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TABLE OF CONTENTS OF VOLUME VII (1938)

	Page
An Eighth Analytical Review of Reports from Pasteur Institutes on the Results of Anti-Rabies Treatment, by A. G. MCKENDRICK, M.B., Ch.B., D.Sc., F.R.C., P.E., F.R.S.E., Lieut.-Col., Indian Medical Service (ret.)	1
Experiments in Malaria Treatment and Prevention carried out in Roumania with Certain Synthetic Drugs :	
Foreword, by M. CIUCA	43
I. Studies on the Treatment of Experimental Malaria Infection with Synthetic Drugs compared with Quinine Sulphate, by M. CIUCA, I. BALLIF, M. CHELARESCO and M. LAVRI-NENKO	47
II. Research on the Treatment of Naturally Acquired Malaria :	
(a) In Hospital : Experiments to ascertain the Efficacy of Synthetic Drugs as compared with Quinine, by M. CIUCA, I. BALTEANU, M. FRANCKE, E. ALEXA and I. MICU	64
(b) Treatment Experiments carried out in the Field, by M. CIUCA, I. BALTEANU and I. ALEXA, with the collaboration of V. BOERIU, I. RUGINA, I. STRETCU and A. RADIANOV	73
III. Efficacy of Atebrin and Quinine in the Prophylactic Treatment of Malaria, by D. MEZINCESCO and D. A. CORNELSON, assisted by C. LAZAR and L. BUSILA	96
IV. Experiments in eradicating Malaria by Means of Synthetic Drugs, carried out by M. CIUCA, I. BALTEANU and I. ALEXA, in collaboration with R. BALTEANU, V. BOERIU and A. RADIANOV	111
Health Indices established in an Experimental Study of the City of Brussels, by K. STOUMAN	122
Report on the Meeting of Directors of Institutes and Schools of Hygiene held at Geneva from November 22nd to 27th, 1937	169

	Page
Second General Report on Certain European Schools and Institutes of Hygiene	191
<i>Annexes :</i>	
1. The Ankara Institute and School of Hygiene	231
2. The Athens School of Hygiene	248
3. The Budapest Institute of Hygiene	264
4. The London School of Hygiene and Tropical Medicine	279
5. The School of Health and National Institute of Hygiene, Madrid	309
6. The Nancy Institute of Hygiene	313
7. The Prague Institute of Hygiene	328
8. The Rome Institute of Public Health	344
9. The Institutes of Hygiene in Roumania	358
10. The Institute of Public Health in Sofia	382
11. The Warsaw State Institute of Hygiene	386
12. The Yugoslav Institutes of Hygiene and School of Public Health	407
Methods of assaying the Content of Morphine in Opium and of Cocaine in Raw Cocaine and in Coca Leaves	429
Sensitiveness and Specificity of a Bordet-Wassermann Reaction (Mørch) and Kahn's Standard Reaction, by P. KRAG	451
Report by the Technical Commission on Nutrition on the Work of its Third Session held in London from November 15th to 20th, 1937	460
Investigations on Undulant Fever in France, by R. M. TAYLOR, M. LISBONNE, L. F. VIDAL and R. H. HAZEMANN.	503
The Significance of Codeine as a Habit-forming Drug, by P. WOLFF	546
Insolation and Natural and Artificial Lighting in Relation to Housing and Town Planning	581
Report of the Group of Experts of the Commission on Physical Education (Geneva, July 6th-8th, 1938)	609
Report on the Work of the Health Organisation between June 1937 and May 1938, and on its 1938 Programme	622
Technical Commission on Nutrition (Report by a Special Committee which met in Geneva from August 22nd to 24th, 1938)	666
Some Preliminary Remarks on the Question of the Standardisation of Smallpox Vaccine, by J. ØRSKOV, M.D.	679

	Page
I. Report on the Meeting of Serologists of the Permanent Commission on Biological Standardisation (Paris, October 19th-22nd, 1938)	683
<i>Annexes :</i>	
<i>Tetanus Antitoxin :</i>	
1a The Assay of Tetanus Antitoxin—Results of Investigations Performed in Five Institutes : Report submitted by the Department of Biological Standards of the State Serum Institute, Copenhagen	713
1b Assay of Three Tetanus Antitoxins, by Professor A. SORDELLI	733
1c The Standardisation of Tetanus Antitoxin : Factors influencing the Assay, by Margaret LLEWELLYN SMITH	739
1d Comparative Assays of International and American Standard Tetanus Antitoxins with Washington and Copenhagen Test Toxins, by Johs. IPSEN and O. ROSTOCK	770
1e The Results of Twenty Different Assays of Five Samples of Tetanus Antitoxin	776
1f Note on Tetanus Antitoxin, by Professor A. SORDELLI	783
<i>Anti-Snake-Venom Serum :</i>	
2. Progress Report on the Possibility of Standardising Anti-Snake-Venom Sera : Submitted by the Department of Biological Standards of the State Serum Institute, Copenhagen	785
<i>Gas Gangrene Antitoxins :</i>	
3a Studies on <i>Perfringens</i> Toxin : Communication from Dr. Ida A. BENGTSON on Work done by Sarah E. STEWART and J. Marion CLAMPIT	802
3b The Necessity and Possibility of Establishing a Standard for Sordelli Antitoxin: Note submitted by the Department of Biological Standards of the State Serum Institute, Copenhagen	807
3c Gas Gangrene Antitoxin (<i>Vibrio septique</i>) : Proposal to change the Strength of the Standard Solution : Note submitted by the Department of Biological Standards of the State Serum Institute, Copenhagen	815
3d The Necessity for Changing the Technique of <i>Perfringens</i> Antitoxin Assay, by M. WEINBERG and M. GUILLAUMIE	818
<i>Anti-Anthrax Serum :</i>	
4a Assays of Anti-Anthrax Serum carried out at the	

	Page
Cantacuzino Institute, Bucharest : Preliminary Communication from Professor C. IONESCO-MIHAIESTI	827
4b The Standardisation of Anti-Anthrax Sera, by Dr. G. IVANOVICS (Szeged)	836
<i>Staphylococcus Antitoxin :</i>	
5. The Preparation of a Second International Standard for Staphylococcus Antitoxin, by Margaret LLEWELLYN SMITH	845
<i>Diphtheria Antitoxin :</i>	
6a Report on Comparative Assays of National Standards in the Years 1934-1938 : Submitted by the Department of Biological Standards of the State Serum Institute, Copenhagen	853
6b Standard Diphtheria Antitoxin for Flocculation Test : Note submitted by the Department of Biological Standards of the State Serum Institute, Copenhagen	859
<i>Anti-Dysentery (Shiga) Serum :</i>	
7. Preliminary Note on the Assay of Anti-Dysentery (Shiga) Sera by the Flocculation Test, by Gh. ISTRATI and A. OLARU	864
IIA. Report on the Adoption of a New International Standard of Vitamin B ₁ and on the Definition of the Existing Unit in Terms of that Standard	874
<i>Annex :</i>	
On the Adoption of Synthetic Vitamin B ₁ (Aneurin) Hydrochloride as International Vitamin B ₁ Standard.	877
IIB. Memorandum on the Second International Standard Vitamin B ₁	882
III. Report of the Third International Conference on the Standardisation of Hormones (Geneva, August 11th to 13th, 1938)	887
General Survey of Medico-Social Policy in Rural Areas	901
International Lists of Causes of Death adopted by the Fifth International Conference for Revision, Paris, October 3rd-7th, 1938	944
Curative Medicine in Rural Areas, by Dr. João de BARROS BARRETO	988
The Present Use of Naturalistic Measures in the Control of Malaria, by L. W. HACKETT, P. F. RUSSELL, J. W. SCHARFF and R. SENIOR WHITE	1016

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**AN EIGHTH ANALYTICAL REVIEW¹ OF
REPORTS FROM PASTEUR INSTITUTES ON
THE RESULTS OF ANTI-RABIES TREATMENT**

by

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I. GENERAL.

The statistics dealt with in this review relate almost entirely to the year 1935. A few reports relating to the previous year, and one for the year 1933, received since the publication of the seventh review, are included.

Schedules which reached Geneva later than July 1st, 1937, will be dealt with in the next review, together with the bulk of the statistics for 1936.

The present analysis deals with a total of 123,040 treated persons. The following table gives the number of cases included in previous reviews, together with the total for all eight reviews.

Review	Persons	Review	Persons
First	31,656	Sixth	118,062
Second	69,707	Seventh	110,884
Third	69,541	Eighth	123,040
Fourth	119,433		
Fifth	115,859	Total	758,182

The general characteristics of each schedule are given below.

¹ For previous reviews, see document C.H.844, and the *Quarterly Bulletin*, 1932, 1, pages 110 and 725; 1933, 2, page 553; 1934, 3, page 613; 1935, 4, page 752; 1937, 6, page 17.

METHODS USED AND RESULTS OBTAINED.

Institute	Year	Vaccine	Days of treatment	Number treated	Deaths	Mortality %	Paralytic accidents	
(1) Dried or glycerinated cords.								
1. Algiers	1935	Dried 5-2 days : glyc.	15-25	2,822	0	0.32	1 (recovered)	
2. Antananarivo (Madagascar) ..	1935	Dried 5-1 days : glyc.	12-20	84	0	0	0	
3. Bangkok, Institute (non-Europeans)	1935	Dried — : glyc.	18-25	339	1	0.29	0	
4. Beirut (Lebanon)	1935	Dried 4-2 days : glyc.	15-25	147	0	0	0	
5. Berne	1935	Dried 10-2 days : glyc.	18-21	6	0	0	0	
6. Bologna	1935	Dried 8-2 days : glyc.	15-20	184	0	0	0	
7. Bordeaux	1935	Dried 5-2 days : glyc.	14-21	144	0	0	0	
8. Casablanca (Morocco)	1935	Dried 5-2 days : glyc.	15-25	1,031	6	0.58	0	
9. Ceara (Brazil)	1935	Dried 6-2 days : glyc.	20-25	275	1	0.36	0	
10. Cordoba (Argentina)	1935	Dried 6-2 days	28-38	460	0	0	0	
11. Dakar (Europeans)	1935	Dried 4-1 days : glyc.	15-20	22	0	0	0	
12. Dakar (non-Europeans)	1935	Dried 4-1 days : glyc.	15-20	65	1	1.5	0	
13. Hanoi (Tongking) (Europeans)	1935	Dried 6-0 days : glyc.	15-20	183	0	0	0	
14. Hanoi (Tongking) (non-Europeans)	1935	Dried 6-0 days : glyc.	15-20	1,184	6	0.51	0	
15. Hue (Annam)	1934	Dried — : glyc.	15-21	549	1	0.18	0	
16. Hue (Annam)	1935	Dried — : glyc.	15-21	542	0	0	0	
17. Keijo (Chosen)	1935	Dried 3-1 days : glyc.	18	2,609	21	0.80	0	
18. La Plata	1935	Dried 6-2 days	12-26	1,006	2	0.2	1 (recovered)	
19. Lille	1935	Dried 30-2 days : glyc.	14-24	75	0	0	0	
20. Lyons	1935	Dried 4-2 days	15-25	101	0	0	0	
21. Montevideo	1935	Dried 8-1 days	14-20	1,120	0	0	0	
22. Montpellier	1935	Dried — : glyc.	13-24	141	0	0	0	
23. Paris	1935	Dried 4-2 days : glyc.	15-25	510	0	0	0	
24. Phnom-Penh (Cambodia)	1934	Dried 5-2 days : glyc.	15-21	371	1	0.27	0	
25. Phnom-Penh (Cambodia). ...	1935	Dried — : glyc.	?	459	0	0	0	
26. Saigon (Europeans)	1933	Dried 6-1 days : glyc.	15-21	178	0	0	0	
27. Saigon (non-Europeans)	1933	Dried 6-1 days : glyc.	15-21	1,443	6	0.42	0	
28. Saigon (Europeans)	1934	Dried 6-1 days : glyc.	15-21	74	0	0	0	
29. Saigon (non-Europeans)	1934	Dried 6-1 days : glyc.	15-21	1,575	4	0.25	0	
30. Saigon (Europeans)	1935	Dried 6-1 days : glyc.	15-21	107	0	0	0	
31. Saigon (non-Europeans)	1935	Dried 6-1 days : glyc.	15-21	1,897	3	0.16	0	
32. Tartu (Estonia)	1935	Dried 4-2 days : glyc.	?	41	0	0	0	
33. Tokio	1935	Dried 5-1 days : glyc.	18	61	0	0	0	
34. Tunis	1935	Dried 4-1 days : glyc.	12-16	1,949	8	0.41	0	
35. Vientiane (Laos) (non-Europeans)	1935	Dried 6-0 days	15-20	77	0	0	0	
36. Vilno (Poland)	1935	Dried 8-2 days : glyc.	14-20	20	0	0	0	
					21,851	70	0.32	2 (both recovered)

(2) *Modified dilution methods.*

1. Barcelona	1935	Högyes modified : 1/5000-1/100	20	691	0	0	0
2. Budapest	1935	Högyes modified : 100-270 mg.	6-10	4,028	1	0.02	1 (recovered)
3. Certain Bulgarian institutes ..	1935	Boecker's vaccine : 90 mg.	20	3,016	7	0.23	0
4. Riga (at institute)	1935	Dilution	14-21	14	0	0	0
5. Riga (outside institute)	1935	Dilution	14-21	230	0	0	0
				7,979	8	0.10	1 (recovered)

(3-6) *Phenol vaccines : modifications of Fermi's method.*(3) *Killed phenol vaccines.*

1. Baghdad (Europeans)	1935	700-3500 mg. : Semple	7-14	2	0	0	0
2. Baghdad (non-Europeans) ...	1935	700-3500 mg. : Semple	7-14	298	1	0.34	0
3. Bangkok, institute.....	1935	Phenolised vaccine	14	1,059	3	0.28	0
4. Bangkok (outside institute) (non-Europeans)	1935	Phenolised vaccine	14	1,645	3	0.18	0
5. Beirut (Lebanon)	1935	700 mg. : Semple	14	20	0	0	0
6. Bombay (Europeans)	1935	700-7000 mg. : Semple	7-14	376	0	0	0
7. Bombay (non-Europeans) ...	1935	700-7000 mg. : Semple	7-14	7,746	36	0.46	0
8. Cairo (Europeans)	1935	3750-8500 mg. : Semple	15-20	100	0	0	0
9. Cairo (non-Europeans)	1935	3750-8500 mg. : Semple	15-20	3,462	6	0.17	0
10. Calcutta, institute (Europeans)	1935	350-700 mg. : Semple	7-14	79	1	1.27	0
11. Calcutta, institute (non-Euro- peans)	1935	350-700 mg. : Semple	7-14	754	2	0.27	0
12. Calcutta, out-centres (Euro- peans)	1935	350-700 mg. : Semple	7-14	227	0	0	0
13. Calcutta, out-centres (non-Eu- ropeans)	1935	350-700 mg. : Semple	7-14	4,188	26	0.62	0
14. Cernauti (Roumania)	1935	1800-2700 mg. : Semple	12-18	1,022	5	0.48	0
15. Colombo	1935	Semple	14	1,875	12	0.64	Number not stated, but all recovered.
16. Coonoor (Europeans)	1935	700-7000 mg. : Semple	7-14	354	0	0	0
17. Coonoor (non-Europeans) ...	1935	700-7000 mg. : Semple	7-14	12,361	20	0.16	0
18. Cracow	1934	? : Semple	20	104	0	0	0
19. Cracow	1935	? : Semple	20	140	0	0	0
20. Hong-Kong	1935	1400 mg. : Semple	14	435	3	0.69	0
21. Kasauli, institute (Europeans)	1935	1200-7000 mg. : Semple	14	9	0	0	0
22. Kasauli, out-centres (Euro- peans)	1935	1200-7000 mg. : Semple	14	1,464	0	0	0
23. Kasauli, institute (non-Euro- peans) : Class II	1935	1200 mg. : Semple	14	146	0	0	0
24. Kasauli, out-centres (non-Eu- ropeans) : Class II	1935	1200 mg. : Semple	14	2,023	2	0.10	0

Institute	Year	Vaccine	Days of treatment	Number treated	Deaths	Mortality %	Paralytic accidents
25. Kasauli, institute (non-Europeans) : Class III	1935	3500 mg. : Semple	14	319	1	0.31	0
26. Kasauli, out-centres (non-Europeans) : Class III	1935	3500 mg. : Semple	14	7,370	23	0.31	0
27. Kasauli, institute (non-Europeans) : Class IV	1935	7000 mg. : Semple	14	343	3	0.87	0
28. Kasauli, out-centres (non-Europeans) : Class IV	1935	7000 mg. : Semple	14	3,617	57	1.58	2 (both recovered)
29. Kuala Lumpur	1935	1400-2100 mg. : Semple	14-21	60	0	0	0
30. Lisbon	1935	2500-10000 mg. : Semple	10-40	945	0	0	0
31. Milan	1935	4500-7500 mg. : Semple	15-25	50	0	0	0
32. New Orleans (Europeans)	1935	? : Semple	?	225	0	0	0
33. New Orleans (non-Europeans)	1935	? : Semple	?	44	0	0	0
34. New York	1935	? : Semple	14-21	1,609	0	0	1 (recovered)
35. Palestine	1935	700-2100 mg. : Semple	14-21	1,685	1	0.06	0
36. Rangoon (Europeans)	1935	700-7000 mg. : Semple	7-14	232	0	0	1 (fatal)
37. Rangoon (non-Europeans)	1935	700-7000 mg. : Semple	7-14	1,336	3	0.22	0
38. Santa Clara (Cuba)	1935	1920-3360 mg. : Semple	15-21	371	0	0	0
39. Santiago (Chile)	1935	2240-4800 mg. : Semple	?	983	2	0.20	0
40. Shanghai (Europeans)	1935	1125-1575 mg. : Semple	15-21	190	0	0	0
41. Shanghai (non-Europeans)	1935	1125-1575 mg. : Semple	15-21	559	2	0.36	0
42. Shillong, at institute	1935	700-4200 mg. : Semple	7-14	173	1	0.58	0
43. Toronto	1935	— : Semple	?	12	0	0	0
44. Warsaw, at institute	1935	1200 mg. : Semple	20	125	0	0	1 (fatal)
45. Warsaw, outside institute	1935	1200 mg. : Semple	20	2,372	3	0.13	0
				62,509	216	0.35	5 (2 fatal)

(4) *Live phenol vaccines : Puntoni's modification.*

1. Ancona	1935	Puntoni's modification	16-24	8	0	0	0
2. Catania	1935	Puntoni's modification	15-25	107	0	0	0
3. Florence	1935	Puntoni's modification	?	41	0	0	0
4. Palermo	1935	Puntoni's modification : 3200-9600 mg.	20-31	356	0	0	0
5. Rome	1935	Puntoni's modification	15-25	91	0	0	0
6. Trapani	1935	Puntoni's modification : 3200-9600 mg.	15-25	4	0	0	0
7. Turin	1935	Puntoni's modification : 3200-9600 mg.	15-25	27	0	0	0
				634	0	0	0

(5) *Fermi's original vaccine.*

1. Buenos Aires	1935	Fermi : 9000-9150 mg.	20-28	818	0	0	0
2. Genoa	1935	Fermi : 3750-6250 mg.	?	3	0	0	0
3. Kosice (Czechoslovakia)	1935	Fermi : ?	14-21	406	1	0.25	0
				1,227	1	0.08	0

(7) *Heated vaccines : Babes' method.*

1. Bucharest	1935	Dried 6-0 days + heated 50°-60°C.	10-24	7,418	14	0.19	0
2. Chisinau (Roumania)	1935	Högyes in light cases, heated 60°C. in severe cases	14-23	2,112	3	0.14	0
3. Jassy	1935	Heated 60°-65°C. + Fermi	12-18	3,887	3	0.07	0
				13,417	20	0.15	0

(8) *Killed ether vaccine : Hempt's method.*

1. Yugoslavian institutes	1935	Hempt's standard method	1-6	9,110	6	0.06	1 (fatal)
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(9) *Mixed treatments.*

(a) 1. Athens	1935	} Boecker +, in severe cases, Alivisatos	20	1,796	1	0.06	0
2. Certain Bulgarian institutes	1935						
3. Vienna	1935	Högyes + Alivisatos	13-21	197	1	0.51	3 (1 fatal)
				3,642	4	0.11	3 (1 fatal)
(b) 1. Buenos Aires	1935	Cords dried 6-1 days : glyc. +, in severe cases, Fermi's original vaccine		2,671	7	0.26	1 (recovered)

II. METHODS OF TREATMENT.

The methods of treatment employed at each institute, its duration and, where available, its dosage are given in the preceding table.

For purposes of comparison, the various methods of treatment have been classified under the following headings :

1. *Dried or glycerinated cords* (Pasteur's original method and Calmette's modification).
2. *Modified dilution methods* (Högyes).
- 3-6. *Phenol : Modifications of Fermi's method.*
3. *Killed phenol vaccines* (Semple and Mulford's modifications).
4. *Live phenol vaccines* (Puntoni's modification).
5. *Fermi's original method.*
6. *Fermi's sero-vaccine.*
7. *Heated vaccines* (Babes).
8. *Killed ether vaccines* (Hempt).
9. *Mixed treatments :*
 - (a) (dilutions *plus*, in severe cases, Alivisatos) ;
 - (b) (dried cords *plus*, in severe cases, Fermi's original vaccine).
10. *Yatren vaccine.*

In certain instances, the following shortened system of classification has been employed :

- (a) *Killed vaccines* : comprising 3 and 8 above.
- (b) *Live vaccines* : comprising 1, 2, 4 and 9 above.
- (c) *Heated vaccines* :
- (d) *Other* : comprising 5, 6 and 10 above.

III. NUMBER OF PERSONS TREATED.

The total number of treated persons regarding whom information has been received was 123,040. The adjoining table gives the distribution of these according to the method of treatment, the number of institutes concerned, and the average annual number of

patients per institute. In certain places, the table is incomplete. This arises from the fact that the statistics from a group of institutes are sometimes submitted on one schedule. Where no entry is made, the detail will be found in the table on pages 2-5.

	Patients	Institutes	Average per institute
1. Cords	21,851	31	705
2. Dilutions	7,979	—	—
3. Killed phenol	62,336*	25	2,493
4. Live phenol	634	7	91
5. Fermi's vaccine	1,227	3	409
6. Fermi's S.V.	—	—	—
7. Heated	13,417	3	4,472
8. Killed ether	9,110	—	—
9. Mixed (a and b)	6,313	—	—
Total	122,867*		

* Omitting Shillong, as the statistics for patients treated at out-centres served from this institute were not received.

IV. MORTALITIES FOR ALL PATIENTS.

Of the total of 123,040 treated persons, 332 died of rabies. The percentage mortality was thus 0.27 as compared with 0.49 in the first, 0.48 in the second, 0.23 in the third, 0.48 in the fourth, 0.38 in the fifth, 0.35 in the sixth, 0.30 in the seventh, and 0.36 over the whole period covered by the eight reviews.

The detailed figures for the present statistics and for the set of eight reviews, are as follows :

	Eighth review			All eight reviews			
	Number treated	Deaths	Mortality %	Number treated	Deaths		Mortality %
					Observed	Calculated*	
1. Cords	21,851	70	0.32	114,240	427	413	0.37
2. Dilutions ...	7,979	8	0.10	62,857	124	227	0.20
3. Killed phenol	62,509	216	0.35	355,612	1,860	1,287	0.52
4. Live phenol.	634	0	0	3,464	6	13	0.17
5. Fermi's vacc.	1,227	1	0.08	7,319	13	26	0.18
6. Fermi's S.V.	—	—	—	390	0	1.4	0
7. Heated	13,417	20	0.15	93,145	154	337	0.17
8. Killed ether.	9,110	6	0.06	63,444	79	230	0.12
9. Mixed (a) ..	3,642	4	0.11	49,656	60	180	0.12
(b) ..	2,671	7	0.26	2,671	7	9	0.26
10. Yatren	—	—	—	5,384	13	19	0.24
Total	123,040	332	0.27	758,182	2,743	2,741.4	0.36

P < 1 in a million.

* Calculated from the mortality of the total of the eleven groups (i.e., from 0.3618%).

STATISTICS ON RABIES

According to the shortened system of classification, the figures are :

	Eighth review			All eight reviews			Mortality %
	Number treated	Deaths	Mortality %	Number treated	Deaths		
					Observed	Calculated	
(a) Killed	71,619	222	0.31	419,056	1,939	1,516	0.46
(b) Live	36,777	89	0.24	232,888	624	843	0.27
(c) Heated	13,417	20	0.15	93,145	154	337	0.17
(d) Other	1,227	1	0.08	13,093	26	47	0.20
Total	123,040	332	0.27	758,182	2,743	2,743	0.36

P < 1 in a million.

The percentage mortalities in the successive reviews and in the whole set have been :

	First	Second	Third	Fourth	Fifth	Sixth	Seventh	Eighth	All eight
(a) Killed .	0.65	0.80	0.28	0.66	0.51	0.40	0.35	0.31	0.46
(b) Live ..	0.27	0.26	0.21	0.26	0.23	0.31	0.28	0.24	0.27
(c) Heated.	—	0.15	0.08	0.04	0.24	0.18	0.11	0.15	0.17
(d) Other .	—	—	—	0.22	0.27	0	0	0.08	0.20
Total .	0.49	0.48	0.23	0.48	0.38	0.35	0.30	0.27	0.36

The same tests of significance of differences as were employed and described in previous reviews have been used. It will be remembered that a value P is obtained from the statistics which measures the probability that equal or greater differences than those observed would be likely to occur in samples of a population which was admittedly homogeneous. The underlying idea is to test the assumption that the various figures derived from different methods of treatment refer to samples selected at random from a very large homogeneous population. When the results of the statistical analysis indicate that the figures do not agree with this assumption, the data will be referred to as *heterogeneous* or as showing a *significant difference*. The dividing-line between *homogeneity* and *heterogeneity* may conveniently be taken as being defined by $P = 0.05$, any lesser value indicating a real discrepancy and, in the present comparison, significant differences in the efficacy of the various vaccination methods employed.

V. RACIAL STATISTICS.

Information regarding race type was lacking in the case of 4,943 persons, one of whom died of rabies.

Of the remainder, 53,423 were Europeans (45.2%) and 64,674 were of non-European birth (54.8%).

The percentages of Europeans in the various groups for this and former years were as follows :

	First	Second	Third	Fourth	Fifth	Sixth	Seventh	Eighth	All eight
1. Cords	57.6	52.7	50.2	62.5	56.1	49.5	49.1	29.8	49.0
2. Dilutions	100	100	100	94.8	96.6	100	89.0	100	97.2
3. Killed phenol.	19.7	11.9	62.1	10.3	15.6	12.9	21.5	15.6	16.5
4. Live phenol ..	—	100	100	100	100	100	100	100	100
5. Fermi's vacc. .	—	—	—	100	100	100	100	100	100
6. Fermi's S.V. .	—	—	—	100	100	—	100	—	100
7. Heated	—	100	100	100	100	100	100	100	100
8. Killed ether ..	99.7	—	100	100	100	100	100	100	100
9. Mixed (a) & (b)	100	100	100	100	100	100	100	100	100
10. Yatren	—	—	—	100	100	—	—	—	100
Total	52.4	53.5	81.1	48.9	58.0	52.0	50.8	45.2	53.9

The figures relating to mortality are given in the following table :

	Number treated	Eighth review			Mortality %	Number treated	All eight reviews			Mortality %
		Deaths		Calculated			Deaths		Calculated	
		Observed	Calculated				Observed	Calculated		
<i>Europeans.</i>										
1. Cords	6,370	4	7.3	0.06	53,773	77	82	0.14		
2. Dilutions ...	7,979	8	9.1	0.10	61,080	108	93	0.18		
3. Killed phenol	9,191	11	10.5	0.12	55,644	82	84	0.15		
4. Live phenol.	634	0	0.7	0	3,464	6	5	0.17		
5. Fermi's vacc.	409	1	0.5	0.24	6,500	13	10	0.20		
6. Fermi's S.V.	—	—	—	—	390	0	0.6	0		
7. Heated	13,417	20	15.3	0.15	93,145	154	141	0.17		
8. Killed ether.	9,110	6	10.4	0.07	63,444	79	96	0.12		
9. Mixed (a) ..	3,642	4	4.2	0.11	49,656	60	75	0.12		
(b) ..	2,671	7	3.0	0.26	2,671	7	4	0.26		
10. Yatren	—	—	—	—	5,384	13	8	0.24		
Total	53,423	61	61.0	0.11	395,151	599	598.6	0.15		
	P = 0.32					P = 0.12				
<i>Non-Europeans.</i>										
1. Cords	15,021	66	63	0.44	56,044	341	351	0.61		
2. Dilutions	—	—	—	—	1,777	16	11	0.90		
3. Killed phenol.	49,653	204	207	0.41	280,696	1,761	1,756	0.63		
Total	64,674	270	270	0.42	338,517	2,118	2,118	0.63		
	P = 0.53					P = 0.3				

Or, using the shortened system of classification :

	Eighth review				All eight reviews			
	Number treated	Deaths		Mortality %	Number treated	Deaths		Mortality %
		Observed	Calculated			Observed	Calculated	
<i>Europeans.</i>								
(a) Killed	18,301	17	21	0.09	119,088	161	181	0.14
(b) Live	21,296	23	24	0.11	170,644	258	259	0.15
(c) Heated	13,417	20	15	0.15	93,145	154	141	0.17
(d) Other	409	1	0.5	0.24	12,274	26	19	0.21
Total	53,423	61	60.5	0.11	395,151	599	600	0.15
	P = 0.7				P = 0.11			
<i>Non-Europeans.</i>								
(a) Killed	49,653	204	207	0.41	280,696	1,761	1,757	0.63
(b) Live	15,021	66	63	0.44	57,821	357	362	0.62
Total	64,674	270	270	0.42	338,517	2,118	2,119	0.63
	P = 0.7				P = 0.79			

The mortalities as compared with previous reviews are as under :

<i>Europeans.</i>	First	Second	Third	Fourth	Fifth	Sixth	Seventh	Eighth	All eight
(a) Killed ..	0.10	0.14	0.10	0.12	0.19	0.22	0.14	0.09	0.14
(b) Live ...	0.20	0.11	0.13	0.15	0.17	0.22	0.13	0.11	0.15
(c) Heated .	—	0.15	0.08	0.04	0.24	0.18	0.11	0.15	0.17
(d) Other ..	—	—	—	0.19	0.27	0	0	0.24	0.21
Total..	0.17	0.13	0.10	0.14	0.21	0.21	0.13	0.11	0.15
<i>Non-Europeans.</i>									
(a) Killed ..	0.83	0.89	0.93	0.85	0.65	0.52	0.45	0.41	0.63
(b) Live ...	1.02	0.82	0.71	0.74	0.46	0.65	0.67	0.44	0.62
Total .	0.84	0.88	0.78	0.83	0.62	0.54	0.48	0.42	0.63

Each of the values of P, in the figures for either race type in this review and in the figures relating to all eight reviews, is greater than 0.05. Consequently, there is no evidence of heterogeneity arising from the method of treatment—that is to say, there is no evidence of significant differences in the efficacies of the various methods.

It appears from the combined figures that the mortality amongst non-Europeans is 4.2 times as great as that amongst Europeans.

VI. SPECIES OF BITING ANIMAL.

The percentages of persons bitten by the different species of animals are as under :

	Dog	Cat	Wolf	Jackal	Solipeds	Ruminants	Other	Human
1. Cords	92.4	5.0	0.03	0.05	0.5	0.2	1.5	0.4
2. Dilutions	76.9	11.2	0.01	0	0.7	7.7	1.5	1.9
3. Killed phenol	88.7	2.2	0.09	5.8	0.6	0.8	1.2	0.6
4. Live phenol	75.9	18.9	0	0	1.4	0	3.3	0.5
5. Fermi's vacc.	89.4	6.5	0	0	0.8	2.2	1.2	0
6. Fermi's S.V.	—	—	—	—	—	—	—	—
7. Heated	87.4	6.6	0.1	0	0.7	3.4	1.3	0.5
8. Killed ether	83.1	5.9	0.2	0	0.5	4.8	2.0	3.5
9. Mixed (a)	88.7	7.9	0.2	0	0.5	2.1	0.2	0.2
(b)	86.8	10.8	0	0	0.4	0.2	1.5	0.3
Total	87.9	4.5	0.1	3.0	0.6	1.7	1.4	0.8

The figures relating to mortality are as follows :

	(a) Dog			(b) Cat		
	Number treated	Deaths	Mortality %	Number treated	Deaths	Mortality %
1. Cords	19,496	68	0.35	1,048	0	0
2. Dilutions	6,139	8	0.13	893	0	0
3. Killed phenol	54,942	157	0.29	1,388	1	0.07
4. Live phenol	481	0	0	120	0	0
5. Fermi's vacc.	1,005	1	0.10	73	0	0
6. Fermi's S.V.	—	—	—	—	—	—
7. Heated	11,725	17	0.14	891	3	0.34
8. Killed ether	7,567	5	0.06	541	0	0
9. Mixed (a)	3,233	4	0.12	288	0	0
(b)	2,319	7	0.30	289	0	0
Total	106,907	267	0.25	5,531	4	0.07

(c) Wolf

	Eighth review			Number treated	All eight reviews		Mortality %
	Number treated	Deaths	Mortality %		Deaths		
					Observed	Calculated	
1. Cords	6	0	0	76	4	6.2	5.26
2. Dilutions ...	1	0	0	57	11	4.6	19.30
3. Killed phenol	56	3	5.36	478	42	38.9	8.79
5. Fermi's vacc.	0	0	0	5	0	0.4	0
6. Fermi's S.V.	—	—	—	0	0	0	0
7. Heated	11	0	0	87	6	7.1	6.90
8. Killed ether.	17	1	5.88	217	15	17.7	6.91
9. Mixed (a)...	8	0	0	76	5	6.2	6.58
10. Yatren	—	—	—	23	0	1.9	0
Total	99	4	4.04	1,019	83	83.0	8.15

P = 0.07

STATISTICS ON RABIES

(d) *Jackal*

	Eighth review			Number treated	All eight reviews		Mortality %
	Number treated	Deaths	Mortality %		Deaths		
					Observed	Calculated	
1. Cords	10	1	10	125	3	2	2.40
2. Dilutions ...	0	0	0	77	0	1	0
3. Killed phenol	3,620	54	1.49	23,290	373	372	1.60
7. Heated	0	0	0	70	0	1	0
8. Killed ether.	0	0	0	4	0	0	0
9. Mixed	0	0	0	35	1	0.6	2.86
Total	3,630	55	1.52	23,601	377	376.6	1.60

$$P = 0.6$$

(e) *Solipeds, Ruminants, Human and Other*
 (The figures in parentheses indicate deaths)

	Solipeds	Ruminants	Other	Human	Missing
1. Cords	106 (1)	44	313	89	739
2. Dilutions	57	612	122	155	0
3. Killed phenol	380	467	766 (1)	361	529
4. Live phenol	9	0	21	3	0
5. Fermi's vacc.	9	25	13	0	102
6. Fermi's S.V.	—	—	—	—	—
7. Heated	94	453	177	66	0
8. Killed ether ...	50	434	184	317	0
9. Mixed (a).....	19	76	9	9	0
(b).....	11	5	40	7	0
Total	735 (1)	2,116	1,645 (1)	1,007	1,370

Information regarding the biting animal was lacking in the case of 1,370 persons, of whom none died of rabies.

The death amongst those bitten by solipeds occurred at Tunis, the animal being an ass. Amongst "other animals", the death was following a mongoose bite (Kasauli).

From the combined figures for the eight reviews, it appears that, of 17,794 persons bitten by solipeds and ruminants, only two cases (one from Chosen and one from Tunis) have developed rabies. Os 5,562 persons who have come in contact with cases of human rabies, only one (Kasauli) has been reported as having contracted the disease.

VII. EVIDENCE OF RABIES IN THE BITING ANIMAL.

The percentages of treated persons in the different categories¹ are as follows :

	A	B	C	D
1. Cords	11.0	11.0	72.0	5.9
2. Dilutions	17.3	17.2	50.4	15.0
3. Killed phenol	5.9	8.1	84.5	1.5
4. Live phenol	7.9	13.8	77.4	0.8
5. Fermi's vacc.	15.4	67.8	16.8	0
6. Fermi's S.V.	—	—	—	—
7. Heated	6.1	28.9	57.5	7.5
8. Killed ether	20.1	10.3	69.7	0
9. Mixed (a)	22.9	42.9	21.4	12.8
(b)	24.7	2.3	73.0	0
Total	9.7	13.2	73.2	4.0

The figures relating to mortality in the different categories are as under :

Category A.

	Eighth review			All eight reviews		
	Number treated	Deaths	Mortality %	Number treated	Deaths	Mortality %
1. Cords	2,259	10	0.44	8,940	58	0.65
2. Dilutions	1,384	0	0	7,817	14	0.18
3. Killed phenol	3,649	15	0.41	17,314	95	0.55
4. Live phenol	50	0	0	288	0	0
5. Fermi's vacc.	189	1	0.53	597	2	0.34
6. Fermi's S.V.	0	0	0	24	0	0
7. Heated	824	5	0.61	6,506	23	0.35
8. Killed ether	1,832	3	0.16	8,402	20	0.24
9. Mixed (a)	833	0	0	6,778	10	0.15
(b)	660	4	0.61	660	4	0.61
10. Yatren	0	0	0	298	0	0
Total	11,680	38	0.33	57,624	226	0.39

Category B.

1. Cords	2,261	8	0.35	18,057	106	0.59
2. Dilutions	1,373	4	0.29	12,974	41	0.32
3. Killed phenol	4,978	8	0.16	23,987	78	0.33
4. Live phenol	87	0	0	611	2	0.33
5. Fermi's vacc.	832	0	0	1,816	2	0.11
6. Fermi's S.V.	0	0	0	60	0	0
7. Heated	3,878	5	0.12	24,000	31	0.13
8. Killed ether	934	0	0	6,231	8	0.13
9. Mixed (a)	1,564	4	0.26	19,842	33	0.17
(b)	61	1	0.14	61	1	0.14
10. Yatren	0	0	0	2,644	9	0.34
Total	15,968	30	0.19	110,283	311	0.28

¹ A = proved rabid by experiment.

B = certified rabid by medical or veterinary physician.

C = suspected to be rabid.

D = non-suspected to be rabid.

STATISTICS ON RABIES

Category C.

	Eighth review			All eight reviews		
	Number treated	Deaths	Mortality %	Number treated	Deaths	Mortality %
1. Cords	14,787	50	0.34	71,097	233	0.33
2. Dilutions	4,024	3	0.07	30,539	44	0.14
3. Killed phenol	52,193	191	0.37	284,713	1,635	0.57
4. Live phenol	488	0	0	2,061	3	0.15
5. Fermi's vacc.	206	0	0	1,895	3	0.16
6. Fermi's S.V.	0	0	0	52	0	0
7. Heated	7,715	10	0.13	56,312	97	0.17
8. Killed ether	6,344	3	0.05	33,081	44	0.13
9. Mixed (a)	779	0	0	12,368	9	0.07
(b)	1,950	2	0.10	1,950	2	0.10
10. Yatren	0	0	0	1,486	4	0.27
Total	88,486	259	0.29	495,554	2,074	0.42

Category D.

1. Cords	1,209	0	0	7,803	3	0.04
2. Dilutions	1,198	1	0.08	6,952	9	0.13
3. Killed phenol	934	2	0.21	15,262	20	0.13
4. Live phenol	5	0	0	98	0	0
5. Fermi's vacc.	0	0	0	18	0	0
6. Fermi's S.V.	0	0	0	0	0	0
7. Heated	1,000	0	0	4,894	0	0
8. Killed ether	0	0	0	12,732	0	0
9. Mixed (a)	466	0	0	6,976	3	0.04
10. Yatren	0	0	0	956	0	0
Total	4,812	3	0.06	55,691	35	0.06

Details regarding 2,094 persons, of whom two died of rabies, are lacking. Three fatal cases are reported as having occurred in category D. Of these, two are reported from Shanghai, and one from Bulgaria.

As in former reviews, in this and in the succeeding sections, statistics of the two race-types—European and non-European—will be treated separately, as the degree of heterogeneity introduced when they are taken together is so great as to mask other effects. This has involved a great deal of labour, both for those preparing and submitting schedules for the two race-types separately, and in the subsequent treatment of the statistics. The reviewer desires again to thank those directors of institutes who have collaborated in this matter.

In the following table the statistics for categories A and B combined—that is, statistics of those bitten by animals proved or certified to be rabid—and those of category C—relating to those

bitten by animals suspected to be rabid—are given for the eighth and for the total of all eight reviews.

Categories A and B (combined).

<i>Europeans.</i>	Eighth review			Number treated	All eight reviews		Mortality %
	Number treated	Deaths	Mortality %		Deaths		
					Observed	Calculated	
1. Cords	1,162	1	0.09	9,954	18	20	0.18
2. Dilutions . . .	2,757	4	0.15	22,513	55	45	0.24
3. Killed phenol	4,031	4	0.10	20,128	40	40	0.20
4. Live phenol.	137	0	0	1,205	3	2	0.25
5. Fermi's vacc.	203	1	0.49	1,595	4	3	0.25
6. Fermi's S.V.	0	0	0	84	0	0.2	0
7. Heated	4,702	10	0.21	31,516	57	63	0.18
8. Killed ether.	2,766	3	0.11	17,631	35	35	0.20
9. Mixed (a) ..	2,397	4	0.17	28,948	47	58	0.16
(b) ..	721	5	0.69	721	5	1.4	0.69
10. Yatren	0	0	0	2,942	9	6	0.31
Total	18,876	32	0.17	137,237	273	273	0.20
P = 0.05							
<i>Non-Europeans.</i>							
1. Cords	545	5	0.92	3,139	44	24	1.40
2. Dilutions	0	0	0	474	2	4	0.42
3. Killed phenol	1,569	7	0.45	10,913	63	82	0.58
Total	2,114	12	0.57	14,526	109	110	0.75
P = 0.00002							

Category C.

<i>Europeans.</i>	Eighth review			Number treated	All eight reviews		Mortality %
	Number treated	Deaths	Mortality %		Deaths		
					Observed	Calculated	
1. Cords	1,148	0	0	13,606	15	20	0.11
2. Dilutions . . .	4,024	3	0.07	29,332	35	43	0.12
3. Killed phenol	4,794	7	0.15	27,449	50	40	0.18
4. Live phenol.	488	0	0	2,061	3	3	0.15
5. Fermi's vacc.	206	0	0	1,900	3	3	0.16
6. Fermi's S.V.	0	0	0	52	0	0.8	0
7. Heated	7,715	10	0.13	56,312	97	82	0.17
8. Killed ether.	6,344	3	0.05	33,081	44	48	0.13
9. Mixed (a) ..	779	0	0	12,368	9	18	0.07
(b) ..	1,950	2	0.10	1,950	2	3	0.10
10. Yatren	0	0	0	1,486	4	2	0.27
Total	27,448	25	0.09	179,597	262	262.8	0.15
P = 0.03							
<i>Non-Europeans.</i>							
1. Cords	5,648	16	0.28	15,382	69	86	0.45
2. Dilutions	0	0	0	680	0	3.8	0
3. Killed phenol	44,110	176	0.40	169,798	975	954	0.57
Total	49,758	192	0.39	185,860	1,044	1,043.8	0.56
P = 0.02							

The values of P are, with one exception, of doubtful significance ; that is to say, they are of the order of 0.05. The exception is the case of non-Europeans belonging to the A and B group. This variation is largely a reflection of the relatively high mortalities amongst those treated at Keijo and Tonkin by cords, an occurrence which was referred to in last year's review ; but it is to be noted that the present figures also show similar high mortalities, and that these occurred at a number of Asian institutes.

It is as well at this point to study the following table, in which all three categories are combined. The difference between this table and that in Section V is simply that category D—that is, those bitten by dogs *not* suspected to be rabid—is excluded. The figures are as follows :

<i>Europeans.</i>	Number treated	All eight reviews Deaths		Mortality %
		Observed	Calculated	
1. Cords	23,560	33	40	0.14
2. Dilutions	51,845	90	88	0.17
3. Killed phenol	47,577	90	80	0.19
4. Live phenol	3,266	6	6	0.18
5. Fermi's vacc.	3,495	7	6	0.20
6. Fermi's S.V.	136	0	0.2	0
7. Heated	87,828	154	148	0.18
8. Killed ether	50,712	79	86	0.16
9. Mixed (a)	41,316	56	70	0.14
(b)	2,671	7	5	0.26
10. Yatren	4,428	13	7	0.29
Total	316,834	535	536.2	0.17
		P = 0.28		
<i>Non-Europeans.</i>				
1. Cords	18,521	113	107	0.61
2. Dilutions	1,154	2	6.6	0.17
3. Killed phenol	180,711	1,038	1,040	0.57
Total	200,386	1,153	1,153.6	0.58
		P = 0.20		

Also in the abbreviated form of classification :

<i>Europeans.</i>				
(a) Killed	98,289	169	166	0.17
(b) Live	122,658	192	207	0.16
(c) Heated	87,828	154	148	0.18
(d) Other	8,059	20	14	0.25
Total	316,834	535	535	0.17
		P = 0.26		

Non-Europeans.	Number treated	All eight reviews		Mortality %
		Deaths		
		Observed	Calculated	
(a) Killed	180,711	1,038	1,040	0.57
(b) Live	19,675	115	113	0.58
Total	200,386	1,153	1,153	0.58

$P = 0.84$

It is to be noted that there is no evidence of heterogeneity in any of the groups of this table, and that the values of the Ps in this section are, if anything, lower than those of Section V. The omission of category D may thus have led to some clarification, evidenced in an increasing probability of homogeneity. As regards the division of cases into categories, it would appear that the important division is between suspected of rabies and not suspected of rabies—or, in other words, that entrance into category C is a very strong indication that the biting animal was rabid. This is not to be wondered at, as the judgment in this case depends upon the decision, arrived at from the evidence, by the director of a Pasteur Institute.

VIII. SEVERITY OF BITE.

The percentage proportions in the several groups are as follows :

	Deep	Superficial	No visible lesion
1. Cords	23.4	59.5	17.1
2. Dilutions	16.6	70.3	13.1
3. Killed phenol	51.8	41.8	6.3
4. Live phenol	22.9	73.3	3.8
5. Fermi's vacc.	47.0	37.2	15.8
6. Fermi's S.V.	—	—	—
7. Heated	13.7	75.6	10.6
8. Killed ether	19.0	48.5	32.6
9. Mixed (a)	35.3	42.6	22.0
(b)	4.4	95.5	0
Total	35.9	52.5	11.5

The percentages with no visible lesion treated by killed ether and mixed (a) (dilution and Alivisatos) are, as in the last two reviews, rather high.

STATISTICS ON RABIES

The figures relating to mortalities are as follows :

	(a) <i>Deep</i>			(b) <i>Superficial</i>			(c) <i>No visible lesion</i>	
	Number treated	Deaths	Mortality %	Number treated	Deaths	Mortality %	Number treated	Deaths
1. Cords	5,094	53	1.04	12,957	17	0.13	3,727	0
2. Dilutions	1,324	4	0.30	5,613	4	0.07	1,042	0
3. Killed phenol	31,614	172	0.54	25,495	44	0.17	3,871	0
4. Live phenol	145	0	0	465	0	0	24	0
5. Fermi's vacc.	191	1	0.52	151	0	0	64	0
6. Fermi's S.V.	0	0	0	0	0	0	0	0
7. Heated	1,841	14	0.76	10,147	6	0.06	1,429	0
8. Killed ether	1,728	3	0.17	4,414	3	0.07	2,968	0
9. Mixed (a)	1,287	3	0.23	1,552	1	0.06	803	0
(b)	119	1	0.84	2,552	6	0.24	0	0
Total	43,343	251	0.58	63,346	81	0.13	13,928	0

Information is not available regarding 2,423 persons, of whom none developed rabies.

In the following tables, the statistics, as in former reviews, are subdivided according to race type :

(a) *Deep.*

	Eighth review			All eight reviews			
	Number treated	Deaths	Mortality %	Number treated	Deaths		Mortality %
<i>Europeans.</i>					Observed	Calculated	
1. Cords	376	0	0	5,329	27	27	0.51
2. Dilutions ...	1,324	4	0.30	10,459	78	54	0.75
3. Killed phenol	2,823	9	0.32	9,197	75	47	0.82
4. Live phenol.	145	0	0	921	3	5	0.33
5. Fermi's vacc.	191	1	0.52	1,177	7	6	0.59
6. Fermi's S.V.	0	0	—	22	0	0.1	0
7. Heated	1,841	14	0.76	15,994	72	82	0.45
8. Killed ether.	1,728	3	0.17	12,993	54	67	0.42
9. Mixed (a) ..	1,287	3	0.23	14,668	42	76	0.29
(b) ..	119	1	0.84	119	1	0.6	0.84
10. Yatren	0	0	—	187	7	1	3.74
Total	9,834	35	0.36	71,066	366	365.7	0.52

P < 1 in a million.

Non-Europeans.

1. Cords	1,271	17	1.34	3,136	75	26	2.39
3. Killed phenol	27,928	148	0.53	112,307	881	930	0.78
Total	29,199	165	0.57	115,443	956	956	0.83

P < 1 in a million.

(b) *Superficial.*

<i>Europeans.</i>	Eighth review			Number treated	All eight reviews		Mortality %
	Number treated	Deaths	Mortality %		Deaths		
					Observed	Calculated	
1. Cords	1,274	1	0.08	18,938	10	16	0.05
2. Dilutions . . .	5,613	4	0.07	32,520	25	27	0.08
3. Killed phenol	3,987	2	0.05	27,818	15	23	0.05
4. Live phenol.	465	0	0	2,155	3	2	0.14
5. Fermi's vacc.	151	0	0	2,099	0	2	0
6. Fermi's S.V.	0	0	—	339	0	0.3	0
7. Heated	10,147	6	0.06	70,415	80	59	0.11
8. Killed ether.	4,414	3	0.07	37,625	25	32	0.07
9. Mixed (a) ..	1,552	1	0.06	25,706	18	22	0.07
(b) ..	2,552	6	0.24	2,552	6	2	0.24
10. Yatren	0	0	—	3,334	6	3	0.18
Total	30,155	23	0.08	223,501	188	188.3	0.08
					P = 0.005		
<i>Non-Europeans.</i>							
1. Cords	4,855	4	0.08	12,898	28	33	0.22
3. Killed phenol	17,135	37	0.22	75,039	196	191	0.26
Total	21,990	41	0.19	87,937	224	224	0.25
					P = 0.34		

From the above it will be seen that, with the exception of the group of superficially bitten non-Europeans, there is evidence of heterogeneity. There is evidently considerable variation in the interpretation of the phrase "severely bitten".

(c) *Deep and Superficial Combined.*

<i>Europeans.</i>	Number treated	All eight reviews		Mortality %
		Deaths		
		Observed	Calculated	
1. Cords	24,267	37	45	0.15
2. Dilutions	42,979	103	81	0.23
3. Killed phenol	37,015	90	70	0.24
4. Live phenol	3,076	6	6	0.20
5. Fermi's vacc.	3,276	7	6	0.21
6. Fermi's S.V.	361	0	0.7	0
7. Heated	86,409	152	163	0.18
8. Killed ether	50,618	79	95	0.16
9. Mixed (a)	40,374	60	76	0.15
(b)	2,671	7	5	0.26
10. Yatren	3,521	13	7	0.37
Total	294,567	554	554.7	0.19
		P = 0.0026		
<i>Non-Europeans.</i>				
1. Cords	16,034	103	93	0.64
3. Killed phenol	187,346	1,077	1,087	0.57
Total	203,380	1,180	1,180	0.58
		P = 0.27		

The above table differs from that in Section V only in the fact that from this table the statistics regarding those showing "no visible lesion" are excluded. In the European group there is evidence of heterogeneity, whilst in the non-European group there is none. It is to be noted that in the European group the mortality for those treated by cords is less than that for those treated by killed phenol methods, whilst in the case of non-Europeans the reverse is found—viz., the higher mortality relates to those treated by cords. In general this table is not very satisfactory, and it is suggested that the apparent inconsistencies depend upon vagueness, not only in the demarcation between deep and superficial bites, but also on the demarcation between superficial bites and "no visible lesion".

Finally, it appears that for the deeply bitten the mortality amongst non-Europeans is about 1.6 times as great as amongst Europeans, whilst for those bitten superficially the ratio is about 3 times.

Also amongst Europeans the mortality from deep bites is 6.5 times as great as from superficial, whilst in the case of non-Europeans it is 3.3 times as great.

IX. INTERVENTION OF CLOTHING.

The percentage proportions of those bitten on the bare skin and through clothing are as follows :

	On bare skin	Through clothing
1. Cords	68.1	31.8
2. Dilutions	72.1	27.8
3. Killed phenol	79.9	20.1
4. Live phenol	60.4	39.5
5. Fermi's vacc.	53.6	46.4
6. Fermi's S.V.	—	—
7. Heated	63.0	37.0
8. Killed ether	52.7	47.3
9. Mixed (a)	67.8	32.1
(b)	73.4	26.6
Total	73.5	26.6

The figures relating to mortality are :

	(a) On bare skin			(b) Through clothing		
	Number treated	Deaths	Mortality %	Number treated	Deaths	Mortality %
1. Cords	12,352	54	0.44	5,773	6	0.10
2. Dilutions	5,758	8	0.14	2,221	0	0
3. Killed phenol	48,659	200	0.41	12,240	16	0.13
4. Live phenol	367	0	0	240	0	0
5. Fermi's vacc.	185	1	0.54	160	0	0
6. Fermi's S.V.	0	0	0	0	0	0
7. Heated	7,548	18	0.24	4,442	2	0.05
8. Killed ether	3,237	5	0.15	2,905	1	0.03
9. Mixed (a)	2,471	4	0.16	1,171	0	0
(b)	1,961	7	0.36	710	0	0
Total	82,538	297	0.36	29,862	25	0.08

Information regarding 10,640 treated persons, of whom ten died of rabies, is lacking.

The corresponding statistics subdivided according to race type are as under :

(a) On bare skin.

	Eighth review			All eight reviews			
	Number treated	Deaths	Mortality %	Number treated	Deaths		Mortality %
<i>Europeans.</i>					Observed	Calculated	
1. Cords	2,137	1	0.05	19,685	36	48	0.18
2. Dilutions ...	5,758	8	0.14	38,507	99	93	0.26
3. Killed phenol	7,021	11	0.16	35,362	85	85	0.24
4. Live phenol.	367	0	0	2,159	5	5	0.23
5. Fermi's vacc.	185	1	0.54	2,009	6	5	0.30
6. Fermi's S.V.	0	0	—	179	0	0.4	0
7. Heated	7,548	18	0.24	57,170	142	138	0.25
8. Killed ether.	3,237	5	0.15	22,260	76	54	0.34
9. Mixed (a) ..	2,471	4	0.16	32,715	54	79	0.16
(b) ..	1,961	7	0.36	1,961	7	5	0.36
10. Yatren	0	0	—	3,767	11	9	0.29
Total	30,685	55	0.18	215,774	521	521.4	0.24

P = 0.014

Non-Europeans.

1. Cords	4,927	21	0.43	10,427	87	69	0.83
3. Killed phenol	37,126	172	0.46	154,313	1,006	1,024	0.65
Total	42,053	193	0.46	164,740	1,093	1,093	0.66

P = 0.025

STATISTICS ON RABIES

(b) Through clothing.

	Eighth review			All eight reviews			
	Number treated	Deaths	Mortality %	Number treated	Deaths		Mortality %
Europeans.					Observed	Calculated	
1. Cords	330	0	0	7,420	1	2.2	0.013
2. Dilutions . . .	2,221	0	0	14,327	5	4.2	0.035
3. Killed phenol	1,651	0	0	12,533	4	3.7	0.032
4. Live phenol.	240	0	0	1,241	1	0.4	0.081
5. Fermi's vacc.	160	0	0	1,440	1	0.4	0.069
6. Fermi's S.V.	0	0	—	211	0	0.06	0
7. Heated	4,442	2	0.05	33,178	12	9.8	0.036
8. Killed ether.	2,905	1	0.03	25,501	2	7.6	0.008
9. Mixed (a) . .	1,171	0	0	16,493	6	4.9	0.036
(b)	710	0	0	710	0	0.2	0
10. Yatren	0	0	—	1,617	2	0.5	0.124
Total	13,830	3	0.02	114,671	34	33.96	0.030
					P = 0.15		
Non-Europeans.							
1. Cords	1,714	0	0	7,061	17	13.8	0.24
3. Killed phenol	9,085	13	0.14	37,840	71	74.2	0.19
Total	10,799	13	0.12	44,901	88	88.0	0.20
					P = 0.35		

There is thus no evidence of heterogeneity amongst those bitten through clothing in either race type. For those bitten on the bare skin, there is in each case some evidence of heterogeneity, though it is not very convincing.

The mortality amongst those bitten on the bare skin is, in the case of Europeans, 8 times and, in the case of non-Europeans, 3.3 times as great as that observed amongst those bitten through clothing. The mortality amongst non-Europeans, in the case of those bitten on the bare skin, is 2.7 times and, in the case of those bitten through clothing, is 1.5 times as great as amongst Europeans.

X. POSITION OF BITE.

The percentages of those bitten in the various positions are as follows :

	Head	Arm	Trunk	Leg
1. Cords	4.2	38.1	6.2	51.6
2. Dilutions	6.7	57.8	2.6	32.9
3. Killed phenol	5.3	35.9	3.6	55.2
4. Live phenol	4.1	43.2	5.4	47.3
5. Fermi's vacc.	4.7	54.5	1.6	39.1
6. Fermi's S.V.	—	—	—	—
7. Heated	5.0	44.1	5.4	45.5
8. Killed ether	6.1	43.0	3.4	47.4
9. Mixed (a)	4.0	49.8	4.0	42.2
(b)	4.4	56.8	5.9	32.9
Total	5.1	40.1	4.2	50.5

The figures relating to mortality are as follows :

	(a) Head			(b) Arm		
	Number treated	Deaths	Mortality %	Number treated	Deaths	Mortality %
1. Cords	868	29	3.34	7,939	25	0.31
2. Dilutions	531	4	0.75	4,613	4	0.09
3. Killed phenol	3,229	61	1.89	21,967	83	0.38
4. Live phenol	26	0	0	274	0	0
5. Fermi's vacc.	50	1	2.00	577	0	0
6. Fermi's S.V.	0	0	—	0	0	—
7. Heated	600	8	1.33	5,247	10	0.19
8. Killed ether	377	3	0.80	2,644	3	0.11
9. Mixed (a)	145	1	0.70	1,813	3	0.16
(b)	117	2	1.71	1,517	5	0.33
Total	5,943	109	1.83	46,591	133	0.29

	(c) Trunk			(d) Leg		
	Number treated	Deaths	Mortality %	Number treated	Deaths	Mortality %
1. Cords	1,300	1	0.08	10,754	15	0.14
2. Dilutions	206	0	0	2,629	0	0
3. Killed phenol	2,199	5	0.22	33,797	67	0.20
4. Live phenol	34	0	0	300	0	0
5. Fermi's vacc.	17	0	0	414	0	0
6. Fermi's S.V.	0	0	—	0	0	—
7. Heated	638	0	0	5,406	2	0.04
8. Killed ether	209	0	0	2,912	0	0
9. Mixed (a)	145	0	0	1,539	0	0
(b)	158	0	0	879	0	0
Total	4,906	6	0.12	58,630	84	0.14

Information regarding 6,970 persons, of whom none died of rabies, is lacking.

The statistics subdivided according to race type are as under :

	(a) Head.			All eight reviews			
	Eighth review			Number treated	Deaths		Mortality %
	Number treated	Deaths	Mortality %		Observed	Calculated	
<i>Europeans.</i>							
1. Cords	144	0	0	1,656	12	22	0.72
2. Dilutions ...	531	4	0.75	4,137	61	55	1.47
3. Killed phenol	467	3	0.64	3,146	41	42	1.30
4. Live phenol.	26	0	0	203	2	3	0.99
5. Fermi's vacc.	16	1	6.25	349	8	5	2.29
6. Fermi's S.V.	0	0	—	19	0	0.3	0
7. Heated	600	8	1.33	4,446	70	59	1.57
8. Killed ether.	377	3	0.80	3,130	44	42	1.41
9. Mixed (a) ..	145	1	0.69	2,537	20	34	0.79
(b) ..	117	2	1.71	117	2	2	1.71
10. Yatren	0	0	—	180	6	2	3.33
Total	2,423	22	0.91	19,920	266	266.3	1.34

P = 0.05

STATISTICS ON RABIES

	Eighth review			All eight reviews			Mortality %
	Number treated	Deaths	Mortality %	Number treated	Deaths		
<i>Non-Europeans.</i>					Observed	Calculated	
1. Cords	288	12	4.17	778	49	30	6.30
2. Dilutions ..	0	0	—	48	1	1.8	2.08
3. Killed phenol	2,298	54	2.35	9,683	351	369	3.62
Total	2,586	66	2.55	10,509	401	400.8	3.82

P = 0.08

(b) *Arm.*

	Eighth review			All eight reviews			Mortality %
	Number treated	Deaths	Mortality %	Number treated	Deaths		
<i>Europeans.</i>					Observed	Calculated	
1. Cords	1,640	0	0	16,818	19	24	0.11
2. Dilutions ...	4,613	4	0.09	35,441	47	50	0.13
3. Killed phenol	5,801	8	0.14	30,146	39	42	0.13
4. Live phenol.	274	0	0	1,699	3	2	0.18
5. Fermi's vacc.	176	0	0	2,414	1	3	0.04
6. Fermi's S.V.	0	0	—	231	0	0.3	0
7. Heated	5,247	10	0.19	34,152	59	48	0.17
8. Killed ether.	2,644	3	0.11	19,017	34	27	0.18
9. Mixed (a) ...	1,813	3	0.16	25,268	27	35	0.11
(b) ...	1,517	5	0.33	1,517	5	2	0.33
10. Yatren	0	0	—	3,393	5	5	0.15
Total	23,725	33	0.14	170,096	239	238.3	0.14

P = 0.18

<i>Non-Europeans.</i>							
	Number treated	Deaths	Mortality %	Number treated	Observed	Calculated	Mortality %
1. Cords	1,464	7	0.48	4,196	26	24	0.62
2. Dilutions ..	0	0	—	408	1	2	0.25
3. Killed phenol	13,560	67	0.49	57,050	329	329	0.58
Total	15,024	74	0.49	61,654	356	355	0.58

P = 0.6

(c) *Trunk.*

	Eighth review			All eight reviews			Mortality %
	Number treated	Deaths	Mortality %	Number treated	Deaths		
<i>Europeans.</i>					Observed	Calculated	
1. Cords	44	0	0	655	0	0	0
2. Dilutions ...	206	0	0	1,413	0	0	0
3. Killed phenol	161	0	0	1,426	0	0	0
4. Live phenol.	34	0	0	171	0	0	0
5. Fermi's vacc.	10	0	0	370	0	0	0
6. Fermi's S.V.	0	0	0	15	0	0	0
7. Heated	638	0	0	4,951	0	0	0
8. Killed ether.	209	0	0	2,325	0	0	0
9. Mixed (a) ..	145	0	0	1,724	3	0	0.17
(b) ..	158	0	0	158	0	0	0
10. Yatren	0	0	0	112	0	0	0
Total	1,605	0	0	13,320	3		0.02

	Eighth review			All eight reviews				
	Non-Europeans.	Number treated	Deaths	Mortality %	Number treated	Deaths		Mortality %
						Observed	Calculated	
1. Cords	417	0	0	1,167	5	3	0.43	
2. Dilutions	0	0	0	101	0	0.2	0	
3. Killed phenol	1,746	4	0.23	7,155	15	17	0.21	
Total	2,163	4	0.18	8,423	20	20.2	0.24	

P = 0.4

(d) Leg.

	Eighth review			All eight reviews				
	Europeans.	Number treated	Deaths	Mortality %	Number treated	Deaths		Mortality %
						Observed	Calculated	
1. Cords	823	1	0.12	8,806	8	4	0.09	
2. Dilutions	2,629	0	0	19,222	14	9	0.07	
3. Killed phenol	2,161	0	0	16,060	10	8	0.06	
4. Live phenol.	300	0	0	1,354	1	0.6	0.07	
5. Fermi's vacc.	143	0	0	2,302	1	1	0.04	
6. Fermi's S.V.	0	0	0	122	0	0.05	0	
7. Heated	5,406	2	0.04	29,218	12	14	0.04	
8. Killed ether.	2,912	0	0	26,311	1	12	0.004	
9. Mixed (a)	1,539	0	0	18,581	10	9	0.05	
(b)	879	0	0	879	0	0.4	0	
10. Yatren	0	0	—	1,699	2	0.8	0.12	
Total	16,792	3	0.02	124,554	59	58.85	0.05	

P = 0.0013

Non-Europeans.

1. Cords	4,472	2	0.04	11,464	24	35	0.21
2. Dilutions	0	0	—	597	0	2	0
3. Killed phenol	28,607	60	0.21	103,094	326	313	0.32
Total	33,079	62	0.19	115,155	350	350	0.30

P = 0.05

In the fourth, fifth and sixth reviews, the values of P from the combined figures gave no evidence of heterogeneity amongst non-Europeans in any of the four localities. In the seventh review, evidence of heterogeneity amongst those bitten on the head appeared, but in the combined figures as given in this review ($P = 0.08$) the evidence of heterogeneity is again lacking.

With regard to Europeans, evidence of heterogeneity is now found only amongst those bitten on the leg. This observation is again a result of the remarkably low mortality amongst those bitten on the leg and treated by killed ether vaccines at the Yugoslavian institutes (1 fatal case amongst 26,311 persons treated during the period covered by the eight reviews as compared with an expected 12).

The mortalities for the two race types classified according to position are as follows :

	Europeans	Non-Europeans	Ratio : $\frac{\text{Non-European mortality}}{\text{European mortality}}$
Head	1.34	3.82	2.9
Arm	0.14	0.58	4.1
Trunk	0.023	0.24	10.4
Leg	0.047	0.30	6.4

Also, the mortalities of those bitten on head, arm, trunk and leg are, for Europeans, in the ratio of 100 : 10 : 2 : 4 and, for non-Europeans, in the ratio 100 : 15 : 6 : 8.

XI. DELAY IN COMMENCEMENT OF TREATMENT.

The percentage proportions of those commencing treatment during the various periods are as follows :

	0 to 4 days	5 to 7 days	8 to 14 days	More than 14 days
1. Cords	59.6	22.0	11.9	6.6
2. Dilutions	53.0	24.9	15.6	6.5
3. Killed phenol	65.5	16.2	11.4	6.9
4. Live phenol	63.2	15.5	15.1	6.2
5. Fermi's vacc.	54.1	21.2	17.6	7.1
6. Fermi's S.V.	—	—	—	—
7. Heated	71.3	17.7	8.3	2.7
8. Killed ether	72.3	13.8	8.1	5.8
9. Mixed (a)	49.4	24.9	17.5	8.2
(b)	76.6	12.5	8.5	2.3
Total	64.5	18.0	11.4	6.2

The figures relating to mortality are as under :

	(a) 0 to 4 days			(b) 5 to 7 days		
	Number treated	Deaths	Mortality %	Number treated	Deaths	Mortality %
1. Cords	12,904	39	0.30	4,768	17	0.36
2. Dilutions	4,228	8	0.19	1,986	0	0
3. Killed phenol	40,477	129	0.32	10,005	24	0.24
4. Live phenol	401	0	0	98	0	0
5. Fermi's vacc.	625	1	0.16	245	0	0
6. Fermi's S.V.	0	0	—	0	0	—
7. Heated	9,565	18	0.19	2,374	2	0.08
8. Killed ether	6,588	6	0.09	1,254	0	0
9. Mixed (a)	1,798	3	0.17	907	1	0.08
(b)	2,047	7	0.34	335	0	0
Total	78,633	215	0.27	21,972	44	0.20

	(c) 8 to 14 days			(d) More than 14 days		
	Number treated	Deaths	Mortality %	Number treated	Deaths	Mortality %
1. Cords	2,568	8	0.31	1,427	6	0.42
2. Dilutions	1,247	0	0	518	0	0
3. Killed phenol	7,038	26	0.37	4,238	37	0.87
4. Live phenol	96	0	0	39	0	0
5. Fermi's vacc.	203	0	0	82	0	0
6. Fermi's S.V.	0	0	—	0	0	—
7. Heated	1,119	0	0	359	0	0
8. Killed ether	740	0	0	528	0	0
9. Mixed (a)	639	0	0	298	0	0
(b)	227	0	0	62	0	0
Total	13,877	34	0.25	7,551	43	0.57

Information was not available regarding 1,007 persons, of whom none died.

The figures subdivided according to race type are as under :

(a) 0 to 4 days.

	Eighth review			All eight reviews			
	Number treated	Deaths	Mortality %	Number treated	Deaths		Mortality %
<i>Europeans.</i>					Observed	Calculated	
1. Cords	1,292	0	0	15,802	26	28	0.16
2. Dilutions ...	4,228	8	0.19	34,158	81	61	0.24
3. Killed phenol	5,211	10	0.19	32,835	68	59	0.21
4. Live phenol.	401	0	0	1,967	5	4	0.25
5. Fermi's vacc.	260	1	0.38	2,641	7	5	0.27
6. Fermi's S.V.	0	0	—	234	0	0.4	0
7. Heated	9,565	18	0.19	52,523	80	94	0.15
8. Killed ether.	6,588	6	0.09	46,368	69	83	0.15
9. Mixed (a) ..	1,798	3	0.17	25,897	37	46	0.14
(b) ..	2,047	7	0.34	2,047	7	4	0.34
10. Yatren	0	0	—	2,080	8	4	0.38
Total	31,390	53	0.17	216,552	388	388.4	0.18

P = 0.015

	Eighth review			All eight reviews			
	Number treated	Deaths	Mortality %	Number treated	Deaths		Mortality %
<i>Non-Europeans.</i>					Observed	Calculated	
1. Cords	4,131	13	0.31	9,998	50	51	0.50
2. Dilutions ...	0	0	—	801	0	4	0
3. Killed phenol	30,231	103	0.34	122,123	628	623	0.51
Total	34,362	116	0.34	132,922	678	678	0.51

P = 0.14

STATISTICS ON RABIES

(b) 5 to 7 days.

	Eighth review			Number treated	Deaths		Mortality %	
	Europeans.	Number treated	Deaths		Mortality %	Observed		Calculated
1. Cords		632	1	0.16	5,314	7	6	0.13
2. Dilutions ...		1,986	0	0	13,982	23	16	0.16
3. Killed phenol		1,869	0	0	9,506	8	11	0.08
4. Live phenol.		98	0	0	626	1	0.7	0.16
5. Fermi's vacc.		70	0	0	958	1	1	0.10
6. Fermi's S.V.		0	0	—	80	0	0.09	0
7. Heated		2,374	2	0.08	17,895	17	20	0.09
8. Killed ether.		1,254	0	0	8,979	4	10	0.04
9. Mixed (a) ..		907	1	0.08	11,456	14	13	0.12
(b) ..		335	0	0	335	0	0.4	0
10. Yatren		0	0	—	1,500	4	2	0.27
Total		9,525	4	0.04	70,631	79	80.19	0.11
P = 0.23								
Non-Europeans.								
1. Cords		1,263	6	0.48	4,437	27	23	0.61
2. Dilutions		0	0	—	129	0	0.7	0
3. Killed phenol.		7,341	24	0.33	34,405	171	175	0.50
Total		8,604	30	0.35	38,971	198	198.7	0.51
P = 0.45								

(c) 8 to 14 days.

	Eighth review			Number treated	Deaths		Mortality %	
	Europeans.	Number treated	Deaths		Mortality %	Observed		Calculated
1. Cords		398	0	0	4,832	3	4	0.06
2. Dilutions ...		1,247	0	0	9,307	8	7	0.09
3. Killed phenol		1,216	0	0	6,461	9	5	0.14
4. Live phenol.		96	0	0	538	0	0.4	0
5. Fermi's vacc.		47	0	0	609	0	0.6	0
6. Fermi's S.V.		0	0	0	64	0	0.05	0
7. Heated		1,119	0	0	7,138	4	6	0.06
8. Killed ether.		740	0	0	4,939	5	4	0.10
9. Mixed (a) ..		639	0	0	8,196	6	7	0.07
(b) ..		227	0	0	227	0	0.2	0
10. Yatren		0	0	0	1,189	0	0.9	0
Total		5,729	0	0	43,500	35	35.15	0.08
P = 0.35								
Non-Europeans.								
1. Cords		744	0	0	2,092	10	11	0.48
2. Dilutions		0	0	—	101	0	0.5	0
3. Killed phenol.		5,327	23	0.43	22,823	123	121	0.54
Total		6,071	23	0.38	25,016	133	132.5	0.53
P = 0.7								

(d) *More than 14 days.*

<i>Europeans.</i>	Eighth review			All eight reviews			Mortality %
	Number treated	Deaths	Mortality %	Number treated	Deaths		
					Observed	Calculated	
1. Cords	145	0	0	1,465	1	2	0.07
2. Dilutions . . .	518	0	0	4,004	9	5	0.22
3. Killed phenol	516	1	0.19	2,852	7	4	0.25
4. Live phenol.	39	0	0	296	0	0.4	0
5. Fermi's vacc.	32	0	0	286	0	0.4	0
6. Fermi's S.V.	0	0	—	12	0	0.02	0
7. Heated	359	0	0	2,215	3	3	0.14
8. Killed ether.	528	0	0	3,158	1	4	0.03
9. Mixed (a) ..	298	0	0	3,659	3	5	0.08
(b) ..	62	0	0	62	0	0.08	0
10. Yatren	0	0	—	615	1	0.8	0.16
Total	2,497	1	0.04	18,624	25	24.70	0.13
P = 0.17							
<i>Non-Europeans.</i>							
1. Cords	503	2	0.40	1,105	17	14	1.54
2. Dilutions	0	0	—	123	2	1.5	1.63
3. Killed phenol.	3,312	35	1.06	12,832	154	158	1.20
Total	3,815	37	0.97	14,060	173	173.5	1.23
P = 0.60							

The only evidence of heterogeneity in the above tables is found in the group "Europeans, arriving within four days", where the value of P is 0.015, and this is due mainly to a rather high mortality amongst those treated by dilution methods.

If this not very definite evidence of heterogeneity be neglected, the figures may be summed up as under :

<i>Europeans.</i>	Number treated	Deaths		Mortality %
		Observed	Calculated	
Less than 14 days	330,683	502	499	0.15
More than 14 days	18,624	25	28	0.13
Total	349,307	527	527	0.15
P = 0.56				
<i>Non-Europeans.</i>				
Less than 14 days	196,909	1,009	1,103	0.51
More than 14 days	14,060	173	79	1.23
Total	210,969	1,182	1,182	0.56
P < one in a million.				

And so, as in former reviews, the fact is emphasised that, for some reason which does not appear, the handicap of late arrival, though pronounced in the non-European, is not evident in the European, statistics.

Again it may be noted that in the successive periods 0-4, 5-7, 8-14 and more than 14 days, the ratios of non-European to European mortalities are 2.8, 4.6, 6.6 and 9.5 respectively, so that the relative mortality increases progressively with lateness of arrival.

XII. PARALYTIC ACCIDENTS.

The figures relating to the occurrence of post-vaccinal paralyses are as follows :

	Number treated	Accidents	Proportion 1 in	Percentage	Deaths
1. Cords	21,851	2	10,925	0.009	0
2. Dilutions	7,979	1	7,979	0.013	0
3. Killed phenol ..	60,634	5	12,127	0.008	2
4. Live phenol	634	0		0	0
5. Fermi's vacc....	1,227	0		0	0
7. Heated	13,417	0		0	0
8. Killed ether ...	9,110	1	9,110	0.011	1
9. Mixed (a)	3,642	3	1,214	0.083	1
(b)	2,671	1	2,671	0.037	0
Total	121,165	13	10,729	0.009	4

In the schedule received from Colombo, it is stated that "larger doses of the vaccine were given following the introduction of this practice into the Indian institutes ; but because paralytic accidents occurred for the first time since the opening of the institute in 1918, it was decided to return to the smaller doses". It is stated that none of these accidents were fatal, but their number is not given. The total treated at Colombo (1,875) has consequently been excluded in the above computation.

The figures over the period covered by all eight reviews are :

	Number treated	Accidents	Proportion 1 in	Percentage	Deaths	Percentage fatal	Percentage non-fatal
1. Cords	114,240	31	3,685	0.027	3	0.002	0.025
2. Dilutions	62,857	24	2,619	0.038	17	0.027	0.011
3. Killed phenol ..	353,737	35	10,107	0.010	11	0.003	0.007
4. Live phenol	3,464	0	—	0	0	—	—
5. Fermi's vacc. ...	7,319	3	2,440	0.041	2	0.027	0.014
6. Fermi's S.V. ...	390	0	—	0	0	—	—
7. Heated	93,145	8	11,643	0.009	2	0.003	0.006
8. Killed ether ...	63,444	8	7,931	0.013	3	0.005	0.008
9. Mixed (a)	49,656	28	1,910	0.052	3	0.006	0.046
(b)	2,671	1	2,671	0.037	0	0	0.037
10. Yatren	5,384	3	1,795	0.056	0	0	0.056
Total	756,307	139	5,441	0.018	41	0.005	0.013

These may be abbreviated as follows :

	Number treated	Accidents		Proportion 1 in	Percentage	Deaths	Percentage fatal	Percentage non-fatal
		Observed	Calculated					
(a) Killed	417,181	43	77	9,702	0.010	14	0.003	0.007
(b) Live	232,888	82	43	2,840	0.035	23	0.010	0.025
(c) Heated ...	93,145	8	17	11,643	0.009	2	0.003	0.006
(d) Other	13,093	6	2	2,182	0.046	2	0.015	0.031
Total ...	756,307	139	139	5,441	0.018	41	0.005	0.013

P < 1 in a million.

These results may be roughly summarised as follows :

	All accidents	Fatal accidents	Non-fatal accidents
1. Cords	High	Low	High
2. Dilutions	High	High	Low
3. Killed phenol	Low	Low	Low
5. Fermi's vacc.	High	High	Average
7. Heated	Low	Low	Low
8. Killed ether	Low	Average	Low
9. Mixed (a)	High	Average	High
(b)	High	Low	High
10. Yatren	High	Low	High

It is to be observed that killed phenol, heated, and killed ether methods are alike satisfactory regarding the incidence of accident, in that few accidents are likely to occur, and that such as do occur are not likely to be fatal. Cord and mixed (b) methods, which both depend largely on cord treatment, give similar results as would be expected. On the other hand, dilution and mixed (a) methods, in both of which fresh diluted virus is the main ingredient, a curious anomaly is observed ; for it appears that, whilst in both accidents are relatively frequent, with simple dilution treatment these are likely to be fatal, whereas with dilutions plus in severe cases Alivisatos, they are likely to be non-fatal. This is a surprising result, for which no explanation is forthcoming.

XIII. SUMMARY AND CONCLUSIONS.

In the following table, certain of the percentage mortalities are compared with those of previous reviews.

	First review	Second review	Third review	Fourth review	Fifth review	Sixth review	Seventh review	Eighth review
All patients	0.49	0.48	0.23	0.48	0.38	0.35	0.30	0.27
(a) Live vaccines ...	0.27	0.26	0.21	0.26	0.23	0.31	0.28	0.24
(b) Killed vaccines ..	0.65	0.80	0.28	0.66	0.51	0.40	0.35	0.31
Europeans	0.17	0.13	0.10	0.14	0.21	0.20	0.13	0.11
(a) Live vaccines ...	0.20	0.11	0.13	0.15	0.17	0.22	0.13	0.11
(b) Killed vaccines ..	0.10	0.14	0.10	0.12	0.19	0.16	0.14	0.09
Non-Europeans	0.84	0.88	0.78	0.83	0.62	0.54	0.48	0.42
(a) Live vaccines ...	1.02	0.82	0.71	0.74	0.46	0.65	0.67	0.44
(b) Killed vaccines ..	0.83	0.89	0.93	0.85	0.65	0.52	0.45	0.41
Biting animal :								
Dog	0.42	0.44	0.24	0.47	0.36	0.33	0.28	0.25
Cat	0	0.07	0.04	0.06	0.03	0.03	0.04	0.07
Wolf	18.31	0	5.52	7.3	10.2	11.2	5.41	4.04
Jackal	1.58	1.64	5.56	2.2	1.48	1.19	1.49	1.52
Category :								
A	0.29	0.34	0.47	0.44	0.49	0.37	0.32	0.33
B	0.18	0.38	0.31	0.34	0.28	0.29	0.23	0.19
C	0.60	0.57	0.25	0.62	0.41	0.37	0.35	0.29
D	0.10	0.05	0.02	0.01	0.14	0.06	0.12	0.06
Deep bites	1.18	1.06	0.74	1.10	0.85	0.75	0.69	0.58
Superficial bites	0.12	0.24	0.09	0.18	0.16	0.16	0.13	0.13
On bare skin	0.66	0.62	0.38	0.66	0.50	0.46	0.40	0.36
Through clothing	0.10	0.13	0.04	0.12	0.09	0.08	0.11	0.08
Locality :								
Head	2.85	2.42	1.24	3.17	2.84	2.64	2.22	1.83
Arm	0.40	0.49	0.25	0.35	0.29	0.29	0.26	0.29
Trunk	0.42	0.11	0.10	0.31	0.11	0.14	0.11	0.12
Leg	0.30	0.40	0.11	0.30	0.21	0.17	0.18	0.14
Delay in commencing treatment :								
0 to 4 days	0.35	0.46	0.18	0.53	0.40	0.35	0.28	0.27
5 to 7 days	0.59	0.46	0.16	0.38	0.31	0.29	0.27	0.20
8 to 14 days	0.64	0.49	0.28	0.40	0.35	0.27	0.23	0.25
More than 14 days ..	1.04	0.69	0.33	0.73	0.52	0.63	0.83	0.57
Post-vaccinal paralysis	0.025	0.009	0.027	0.021	0.019	0.018	0.023	0.009
(a) Cords	0.22	0.019	0.048	0.025	0.022	0.014	0.021	0.009
(b) Dilutions	0.03	0.03	0	0.105	0.058	0.036	0.045	0.013
(c) Killed phenol ...	0.006	0.003	0.026	0.008	0.014	0.010	0.012	0.008

In discussing the figures relating to previous reviews, the influence of race type upon mortality rate has been in each case emphasised.

The race types have consequently been dealt with separately and the resulting figures examined for differences in the efficacies of the different methods of treatment. Three such tables have, in particular, been considered.

The first is that given in Section V, referring to all cases treated. In this, no evidence of differences of efficacy has been found.

The second is that given for categories A, B and C in Section VII; that is to say, the table includes all persons treated, with the exception of those bitten by dogs *not* suspected to be rabid. The effect of the removal of this diluent of persons at a very low degree of risk does not aid us; again, there is no evidence of any significant differences in the efficacies of the various methods of treatment.

The third table is that relating to the severely and the superficially bitten given in Section VIII. It differs from the first in that those with "no visible lesion" have been excluded. This attempt to find evidence of variation in efficacy by the exclusion of another set of persons who are at a negligible degree of risk has not been successful. Evidence of heterogeneity has been found amongst the European moiety, but points emerge which suggest that this heterogeneity arises from influences other than difference of method. For example, amongst Europeans the killed-phenol method appears to be less efficacious than the method of dried cords, whilst amongst non-Europeans the reverse seems to be the case. The more probable explanation of the heterogeneity seems to be that the grouping of cases in the classes deep, superficial, and with no visible lesion differs markedly in the various institutes. The vagueness of the line between deep and superficial has already been referred to; it would seem that there exists also vagueness in the line of demarcation between the superficially bitten and those with no visible lesion.

The more powerful method of analysis introduced in the seventh review may now be applied. It will be remembered that it was pointed out in that review that, employing the idea of "fiduciary probability" or "confidence coefficients", it was possible to make statements as to the limits within which any presumed superiority of one treatment over another must lie. Such statements may have any assigned degree of reliability—95%, 99%, etc. Where the number of observations is small, the range between lower and upper limit will obviously be large, and where the observations are many,

the range will be contracted, and the statement will be "more precise". (In the present analysis, it has been found more convenient to state the degree of superiority of any one treatment over the *mean* of the whole group of treatments.)

The approximate formula (applicable when the differences are not too large, as is the case in the rabies statistics) is

$$p_1 - p_m = p'_1 - p'_m \pm \frac{c}{N} \sqrt{\frac{n_2 n_3 n_4}{n_1 N}}$$

When p_1 is the probability of death for the treatment in question, p_m is that for all methods of treatment. The dashed p 's are the observed values, and the undashed the estimated values. n_1 is the number treated by the particular method in question, n_2 the number treated by the *remaining* methods, $N = n_1 + n_2$ is the total treated population. n_3 is the total number of deaths, n_4 the total number of escapes ($N = n_3 + n_4$). c is a constant which varies according to the degree of reliability required. For a 90% reliability, it is 1.64; for a 95%, it is 1.96; and for a 99% reliability, it is 2.57. In what follows, the value $c = 1.96$, corresponding to a 95% reliability, has been adopted. It should be again emphasised that the above formula is only approximate; it is applicable when $p'_1 - p'_m$ is not too large, and we believe that it may safely be applied to the figures with which we have to deal.

The values of $p_1 - p_m$ so calculated are tabulated below for Europeans and non-Europeans respectively :

- (1) For all cases ;
- (2) For all, excluding category D (*i.e.*, those bitten by dogs not suspected to be rabid) ;
- (3) For all, excluding those in whom " no visible lesion " was observed.

In interpreting such a table as the following, it is to be noted that, when the upper limit is positive and the lower limit is negative, a zero value is allowable; that is to say, it is possible that the treatment in question is neither better nor worse than the mean. When both limits are of like sign, then the treatment in question is significantly better, or worse as the case may be, than the mean. When one or other limit is zero, the difference becomes just significant. This corresponds to a value of $P = 0.05$ (for a 95% reliability), as obtained by ordinary methods.

	(1) All cases		(2) Excluding category D		(3) Excluding "no visible lesion"	
	Upper limit	Lower limit	Upper limit	Lower limit	Upper limit	Lower limit
<i>Europeans.</i>						
1. Cords	+0.0222	-0.0390	+0.0218	-0.0794	+0.0166	-0.0878
2. Dilutions	+0.0570	-0.0040	+0.0304	-0.0210	+0.0895	-0.0137
3. Killed phenol ..	+0.0258	-0.0342	+0.0549	-0.0131	+0.0963	+0.0137
4. Live phenol	+0.1506	-0.1074	+0.1550	-0.1254	+0.1594	-0.1454
5. Fermi's vacc. ..	+0.1340	-0.0380	+0.1666	-0.1038	+0.1733	-0.1221
6. Fermi's S.V ..	+0.2347	-0.5381	+0.5313	-0.8591	+0.2588	-0.6350
7. Heated	+0.0395	-0.0037	+0.0216	-0.0288	+0.0127	-0.0371
8. Killed ether ...	-0.0006	-0.0548	+0.0212	-0.0454	+0.0016	-0.0656
9. Mixed (a)	+0.0012	-0.0628	-0.0035	-0.0703	-0.0002	-0.0788
(b)	+0.2576	-0.0366	+0.2494	-0.0610	+0.2375	-0.0895
10. Yatren	+0.1929	-0.0131	+0.2447	-0.0047	+0.3234	-0.0388
<i>Non-Europeans.</i>						
1. Cords	+0.1179	-0.1495	+0.1405	-0.0757	+0.1750	-0.0506
2. Killed phenol ..	+0.0083	-0.0023	+0.0072	-0.0138	+0.0044	-0.0150

It will be seen from the above table that, in almost every instance, the zero point is included within the range. The exceptions are :

- (a) Those treated by the killed-ether method in Table (1);
- (b) Those treated by the mixed (a) method in Table (2);
- (c) Those treated by killed-phenol and mixed (a) methods in Table (3).

None of these exceptions occur in the figures relating to non-Europeans treated by cords and killed phenol.

The range for the mixed (a) method of treatment lies in Tables (2) and (3) just on the negative side, and in Table (1) one limit lies just to the positive side of the mean. It would appear, then, that this method is possibly just significantly more effective than the other methods.

The killed-ether method tends to take up a similar position, but not so definitely.

No evidence of difference in efficacy between cords and killed-phenol methods can be detected. The suggested superiority of cords in the case of Europeans in Table (3) is balanced by a suggestion of inferiority in the case of non-Europeans.

No conclusion can be drawn regarding those treated by live phenol vaccine, Fermi's original or Fermi's sero-vaccine ; the limits are widely separated on account of the paucity of the data, and, as stated in the last review, it is not likely that, in the near future, it will be possible to draw any conclusions as to their real efficacy.

Thus, from the evidence available, there seems to be little to choose between the cord, dilution, killed-phenol, heated, and killed-ether methods as regards their immunising properties ; whilst the mixed (a) system of treatment (dilutions plus Alivisatos in severe cases) is apparently associated with a reduction of mortality which does not exceed 42% and may actually be zero.

It must be remembered, as before, that these statements are made on a basis of reliability of 95%. This means that one of twenty statements is likely to be wrong. As only the Europeans treated by mixed (a) method out of a considerable number of treatment groups has shown any evidence of real superiority, it is necessary not to attach undue weight to this positive result. It may eventually prove to be important, but, on the other hand, it may be merely the emergence of the one-in-twenty chance.

It thus appears that from statistics relating to some 732 thousand persons treated by various methods, there is little evidence of superiority of one method over another, with the possible exception of a superiority in favour of the live-vaccine treatment described as mixed (a) (that is, a dilution treatment with, in severe cases, the addition of Alivisatos ether vaccine).

It may seem remarkable that in such large statistics differences in efficiencies have not become evident, but it must be remembered, as stated in a previous review, that the controlling factor is the mortality rate. The lower this may be, the greater the number of patients required to demonstrate variations. In the case of Europeans, the mortality rate is of the order of 0.17%, and, in the case of non-Europeans, of 0.58%.

It may be said in general terms that, with regard to the treatment methods—cords, dilutions, killed phenol, heated and killed ether vaccines—it is unlikely that a difference in efficiency of more than 25% between any two of these methods exists. The possible limit of superiority of the mixed (a) method has already been alluded to.

Finally, having examined the statistics with regard to immunising efficiency, we turn to the likelihood of occurrence of paralytic accidents. The results arrived at in the last review continue to hold, and are summarised in the discussion at the end of Section XII. The occurrence of accidents is less than 1 in 8,000 amongst those treated by killed phenol, killed ether, and heated vaccines, and is

more than 1 in 2,700 amongst those treated by methods in which living vaccines are employed—viz., cords, dilutions, mixed (a) and (b). The percentage of fatal accidents is high amongst those treated by dilutions and Fermi's original method.

Anti-Rabies Treatment in the Union of Soviet Socialist Republics.

The statistics from the Union of Soviet Socialist Republics relating to the years 1927-1932 have already been dealt with, in the first, fourth and fifth of this set of reviews. Statistics are now available regarding the years 1933 and 1934. As previously explained, a number of methods of treatment have been employed at a number of institutes. Detailed statistics relating to all the methods *combined* have been furnished according to the schedule adopted at the Paris Conference, but with regard to individual methods the only figures available are those relating to all patients. Consequently, the detailed system of analysis employed in the main report could not be followed, and the statistics are treated separately.

The schedules are based upon the statistics of the forty-seven Russian Pasteur institutes, excluding in 1933 Koursk, and in 1934 Semipalatinsk, from which reports were not received. Most of the forty-seven institutes serve a number of sub-centres at which treatment is given. The director writes : " It has been established that, during the period covered by the reports, the number of persons asking for treatment continues to decline all over the country. This is due to an abrupt diminution of rabies in animals in the Union of Soviet Socialist Republics." This view is supported by the following figures :

	Number of institutes	Number of persons bitten and treated	Average number per institute
1927	72	74,430	1,034
1928	60	66,154	1,103
1929	53	53,518	1,010
1930	55	49,399	898
1931	52	38,961	749
1932	50	27,647	553
1933	46	17,410	378
1934	46	15,630	340
		343,149	791

In the following tables are recapitulated the main facts relating to methods of treatment for the years 1933, 1934, and the whole

	1933					1934				
	Total treated	Bitten persons treated	Number of deaths	Deaths ; percentage of persons bitten	Post-vaccinal complications	Total treated	Bitten persons treated	Number of deaths	Deaths ; percentage of persons bitten	Post-vaccinal complications
Number treated	26,689	17,410	35	0.20	5	24,724	15,630	21	0.13	1
Methods :										
Philipps-Högyes	17,335	10,980	16	0.15	5	14,560	8,632	10	0.12	0
Mixed method (Philipps-Högyes + Fermi or Alivisatos)	1,909	1,357	7	0.52	0	2,972	1,852	—	0	0
Fermi	4,132	3,050	5	0.16	0	4,480	3,512	6	0.17	1
Pasteur-Calmette	2,912	1,772	6	0.34	0	2,535	1,484	5	0.34	0
Pasteur-Remlinger	401	251	1	0.40	0	177	150	—	0	0
Biting animal : Dog	18,440	13,051	26	0.20	3	17,093	11,967	16	0.13	1
Cat	1,608	1,215	1	0.09	2	1,673	1,148	0	0	0
Wolf	39	33	5	1.52	0	37	22	4	1.82	0
Other	2,238	1,204	—	0	0	1,889	1,306	—	—	—
Not specified ...	4,364	1,907	3	0.16	0	4,032	1,187	1	0.08	0
Category : A	2,777	1,384	8	0.58	0	3,650	1,717	8	0.47	1
B	3,158	1,586	5	0.32	1	3,634	1,766	2	0.11	0
C	15,648	11,871	21	0.18	4	12,807	9,528	10	0.11	0
Not specified	5,106	2,569	1	0.04	—	4,633	2,619	1	0.04	0
Bites : Simple			2		2			3		0
Multiple			32		1			15		0
Not specified			1		2			2		0
No visible lesion								1		1
Interposition of clothing :										
On bare skin			32		2			17		1
Through clothing			3		2			3		0
Not specified			—		1			1		0
Position :										
Head		1,399	16	1.14	0		1,218	10	0.83	0
Hands		4,592	8	0.17	2		4,042	6	0.15	1
Arms and shoulder		1,573	5	0.32	0		1,665	1	0.06	0
Lower limbs		6,462	2	0.03	1		5,620	2	0.04	0
Other parts		714	1	0.14	1		650	1	0.15	0
Not specified		2,070	3	0.15	1		2,435	1	0.04	0
Delay in arrival :										
0-4 days	12,207	9,250	24	0.26	2	11,559	8,258	16	0.19	1
5-7 days	6,072	3,971	5	0.13	1	4,885	2,671	2	0.08	0
8-14 days	3,001	1,546	2	0.13	2	2,781	1,455	1	0.07	0
15-21 days	978	505	—	0	0	822	416	0	0	0
More than 22 days	290	203	1	0.49	0	386	202	1	0.50	0
Not specified	4,141	1,935	3	0.16	0	4,291	2,628	1	0.04	0

	1933			1934			1927-1934 Deaths			
	Number bitten	Deaths	Mor- tality	Number bitten	Deaths	Mor- tality	Number bitten	Observed	Calcu- lated	Mor- tality
Pasteur	1,772	6	0.34	1,484	5	0.34	79,591	187	135	0.2350
Fermi	3,050	5	0.16	3,512	6	0.17	50,019	92	85	0.1839
Högyes-Philipps	10,980	16	0.15	8,632	10	0.12	196,238	263	334	0.1340
Remlinger	251	1	0.40	150	0	0	3,560	13	6.1	0.3652
Pasteuff plus Fermi	—	—	—	—	—	—	1,872	11	3.2	0.5876
Philipps plus Fermi or Ali- visatos	1,357	7*	0.52	1,852	0	0	11,869	18	20	0.1517
	<u>17,410</u>	<u>35</u>	<u>0.20</u>	<u>15,630</u>	<u>21</u>	<u>0.13</u>	<u>343,149</u>	<u>584</u>	<u>583.3</u>	<u>0.1702</u>

* Three of the seven fatal cases reported were from wolf bite.

P < 1 in a million.

period 1927-1934. The corresponding figures for the individual years 1927 to 1932 will be found in the fifth review.

The director writes :

“ In comparing the figures for the years 1933 and 1934 with the preceding years, one notes that the institutes of the Union of Soviet Socialist Republics have progressively continued to abandon the use of the dried-cord method (Pasteur method) and have adopted almost entirely either the method of dilutions (method of Högyes-Philipps) or the phenol-vaccine method of Fermi. In 1934, only three institutes (Tiflis, Kiroff-Ukraine and Irkutsk) have continued to employ dried cords. At Irkutsk, for many years, this method, intensified according to the procedure of Remlinger, has been employed. For this reason, this institute has been included in a distinct group. Of the forty-seven institutes which have furnished statistics, twenty-nine employed in 1934 the dilution method, and fifteen Fermi's phenol vaccine. Four of these institutes intensify the treatment, in the case of the severely bitten, by another method. Thus the institutes at Odessa, Vinnitsa and Gorki have reinforced the method of Högyes-Philipps by the method of Fermi, whilst at the Institute of Tamboff it is reinforced by the method of Alivisatos.”

The value of P for the whole table is less than one in a million, which shows that the statistics according to the various methods of treatment vary markedly.

The efficacies of the various methods have been examined by the method of limits used in the last section of the main paper, and the results are given in the following table.

	Upper limit	Lower limit
Pasteur	+0.0899	—0.0397
Fermi	+0.0471	—0.0197
Högyes-Philipps	—0.0143	—0.0381
Remlinger	+0.3304	+0.0608
Pasteur plus Fermi	+0.6050	+0.2298
Philipps plus Fermi or Alivisatos	+0.0544	—0.0914

It appears from this analysis that the method of Högyes-Philipps is significantly superior to the aggregate, and that the methods of Remlinger, and Pasteur, plus Fermi are inferior, whilst the efficacies of the methods of Pasteur, Fermi and Philipps plus Fermi or Alivisatos are in agreement with the aggregate.

This result, in so far as it supports the view that better immunising effects have been obtained amongst those treated by the dilution method than amongst those treated by dried cords, or Fermi's vaccine, is in agreement with that arrived at in the main report.

Six accidents are reported ; five occurred amongst those treated in 1933 by the Högyes Philipps method and one amongst those treated in 1934 by Fermi's vaccine. Only one of the six was a case of Landry's paralysis. Unfortunately, no statement is made regarding the mortality amongst these six cases.

Adding this set of statistics to those of former years (see the fourth review, *Quarterly Bulletin of the Health Organisation of the League of Nations*, 1933, 2, 599), we arrive at the following table. (Statistics for the years 1931 and 1932 dealt with in the fifth review cannot be included, as no information is given regarding the method of treatment used in the single case of paralytic accident which occurred.)

	Number treated	Accidents	Proportion
Pasteur	113,477	22	1 in 5,158
Fermi	53,042	6	1 in 8,840
Högyes-Philipps	234,787	30	1 in 7,826
Remlinger	3,226	0	—
Pasteur plus Fermi	2,500	0	—
Philipps plus Fermi or Alivisatos.	14,092	1	1 in 14,092
	<hr/> 421,124	<hr/> 59	<hr/> 1 in 7,138

It will be noted that the above proportions are in general considerably lower than those given in Section XII of the main review. In particular, the proportion with dilution treatment (Högyes-Philipps) is 1 in 7,826, as compared with 1 in 2,619 in the main review.

CONCLUSIONS.

1. There has been a steady decline in the number of those presenting themselves for treatment. This, in the opinion of the authorities, is due to an " abrupt diminution of rabies in animals in the Union of Soviet Socialist Republics".

2. The mortality rate amongst the bitten since 1928 shows no significant variation. The rates from 1927 to 1934 are, respectively, 0.23, 0.20, 0.15, 0.11, 0.14, 0.15, 0.20 and 0.13%.

3. As regards the immunising properties of the various methods of treatment employed, it would appear that the methods fall into three groups : (1) The live vaccine of Högyes-Philipps being superior, (2) the methods of Pasteur, Fermi and Philipps plus Fermi or Alivisatos being nearly equal to, and (3) the methods of Remlinger and Pasteur plus Fermi being inferior to, the aggregate.

EXPERIMENTS IN MALARIA TREATMENT AND PREVENTION CARRIED OUT IN ROUMANIA WITH CERTAIN SYNTHETIC DRUGS.¹

FOREWORD

by

M. CIUCA.

The preliminary results of these investigations are embodied in document C.H. /Malaria /239, the conclusions of which went up to April 30th, 1936. Since that date, new cases have been treated in the field and in hospital, and there has been an opportunity of supplementing the data on relapses and reinfections during the epidemic season of 1936 ; certain figures have been corrected accordingly. Attention should, however, be directed, when interpreting the results concerning prevention of relapses, to the fact that the period during which patients were under observation varied very considerably.

The researches carried out at the experimental stations for the study of malarial infection in Roumania are grouped as follows :

I. Research into the treatment of experimental malarial infection, at the malariatherapy station attached to the Socola Hospital (Jassy).

¹ Final results at September 30th, 1936.

II. Research into treatment with synthetic products as compared with quinine.

(a) Cases treated at the Izolarea Hospital ;

(b) Cases treated in the field at the Tomesti Malaria Research Centre.

III. Eradication experiments carried out in the village of Opriseni by treatment with atebtrin and plasmoquine.

IV. Comparative experiments in clinical prophylaxis with atebtrin and quinine. These were carried out at the Gurbanesti Experimental Station under the direction of Professor MEZINCESCO.

Details of the plan of work will be found in the chapters dealing with the different groups of experiments.

The general conclusions are derived from observations on 476 cases of experimental infection, 418 cases of natural infection treated in hospital, and 740 cases treated in the field.

The malaria eradication experiments at Opriseni included a complete survey and the continuous observation and supervision of a population of 725 persons, 73% of whom were subjected to complete treatment in accordance with the indications given in the plan of research.

The Codreni prophylactic experiments, carried out by Professors MEZINCESCO and CORNELSON, were conducted among a population of about 300.

* * *

During these researches, four schizontocides—*quinine*, *aristoquine*, *atebtrin*, and *acriquine*—and one gametocide—*plasmoquine*—were used in varying quantities, singly or in combination.

All three species of parasite were represented among the cases treated. Given the conditions under which our experiments were carried out, the following conclusions may be deduced :

The therapeutic efficacy of quinine hydrochloride, atebtrin, and acriquine, in the treatment of an attack, appears to be equal, while that of aristoquine is slightly less.

The effective therapeutic dose, both in *aborting the attack* (single dose) and for its *treatment*, should not be less than 1 grm. of quinine

or 0.30 grm. of atebtrin per adult per day. The inadequacy of smaller doses of atebtrin—0.10 grm. per adult—has been demonstrated.

The length of the treatment of an attack should not be less than seven days. In quartan fever, in particular, an examination of the blood after the administration of the seventh dose of the drug may possibly point to the necessity of continuing the schizontocidal treatment until the parasites disappear (if the patient's state of tolerance for acridine derivatives permits).

It is inadvisable, in an attack of malaria, to use mixtures of different schizontocides, or mixtures of schizontocides and gametocides. A mixture of atebtrin + plasmoquine should be particularly avoided. These two substances, if administered *simultaneously*, produce a high percentage of toxic disturbances.

None of these schizontocides prevents the appearance of the gametocytes of malignant tertian, when those forms were absent at the beginning of the treatment.

From the point of view of the prevention of relapses, atebtrin, and particularly atebtrin followed by plasmoquine, appears to be more effective in quartan fever and malignant tertian. Definite conclusions could only be deduced from comparable groups kept under observation for an equal period of time.

The gametocidal action of a daily sub-toxic dose of 0.02 grm. of plasmoquine in malignant tertian is confirmed; 25% to 33% of the gamete-carriers still exhibit crescents after the administration of the fifth dose of that drug. The devitalising action is apparent in the majority of cases two days after the administration of the first dose.

It appears to be clearly superfluous to administer a daily sub-toxic dose of plasmoquine in order to devitalise the gametocytes. A single dose of 0.02 grm., repeated *if necessary* every five days (but only in the rare cases in which the gametocytes still persist), will have the same effect.

The regular treatment, three years in succession, of all malaria cases—attacks and relapses—in two villages in which no measures were taken against mosquitoes, produced a certain falling-off in the malarial morbidity. The number of cases of malignant tertian, in particular, dropped in three years by about 60%. The morbidity curve was, however, maintained in the case of benign tertian : the

number of relapses declined, but the number of new cases remained at the peak. The endemic indices declined.

Eradication experiments through treatment and prophylaxis with atebtrin and plasmoquine in one village—Opriseni, where 73% of the population followed the treatment regularly—saved the people treated from clinical symptoms, and caused a big decline in the endemic indices. The influence of this method was again revealed in the following year, notwithstanding a tendency towards higher indices, under the conditions of an anti-malarial campaign restricted on this occasion to the treatment of attacks and relapses.

Secondary disturbances.—Children under 1 year of age do not tolerate atebtrin ; signs of intolerance may appear immediately after the administration of the drug, or some little time afterwards. The administration of atebtrin in the morning before any food has been taken predisposes the patient to these disturbances.

The percentage of secondary disturbances in adults after the administration of atebtrin was very small, and necessitated the cessation of treatment in only one case.

The administration of a sub-toxic dose of 0.02 grm. of plasmoquine during five days, notwithstanding certain cyanotic disturbances, was continued without further incident. Synthetic drugs should only be administered under medical supervision.

I. STUDIES ON THE TREATMENT OF
EXPERIMENTAL MALARIA INFECTION
WITH SYNTHETIC DRUGS COMPARED WITH
QUININE SULPHATE.¹

By

M. CIUCA, L. BALLIF, M. CHELARESCO and M. LAVRINENKO.

In document C.H./Malaria/239 (Part I), we set out the results of our preliminary experiments, concluded on May 30th, 1936. The present note contains the results of our observations up to September 30th, 1936, together with remarks on earlier research conducted under similar experimental conditions.

We append the details of the plan followed, with the slight modification required by local conditions :

Benign tertian.—Study the action of a single dose of 0.50 gm. of quinine administered after the first four or five fever paroxysms, and the evolution of fever, parasites and relapses.

Establish the efficacy of a single dose of 0.1 gm. atebtrin as compared with a single dose of 0.5 gm. quinine.

Establish in the same way the efficacy of a single dose of 0.5 gm. quinine associated with 0.02 gm. plasmquine.

Study the action of a single dose of 0.25 gm. quinine plus 0.05 gm. atebtrin.

Study the therapeutic efficacy of a short treatment with quinine : 0.5 gm. daily for seven days and its effect in reducing relapses.

Repeat afterwards the same experiment with atebtrin 0.1 gm. daily for seven days.

¹ The present note is a summary of the experiments in treatment which have been undertaken according to a plan drawn up together with Colonel JAMES and Professor BALLIF, in May 1933, during a study mission organised under the auspices of the Health Organisation.

If relapses occur, study the efficacy of a therapeutic course of treatment with quinine : 0.5 gm. daily for fifteen days.

Malignant tertian.—The action of a single dose of 1 gm. of quinine administered on the fifth day of fever ; the course of the disease and relapses.

Action of a small dose of quinine (0.15 gm.) on the disappearance of asexual parasites in febrile cases.

Therapeutic efficacy of a seven-day course of quinine with daily doses of 1 gm.

Therapeutic efficacy of a seven-day course of atebtrin with daily doses of 0.3 gm.

Efficacy of a very small dose of plasmoquine in devitalising gametocytes. Begin with a dose of 0.02 gm. The minimum of exflagellation forms in the blood should be 25 per cubic millimetre. Groups of from 20 to 25 mosquitoes to be fed before treatment and four hours after the administration of the drug on four to five consecutive days. The results of the mosquito infection to be compared with the number of exflagellation forms per cubic millimetre (daily count).

Quartan.—Therapeutic action of :

Atebrin : 0.3 gm. for seven days.

Atebrin : 0.3 gm. + plasmoquine 0.02 gm. for seven days.

Atebrin : 0.3 gm. + quinine 0.5 gm. for seven days.

Observe the course of relapses.

A. Benign Tertian.

The benign tertian cases treated were cases of infection induced with three benign tertian strains of which BT^R102 and BT^{AP} are indigenous. The third (BT^H) is a strain from Madagascar, well known in the Malariatherapy Services of London, Amsterdam and Italy.

The BT^R102 strain (autochthonous strain) had undergone 117 passages direct through man before being passed through the

mosquito ; this strain has so far undergone 154 passages.¹ The BT^R Apostol strain—a recent indigenous strain—underwent forty alternate passages² through man and the mosquito. The passages through man took place during the same period in a malarious country and a non-malarious country (two years).

The “ human host ” medium does not appear to have produced any changes in virulence or any special sensitiveness to the anti-malarial drugs used.

The BT^H strain from Madagascar has been maintained in man and the mosquito alternatively for three years at Socola ; it has so far undergone forty-one passages.³

The comparative studies carried out with these strains have shown no variations with regard to the sensitiveness to different drugs.

The cases infected either by sporozoites or by virulent blood behaved in the same way in regard to their sensitiveness to the same anti-malarial drug.

For this reason, we have taken all the benign tertian cases together, when studying the immediate action upon fever and parasites.

The exigencies of malariatherapy necessities precluded us from applying the treatment in all cases on the fifth or seventh day of fever. Our observations on some hundreds of cases (infected with sporozoites or inoculated with virulent blood) have not shown any marked differences in a first attack, with regard to the immediate action of the drug, upon the disappearance of the fever and of the parasites.

COMPARATIVE ABORTIVE ACTION OF A SINGLE DOSE OF A DRUG.

These experiments were designed to study the comparative efficacy of a single small dose of a drug, with the object of allowing severely infected patients a temporary rest and enabling them to benefit later by pyrexia treatment in the event of a possible recurrence.

¹ 151 passages by inoculation with virulent blood and three through the mosquito.

² Twelve passages through the mosquito and twenty-eight by inoculation with virulent blood.

³ Seventeen passages through the mosquito and twenty-four by inoculation with virulent blood.

107 cases of *benign tertian* with fever and parasites in the blood consequently received a single dose of the following drugs, during their first febrile attack.

- (a) Quinine (sulphate) 0.5 gm. for one day ;
- (b) Quinine 0.5 gm. + plasmoquine 0.02 gm. for one day;
- (c) Atebrin 0.1 gm. for one day;
- (d) Atebrin 0.05 gm. + quinine 0.25 gm. for one day.

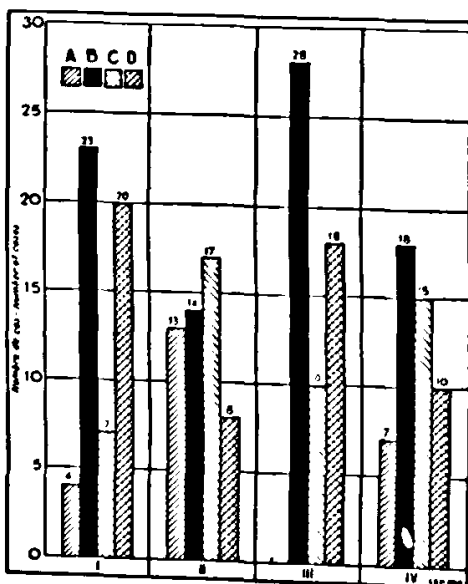
A daily blood analysis was carried out, including the examination of three thick drops and of a smear ; the parasites were counted over a hundred microscopic fields and the temperature taken every four hours.

Action upon the fever.—In 4 out of 27 cases treated with a single dose of 0.50 gm. quinine sulphate, no immediate action upon the fever could be observed ; in the other 23 patients, fever had disappeared after the administration of the drug.

In a like number of patients (27) treated with a single dose of 0.1 gm. atebrin, no immediate action upon the fever was noted in 13 cases.

Figure 1.

ABORTIVE ACTION OF A SINGLE DOSE OF QUININE (I), ATEBRIN (II), PLASMOQUINE + QUININE (III) AND ATEBRIN + QUININE (IV) IN BENIGN TERTIAN.



- A : No action on fever.
- B : Action on fever.
- C : No action on parasites.
- D : Action on parasites.

- I. Quinine : 0.50 gm. for one day.
- II. Atebrin : 0.10 gm. for one day.
- III. Plasmoquine : 0.02 gm. + quinine 0.50 gm. for one day.
- IV. Atebrin : 0.05 gm. + quinine 0.25 gm. for one day.

Among the patients (28) who received a single dose of 0.50 gm. quinine + 0.02 gm. plasmoquine, the fever fell in all cases. *This mixture seems thus to be the most active as regards direct action.*

The association of a very small dose of atebtrin (0.05 gm.) with 0.25 gm. of quinine was efficacious in 18 cases out of 25 cases treated.

In the doses used, the association of 0.50 gm. quinine + 0.02 gm. plasmoquine is therefore the most efficacious against fever, 0.10 gm. atebtrin administered alone being the less effective. Average time elapsing for the disappearance of fever varied between 1.5 days (after quinine + plasmoquine) and 2.2 days (after atebtrin alone).

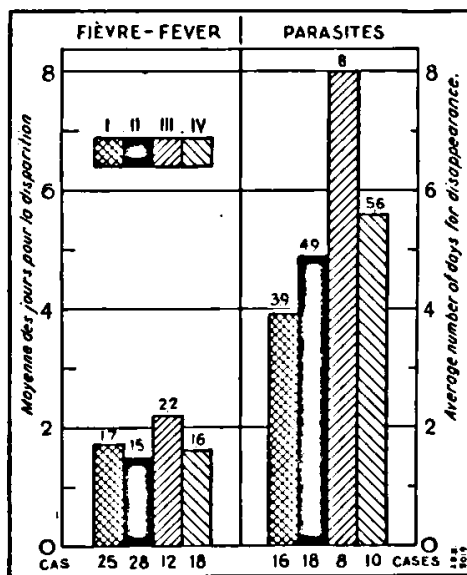
Immediate action on the disappearance of parasites.

In 7 cases out of 27 treated with a single dose of quinine sulphate, the parasites did not disappear; in the 20 other cases, the disappearance of the parasites from the circulation after this single dose was observed within a variable period, averaging 3.9 days.

Figure 2.

ABORTIVE ACTION OF A SINGLE DOSE OF QUININE (I), QUININE + PLASMOQUINE (II), ATEBRIN (III) AND ATEBRIN + QUININE (IV) IN BENIGN TERTIAN.

- I. Quinine : 0.50 gm. for one day.
- II. Quinine : 0.50 gm. + plasmoquine 0.02 gm. for one day.
- III. Atebrin : 0.10 gm. for one day.
- IV. Atebrin : 0.05 gm. + quinine 0.25 gm. for one day.



In a group of 25 patients treated with a single dose of 0.1 gm. atebtrin, no action on the parasites was observed in 17 cases. In the 8 others, the disappearance of the parasites after this single dose was observed after an average of 8 days. Patients Nos. 680 and 319 were only free from parasites after 23 and 70 days respectively; these two cases have not been counted.

Among the 28 cases who were given a single dose of 0.5 gm. quinine + 0.02 gm. plasmoquine, there were 10 cases in which the disappearance of the fever was not followed by that of the parasites. In 18 cases this disappearance was observed after variable intervals, the average being 4.9 days.

In 15 out of 25 cases treated with 0.05 gm. atebirin + 0.25 gm. quinine, the parasites had not disappeared. Their disappearance in the 10 other cases was observed after an average of 5.6 days.

Conclusions.

These experiments prove the insufficiency of too small doses of quinine or atebirin for the abortion of attacks.

The therapeutic doses of 0.5 gm. quinine sulphate and 0.1 gm. atebirin are not equivalent ; the latter seems to be too small.

The mixture of quinine sulphate (0.5 gm.) + plasmoquine (0.02 gm.) has proved in our cases to be the most efficacious.

COMPARATIVE TREATMENT OF THE ATTACKS.

Ninety-five patients all suffering from attacks and showing parasites in the circulation were treated as follows :

Quinine : 0.5 gm. for seven days : 30 patients ;
 Quinine : 1 gm. for seven days : 34 patients ;
 Atebrin : 0.1 gm. for seven days : 31 patients.

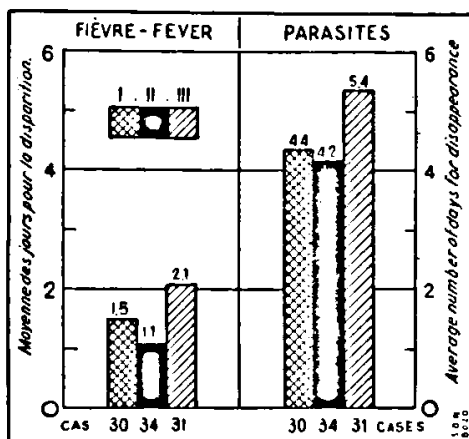
Action upon the fever.—With the doses used, the disappearance of fever occurred after an average of 1.5 days, when 0.5 gm. quinine was administered, of 1.1 days when the therapeutic dose of 1 gm. was administered and of 2.1 when atebirin was used.

Action upon the parasites.—The disappearance of the parasites occurred after an average of 4.4 days with quinine (0.5 gm.), of 4.2 after the therapeutic dose (1 gm.), of 5.4 days after atebirin (0.1 gm., a dose which we consider to be too small).

Relapses.—The incidence of relapses having been found to be far higher in patients infected by sporozoites than in patients inoculated with virulent blood, the results will be shown separately. The monthly distribution of relapses is given in relation to the period for which each patient was under observation.

Figure 3.
TREATMENT COMPARED IN
BENIGN TERTIAN; ACTION UPON
THE FEVER AND PARASITES.

- I. Quinine : 0.50 grm. for seven days.
- II. Quinine : 1 grm. for seven days.
- III. Atebrin : 0.10 grm. for seven days.



Among 18 patients infected with sporozoites and treated with 0.10 grm. atebrin for seven days, there were 10 clinical or parasitic relapses during the nine-month period of observation, and only 2 among the 12 patients inoculated with virulent blood, who were treated under the same conditions. In similar groups treated with quinine, there were 3 relapses among 12 patients and 1 among 18. As our patients were under observation for varying periods, we show the distribution of relapses in tabular form.

Period of observation Months	Atebrin 0.10 grm. for seven days				Quinine 0.50 grm. for seven days			
	Sporozoites		Virulent blood		Sporozoites		Virulent blood	
	Number of patients under observation	Re-lapses	Number of patients under observation	Re-lapses	Number of patients under observation	Re-lapses	Number of patients under observation	Re-lapses
1	18	2	12	1	12	2	18	0
2	13	0	10	1	9	0	15	0
3	12	0	6	0	6	0	13	0
4	10	2	5	0	4	0	11	0
5	7	1			2	0	10	0
6	6	0			2	0	10	0
7	6	1			2	0	9	0
8	5	2	4	0	2	0	9	1
9	3	2			2	1	7	0

Considering the number of relapses in relation to the total number of patients in each group, we may tabulate the results as follows :

- (a) Atebrin — 18 patients infected by sporozoites, 10 relapses ;
- (b) Atebrin — 12 patients infected by virulent blood, 2 relapses ;
- (c) Quinine — 12 patients infected by sporozoites, 3 relapses ;
- (d) Quinine — 18 patients infected by virulent blood, 1 relapse.

We would direct the reader's attention to the period of observation for patients in groups (a) and (b). The group treated with quinine was reduced by 50% for observation purposes in the third month of observation, while the number of relapses was higher in the atebtrin group from the fourth to the ninth month. The period of observation was longer, in the last group, in a larger number of cases. From the point of view of the prevention of relapses, therefore, our data are not comparable. At the same time, a dose of 0.10 gm. of atebtrin seems to us to be too near the minimum for efficacy.

Conclusions.

With regard to the efficacy of quinine administered in various doses, there was hardly any difference between the therapeutic dose (1 gm.) and half of that dose (0.5 gm.) in a seven-day treatment.

Quinine and atebtrin administered in the doses above mentioned for seven days are, within one day, equally efficacious.

The duration of seven days for the treatment of attacks of benign tertian appears to be a minimum.

Figure 4.

INCIDENCE OF RELAPSES IN SUBJECTS INFECTED BY SPOROZOITES (atebtrin 0.10 gm. for seven days).

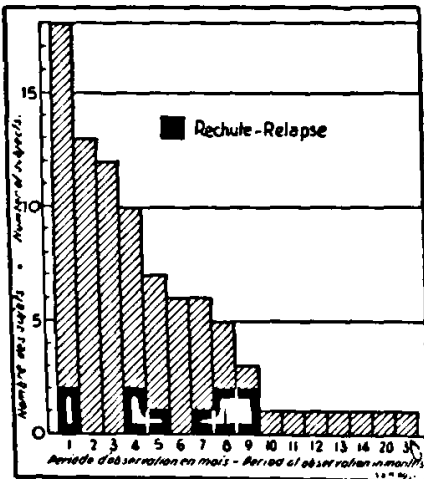


Figure 5.

INCIDENCE OF RELAPSES IN SUBJECTS INOCULATED WITH VIRULENT BLOOD (atebtrin 0.10 gm. for seven days).

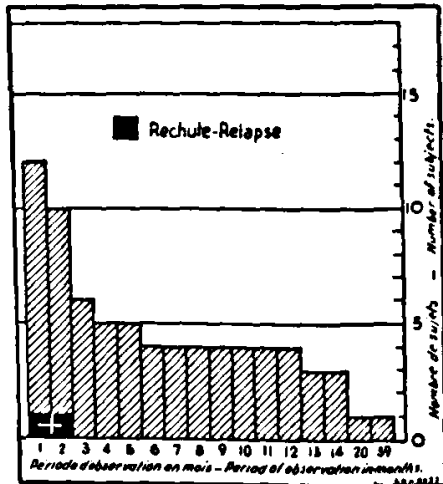


Figure 6.

INCIDENCE OF RELAPSES IN SUBJECTS INFECTED BY SPOROZOITES (quinine 0.50 grm. for seven days).

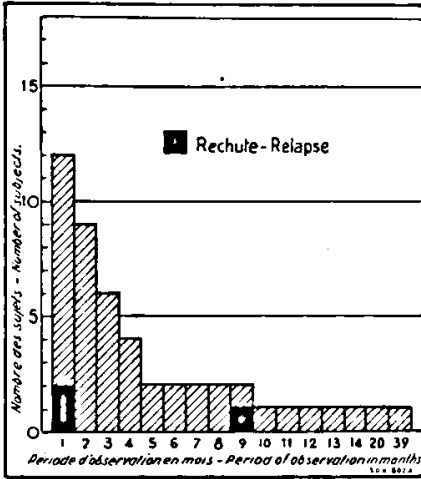
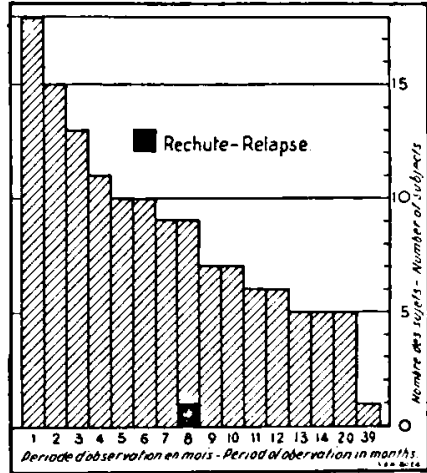


Figure 7.

INCIDENCE OF RELAPSES IN SUBJECTS INOCULATED WITH VIRULENT BLOOD (quinine 0.50 grm. for seven days).



B. Quartan Fever.

The cases treated according to the established plan were infected—for malaritherapy purposes—by inoculation of virulent blood from two quartan malaria strains (one being indigenous¹).

All our cases were treated during febrile attacks with one of the following drugs :

- 28 cases with 0.3 grm. atebriin for seven days ;
- 22 cases with 0.3 grm. atebriin + 0.5 grm. quinine for seven days ;
- 21 cases with 0.3 grm. atebriin + 0.02 grm. plasmoquine for seven days.

¹ The Q^R strain (indigenous) had undergone sixty-eight direct passages ; the Q^H strain, given us by Colonel JAMES, has only undergone twenty-three passages in Socola.

With regard to the receptivity of our patients and their sensitiveness to the treatment, the two strains were about equal. The clinical course of the disease appears to be more severe in cases inoculated with Q^R. A complete cross immunity exists between these two strains.

Action upon the fever.—The fall of the temperature was observed to occur after an average of 1.4 days in the group of 28 patients treated with atebrin ; after an average of 2 days in the 22 patients who were given 0.30 gm. atebrin + 0.5 gm. quinine sulphate and after an average of 1.8 days in the 21 patients who received atebrin associated with plasmoquine. *The action upon the fever appears to be determined in all three kinds of treatment by the atebrin.*

Action upon the parasites.—In the same groups, the average lapse of time after which the disappearance of the parasites occurred was 4.5 days when the patients were treated with atebrin and plasmoquine ; 4.8 days, in those who received atebrin alone. In the group of patients treated with atebrin and quinine, the average was 6.8 days. This difference is due to a *series of cases more resistant* to treatment ; this, however, can also be observed in the treatment of naturally contracted quartan fever.

In a small group of 5 patients treated with 1 gm. of quinine for seven days, the fever disappeared after an average of 2.5 days and the parasites after 5.3 days.

These results have been confirmed by the treatment of 25 parasite carriers (without fever) as follows :

- 16 patients with atebrin 0.3 gm. + quinine 0.5 gm. for seven days ;
- 4 patients with atebrin 0.3 gm. + plasmoquine 0.02 gm. for seven days ;
- 5 patients with quinine 1 gm. for seven days.

The parasites disappeared after an average of 4.5, 4.3 and 4.5 days respectively.

Two more persons who had been treated with 0.5 gm. quinine sulphate for 15 days relapsed after 15 and 35 days. ●

Secondary phenomena.—Out of a total of 90 patients (not all included in the graph) who were treated with atebrin, alone or associated with quinine or plasmoquine, 14 showed distinct pigmentation of the skin and scleræ. One case (No. 201) showed total intolerance to atebrin : vomiting and gastric pains.

Relapses.—In case No. 491 (atebrin group), there was a parasitic relapse thirty-one months after inoculation ; in case No. 461 (atebrin + plasmoquine group), there was a clinical relapse after sixteen weeks.

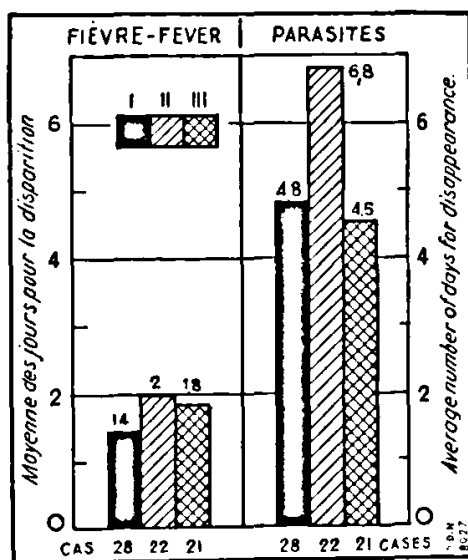
Here would we draw attention to the results of our earlier researches¹ into the treatment of experimental quartan fever (same strain). During these experiments, carried out on 83 patients, the treatment used was : quinine sulphate, pure plasmoquine, compound plasmoquine + pure plasmoquine, etc. The period of treatment was from seven to fifteen days. The average time required for the disappearance of the fever varied, in the case of quinine sulphate, from 1 to 2.4 days, and for the disappearance of the parasites from 4 to 6.2 days. In the last group, we observed 10 relapses among 54 cases treated with quinine sulphate ; 2 relapses among 18 cases treated with compound plasmoquine + pure plasmoquine.

Conclusions.

Upon the fever and parasites, the efficacy of the drugs used is approximately the same. There appears to be no advantage in associating quinine or plasmoquine with a therapeutic dose of atebtrin.

Figure 8.
TREATMENT COMPARED IN QUARTAN : ACTION UPON THE FEVER AND PARASITES.

- I. Atebrin : 0.30 grm. for seven days.
- II. Atebrin : 0.30 grm. + quinine 0.50 grm. for seven days.
- III. Atebrin : 0.30 grm. + plasmoquine 0.02 grm. for seven days.



With regard to relapses, the difference between atebtrin and quinine is evident ; *relapses have been more numerous in cases treated with quinine.*

¹ Archives roumaines de Pathologie expérimentale, 1932, 5, No. 1.

Plasmoquine associated with quinine does not shorten the lapse of time after which parasites disappear ; *it diminishes, however, the number of relapses.*

In view of the somewhat numerous cases of slow disappearance of the parasites, the treatment of experimental quartan malaria should in no case be applied for less than seven days.

Control examination after seven days will show if this treatment needs to be prolonged. *In 8 cases out of the total number of patients subjected to the experiment, the parasites were present till the twelfth day of treatment ; such resistance is an individual matter and has no relation to the drug used.*

C. Malignant Tertian.

The cases of malignant tertian¹ which have been studied according to the plan established include 67 *patients infected by sporozoites* and 98 *inoculated with virulent blood.*

Only 66 of them had to be treated.

ABORTIVE ACTION OF A SINGLE DOSE OF 1 GRM. QUININE.

The single dose of quinine was usually administered between the third and ninth day of fever.

No action upon the fever was observed only in 4 cases out of 26 treated in that way. In the 22 other cases, action by the quinine on the fever was observable during the four days following treatment, the average being 1.7 days in patients infected with sporozoites and 2.3 days in those inoculated with virulent blood.

Parasites.—In 14 cases, the trophozoites did not disappear after a single dose of 1 grm. quinine. In the other 12 cases, the trophozoites disappeared after varying lapses of time, the average being 3.5 days in patients infected with sporozoites and 5.3 in those inoculated with virulent blood.

¹ The M.T. strain used had undergone 116 passages direct and nine through the mosquito. The anopheles were infected for the first time with the seventy-eighth passage. In malignant tertian, more particularly, there is no difference in sensitiveness to treatment as between the patients inoculated by virulent blood and those infected by sporozoites. The two groups are also similar from the point of view of the incidence of relapses.

TREATMENT OF THE ATTACK.

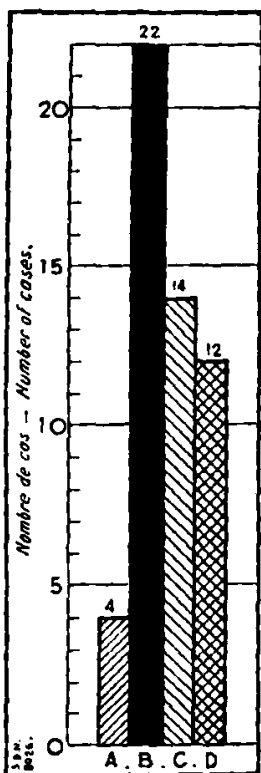
Comparative treatment of 66 clinical cases with fever and parasites was applied as follows :

- 41 patients received 1 grm. quinine for seven days ;
- 25 patients received 0.3 grm. atebtrin for seven days.

The average time required for the disappearance of the fever was 1.8 days in the 41 cases treated with quinine, and 1.5 days in the 25 treated with atebtrin. The trophozoites disappeared after an average of 3.2 and 4.1 days respectively in the two groups.

Figure 9.

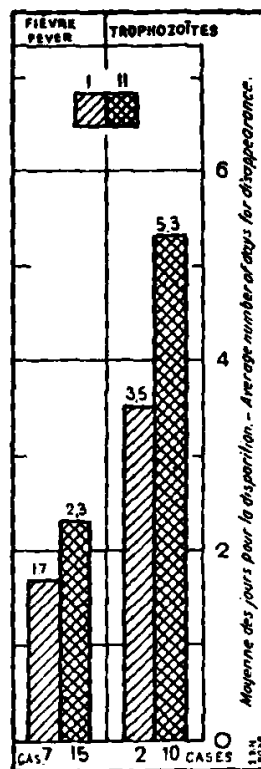
ABORTIVE ACTION OF A SINGLE DOSE OF 1 GRM. QUININE (SULPHATE) IN MALIGNANT TERTIAN (T.M.²⁷⁸).



- A : No action on fever.
- B : Action on fever.
- C : No action on trophozoites.
- D : Action on trophozoites.

Figure 9bis.

ACTION, UPON THE FEVER AND TROPHOZOITES, OF A SINGLE DOSE OF 1 GRM. QUININE (SULPHATE) IN MALIGNANT TERTIAN (T.M.²⁷⁶).



- I. Cases infected by mosquito bites.
- II. Cases inoculated with virulent blood.

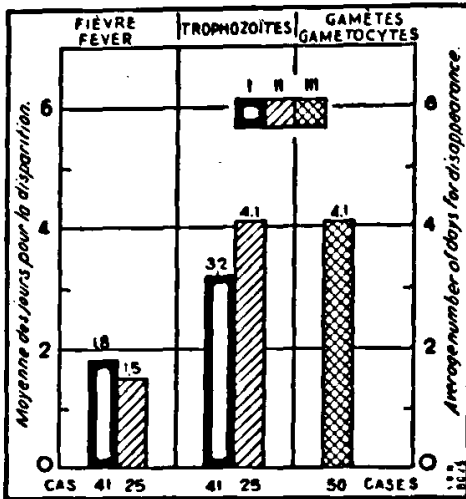


Figure 10.
TREATMENT COMPARED IN MALIGNANT TERTIAN (all cases).

- I. Quinine : 1 grm. for seven days.
 II. Atebrin : 0.30 grm. for seven days.
 III. Plasmoquine : 0.02 grm. for one day.

Whilst there was no obvious difference between the groups treated with quinine and those treated with atebrin, we observed nevertheless a marked difference with regard to relapses : 2 of the 25 cases treated with atebrin and 14 of the 41 cases treated with quinine. Graphs Nos. 11, 12, 13, 14, 15 and 16 show the monthly distribution of relapses according to the drug used and the method of infection.

The efficacy of quinine and atebrin administered in therapeutic doses is equivalent in respect of action upon the fever and the disappearance of trophozoites from the general circulation.

The action of atebrin upon the prevention of relapses appears to be superior to that of quinine alone or of atebrin associated with quinine.

For the attack, a treatment of seven days appears to be a minimum.

GAMETOCIDAL ACTION OF A SINGLE DOSE OF 0.02 GRM. PLASMOQUINE.

Document C.H. /Malaria /235 on the sterilising action of a single dose of 0.02 grm. plasmoquine on the gametocytes has confirmed the data previously obtained. The sterilising action is observed in most of the cases two days after the administration.

The thick-drop blood examination of 50 gametocyte carriers has enabled us to confirm the previous studies and has showed that the

Figure 11.

INCIDENCE OF RELAPSES IN THE SUBJECTS INFECTED BY SPOROZOITES OR INOCULATED WITH VIRULENT BLOOD (quinine 1 grm. for seven days).

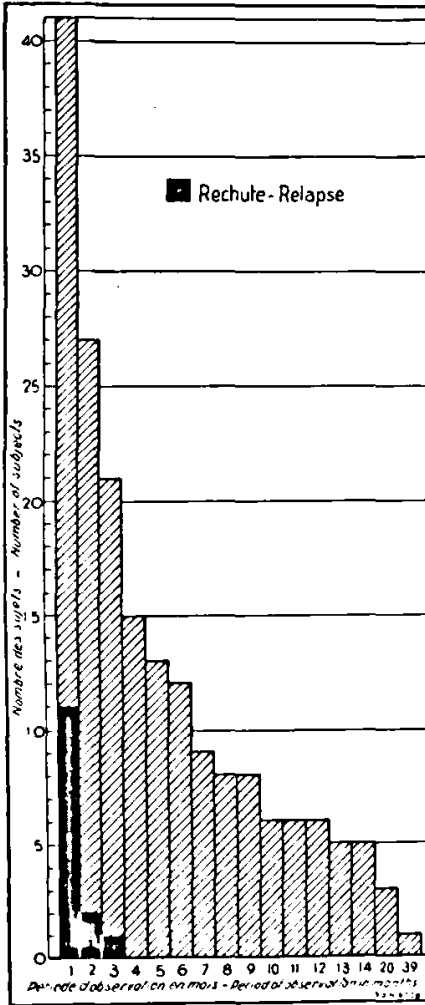
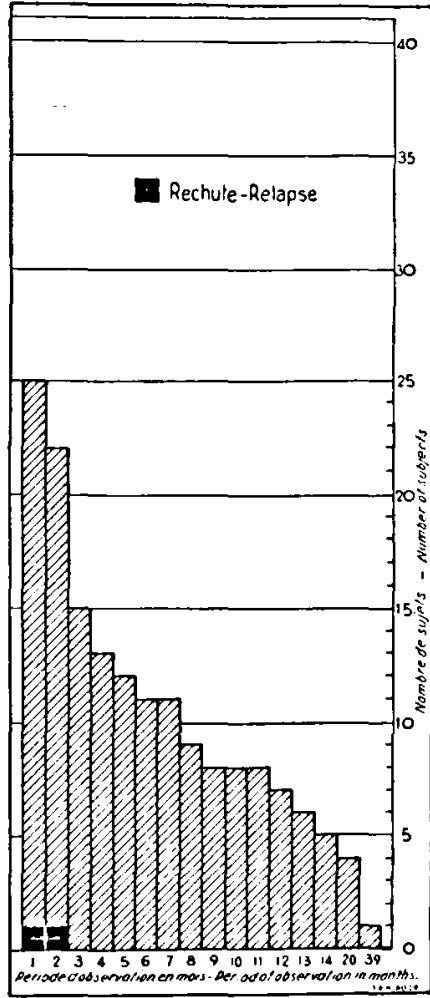


Figure 12.

INCIDENCE OF RELAPSES IN THE SUBJECTS INFECTED BY SPOROZOITES OR INOCULATED WITH VIRULENT BLOOD (atebrin 0.30 grm. for seven days).



gametocytes could remain in the circulation for lapses of time averaging 4.1 days after the administration of a single dose.

We should like, however, to recall here once more that the sterilising action of plasmoquine is evident in spite of the presence (in some cases) in the blood of an important number of gametocytes which are no more capable of infecting the anopheles.

Figure 13.

INCIDENCE OF RELAPSES IN SUBJECTS INFECTED BY SPOZOITES (atebrin 0.30 gm. for seven days).



Figure 14.

INCIDENCE OF RELAPSES IN SUBJECTS INOCULATED WITH VIRULENT BLOOD (atebrin 0.30 gm. for seven days).

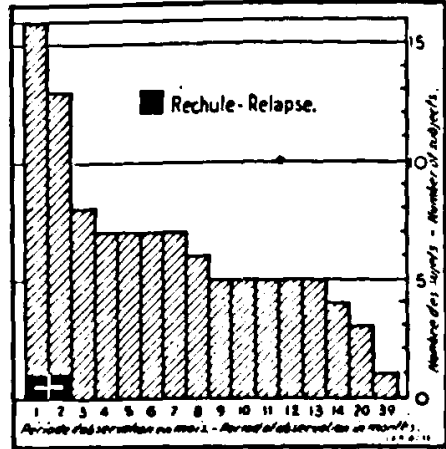


Figure 15.

INCIDENCE OF RELAPSES IN SUBJECTS INOCULATED WITH VIRULENT BLOOD (quinine 1 gm. for seven days).

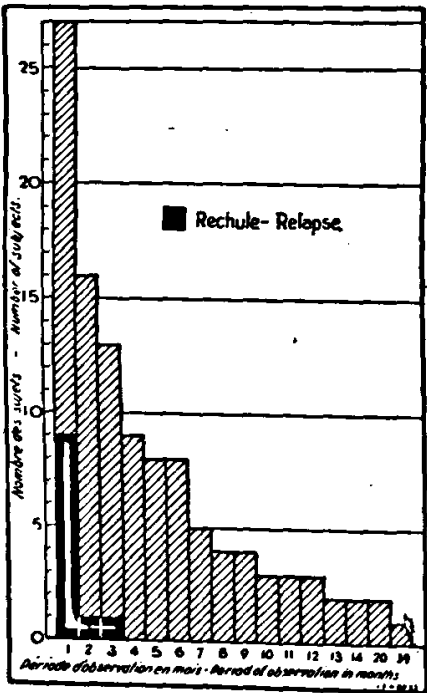
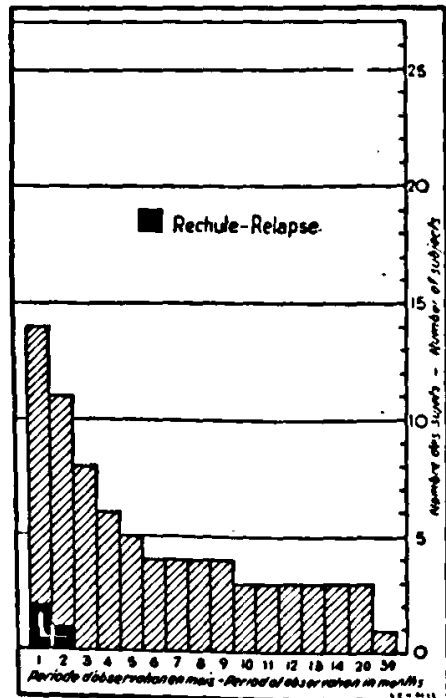


Figure 16.

INCIDENCE OF RELAPSES IN SUBJECTS INFECTED BY SPOZOITES (quinine 1 gm. for seven days).



The conclusion to be drawn from these observations (as well as those collected in the field) is that *it is futile* to administer plasmoguinine *daily* for the only reason that gametocytes are still present in the blood. A single dose of 0.02 gm. plasmoguinine, repeated at intervals of four or five days, yields results similar to those obtained with the same dose repeated daily.

II. RESEARCH ON THE TREATMENT OF NATURALLY ACQUIRED MALARIA.

(a) IN HOSPITAL : EXPERIMENTS¹ TO ASCERTAIN THE EFFICACY OF SYNTHETIC DRUGS AS COMPARED WITH QUININE.

By

M. CIUCA, I. BALTEANU, M. FRANCKE, E. ALEXA and I. MICU.

(Second Note.)

In a first note² prepared in collaboration with M. FRANCKE, E. ALEXA, C. AGAPI, E. LUPU and E. MANOLIU, we gave the results of the comparative treatment of 110 cases of malaria (spontaneous natural infection) carried out in hospital under the best possible conditions of control : temperature taken every four hours, daily blood tests with parasite count, kidney permeability tests, tests to determine the functioning of the liver, etc.

Experiments were conducted with the following drugs :

Atebrin 0.3 grm. per diem for seven days ;

Atebrin 0.3 grm. + plasmoquine 0.02 grm. for seven days ;

Quinine sulphate 0.5 grm. + atebrin 0.3 grm. for seven days ;

Quinine sulphate 1 grm. for seven days ;

Quinine sulphate 0.5 grm. + plasmoquine 0.02 grm. for seven days.

The conclusions set out in this note were :

“Our observations confirm previous data regarding the efficacy of atebrin in cases of natural infection due to one of the three types of parasite and its innocuousness during the acute period of the disease.

¹ Carried out at the “ Izolarea ” Hospital, Jassy.
² *Arch. roum. Path. expér.*, 1935, 8, No. 1.

"As regards direct action on the fever and the disappearance of the schizonts, there would seem to be little to choose between quinine and atebtrin.

"Atebrin resembles quinine in that its efficacy (direct action on the fever and elimination of parasites) varies according to the period in the course of the disease at which it is administered—*i.e.*, to the degree of immunity acquired by the patient.

"Discoloration of the skin was observed in our subjects to be more pronounced in the more serious cases.

"A combination of atebtrin (0.3 grm.) with a sub-toxic dose of plasmoquine (0.02 grm.) gives rise, in some cases, to the toxic symptoms of plasmoquine on and after the second day of treatment. In our opinion this combination should, in the treatment of acute forms of the disease, be administered only under the strict supervision of a doctor.

"The combination atebtrin (0.3 grm.) plus 0.5 grm. quinine does not seem to us to possess any particular advantage over the use of either drug singly. In some cases, atebtrin causes secondary disturbances such as gastro-intestinal disorders, vomiting and gastric pains ; in one isolated instance, we observed slight mental excitement in a patient then in the fourth month of her pregnancy.

"In spite of the relatively small number of patients it may be observed that, as regards the prevention of relapses in malignant tertian, in a third of the cases which had relapses, the combination atebtrin *plus* plasmoquine apparently produced no better results than atebtrin used alone. The combination seems to be more effective in quartan cases."

Document C.H. /Malaria /239 contains a summary of the results of the experiments on the efficacy of synthetic drugs administered to *160 malaria patients in hospital* ; these observations ceased on June 1st, 1935. Since that date, *127 new malaria patients* have been treated, and we have continued to control relapses as far as possible.

The local epidemiological conditions of the 287 patients who have formed the subject of our investigations are the same as those obtaining at the Tomesti Research Centre. (Most of the patients come from this district.) The reader will therefore be able to compare the relative efficacy of the drugs when administered to patients in hospital and to persons outside carrying on with their ordinary occupations in the intervals between attacks.

METHOD OF EXPERIMENTAL TREATMENT.

Two hundred and sixty-six malaria patients and 21 parasite carriers were treated either with acriquine, atebtrin or quinine.

In 57 cases out of the 287 (which received treatment for seven days), schizonticide treatment was followed, after three days' rest, by five days' treatment with plasmoquine, the dose being 0.02 gm. per diem.

Classified according to type of parasite and drug administered, the figures for our cases are as follows :

Clinical cases.

Quinine (for seven days) :	}	Benign tertian	56
		Malignant tertian	21
Acriquine (for seven days) :	}	Benign tertian	52
		Malignant tertian	49
		Quartan	4
		Quartan plus malignant tertian	1
Atebrin (for seven days) :	}	Benign tertian	22
		Malignant tertian	20
		Quartan	3
		Malignant tertian plus benign tertian	1
Acriquine (for seven days) + plasmoquine (for five days) :		Malignant tertian	21
Atebrin (for seven days) + plasmoquine (for five days) :	}	Malignant tertian	26
		Quartan	1
		Quartan plus benign tertian...	1
		Malignant tertian plus benign tertian	2
Quinine (for seven days) + plasmoquine (for five days) :		Malignant tertian	6

The drugs were administered twice daily during or after meals ; the temperature was taken every four hours ; the blood was examined daily (thick drops and smears).

During these experiments, the drugs employed were taken from the stocks used for the other experiments. The acriquine¹ was offered us for experimental purposes by Professor SERGUIEFF, of Moscow, in February 1935.

¹ Acriquine, a derivative of acridine, is a bihydrochloride : 2-methoxy 6-chloro 9-diethylamino-pentylamino-acridine.

TAREJEV, in a report submitted at Moscow, says that the experiments conducted by the Moscow Institute of Tropical Medicine prove the absolute therapeutical equivalence of atebrin and acriquine (F = 3).

The period within which temperature reverted to normal was 3.2 days ; the parasites disappeared in 4.8 days. There were 35% relapses in benign tertian. In quartan : fever and parasites disappeared in 3.6 and 6.3 days respectively ; no relapse was noted. In malignant tertian, fever and parasites disappeared in 3.6 and 4.8 days respectively.

Table 1 shows the clinical aspects of the cases treated with each drug experimented with.

Secondary symptoms.—Among 106 patients treated with acriquine and 21 with acriquine plus plasmoquine, pigmentation appeared in 22 cases between the first and eleventh days of treatment. Two patients suffered from giddiness ; one only experienced nausea. Of 46 patients treated with atebtrin alone and 30 patients treated with atebtrin plus plasmoquine, 20 showed the yellow discoloration, which appeared between the first and sixteenth days and in some cases continued for twenty to twenty-five days after the end of treatment. Nausea was observed in 3 cases, disturbances of the heart rhythm in 1 case and gastric pains in 2 cases ; in only 1 case was there vomiting.

Comparative efficacy.—Information concerning the comparative efficacy of the drugs will be found in Tables 2 and 3, in which the case records are summarised.

Benign Tertian.

130 cases of benign tertian and 14 parasite carriers were considered. Under the local conditions of treatment, acriquine had on an average a more effective direct action on the fever than atebtrin or quinine. The difference is less marked in the case of immediate action on schizonts ; in fact, there was practically no difference in the time taken to eliminate all parasites from the blood stream. In our subjects, quinine seemed to be rather slower than the other drugs in its action on the spleen.

Relapses.—More than 50% of the patients were re-examined once or more during the eight to fourteen months' observation period. The number of relapses among those who presented themselves for examination is given for the three groups. It was not possible to control all the relapses.

Malignant Tertian.

143 clinical cases and 6 parasite carriers were considered. The results summarised in Table 4 clearly prove that all three schizontocides are equally efficacious whether followed with plasmoquine for five days or not ; the averages are shown in the table.

The average period after which trophozoites had disappeared was 2.7 days in the case of atebtrin, 3.3 days in that of acriquine, and 3.6 days in that of quinine hydrochloride.

None of the three schizontocides is effective in preventing during the schizontocide treatment the appearance of gametocytes where originally there were none. In 3 cases out of 21 treated with acriquine plus plasmoquine, gametocytes were still present in the blood at the end of the plasmoquine treatment ; in 4 cases out of 30 treated with atebirin plus plasmoquine, the same condition obtained.

Conclusions.

Our experiments confirm the experiments of KRITCHEWSKI, TAREJEV, and others, concerning the equivalency of acriquine and atebirin.

Continuous treatment of 287 malaria patients in hospital did not reveal any difference between the respective schizontocide properties of acriquine, atebirin, and quinine in benign tertian. In malignant tertian, atebirin acted more quickly on the trophozoites.

Certain similar secondary symptoms were noted after the administration of acriquine and of atebirin ; no ill effects followed the administration of quinine.

None of the three schizontocides prevented the appearance of crescents where originally there were none. In approximately 25% of malignant tertian gametocyte carriers, the crescents were still present until the administration of the fifth dose of plasmoquine.

The control of relapses was too irregular to permit of conclusions ; the data obtained are shown in the following tables :

Table 1.

TREATED CASES AND EXPERIMENTED DRUGS.

Total number of cases treated	Acriquine				Atebrin				Quinine			Acriquine + plas- moquine	Atebrin + plasmoquine			Quinine + plas- moquine
	106				46				78			21	30			6
Clinical forms	B.T. 52	M.T. 49	Q. 4	M. 1	B.T. 22	M.T. 20	Q. 3	M. 1	B.T. 56	M.T. 21	Q. 1	M.T. 21	M.T. 26	Q. 1	M. 3	M.T. 6
Primary infection	1	1	—	—	—	—	—	—	1	—	—	—	3	—	—	—
Quotidian	21	26	1	1	10	6	1	—	15	6	—	13	14	1	1	2
Tertian	16	8	—	—	10	6	—	1	23	7	—	2	9	—	—	1
Sub-febrile cases	1	2	1	—	2	1	—	—	3	2	—	2	—	—	—	—
Quartan	—	—	2	—	—	—	2	—	—	—	—	—	—	—	—	—
Parasite carriers	5	3	—	—	—	—	—	—	9	1	1	2	—	—	—	—
Irregular febrile attacks	8	9	—	—	—	7	—	—	5	5	—	2	—	—	2	3

Table 2. — COMPARATIVE EFFICACY OF THE DRUGS

	BENIGN TERTIAN			BENIGN TERTIAN : PARASITE CARRIERS		QUARTAN		
	Acridine (0.30 grm. for seven days)	Atebrin (0.30 grm. for seven days)	Quinine hydrochloride (1 grm. for seven days)	Acridine (0.30 grm. for seven days)	Quinine hydrochloride (1 grm. for seven days)	Acridine (0.30 grm. for seven days)	Atebrin (0.30 grm. for 7 days) followed after 3 days' interval by plasmoquine (0.02 grm. for 5 days)	Atebrin (0.30 grm. for seven days)
FEVER.								
Number of cases considered	47	22	47	5	9	4	1	3
Fever and parasites at the beginning of the treatment	33	19	29	—	—	3	1	2
No fever at the beginning of the treatment	14	3	18	5	9	1	—	1
Number of cases in which the fever disappeared after								
1 dose	13	14	23	—	—	—	—	—
2 doses	21	4	6	—	—	1	1	1
3 doses	2	—	1	—	—	2	—	—
4 doses	1	—	—	—	—	—	—	—
5 doses	—	—	—	—	—	—	—	—
6 doses	—	—	—	—	—	—	—	—
7 doses	—	—	—	—	—	—	—	—
Average	1.75	1.22	1.26	—	—	3	2	1.5
SCHIZONTS.								
No schizonts at beginning of treatment ..	1	2	3	—	—	1	1	—
Number of cases in which the schizonts disappeared after								
1 dose	12	7	19	3	3	1	—	2
2 doses	25	10	20	2	5	1	1	1
3 doses	8	3	4	—	1	1	—	—
4 doses	2	—	1	—	—	—	—	—
5 doses	—	—	—	—	—	1	—	—
6 doses	—	—	—	—	—	—	—	—
7 doses	—	—	—	—	—	—	—	—
Average	1.57	1.8	1.7	1.4	1.7	2.75	2	1.33
GAMETOCYTES.								
Number of cases in which the gametocytes disappeared after								
1 dose	3	4	8	4	3	1	1	1
2 doses	23	8	20	1	3	—	—	—
3 doses	11	8	9	—	2	2	—	1
4 doses	8	2	6	—	—	—	—	—
5 doses	2	—	—	—	1	1	—	—
6 doses	—	—	2	—	—	—	—	—
7 doses	—	—	—	—	—	—	—	—
Average	2.63	2.36	2.46	1.20	2.22	3	1	2
SPLEEN.								
Enlarged before treatment	37	20	40	5	8	4	1	3
Reduced after treatment	35	16	30	4	7	4	1	3
RELAPSES.								
Number of persons re-examined	36	17	24	4	3	—	—	—
Period of observation (months)	1-13	2-14	1-10	3-11	3-10	—	—	—
Total relapses : Number	9	7	7	1	1	—	—	—
Forms A+P+	7	7	7	1	1	—	—	—
Ao P+	2	—	—	—	—	—	—	—
Percentage	23	31	14	—	—	—	—	—

Table 3.

DISTRIBUTION OF RELAPSES DURING THE FOURTEEN MONTHS FOLLOWING TREATMENT.

Drug	Type of parasite	Total number of cases	Total number of cases		Number of cases re-examined and relapses after a period of 1 to 14 months																													
			Re-examined	Relapses	1		2		3		4		5		6		7		8		9		10		11		12		13		14			
					r	R	r	R	r	R	r	R	r	R	r	R	r	R	r	R	r	R	r	R	r	R	r	R	r	R	r	R		
Acriquine	B.T.	47	36	9	3	3	7	3	1	—	—	—	1	—	1	—	3	1	3	—	2	1	8	—	3	—	3	—	1	1	—	—	—	—
Atebrin	B.T.	22	17	7	—	—	1	—	4	1	4	2	2	1	—	—	1	—	1	—	1	—	—	—	1	1	1	1	—	—	—	—	1	1
Quinine	B.T.	47	24	7	4	1	2	1	4	3	3	—	1	—	—	—	2	1	3	—	4	1	1	—	—	—	—	—	—	—	—	—	—	—
Acriquine	M.T.	46	16	10	5	3	7	6	1	—	1	1	—	—	—	—	—	—	—	—	1	—	—	—	1	—	—	—	—	—	—	—	—	—
Atebrin	M.T.	20	8	5	1	1	3	2	—	2	2	1	2	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Quinine	M.T.	20	7	2	3	—	1	1	—	—	1	—	—	—	—	—	—	—	2	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Acriquine + plasmoquine	M.T.	19	8	4	2	1	2	2	1	—	—	—	1	1	—	—	—	—	1	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—
Atebrin + plasmoquine	M.T.	26	15	5	—	—	2	1	2	1	5	—	4	2	1	—	—	—	—	—	1	1	—	—	—	—	—	—	—	—	—	—	—	—

r = re-examined.
R = Relapses.

Table 4.—MALIGNANT TERTIAN.

	Acricquine (0.30 grm. for seven days)	Atebrin (0.30 grm. for seven days)	Quinine hydrochloride (1 grm. for seven days)	Acricquine (0.30 grm. for seven days) followed after three days' interval by plasmoquine (0.02 grm. for five days)	Atebrin (0.30 grm. for seven days) followed after three days' interval by plasmoquine (0.02 grm. for five days)	Quinine hydrochloride (1 grm. for seven days) followed by plasmoquine (0.02 grm. for five days)
FEVER.						
Number of cases considered	46	20	20	19	26	6
With attacks and parasites at the beginning of the treatment	43	15	16	18	19	4
No fever at the beginning of the treatment	3	5	4	1	7	2
Disappearance of fever after						
1 dose	9	3	6	5	3	—
2 doses	17	7	11	6	13	5
3 doses	13	5	1	4	6	—
4 doses	3	2	—	2	1	—
5 doses	1	—	1	1	—	1
6 doses	—	—	—	—	—	—
7 doses	—	—	—	—	—	—
Average	2.3	2.35	1.89	2.33	2.21	2.5
TROPHOZOITES.						
No trophozoites at beginning treatment	1	1	2	3	1	—
Disappearance of fever after						
1 dose	2	2	1	—	2	—
2 doses	11	8	4	7	6	1
3 doses	18	4	4	5	11	1
4 doses	8	3	6	6	5	3
5 doses	5	2	1	1	1	—
6 doses	1	—	1	—	—	1
7 doses	1	—	1	—	—	—
Average	3.20	2.73	3.5	3.05	2.8	3.8
GAMETOCYTES.						
No gametocytes at the beginning of the schizontocidal treatment	35	14	9	11	20	1
No gametocytes at the beginning of the schizontocidal treatment and no appearance during treatment	8	5	3	—	5	—
Presence of gametocytes at the beginning of the treatment	11	6	11	8	6	5
Appearance of gametocytes during treatment after						
1 dose	10	2	—	4	3	—
2 doses	4	4	3	1	5	1
3 doses	4	1	1	—	3	—
4 doses	6	1	1	4	2	—
5 doses	2	1	1	2	1	—
6 doses	1	—	—	—	1	—
7 doses	—	—	—	—	—	—
Disappearance of gametocytes after						
1 dose of quin. or atebr.	—	1	—	—	—	—
2 doses of quin. or atebr.	—	1	1	—	—	—
3 doses of quin. or atebr.	—	—	1	—	1	—
4 doses of quin. or atebr.	1	1	1	—	1	—
5 doses of quin. or atebr.	3	—	—	—	—	—
6 doses of quin. or atebr.	3	—	1	—	1	—
7 doses of quin. or atebr.	4	—	—	—	—	—
Persistence after the seventh dose of quinine or atebrin	27	12	13	10	18	6
Disappearance during treatment with plasmoquine				14	13	0
Persistence 24 hours after the fifth dose of plasmoquine				3	4	—
SPLEEN.						
Enlarged before treatment	35	17	16	14	20	6
Reduced after treatment	31	11	10	12	17	5
RELAPSES.						
Number of cases re-examined	16	8	7	8	15	—
Period of observation (months)	1-11	1-5	1-8	1-9	2-9	—
Number of patients having relapses	10	5	2	4	5	—
Total relapses: Forms A + P+	8	5	2	4	5	—
Ao P+	2	—	—	—	—	—

(b) TREATMENT EXPERIMENTS CARRIED
OUT IN THE FIELD.¹

By

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Experiments.—A. In a village suffering from endemic malaria, all attacks and relapses to be treated with atebryn, followed or not by plasmoguinine.

B. In another village, all attacks and relapses to be treated according to the same criteria, with quinine hydrochloride, followed or not by plasmoguinine.

The experiments on treatment have been carried out in two villages : Osoi (2,067 inhabitants) and Costuleni (1,572 inhabitants) with like epidemiological conditions (detailed information on these two villages will be found in document C.H. /Malaria /234).

A third village, Comarna, belonging to the same epidemiological complex, was chosen as control.

The three villages are situated in an area of average malaria endemicity.

It may be mentioned here that the number of births at Osoi in 1935, among a population of 2,067, was 81 ; there were 29 deaths, including 20 of children under one year.

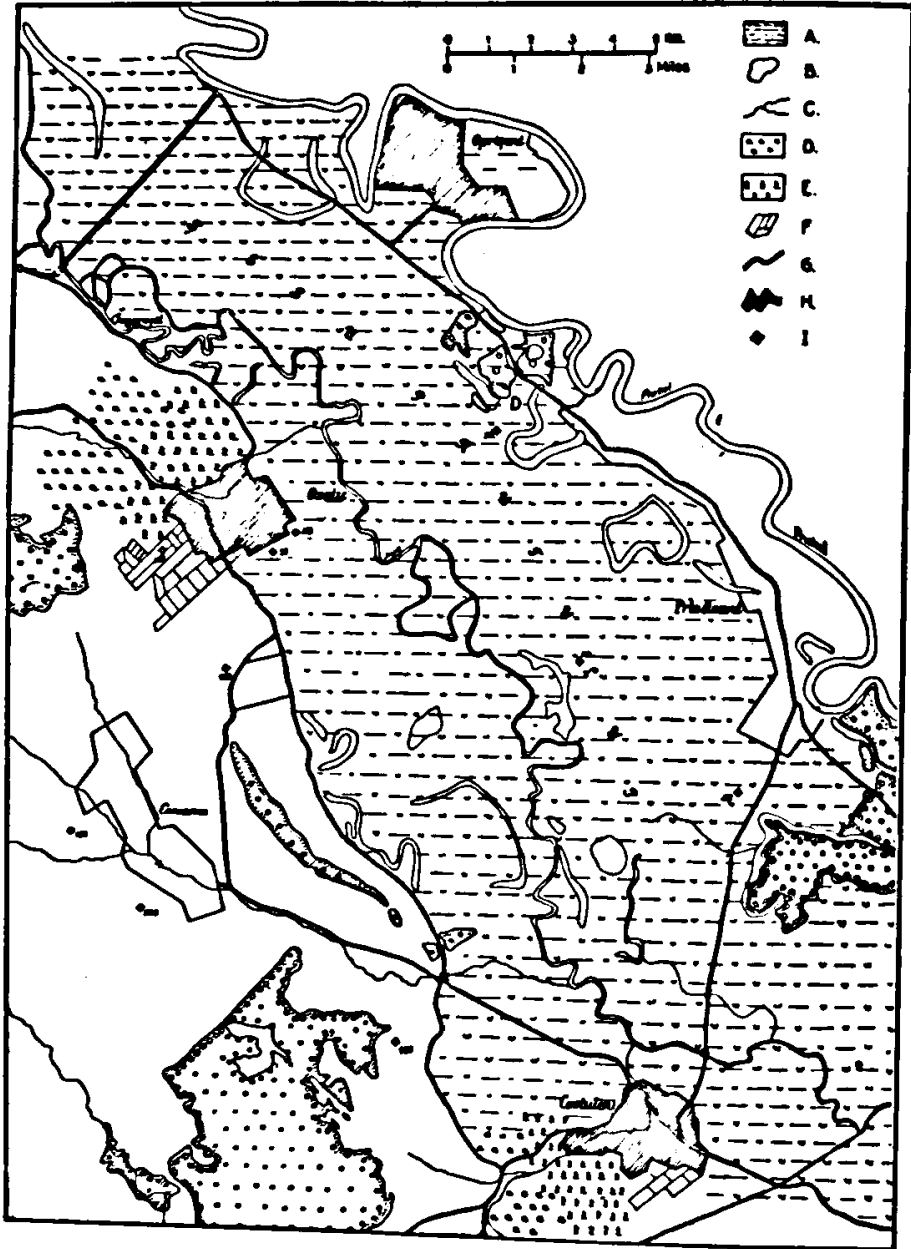
At Costuleni (population 1,572) in 1935 there were 63 births, and 42 deaths, including 14 under one year.

The individual economic situation of the inhabitants was below the average ; it will suffice to point out that the number of cases of pellagra in the two villages is fairly high.

¹ The preliminary data contained in document C.H. /Malaria /239 concerned only the results up to April 30th, 1936. The figures and percentage now given in the present report comprise the data obtained up to September 30th, 1936.

Figure 1.

MAP OF THE VILLAGES COSTULENI, OSOI AND OPRISANI.



A : Land liable to flooding.
 B : Marshes.
 C : Stream.
 D : Orchards.
 E : Vineyards.

F : Arable land.
 G : Public road.
 H : Village.
 I : Height.

The reader will find in the monograph¹ by AYKROYD, ALEXA, and NITZULESCU fuller details concerning the economic situation in Osoi ; the conditions at Costuleni are very much the same.

Live-stock.—In the village of Osoi, there are 420 dwelling-houses and 360 byres or sheds for animals, situated as a rule in the immediate vicinity of the houses.

In the village of Costuleni, there are 340 houses, and 244 byres or sheds of various kinds for live-stock also are in the immediate vicinity of the houses.

EXPERIMENTAL CONDITIONS.

Document C.H. /Malaria /234 gives particulars of the anti-malaria measures applied during 1933 and 1934 which preceded the carrying-out of our programme. We should like to recall here that, during this period, all malaria cases (traced during house visits or at the dispensary)—attacks and relapses—have been regularly treated for seven successive days either with quinine or atebrin alone or associated with plasmoquine.

No other anti-malaria measures have been applied.

Organisation of the Field Work in 1935.

One doctor was responsible for each village and had to co-ordinate the work in connection with the detection of patients, the taking of blood samples, the treatment and control.

The villages were dealt with in three areas with a health worker for each who had been trained for the task he would have to accomplish. Each area was divided into thirty groups of houses occupied by four or five families. Each month the blood was tested at the same date.

Two distributing agents administered the drugs and took the temperatures of the patients twice a day. The blood examination was carried out daily during treatment and repeated regularly once a month.

The endemic indices and splenometric data, according to the method of Catanei and Parrot, were established four times in the year.

¹ *Archives roumaines de Pathologie expérimentale*, 1936, 8, No. 4.

Table 1.
MALARIA IN THE VILLAGES OF OSOI AND COSTULENI.*

Month	1935							
	OSOI				COSTULENI			
	Population	Total	New cases	Re-lapses	Population	Total	New cases	Re-lapses
Total.....	2,067	331	179	152	1,572	373	204	169
January.....		1	—	1		8	2	6
February.....		4	1	3		7	3	4
March.....		20	6	14		18	12	6
April.....		14	4	10		7	5	2
May.....		74	38	36		84	35	49
June.....		86	47	39		77	41	36
July.....		54	36	18		69	45	24
August.....		34	20	14		52	34	18
September.....		29	20	9		30	14	16
October.....		12	6	6		17	12	5
November.....		2	1	1		2	1	1
December.....		1	—	1		2	—	2
	1936							
Total.....		161	84	77		164	60	104
January.....		2	1	1		3	—	3
February.....		1	—	1		2	1	1
March.....		7	2	5		8	3	5
April.....		18	9	9		7	2	5
May.....		15	6	9		40	16	24
June.....		15	4	11		10	4	6
July.....		16	10	6		12	5	7
August.....		78	45	33		72	22	50
September.....		9	7	2		10	7	3

* See also Figure 2.

Malaria incidence.—In the village of Osoi, 331 cases positive at the blood examination were registered in 1935 (i.e., 91 cases less than in 1933, despite the fact that the registration has been continually improved during this period).

At Costuleni, the number of cases decreased from 465 (in 1933) to 373 (in 1935) (of which 63 were parasite carriers).

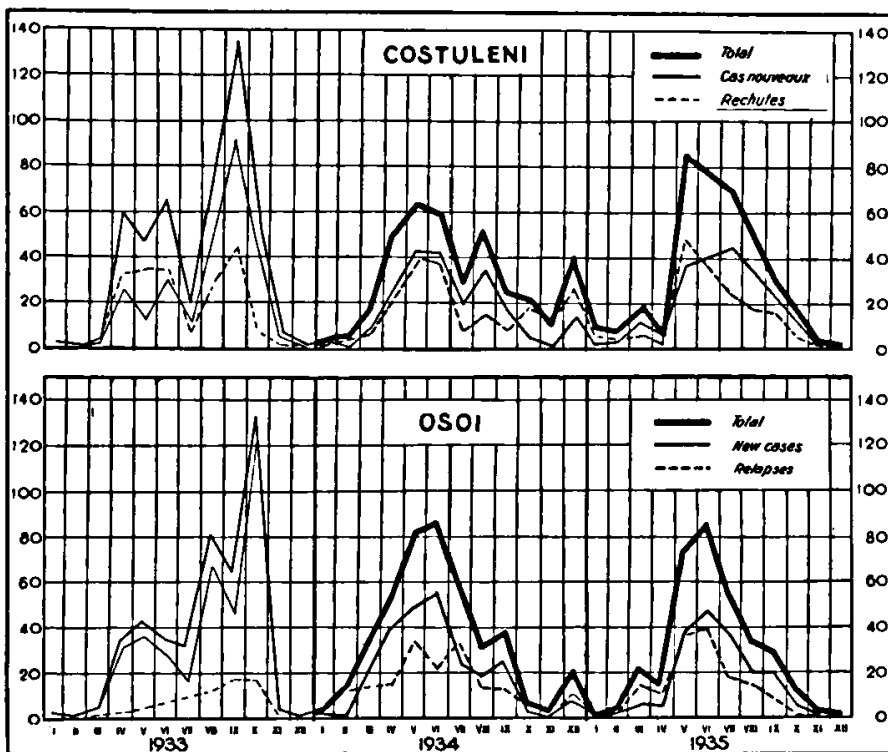
Parasite species.—In Osoi and Costuleni, the parasite findings were :

<i>Plasmodium vivax</i>	589 or 83.66%
<i>Plasmodium falciparum</i>	88 or 12.50%
<i>Plasmodium malariae</i>	26 or 3.69%
Mixed forms	1 or 0.14%

The seasonal curve of parasite types shows a benign tertian peak in May-June and a malignant tertian peak in August-September.

Figure 2.

MONTHLY EVOLUTION OF MALARIA IN THE VILLAGES OF COSTULENI AND OSOI.



TREATMENT EXPERIMENTS.

The experiments began on May 1st, 1935. A blood sample was taken every morning, the drug being administered in two daily doses after the blood had been taken.

The population remained under medical observation until April 30th, 1936.

The relapses were treated with the same drug as that used for the first attack.

In the village of Osoi, all clinical malaria cases were treated for seven days with atebirin alone or followed by a five days' treatment with plasmoquine.

In the village of Costuleni, in another group of patients, the seven-day course with quinine was followed by five-day treatment with plasmoguinine.

The immediate action on the fever and parasites is shown in Tables 2 and 3. The word "dose" should be read *to mean the total daily dose of the drug*.

Under the heading "no fever", the number of patients having no fever on the day of starting treatment is shown.

Under the heading "relapses", the clinical relapses are indicated by A+P+; the parasitic relapses, by AoP+.

Atebrin.

In the village of Osoi, 207 *malaria cases* (attacks and parasites) were treated:

Benign tertian, 173 cases	}	140 : atebrin for seven days ;
		33 : atebrin for seven days—three days' rest—plasmoguinine for five days.
Sub-tertian, 28 cases.....	}	14 : atebrin for seven days ;
		14 : atebrin for seven days—three days' rest—plasmoguinine for five days.
Quartan : 4 cases	}	1 : atebrin for seven days.
		3 : atebrin for seven days—three days' rest—plasmoguinine for five days.
Mixed infections : 2 cases .		2 : atebrin for seven days.

Benign Tertian.

Among 119 cases with fever and parasites at the beginning of the treatment, the *average* number of doses needed for the disappearance of fever was 1.7. This average is confirmed by the results obtained in a second group of 33 patients treated in the same conditions with atebrin and subjected, after three days' rest, to treatment with plasmoguinine. The average of that group was 1.8 doses.

The *average* number of doses necessary to clear out trophozoites and schizonts from the general circulation were respectively 1.5 and 1.4; for the gametocytes, 2.1 to 2.3.

Spleen enlargement.—Among 87 cases observed, the size of the spleen was reduced in 51 cases after the use of atebrin, while it had remained unchanged in 36 cases. Among the cases treated with atebrin followed by plasmoguinine, the proportion was 20 spleens reduced to only 2 unchanged.

Table 2.

BENIGN TERTIAN : DISTRIBUTION OF TREATED CASES ACCORDING TO THE NUMBER OF DAILY DOSES AFTER WHICH THE SYMPTOMS TAKEN INTO CONSIDERATION HAVE DISAPPEARED.

	Atebrin (0.30 grm. x 7 days)	Atebrin (0.30 grm. x 7 days) followed after 3 days' rest by plasmoquine (0.02 grm. x 5 days)	Quinine hydrochloride (1 grm. x 7 days)	Quinine hydrochloride (1 grm. x 7 days) followed after 3 days' rest by plasmoquine (0.02 grm. x 5 days)	Aristoquine (0.30 grm. x 7 days)	Aristoquine (0.30 grm. x 7 days) followed after 3 days' rest by plasmoquine (0.01 grm. x 5 days)
FEVER.						
Number of cases taken into consideration	140	33	147	61	87	17
No fever at beginning of treatment	21	3	10	2	7	1
Number of cases in which fever disappeared after						
1 dose	46	15	56	17	19	2
2 doses	54	12	49	26	37	7
3 doses	17	2	25	12	20	7
4 doses	1	1	4	2	3	—
5 doses	1	—	1	1	1	—
6 doses	—	—	2	1	—	—
7 doses	—	—	—	—	—	—
Average	1.7	1.8	1.9	2.1	2.2	2.3
SCHIZONTS.						
No schizonts at beginning of treatment	23	3	16	6	7	—
Number of cases in which the schizonts disappeared after						
1 dose	56	18	45	13	17	3
2 doses	56	11	66	29	39	9
3 doses	4	1	17	7	10	2
4 doses	1	—	3	4	11	2
5 doses	—	—	—	1	2	—
6 doses	—	—	—	1	1	1
7 doses	—	—	—	—	—	—
Average	1.5	1.4	1.8	2.1	2.2	2.4
GAMETOCYTES.						
No gametocytes at beginning of treatment	23	6	2	1	—	1
Number of cases in which the gametocytes disappeared after						
1 dose	31	8	6	1	1	—
2 doses	39	6	45	12	20	6
3 doses	40	9	57	23	31	6
4 doses	7	4	22	12	20	2
5 doses	—	—	10	4	12	1
6 doses	—	—	4	8	1	1
7 doses	—	—	1	—	1	—
Average	2.1	2.3	3.0	3.5	3.3	3.0
SPLEEN.						
Enlarged before treatment	87	22	89	40	21	6
Reduced after treatment	51	20	52	11	10	3
RELAPSES.						
Re-examined	140	33	147	61	87	17
Period of observation (months)	9-17	9-17	9-17	9-17	9-17	9-17
Number of cases with relapses : Number	26	1	39	11	28	3
Per cent.	18.5	3.03	26.5	18.3	32.1	17.6
Total number of relapses : Number	29	4	55	14	38	5
Type A+P+	21	3	51	12	38	5
Ao P+	8	1	4	2	—	—
Percentage ..	20.7	12.12	37.4	22.9	43.6	29.4

Table 3.

SUBTERTIAN : DISTRIBUTION OF TREATED CASES ACCORDING TO THE NUMBER OF DAILY DOSES AFTER WHICH THE SYMPTOMS TAKEN INTO CONSIDERATION HAVE DISAPPEARED.

	Atebrin (0.30 grm. x 7 days)	Atebrin (0.30 grm. x 7 days) followed after 3 days' rest by plasmoquine (0.02 grm. x 5 days)	Quinine hydrochloride (1 grm. x 7 days)	Quinine hydrochloride (1 grm. x 7 days) followed after 3 days' rest by plasmoquine (0.02 grm. x 5 days)	Aristoquine (0.30 grm. x 7 days)	Aristoquine (0.30 grm. x 7 days) followed after 3 days' rest by plasmoquine (0.01 grm. x 5 days)
FEVER.						
Cases taken into consideration	14	14	39	52	10	17
No fever at beginning of treatment	1	1	3	6	2	4
Number of cases in which fever disappeared after						
1 dose	2	3	12	2	2	1
2 doses	7	3	18	26	3	5
3 doses	4	1	6	16	3	5
4 doses	—	1	—	—	—	2
5 doses	—	1	—	—	—	—
6 doses	—	—	—	—	—	—
7 doses	—	—	—	—	—	—
Average	2.1	2.2	1.8	2.1	2.1	2.3
TROPHOZOITES.						
No schizonts at beginning of treatment	1	2	3	3	3	3
Number of cases in which trophozoites disappeared after						
1 dose	2	1	2	4	2	—
2 doses	5	4	20	26	3	4
3 doses	5	5	6	15	1	4
4 doses	1	1	2	3	1	4
5 doses	—	1	—	—	—	2
6 doses	—	—	1	1	—	—
7 doses	—	—	—	—	—	—
Average	2.3	2.7	2.3	2.4	2.1	3.2
GAMETOCYTES.						
No gametocytes at beginning and during treatment	8	3	15	9	2	2
Gametocytes present at beginning of treatment	4	4	13	18	5	4
Cases in which gametocytes appeared during treatment after						
1 dose	—	—	—	1	—	—
2 doses	—	—	3	3	1	4
3 doses	1	2	3	6	—	—
4 doses	—	1	3	6	—	4
5 doses	1	1	—	4	1	2
6 doses	—	3	2	5	1	1
7 doses	—	—	—	—	—	—
Disappearance of gametocytes after						
1 dose of quin. or atehr.	1	—	—	—	—	—
2 doses of quin. or atehr.	—	1	3	1	1	—
3 doses of quin. or atehr.	2	1	5	1	2	1
4 doses of quin. or atehr.	—	—	2	2	—	—
5 doses of quin. or atehr.	1	—	3	3	1	—
6 doses of quin. or atehr.	—	—	1	2	—	—
7 doses of quin. or atehr.	1	1	1	2	2	—
Still present after seventh dose of quinine or atehrin	1	8	9	32	2	—
Disappeared during plasmoquine treatment. Still present after plasmoquine treatment. Disappearance of gametocytes during seven days following treatment	—	5	—	24	—	11
3	—	3	—	8	—	3
3	—	3	—	8	—	3
SPLEEN.						
Enlarged before treatment	9	10	13	29	4	9
Reduced after treatment	6	4	7	20	3	7
RELAPSES.						
Re-examined	14	14	39	52	10	17
Period of observation (months)	9-17	9-17	9-17	9-17	9-17	9-17
Cases with relapses : Number	3	—	6	2	2	3
Percentage	21.3	—	15.3	3.8	20.0	17.6
Total number of relapses : Number	4	—	6	2	3	3
Type A+ P+	4	—	6	2	3	3
AoP+	—	—	—	—	—	—
Percentage	28.5	—	15.3	3.8	30.0	17.6

Relapses.—All clinical or parasitic relapses were carefully detected. In the group of 140 patients treated with atebirin, we observed 21 clinical relapses (A+P+) and 8 parasitic relapses (AoP+)—*i.e.*, a percentage of 20.7. In the 33 patients treated with atebirin followed by plasmoquine, the percentage was 12.2 only.

Malignant Tertian.

The number of cases of malignant tertian in the village of Osoi was particularly low during 1935, probably because of the tracing and systematic treatment of malaria cases during preceding years (see document C.H./Malaria/234). 14 cases were treated with atebirin, 14 were given a further five-day course of plasmoquine three days after the atebirin treatment.

Fever disappeared after an average of 2.1 and 2.2 doses respectively, the *trophozoites* after 2.3 and 2.7 doses.

Gametocytes.

A. In the first group treated with atebirin, 8 patients out of 14 did not show any gametocytes at the beginning of, or during, treatment : their appearance was observed in 2 cases. Among the 4 cases which showed gametocytes at the beginning, 2 were rid of them after 3 doses of atebirin, 1 after the seventh, while in the fourth patient they were still present at the end of the treatment.

Among those in whom gametocytes appeared during treatment, the disappearance occurred in 1 case after five days ; in another, the presence of gametocytes was transient (one day only).

Of 6 cases in which gametocytes appeared during treatment with atebirin, 1 only still showed them at the end of treatment.

B. Among the 14 cases treated with atebirin followed by plasmoquine, the following results were obtained :

(a) 3 never showed gametocytes from the beginning to the end of the treatment.

(b) 4 crescent carriers at the beginning of treatment behaved as follows : the gametocytes disappeared in one case after 2 doses of atebirin, in a second after 3, in one after the fifth dose ; in the last, gametocytes were still present after the end of the treatment.

(c) In 7 cases, gametocytes, absent at the beginning, appeared during the treatment and remained for a variable period of time; in 2 cases, they were present after the third dose of atebirin and disappeared in 1 after the fifth dose; in the other, they were still present at the end of treatment. In 1 case, their appearance was noticed after the fifth atebirin dose and their disappearance after the fifth plasmoquine dose. In another case, the gametocytes were noticed for the first time after the fifth atebirin dose and persisted at the end of the treatment. In 3 cases, the gametocytes appeared after the sixth dose of atebirin and disappeared in 1 case twenty-four hours later; in 2 cases, after the fifth dose of plasmoquine.

To sum up, in 8 of 11 cases in which gametocytes were present, these disappeared during the treatment; in 3 cases, gametocytes were still present in the blood after the fifth day of treatment with plasmoquine and only disappeared during the following seven days.

Action on the spleen.—Of 9 enlarged spleens, 6 were reduced in size after the treatment with atebirin.

In group B, of 10 enlarged spleens, 4 were reduced.

Relapses.—In a total of 26 cases, no relapses were observed up to May 1936. We should like to recall here that the malignant tertian season begins late in June and reaches its maximum in September. These figures have therefore no value. Relapses occurred during the period July-October 1936; details will be found in Table 3 on page 80.

Quartan.

In 4 cases of quartan, 1 case only was treated with atebirin. The 3 other cases were treated with plasmoquine for five days, three days after the end of the atebirin treatment. Fever and parasites disappeared after the first 3 doses.

Secondary Effects and Toxic Symptoms.

Out of a total of 154 patients treated with atebirin, 21 presented a yellow discoloration of the skin—*i.e.*, 13.6%. Out of 50 cases treated with atebirin followed by plasmoquine, 9 showed this discoloration (*i.e.*, 18%). It lasted from one to twenty days.

We further observed 3 cases of vertigo which lasted from one to three hours and occurred half-an-hour after the ingestion of the drug, 5 cases of nausea and vomiting, 1 case of gastralgia which lasted half-an-hour after the ingestion of the drug, and 2 cases of mental excitement.

Out of 50 cases treated with plasmoquine, 3 showed cyanosis ; the treatment was continued without further symptoms.

Here are the particulars of one of the cases of mental excitement : Coj. V. (Osoi), first attack of malaria in 1934, treated with atebtrin (0.15 grm.) + plasmoquine 0.02 grm. for seven days without any symptoms of intolerance.

Relapse in 1935 : bad general state of health, very weakened, fever 39.3°C. ; spleen : 2. Two hours after the first dose of atebtrin, vomiting, headache, giddiness, pain in the eyes. These symptoms did not improve during the treatment, in spite of the disappearance of fever and parasites after forty-eight hours ; furthermore, discoloration of the skin began on the sixth day together with pronounced mental excitement which lasted for forty-eight hours without other phenomena.

To sum up, the schizontocidal efficacy of atebtrin was confirmed in 207 malaria cases assignable to the three types of parasite.

Atebtrin has no gametocidal action in malignant tertian and does not always prevent the appearance of crescents in cases in which they were not present at the beginning of the treatment.

In the doses used, the gametocidal action of plasmoquine has also been confirmed ; in 3 out of 14 cases, crescents still persisted after the fifth dose of plasmoquine ; they disappeared during the seven days following treatment.

With regard to the preventive action against the appearance of relapses, atebtrin seems to be more efficacious in benign tertian than quinine hydrochloride : 20.7% against 37.4%. The percentage among the benign tertian cases treated with atebtrin followed by plasmoquine is only 12.12.

The efficacy of atebtrin, in the prevention of relapses, is still more evident in malignant tertian, in spite of the small number of cases treated.

A course of seven days for the treatment of the attack appears to be a minimum.

The percentage of toxic symptoms observed among our cases is slightly inferior to those given by different authors. These symptoms are more frequent if the drug is absorbed on an empty stomach.

Quinine.

In Costuleni, 430 cases of malaria were treated according to the dosage established by the programme : adults receiving quinine hydrochloride ; children, aristoquine.

Benign Tertian.

- 147 cases treated with quinine hydrochloride for seven days.
- 87 cases treated with aristoquine for seven days.
- 61 cases treated with quinine hydrochloride for seven days—three days' rest—plasmoquine for five days.
- 17 cases treated with aristoquine for seven days—three days' rest—plasmoquine for five days.

Malignant Tertian.

- 39 cases treated with quinine hydrochloride for seven days.
- 10 cases treated with aristoquine for seven days.
- 52 cases treated with quinine hydrochloride for seven days—three days' rest—plasmoquine for five days.
- 17 cases treated with aristoquine for seven days—three days' rest—plasmoquine for five days.

Benign Tertian.

A. 147 cases were treated with quinine hydrochloride : 1 grm. for seven days. In 10 cases, there was no fever at the beginning of treatment. The action of quinine on fever was shown in 105 cases after the first two doses ; in 25 cases, after the third dose ; in 7 cases, after four, five and six doses respectively.

The average for the 147 cases was two doses.

Schizonts.—In 16 cases, no schizonts were observed on the first day of treatment. When they were present, they disappeared in 117 cases after the first two doses, in 17 after the third dose, in 3 after the fourth dose. The average was 1.8 doses.

Gametocytes disappeared in 51 cases after the first two doses, in 57 after the third, in 22 after the fourth, in 10 after the fifth, in 4 after the sixth and in 1 after the seventh dose. The average was 3 doses.

Spleen.—Out of 89 enlarged spleens, 52 were reduced in size at the end of the treatment.

Relapses.—Among the 147 cases, 51 clinical relapses and 4 parasitic ones were observed—*i.e.*, 37.4%. This percentage includes, of course, numerous re-infections with the same type of parasite.

B.—Among 61 cases, to whom 0.02 grm. of plasmquine was administered during five days, three days after the quinine treatment, the temperature had returned to normal in 43 cases after the first two doses of quinine, in 12 after the third, in 4 after the fourth, fifth and sixth dose respectively. The average of 2.1 doses was equivalent to that obtained in group A.

Schizonts.—In 42 cases schizonts disappeared after the first two doses, the average being 2.1 doses (1.8 in group A).

Gametocytes.—The average for their disappearance in that group was after 3.5 doses (3.2 in the first group); in 36 cases out of 61, gametocytes disappeared after the first three doses.

Out of 40 *enlarged spleens*, only 11 were reduced in size after treatment.

Relapses.—12 clinical relapses and two parasitic ones were observed in a total of 61 cases treated, corresponding to a percentage of 22.9 (37.04 in group A).

Aristoquine.

87 children were treated with aristoquine in chocolates. Fever disappeared in 56 cases after the first two doses of the drug; in 20, after the third dose: average: 2 doses.

Schizonts.—In 56 cases, schizonts disappeared after the first two doses; in 10 after the third, in 11 after the fourth. Average 2.2 doses.

Gametocytes disappeared in 21 cases after the first two doses, in 31 after the third, in 20 after the fourth, in 12 after the fifth dose. Average: 3.3 doses.

Out of 21 *enlarged spleens*, 10 were reduced in size at the end of the treatment.

Relapses.—Among 87 cases treated, 38 relapse cases were registered—*i.e.*, a percentage of 43.6.

Aristoquine followed by Plasmoquine.

This treatment was applied to 17 children.

The average number of doses required for the disappearance of fever, schizonts and gametocytes were 2.3 (2 in group C), 2.4 (2.2 in group C) and 3 (3.3 in group C) respectively.

Out of 6 enlarged spleens, 3 were reduced after treatment.

Relapses.—5 clinical relapses occurred among these 17 cases (29.4%).

Malignant Tertian.

A.—39 cases were treated with quinine hydrochloride. One of them had no fever. The temperature returned to normal in the others in 30 cases after the first two doses, in 6 after the third, the average being 1.8 doses.

Trophozoites.—In 22 cases, trophozoites disappeared after the second dose, in 6 after the third, in 2 after the fourth, in 1 after the sixth, while in 8 cases no trophozoites were observed at the beginning of treatment.

Gametocytes.—15 cases out of the 39 never showed gametocytes in the circulation; these were present in 13 cases on the first day of treatment, and appeared in the 11 others during the treatment. Their disappearance was observed in 15 cases during the schizontocidal treatment and occurred between the third and eighth day; in 9 cases, gametocytes still persisted at the end of treatment. We consider this disappearance as a fact independent of the schizontocidal treatment in a particular group of patients.

Out of 13 *enlarged spleens*, 7 were reduced after treatment.

Relapses.—In 6 out of 39 cases, relapses occurred.

B.—Plasmoquine was administered for five days to 52 patients after a seven-day quinine treatment.

Fever disappeared in 35 cases after the first two doses of quinine; in 16, after the third dose. Average: 2.1 (1.8 in group A).

Trophozoites.—3 cases out of 52 did not show any trophozoites on the first day of treatment; in 30, they disappeared after the first two doses; in 15, after the third. Average 2.4 (2.3 in group A).

Gametocytes.— In 9 cases, out of 52, gametocytes were absent from the beginning to the end of treatment ; in 19 cases, gametocytes were detected at the beginning of treatment ; in 25, they were absent at the beginning and appeared during the schizontocidal treatment.

The gametocytes were eliminated in 11 out of 43 cases during the schizontocidal treatment, and after the fifth dose of plasmoquine in 24 cases ; in 8 cases, gametocytes were still observed at the end of the treatment, but all these cases were negative seven days later.

Spleen.—Out of 29 enlarged spleens, 20 were reduced in size at the end of treatment.

Relapses.—2 cases occurred out of the 52 treated.

Aristoquine.

This group includes 10 cases. The disappearance of fever and of trophozoites was observed after an average of 2.1 doses.

In 2 cases, there were no gametocytes at the beginning of the treatment ; in 5 cases, gametocytes were observed at the beginning ; in 3 cases, they appeared during the treatment ; in 6 cases, they were eliminated during the schizontocidal treatment ; in 2 cases, the gametocytes remained to the end of the treatment ; seven days later, all these cases were negative.

3 out of 4 enlarged spleens were reduced at the end of the treatment.

3 relapses were observed among 10 cases treated with this drug.

Aristoquine followed by Plasmoquine.

17 cases were treated according to this method. The average number of doses for the disappearance of fever and trophozoites was 2.3 and 3.2 respectively. In 4 of these 17 cases, gametocytes were in the circulation at the beginning of treatment. In 11, they appeared during the schizontocidal treatment. Their disappearance occurred in 1 case during the schizontocidal treatment ; in 11 cases, during the gametocidal treatment ; in 3 cases, during the seven days following the treatment.

Spleen.—Out of 9 enlarged spleens, 7 were reduced in size after treatment.

Among 17 cases treated, 3 relapses were registered.



Quartan.

A single case of quartan was treated, first with quinine hydrochloride, afterwards with plasmoquine for five days. Fever and schizonts disappeared after the first two doses ; gametocytes after the fifth dose.

Mixed Infections.

6 cases of mixed infections (benign tertian and malignant tertian) were treated either with quinine hydrochloride for seven days (1 case), or with the same drug followed by a five-day treatment with plasmoquine. The first case showed the characteristics of chronic infection.

Fever and schizonts disappeared after the first dose ; gametocytes after the third dose.

No relapses occurred during the nine months of observation.

In the 5 cases treated with quinine followed by plasmoquine, the fever disappeared after an average of 2.2 doses, schizonts after an average of 2.7 doses. Gametocytes of benign tertian disappeared in 2 cases after the third and fifth dose respectively ; the crescents only disappeared after the gametocidal treatment.

Spleen.—Enlarged spleen was observed in 9 cases ; it was reduced at the end of treatment.

A single case of relapse was observed.

Acriquine.

The following cases were also treated during the summer of 1936 : 90 cases with acriquine and 6 with acriquine followed by plasmoquine. Observation of these cases only ceased on September 30th, and it is too soon to say anything about relapses.

Benign tertian, 37 cases..	{	34 acriquine for seven days ; 3 acriquine for seven days, three days' interval, plasmoquine for five days.
Malignant tertian, 59 cases	{	56 acriquine for seven days ; 3 acriquine for seven days, three days' interval, plasmoquine for five days.

Benign Tertian.

Out of 34 cases treated, 23 had no fever after the first two doses of the drug ; the average number of doses before the fever disappeared was 2.6.

In the second group, consisting of 3 patients treated under the same conditions with acriquine, followed, after three days' interval, by five days of plasmoguin, the average was 1.

The average number of doses before the trophozoites and schizonts disappeared from the general circulation was 1.3 and 1.5 respectively, and in the case of gametocytes 2 and 2.5.

15 cases of enlarged *spleen* : the spleen was reduced in 7 cases and remained unchanged in 8 cases. For the cases treated with acriquine followed by plasmoguin, the figures were one enlarged spleen, reduced after treatment.

Relapses (early).—In the group of 34 patients treated with acriquine, we observed 3 clinical relapses (A+P+) or 8.8%. In the second group, none was observed.

Malignant Tertian.

56 cases were treated with acriquine ; 3 other cases were treated in addition for five days with plasmoguin, three days after the acriquine treatment.

The fever disappeared after an average of 1.8 and 1.5 doses.

The trophozoites disappeared after 2.1 and 2 doses.

Gametocytes.

(a) In the first group treated with acriquine, 32 out of 56 patients exhibited no gametocytes either at the beginning or during the treatment ; gametocytes were only observed during treatment in 11 cases. There were 13 cases with gametocytes at the beginning of treatment. In 23 cases, the gametocytes disappeared during the schizontocidal treatment ; in 1 case, they persisted to the end of the treatment.

(b) Of the 3 cases treated with acriquine followed by plasmoguin :

In 2 cases exhibiting crescents at the beginning of treatment, the gametocytes disappeared—in the first case, after the third dose of acriquine ; in the second, after the fourth dose.

In 1 case, no gametocytes were detected at the beginning; they appeared during the treatment, after the sixth dose of acriquine, and disappeared again during the plasmoquine treatment.

Action on the spleen.—Of 31 enlarged spleens, 8 were reduced after treatment with acriquine.

In group (b), of 2 enlarged spleens, only 1 was reduced.

As regards schizontocidal and gametocidal action, from the cases treated, the efficacy of acriquine appears to be equal to that of atebtrin.

ENDEMIC INDICES.

Splenic and splenometric indices were calculated in April, October 1935 and in April 1936 according to the methods indicated in the programme, modified as regards spleen enlargement, which has been determined according to Schüffner's method. This same method was used in the control village—Comarna—where anti-malarial work by treatment was not carried out systematically.

The following graph shows a very important decline in the splenometric index. In Osoi (atebtrin), from 30.17 in December 1933, it fell to 1.60 in December 1935; in Costuleni (quinine), from 18.30 to 1.10. We recall here that, already in 1933 and 1934, these two villages had the benefit of systematic treatment of all cases of attacks and relapses.

The very sharp decline at the end of the first two years of treatment was much less marked during 1935 and at the beginning of 1936.

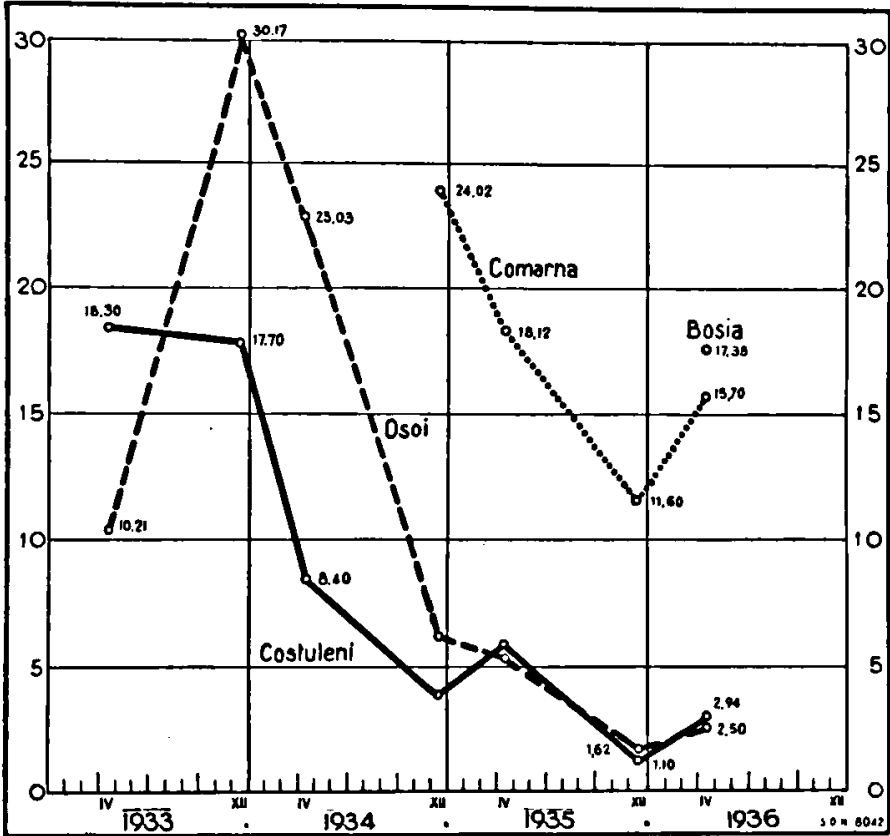
In the control villages Comarna and Bosia—where no systematic malaria control was carried out—the splenometric index only fell to 11.60 in December 1935 to rise again to 15.70 in April 1936 at Comarna; this index was 17.35 at the same date in the second control village.

Parasite Rate.

A blood examination of the entire population was carried out on April 1st, 1935, followed by a monthly examination at the same date for each family.

Figure 3.

SPLENOMETRIC INDEX IN THE VILLAGES OF OSOI, COSTULENI, COMARNA (CONTROL) AND BOSIA (CONTROL), 1933-1936.



Results.—The number of parasite carriers, very low during post- and pre-epidemic periods, subsequently rises, the maximum being in June-July. The highest percentage of parasite carriers is found in the age-groups from 1 to 15 (approximately two-thirds of the total number). *No difference between the parasite rates in April 1935 and April 1936 was noted, in spite of the systematic treatment applied to all cases of malaria (attacks and relapses).*

In OsOI, where atebriin alone or followed by plasmoquine was used, the parasite rate remained a little lower.

The total number of cases has hardly diminished; that of new cases has slightly increased; a decrease was observed only in respect of the number of relapses.

No cases of death were recorded.

The decline of spleen and splenometric indices is more marked than that of the parasite rate.

Summary and Conclusions.

Two villages—Osoi and Costuleni—belonging to a malaria area with an average endemicity where the inhabitants enjoy a certain degree of immunity, were used from May 1st, 1935, for trials in malaria treatment with atebtrin compared with quinine alone or followed by a plasmoquine treatment.

In these villages, the systematic treatment of malaria cases applied during the *three years preceding these trials* had resulted in an important decline of malignant tertian.

The treatment of malaria cases is the only method of malaria control applied.

389 benign tertian, 77 malignant tertian, 5 quartan and 8 cases of mixed infection were treated from May 1st, 1935, to April 30th, 1936 ; we also treated 133 cases of benign tertian and 128 cases of malignant tertian between May 1st and October 1st, 1936.

Tables Nos. 1, 2 and 3 recapitulate data concerning the comparative efficacy of the drugs used.

The schizontocidal action of these drugs is nearly identical.

The action of atebtrin on gametocytes of benign tertian is quicker by one day than that of quinine.

The action of aristoquine on fever and parasites seems to be a little slower.

The efficacy of atebtrin in the prevention of relapses of benign tertian appears in our cases to be superior to that of quinine and of aristoquine.

The adjuvant treatment with plasmoquine further lowers the percentage of relapses. In the cases treated with atebtrin followed by plasmoquine, the percentage of relapses was 3.03 ; in cases treated with quinine hydrochloride followed by plasmoquine, the percentage was 18.3 ; and in cases treated with aristoquine followed by plasmoquine, it was 17.6.

None of the schizontocides used prevented the appearance of gametocytes in cases in which these forms were absent at the beginning of treatment.

The well-established gametocidal action of plasmoquine in malignant tertian is confirmed once more.

In 33% of the cases exhibiting gametocytes which were treated with plasmoquine after schizontocidal treatment, gametocytes were still present after five doses of plasmoquine ; they disappeared spontaneously during the seven days following.

From the epidemiological point of view, the systematic treatment applied during three years has resulted in the suppression of malaria mortality and in a decline of malaria morbidity.¹

The percentage of relapses (including re-infections) is declining ; the number of new cases maintains, however, the peak of the curve.

Malignant tertian has been hardest hit by this treatment campaign ; out of the total number of positive blood tests, the percentages for *P. falciparum* were 53.54 in 1932, 24.68 in 1933, 18.29 in 1934 and 12.08 in 1935.

¹ It should be added, however, that, in 1935, anophelism was far less intense owing to the drought.

Table 4.

RATE OF DISAPPEARANCE OF SYMPTOMS TAKEN INTO CONSIDERATION ACCORDING TO THE NUMBER OF DAILY DOSES ADMINISTERED (PERCENTAGE).

PLASMODIUM VIVAX		Atebrin	Atebrin followed by plasmoquine	Quinine hydrochloride	Quinine hydrochloride followed by plasmoquine	Aristoquine	Aristoquine followed by plasmoquine
FEVER.							
Cases taken into consideration		119	30	137	59	80	16
Percentage of cases in which the fever disappeared after	1 dose	38.66	50.00	40.88	28.81	23.75	12.50
	2 doses	84.63	90.00	76.64	72.88	70.00	56.25
	3 doses	98.03	96.66	94.89	93.22	95.00	100.00
	4 doses	99.16	100.00	97.81	96.61	98.75	—
	5 doses	100.00	—	98.54	98.30	100.00	—
	6 doses	—	—	100.00	100.00	—	—
	7 doses	—	—	—	—	—	—
SCHIZONTS.							
Cases taken into consideration		117	30	131	55	80	17
Percentage of cases in which the schizonts and the trophozoites disappeared after	1 dose	47.85	60.00	34.35	23.00	21.25	17.65
	2 doses	95.73	96.66	84.73	76.36	70.00	70.59
	3 doses	99.01	100.00	97.70	89.09	82.50	82.35
	4 doses	100.00	—	100.00	96.36	96.25	94.12
	5 doses	—	—	—	98.18	78.75	—
	6 doses	—	—	—	100.00	100.00	100.00
	7 doses	—	—	—	—	—	—
GAMETOCYTES.							
Cases taken into consideration		117	27	145	60	86	16
Percentage of cases in which the gametocytes disappeared after	1 dose	26.50	29.62	4.14	1.67	1.16	0
	2 doses	57.82	51.85	35.17	21.66	24.42	37.50
	3 doses	94.01	85.18	74.48	66.00	60.47	75.00
	4 doses	100.00	100.00	89.66	80.00	83.72	87.50
	5 doses	—	—	96.55	86.66	97.67	13.75
	6 doses	—	—	99.31	100.00	98.84	100.00
	7 doses	—	—	100.00	—	100.00	—
SPLEEN.							
Cases taken into consideration		87	22	89	45	21	6
Percentage of cases where the spleen was reduced after treatment		58.62	90.91	58.42	27.50	47.61	50.00
RELAPSES.							
Observation over a period of 12 months.		20.7	12.12	37.4	22.9	43.8	29.4

Table 4 (continued).

RATE OF DISAPPEARANCE OF SYMPTOMS TAKEN INTO CONSIDERATION ACCORDING TO THE NUMBER OF DAILY DOSES ADMINISTERED (PERCENTAGE).

PLASMODIUM FALCIPARUM		Atebrin	Atebrin followed by plasmoquine	Quinine hydrochloride	Quinine hydrochloride followed by plasmoquine	Aristoquine ¹	Aristoquine followed by plasmoquine
FEVER.							
Cases taken into consideration		13	13	36	51	8	16
Percentage of cases in which the fever disappeared after	1 dose	15.38	23.07	33.33	17.65	25.00	25.00
	2 doses	69.23	76.92	83.33	68.62	62.50	56.25
	3 doses	100.00	84.61	100.00	100.00	100.00	87.50
	4 doses	—	92.30	—	—	—	100.00
	5 doses	—	100.00	—	—	—	—
	6 doses	—	—	—	—	—	—
	7 doses	—	—	—	—	—	—
SCHIZONTS.							
Cases taken into consideration		13	12	31	49	7	14
Percentage of cases in which the schizonts and the trophozoites disappeared after	1 dose	15.38	8.33	6.45	8.16	28.57	0
	2 doses	53.85	41.66	70.96	61.22	71.42	28.57
	3 doses	92.31	83.33	90.32	91.83	85.71	57.14
	4 doses	100.00	91.66	96.77	97.95	100.00	85.71
	5 doses	—	100.00	—	—	—	—
	6 doses	—	—	100.00	100.00	—	—
	7 doses	—	—	—	—	—	—
GAMETOCYTES.							
Cases taken into consideration							
Percentage of cases in which the gametocytes disappeared after	1 dose						
	2 doses						
	3 doses						
	4 doses						
	5 doses						
	6 doses						
	7 doses						
SPLEEN.							
Cases taken into consideration		9	10	13	29	4	9
Percentage of cases where the spleen was reduced after treatment		66.66	40.00	33.33	55.76	75.00	77.77
RELAPSES.							
Observation over a period of 12 months.		28.5	7.1	15.3	6.25	30.00	17.6

¹ The small number of sub-tertian cases treated with aristoquine does not permit of the establishment of percentages.

Cases "taken into consideration" are those in which fever, schizonts, gametocytes (smears) or spleen enlargement were present at the beginning of treatment and for which sufficient data are available.

III. EFFICACY OF ATEBRIN AND QUININE IN THE PROPHYLACTIC TREATMENT OF MALARIA.

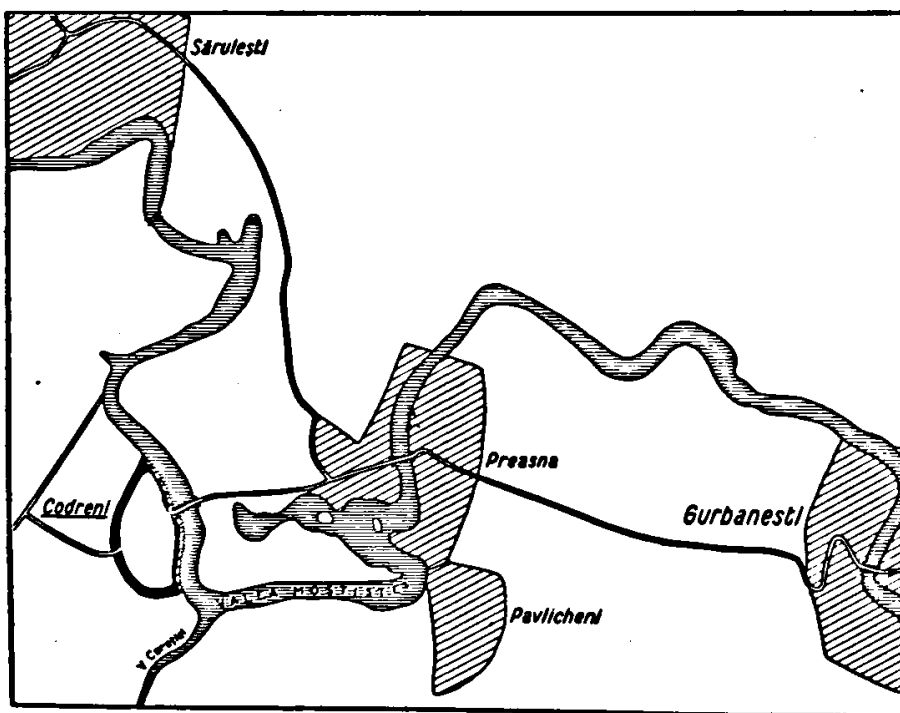
(Second Memorandum.)

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We described in an earlier paper¹ the results of the trials in the matter of clinical prophylaxis carried out with atebtrin and quinine in 1933 and 1934 in the village of Codreni, which lies within the area of operations of the Gurbănești Malaria Research Station (see Figure 1).

Figure 1. — MAP OF THE VILLAGES OF GURBĂNEȘTI AND CODRENI.



¹ The paper appeared in the *Archives roumaines de Pathologie expérimentale et de Microbiologie*, 8, No. 4 (1935) and in the publication of the League of Nations Malaria Commission (document C.H./Malaria/233.)

In 1933 and 1934, during the whole of the epidemic period proper, half the population of the village were treated with atebrin and the other half with quinine. The preventive treatment with the two drugs, administered strictly to the whole population, brought about a considerable reduction in the number of parasite carriers and did away almost entirely with clinical cases, but did not prevent fresh infection. Moreover, a marked recrudescence of clinical cases and a considerable increase in the number of parasite carriers were noticeable each spring, during April and May, before the resumption of preventive treatment.

It seemed clear to us in the circumstances that, in spite of preventive treatment, the endemic-epidemic of malaria, though confined to non-apparent forms, was still continuing in precisely the same way as in the other villages in the area.

* * *

During the year 1935, preventive treatment was carried on from June 1st to November 1st on much the same lines as in the preceding years. In 1935, however, we kept a control group of about 70 of the inhabitants, who were given no treatment. For full particulars of these experiments, readers are referred to our first publication, which also contains data on the epidemiological conditions of malaria before the experiments began.

In an appendix to this memorandum will be found the doses administered, together with data on anophelism and meteorological conditions during the period 1932-1935.

Table 1 gives the composition of the groups treated and of the control groups, and the distribution of the members by age-groups.

Table 1.
NUMBER OF INHABITANTS TREATED WITH ATEBRIN (SECTOR I)
AND WITH QUININE (SECTOR II) AND NUMBER OF INHABITANTS FORMING
THE CONTROL GROUPS.

Age-group (Years)	Sector I		Sector II		Totals		
	Preven- tive treatment with atebrin	Controls	Preven- tive treatment with quinine	Controls	Given preven- tive treatment	Controls	Popula- tion of village
0-14	38	18	39	10	77	28	105
15-80	63	18	60	25	123	43	166
Total	101	36	99	35	200	71	271

As will be seen from the table, 101 inhabitants were given preventive treatment with atebrin and 99 treatment with quinine.

The control groups consisted respectively of 36 and 35 persons, 71 in all.

It should be noted that, whereas in previous years parasite carriers, directly they were traced, were given curative treatment with higher doses than were administered in preventive treatment—which lasted for thirty-six days in 1933 and twelve days in 1934—only those exhibiting definite clinical symptoms were given curative treatment in 1935.

As in previous years, periodical blood tests were carried out twice a month during the period of clinical prophylaxis (June 1st-November 1st, 1935), and once a month for the rest of the period (December 1st, 1935-December 31st, 1936).

We give below in tabular form the results of the blood tests carried out before and during the 1935 campaign and during the year 1936 (Table 3 and Figure 2).

As in previous years, the number of parasite carriers during the inter-epidemic period was fairly low in 1935. It began to rise in April, and in May (at the beginning of the epidemic period) the parasite rate was 14.4% in Sector I (atebrin) and 11.3% in Sector II (quinine).

Table 2.

PARASITE RATES BEFORE THE BEGINNING OF THE EXPERIMENTS IN CLINICAL PROPHYLAXIS IN 1935.

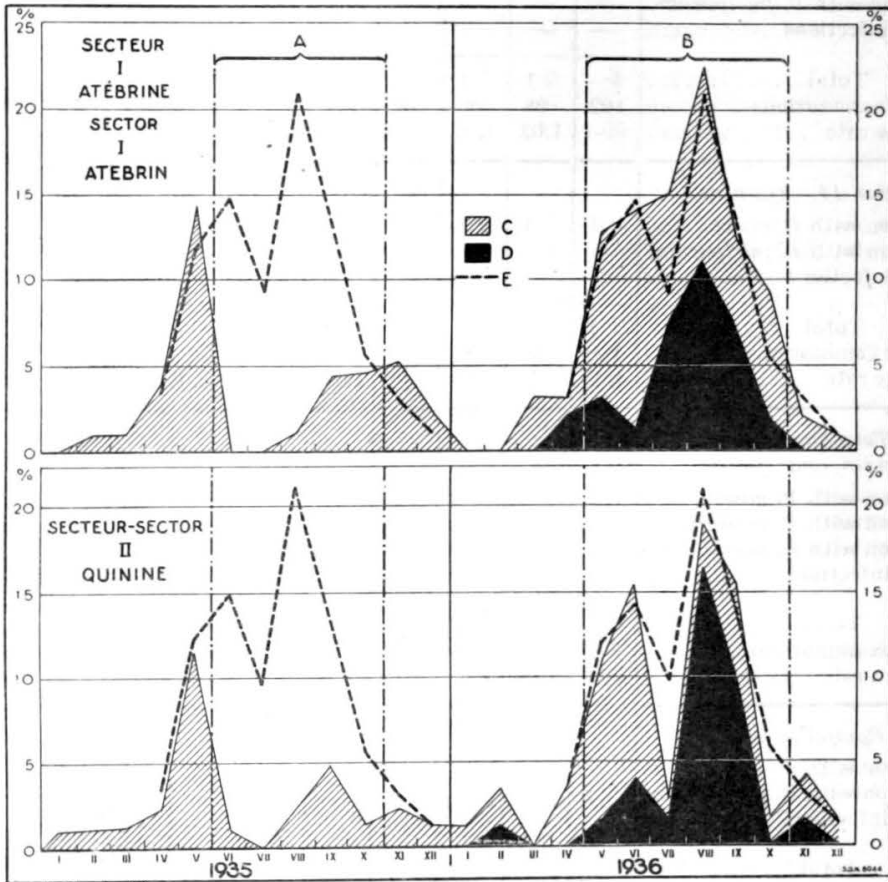
Group	April			May		
	Blood tests	Parasite carriers	Parasite rate	Blood tests	Parasite carriers	Parasite rate
I. Atebrin ...	100	4	4.0	104	15	14.4
II. Quinine ...	91	2	2.2	97	11	11.3
Control	45	7		59	7	

In the persons forming the groups subjected to preventive treatment, the parasite rate was reduced to 0.49% by June, and remained at about that figure during July and August.

In September and October, a slight increase in the number of parasite carriers was observed. In September, the parasite rates were 4.49% in the atebrin sector and 4.81% in the quinine sector.

Figure 2.

MONTHLY VARIATIONS OF THE PARASITE RATE AND OF THE INCIDENCE OF CLINICAL CASES.



A : Third experiment of clinical prophylaxis (1935).

B : No preventive treatment.

C : Parasite carriers.

D : Clinical attacks of malaria.

E : Probable Monthly Rate.

MONTHLY VARIATIONS OF PARASITE RATE IN THE VILLAGE OF CODRENI :
II (QUININE) AND

Comparative variations of parasite index in the three sectors	1935											
	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII
<i>Sector I.—Atebrin.</i>	Third preventive treatment											
Infection with <i>P. vivax</i>	—	1	1	4	15	—	—	—	2	—	3	1
Infection with <i>P. malariae</i>	—	—	—	—	—	—	—	—	—	—	—	—
Infection with <i>P. falciparum</i>	—	—	—	—	—	—	—	1	2	3	2	1
Mixed infections	—	—	—	—	—	—	—	—	—	1	—	—
Total	—	1	1	4	15	—	—	1	4	4	5	2
Blood examinations	102	98	96	100	104	103	99	91	89	86	96	82
Parasite rate	—	1.02	1.04	4.00	14.42	—	—	1.09	4.49	4.65	5.21	2.44
<i>Sector II.—Quinine.</i>												
Infection with <i>P. vivax</i>	1	1	1	2	11	1	—	1	3	—	—	—
Infection with <i>P. falciparum</i>	—	—	—	—	—	—	—	1	1	1	2	1
Mixed infections	—	—	—	—	—	—	—	—	—	—	—	—
Total	1	1	1	2	11	1	—	2	4	1	2	1
Blood examinations	100	90	92	91	97	100	88	87	83	77	93	78
Parasite rate	1.00	1.11	1.09	2.20	11.34	1.00	—	2.29	4.81	1.29	2.15	1.28
<i>Total for Sectors Atebrin and Quinine.</i>												
Infection with <i>P. vivax</i>	1	2	2	6	26	1	—	1	5	—	3	1
Infection with <i>P. malariae</i>	—	—	—	—	—	—	—	—	—	—	—	—
Infection with <i>P. falciparum</i>	—	—	—	—	—	—	—	2	3	4	4	2
Mixed infections	—	—	—	—	—	—	—	—	—	1	—	—
Total	1	2	2	6	26	1	—	3	8	5	7	3
Blood examinations	202	188	188	191	201	203	187	178	172	163	189	160
Parasite rate	0.50	1.06	1.06	3.14	12.94	0.49	—	1.69	4.65	3.07	3.70	1.88
<i>Control Group.</i>												
Infection with <i>P. vivax</i>	—	—	2	6	7	5	8	3	6	5	4	1
Infection with <i>P. falciparum</i>	1	2	1	1	—	—	—	—	1	3	1	1
Mixed infections	—	—	—	—	—	—	—	—	—	—	—	—
Total	1	2	3	7	7	5	8	3	7	8	5	2
Blood examinations	43	45	44	45	59	37	44	39	44	41	45	47
<i>New-born Children and New Inhabitants.</i>												
Infection with <i>P. vivax</i>	—	—	—	—	—	—	—	—	—	—	—	—
Infection with <i>P. falciparum</i>	—	—	—	—	—	—	—	—	—	—	—	—
Mixed infections	—	—	—	—	—	—	—	—	—	—	—	—
Total	—	—	—	—	—	—	—	—	—	—	—	—
Blood examinations	—	—	—	—	—	—	—	—	—	—	4	3
<i>Total.</i>												
Infection with <i>P. vivax</i>	1	2	4	12	33	6	8	4	11	5	7	2
Infection with <i>P. malariae</i>	—	—	—	—	—	—	—	—	—	—	—	—
Infection with <i>P. falciparum</i>	1	2	1	1	—	—	—	2	4	7	5	3
Mixed infections	—	—	—	—	—	—	—	—	—	1	—	—
Total	2	4	5	13	33	6	8	6	15	13	12	5
Blood examinations	245	233	232	236	260	240	231	217	216	204	238	210
Parasite rate	0.82	1.72	2.16	5.51	12.69	2.50	3.46	2.76	6.94	5.88	5.04	2.38

2.

PARASITE CARRIERS DETECTED BY BLOOD EXAMINATIONS, IN SECTORS I (ATEBRIN), III (CONTROLS).

1936												Comparative variations of parasite index in the three sectors
I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	
—	—	2	3	12	13	10	7	5	7	1	1	<i>Sector I.—Atebrin.</i> Infection with <i>P. vivax</i> . Infection with <i>P. malarix</i> . Infection with <i>P. falciparum</i> . Mixed infections.
—	—	—	—	—	—	—	—	—	1	—	—	
—	—	1	—	—	—	3	15	7	1	1	—	
—	—	—	—	—	—	1	—	—	—	—	—	
—	—	3	3	12	13	14	22	12	9	2	1	Total. Blood examinations. Parasite rate.
97	94	96	93	92	91	92	97	95	95	90	92	
—	—	3.12	3.23	13.04	14.28	15.22	22.68	12.63	9.47	2.22	1.09	
1	3	—	3	8	12	1	4	2	1	1	—	<i>Sector II.—Quinine.</i> Infection with <i>P. vivax</i> . Infection with <i>P. falciparum</i> . Mixed infections.
—	—	—	—	1	—	1	9	8	—	2	1	
—	—	—	—	—	—	—	1	1	—	—	—	
1	3	—	3	9	12	2	14	11	1	3	1	Total. Blood examinations. Parasite rate.
87	91	88	85	84	78	76	74	72	79	73	71	
1.15	3.30	—	3.53	10.71	15.38	2.63	18.92	15.28	1.27	4.11	1.41	
1	3	2	6	20	25	11	11	7	8	2	1	<i>Total for Sectors Atebrin and Quinine.</i> Infection with <i>P. vivax</i> . Infection with <i>P. malarix</i> . Infection with <i>P. falciparum</i> . Mixed infections.
—	—	—	—	—	—	—	—	—	1	—	—	
—	—	1	—	1	—	4	24	15	1	3	1	
—	—	—	—	—	—	1	1	1	—	—	—	
1	3	3	6	21	25	16	36	23	10	5	2	Total. Blood examinations. Parasite rate.
184	185	184	178	176	169	168	171	167	174	163	163	
0.54	1.62	1.62	3.37	11.93	14.79	9.52	21.05	13.77	5.75	3.07	1.23	
2	2	1	—	2	6	3	4	3	1	3	1	<i>Control Group.</i> Infection with <i>P. vivax</i> . Infection with <i>P. falciparum</i> . Mixed infections.
2	3	2	1	1	1	2	3	1	3	—	—	
—	—	—	—	1	1	—	1	1	—	—	—	
4	5	3	1	4	8	5	8	5	4	3	1	Total. Blood examinations.
57	55	51	50	47	49	42	43	47	44	43	47	
—	—	—	—	1	1	1	—	1	1	1	—	<i>New-born Children and New Inhabitants.</i> Infection with <i>P. vivax</i> . Infection with <i>P. falciparum</i> . Mixed infections.
—	—	—	3	1	—	1	4	10	3	1	—	
—	—	—	—	—	—	—	1	1	—	—	—	
—	—	—	3	2	1	2	5	12	4	2	—	Total. Blood examinations.
4	6	6	11	11	7	13	19	30	18	30	22	
3	5	3	6	23	32	15	15	11	10	6	2	<i>Total.</i> Infection with <i>P. vivax</i> . Infection with <i>P. malarix</i> . Infection with <i>P. falciparum</i> . Mixed infections.
—	—	—	—	—	—	—	—	—	1	—	—	
2	3	3	4	3	1	7	31	26	7	4	1	
—	—	—	—	1	1	1	3	3	—	—	—	
5	8	6	10	27	34	23	49	40	18	10	3	Total. Blood examinations. Parasite rate.
245	246	241	239	234	225	223	233	244	236	236	232	
2.04	3.25	2.49	3.35	10.68	14.67	10.31	21.03	16.39	7.63	4.24	1.29	

A comparison between the figures for the groups subjected to preventive treatment and those for the control group gives fairly conclusive results ; an appreciable reduction will be observed in the parasite rate for the groups treated, whereas in the control group the parasite rate remained fairly high (see Table 4).

Table 4.

PARASITE RATES BEFORE, DURING, AND AFTER THE EXPERIMENTS IN CLINICAL PROPHYLAXIS IN 1935.

Group	May			June, July, August September, and October			November		
	<i>Before</i> prophylaxis experiments			<i>During</i> prophylaxis experiments			<i>After</i> prophylaxis experiments		
	Blood tests	Parasite carriers	Parasite rate	Blood tests	Parasite carriers	Parasite rate	Blood tests	Parasite carriers	Parasite rate
I. Atebrin	104	15	14.4	468	9	1.9	96	5	5.2
II. Quinine	97	11	11.3	435	8	1.8	93	2	2.2
Control	59	7		205	31	15.1	45	5	

In the two sectors subjected to preventive treatment, the parasite rates for the period of clinical prophylaxis (June 1st-November 1st, 1935) are almost the same—1.9% and 1.8%. The corresponding parasite rate in the control group is 15.1%. The difference between the average parasite rate in the groups subjected to preventive treatment and the group not treated would appear to be significant, as indicating a considerable fall in the number of parasite carriers in the sectors subjected to prophylactic treatment.

There is very little difference between the parasite rate for the "atebrin" sector and that for the "quinine" sector. This would seem to show that the two drugs are of equal prophylactic value.

It should be noted that, although preventive treatment with atebrin and quinine brought about a very considerable reduction in the parasite rates, parasite carriers were not completely eliminated by the use of either drug.

As in previous years, the preventive treatment led to a very considerable fall in the number of clinical cases of malaria. In

1935, during the period of clinical prophylaxis, their incidence was almost nil.

* * *

With a view to obtaining as accurate a term of comparison as possible for our experiments, we suspended preventive treatment during 1936, while continuing blood tests of the inhabitants of the village and watching for the appearance of clinical cases of malaria. Clinical cases were treated, as formerly, with atebrin in Sector I and with quinine in Sector II.

The results of the blood tests made in 1936 will be found in Table 3.

The incidence of clinical cases of malaria is given in Table 5.

Table 5.

MONTHLY INCIDENCE OF ATTACKS OF CLINICAL MALARIA DURING
THE YEAR 1936 (NO PREVENTIVE TREATMENT).

	Former groups			Total	Infections with		
	I. Atebrin	II. Quinine	Control		<i>P. vivax</i>	<i>P. falciparum</i>	Mixed
February	—	1	—	1	1	—	—
March	—	—	—	—	—	—	—
April	2	—	—	2	2	—	—
May	3	1	—	4	4	—	—
June	1	3	3	7	5	1	1
July	7	1	3	11	4	6	1
August	11	12	4	27	7	18	2
September	7	7	2	16	4	10	2
October	2	—	1	3	2	1	—
November	—	1	—	1	1	—	—
Total	33	26	13	72	30	36	6

Table 5 shows that the suspension of preventive treatment was responsible for the appearance of a large number of clinical cases of malaria, especially in the epidemic period. Most of these cases were from earlier infections which treatment had not eliminated but had merely maintained in a latent state. The average incidence

of clinical cases during the year 1936 was 2.7%. The average parasite rate for the same period was 7.6%. Hence, about 30% of the parasite carriers had clinical attacks. The plan on the next page (Figure 3) shows the geographical distribution of clinical cases and parasite carriers in relation to the corresponding conditions during the period of prophylactic treatment. The distribution of clinical cases and parasite carriers between the different experimental groups will be found in Table 6.

Table 6.

AVERAGE INCIDENCE OF ATTACKS OF CLINICAL MALARIA AND AVERAGE PERCENTAGE OF PARASITE CARRIERS DURING THE YEAR 1936 (NO PREVENTIVE TREATMENT).

Former groups	Total number of blood tests	Parasite carriers	Average parasite rate	Clinical attacks of malaria	Average incidence of clinical attacks
			%		%
I. Atebrin	1,125	91	8.1	33	2.9
II. Quinine	958	60	6.3	26	2.7
Control	575	51	8.9	13	2.2
Total	2,658	202	7.6	72	2.7

Table 7 shows the distribution of clinical cases by age-groups. As usual, there are more clinical cases in children under 15.

Table 7.

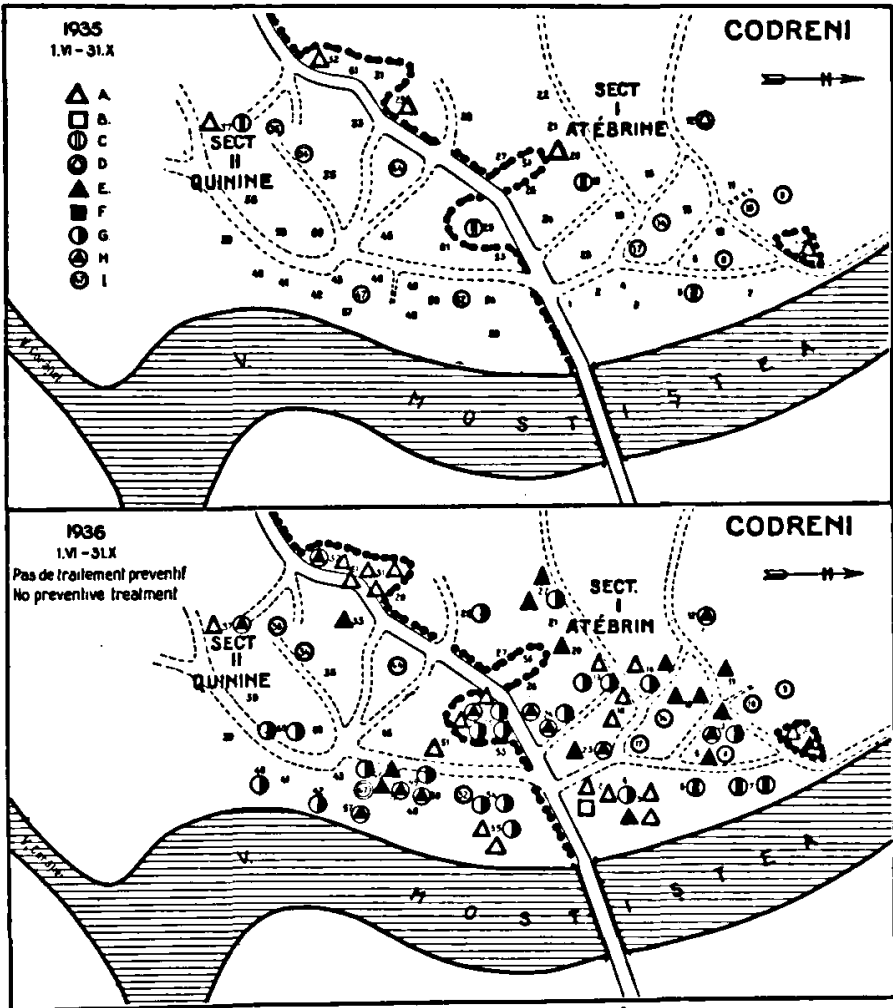
DISTRIBUTION BY AGE-GROUPS OF CLINICAL CASES OF MALARIA OCCURRING DURING THE YEAR 1936.

Age-group (years)	Former groups			Total
	I. Atebrin	II. Quinine	III. Control	
0-14	23	20	12	55
15-80 and over	10	6	1	17
Total	33	26	13	72

With regard to parasite carriers, it should be observed in the first place that the evolution of the parasite rate was not influenced by previous treatment. As in the years preceding the prophylactic treatment, a considerable increase was observed in the number of

Figure 3.

DISTRIBUTION OF PARASITE CARRIERS AND OF CLINICAL CASES, CORRESPONDING TO THE PERIOD OF PREVENTIVE TREATMENT (YEARS 1935-1936).



- A : Parasite carriers : infection with *P. vivax*.
- B : Parasite carriers : infection with *P. malarix*.
- C : Parasite carriers : infection with *P. falciparum*.
- D : Parasite carriers : mixed infections.
- E : Clinical attacks of malaria : infection with *P. vivax*.
- F : Clinical attacks of malaria : infection with *P. malarix*.
- G : Clinical attacks of malaria : infection with *P. falciparum*.
- H : Clinical attacks of malaria : mixed infections.
- I : Houses of the control group.

parasite carriers in May, at a time when the parasite rate was beginning its upward movement. The curve reached its peak in August, and then fell gradually in September and October and during the inter-epidemic period.

The prophylactic treatment administered in the preceding years does not seem to have had any influence on the parasite rate. As will be seen from Summary Table 8 and Figure 4 (see also Table 3 and Figure 2), the parasite rates for the epidemic period of the year 1936 were : for the former atebtrin group, 14.9% ; for the former quinine group, 10.5% ; and for the former control group, 13.3%. These figures give an average of 13.6%. During the third year of prophylactic treatment, the parasite rate for the control group was 15.1%. It will be seen that there is very little difference between the two figures. They are normal for the endemic-epidemic conditions of the area.

Table 8.

COMPARISON BETWEEN THE PARASITE RATE FOR THE EPIDEMIC PERIOD OF THE YEAR 1935, DURING THE EXPERIMENTS IN CLINICAL PROPHYLAXIS, AND THE PARASITE RATE FOR THE SAME PERIOD OF THE YEAR 1936 (NO PREVENTIVE TREATMENT).

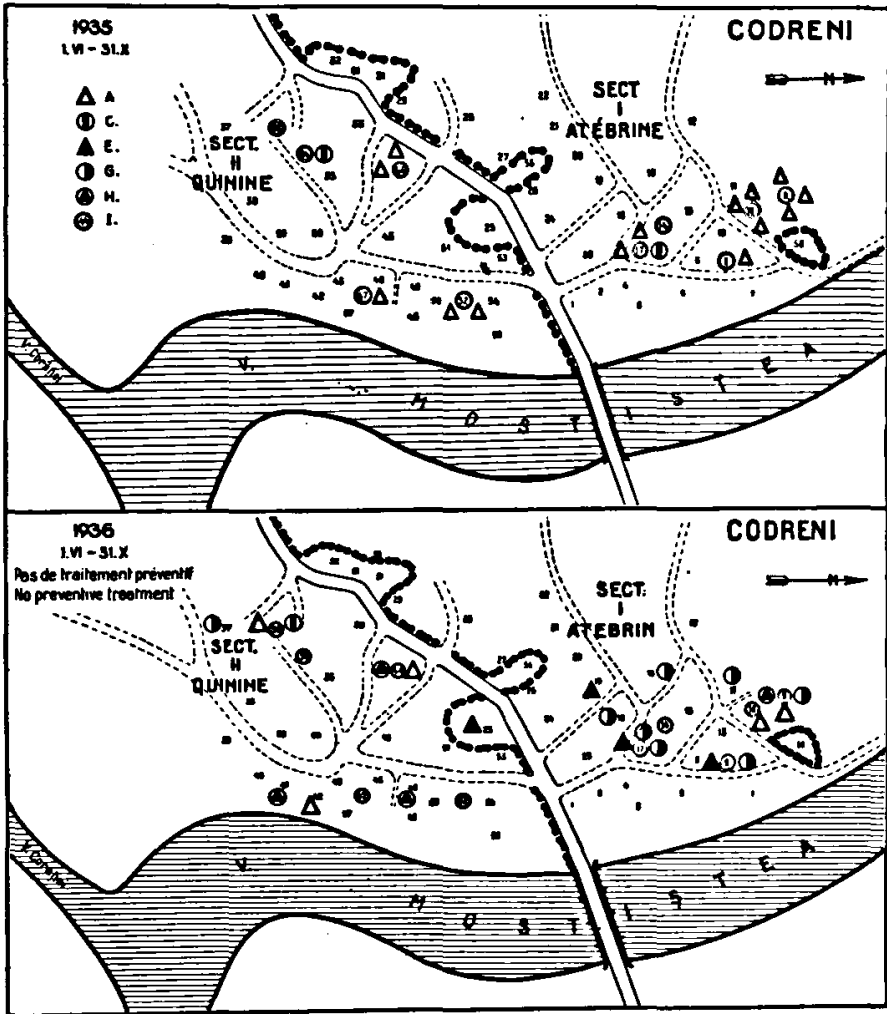
Group	1935 : June 1st-Nov. 1st Preventive treatment			1936 : June 1st-Nov. 1st No preventive treatment		
	Blood tests	Parasite carriers	Parasite rate %	Blood tests	Parasite carriers	Parasite rate %
I. Atebrin	468	9	1.9	470	70	14.9
II. Quinine	435	8	1.8	379	40	10.5
Control	205	31	15.1	225	30	13.3
				1,074	140	13.0

Apart from the fall in the number of clinical cases and in the parasite rate observed during the period of prophylactic treatment, there would seem again to be only one effect—a reduction in the parasite rate in the inter-epidemic period immediately following. Thus, as will be seen from Table 9, the average parasite rate for the inter-epidemic period following the prophylactic treatment administered in 1935 was 2.3% for the atebtrin sector and 1.9% for the quinine sector, whereas it was 6.2% for the control group.

The difference, which is fairly large, is the same as that recorded in our previous work.

Figure 4.

DISTRIBUTION OF PARASITE CARRIERS AND OF CLINICAL CASES IN THE CONTROL GROUPS, CORRESPONDING TO THE PERIOD OF PREVENTIVE TREATMENT (YEARS 1935-1936).



- A : Parasite carriers : infection with *P. vivax*.
- C : Parasite carriers : infection with *P. falciparum*.
- E : Clinical attacks of malaria : infection with *P. vivax*.
- G : Clinical attacks of malaria : infection with *P. falciparum*.
- H : Clinical attacks of malaria : mixed infections.
- I : Houses of the control group.

Figure 5.

COMPARISON BETWEEN THE PARASITE RATE FOR THE EPIDEMIC PERIOD OF 1935, DURING THE EXPERIMENTS OF CLINICAL PROPHYLAXIS, AND THAT OF THE SAME PERIOD IN 1936 (NO PREVENTIVE TREATMENT).

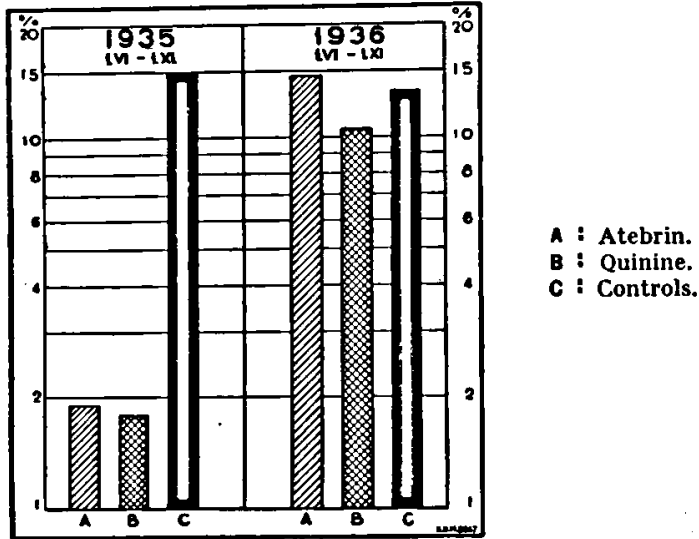


Table 9.

AVERAGE PARASITE RATES FOR THE INTER-EPIDEMIC PERIOD (NOVEMBER, DECEMBER 1935, JANUARY, FEBRUARY, MARCH AND APRIL 1936) FOLLOWING THE CESSATION OF PREVENTIVE TREATMENT.

Group	Number of blood tests	Parasite carriers	Average parasite rates
I. Atebrin	558	13	2.3
II. Quinine	552	10	1.9
Control	305	19	6.2

CONCLUSIONS.

1. Prophylactic treatment with atebtrin or quinine appreciably reduces the incidence of clinical malaria during the period of treatment. From the first year of treatment, clinical cases are almost eliminated.

2. Prophylactic treatment considerably reduces the parasite rate during the period in which the drug is administered regularly. The reduction also continues in the subsequent inter-epidemic period.

3. The suspension, in 1936, of the prophylactic treatment administered during the three preceding years was followed by a recrudescence of clinical cases and a rise in the parasite rate. In the epidemic period following the suspension of the treatment, the incidence of clinical cases, as well as the parasite rate, reverted to the figures usual in such endemic-epidemic conditions as prevailed locally.

Appendix.

A. DOSES OF DRUGS.

In accordance with the recommendations of the Malaria Commission (Programme of Co-ordinated Experiments to be made in the Field—document CH. /Malaria /227), we administered the doses set forth below to different age-groups.

Doses of Atebrin and Quinine administered for Preventive Treatment.

Age-group (years)	Sector I. Atebrin	Sector II. Quinine
0-2	0.025 grm. every other day	0.10 grm. daily
3-4	0.025 " " " "	0.20 " "
5-8	0.025 grm. daily	0.20 " "
9-12	0.050 " "	0.20 " "
12-80	0.050 " "	0.40 " "

The treatment was administered to all the inhabitants of the village, except the control groups, from June 1st to November 1st, 1935. Atebrin was administered in tablets, and quinine in sugar-coated pills and chocolates. Our task was made much easier by the circumstance that the earlier experiments had accustomed the people to the treatment we were administering.

Quinine was administered by two specially trained assistants. It had to be taken in their presence, and they were responsible for the accuracy of the doses and the continuity of the treatment. Regular notes were kept of persons who did not attend and doses not taken. Two doctors paid surprise visits in order to ensure the regularity of the treatment and to check cases of intolerance.

During their daily visits, the assistants collected blood smears and thick drops from all persons who complained of fever or were seen to be ill.

Clinical attacks of malaria were treated for seven days with the drug used for prophylaxis—atebrin or quinine, as the case might be—without the addition of plasmoquine.

Doses of Atebrin and Quinine administered for Curative Treatment.

Age-group (years)	Sector I. Atebrin	Sector II. Quinine
0-2	0.10 grm.	0.30 grm.
3-4	0.10 " "	0.50 " "
5-8	0.20 " "	0.60 " "
9-11	0.30 " "	0.80 " "
12-80	0.30 " "	1.00 " "

Parasite carriers who had no clinical attacks were not subjected to curative treatment.

B. DATA REGARDING ANOPHELSM IN 1935.

Differentiation according to the different ovipositions of *A. maculipennis* collected at Codreni during the summer of 1935 gave the following results :

Month	Races of <i>A. maculipennis</i>			Total
	<i>Messeæ</i>	<i>Atroparvus</i>	<i>Typicus</i>	
July	150	53	7	210
August	227	66	10	303
September	62	83	2	147
Total	439	202	19	660
Percentage	66.5	30.6	2.9	100

As will be seen from these figures, the most widespread variety was *A. maculipennis messeæ*. *A. maculipennis atroparvus* was fairly frequent, and *A. maculipennis typicus* was somewhat rare.

Throughout the experiments in clinical prophylaxis, no anti-larval measures were taken, nor were any steps taken to destroy adult mosquitoes.

C. CLIMATIC CONDITIONS IN THE GURBĂNEȘTI AREA.

The Gurbănești area is situated in the Wallachian anti-steppe, and has all its climatic features. As will be seen from the following figures summarising the meteorological observations taken at the Gurbănești station during the years 1932-1935, the annual variations in temperature, the rainfall, and the variations in the relative humidity of the air are of the continental type.

Summary of Meteorological Observations taken at the Gurbănești Station, 1932-1935.

	Average temperature	Atmospheric precipitation mm.	Relative humidity of the air %
Winter (December-February)	2.9°C.	84.25	84
Spring (March-May)	10.3°C.	119.33	70
Summer (June-August) ...	21.0°C.	154.23	66
Autumn (September-November)	12.7°C.	74.45	71
Yearly average	10.2°C.	434	73

IV. EXPERIMENTS IN ERADICATING MALARIA BY MEANS OF SYNTHETIC DRUGS

carried out by

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According to the Health Organisation's plan, these experiments required :

(a) A preliminary treatment of the whole population of a village with atebirin for five days (0.3 grm. per day per adult).

(b) The subsequent administration during the malarial season of plasmoquine twice weekly at the rate of 0.02 grm. per adult and atebirin once weekly at the rate of 0.2 grm. per adult.

Situation.—Opriseni, a village of 725 inhabitants isolated in a bend of the River Pruth in the midst of an area subject to spring and autumn flooding, was chosen for the experiment.

In the immediate neighbourhood of the village there is a permanent weed-infested pond and in the middle of the village a hollow full of water in the rainy season and dry in the summer.

We give below the result of a census of the population taken before the beginning of the experiment (April 1935).

In 1935, there were 26 births (with 14 survivals) and 23 deaths for the whole population.

During the same year, there was an epidemic of whooping-cough. There were also 79 cases of influenza.

Social diseases—29 cases of pellagra, 4 cases of tuberculosis.

The village consists of 136 houses, mostly built of sun-dried mud with a rush or wooden roof.

THE TREATMENT OF MALARIA

Age (years)	Men	Women	Total
0-1	10	15	25
1-2	15	17	32
2-3	13	10	23
3-4	11	11	22
4-5	15	17	32
5-10	44	44	88
10-15	40	35	75
15-20	34	29	63
20-25	41	33	74
25-30	29	34	63
30-35	20	21	41
35-40	21	22	43
40-45	14	13	27
45-50	19	13	32
50-55	13	12	25
55-60	11	15	26
Over 60	17	17	34
Total	367	358	725

The economic condition of the population is good, generally speaking ; nutrition is poor ; the inhabitants sell their agricultural produce.

There are 117 stables and shelters for animals in the immediate neighbourhood of these houses ; 127 horses, 32 head of cattle, 162 sheep and 207 pigs make up the total live-stock of the village.

Crops.—The area cultivated is 797 hectares—34 hectares under wheat ; 7 hectares, oats ; 36 hectares, barley ; 473 hectares, maize ; 127 hectares, various ; 120 hectares, grass-land.

* * *

The organisation of the campaign was difficult, because the malarial season coincides with the busy farming season.

A permanent anti-malarial dispensary was also set up in the village.

The village was divided up into seven areas, each including twelve to fifteen houses under the supervision of a specially trained health agent. It was the duty of this agent to distribute drugs according to the plan agreed upon.

One health agent was responsible for blood sampling. He took about twenty-four samples a day. *The blood of the whole population was examined monthly.*

All the information obtained, the doses of drugs administered, accidents, etc., were recorded every day.

The field staff was as follows : one resident medical officer, nine health agents and one assistant.

The blood tests were made by the Jassy Institute of Hygiene.

Investigations.—The advantages of an anti-malaria campaign were first explained to the people, and they were shown a special propaganda film.

In April and in November 1935, as well as in April 1936, the spleens of all the inhabitants between the ages of 0 and 14 years were examined. Cases were regularly traced and the blood was tested monthly. Owing to the agricultural work, the blood samples had to be taken and the drugs administered very early in the morning and mostly before breakfast.

To part of the population, the drugs were administered in the fields. The operations were considerably facilitated by the assistance of the schoolmaster and of the priest : their help was greatly appreciated.

* * *

Difficulties encountered.—There can be no doubt that, according to the Health Organisation's plan, the *whole population* should have been subjected to prophylaxis and possibly steps ought to have been taken to prevent the immigration of fresh reservoirs of infection for the mosquitoes. The impossibility of carrying out such a plan can readily be understood. In point of fact, in spite of all efforts, only 651 out of the 725 inhabitants agreed to undergo treatment ; 74 inhabitants—refractory persons, cartmen and aged and infirm persons—received no treatment and therefore served as controls.

Of the 651 persons subjected to prophylaxis, 530 (81.57%) followed the treatment very regularly ; 39 interrupted it for various unavoidable reasons, 31 children under 2 years of age on account of the disorders observed, in particular, vomiting ; 36, because they left the village ; 10 old men of more than 60, because they did not wish to continue the treatment ; and 5 persons, because they died from various causes.

Treatment was applied as follows : From May 1st to May 5th, the whole population received 0.3 gm. of atabrin daily ; then, until October 31st, on Tuesdays and Thursdays, plasmoquine ; on Satur-

days, atebtrin 0.2 gm. The doses in the various age-groups were as follows :

Atebrin.

From 0 to 5 years of age	0.1 gm.
From 5 to 12 years of age	0.2 gm
Over 12 years of age	0.3 gm.

Plasmoquine.

From 0 to 2 years of age	0.005 gm.
From 2 to 8 years of age	0.01 gm.
Over 8 years of age	0.02 gm.

Toxic accidents.—Some of the accidents observed made it necessary to discontinue the treatment. Thirty-one children under 2 years of age began to vomit immediately after swallowing the atebtrin. As these accidents occurred several times after the administration of the drug, we were obliged to discontinue it in these cases.

In another group, also of 31 persons, but of all ages, disorders set in between thirty minutes and one hour after swallowing the drug : malaise, headaches and a feeling of heaviness in the epigastric region. These symptoms were more frequently met with among the numerous persons who took the drug on an empty stomach.

In order to make sure of this fact, the resident medical officer and eight sanitary agents took 0.15 gm. of atebtrin on an empty stomach ; all felt malaise, a disagreeable sense of slight indisposition, headache and heaviness in the epigastric region. These symptoms lasted from four to six hours.

Forty-three persons showed a yellow discoloration of the scleræ and the skin which lasted throughout the whole period of prophylaxis. This coloration, although particularly disagreeable for the young girls, did not lead to discontinuance of the treatment. It was much less intense than the coloration observed in Sardinia.

In the doses administered, the plasmoquine did not cause any toxic accidents and there was no need on any occasion to discontinue the treatment.

We give below in tabular form the results of the malarial investigations before the beginning of the treatment, during the period of prophylaxis (May 1st to October 31st, 1935), in the pre-epidemic and in the epidemic period, 1936.

Table 1.
SPLEEN INDEX.

Age-group :	0-1 year	2-5 years	6-10 years	11-14 years	Total
April 1935 : before the experiment :					
Number of inhabitants examined..	19	71	82	41	213
Number of enlarged spleens	1	4	9	5	19
Spleen index					8.92%
November 1935 : at the end of the experiment :					
Number of inhabitants examined..	18	79	80	31	208
Number of enlarged spleens	—	1	1	1	3
Spleen index					3.26%
April 1936 : five months after the experiment :					
Number of inhabitants examined..	21	87	89	47	244
Number of enlarged spleens	1	—	6	2	9
Spleen index					3.68%
July 1936 : during the epidemic season					
Number of inhabitants examined..	20	73	85	48	226
Number of enlarged spleens	2	4	5	2	13
Spleen index					5.75%

This table shows that the spleen index fell as a result of the treatment from 8.92% in April 1935 to 3.26% in November (prophylaxis ceased on October 31st, 1935), rose to 3.68% during the pre-epidemic period (April 1936) and to 5.75% during the epidemic period (July 1936).

Table 2.
SPLENOMETRIC INDEX.

Date	Number of children examined (0-14 years)	Number with enlarged spleens	Average spleen figures	Spleen index	Spleno- metric index
1935 :					
April	213	19	1.63	8.92	14.54
November.	208	3	1.33	3.26	4.34
1936 :					
April	244	9	1.55	3.68	5.70
July.....	226	13	1.46	5.75	8.39

The splenometric index fell as a result of the prophylaxis from 14.54% to 4.34% in November, then rose to 5.7% in April 1936 and to 8.39% during the epidemic period (July 1936).

Table 3.

PARASITE INDEX AND RATE.

	0-14 years	Over 14 years	Total
April 1935, before the experiment :			
Number of inhabitants examined	244	366	610
Number of parasite carriers	9	8	17
Parasite rate	3.68	2.18	2.58
November, at the end of the experiment :			
Number of inhabitants examined	208	302	510
Number of parasite carriers	1	1	2
Parasite rate	0.48	0.33	0.39
April 1936, five months after the end of the experiment :			
Number of inhabitants examined	238	290	528
Number of parasite carriers	1	—	1
Parasite rate	0.42	—	0.19
July 1936 :			
Number of inhabitants examined	231	353	584
Number of parasite carriers	3	2	5
Parasite rate	1.30	0.57	0.86

The parasite index, which was 3.68% in April, fell to 0.48% at the end of prophylaxis and to 0.42% during the pre-epidemic period of 1936. It started to rise during the epidemic season, reaching 1.30% in July. The parasite rate followed the same curve.

In order to show the part played by prophylaxis in decreasing the parasite indices and rates, we set out in Table 4 the distribution of parasite carriers among the treated persons and the controls.

This table shows that the percentage of parasite carriers during prophylaxis was 0.42 among children from 0 to 14 years of age who followed the treatment (1,465 blood tests) and 0.30 in the age-groups above 14 years of age (1,992 blood tests).

Among the untreated controls, the percentage was 5.11 under 14 years of age (137 blood tests) and 0.94 above 14 years of age (213 blood tests). Between the ages of 0 and 14, it was therefore five times greater in the control group than in the groups subjected to prophylaxis. The following graph shows this difference.

Figure 1.
PERCENTAGE OF PARASITE CARRIERS
COMPARED IN THE TREATED
AND UNTREATED GROUPS (1935).

I. Epidemic period.
II. Post-epidemic period.

A : Treated.
B : Untreated.

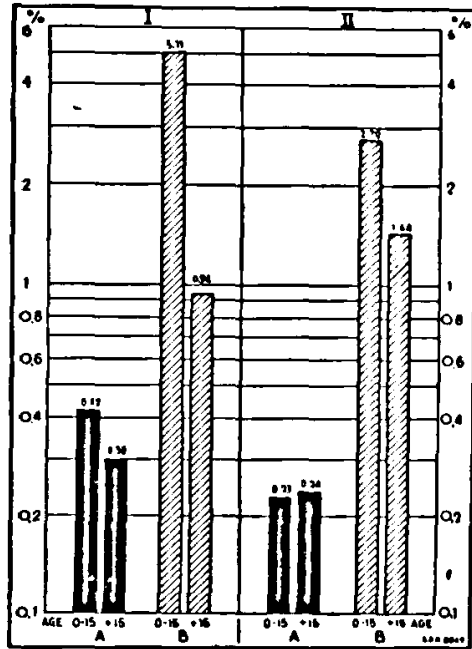


Table 4.
MONTHLY DISTRIBUTION OF PARASITE CARRIERS AMONG TREATED CASES
AND NON-TREATED CONTROLS.

	Population treated : May 1st-October 30th, 1935			Non-treated population : May 1st-October 30th, 1935		
	Total	0-14 years	Over 14 years	Total	0-14 years	Over 14 years
Total	3,457	1,465	1,992	350	137	213
May :						
Blood tests	608	267	341	34	14	20
Parasite carriers	1	—	1	1	1	—
June :						
Blood tests	616	259	357	54	18	36
Parasite carriers	5	2	3	2	2	—
July :						
Blood tests	609	254	355	48	21	27
Parasite carriers	4	2	2	1	1	—
August :						
Blood tests	593	250	343	46	19	27
Parasite carriers	1	1	—	—	—	—
September :						
Blood tests	519	226	293	108	38	70
Parasite carriers	1	1	—	2	1	1
October :						
Blood tests	512	209	303	60	27	33
Parasite carriers	—	—	—	3	2	1
Percentage	0.34	0.42	0.30	2.57	5.11	0.94

Table 5.

VARIATION IN THE NUMBER OF PARASITE CARRIERS FROM OCTOBER 30TH, 1935, TO APRIL 30TH, 1936 (AFTER PROPHYLAXIS).

	Treated group			Untreated group		
	Total	0-14 years	Over 14 years	Total	0-14 years	Over 14 years
Total	2,986	1,295	1,691	457	179	278
November 1935 :						
Blood tests	457	187	270	53	21	32
Parasite carriers	—	—	—	2	1	1
December 1935 :						
Blood tests	534	235	299	76	31	45
Parasite carriers	1	—	—	1	1	—
January 1936 :						
Blood tests	523	218	305	91	36	55
Parasite carriers	1	1	—	2	1	1
February 1936 :						
Blood tests	512	224	288	82	30	52
Parasite carriers	1	1	—	4	2	2
March 1936 :						
Blood tests	509	225	284	78	29	49
Parasite carriers	3	—	3	—	—	—
April 1936 :						
Blood tests	451	206	245	77	32	45
Parasite carriers	1	—	—	—	—	—
Percentage	0.23	0.23	0.24	1.96	2.79	1.44

The difference in the ratio of parasite carriers between the treated group and the non-treated group continued to be the same throughout the winter and the pre-epidemic period. We would draw attention to the decrease in the percentage of parasite carriers in the non-treated group—decrease which seems to us to be very important and which can only be explained by a decrease in the number of reservoirs of infection for the mosquitoes, as a result of the prophylaxis applied to 75% of the population.

Here we would point out that, despite a tendency to rise, the rates (spleen and parasite) in July 1936 (5.75 ; 0.86) remained below the rates for the pre-epidemic season of 1935 before the experiment (8.92 ; 2.58).

Malaria incidence.—The village of Opriseni was only attached to the Tomesti rural Health Centre as from January 1st, 1935, and no malaria investigations had been conducted there before that date.

Nevertheless, 178 clinical cases of malaria were registered in 1934—i.e., 24.6% of the population; these cases had received incomplete treatment with quinine sulphate.

The following is the distribution of clinical cases and parasite carriers as from May 1st, 1935, the date on which the eradication experiments began, to November 1st, 1936.

Table 6.
INCIDENCE OF MALARIA IN THE VILLAGE OF OPRISANI
FROM MAY 1ST, 1935, TO NOVEMBER 1ST, 1936 (PERCENTAGE).
Population treated (530).

Age (years)	May 1st- Oct. 30th, 1935			Nov. 1st, 1935- May 1st, 1936			May 1st- Nov. 1st, 1936		
	A+ P+	Ao P+	Total	A+ P+	Ao P+	Total	A+ P+	Ao P+	Total
0-1 ...	—	—	—	—	—	—	—	—	—
2-5 ...	—	2	2	—	—	—	3	1	4
6-10 ...	—	1	1	—	1	1	2	1	3
11-15 ...	—	3	3	1	—	1	4	—	4
16-20 ...	—	—	—	1	1	2	2	—	2
21-30 ...	—	4	4	1	—	1	7	—	7
31-40 ...	—	2	2	—	1	1	3	—	3
41-50 ...	—	—	—	1	—	1	4	—	4
51-60 ...	—	—	—	—	—	—	—	—	—
61 and over	—	—	—	—	—	—	—	—	—
Total ...	—	12 2.26	12 2.26	4 0.76	3 0.56	7 1.32	25 4.72	2 0.37	27 5.09
<i>Population not treated (control) (121)</i>									
0-1 ...	—	—	—	—	—	—	1	—	1
2-5 ...	6	—	6	1	2	3	5	—	5
6-10 ...	—	—	—	1	—	1	3	—	3
11-15 ...	1	—	1	—	—	—	4	—	4
16-20 ...	—	—	—	—	2	2	—	—	—
21-30 ...	1	—	1	2	1	3	3	1	4
31-40 ...	—	—	—	—	—	—	1	1	2
41-50 ...	—	—	—	—	—	—	—	—	—
51-60 ...	—	—	—	1	—	1	—	—	—
61 and over	—	—	—	—	—	—	1	—	1
Total ...	8 6.61	—	8 6.61	5 4.13	5 4.13	10 8.26	18 14.87	2 1.65	20 16.52

This table shows that no clinical cases of malaria were observed among the population submitted to treatment (May 1935-October

1935), but only 2.26% of parasite carriers ; whereas there were 6.61% clinical cases of malaria among the controls.

The percentage of cases appearing during the post-epidemic period (November 1935-April 1936), after the end of the treatment, was 1.32% of the population treated (0.76% clinical cases and 0.56% parasite carriers), the percentage in the control population being 8.26 (4.13% clinical cases and 4.13% parasite carriers).

In the epidemic period (May-October 1936), the percentage of clinical cases appearing in the population treated was 5.09 (4.72% clinical cases and 0.37% parasite carriers) ; at the same time, the percentage of cases appearing in the control population was 16.52 (14.87% clinical cases and 1.65 parasite carriers).

GENERAL CONCLUSIONS.

In the conditions obtaining in our villages, an experiment in total malaria eradication by treatment seems to us to be a very difficult proposition. At Opriseni, in spite of the efforts of a numerous staff (twelve persons), only 73% of the population received the complete treatment during the whole epidemic season. It was evident throughout the period of prophylaxis that the method adopted was efficacious ; malaria morbidity fell considerably in comparison with previous years.

Complete treatment (in accordance with the recommendations of the programme of experiments) administered to only 73% of the population prevented the appearance of clinical cases during the treatment (May 1935-October 30th, 1935) ; but 2.26% of parasite carriers were discovered among the population treated. The percentage of cases appearing after the cessation of treatment, in the post-epidemic period (November 1935-April 1936), was 1.32 (0.76% clinical cases and 0.56% parasite carriers). The incidence of malaria was far higher in the epidemic period of 1936 (May-October) ; in fact, we found 5.09% cases of malaria among the same population as was treated in the previous year (4.72% clinical cases and 0.37% parasite carriers).

There was a clear drop in the endemic indices. The spleen and parasite rates in July 1936 remained below the rates for April 1935 (before the experiment), although they showed a tendency to rise.

The fact that there was also a fall in the untreated group would seem to indicate that there were fewer sources of infection for mosquitoes,¹ for which the gametocidal treatment was responsible.

Prophylaxis carried out under these conditions was effective ; the eradication experiments in the circumstances described above were not successful in clearing a given area in which epidemiological conditions continue.

The expense of maintaining so large a staff would be too heavy in a more extensive malarious area. It would be increased still further by the cost of drugs, which we received free of charge this time, through the Health Organisation, for experimental purposes.

The drugs should be administered under the supervision of a medical officer.

¹ Here we would point out that there was a prolonged drought in the year 1935.

HEALTH INDICES ESTABLISHED IN AN EXPERIMENTAL STUDY OF THE CITY OF BRUSSELS

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INTRODUCTION.

The present study is the third experimental application of a system of health indices elaborated by Dr. I. S. FALK, of the Social Security Board, Washington, D.C., and the author, under the auspices of the Health Section of the League of Nations Secretariat and the Milbank Memorial Fund of New York.¹ The first experimental study was made in 1936 in the city of New Haven, Conn. ;² the second in the rural district of Mezökövesd in Hungary.³

It was considered advisable, before the system of indices was submitted for the consideration of international experts in this field, to undertake an experimental study of the application of the indices to a European city where the development of the health service had followed lines differing from those usually governing the conception of public health administration in the United States. The kind offer of Dr. René SAND, Secretary-General of the Belgian Ministry of Health, to pursue the study in a Belgian city was therefore warmly appreciated.

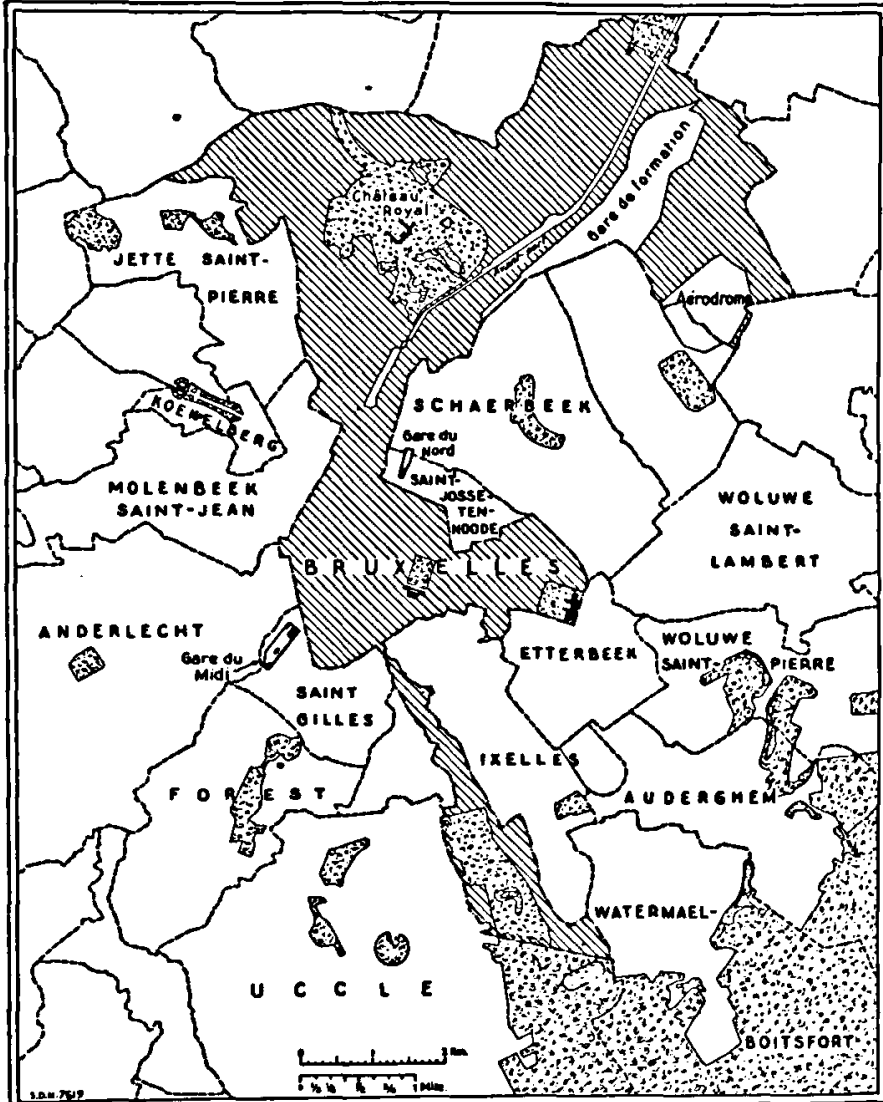
¹ *Quart. Bull. Health Org.*, 1936, 5, pages 901-996.

² *Ibid.*, pages 997-1081.

³ *Bull. Health Org.*, 1937, 6, 766.

Figure 1.

MAP OF THE URBAN AREA OF BRUSSELS.



The City of Brussels was chosen for this experiment rather for the difficulties which a study presented there than on account of the abundance of material available. The administrative organisation of the Brussels area is extremely complicated, and the protection of its health is organised along lines entirely different from those of the two areas previously studied. This application represents therefore a particularly severe test for the adaptability of the health indices, and the present study is consequently far from being a simple repetition of the previous two experiments.

Certain parts of the report may seem meagre on account of the scarcity of obtainable information. It must be remembered, however, that, while American city health administrations are usually able to make such information available on account of the annual "health contests" and the periodical Appraisal Form surveys, such surveys had never been in the minds of the Brussels administration any more than in those of most other European city administrations. The material which is now wanting could easily be procured if it was known that it would be required, and it would undoubtedly be demanded once its utility had been recognised.

Adequate records of work performed can be kept without great difficulty no matter what general conceptions guide the administrative organisation. The present study has brought out various facts concerning the health conditions in Brussels which were not hitherto known. Future studies, which may be undertaken when more complete and detailed data have become available, will undoubtedly contribute much more precise indications of the results of work performed as well as of future needs in the field of public health. It is hoped that the present study will at least illustrate the utility, nay even the necessity of such investigations.

As far as the health indices themselves are concerned, a comparison between the New Haven and the Brussels indices illustrates the need of a considerable degree of flexibility in any system of indices for international use capable of adaptation to the varying conceptions which rule the organisation of public health in the different countries. Such a system can be based only upon a clear presentation of environmental factors and results obtained in public health as shown by the vital statistics and the mortality records. These factors, which are brought out in parts A and B of the present system,

must be the corner-stone of any international appraisal of public health activities. It is hoped that these studies will encourage institutions charged with the protection and betterment of public health in other countries to undertake similar investigations. It is essential, however, that such studies should be co-ordinated from an international centre such as the Health Organisation of the League of Nations in order to promote cohesion and international comparability. Once the means of objective comparison are established through a flexible and comprehensive system of international health indices, a powerful tool will have been forged for comparative study and friendly competition in a field which concern the health and welfare of every inhabitant of the globe.

This study owes its existence particularly to the interest taken in the matter by Dr. René SAND, who has not only contributed valuable advice but also helped to procure the necessary information from the many sources which had to be consulted. Special thanks are due also to M. Edm. LESOIR, Director-General of the Central Statistical Office of Belgium, and to Dr. André BECH, Health Officer of the City of Brussels, who have taken an active interest in the study and furnished much of the information upon which it is based.

A. INDICES OF ENVIRONMENT.

I. CLIMATE AND TOPOGRAPHY.

Brussels, ancient capital of Brabant and, since 1831, of the Kingdom of Belgium, is situated in the very centre of this densely populated country, just where the lowlands of Flanders merge into the rolling plains of Brabant. A large part of the urban area is hilly but not so much as to interfere with traffic. The ancient town itself inside the boulevards is commonly divided into the "High Town" standing on the rising ground toward the south-east and the "Low Town" in the valley. The High Town includes the palatial buildings of the Kingdom and Finance, the Low Town the City Hall and other buildings of ancient municipal life as well as the main business district. During the last century the suburbs have spread out over an area many times that of the old city.

Brussels has many large parks and much open space, but seriously congested areas still exist, especially in the lower part of the old town. A constant effort at rebuilding has been in evidence for over a generation. The height above sea-level is from 100 to 300 feet. The soil and subsoil consist mostly of a fine red sand.

Brussels differs from most ancient cities in that it stands on no river of any commercial importance. It is traversed by the Senne, which is so small, however, that it was vaulted over in 1874 and led underground through the town. A port communicates by canal with the Schelde and the Sambre, tributary of the Meuse.

The climate is that of the North Sea area : cool summers, mild winters, frequent rains and sudden changes of weather. The mean temperature of the warmest month is 66° F., that of the coldest month 36° F. The range between the warmest and the coldest month is thus only 30° F. as compared with 44° F. for New Haven, Conn. Rains occur in all seasons but are usually not very heavy, the annual rainfall being 36 inches. The sky is frequently overcast, and hours of sunshine amounted to only 31% of the possible total as against 60% for New Haven. In spite of the latter drawback, the climate is clearly one which favours health and promotes energy. The proximity of salt water should increase its stimulating power.

Considering further the easy slope of the ground and the porous nature of the soil, it is clear that the site of Brussels is highly favoured by the hand of nature and very suitable for the development of a large city.

INDICES TO CHAPTER A, I.

1. *Temperature (1935) :*
 - (a) Mean annual : 51.4° F.
 - (b) Highest monthly mean (July) : 65.8° F.
 - (c) Lowest monthly mean (January) : 36.3° F.
2. *Annual rainfall :* 36 inches.
3. *Hours of sunshine :*
 - (a) Actual : 1,371 hours.
 - (b) Proportion of possible total : 31.3%.
4. *Altitude above sea-level :* 100-300 feet.
5. *Nature of soil and subsoil :* Sandy.

II. METROPOLITAN AREA AND DENSITY OF POPULATION.

The urban agglomeration of Brussels covers an area of 59 square miles, and its population was 916,275 at the end of 1936. Brussels should thus be one of the large towns of Europe and second, in the French-speaking part of the world, only to Paris. As administrative divisions now stand, the City of Brussels has, however, only 193,481 inhabitants on an area of 13 square miles. The remainder of the urban area consists of fifteen communes each with its own administration and institutions, associated only through a weekly conference of their mayors. Outside this area there are yet a few more communes which are due to be included within the metropolitan area.

The City of Brussels comprised up to 1921 only the old town inside the boulevards which have replaced the ancient fortifications, the aristocratic Quartier Léopold to the east and a small section around the North Station. In 1921, Laeken and some smaller suburban communes were annexed forming a long tentacle toward the north and another smaller to the south-east. This movement toward administrative consolidation was not continued, and there has been no change during the last sixteen years. Administrative consolidation of urban areas is usually slow in most countries, but there are few towns throughout the world where it lags so far behind the actual urban growth as in Brussels. This constitutes naturally a serious handicap for efficient administration in general and for the protection of health in particular.

The present area of the City of Brussels included, at the census of 1880, 42.5% of the population of the urban agglomeration. In 1936, it included only 21.1% of it. Nearly four-fifths of the Brussels people thus lived in the other fifteen communes, although a large proportion of them had their work in the city. The rational adjustment of this situation is made difficult by the Belgian legislation on municipal autonomy.

Similar difficulties are met with in other large Belgian cities, but nowhere is it as serious as in Brussels. At the census of 1930, the City of Antwerp included 58.7%, Ghent 77.9% and Liège 65.6% of the population of their respective built-up areas.

Within the metropolitan area of Brussels, the density of population is greatest in the low part of the inner town and in the old suburban communes of St. Gilles and St. Josse-ten-Noode (104 to 144 inhabitants per acre). A moderate density (44 to 59 per acre) about equal to that of the Quartier Léopold and the High Town is found in the communes of Etterbeek, Ixelles, Koekelberg, Molenbeek-St. Jean and Schaerbeek. The last-named commune has a population equal to that of the city area less the 1921 annexations. The eight other communes are more truly suburban and have, like the two long tentacles of the city, a low population density varying from 5 to 25 inhabitants per acre. In the city itself, the density varies from 144 per acre in the second district, which includes the central and southern parts of the old town, to 2.5 per acre in the tenth district, which is the most distant part of the northern extension.

The City of Brussels is thus within its present area a fairly representative sample of various forms of settlement met with within the limits of the entire urban district. This is all the more fortunate since, for the most part, statistics are not available for the suburban communes. At the end of 1936, the density of population of the City of Brussels was 23 per acre, that of the fifteen suburban communes was 24 per acre.

The built-over area of the city proper was 1,899 acres at the end of 1935 or 22.6% of the total area. Roads and streets covered 13.3% of the city area, public parks 6.3%, the Crown Land 4.7% and the railway formation yard 5.4%. The City of Brussels taken as a whole is thus abundantly provided with open space. Just beyond the city limits there is, moreover, the large forest of Soignes, which is available for the public.

INDICES TO CHAPTER A, II.

1. *Density of population* (1936) :

	Acres	Inhabitants per acre
Districts II, III and IV ("Low Town")	788	105
Districts I and V ("High Town" and Quartier Léopold)	880	51
Districts VI to X (outer extensions)	6,714	10
Total city area	8,382	23
Fifteen suburban communes	29,565	24
Total urban area	37,947	24

2. *Proportion of urban area included within city limits (1936) : 21.1%.*
3. *Built-over area and open public spaces within city limits (1935) :*

	Acres	Percentage of city area
Built-over area	1,899	22.6
Roads and streets	1,115	13.3
Public parks	528	6.3
Crown Land	397	4.7
Railway formation yard	452	5.4

III. SOCIAL AND ECONOMIC CONDITIONS.

The revenue *per caput* from real estate and buildings is greater in Brussels than in any other Belgian city. In 1930, it was 1,666 francs (56.86 American dollars) *per caput* for the city and 992 francs for the suburbs, the average for the whole urban district being 1,148 francs. The corresponding *per caput* revenue for the other three big Belgian urban centres was 833 francs for Antwerp, 642 francs for Liège and 443 francs for Ghent. It was less for the smaller towns—as, for example, 256 francs for Malines and 227 francs for Lierre. Brussels must therefore be considered a wealthy city easily capable of paying for adequate health protection. This opulence constitutes in itself an important environmental factor.

No data are available upon which exact indices for the distribution of this wealth could be based. There are certainly poor sections of the town where living conditions must influence health adversely. This is so especially in the narrow blind alleys and in the southern part of the old town, but there is probably no more extreme poverty in Brussels than in other large European cities. The general impression is that a more or less comfortable middle class predominates in the greater part of the town. This general remark is merely comparative and must not be construed to mean that social conditions are ideal. This impression cannot be condensed into an index, but is borne out by the census returns of occupational and social distribution.

The census does not specify transport and communications as one of its main groups, but includes workers in this field under the headings of Industry, Commerce or Public Administration according to the branch of economy with which they are principally connected. One-half of the occupied men are engaged in industry

and 30% in commerce. This may be considered normal for a large town and gives the same total of 80% of the male population as for these groups—including transportation—in New Haven. The proportion engaged in public service is somewhat high, which is natural, as Brussels is the seat of the national government.

Fifty-six women were engaged in gainful occupations for every 100 men. This is a high proportion which is not equalled even in most American cities. The corresponding ratio for New Haven was 38. The women are engaged mostly in commerce, industry and domestic service, the three groups being approximately equal. The proportion of domestic servants is high—55 per 1,000 population as against 28 in New Haven—and the proportion of women engaged in commerce is also considerably higher than there. On the other hand, only 5.8% of the occupied women were engaged in liberal professions in Brussels as against 18.4% in New Haven.

The Belgian census contains valuable information regarding the social distribution of the population into employers, employees, labourers, etc. It appears that roughly half of the population can be regarded as belonging to the labouring classes, including domestic servants. Taking both sexes together, 36.4% of the persons engaged in commerce and 11.5% of those engaged in industry were employers or at least independently established. This shows that the small or medium-sized business concerns prevail and that a considerable proportion of industry is still in the nature of artisan concerns. Female industrial labourers numbered 36.2 for every 100 male workers of the labouring classes. This rather high proportion is probably due to the relative importance of the dressmaking and millinery industries. The proportion of women employers was high (37 per 100 men). It is noteworthy that only 14 women were employed in public service for every 100 men.

Unemployment is naturally variable, but it is of interest that, out of 1,909 unemployed enumerated by the social assistance service of the city, 1,155 (60.5%) had been unemployed for over a year and 814 (42.6%) for over two years. Of the total, 20% were between 50 and 65 years of age. There is thus evidence of the formation of a group of chronically unemployed, but this group amounts to only 1.1% of the total number of wage-earners.

INDICES TO CHAPTER A, III.

1. *Revenue per caput from real estate and buildings (1930) :*

	Belgian francs
Brussels City	1,666
Suburban communes	992
Whole agglomeration.....	1,148
Antwerp agglomeration.....	833
Liège agglomeration.....	642
Ghent agglomeration.....	413
Malines agglomeration.....	256

2. *Percentage distribution of occupations by sex (1930) :*

	Men		Women	
	Number	Percentage	Number	Percentage
Agriculture and fishery	856	1.2	220	0.6
Industry	34,548	50.3	11,972	31.0
Commerce	20,281	29.6	12,166	31.5
Liberal professions	4,056	5.9	2,257	5.8
Public service	4,847	7.1	683	1.8
Domestic service, hotels	2,924	4.3	11,021	28.6
Undefined	1,103	1.6	261	0.7
Total	68,615	100.0	38,580	100.0

3. *Number of women engaged in gainful occupations per 100 men (1930) : 56.2.*4. *Female domestic servants per 1,000 population (1930) : 55.*5. *Female industrial labourers per 100 male industrial labourers (1930) 36.2*6. *Female employers (all occupations) per 100 male employers (1930) : 36.9.*7. *Number of women employed in public service per 100 men (1930) : 14.*8. *Distribution of occupied persons according to their position in the profession (1930) :*

	Men	Women
Employers	22.5	14.9
Employees	18.0	16.9
Labourers	48.5	39.9
Assisting ¹	1.6	7.4
Public service	6.1	1.7
Servants	3.3	28.2
Total	100.0	100.0

9. *Percentage of employers in total number of workers of both sexes (1930) :*

Industry.....	11.5
Commerce	36.4

10. *Persons recorded by the public assistance service of the city as having been unemployed for over a year per 100 wage-earners (1935) : 1.1.*¹ Mostly members of the family assisting in the work.

IV. CULTURAL LEVEL.

The boundary between the Flemish and the French languages runs some distance to the south of Brussels, but the urban agglomeration is bilingual with French predominating. In the city proper, 62% spoke French most frequently, 35% Flemish most frequently, but 48% spoke both languages. Only 13% of the population understood but Flemish (1930).

Illiteracy has not disappeared altogether. In Brussels City and Schaerbeek, 5.3% of the inhabitants over 7 years of age were returned as illiterate at the census of 1930. The proportion of illiterates ranged from 1% at the ages 15-20 to 13% at ages over 60.

Primary school attendance is fairly well enforced from 6 to 14, but control, especially as far as hygiene is concerned, is complicated by the fact that there are two school organisations, the public schools and the denominational schools. There were 11,820 pupils in the public primary schools, 1935/36, and probably about 8,000 in the denominational schools.

Pupils in the State and City middle schools numbered 4,172 and in higher educational institutions 2,745. It is not known how many of these were from outside the city limits, so that the exact rates of school attendance over 14 years of age cannot be established.

Professional and artistic education is abundantly provided for, as well as special evening courses. The educational level is therefore undoubtedly high in spite of difficulties from the dual system of denominational and non-denominational schools.

Prostitution was officially abolished in the city in 1924 and no new inscriptions are made. Taverns resembling closely disorderly houses are, however, tolerated and are to some extent under medical supervision.

INDICES TO CHAPTER A, IV.

1. *Languages spoken* (1930) :

	Percentage
French most frequently.....	62.3
Flemish most frequently.....	34.7
Both equally	47.9

2. *Percentage of illiterates in the communes of Brussels and Schaerbeek (1930) :*

Ages	Percentage
7-15	2.75
15-21	0.97
21-60	4.66
60 and over	13.04
Total 7 and over	5.31

V. HOUSING.

The number of dwelling-houses in the City of Brussels increased by 5.8% from 1920 to 1930, while the population decreased by 1.3%. The housing situation must thus have improved during this period, the more so as the new houses were undoubtedly better on the average than the old ones that were demolished. The same is true for the whole of the urban agglomeration, as the number of dwelling-houses there increased by 19.1% during these ten years, while the population increased only by 9.9%.

The ancient style of dwelling-house is rather small and generally houses only a few families. The average number of families per house was 2.8 in 1930. Two-, three- and four-roomed apartments were most numerous. Apartments of five rooms or more made up 27% of the total in the whole built-up area. In these large apartments there is very little overcrowding. Overcrowding is most serious in the one- and two-roomed apartments, which together made up 35.5% of the total. Many of these very small apartments which housed 26.4% of the population are probably not very satisfactory, but the distribution of apartments in relation to the population is nevertheless better than in most French and many other continental towns. In Brussels, 26.2% of the population lived with more than one person per room, which cannot be considered satisfactory, but the corresponding percentage for Paris is 42.3.

An unsatisfactory element in Brussels housing is the frequency of basement apartments, many of which have the top of their windows only a few inches over the street-level. No statistics are available concerning this form of accommodation.

It is naturally in certain parts of the old town that housing conditions are the least favourable. In 1920, there were here 156 blind alleys, some of them so narrow that one could touch both

sides with outstretched arms. Some of these have since disappeared, and demolition is carried on actively in the worst areas. In 1935, 131 houses were pulled down and 272 new ones constructed, giving an incidence of clearance of 4.7 per 1,000 houses and of new construction of 9.7 per 1,000. This must be considered satisfactory, the more so as the demolition of old houses has been added to by the work on the railway connection through the old town.

It might be considered whether at least a part of the low basement apartments could not be condemned as unfit for habitation even though the house otherwise remains inhabited.

INDICES TO CHAPTER A, V.

1. Increase of the number of houses in Brussels from 1920 to 1930 :

	City	Agglomeration
Houses	5.8	19.1
Population	-1.3	9.9

2. Number of families per house (1930) :

City	2.8
Urban area	2.5

3. Number of inhabitants per house (1930) :

City	7.2
Urban area	6.7

4. Houses demolished and new houses constructed per 1,000 houses existing in the city of Brussels (1935) :

Demolitions	4.7
New constructions	9.7

5. Distribution of apartments by size and by inhabitants living in each category in the Brussels urban area (1930) :

Number of rooms	Apartments	Inhabitants	Persons per room
1	12.38	6.66	1.46
2	23.11	19.75	1.16
3	21.71	21.29	0.89
4	15.79	17.06	0.73
5	8.93	10.34	0.63
6	5.43	6.48	0.54
7	3.29	4.11	0.49
8	2.36	3.09	0.44
9	1.65	2.30	0.42
10 and over	5.35	8.92	0.36
Total	100.00	100.00	0.70

6. Percentage of population living in apartments with more than one person per room (1930) : 26.2.

B. INDICES OF VITALITY AND HEALTH.

I. POPULATION.

The population of the metropolitan area of Brussels increased during the thirty years up to 1910 at an annual rate of about 2%. During the intercensal period 1910-1920, which included the war years, the annual rate of growth fell to about $\frac{1}{2}$ %, while from 1920 to 1930 it was 1%.

The growth of the population of the city proper including the annexed territories, on the other hand, came to a standstill as early as 1900 or thereabouts since which date there has been a continuous decrease. During recent years the population decrease has been accentuated in part by extensive demolition in old congested areas through which the railway connection between the north and the south stations is being prepared. The point of saturation seems to have been reached also in some of the older suburbs, and growth is now practically confined to the outer residential belt. The population of Ixelles has remained stationary since 1920, and that of Molenbeek-St. Jean, St. Gilles and St. Josse-ten-Noode is actually decreasing.

The composition of the population both of Brussels proper and of the remainder of the metropolitan area is remarkable for its heavy excess of inhabitants of female sex. At the census of 1930, there were 115 female inhabitants per 100 males, while the corresponding ratio for the Antwerp metropolitan area was only 107. The excess of female population is not particularly heavy in youth or in the age groups in which the men participated in the war, as is frequently the case in French towns. It exceeds the average only after the age of 50 and seems to be largely due, in these age groups, to the considerable excess of male mortality.

The female excess begins at the age of 15 to 20 (domestic servants), where it is of 8%, and increases steadily with the age.

Women of child-bearing age (15-45) made up 26.4% of the total population, which is only little above the normal for a large city. The causes of the abnormally low birth rate are certainly not to be found in the composition of the population.

The most striking feature of the age distribution of the population is the extremely small number of children. Children under 15 formed only 15.8% of the population in 1930, as compared with 29.4% in the United States and 30.6% in the Netherlands. Adequate protection of health in infancy and childhood and good schools would thus constitute a smaller financial burden *per caput* than in most other localities.

Children under 10 numbered in 1930 only 61.7% of the adults from 30 to 40. As some of the children will die before they grow up, there would be a decrease of over 40% from one generation to the next if there were no immigration. The children under 10 at the census of 1930 were born from 1921 to 1930, since when there has been a further fall of the birth rate of about 30%. In reality, the reproduction rate is therefore a good deal lower than would appear from the above figures. This is an exceptionally striking example of how a large city consumes the population of other districts in order to grow or even just to exist.

The City of Brussels possesses a population register at the Registrar's Office for births, deaths and changes of residence which is kept constantly up to date. It has to be corrected at each census, as all population registers must be, but it gives nevertheless a good indication of current population movements. There is a considerable amount of moving about between Brussels and the suburban communes which would make it impossible to keep track of the population without a population register. In 1935, 29,619 persons coming from other communes took up residence in Brussels and 27,731 residents left to live in other communes. Furthermore, 36,581 persons changed address within the city limits. Nearly half of the population thus changed domicile within a year. During the years 1931-1935, the net annual rate of emigration was 1.47 per 1,000 population, that of natural decrease 3.75 per 1,000, giving a total annual population decrease of 5.22 per 1,000. It is thus seen that the low birth rate is responsible for nearly three-fourths of the population decrease.

This is also reflected in a diminution of the size of the households. The average household was found at the census of 1930 to be 2.6 persons as against 3.1 in 1910 and 3.6 in 1890. The average was about the same for the whole metropolitan district—2.66 in 1930—but there are considerable differences between the various

communes, the smallest average household being of 2.2 persons in St. Josse-ten-Noode, the largest of 3.4 in Woluwe-St. Pierre. The "average household" of Antwerp was of 3.1 or the same as that of Brussels in 1910.

INDICES TO CHAPTER B, I.

1. *Resident population* (December 31st, 1936) :

City proper (from population register)	193,481
Fifteen suburban communes (estimate)	722,794
Total, metropolitan area	916,275

2. *Growth of the population* :

(a) Increase or decrease of population :

Years	Brussels City ¹	Annual increase per 1,000 from previous census	Entire metro- politan area ¹	Annual increase per 1,000 from previous census
1890	205,096	11.9	514,013	19.0
1900	218,623	6.6	617,466	20.1
1910	218,969	0.2	748,654	21.3
1920	203,058	-7.3	790,957	5.7
1930	200,433	-1.3	869,281	9.9
1936	193,481	-5.9	916,275	9.0

(b) Migration and natural increase of population, city of Brussels only (1931-1935) :

	Actual number	Annual rate per 1,000 population
Net emigration	1,459	1.47
Natural decrease	3,708	3.75
Actual decrease	5,167	5.22

3. *Age and sex distribution of the population of the City of Brussels* (1930) :

Age	Males	Females	Total	Female population per 100 males
Under 5	2.56	2.57	5.13	100
5-14	5.31	5.34	10.65	100
15-29	11.41	12.44	23.85	109
30-49	15.87	18.17	34.04	115
50-69	9.73	12.02	21.75	123
70 and over	1.64	2.94	4.58	179
Total	46.52	53.48	100.00	115

¹ Population for areas as established after the annexations of 1921.

4. *Percentage of women of child-bearing age (15-45), City of Brussels (1930) :*
26.4.

5. *Percentage of children under 15 (1930) :* 15.8.

6. *Children under 10 per 100 adults of ages 30 to 40 (1930) :* 61.7.

7. *Number of persons per household :*

	1890	1900	1910	1920	1930
City proper	3.6	3.4	3.1	2.8	2.6
Metropolitan area	3.8	3.4	3.1	2.9	2.7

II. NATALITY.

Vital statistics of cities always present considerable difficulties in dealing with the question of non-residents, notably in regard to the proper classification of births occurring in maternity homes and deaths in hospitals. Where the city is only a part of a much larger urban area, as in the case of Brussels, this difficulty becomes very serious and its correct solution indispensable.

Statistics of births and deaths of non-residents occurring in the territory of the City of Brussels can be obtained in full detail from the City Health Service. This service has, however, no record of the births and deaths of Brussels residents occurring in other communes and this lacuna invalidates the data to a considerable extent. Records of such births and deaths are available in the Registrar's Office of the City of Brussels, but they contain no details as to sex, age, cause of death, etc. A fully corrected live-birth rate and general death rate can therefore be obtained, but all other statistics will be uncorrected and thus give little more than rough indications.

The importance of the problem is shown by the fact that 28.2% of the live births and 32.2% of the deaths occurring in the territory of the City of Brussels in 1935 were of non-residents. The number of births to mothers resident in Brussels occurring outside the city territory was approximately equal to that of births by non-resident mothers occurring in Brussels. The deaths of Brussels residents occurring outside the city numbered, on the other hand, only 37.7% of the deaths of non-residents occurring in the city. In order to obtain the full benefit of the considerable amount of work performed on vital statistics in the City of Brussels, it is indispensable that an arrangement should be made by which a complete correction for residence can be made in all the tables.

The live-birth rate duly corrected for residence was 16.4 per 1,000 population in 1921. It remained above 15 up to 1924 and above 12 up to 1931, since when it sank as low as 9.4 in 1936. Very few cities throughout the world show a lower birth rate. That of Antwerp is 11.2 and that of Ghent 14.4.

The corrected live-birth rate based upon the female population from 15 to 44 was 35.8 per 1,000 in 1936 as compared with 52.6 in New Haven, Conn., although this latter rate is fairly low for an American city.

In Belgium, infants dying before being registered are reported as still-births. A correction must therefore also be made for this source of error if international comparisons are desired. In 1936, thirty-three infants known to have lived were reported as still-births in the City of Brussels. The correction is not very important for the live-birth rate, because it increases it by only 1.8%. It has been made in the rates given above. The correction is of extreme importance, however, when dealing with the still-birth or infant mortality rate, as it diminishes the former by a third and augments the latter by 17%.

The birth rate is considerably lower in the well-to-do sections than elsewhere. The rate can be established by administrative districts only for residents born in the city proper, and results are therefore only approximate. It is clear, nevertheless, that they are much below the average in the wealthy Quartier Léopold to the east of the old town and in the southern extension along the Avenue Louise. The birth rate is below the average also in the northern half of the old town as well as in the not very desirable district behind the North Station. It is somewhat above the average in the populous southern half of the old town and in Laeken and highest in the outer part of the northern extension. Nevertheless, the rate cannot be said to be even moderately high anywhere.

The problem of the differential birth rate is important in most large cities, although in some, such as Stockholm, the difference between the social classes seems to be disappearing. In Brussels, this difference is evidently very considerable and adds to the urgency of adequate measures for the protection of infant life in classes where this cannot be held to be assured through favourable conditions of life. In 1935, 1,153 infants, or 61.4% of the total born, were classified by the City Health Service as born to families of

the poor. The definition of such families is of necessity somewhat vague and based largely upon the living quarters, but even superficial observation makes it obvious that children are much less numerous in the well-to-do than in the poor districts.

The proportion of illegitimate births is rather high. It was 15.3% in 1933-1935. The corresponding ratio was 7.5 for Antwerp and 5.5 for Ghent. For the whole Kingdom it was 3.1. The incidence of illegitimate births is lower—7.9%—in the suburban area than in the city proper. It may be added that the above ratio for the City of Brussels has been corrected for births of non-residents in maternity homes.

The marriage rate was 8.5 per 1,000 inhabitants in 1935, which is about normal for a large city.

INDICES TO CHAPTER B, II.

1. *Marriages* :

Rate per 1,000 inhabitants (1935) : 8.5.

2. *Birth rate* :

(a) Live births per 1,000 inhabitants fully corrected for residence :

1921-1925	15.0
1926-1930	12.3
1931-1935	10.6
1936	9.4

(b) Decrease of birth rate in ten years (from 1921-1925 to 1931-1935) : 29.3%.

(c) Live births per 1,000 women, 15-44 (1936) : 35.8.

3. *Resident live births (not including those born outside of city limits) per 1,000 inhabitants by administrative districts (1933-1935) :*

District	
I. (Old Town)	9.0
II. (Old Town)	9.0
III. (Old Town)	6.7
IV. (Old Town)	4.9
V. (Quartier Léopold)	3.9
VI. (Southern Extension)	4.2
VII. (North Station District)	6.3
VIII. (Northern Extension)	9.3
IX. (Northern Extension)	10.4
X. (Northern Extension)	12.7
Total	7.4

4. *Proportion of infants classified as born to parents of the poor classes (1935) :* 61.4%.

5. *Proportion of illegitimate resident live births (1933-1935) :* 15.3%.

III. STILL-BIRTHS, INFANT MORTALITY AND MATERNAL MORTALITY.

Statistics of still-births and infant deaths cannot be obtained fully corrected for residence. For still-births, the only data available relate to those registered on the city territory. This will cause no serious error, however, so long as the still-births are measured in relation to the total number of births, which is the proper way as they are essentially ante-natal deaths. The still-birth rate based on the population is of little interest.

Still-births are counted as such from the sixth month of pregnancy. Previous to that time, they are considered abortions, the registration of which is also compulsory, but the reporting is naturally very incomplete. The abortions reported amount to only about one-fourth of the real still-births. A birth is considered a still-birth if the child was dead when registered (Decree of 1806) and children born alive but "presented without life" must be deducted from the records in order to obtain the real still-birth rate. This correction can be made fairly exactly, as a distinction is made between still-births dead before, during and after delivery. If this distinction is exactly made, the two first groups should be real still-births, the third infant deaths. During the three years 1933-1935, 169 still-births were reported to be dead before and 97 during delivery, while 45 reported as still-births were, in reality, born alive.

The corrected still-birth rate for the City of Brussels was 39.2 per 1,000 total births during the three years 1934-1936. This is not an excessive rate, although it is somewhat higher than for the whole of Belgium, where the corresponding rate was 32.5. The still-birth rate for the United States was 34.9 and that of the City of New Haven 28 per 1,000 births.

There has been an appreciable decrease of the still-birth rate during the last ten years. The rate was 47.4 per 1,000 births in 1924-1926 and the decrease has thus been 17.3%.

The still-birth rate was 37.3 per 1,000 for legitimate and 53.2 per 1,000 for illegitimate births in 1933-1935. The excess of the illegitimate over the legitimate rate was 42.6%.

So far as the infant mortality under one month is concerned, it is preferable to use the deaths and births including non-residents, not only because the figures for the "children presented without life" are available only for both combined but also because the majority of the deaths under one month occur during the first week or two of life, when the infants are still in the maternity homes where they were born. The neo-natal mortality thus obtained is consequently as close to reality as it can be under the present registration system, and any errors will be negligible.

The infant mortality under one month thus computed was 35 per 1,000 live births during the three years 1934-1936. The corresponding rate was 36.3 in 1924-1926, and the decrease has accordingly been only 3.6% in ten years. This rate cannot be considered excessive, however, and it differs but little from that of the whole of Belgium (32) or of the United States (33.5).

All uncertainty in regard to the distinction between still-births and infant deaths may be eliminated by combining the still-birth rate and the neo-natal death rate. This "birth mortality rate" was 74.2 per 1,000 in 1934-1936 as compared with 83.7 in 1924-1926. The decrease in ten years was thus 11.4%. This is not much, but the rate cannot be said to be excessive. There is, however, still room for improvement, as a comparison, for example, with Dutch or Swiss towns will show. This rate should give some indication of the state of the obstetrical organisation and of pre-natal care and is of interest particularly in this connection.

There is no significant difference between the neo-natal mortality of legitimate and illegitimate infants. In 1933-1935, the former was 29.6 and the latter 28.4 per 1,000 live births. The favourable rate of the illegitimate infants in this first month of life is undoubtedly due to the fact that about 90% of the illegitimate births occur in the Public Assistance maternity home and that the infants are therefore properly cared for during the first ten or twelve days of their existence. Bad care to which they may be exposed later will show its effects only in the mortality of subsequent months.

The question of correction for residence becomes much more difficult after the first month of life. It may be assumed that practically all the infants of Brussels residents born in maternity homes outside the limits have returned home in course of the first month of life and that most of those born to non-resident mothers

in the maternity homes of the city have left for their communes of residence. Consequently, it seems preferable to use the live births corrected by the Registrar's office as a basis for the later infant mortality rate.

The change in the aspect of the residence question after the first month of life is seen from the fact that, of the infant deaths under one month occurring on Brussels City territory, 48.2% were of non-residents (1934-1936) while the corresponding percentage for infant deaths from 1 to 12 months was only 16.9. If only the resident infant deaths were included, the later infant mortality would be 65.5 per 1,000 live births, while, if the non-resident deaths were added, it would be 78.9. The former figure is certainly too low, as there will undoubtedly be some infants of residents dying outside the city limits. The latter rate is likely to be too high, as these infants are probably less numerous than those of non-residents dying in city hospitals. It is probable, therefore, that the true infant death rate from 1 to 12 months of age of the City of Brussels was somewhere between 70 and 75 in 1934-1936. This is a high rate which compares unfavourably with the whole of Belgium, where the corresponding rate was 54.5 in 1933-1935, and still more so with countries where the reduction of infant mortality has been actively pursued (the United States, 24.1 ; Dutch towns over 100,000 inhabitants, 19.6).

The reconstruction of the true total infant mortality from the above rates for neo-natal and later infant mortality, shows that it cannot have been less than 105 per 1,000 live births in 1934-1936. Equally high or higher infant death rates in large cities are found only at Quebec in North America and in Europe only in cities of Poland, Hungary, the Balkans and farther east. The infant death rate for The Hague was only 31 per 1,000 during the same years and that of Oslo 26. This unfavourable situation of Brussels is entirely due, as shown above, to the later infant mortality and not to the neo-natal mortality. The high infant mortality is all the more noteworthy as the natality is exceptionally low.

There has been some improvement during the last ten years, but it might have been greater. In 1924-1926, the later infant mortality was 85.2 per 1,000 live births excluding non-resident deaths and 101.7 if including them. There has thus been a reduction of 23% since then, but the birth rate fell by 30% during the

same period. The reduction of infant mortality as a whole during this period was 17%.

Considering only the resident deaths, the later infant mortality was (1933-1935) 93.8 per 1,000 live births for the illegitimate and 64.2 per 1,000 for legitimate births, which gives an excess of 46% of the mortality of the illegitimate over the legitimate infants at the ages of 1 to 12 months. This is about the same excess as was found for the still-births.

The infant mortality varies greatly from one part of the city to another, as might be expected. Full correction for residence could not be made by administrative districts, and the infants born alive but "presented without life" could not be included in the infant deaths. The rates relate therefore to total infant mortality of resident deaths based on births to Brussels residents. Nevertheless, they bring out striking differences between the poorer and the more well-to-do districts. The infant mortality rates thus established vary from 54-67 in the Quartier Léopold, Laeken and the southern extension to 150-173 per 1,000 live births in Districts I and II (southern half of the old town) and VII around the North Station. In the other districts, they vary from 91 to 109. The infant mortality is thus roughly three times as high in the worst districts as in the best. In view of the fact that the natality is much higher in the poor districts than in the well-to-do areas, it is evident that the causes of the high infant mortality of Brussels must be looked for primarily in social conditions.

Statistics of causes of infant mortality can be obtained only for deaths of residents occurring in the territory of the City of Brussels.

Rates have been worked out—under 1 month on a basis of live births of residents occurring in the city territory, from 1-12 months on a basis of resident live births fully corrected by inclusion of resident births occurring outside the city territory. In both cases, the rates are probably a little too low, but they represent undoubtedly the nearest approach to reality which can be effected.

The causes of death under one month of age call for little comment. The mortality from premature birth, malformation, congenital debility and other causes peculiar to the earliest infancy is quite moderate. There are, however, even in this group some deaths from diarrhoea and broncho-pneumonia which might have been avoided.

The mortality from 1 to 12 months of age, on the other hand, presents a heavy loss of life due to preventable causes and notably diarrhœa (19.3 per 1,000), broncho-pneumonia (13.4) and convulsions. The mortality from measles and whooping-cough is also heavy and may, as usual, be attributed largely to avoidable complications. These statistics show that the high mortality at this age could be greatly reduced simply by proper care and nutrition. Comparison with the statistics for New Haven shows similarity in the causes of death under one month but radically different conditions for the later infant mortality. Spot maps of deaths from infant diarrhœa published annually by the city health service show, as might be expected, that these deaths are concentrated in the poorer districts, while there are none in the well-to-do districts.

Statistics are available for maternal deaths occurring in the city territory and can be divided into deaths of residents and those of non-residents. As the corresponding number of births including still-births can be obtained, the rates for each of the two groups should be exact.

These two groups have been kept separate as the incidence of mortality seems to be quite different, in fact surprisingly different.

The maternal death rate of residents was 3.1 per 1,000 births in 1931-1935 which is a wholly favourable rate and distinctly lower than those prevailing in the United States. Puerperal septicæmia, however, made up half of it, and this could probably be reduced.

The maternal death rate of non-residents, on the other hand, was 10.9 per 1,000 births, which is an abnormally high incidence. Puerperal septicæmia caused 2.8 per 1,000 births and puerperal hæmorrhages 2, which is excessive. The number of deaths (3.9 per 1,000) attributed to ectopic gestation seems abnormally high, and one wonders if this is not simply induced abortion thus described for legal reasons. If so, it is possible that one half or more of this excessive maternal mortality was due to cases of abortion coming into hospital in a desperate condition. It would seem that this point should be cleared up since the effect might be to reduce the maternal mortality rate, a rate which would be favourable were it not for these oddly described non-resident deaths.

INDICES TO CHAPTER B, III.

1. *Still-births per 1,000 total births (1934-1936) : 39.2.*
2. *Decrease of still-birth rate in ten years (1924-1926 to 1934-1936) : 17.3%.*
3. *Still-births per 1,000 total births by legitimacy (1933-1935) :*
 - (a) Legitimate : 37.3.
 - (b) Illegitimate : 53.2.
 - (c) Excess of illegitimate over legitimate rate : 42.6%.
4. *Neo-natal mortality per 1,000 live births (1934-1936) : 65.*
5. *Decrease of neo-natal mortality in ten years (1924-1926 to 1934-1936) : 3.6%.*
6. *"Birth mortality" (still-births plus neo-natal mortality) (1934-1936) : 74.2.*
7. *Neo-natal mortality per 1,000 live births by legitimacy (1933-1935) :*
 - (a) Legitimate : 29.6.
 - (b) Illegitimate : 28.4.
8. *Later infant mortality (1-12 months) per 1,000 live births (1934-1936) :*
 - (a) Excluding non-residents : 65.5.
 - (b) Including non-residents : 78.9.
9. *Decrease of later infant mortality in ten years (1924-1926 to 1934-1936) : 23.1%.*
10. *Decrease of whole infant mortality in ten years (same period) : 17.3%.*
11. *Later infant mortality per 1,000 live births by legitimacy (resident deaths only) (1933-1935) :*
 - (a) Legitimate : 64.2.
 - (b) Illegitimate : 93.8.
 - (c) Excess of illegitimate over legitimate rate : 46.1%.
12. *Infant mortality (resident births and deaths without children born alive but presented without life) per 1,000 live births by administrative districts (1931-1935) :*

District	
I.	161
II.	150
III.	103
IV.	91
V.	67
VI.	54
VII.	173
VIII.	64
IX. and X.	109
Total	111

13. *Deaths under one month (residents only) from principal causes per 1,000 live births (1933-1935) :*

Causes	Brussels	New Haven
Epidemic diseases	0.0	0.3
Syphilis	0.5	0.5
Broncho-pneumonia	1.1	0.6
Diarrhœa	2.7	0.0
Convulsions	2.3	—
Premature births, debility, etc.	18.0	24.8
Other known causes	1.6	1.8
Unknown	3.2	0.2
Total	29.4	28.3

14. *Infant deaths from 1 to 12 months (residents only) from principal causes per 1,000 live births (including those born outside of city) (1933-1935) :*

Causes	Brussels	New Haven
Measles	4.4	1.1
Whooping-cough	3.2	
Other epidemic diseases	1.4	
Tuberculosis	1.0	0.2
Syphilis	1.2	0.2
Broncho-pneumonia	13.4	3.3
Other respiratory diseases	5.1	—
Diarrhœa	19.3	1.4
Convulsions	10.9	—
Congenital debility, etc.	3.9	4.0
Other known causes	3.9	3.4
Unknown	1.0	0.0
Total	68.7	13.5

15. *Maternal mortality by causes per 1,000 total births of residents and non-residents occurring on the city territory (1931-1935) :*

Causes	Residents	Non-residents
Abortion	0.5	0.6
Ectopic gestation	0.6	3.9
<i>Placenta prævia</i> and puerperal hæmorrhage.	0.1	2.0
Puerperal septicæmia	1.4	2.8
Albuminuria and other toxæmias	0.2	0.3
Other accidents of childbirth	0.2	1.4
Total	3.1	10.9

IV. GENERAL MORTALITY AND CAUSES OF DEATH.

The general death rate has exceeded the birth rate every year since 1924, although the age constitution favours a low death rate.

In 1936, the death rate fully corrected for residence and with inclusion of live-born infants "presented without life" was 14.3 per 1,000 population, or 52% higher than the live-birth rate. The general death rate averaged 13.4 for the years 1934-1936. Ten years earlier (1924-1926) it was 15.2, and the decrease has thus been 11.8%.

The distribution by sex and age can be obtained only for deaths occurring on the city territory. If, of these deaths, those of non-residents were included, the death rates would become much too high; if, on the other hand, only those of residents were included, they would become too low. The procedure followed to obtain as close an approximation as possible to the real specific death rates by age and sex has therefore been to take the deaths of residents occurring in the city territory and to add to them those occurring outside the city limits, assuming that their age and sex distribution are the same. For the years 1931-1935, this increases the resident deaths occurring within the city limits by 13.365%. It is entirely possible that the age distribution of the deaths occurring outside the city is not quite the same as that of those occurring in the city, but the error is probably not very large, and it is the best approximation which can be obtained under the circumstances. The population in the second year of life is estimated from births and infants deaths during the previous year. No distinction of sexes has been made under 15 years of age, as this is of little interest in connection with health conditions.

On the basis of these estimates, the specific death rate is found to be 25.5 per 1,000 for the second year of life and 4.3 per 1,000 for the ages 2 to 5, during the five years 1931-1935. This is a high rate for the second year of life. It would have been very high even if it had not been increased by 13% for the deaths occurring outside the city limits. It is about twice as high as for the whole of Belgium, where the corresponding rate was 12.4 for the years 1933-1935. The death rate in the second year of life was 8.6 per 1,000 in

Dutch cities over 100,000 inhabitants (1930-1932) and 9.8 in Copenhagen (1931-1933). The mortality during this year of life is not so excessive, however, as that of the later infant mortality, and similar rates were found ten years ago in large English cities. Improvement seems to have been rather slight at this age, except when compared to quite unfavourable years, such as 1921, 1926 and 1927.

The specific death rate of the ages 2 to 5 was 4.3 per 1,000. This is a more favourable rate, which does not exceed that prevailing in large English cities, although there is still room for improvement.

The combined death rate for the ages 1 to 5 was 9 per 1,000, which is twice that of the United States (4.5 in 1934) and about four times that of New Haven (2.2 in 1932-1934). It is lower than the rates prevailing in Southern, East Central and Eastern Europe, but distinctly higher than the rates of Northern and Central Europe.

The mortality of school age (the groups 5 to 15), on the other hand, was only 1.6 per 1,000, which indicates conditions similar to those of the Netherlands, the Scandinavian countries, Switzerland, Germany and the United States. The other European countries have a higher death rate at this period of life.

It appears from this analysis, therefore, that efforts at saving human life in Brussels ought to be directed especially toward an amelioration of the later infant mortality and the mortality of pre-school age, notably the second year of life.

The specific death rates of the ages from 15 to 30 are similar to those of countries with advanced health conditions and fully as favourable as in the United States. This satisfactory situation continues throughout life for the female sex, but, after the age of 30, there is a very marked excess of male mortality. This excess over the corresponding female death rate is 51.5% in the age-groups 30 to 50 and rises to 92.1% at the ages of 50 to 60, after which it diminishes. This large excess of the male mortality cannot be due to a faulty distribution by age of the deaths of Brussels residents occurring outside the city territory. It does not exist previous to the age of 30, and there is no reason why women of middle and advanced ages should be more liable to die out of town than men.

It is not uncommonly observed that city life has a more injurious effect upon men than upon women once youth is passed. This is commonly attributed to the frequently unhealthy nature of the

work of men. In Brussels proper, there are, however, no large industries which might be particularly injurious to health, and workshops and factories are closely inspected. The excess mortality is nevertheless abnormally heavy, and there must be reasons for this. We shall not venture to suggest any such possible reasons, but a thorough analysis of this situation might furnish useful indications for future health work.

There seems to have been but little change in the adult death rate in recent years. Including only resident deaths occurring in the city territory, the death rate of ages 15 and over was 13.1 per 1,000 in 1930-1932 and 12.9 in 1933-1935. These were normal years without serious influenza outbreaks which could influence the rates materially.

Statistics of causes of death by age and sex can be obtained only for deaths of residents occurring on the territory of the City of Brussels. As it is not unlikely that deaths of residents occurring in the city territory may be due particularly to certain diseases or accidents which are more likely to entail hospital treatment than others, it seems preferable not to make estimates as to the causes of these deaths, but to give the death rates for those occurring in the city only. It should be remembered that most of these must be lower than the death rates fully corrected for residence would be.

The causes of death in the second year of life are clearly a continuation of those of the later infant mortality less those peculiar to early infancy. The rates are naturally lower on the whole than during the first year of life, but there is still a very high mortality from broncho-pneumonia and from diarrhoea, diseases which are certainly preventable to a large extent. There is also a high mortality from other respiratory diseases and from the current epidemic diseases of childhood.

During the following three years of life up to the age of 5, diarrhoea disappears as a cause of death and the importance of broncho-pneumonia and other respiratory diseases is greatly diminished. Measles and whooping-cough also cause fewer deaths, but diphtheria has become the most important single cause of death. This is of particular interest, because immunisation against diphtheria is actively pursued only when children enter a school or kindergarten and not during the second year of life, when protection begins to become necessary.

The causes of death at the ages 5-14 call for little comment. Diphtheria, as well as the other epidemic diseases of childhood, has lost its importance as a cause of death, and the same is the case with broncho-pneumonia. There are still some deaths from tuberculosis, but less than at pre-school ages. Death seems at this period of life to be more or less accidental and spread over a great many causes, none of which is in any way predominant. The low diphtheria mortality in comparison with that of children from 1 to 5 years is noteworthy.

When analysing the causes of death of adults, it should be kept in mind that at least some of the rates are certainly too low through the deaths of residents occurring outside the city territory not being included. This seems to be the case notably with deaths from accidents. It is true that there are no big industries and that traffic accidents are less common than in many other towns; nevertheless, the accident death rate shown below is certainly too good to be true for a large town.

The female death rates are favourable throughout life and especially at the ages 50 to 70. None of the causes of death can be said to be more common than might be expected. The female rates are therefore useful as a basis of comparison for the male rates, the more so as errors due to residence are probably about the same for the two sexes.

The only causes of death showing a female excess are cancer and diabetes, and this is normal. The male excess of deaths from accidents, suicide and cirrhosis of the liver is equally normal and calls for no comment. It is not normal, on the other hand, that the male tuberculosis death rate should be three times the female rate at the ages 30 to 50 and five times at the ages 50 to 70. This is the most striking feature of the male excess mortality and calls for further investigation. Tuberculosis alone is not capable, however, of causing the entire excess mortality that we find for males. It is equally worthy of attention that the male death rate from nephritis is more than twice as high as the female rate after the age of 50. There is also a heavy male excess mortality from pneumonia, heart disease and cerebral hæmorrhage at the ages from 30 to 70, which seems to be rather abnormal. It would thus appear that the trouble comes not from conditions affecting the lungs directly, such as dusty industries, but rather from causes injurious to the

organism in general and to the blood vessels and related organs in particular. These conditions have no effect upon malignant growths or metabolism as influenced by diabetes. Whatever they are, they seem to be peculiar to the male sex and should be looked for in fields where the life of men, especially between 30 and 70, differs from that of women.

The unusually large excess of male suicides is also striking. Suicide is everywhere more frequent among men than among women, but it is certainly unusual to see male rates as much as five times the female rates after the age of fifty. These rates are of interest also in that they dispel any doubts that might remain as to the influence of the question of residence, for it is not to be supposed that women are particularly prone to go out of town to commit suicide. The female suicide rate was normal, the male rate very high after the age of thirty. The parallelism of the male excess mortality from suicide and from tuberculosis up to the age of 70 is striking.

INDICES TO CHAPTER B, IV.

1. *General death rate corrected for residence per 1,000 resident inhabitants :*

1924-1926 : 15.2.

1934-1936 : 13.4.

2. *Decrease of general death rate in ten years : 11.8%.*

3. *Specific death rates in childhood per 1,000 children of each age (1931-1935) :*

1-2 years	25.5
2-5 years	4.3
5-15 years	1.6
15-20 years	1.7

4. *Specific death rates of adults by sex and age per 1,000 population, and percentage excess of male over female mortality at each age (1931-1935) :*

Ages	Males	Females	Percentage of male excess
20-30	2.7	2.6	3.8
30-40	5.0	3.3	51.5
40-50	9.7	5.7	70.2
50-60	21.9	11.4	92.1
60-70	45.8	27.5	66.5
70 and over	122.1	103.7	17.7

5. *Principal causes of death in childhood occurring among residents of Brussels on the city territory per 100,000 inhabitants of these ages (1933-1935) :*

	1-2 years	2-5 years	5-15 years
Measles	290.9	37.7	0.0
Whooping-cough	145.5	16.2	0.0
Diphtheria	36.4	64.6	1.6
Scarlet fever	0.0	21.5	1.6
Tuberculosis	72.7	48.5	17.5
Simple meningitis	90.9	48.5	3.2
Broncho-pneumonia	600.0	26.9	0.0
Other respiratory diseases	200.0	26.9	8.0
Diarrhoea	509.1	0.0	0.0
Appendicitis	0.0	21.5	11.2
Accidents	0.0	5.4	12.8
Other causes	290.9	48.5	57.4
Unknown	0.0	0.0	0.0
Total	2,236.4	366.2	113.2

6. *Principal causes of death among adults by sex and age occurring among residents of Brussels on the city territory per 100,000 inhabitants of each sex and age (1933-1935) :*

(a) Males :	15-30	30-50	50-70	70 and over	15 and over (total)
Tuberculosis	80.6	197.5	276.6	166.2	181.6
Cancer	3.0	22.5	308.1	934.7	127.4
Diabetes	1.5	4.3	36.8	93.5	15.4
Cerebral hæmorrhage, embolism and thrombosis ..	3.0	21.5	255.6	1,474.7	136.6
Diseases of the heart, pericardium, etc.	9.0	88.0	617.9	3,053.3	323.9
Influenza, bronchitis and pneumonia	9.0	53.7	187.3	706.2	101.8
Cirrhosis of liver	0.0	17.2	68.3	0.0	24.2
Nephritis	3.0	16.1	129.5	623.1	66.5
Suicide	14.9	34.3	98.0	207.7	52.0
Accidents	13.4	11.8	38.5	72.7	21.6
Senility	0.0	0.0	49.0	1,817.4	89.5
Other causes	50.7	135.2	518.1	1,703.2	273.2
Unknown	1.5	23.6	110.3	166.2	44.9
Total	189.6	625.7	2,694.0	11,018.9	1,458.6

HEALTH INDICES

(b) Females :	15-30	30-50	50-70	70 and over	15 and over (total)
Tuberculosis	68.5	65.6	55.3	133.2	68.0
Cancer	6.8	48.7	290.5	706.8	143.5
Diabetes	0.0	1.9	46.8	121.7	20.9
Cerebral hæmorrhage, embolism and thrombosis ..	0.0	17.8	164.4	1,089.1	120.7
Diseases of the heart, pericardium, etc.	20.5	67.5	388.2	2,635.8	305.0
Influenza, bronchitis and pneumonia	9.6	26.2	100.6	712.5	85.6
Cirrhosis of liver	0.0	8.4	9.9	40.6	8.6
Nephritis	5.5	15.0	55.3	283.9	40.4
Suicide	9.6	10.3	19.8	40.6	14.6
Accidents	1.4	2.8	19.8	57.9	10.5
Senility	0.0	0.0	34.0	2,247.7	154.0
Other causes	53.4	113.4	277.7	1,141.2	206.7
Unknown	1.4	12.2	25.5	69.5	16.4
Total	176.6	389.9	1,487.8	9,280.5	1,194.9

7. *Percentage excess of male death rate from certain causes over corresponding female rate (1933-1935) :*

	15-30	30-50	50-70	70 and over	15 and over (total)
Tuberculosis	17.7	201.1	400.2	24.8	167.1
Cancer	-55.9	-53.8	6.1	32.2	-12.2
Cerebral hæmorrhage	—	20.8	55.5	35.4	13.2
Diseases of the heart	-56.1	30.4	59.2	15.8	5.9
Pneumonias, etc.	- 6.3	105.0	86.2	-0.9	18.9
Nephritis	-45.5	7.3	134.2	119.5	64.6
Suicide	55.2	233.0	394.9	411.6	256.2
All causes	7.4	60.5	81.1	18.7	22.1

V. MORBIDITY.

Very little information can be obtained concerning morbidity except from the notification of contagious diseases. The notification of tuberculosis cases is obviously quite incomplete and case records cannot be obtained from the various social insurance organisations.

Notification of contagious diseases is not compulsory for practising physicians, except for the quarantine diseases, which are practically unknown in Belgium. The notifications received by the Brussels Health Service came mostly from the hospitals and schools.

Practising physicians seemed to be in the habit of reporting only typhoid fever, diphtheria and scarlet fever. Judging from the case-mortality rates, the reporting of these three diseases seems to be fair. For the minor epidemic diseases, the reporting is probably of value only at school ages.

No case of smallpox has occurred since 1929, and typhus fever is unknown. The incidence of typhoid fever is low ; the case incidence was 0.5 per 10,000 inhabitants and the mortality 1.4 per 100,000 (1932-1936). The high case-mortality rate (29.8%) suggests that some cases may have escaped notification. Paratyphoid fevers seem to be rare ; only two cases were reported during the last five years. There seems to have been some improvement during the last ten years in respect of typhoid fever, as the resident death rate from this cause was 3.4 per 100,000 in 1922-1926. Both the case rate and the death rate have decreased by 58% during these ten years.

The reported incidence of diphtheria cases was 4.4 per 10,000 inhabitants during the same five years (1932-1936) and the death rate was 2.5 per 100,000, as compared with a case rate of 0.4 per 10,000 in New Haven. The reported case-mortality rate was 5.7%. There seems to have been no substantial progress in regard to diphtheria control during the last ten years, as the reported case incidence was 2.9 per 10,000 and the mortality 2.2 per 100,000 ten years ago (1922-1926) ; that is, considerably lower than it is now. The diphtheria immunisation in the schools has obviously given good results, as only 6.7% of the diphtheria cases were reported by the primary schools (1933-1935), while 22.1% of the scarlet fever cases were reported by these. Further reduction of the diphtheria incidence seems therefore to be dependent on early immunisation of pre-school children.

Both the incidence (11.1 per 10,000) and the case mortality rate (0.8%) of scarlet fever are the same as in New Haven. The disease is of common occurrence, but quite mild in type. The case rates for the minor epidemic diseases of childhood are of little interest as the reporting is incomplete ; they are prevalent as elsewhere. The high mortality caused by measles is worthy of mention, however, as it depends in the main upon avoidable complications. In Brussels, the measles mortality (1932-1936) was 24 per 10,000 children under 5, while the corresponding rate for New Haven was

only 1.8, although measles is as widespread in the latter town as it can be.

Poliomyelitis and the other epidemic diseases of the central nervous system are rare.

Notifications of tuberculosis cases amounted to only half of the deaths (507 cases and 1,046 deaths in 1932-1936). The number of cases attending the tuberculosis dispensary of the National Belgian League against Tuberculosis gives a better idea of the incidence of this disease. In 1936, 1,513 persons diagnosed as suffering from pulmonary tuberculosis were treated at this dispensary. The area served by this dispensary includes the old town and some of the adjoining territory toward St. Gilles, with probably about 200,000 inhabitants. The rate of active cases would thus be about 75 per 10,000 inhabitants, but this would naturally include only the poorer part of the population.

Venereal diseases are not notifiable, and no definite information is available concerning their incidence.

INDICES TO CHAPTER B, V.

1. Cases of epidemic diseases reported and case rates per 10,000 population (1932-1936) :

	Cases	Case rate per 10,000 population	Deaths	Death rate per 100,000 population
Typhoid fever	47	0.5	14	1.4
Paratyphoid fever	2	—	0	—
Diphtheria	435	4.4	25	2.5
Scarlet fever	1,096	11.1	9	0.9
Measles	2,556	26.0	120	12.2
Whooping-cough	781	7.9	42	4.3
Chicken-pox	1,366	13.9	0	—
Mumps	823	8.4	0	—
Poliomyelitis	14	0.1	0	—
Cerebro-spinal meningitis	0	—	9	0.9

Note.—Cases reported only from the Registrar's Office after death are not included as cases.

2. Reported case-mortality rate of certain epidemic diseases (1932-1936) :

	Percentage rate
Typhoid fever	29.8
Diphtheria	5.7
Scarlet fever	0.8
Measles	4.7
Whooping-cough	5.4

3. *Percentage increase or decrease in ten years of :*

	Case rate	Death rate
Typhoid fever	-57.5	-57.7
Diphtheria	+50.9	+16.5

VI. INSANITY AND ALCOHOLISM.

The responsibility for internment of the insane rests with the mayor and the council of aldermen (Collège des Bourgmestres et Echevins). This council ordered the seclusion of 427 persons on account of insanity in 1935, which gives an incidence of 21.9 per 10,000 inhabitants. It may be mentioned that internments for insanity in New Haven, Conn., numbered 11.3 per 10,000 population during the same year, but that they depend to a large extent upon the space available in the asylums for the insane and the general policy pursued in this respect. Direct comparisons therefore require caution. Forty-seven of these internments (2.4 per 10,000 population) were for alcoholism or drug habit. The corresponding rate for New Haven was 2.1 per 10,000, or substantially the same as the Brussels rate.

Another index of interest in connection with the abuse of alcohol is furnished by the convictions for public drunkenness by the police courts of the City of Brussels. In 1935, the police courts of the City of Brussels pronounced 327 convictions for this cause or 16.8 per 10,000 inhabitants ; 610 persons were arrested for drunkenness. International comparison of such rates are not warranted, however, so long as a special comparative study of procedures and definitions has not been made. Retail sale of distilled liquors by cafés, restaurants and other kinds of establishments is prohibited by law, while that of beer, wine and other fermented drinks is permitted. The consumption of beer is particularly high in Belgium.

INDICES TO CHAPTER B, VI.

1. *Internments of insane per 10,000 inhabitants (1935) : 21.9.*
2. *Internments of alcoholics and drug-addicts per 10,000 inhabitants (included above) : 2.4.*
3. *Convictions by police courts for public drunkenness per 10,000 inhabitants (1935) : 16.8.*

C. INDICES OF PUBLIC HEALTH ACTIVITY.

I. HEALTH PERSONNEL AND EXPENDITURE.

In 1936, the following were registered with the City Health Department as exercising a profession connected with health : 347 physicians, 92 dentists, 111 pharmacists and 30 midwives. No record was kept of the nurses. The number of physicians is ample for the needs (1.8 per 1,000 inhabitants) while that of the dentists (0.5 per 1,000 inhabitants) is lower than it would be for an American city of similar size. The number of midwives seems rather low, but it must be remembered that the birth rate is very low and that the majority of births occur in maternity homes.

The health department personnel differs entirely in its composition from that of the normal American city health department personnel. The Brussels Health Department has neither the tuberculosis nor the infant and maternity hygiene work under its control, and the school hygiene and the public health laboratory are also under other departments. The control of venereal disease is only partly under the health department. Its work lies largely in the field of general sanitation and includes, furthermore, most of the factory inspection and the sanitary control of prostitutes. Most of the essential basic activities of the American city health department are therefore outside the sphere of activity of the Brussels Health Department, the functions of which are based on entirely different conceptions.

The personnel consists of 1 full-time medical health officer, 18 part-time physicians, 7 sanitary inspectors, 4 public health nurses, 4 disinfectors and 19 other employees—mostly clerical personnel. The principal function of ten of the part-time medical officers is the verification and medical certification of births and deaths, that of five others vaccination and control of sickness among the personnel of the city administration. Three are chiefly occupied with the V.D. dispensary and the medical control of prostitutes ; each one assists the other in the various activities, except the three V.D. physicians, who keep strictly to their own work. It is thus seen that the activity of these physicians is largely concerned with

matters with which an American city health department would have nothing to do.

The extraordinarily small number of public health nurses is due to the fact that nearly all the fundamental work of the American city health department is outside the sphere of activity of the Brussels Health Department. One nurse is employed at the anti-venereal dispensary, one on the control of prostitutes (*service des mœurs*) and two are engaged in the control of epidemic diseases. The latter activity, together with the general sanitary inspection, are about the only fields in which the work of the Brussels City Health Department does not differ materially from the American conception. The number of sanitary inspectors is about the same as it would be in a health department of an American city of similar size. The latter would generally have a smaller clerical staff, and there would usually be no special disinfectors.

The annual budget of the City Health Department, including its share in the Intercommunal Laboratory, but excluding the school health service, hospitals and other health activities outside of its field, amounts to about two million Belgian francs. This gives about 10 francs or 35 American cents *per caput*. This is only half or a third of what an American city health department would generally command, but the figures are not in the least comparable as their allocation is entirely different. It has not been possible to establish the total amount spent on community health by the various private and official organisations. The most important item in this connection is probably the large deficit of the city hospitals, which is made up by the city administration.

INDICES TO CHAPTER C, I.

1. *Number of persons per 1,000 inhabitants engaged in professions connected with health (1936) :*

Physicians	1.8
Dentists	0.5
Pharmacists	0.6
Midwives	0.15

2. *Health Department budget per caput (1936) : 35 United States cents.*

II. VITAL STATISTICS.

The basis for the compilation of particularly good vital statistics certainly exists, and it would entail no additional expenditure to perfect them so that they would be of real value in analysing and solving the health problems with which the city is confronted.

A complete census is taken every ten years by the national statistical office and supplemented by periodical economic censuses. This work is carried out efficiently under competent direction. There is furthermore a population register which is kept by the office of the city registrar and, even if these records cannot be quite complete, they furnish most valuable help in making intercensal estimates of the population.

All births, still-births and deaths must be seen and verified by the physicians of the health department collaborating with the registrar's office. No burial permit can be issued until one of these physicians has seen the corpse and satisfied himself as to the cause of death. Registration is therefore certainly quite complete. This control covers all births and deaths occurring in the city territory, and reliable records are established in each case whether they relate to residents or to non-residents. This is perfect, and the one weakness of the system is that births and deaths of residents occurring outside the city territory are reported only to the registrar's office, while the health department receives no report. The Brussels vital statistics would be complete if detailed information concerning these births and deaths covering sex, age, cause of death, etc., were currently transmitted by the registrar's office to the health department for inclusion in its records.

Another shortcoming arises from the definition of still-births, which has already been referred to in part B. A reform of this procedure can be effected only on a national basis, as the definition depends upon the registration law. An attempt could be made, however, by the official physicians to establish and record the cause of death for infants born alive which are legally still-births and thus to complete the infant mortality statistics.

The causes of death seem to be carefully established ; only 2.5% of the deaths occurring in the city territory exclusive of still-

births were certified as due to unknown or ill-defined causes in 1935. Senility seems to be rather frequently given as a cause of death, 26.2% of all deaths over 70 being attributed to this cause. The value of the statistics of causes of death is increased by the fact that over a third of the resident deaths occur in hospital, where a more careful diagnosis may be established.

INDICES TO CHAPTER C, II.

1. *Percentage of deaths medically certified* : 100.
2. *Percentage of deaths attributed to unknown cause (1935)* : 2.5.
3. *Percentage of resident deaths over 70 attributed to senility (1935)* : 26.2.
4. *Percentage of resident deaths occurring in hospital (1935)* : 34.5.

III. LABORATORY SERVICES.

The City Health Department is equipped only for diphtheria examinations. Other bacteriological and serological examinations are made by the provincial Pasteur Institute or by private laboratories. No record can be obtained of the total of such examinations for the city territory. Laboratory work relating to food and drink is carried out by the Intercommunal Laboratory, which is a co-operative institution set up by the communes of the metropolitan agglomeration. The water company, which is also a co-operative concern set up by these communes, is doing its own examinations. There is no city bacteriologist, and the health officer does the diphtheria examinations himself.

Diphtheria examinations, mostly of specimens from the schools, numbered 3,650 or 50 per reported case in 1936 ; 7.3% of them were positive. This reaches the standard requirements of the American Appraisal Form, which is 40 diphtheria examinations per reported case. This standard is, however, greatly exceeded by many American cities.

Not only the milk examinations, but also the milk inspection is made by the Intercommunal Laboratory. In 1935, 27,199 milk samples were examined, of which 21,878 were taken in town and 5,321 in the stables. This gives 3 milk examinations per 100 inhabitants. As the milk consumption is probably less than 100 quarts

a year *per caput*, this gives over 30 examinations per 100,000 quarts of milk consumed—a rate indicating a very efficient control. The result of these examinations will be given in the chapter for milk and food control.

The Intercommunal Laboratory furthermore examined 4,510 samples of butter and other fats and 14,781 samples of other food products.

INDICES TO CHAPTER C, III.

1. *Diphtheria examinations made by the City Health Department per case notified (1936) : 50.*
2. *Milk examinations made by the Intercommunal Laboratory per 100 inhabitants (1935) : 3.*
3. *Other food analyses made by the Intercommunal Laboratory per 100 inhabitants (1935) : 2.1.*

IV. ACUTE COMMUNICABLE DISEASES.

It is a peculiarity of Belgian sanitary legislation that the notification of contagious diseases cannot be imposed on practising physicians except so far as the quarantine diseases—smallpox, typhus, plague, cholera and yellow fever—are concerned. As no case of these diseases has occurred for many years, compulsion to notify exists practically only for state schools, hospitals, dispensaries and public assistance institutions.

Practising physicians voluntarily reported a fair number of typhoid-fever, diphtheria and scarlet-fever cases, but only rarely cases of other epidemic diseases. During the three years 1933-1935, 39.3% of the typhoid fever cases, 19.3% of the diphtheria cases and 27.5% of the scarlet-fever cases notified were reported by practising physicians, apart from the cases known only from the death certificates. As the percentage of removals to hospital is relatively high, particularly for diphtheria, this may be considered as satisfactory in view of the absence of any compulsion.

The number of cases reported per death was, during the same three years, 7 for typhoid fever, 14.2 for diphtheria, 127.5 for scarlet fever, 26.2 for measles and 16.9 for whooping-cough. The

requirements of the American Appraisal Form in this respect are 8 cases per death for typhoid fever, 10 for diphtheria, 100 for scarlet fever, 120 for measles and 50 for whooping-cough. These standards are rather arbitrary, because the case mortality rate varies from one part of the world to another, but it is nevertheless clear that the reporting is fairly good for the three first diseases, but incomplete for the latter two.

The two visiting nurses of the City Health Department made 1,321 home visits on account of contagious diseases in 1935. These visits are not specified by disease and their adequacy cannot, therefore, be directly appreciated. Considering only cases of typhoid fever, diphtheria, scarlet fever, measles, whooping-cough and acute poliomyelitis, and leaving out of consideration chickenpox and mumps, as well as cases known only from the death certificates, this gives 2.1 visits per case. Assuming that one home visit would have sufficed for hospitalised cases, it would give 3 nursing visits at domicile for the remaining cases. Given the composition of the group of non-institutionally treated cases in this instance American standards (4 visits per typhoid-fever, diphtheria and scarlet-fever case, and 2 visits per measles and whooping-cough case) would work out to 2.6 visits per case ; it may be assumed therefore that this part of the control of epidemic diseases is well provided for.

Hospitalisation of cases of contagious diseases is much more actively aimed at than in the United States. Up to October 1935, such cases were hospitalised at the Hôpital St. Jean ; since then, this service has been transferred to the Hôpital St. Pierre. It is highly satisfactory that, in 1935, nearly two-thirds of the typhoid-fever and the diphtheria cases and 38% of the scarlet-fever cases were hospitalised. The high percentage of measles and whooping-cough cases which were hospitalised must be considered in the light of the incomplete notification of these diseases, but is nevertheless significant.

The high proportion of the contagious disease cases hospitalised is further brought out by the fact that 72.2% of the resident deaths (1933-1935) from contagious diseases occurred in hospital. This denotes a serious effort to get the more severe cases even of measles and whooping-cough into hospital.

The search for diphtheria carriers is actively pursued in the schools as well as in families where a diphtheria case has occurred. In 1936,

3,650 specimens were taken for bacteriological examinations in the public schools, 963 in the denominational schools and 260 among other contacts, which gives a total of 66.8 examinations per case notified ; 6.7 % of these were found positive.

Immunisation of school-children by the Ramon method has been carried out since 1930. The immunisation, for which written authorisation from the parents is required, is carried out partly among children entering primary public schools at the age of 6, partly in the kindergartens, which children of from 3 to 6 years of age attend. It is only performed irregularly in the denominational schools. No attempt is made to extend the immunisation to children in their second year of life. About three-fourths of the children received all three injections, while 10% received only one injection.

In 1936, 1,121 diphtheria immunisations were made. The annual average for the seven years 1930-1936 was 1,174, including those who had had only one or two injections. The average annual number of births less infant deaths was 1,905 during this period. Immunisations were therefore not sufficiently numerous to protect the whole of the children of the new generations, but only 61.6% of these. This is confirmed by the fact that diphtheria immunisations numbered only 54.6% of the smallpox vaccinations performed on entering school. This percentage of immunisations should be sufficient, however, materially to impede the spread of diphtheria epidemics if they were made early enough. As it is, they have undoubtedly helped to check the spread of diphtheria in the public primary schools, as a comparison with the proportion of scarlet-fever cases in schools clearly shows.

Anti-typhoid vaccination is carried out on a small scale among contacts of typhoid cases. In 1935, there were 12 such vaccinations, in 1934, 19.

Smallpox vaccination is compulsory on entering school, and the population seems to be well protected against this disease. During the year ending August 31st, 1936, 2,538 vaccinations and revaccinations were made as against 2,722 during the previous year. The number of vaccinations made on entering school, during the year ended August 31st, 1936, was 2,123, of which 1,996 were revaccinations. A high proportion (61.5%) of the revaccinations proved successful.

INDICES TO CHAPTER C, IV.

1. *Number of cases of epidemic diseases notified per death (1933-1935) :*

Typhoid fever	7.0
Diphtheria	14.2
Scarlet fever	127.5
Measles	26.2
Whooping-cough	16.9

2. *Source of notification in percentages of all cases notified (1933-1935) :*

	Typhoid fever	Diphtheria	Scarlet fever
Practising physicians	39.3	19.3	27.5
Hospitals	50.0	56.2	33.2
Schools	3.6	16.7	32.8
Other sources	7.1	7.8	6.5
Total	100.0	100.0	100.0

3. *Home visits of health department nurses per case of contagious disease (typhoid fever, diphtheria, scarlet fever, measles, whooping-cough and acute poliomyelitis) (1935) :*

(a) For all cases : 2.1.

(b) For non-hospitalised cases counting only one visit per hospitalised case : 3.

4. *Percentage of notified cases of contagious diseases which were hospitalised (1935) :*

Typhoid fever	66.7
Diphtheria	61.8
Scarlet fever	38.2
Measles	26.2
Whooping-cough	54.2

5. *Percentage of resident deaths from contagious diseases which occurred in hospital (1933-1935) :*

Typhoid-fever	50.0
Diphtheria	78.9
Scarlet fever	83.3
Measles	71.4
Whooping-cough	70.0

6. *Examinations for diphtheria carriers per case notified (1936) :* 66.8.7. *Percentage of these diphtheria specimens found positive (1936) :* 6.7.8. *Diphtheria carriers found per case notified (1935) :* 1.2.9. *Diphtheria immunisations per 100 births less infant deaths (1930-1936) :*
61.6.

10. *Percentage of those immunised which had received (1935) :*
- | | |
|-----------------------------------|------|
| First injection only | 9.6 |
| First and second injections | 14.6 |
| All three injections | 75.8 |
11. *Diphtheria immunisations per 100 smallpox vaccinations performed on entering school (1935) : 54.6.*
12. *School-children vaccinated or revaccinated against smallpox (1935-36) : 100%.*
13. *Percentage of these which were revaccinations (1935-36) : 94.*
14. *Percentage of revaccinations which were successful (1935-36) : 61.5.*

V. VENEREAL DISEASES.

The work of the City Health Department in the matter of venereal disease control is concentrated on the medical supervision of prostitutes. This control is carried out by the means of a venereal disease dispensary, four part-time physicians and two public health nurses.

The medical supervision of prostitutes falls into two parts : (a) women reported by the police as accused of inciting to immorality or engaged in prostitution and (b) waitresses in taverns suspected of disorderly morals. In 1935, 265 women were reported by the police under the first category, 221 under the second. Visits were made to these persons by the nurse as far as they could be found, and 96 or 19.8% came to the dispensary. A few furnished medical certificates, but the remainder could not be found or refused to present themselves.

The services of the dispensary, which are free of charge, were extended also to other than prostitutes. In 1935, 47 persons were treated for syphilis, 356 for gonorrhœa ; 110 persons were examined for syphilis and 305 serological tests were made. Dispensary visits for syphilis numbered 1,240 (110 male and 1,130 female), or 26 per case treated ; visits for gonorrhœa numbered 12,994, or 36 per case treated. Of the gonorrhœa cases, 31% were old cases when first seen.

There are furthermore two hospital dispensaries and an inter-communal dispensary (Brussels, Schaerbeek, Molenbeek, St. Josseten-Noode) where venereal cases are treated at low cost. The

information obtained is insufficient for the establishment of significant indices of the total of anti-venereal activities.

The police took action against disorderly conduct in the street and arrested 445 women for infringing the regulations on prostitution in 1935. This gives a ratio of 8.4 per 1,000 female inhabitants aged 15-45.

INDICES TO CHAPTER C, V.

1. *Percentage of women reported by the police des mœurs who came to the Health Department dispensary (1935) : 19.8.*

2. *Persons treated by Health Department Dispensary per 10,000 inhabitants (1935) :*

(a) For syphilis	2.4
(b) For gonorrhœa	18.3

3. *Number of visits per case treated at Health Department Dispensary (1935) :*

(a) Syphilis	26.2
(b) Gonorrhœa	36.5

4. *Number of women arrested for infringing the regulations on prostitution per 10,000 inhabitants of female sex aged 15-45 (1935) : 8.4.*



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**REPORT ON THE
MEETING OF DIRECTORS OF INSTITUTES
AND SCHOOLS OF HYGIENE**

held at Geneva from November 22nd to 27th, 1937.

In accordance with the Health Committee's decision in May 1936, and following the report of Professor JAMESON, Professor PITTALUGA and Dr. STAMPAR on certain European institutes and schools of hygiene, which was submitted to the Health Committee at its session of February 1937, a meeting¹ of directors of institutes and schools of hygiene was convened at Geneva on November 22nd, 1937.

¹ This meeting was attended by :

- Dr. J. PARISOT (*Chairman*), Professor of Hygiene and Preventive Medicine, Director of the Institute of Hygiene, Nancy ;
- Dr. Mahmut Sabit AKALIN, Director of the Institute of Malariology, Adana ;
- Professor J. BALTEANU, of the Institute of Hygiene and Public Health of Jassy University ;
- Dr. Ralph K. COLLINS, Director of the School of Hygiene, Ankara ;
- Dr. L. S. FRIDERICIA, Professor of Hygiene of Copenhagen University ;
- Professor L. HIRSZFELD, Director of the Department of Bacteriology and Experimental Medicine of the State Institute of Hygiene, Warsaw ;
- Dr. J. Axel HÖJER, Director General of Health Services, Stockholm ;
- Professor Bela JOHAN, Secretary of State at the Royal Hungarian Ministry of the Interior, Budapest ;
- Dr. M. KACPRZAK, Chief of the Department of Health Statistics at the State Institute of Hygiene, Warsaw ;
- Dr. M. KAISER, Counsellor of the Federal Ministry of Social Administration, Vienna ;
- Dr. P. KOJOUHAROFF, Chief of the Bacteriological and Epidemiological Department of the Institute of Hygiene, Sofia ;
- Dr. M. KRALJEVIC, of the State School of Hygiene, Zagreb ;
- Professor E. LECLAICHE, Director of the Office international des Épizooties, Paris ;

This meeting was called, not only for the purpose of discussing the above report, but also for the consideration of the following questions : health indices, enteric fever, brucellosis, tuberculosis and nutrition ; these questions to be studied from the point of view of rural hygiene, and the proceedings to form part of the preparatory work for the 1939 Conference on Rural Life.

The various resolutions adopted at the final plenary meetings were as follows :

A. GENERAL REPORT ON INSTITUTES AND SCHOOLS OF HYGIENE.

The health and social welfare of the people cannot be efficiently ensured unless the training of general practitioners and public

-
- Dr. M. P. LISBONNE, Director of the Undulant Fever Research Centre and Professor at the Faculty of Medicine, Montpellier ;
 - Dr. G. LIVADAS, Director of the School of Hygiene of the Health Ministry, Athens ;
 - Professor J. J. VAN LOGHEM, Director of the University Institute of Hygiene, Amsterdam ;
 - Dr. M. MALOJCIC, of the School of Public Health, Zagreb ;
 - Professor H. MOOSER, Director of the University Institute of Hygiene, Zurich ;
 - Colonel G. S. PARKINSON, M.D., of the London School of Hygiene and Tropical Medicine, London ;
 - Dr. Hynek PELC, Professor of Social Medicine at the Charles IV Institute of Social Medicine, Prague ;
 - Dr. René SAND, Secretary-General of the Ministry of Public Health, Brussels ;
 - Dr. S. SAVONEN, Secretary of the Finnish National Anti-Tuberculosis Association, Chairman of the Board of the State School of Public Health Nursing, Helsinki ;
 - Mr. K. STOUMAN, former member of the Health Section of the League of Nations ;
 - Dr. G. SZULC, Director of the State Institute of Hygiene, Warsaw ;
 - Dr. Richard M. TAYLOR, State Hygienic Institute of Hungary, Budapest ;
 - Professor J. TOMCSIK, Director of the State Institute of Public Health, Budapest ;
 - Professor M. ZOŁOG, Inspector of Sanitary Engineering, Institute of Hygiene and Public Health, Cluj.

Mr. LINDBERG, of the Financial Section of the Secretariat of the League of Nations, was also present during the meetings.

The following members of the International Labour Office also attended the session :

- M. F. VON BULOW, Chief of the Agricultural Section ;
- Professor L. CAROZZI, Chief of the Industrial Hygiene Section ;
- Mr. I. W. NIXON, Chief of the Statistical Service ;
- M. O. STEIN, Chief of the Social Insurance Section ;
- Mr. R. M. WOODBURY, of the Statistical Service.

health officers embraces all aspects of preventive and social medicine. This calls for special institutions, which should be adapted to the conditions and needs of each country.

It is necessary, not only to provide special teaching for future health officers, but also to give appropriate instruction to medical students, who will be the practitioners of the future.

An adequate grounding in hygiene and preventive and social medicine is, in fact, a fundamental requirement for that collaboration of the general practitioners in health work and social insurance which is indispensable. Whilst essential everywhere, it is of particular importance in rural areas, and special measures should be taken to attract and retain there a sufficient number of medical men.

The rôle of institutes and schools of hygiene may be defined as follows :

- Teaching ;
- Research ;
- Practical activities in public health ;
- Educative propaganda.

1. ORGANISATION OF TECHNICAL FACILITIES.

Experience shows the necessity of organising, for the benefit of future health officers, practical courses of field work of sufficient duration ; their participation in this field work should be both active and controlled. These courses should be given in the Health Services, and in organisations engaged in protective health and social welfare work (health centres, public health clinics, etc.), both in rural areas and in towns and industrial districts.

Hence it is essential that the teaching staffs of the institutes and schools of hygiene should be in direct contact with the Health Services as well as the organisations engaged in protective health and social welfare work, either by taking an active share in that work, or through close and regular liaison.

2. DIFFERENT TYPES OF INSTITUTES AND SCHOOLS.

While there is no need to revert here to the question of the different types of institutes and schools, which are described in the report,

it is considered essential that they should be co-ordinated within each country as regards, not only their syllabus, but also their activities. This co-ordination presents no difficulty in countries with a national institute and affiliated branches ; where, however, there are a number of separate institutes of hygiene attached to universities, co-ordination should be brought about by the combined action of the controlling central authorities.

3. RÔLE OF THESE INSTITUTIONS.

Teaching.

The syllabus, both theoretical and practical, should be planned in such a way as to keep abreast of new developments in the matter of methods and means of social and preventive health work, and adapted at all times to the needs of the population.

This syllabus should be adjusted to meet the requirements of the various categories of personnel, and to fit the circumstances arising out of the introduction of new labour legislation, measures of public assistance, social insurance, etc.

Research.

These institutes and schools of hygiene should carry out research work, viz. :

- (a) Individual research work of a purely scientific character ;
- (b) Research work relating to the actual problems of public health.

Active Intervention of Institutes and Schools of Hygiene : Practical Collaboration with the Health Authorities.

The institutes under consideration should be empowered :

- (a) To give advice on all questions relating to health and social welfare to the authorities—national, regional or local—which deal with these matters ;
- (b) To carry out any practical work in this field.

Close co-operation between the institutes and social insurance, assistance and welfare institutions is desirable in every way.

Educational Propaganda.

The institutes and schools should take part in the health education of the public through both their own staff and their graduates. They should help both official and voluntary agencies in their efforts towards educational health work.

**4. INTERNATIONAL LIAISON BETWEEN INSTITUTES
AND SCHOOLS OF HYGIENE.**

It is becoming more than ever necessary to maintain permanent liaison between the various schools and institutes of hygiene on the international plane.

To that end, the holding of regular meetings of directors of institutes and schools, under the auspices of the League of Nations' Health Organisation, should be recommended.

The Health Section of the Secretariat of the League of Nations should act as a clearing house to enable these various institutions to pool their experience and exchange all documents relating to their general organisation, functions and activities.

This collaboration would be usefully strengthened, not only by the direct exchange of publications and scientific papers between the institutes themselves, but also by an interchange of professors.

The publication of a periodical concerning the institutes and schools of hygiene would admirably meet the needs of this liaison and collaboration.

**5. SUPERVISION OVER THE HEALTH OF STUDENTS AND THEIR
EDUCATION IN PERSONAL AND COMMUNITY HYGIENE.**

The meeting requests the Director of the Health Section to collect by means of a questionnaire addressed to the universities in the various countries, information regarding what is being done for the control of the health of students and connected subjects. It would also be desirable to know whether any teaching on individual and community hygiene is given to students who do not propose to enter the medical profession or allied professions.

B. HEALTH INDICES.

1. The question of health indices was studied and their utility considered in connection with :

- (a) Teaching in schools of hygiene ;
- (b) Establishment of a uniform classification of subjects for health surveys ;
- (c) Preparation of a general framework for special enquiries ;
- (d) Systematic classification of statistics relating to public health and allied subjects ;
- (e) Administrative statistical enquiries.

Members from Belgium, France, Czechoslovakia, Hungary, Netherlands, Poland, Roumania, Turkey and Yugoslavia expressed their intention to recommend that experimental application of the health indices be undertaken in their respective countries : it would be desirable for the Health Section to act as clearing house for information in this connection and, generally, to co-ordinate the efforts of the participants.

When the new application of the indices has been made, it would be useful to have the delegates of the participating institutes meet in 1938 in order to discuss the adaptation, and, if need be, the improvement of the system.

2. The geographical framework for the enquiries should, as far as possible, correspond to a natural region for the sake of homogeneity, and to an existing administrative division in order to facilitate the collection of statistical data and, possibly, the future organisation of public health and social welfare work.

Beside the data regarding the region considered as a whole (extensive enquiries), detailed investigations should be made in some localities which constitute a fair sample of the whole area (intensive enquiries) or of some distinctive constituent part when the region is not homogeneous.

3. The main headings of the list of " indices ", as well as a certain number of indices under each heading, should be employed systematically in all the surveys made. A certain elasticity should

subsist on other points in order to allow of the necessary local adaptations.

4. Certain sections have been adapted to rural conditions and the essential points which should appear in each survey have been specified.

The following subjects from the Nancy survey forms should be embodied in the system of health indices : Information on agricultural products (page 4 of the survey form) ; buildings for public use (page 5) ; farm buildings (page 6) ; flies, mosquitoes and rodents (page 7) ; nutritional hygiene (pages 8-9) ; hours of work (page 9) ; organisation of leisure (page 10) ; domestic animals (page 11) ; sanitary inspection of green vegetables (page 15) ; diseases common to men and animals (page 18) ; medical supervision of sports (page 20) ; military and temporary population (page 22) ; divorces (page 22).

5. It is suggested that health indices could be used as a general framework for special enquiries on tuberculosis, nutrition, brucellosis, typhoid fever, etc., which are undertaken in preparation of the Conference on Rural Life.

C. ENTERIC FEVER IN THE RURAL ENVIRONMENT.

The research carried out by the institutes and schools of hygiene in pursuance of the resolution of the 1931 Conference on Rural Hygiene suggests that the following points require further investigation.

The term " rural " area would, of course, have to be interpreted in each country according to local circumstances, but it was considered that, in order to maintain comparability of studies on rural enteric fever, " rural " areas *for the purposes of such studies* should be taken to mean areas in which there is no piped water-supply system, sewerage system or satisfactory inspection of foodstuffs, and in which farm animals are kept. The institutes of the following countries have decided to take part in this research : Austria, Bulgaria, Czechoslovakia, France, Greece, Netherlands, Poland, Roumania and Yugoslavia.

1. As national statistics on morbidity and mortality from enteric fever are not comparable at present, institutes and schools of hygiene should enquire into the methods adopted in their countries for :

- (a) Certification of deaths ;
- (b) Notification of communicable diseases ;
- (c) Laboratory diagnostic services in connection with such notification.

These enquiries should have particular reference to rural areas and should cover, not only all the relevant legislation,¹ but also the manner in which it is actually carried out in practice. The conclusions of these enquiries will be communicated through the Health Section to all institutes participating in this research.

2. Studies should be carried out on the prevalence and seasonal variations of rural and urban enteric fever in respect of their origin—viz. :

- (a) Contact ;
- (b) Water ;
- (c) Food ;
- (d) Unknown.

3. Studies should be made of the seasonal fluctuations in rural districts of the enteric curve, together with the curves of temperature and of the abundance of flies. Similarly, variations of other possible biological factors of typhoid, such as the presence of bacteriophage in drinking-water, might also be investigated.

4. In view of recent improvements in bacteriological technique and particularly of the good results obtained with the Wilson-Blair and Müller-Kauffmann media in the culture of the typhoid bacillus, it is desirable to repeat investigations on :

- (a) The detection of the typhoid bacillus in surface water and in milk in rural areas where enteric fever is endemic ;
- (b) Enteric contamination of the various species of flies breeding or feeding on human excreta and their possible rôle as vectors of the typhoid bacillus ;
- (c) The detection of chronic germ-carriers.

¹ Including, *inter alia*, legislation on germ-carriers and measures relating thereto.

5. It is desirable to study the possibility of using the Widal test in low concentration for the detection of chronic germ-carriers.

6. The improvement in our knowledge of antigens best suited to bring about immunity in man makes it desirable to investigate the effects of mass vaccination with these new vaccines on enteric fever incidence.

7. A study should be made of the effects of the removal of patients to hospital on the incidence of enteric fever.

8. In the studies on enteric fever, it is desirable that the Widal test be carried out according to the technique recommended by the Health Organisation's experts on the standardisation of agglutinin tests at their meeting in London in November 1937.¹

9. The classification of *Salmonellæ* on the basis of their antigenic make-up should be reconsidered, taking into account the pathogenic significance of the various antigen-constituents and the epidemiological rôle of the germs.

Certain aspects of this problem have already been taken up by the experts on the standardisation of agglutinin tests appointed by the Health Organisation. There is therefore no need to outline a detailed programme. It would appear desirable to point out, however, that these studies are likely to lead to practical results and that it would be useful to set up an international centre for the classification of *Salmonellæ*.

10. In rural areas where enteric fever is endemic, special attention should be given to the probable occurrence of mild atypical forms amongst children, and efforts should be made to determine the prevalence of such infection by making greater use of laboratory facilities and applying the new methods.

11. It would be highly desirable, in addition to the technical investigation of particular points of enteric fever epidemiology and control, to carry out more general enquiries fitting in with the general

¹ See document C.H.1292.

plan of health indices and capable of bringing to light in rural areas :

(1) The importance of enteric fever as a cause of morbidity and mortality :

Absolute importance : deaths, cases and days of illness per hundred thousand inhabitants ;

Importance relatively to other communicable diseases and other causes of morbidity and mortality ;

(2) The cost of the disease :

(a) To the population itself (cost of medical care, drugs, hospital treatment, etc., loss of wages due to the patient's temporary incapacity and loss of wages of members of the family taking care of the patient ; capital loss represented by deaths, etc.) ;

(b) To insurance funds ;

(c) To public funds, both local and national (cost of hospital treatment, laboratory services, control of germ-carriers, etc.) ;

(3) The cost of various measures against rural enteric fever :

Construction of piped water-supply systems and/or purification and distribution of water ;

Construction of protected wells ;

Protection of springs ;

Sanitary improvements to manure pits, etc. ;

Construction of sanitary privies ;

Systematic removal to hospital of patients ;

Detection and control of chronic germ-carriers ;

Mass vaccination of the population ;

taking into account :

(a) The geographical type of the rural community :

Concentrated or scattered population ;

Size of the villages ;

Accessibility and fitness for human consumption of the water supply, etc. ;

(b) The immediate outlay involved, amortisation and cost of upkeep on the one hand and the cost of continuing to apply the above measures on the other hand ;

- (c) Their relative efficacy as demonstrated by practical experience (it would be useful to cite actual examples) ;
- (4) The relationship between the incidence of enteric fever and that of other diseases and causes of death (changes in general and infantile death rates, tuberculosis mortality, etc., compared with fluctuations in enteric fever mortality) ;
- (5) In consequence, the extent to which the rareness of enteric fever may be considered an index of health.

D. BRUCELLOSIS.

In view of its importance as a human, as well as an animal, disease, and of its influence on rural economics, brucellosis is one of the diseases which might profitably be studied by institutes and schools of hygiene interested in rural hygiene.

It would be advisable to undertake a comprehensive survey of the problem in its different aspects as indicated above.

Such a survey might take the form of either a general enquiry or detailed local surveys wherever there were sufficient cases to justify such an undertaking, which, though complicated, would be of considerable value to both students and health authorities.

The institutes of the following countries have asked to take part in this work : Austria, Czechoslovakia, France, Greece, Poland, Roumania, Switzerland.

As a general rule, the study of this disease more than any other calls for the co-operation of the health, veterinary and agricultural services.

It is suggested that the institutes of hygiene should send to the Health Section of the Secretariat of the League of Nations, which will act as a clearing house, in preparation for the Conference on Rural Life, the general documentary material collected by them and the results of any enquiries they may carry out.

1. GENERAL DOCUMENTARY MATERIAL.

The Institutes should collect any scientific and social and economic documentary material that may be obtainable in countries in which

undulant fever has formed the subject of previous studies. This material should, as far as possible, be presented in the manner described below.

2. ENQUIRIES UNDERTAKEN WITHIN THE FRAMEWORK OF HEALTH INDICES.

A. The distribution and frequency of cases of undulant fever in man should be studied with the help of the available data :

(a) *Number of cases notified* when notification is compulsory or cases brought to the notice of the health authorities by some other method.

Efforts should be made to procure these particulars for a five-year period.

A pathological episode will not be considered as a " case of undulant fever " for the purpose of these studies unless its diagnosis is confirmed by a serological or bacteriological examination.

(b) *Detection of cases by systematic serological tests* : A method of detecting cases which is as valuable for the compilation of figures in a general enquiry as for detailed surveys, consists in the systematic testing for *Brucella* agglutination of all blood samples sent to the laboratories for the diagnosis of typhoid fever or other communicable diseases (such as syphilis).

In presenting the statistical results thus obtained, mention should be made of the reason for which the blood samples were sent to the laboratory (for diagnosis of undulant or typhoid fever ; other reasons, if any) and whether they came from a *rural* or *urban* district.

The tables relating to positive cases should also include the following particulars :

- (1) Sex ;
- (2) Age ;
- (3) Occupation ;
- (4) Clinical symptoms ;
- (5) Probable source of the infection ascertained either by a questionnaire or preferably by an enquiry on the spot.

The probable sources of infection should be stated and classified under the following heads :

- (1) *Indirect contamination* : consumption of raw milk, cheese, whether fresh or not, cream, etc. ;
- (2) *Direct contamination*.

In the case of both these modes of contamination (indirect or direct), the species of animal responsible should be specified and it should be stated whether these animals have aborted or not, and, if so, when.

Any documents which would help to establish the morbidity, mortality and fatality rates should be communicated (relation between the incidence of brucellosis and other infections and causes of death, such as the general death rate, tuberculosis mortality, etc.), the average duration of the disease, its sequelæ, and if necessary any information which can be furnished by social insurance and mutual benefit organisations, together with particulars of the economic and social effects of the disease, with special reference to rural exodus.

The cost of the disease might be established as follows :

- (1) To the population itself (cost of medical treatment, drugs, hospital treatment, etc. ; loss of wages due to patient's temporary or permanent incapacity and wages lost by relatives taking care of the patient, capital loss represented by death, etc.) ;
- (2) To insurance and mutual benefit funds ;
- (3) To public funds, both local and national (cost of treatment in hospital, laboratory services).

B. Particulars should be given of the number of enzootic or epizootic abortions known to be caused by brucellosis, in the same circumstances as in man, in the following animals :

Cows, ewes, goats, sows, mares, etc.

It should be stated whether a serological diagnosis was made and also how many specimens for each species of animal were examined (the proportion of positive cases should be given).

Whenever possible, the particulars should be given in statistical form either for the live-stock as a whole or, better still, *per infected*

byre or herd, divided in five groups according to the number of animals (0 to 4 head, 5 to 19, 20 to 49, 50 to 99, 100 and over).

These documents should be used to show :

(a) The extent of the direct loss to rural economy (abortion, sterility, agalactia and the possible slaughter of infected animals, etc.) ;

(b) The effect of trade or transport on the spread of the disease among animals ; sale, markets, grazing, seasonal movement of herds, etc. ;

(c) What legislation concerning the notification of abortions and what regulations relating to grazing, transport and the seasonal movement of herds, etc., exists or could be introduced.

The cost of the various measures to improve rural conditions should be specified :

(1) Shelter for animals (byres, sheepfolds, accommodation for small live-stock, etc.) ;

(2) The improvement of manure pits, etc. ;

(3) Drinking-water supply :

taking into account :

(a) The geographical type of the rural community : concentrated or scattered population ; size of villages ; accessibility and fitness for consumption of available water, etc. ;

(b) The immediate outlay involved, amortisation and upkeep on the one hand and cost of continuing to apply the measures taken on the other hand ;

(c) Their relative efficacy as demonstrated by practical experience (it would be useful to cite actual examples).

C. *Laboratory research* : The results obtained should be shown in both human and animal cases, in two columns :

(1) Positive results,

(2) Negative results.

The following headings are suggested :

(a) Method of agglutination (quick, slow or other) ; the results to be communicated separately according to the nature of the specimen (blood, milk, other products) ;

- (b) Method of culture ;
- (c) Method of identification and typing of isolated germs (*Br. melitensis*, *abortus*, *suis*, etc.) ;
- (d) Complement fixation method ;
- (e) Method based on allergic reactions ;
- (f) Other methods (to be specified), for instance, precipitation, etc.

D. If this enquiry is to afford a solid basis for further discussion, it would be desirable for laboratories to use identical methods, which have stood the test of experience in previous enquiries, as follows :

- (a) For agglutination, use of an antigen prepared with a specified strain of *Brucella* ;
- (b) For identification and typing, use of the Huddleson methods (bacteriostasis by the dye method—production of H_2S , culture in CO_2 or in the open air—culture on Petraghani's medium) ;
- (c) For allergic reactions, use of a " melitin " prepared from an adequate strain.

E. TUBERCULOSIS.

Without entering into all the details of a programme for a survey on rural tuberculosis, in which the institutions of Bulgaria, Czechoslovakia, France, Hungary, Netherlands, Poland, Roumania and Yugoslavia wish to participate, the following proposals may be advanced :

1. Anti-tuberculosis action, both curative and preventive, must be adapted to local conditions—viz., to the local epidemiology of tuberculosis, the way in which the population is distributed and the social and economic condition of the people.
2. To permit of such adaptation, it is necessary to carry out regional field surveys relating, not only to the incidence and forms of tuberculosis itself, but also to the whole of the social, medical and sanitary conditions in which the population lives, for tuberculosis cannot be regarded as an isolated problem.

3. The geographical area taken for regional field surveys should coincide as closely as possible with both a natural region and an existing administrative division. In addition to data, however, regarding the selected region, considered as a whole, full particulars should be collected in a few localities which are representative samples of the whole (intensive surveys), or which represent distinct factors, if the region is not homogeneous.

4. For the general survey of the social, economic and health conditions of the population, the "Health Indices"¹ system might with advantage be used. Regions in which these indices are to be used experimentally might also be selected for the tuberculosis surveys.

5. A detailed scheme for both regional (extensive) and local (intensive) surveys—one complementing the other—of the incidence of mortality, morbidity and tuberculosis infection has been drafted. In order to determine morbidity, it is necessary, not only to question every inhabitant of one or more localities, but also to subject each to both tuberculin-testing and X-ray examination for pulmonary lesions. In the case of patients and suspects, the X-ray examination should be supplemented by clinical and bacteriological examinations.

6. It is desirable that a single well-defined method should be adopted everywhere for tuberculin testing. The tuberculosis specialists entrusted with the surveys arranged by the institutes of hygiene should agree on a method beforehand. Agreement should similarly be reached as to the classification of clinical forms of tuberculosis for the purposes of the surveys.

7. The local tuberculosis survey should be supplemented by a detailed enquiry into the social factors of tuberculosis (housing, general and hygienic education, nutrition, occupations and social position of the population), and into migratory movements of individuals which may influence the spread and evolution of tuberculosis. Consideration should also be devoted to the position as regards medical and social assistance.

¹ See *Bull. Health. Org.*, 1936, 5, 901.

8. Apart from data on human tuberculosis, data on animal tuberculosis could usefully be collected by the competent veterinary services (tuberculin reactions, frequency of tuberculous lesions in slaughtered animals, sanitary conditions of sheds and possible relationship between human and bovine cases).

9. The programme of tuberculosis control work should be adapted to the requirements and financial resources of the community. These resources should be utilised according to the urgency of the requirements :

- (a) First, instruction of the population in hygiene (propaganda) ;
- (b) Then detection of cases (dispensaries) ; and isolation of the most highly contagious cases ;
- (c) Lastly, removal to sanatoria of cases which are amenable to this method of treatment.

In view of its low cost, BCG vaccination might be included in the programmes even of communities with the smallest budgets.

10. To assist in obtaining the necessary credits for anti-tuberculosis action, it would be desirable to estimate, on the basis of the information collected during the survey :

1. *The cost of tuberculosis :*

- (a) To the population itself (cost of medical treatment, drugs, hospital treatment, etc. ; loss of wages due to the temporary incapacity of the patient and to his lowered efficiency on recovery ; capital loss represented by death, etc.) ;
- (b) To insurance funds ;
- (c) To public funds, both local and national (cost of treatment in hospital, treatment in sanatoria, preventoria, etc., including the amortisation of capital outlay on such institutions, and on dispensaries and district nursing services, etc.).

2. *The cost of the various anti-tuberculosis measures :*

- Organisation of *educative propaganda* ;¹
- Organisation of BCG vaccination ;

¹ Campaign against tuberculosis among agricultural labourers and in industry (silicosis) and campaign against spitting.

Detection of cases by stationary and travelling clinics and their visiting nurses ;

Out-patient treatment by pneumo-thorax ;

Segregation in hospital of the most highly contagious cases (institutional treatment on the spot or at a distance ; hospitals, homes, and special housing accommodation for the tuberculous) ;

Treatment of curable cases in sanatoria ;

Prophylactic treatment for cases of latent tuberculosis (preventoria) and subjects specially exposed to tuberculosis (boarding-out, holiday camps, open-air schools) ;

Social assistance to the tuberculous and their families (supplies in kind for treatment or convalescence in the home) ;

Financial aid and supply of food to patients and their families ;

Vocational re-adaptation for patients who have improved or recovered ;

In calculating the cost of the various antituberculosis measures, account should be taken of the immediate cost of constructing institutions, amortisation and running expenses.

Estimates should take account as far as possible the actual cost of existing institutions in relation to the number of cases and the population served. Where there are no such institutions, or where their number is inadequate, the probable cost of creating them or enlarging them to meet requirements should be estimated.

Estimates should cover the cost of institutions on simple lines, run with the maximum economy compatible with technical efficiency.

F. NUTRITION.

The subject of nutrition is one of the chief topics suggested for the agenda of the proposed 1939 Conference on Rural Life in Europe. Institutes or schools of hygiene and national nutrition committees in the several countries therefore are taking stock of the research already completed and of what still needs to be undertaken to answer such questions as :

- (1) What is the actual food consumption of the different groups of the rural (village and/or farm) population ?

(2) What evidence is there regarding the adequacy or inadequacy of these diets ?

(3) What practical measures can be adopted to improve diets found to be deficient ?

Considerable work has already been done in some countries. But diversity of objectives, of methods and of scope makes it difficult to collate the findings for international comparison. It is urged by the Technical Commission on Nutrition (a)¹ that, in future studies, data should be obtained for the same person or group of persons both on food eaten and on the nutritional state of the body.

Committees of experts (b) have already outlined the type of data which, in their opinion, should be obtained in enquiries of varying degrees of comprehensiveness.

On certain points of technique, the Technical Commission (a) has made recommendations in the interest of uniformity of procedure—e.g., family coefficients and main headings under which foods will be classified. There still are, however, many points concerning the method of collection and of analysis on which no guidance has been given. Some of these techniques are still in the experimental state ; others could be standardised with profit.

1. According to the purpose in view, three main types of nutrition studies may be distinguished :

- (A) Quantitative studies to determine food requirements ;
- (B) Quantitative studies to determine the adequacy of diets of population groups ;
- (C) Qualitative studies as a basis for developing nutritional policies.

A. Painstaking *quantitative studies* of food intake and nutritional status which will add to the sum total of scientific knowledge regarding *food requirements*. These include food intake studies of types 2 (community), 3 (family) and 4 (individual), as recommended by the Technical Commission on Nutrition (a), combined with studies of types 2 or 3, as recommended by the experts on nutritional assessment (b). Studies of the food intake of individuals (type 4) combined with studies of nutritional assessment of type 2 are especially recommended.

¹ The lettering (a), (b), (c) relates to the list of references.

The resulting investigations should answer such questions as :

(a) What composition of diet (stated quantitatively in terms of articles of food and in terms of nutrients) is associated with an excellent state of nutrition or a high degree of physical well-being ?

(b) Under what current dietary regimes (described quantitatively as above) does one observe :

(1) Very slight infraclinical symptoms of a deficiency of any given nutrient ?

(2) Gross clinical symptoms ?

(c) Do the symptoms (see (b) above) disappear when the subject under observation consumes :

(1) Definite quantities of specific foods ?

(2) Definite supplements of a specific nutrient ?

(3) Definite supplements of a combination of nutrients?

This type of study involves continuous or adequately timed quantitative measurements of the actual total food intake, coupled with appropriate measures of nutritional condition made at suitable intervals. Such information is of fundamental importance for the establishment of dietary standards.

B. *Quantitative studies* of dietary adequacy, showing levels of consumption and variations from one social or economic group to another, as well as factors influencing the character of the food supply.

If feasible, data should be obtained on expenditure for purchased food and money value of home-produced food.

This type of investigation consists of food intake studies of types 2 and 3, as recommended by the Technical Commission on Nutrition (a) combined with studies of type 1 or 2, as outlined by the experts on the assessment of nutrition (b).

Rural populations are made up of groups varying in economic status (amount of income and the extent to which this is in cash or in goods ; household composition, etc.). These factors must be considered in developing sampling procedures and in the subsequent compilation and analysis of data. It is recommended to seek expert advice on the method of selecting families, the number of families to be included, and the statistical handling of the data. If possible, the sampling and classification procedures should correspond to those used in general studies of family living.

The results of these studies of groups permit comparisons :

- (1) With one another ;
- (2) With standards based on present knowledge of food requirements ;
- (3) With the results of studies of the nutritional state of the persons.

The questions which the results help to answer include :

(a) To what extent does the food supply satisfy the requirements of the members of the group, as indicated by comprehensive studies of their nutritional state, or as indicated by comparisons with dietary standards based on present knowledge ?

(b) To what extent is the level of adequacy of the diet of a given population group associated with family size and with environmental factors such as degree of urbanisation, general living conditions, occupation, the kind and amount of income, the opportunity for home production of food, etc. ?

C. *Qualitative studies* of food consumption in rural districts on a regional basis can, if interpreted in the light of present knowledge, indicate the general nutritional policies which should be developed. It would seem well to combine this type of food survey with nutritional assessment studies of type 1 (b).

In some countries, surveys have been made by regions, defined according to the prevailing type of farming, general economic conditions, and characteristic levels of living (c). In these studies, in accordance with a carefully planned schedule, estimates are secured from key people in a community (teacher, priest, selected housewives, etc.) of the food production and consumption typical of the region at different seasons. Also information is obtained on the frequency of meals, the kinds of menus served, the methods of food preparation, etc. The general impressions of dietary habits so obtained refer to large population groups, and, together with a demographical survey, suggest the trend for nutritional policies (agricultural, economic or educational) to improve the nutritional situation.

2. All of these types of studies serve useful purposes. Which one any given country decides to undertake within the next few

years probably will depend in part on what it has already accomplished, in part on problems still to be solved and in part on the qualifications of research-workers and the credits available for the work.

Studies of type A are the most fundamental, and are essential to the interpretation of types B and C. They include demonstrations of the effect of improved diets, as well as studies of the effect of current diets on health, nutritional status and physical fitness. The state of nutrition at any given time represents the cumulative effect of long periods of feeding. We have as yet very few specific tests for detecting slight deviations from the optimal nutritional state. A close correlation between indices of *general nutrition* and *food intake for a short period such as a week or month* cannot be expected. However, these studies are indispensable for progress in the knowledge of nutrition.

Studies of type B are needed for a thorough-going understanding of the dietary position of a country. It may be necessary to supplement scientifically adequate studies of this kind with less costly but more extensive studies, for example type C.

Studies of type C are suggested as preliminary surveys. It is recommended that they be supplemented with studies of types A and B.

3. The national nutrition committees and the institutes or schools of hygiene of the following countries have indicated that they will continue present studies or undertake new work on food consumption in relation to health : Belgium, Czechoslovakia, Finland, France, Hungary, Poland, Roumania, Sweden and Yugoslavia. Other schools also are considering the possibility of undertaking such studies.

REFERENCES.

- (a) " Report of Technical Commission on Nutrition of its Meeting held in London, November 15th-20th, 1937 " (in preparation).
 - (b) " Report of Work of the Group of Experts appointed to study Methods of assessing the State of Nutrition in Infants and Adolescents ". *Bull. Health Organ.*, 1937, 6, 129.
 - (c) " Methods of Study of the Nutrition of Rural Populations used by the Institute of Public Health of Czechoslovakia ", by Dr. Hynek PELC and Marie RIEGLOVA-PODZIMKOVA. L.O.N. documents C.H.1291 and 1291(a).
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SECOND GENERAL REPORT ON CERTAIN EUROPEAN SCHOOLS AND INSTITUTES OF HYGIENE.

1. ORIGIN AND OBJECT OF THE ENQUIRY.

At its session held in May 1936, the Health Committee decided to arrange for a meeting of directors of schools and institutes of hygiene in 1937, at which the work of these institutions would be discussed and a review made of the progress achieved since the publication of Professor PRAUSNITZ' report (document C.198.M. 124.1936). The Bureau of the Health Committee, at its meeting held in Paris on October 29th and 30th, 1936, entrusted the preparatory work to Professor W. W. JAMESON, Dean of the London School of Hygiene and Tropical Medicine, Professor G. PITTALUGA, Director of the Madrid School of Hygiene, and Dr. A. STAMPAR, former Director of Health of Yugoslavia. After having visited the European institutes and schools of hygiene during November and December 1936 and January 1937, this Commission prepared the present report.

The first study of European institutes and schools was conducted on behalf of the Health Organisation by Professor C. PRAUSNITZ and published, in 1930, in a document¹ containing an account of the work of the Conferences of Directors of Schools of Hygiene, held at Paris and Dresden. A report on the teaching of hygiene in various European countries was included as well as a memorandum by Professor Léon BERNARD summing up the results of the work of

¹ Document C.H.888.IIL1930.

the Commission on Education in Hygiene and Preventive Medicine, appointed by the Health Organisation in 1924. Professor PRAUSNITZ' report deals with the teaching of hygiene in Czechoslovakia, France, Germany, Great Britain, Hungary, Poland and Yugoslavia. The major part of the report consists of a full description of the organisation and activities of the institutes and schools as central institutions for the teaching of hygiene.

The main object of the present enquiry was : (1) to study the development in the last five years of the institutes and schools already described by Professor PRAUSNITZ, and (2) to inspect the institutes and schools established after Professor PRAUSNITZ' report was published. These latter include the Roumanian Institutes at Bucharest and Jassy, the Athens School of Hygiene, the Ankara Institute and School of Hygiene, the Rome Institute of Public Health and the Sofia Institute of Public Health. The Commission was not able to visit Madrid or Cluj. Nevertheless, descriptions of these institutes are included in order to present a complete picture of recent developments in public health teaching and, in particular, of the training of medical officers of health.

Before the Commission started its study tour a large amount of material had already been collected by means of a questionnaire ; this very much facilitated the local studies and enquiries.

Professor PRAUSNITZ' report dealt with newly established institutions which had been operating for only a short period. The present report includes a description of the changes which have occurred during the past five years, the influence of the economic crisis on the work of the schools, and the relation of the schools to health administrations, public life and the social-economic background of certain countries.

There are many schools for the training of auxiliary personnel, but the members of the Commission were unable to study all of them. The report includes short descriptions of those which form part of the institutes and schools of hygiene, or in which the staff of the institutes and schools teach or take part in the practical training. The question of the training of auxiliary personnel certainly requires further study.

2. FACTORS INFLUENCING THE DEVELOPMENT AND WORK OF THE INSTITUTES AND SCHOOLS OF HYGIENE.

A. THE SOCIAL-ECONOMIC BACKGROUND.

Demographic Statistics.

In order properly to understand the position and rôle of the institutes and schools of hygiene in the different countries, it is necessary to know something of the social and economic conditions of the populations which it is hoped to benefit. The origin of health problems may often be found in social-economic factors ; indeed, there is usually a close relationship between the standard of living and the state of public health.

The countries to which this report refers fall naturally into two groups, a western group (England, France, Italy and the western part of Czechoslovakia) which is largely industrial, and an east-central group (Eastern Czechoslovakia, Poland, Hungary, Yugoslavia, Bulgaria, Greece and Turkey) which is mainly agricultural.

The percentage of the population engaged in agriculture in each country is given in the following table :

	1931
England	19.9
Western part of Czechoslovakia	25.2
France	48.0
Italy	32.0
Greece	67.0
Hungary	54.0
Eastern part of Czechoslovakia	56.6
Poland	72.8
Roumania	79.0
Yugoslavia	80.0
Bulgaria	81.3
Turkey	81.6

It is interesting to compare these countries as regards general mortality, natality and infant mortality.

	General mortality per 1,000 population	1933	
		Birth rate per 1,000 population	Infant mortality per 1,000 births
England	12.3	14.4	64
France	15.8	16.3	75
Italy	13.7	23.7	100
Czechoslovakia	13.6	19.2	127
Greece	16.9	28.8	123
Hungary	14.7	22.0	136
Poland	14.2	26.5	128
Roumania	18.7	32.0	174
Yugoslavia	16.9	31.3	140
Bulgaria	15.5	29.2	146
Turkey	20.8	44.1	125

Agrarian Reform.

In some of the agricultural countries of Europe, after the war, agrarian reforms were introduced, resulting in the breaking-up of large estates and the creation of a class of peasant owners, whose social-economic condition was thereby improved. In these countries, no one is now permitted to own more than a fixed number of acres which varies from State to State. The size of small holdings also varies—e.g., in Poland from 20 to 40 hectares, in Czechoslovakia from 5 to 15 hectares, in Roumania from 5 to 10 hectares and in Yugoslavia up to a maximum of 4 hectares. In these countries, nearly 18% of the agricultural land was affected, nearly two million new farms were created and about one million tenant farmers became landowners.

The effects of the agrarian reforms have been studied by many experts. Immediately after the reform had been carried out, production decreased. As time went on, the new owners began to improve their methods of tilling the land. They were helped extensively by means of cheap credits, material for the construction of new houses and better seeds and agricultural implements. David MITRANY discusses this question in his book, "The Land and the Peasant in Roumania". He found that the peasants as a class had been greatly benefited, having obtained almost all the arable land at a nominal price, and, in consequence, having secured a monopolistic control of agriculture. Speaking generally, the peasants produced more than before; they were short of money because they did not sell more; and they did not sell more because they had eaten more. In Czechoslovakia and Yugoslavia, new settle-

ments with better housing conditions were established for new landowners. However, even the most drastic agrarian reform could not meet the needs of all landless peasants.

In the pre-war period, thousands of peasants from Poland, Czechoslovakia, Hungary, Roumania and Yugoslavia had migrated to overseas countries where they were mostly employed as unskilled workers and supported their families at home by sending back considerable amounts of money. As immigration to overseas countries has been very greatly restricted, the available arable land in their own countries is not sufficient to provide now for the increasing peasant populations. Land holdings have consequently been divided and subdivided among the members of families, thus becoming smaller and less capable of economic exploitation.

There is now a trend towards the establishment of local industries, and attempts are being made to create self-supporting national units. The growth of industries in what were formerly purely agricultural countries has caused an influx of workers from rural to industrial areas. A relatively small number of peasants have emigrated to the Western European countries where they are employed mainly in the mining districts of Belgium, France, Germany and the Netherlands.

In conformity with the terms of the peace treaties, there have been large exchanges of rural populations between Bulgaria, Turkey and Greece. These movements have affected almost two million people and have made exceptional demands upon the financial and public health resources of the three countries. The resettlement schemes have been carried out in accordance with modern hygienic requirements.

Agrarian Situation.

The following facts give some idea of the agrarian situation :

In Poland, there are 3.3 million farms, the size of which varies widely ; according to the census of 1921, two-thirds of the farms are under 5 hectares in size and occupy only 25% of the total area of arable land, while 19,000 farms are over a hundred hectares in size and represent 27% of the arable land.

In Yugoslavia, two-thirds of the 2 million farm holdings are not larger than 3 hectares. About 10% of the rural population possesses no land, its income being derived mainly from agricultural

labour. Bulgaria is also a land of small farms. About 65% of the land holdings are from 2 to 5 hectares, occupying altogether six-tenths of the total arable land. Holdings larger than 30 hectares represent not more than one-twentieth of the arable land area.

The peasant family in Turkey tills on an average from 1 to 3 hectares, and, in exceptional cases, from 15 to 20 hectares. The State owns large areas of land, mainly as a result of the expropriation of the property of religious organisations.

In Hungary, according to data obtained in 1930, 1,644 landed proprietors with holdings larger than 400 hectares (0.1% of all proprietors) own 14.8% and 779,105 proprietors holding not more than 1 hectare (51.9% of all proprietors) only 4.3% of the total arable land. The landless agricultural population forms almost a quarter of the whole population, earning wages which are 25% lower than those earned before the war. Each 100 *hectares* of arable land must support :

100 persons of the rural population in Yugoslavia,	
97 " " " " " " " " Roumania,	
89 " " " " " " " " Bulgaria,	
80 " " " " " " " " Poland,	
72 " " " " " " " " Hungary,	
56 " " " " " " " " Czechoslovakia.	

The density of population is high in the agricultural regions of these countries. For example, it has been calculated that, in Poland in 1930, there was, on the average, a surplus agricultural population of over 3 million persons.

The yield of cereals per *hectare* is two to two and a half times as high in Denmark as in Poland, Yugoslavia, Bulgaria, Roumania or Turkey.

Agricultural Crisis.

Small land holdings, density of agricultural population, primitive methods of tilling the soil, and the large number of landless peasants must naturally affect standards of life. The institutes in Roumania and Yugoslavia have carried out some very important and interesting studies on this subject. They have found that the standard is in many cases much lower than would be suspected from purely statistical data. As regards morbidity, infant mortality, nutrition, housing and incomes, many facts have been collected showing

how acute is rural distress and how urgent is the need for a general improvement. Under such conditions, it goes without saying that medical care is insufficient.

The agricultural crisis, which began in 1930, has aggravated the already difficult social-economic situation of the rural population. This is brought out clearly by a League of Nations publication, "The Agricultural Crisis": "Immediately after the world war, agriculture experienced a period of prosperity, but, in most countries, it passed through a crisis in 1920 and 1921; then a very real improvement took place in 1924 and 1925; finally, a marked depression occurred in the cultivation of cereals, and, from 1928, spread throughout the entire world, after having also affected other branches of agricultural production, such as wool and cotton. Gradually, the situation became distinctly unfavourable. The year 1930 was a year of disappointment in every way, and it has left in the minds of farmers the memory of something approaching disaster. The complaints of the farmers are heard in almost every country."

Official figures compiled by the Agricultural Academy at Prague show how the crisis developed in Czechoslovakia. The cash yield per hectare of corn-land was estimated in 1927 at 1,325 Czech crowns; in 1928, at 1,080 crowns; in 1929, at 658 crowns; in 1931, at 210 crowns; in 1932, at 110 crowns, and, in 1933, income was replaced by an actual loss. Similar statements have been made by the Polish Agricultural Institute. The fall in prices of agricultural products was noticed in every country. The peasants incurred heavy debts and only a series of emergency measures saved them from greater disaster.

Industrial Crisis.

Unemployment is one of the most important indices of industrial depression. The following figures of unemployment in the period from 1929 to 1936 show the extent and development of the crisis. The number of unemployed persons during that time was:

	1929	1932	1933	1934	1935	1936
	(000's omitted)					
In the United Kingdom ...	1,004	2,233	2,310	1,908	1,818	1,639
In Czechoslovakia	50	634	878	790	805	798
In Italy	293	1,053	1,082	1,057	853	
In Poland.....	171	363	280	388	506	475

A series of measures has been adopted to deal with this problem. Public works have been undertaken, social insurance schemes extended, social welfare activities enlarged, the care of children greatly elaborated, the problems of nutrition taken into consideration, housing conditions very much improved and in some countries resettlement on the land of urban population has been attempted.

Recent Economic Improvement.

There was an improvement in economic conditions at the time when these studies on schools and institutes were carried out. The number of unemployed had decreased as compared with the previous year; the prices of agricultural products had increased slightly; the harvest was abundant in agricultural countries; estimates of expenditure on health work were higher. Nevertheless, conditions among the rural population are still very serious.

During the past five years, public interest in health and social problems has greatly increased. But the shock of the agricultural and industrial depression and the slowness of recovery tend to show that it is impossible to improve public health without bringing about other important changes in social and economic conditions.

B. THE INFLUENCE OF THE ECONOMIC DEPRESSION ON PUBLIC HEALTH EXPENDITURE.

The general level of public expenditure was more affected by the economic depression in agricultural than in industrial countries. The total expenditure in the United Kingdom rose from £818 million in 1928/29 to £824.3 million in 1935/36. In Bulgaria, on the other hand, the budget fell from 7,389.3 million leva to 5,695.1 millions; in Hungary from 1,472.8 million pengő to 1,176.1 millions; in Poland from 2,841.1 million złoty to 2,168.4 millions; in Roumania from 32,223.6 million lei to 20,686.8 millions and in Yugoslavia from 11,386.5¹ million dinara to 10,323.5 millions during the same period. The largest decrease took place in Roumania.

¹ In 1930/31, 12,469.6 million.

During the same period, State expenditure for health and social services did not decrease proportionately. There is again a difference between industrial and agricultural countries. The enlarged and newly developed health services have required even an increase in expenditure. In the United Kingdom, this expenditure amounted to 9.84% of the total expenditure in 1936/37; in France, to 6% during the same years; in 1928/29, it amounted to only 7.69% in England and to 2.6% in France. In Czechoslovakia, the trends are similar; in 1928/29, the expenditure for these purposes amounted to 4.10% and, in 1936/37, to 6.61% of the total expenditure.

Even in agricultural countries, the health services have been developed in spite of drastic cuts in the State budgets. Many of the health services formerly provided by the State have been taken over by local administrations. In Roumania, a special fund was created from the proceeds of a lottery and surtaxes; with the help of this, the total expenditure *per caput* on health services has remained practically the same during the past few years. In Poland, the total amount spent out of the State budget decreased from 14.8 million zloty in 1928/29 to 9.7 millions in 1932/33. It was 11.4 millions in 1935/36. In Turkey, the expenditure rose from £T3.1 million in 1928/29 to £T4.8 million in 1935 and to £T8.2 million in 1936. In Czechoslovakia, the amount spent on health services has remained practically the same during the last few years (140 million crowns). The amount devoted to social welfare rose from 330 millions in 1928/29 to 447.5 millions in 1935/36. In Yugoslavia, the expenditure of the Ministry of Social Welfare and Public Health in 1934/35 decreased to 65.9% of the expenditure in 1930/31; in Hungary, the decrease has also been considerable; from 33.1 million pengö in 1928/29 to 20.8 millions in 1933/34.

Examination of the expenditure of the different institutes and schools of hygiene during the past few years shows that, in the countries where there was a tendency to increase general State expenditure, the amounts spent by institutes and schools have increased even in larger proportions.

The total expenditure of the London school in 1930/31 was £64,244 9s. 8d. and, in 1935/36, £82,644 7s. 11d. The contribution from the Treasury amounts to £40,000 and is the same as in recent years; students' fees amounted to an average of about £5,000 per annum; there has been a considerable increase in contributions and

donations for special researches ; these represent almost one-fourth of the total income.

In other cases, it is difficult to separate the expenditure of the schools from that of the institutes, because, in the majority of cases, the schools are only departments of the institute, or the schools are carrying out a programme of national health administration with numerous field activities.

In Nancy, the expenditure of the institute of hygiene represents a relatively small percentage of the total amount expended on the widely developed health services of the department of Meurthe-et-Moselle. In the period from 1930 to 1936, the budget of the Office d'Hygiène sociale rose from 1.1 million to 3 million francs per annum.

Expenditure of the Czechoslovak Institute of Hygiene also shows a tendency to increase : from 6.42 million crowns in 1931 to 8.19 million crowns in 1935. As regards income, mainly derived from the sale of sera and vaccines, the total rose from 3.69 million crowns in 1930 to 5.58 million crowns in 1935 ; the grant from the Treasury remaining practically the same during this period—*i.e.*, an average of 2.6 millions per annum.

The Ankara Institute of Hygiene shows a considerable increase in expenditure : from 114,447 Turkish pounds in 1934 to 381,480 in 1936 ; a good deal of this increase is due to the fact that the Institute was being rapidly developed during these years. In Hungary, the Institute of Hygiene has not followed the tendency shown in the State budget to reduce general expenditure on health ; on the contrary, in 1936/37, two and a half times as much was spent as in 1932/33, mainly on newly organised rural health services and on sanitation.

A different picture is presented by the institutes and schools in Poland, Yugoslavia and Roumania.

At Warsaw, the institute derives an annual income of rather more than one million zloty from the production and sale of sera and vaccines, and receives from the State an annual grant which fell from 771,256 zloty in 1931/32 to 527,836 zloty in 1935/36. The school at Zagreb has experienced even more drastic cuts ; in PRAUSNITZ' report, the budget of the school before the economic crisis showed the expenditure and income balanced in 1929/30 at 7.4 million dinara ; in the same year, the grant from the Treasury

reached as high a figure as 3.5 millions. In 1936/37, the total expenditure amounted to 4.99 millions, but the Treasury contribution was cut down to 1.19 million dinara.

The Roumanian institutes also show considerable decreases in expenditure. The Institute of Hygiene at Bucharest receives for material expenses only 80,000 lei per annum ; at Cluj, the institute spent in 1932/33, 1.25 million lei for salaries and 0.5 million lei for material expenses. In 1936/37, these sums were cut down to 0.94 and 0.08 million lei respectively. At Jassy, in 1936/37, the items for salaries amounted to 1.42 million lei and for material expenses 0.09 million lei, in comparison with 2.5 million lei and 0.4 million lei in 1931.

Nominally, the expenditure of the Athens school of hygiene decreased in 1935/36 to half the amount provided by the budget in 1931/32 ; in practice, however, the expenditure on the newly organised health services outside the school is met by special appropriations and is not now included in the budget of the school. For field activities, especially for anti-malaria work and sanitation, conducted by the corresponding departments of the school, large sums have been appropriated in recent years.

The question naturally arises how the work of the institutes and schools has been affected in cases where there has been a considerable decrease in the budget. First of all, salaries in Poland, Czechoslovakia, Hungary, Yugoslavia and Roumania are now much lower than before the crisis. For this reason, in some countries,¹ the technical staff very often takes on one or more additional appointments. As regards laboratory and routine work, there has been a normal development. The field activities and organisation of local health services have been much restricted and some services have been abandoned. In Poland, new departments have been established in the institute and a new organisation set up for the control and improvement of water-supplies, largely owing to the assistance of local authorities. The school in Zagreb maintains activity in all branches of work in spite of very much decreased expenditure, thanks to the additional support received from local authorities and from peasants, with whom the school had colla-

¹ Czechoslovakia, Poland and Roumania.

borated successfully for years ; health education in general and work on sanitation have developed very satisfactorily.

The Cantacuzène Institute, which derives an income from the sale of its biological products, was not so much affected by the depression, but the institutes of hygiene at Bucharest, Cluj and Jassy have devoted themselves mainly to laboratory work, and to the maintenance of the attached health centres which carry out important field investigations. The rôle of the Rockefeller Foundation, which helped a number of institutes and schools during the emergency with grants for the development of the work, has been of the greatest importance.

C. THE INFLUENCE OF TRADITION IN VARIOUS COUNTRIES.

In each of the countries visited, there has been great interest and considerable activity during the last two decades in the reorganisation and improvement of the existing social and health services. In newly established States, the tradition in health organisation was not deeply rooted and there was a strong movement to develop a social and health service on modern lines.

Great Britain has certainly the longest tradition in public health work. The first public health officer was appointed nearly a hundred years ago, and subsequently a whole-time health service was established. Housing, improvement of nutrition, maternity and child welfare, school hygiene, the control of social diseases, social services for the unemployed, are only parts, even if the most important, of a wider programme for the protection of national health. Public health has become a generally accepted obligation of government, and a matter of real public interest. The position of a health officer has grown stronger with the passage of years ; working with the local authorities, he can do much on his own initiative and, as a rule, is strongly supported by public opinion. The funds for public health are increasing every year. The health services have grown up with the development of local government and now form an important part of local authorities' responsibilities. In this atmosphere, the idea of a school of hygiene gradually developed and took shape, and, at present, the school is in a strong position with a growing number of students.

The case of *France* is quite different. With an excellent tradition in scientific and curative medicine, and particularly in relation to the prevention of infectious disease as evidenced by the work of the Pasteur Institute, this country only recently started to establish public health services. The first steps taken were the organisation of an anti-tuberculosis and anti-venereal campaign and of a scheme for child welfare work. Not until 1902 were steps taken to create Departmental Health Services with whole-time health officers in charge. At a still later date, post-graduate training for medical officers was established, and a rational and standardised system of recruitment of the medical officers introduced.

In *Italy*, the institute of public health represents the concentration of existing special institutions, of which some have had a long and honourable tradition. The general sanitation and reclamation (*bonification*) and the anti-malaria work, in which Italy has such brilliant achievements to her credit and which have been elaborated greatly in recent years, were a powerful stimulus to the establishment of the present institute. The post-graduate training in tuberculosis is a natural development of the special system of insurance against tuberculosis, and is based on sound scientific principles.

In *Spain*, all the health activities of the country have, in reality, been centred, from the technical point of view, in the institute of hygiene, which was created in 1900. Some resistance has from time to time been offered by the large professional associations, seconded by several thousands of doctors who organise a comprehensive and efficient system of medical assistance in rural areas, a system which, since 1931, has been of the most up-to-date kind. This system, however, is, in part, based on the traditions of private medical practice.

In *Czechoslovakia*, there is a long tradition in health administration. The Austrian Health Law of 1870 and the Hungarian Law of 1876 still influence the health services. There is still in force the requirement that medical officers must have the "physicate" certificate. For this, university professors organise post-graduate training on private lines. Social insurance legislation, on the other hand, has been widened in scope, embracing, at present, half of the population. The initiative in medical-social matters is in the hands of social insurance institutions, not in those of the Ministry

of Health. Physicians are more apt to be attracted by employment in social insurance institutions than in that of the State health service. A large amount of health work is also carried out by numerous private agencies. In these circumstances, the institute of hygiene is still seeking its proper place in the health work of the country. It is mainly an institution for diagnostic purposes, field surveys and the production of sera and vaccines, taking, from time to time, a part in the numerous short-term courses for physicians organised throughout the country.

As regards health administration in *Poland*, there are the traditions of the former German, Austrian and Russian medical services. As a result of the establishment of a Ministry of Health in the early days of the Republic and lately of a ministry of social welfare, the general control of health policy is in the hands of a central authority, which is attempting to unify and standardise the health service and to adapt the varying traditions to modern problems and methods. In 1919, an epidemiological institute was opened at Warsaw. This institute was the immediate predecessor of the existing institute of hygiene.

The severe typhus epidemics which occurred fifteen years ago in Russia and Eastern Europe, and the European Sanitary Conference convened at Warsaw in co-operation with the League of Nations to deal with this question, gave a strong impetus to the subsequent development of modern health services in Poland. The severe economic depression has restricted the further development of rural health centres, so successfully established in the beginning. The institute of hygiene created twelve years ago, with its public health school, became a centre for new ideas, and it produced a new type of physician. It not only improved the technical services in the country but also provided a model new health organisation, which developed at Warsaw and in some other districts.

By the Law of 1876, a very progressive health service (for the period) was established in *Hungarian* departments, districts and communities. The Departments enjoyed a great measure of autonomy in health matters. For several decades, the health service performed to some extent the duties of sanitary police and, apart from this, restricted its work to the medical treatment of the poor. Hungary is well known for her child welfare activities, which started at the beginning of this century. The institutions for children, the

methods of dealing with destitute children and the network of institutions for the care and treatment of sick children certainly represent the first elements of a preventive service. The powerful "Stephania" child welfare association carried out extensive work in this field. At Budapest, a special commission of university professors has for years organised post-graduate courses for physicians, consisting of a series of lectures mainly in clinical subjects but also in hygiene. A few years after its organisation, the institute of hygiene became a section of the Ministry, acting as a technical department in the execution of the State health programme. This programme consists mainly of measures directed towards the improvement of the health services in the districts and communes through compulsory training in hygiene of all physicians in public service, of the organisation of rural health centres and of field activities carried out directly by the institute.

The present *Yugoslav* health administration developed in response to a strong national demand for better health conditions after the terrible experiences of the late war. Formed of a number of different constituent parts, Yugoslavia inherited, as regards health organisation, the traditions of Serbia, Montenegro, Croatia, Hungary, Bosnia and Herzegovina, Dalmatia and Slovenia. The Serbian Health Law of 1882 provided to some extent for preventive services, the autonomous Croatian Health Law of 1906 was even more advanced. The autonomous Bosnian-Herzegovinan Law against Epidemics, adopted in 1914, but in force only for a short period, included a great many excellent preventive measures. In Montenegro, there were only the beginnings of a medical service; in other parts of Yugoslavia, the old Hungarian and Austrian laws applied. Under the influence of the war experiences, and with the help of an awakened peasantry, represented in Parliament and in political, economic and cultural peasant organisations, a favourable situation was created which enabled groups of young physicians with modern training to reorganise the existing health services and to establish, in a very short time, a new health organisation as a basis for further developments. The main characteristics of this organisation are the efforts directed towards an improvement in rural health and the close collaboration with the peasant population. This has resulted in a series of experiments conducted by the school at Zagreb and the institute of hygiene at Belgrade, through direct

action in villages or through specially organised health co-operatives.

Roumania, already in possession of an old-established basis of scientific medicine and voluntary hospital organisations, has inherited in Transylvania, in Bukovina and in Bessarabia the traditions of Hungary, of Austria and of Russia. The establishment of rural health services in Roumania became more and more important after the agrarian reform, and, in 1930, a new Public Health Law was enacted providing for the reorganisation of the health services, the appointment of full-time medical officers, regional institutes of hygiene, rural hygiene services and a series of preventive measures. In spite of the fact that this law was later modified and weakened, there still exists a strong desire for a modern health organisation, and the institutes, in the face of serious economic difficulties, are still carrying out excellent demonstration programmes, thereby producing results which can serve as examples and which will have considerable influence when the economic situation improves.

In *Greece*, the establishment of modern health services and of a school of public health is due to some extent to the influence of the worldwide movement in favour of better health conditions, to the influx of refugees in consequence of the war in Asia Minor and to the anti-malaria and sanitation plans that have been taken in hand, notably in the valleys of the Vardar and the Struma.

The Ottoman Empire did not attach sufficient importance to health questions, and, when the Republican regime was established in *Turkey*, the institutions providing care for the sick were totally inadequate for the needs of the country, nor did any organisations exist for the campaign against social diseases.

Thus, in 1920, when the National Government was instituted in Anatolia, a Ministry of Health and Social Welfare was set up. This Ministry found itself faced with important tasks. These included the taking of measures of public health protection and of remedying deficiencies as regards the number of physicians and qualified sanitary personnel, while elaborating, at the same time, laws and regulations indispensable for a modern health and social welfare organisation.

By the production of sera and vaccines, the Ankara Institute of Hygiene takes an active part in the campaign against contagious

diseases. It is, in addition, a national centre for medical and biological research. The institute forms a section of the Central Organisation of the Ministry of Health and Social Welfare. Rural hygiene occupies an important place in the work of the Ministry. Two schools have already been opened for the training of sanitary inspectors, who do good work in improving village hygiene. Schools for the training of midwives for the villages are also being created.

There is no doubt that tradition plays a very important part in every country. The health work conducted in recent years in the countries of Europe is in many respects moulded by traditions which differ from country to country. The progress made in these years has certainly been very rapid and represents a great achievement in applied hygiene. The strong influence exerted by successful health work in neighbouring countries has been evident in many cases. The fellowships granted by the Rockefeller Foundation and by the Health Organisation of the League of Nations and the interchanges organised by the latter body have contributed very greatly towards promoting progress, widening experience and facilitating the study of health work all over the world.

D. INFLUENCE OF INTERNATIONAL HEALTH ORGANISATIONS.

1. *The Health Organisation of the League of Nations.*

The problem of post-graduate training in public health was studied for several years by a special Commission appointed in 1924 by the Health Committee. The Commission was invited to take part in the inauguration of the Warsaw School in 1926 and in similar functions at Budapest and Zagreb in 1927. The third and fourth meetings were held at Paris and Dresden respectively in 1930. The following problems were discussed : (1) the character of the research work of the school ; (2) instruction in sanitary engineering ; (3) methods and extent of field training ; (4) other activities of a school.

The conclusions of these Conferences were described in full by Professor Léon BERNARD and Professor Carl PRAUSNITZ in the

report on the work of the Conferences of Directors of Schools of Hygiene (Geneva, 1930, document C.H.888).

The rôle of the Health Organisation in the establishment of the Athens School of Hygiene was of great importance. In response to a request from the Under-Secretary of Health of the Greek Government, a Commission was despatched to study local conditions and the possibility of developing modern public health services. This Commission spent several months in Greece and presented to the Health Organisation proposals later adopted by the Greek Government. The establishment of the Athens health centre and school of hygiene was the consequence. Dr. F. Norman WHITE, member of the Health Section of the League of Nations, was appointed Director of the Athens centre and school (see document C.162.M.63.1929.III).

The directors and experts of the institutes and schools of hygiene took a very important part in the discussions and proceedings of the European Conference on Rural Hygiene (June 29th to July 7th, 1931). The Conference recommended that a study of subjects of particular interest to rural sanitation should be undertaken, under the auspices of the Health Organisation, by various schools and institutes of hygiene. The meeting of the directors of European schools of hygiene considered this recommendation and decided to study the following problems : (1) The cost and efficiency of rural health services ; (2) manure and flies ; (3) milk in rural districts ; (4) typhoid infections ; (5) methods used for the analysis and expert examination of water supplies and sewage (document C.473.M.202.1931.III). In subsequent years, these field studies were undertaken by schools, the reports being published in the *Quarterly Bulletin of the Health Organisation*.

In March 1935, a meeting of directors and experts of the schools and institutes of hygiene at Zagreb, Warsaw and Nancy, assisted by representatives of the International Labour Office, was convened at Geneva to consider the guiding principles for the study of rural housing (documents C.H.1160/36, C.H./Hyg.rurale/E.H.1).

The European Conference on Rural Hygiene had recommended that enquiries should be made into the conditions of *rural housing*, and the Bureau of the Health Committee, when considering, in November 1934, the technical suggestions made by the last Assembly, which included the study of rural dwellings and farms, decided

to take advantage of the meeting of the directors of schools and institutes of hygiene to ask them to consider this question.

The meeting of directors of European schools and institutes of hygiene held at Geneva from April 24th to 26th, 1935, decided to carry out studies on rural housing and reviewed the work done under the auspices of the League on fly prevention and on nutrition in rural areas.

A meeting of entomologists, convened by the Health Organisation to discuss the fly problem, was held in London on December 16th and 17th, 1935.¹

In the period following the Conference on Rural Hygiene, studies on the other subjects were carried out by different institutes and schools. The institutes at Nancy, Budapest and Warsaw, the school at Zagreb and the Roumanian institutes conducted studies on milk, typhoid, tuberculosis, pellagra and malaria and on social economic conditions in rural areas ; the institute at Nancy worked on brucellosis, and, at the institutes in Denmark and England, studies on milk were carried out by a number of specialists. The Social Medicine Department of the Prague Institute of Hygiene published studies on the cost of health services and on nutrition in rural districts. The Health Organisation financed some of these studies entirely or made certain grants to the institutes and schools for the purpose of facilitating studies which were already being carried out as a part of the regular activities of these institutions.

Beside organising meetings of directors and experts and initiating and financing field studies, the Health Organisation invited members of the staffs of the institutes and schools to take part in interchanges or individual study tours. In this way, many subjects of common interest were discussed and views exchanged and experience pooled. Seventeen directors and experts have been given travel opportunities during the last four years to study general health activities, the organisation and work of the institutes and schools of hygiene, and rural health problems ; these missions lasted from one to eight weeks.

¹ Further studies have been proposed (1) on the influence of the house-fly on the epidemiology of intestinal diseases and (2) on biology and morphology of flies which are attracted by human food and of those breeding in human faeces.

2. *The International Health Division of the Rockefeller Foundation.*

In the last fifteen years, the rôle of the Rockefeller Foundation and its influence in matters of public health have assumed such importance that, in every country of Europe, there is evidence of its activities in different fields—medical education, public health administration, public health institutions and research work. It is no exaggeration to say that many extremely important public health activities have been started only because the Foundation initiated them or strongly supported the proposals submitted by national health administrations, all of which in the post-war period were much interested in the development of modern public health services.

The assistance furnished by the Foundation took three main forms :

- (1) Collaboration with national health administrations in the establishment and maintenance of institutes of hygiene, schools of hygiene and schools of nursing, in the reform of existing health services or in the establishment of new local health services ;
- (2) Granting of fellowships ;
- (3) Grants for research work.

Undoubtedly the institutes and schools of hygiene are the basic institutions of every country for the training of personnel in public health, the creation of a new spirit in the health services and the carrying-out of research work. Practically every administration, in its endeavour to organise a modern health service, was faced with the difficulty of finding properly trained personnel.

The Foundation has helped the national health administrations in the establishment of institutes and schools of hygiene :

- (1) With capital grants, which amounted to a certain percentage of the total expenditure (in the majority of cases, 50%), the rest being paid by the administrations which also undertook to meet all running expenses ; with this help, new buildings for the institutes and schools at Warsaw, Prague, Zagreb, Budapest, London, Ankara, Rome, Bucharest and Sofia have been built ;

- (2) With grants for local health services in demonstration centres for practical training in public health ;
- (3) With grants for the development of special activities of the institutes and schools.

In connection with the work of the institutes and schools, and for the purpose of practical training in public health, the Foundation supported the national health service administrations with grants for studies on health service reforms and for the development of local services and special units for demonstrations. Bulgaria, Czechoslovakia, Greece, Hungary, Italy, Poland, Roumania, Turkey and Yugoslavia received, in this period, substantial grants for these purposes.

Schemes for the training of nurses could not, in many cases, have been carried out without the help of the Foundation. Grants were given for certain nursing schools such as Budapest, Prague, Warsaw and Bucharest.

From the very beginning, the Foundation's policy was to grant fellowships to officers of different administrations and institutions for post-graduate studies of the more important subjects in public health. The majority of these officers were sent to the United States of America and Canada, and, after training in these countries, they returned to take up leading positions, mainly in the institutes and schools. A number of them developed into leaders in the central health administrations. The Foundation also gave shorter study tours to enable experts to meet and exchange views, to make local studies and to collect useful information. The special studies undertaken by the most promising officers were supported with grants-in-aid and the necessary equipment.

Field work and applied research, supported or maintained entirely by the Foundation, and payment of the experts connected with this programme have exerted a marked influence on the work of the institutes and schools. In Italy, Greece, Bulgaria and Spain, the malaria studies and field work carried out respectively by HACKETT, by BALFOUR and BARBER, by COLLINS, and by BAILEY and HILL represent a most important and successful method of co-operating with national institutes. In other cases, the Foundation has established and financed independent services for special studies : at Jassy, on scarlet fever (GORDON and JANNEY) ; at Budapest, on

influenza (TAYLOR); but, in all cases, in close collaboration with the institutes of hygiene. Dr. COLLINS, representative of the Foundation for Bulgaria, Turkey and Yugoslavia, is the Director of the school of hygiene in Ankara, and Mr. WRIGHT, an expert of the Foundation on sanitary engineering, after spending a few years in the Athens School of Hygiene, now teaches in the Ankara school and carries on field work. Undoubtedly, the assistance given by the Rockefeller Foundation has been of great importance.¹

3. DESCRIPTION OF THE INSTITUTES AND SCHOOLS OF HYGIENE.

A. TYPES OF INSTITUTION.

During the past five years, the position of the schools in their relationship to the State health administrations has undergone certain changes. At present, the schools are of different types as regards both their organisation and their position in the health administration and programme of work :

The *first type* includes the schools which are university institutions, organised for public health teaching and for the conduct of pure and applied research work. At present, there is only one example of this type in Europe : the London School of Hygiene and Tropical Medicine. This institution is a school of the University of London which conducts the examinations of, and confers diplomas on, the students of the school. It is an academic institution with all the duties and privileges of a university school. The professors and readers are appointed according to university regulations.

The institutes of hygiene at Nancy, Cluj, Jassy and Bucharest represent the *second type*. In these, the university institutes of hygiene have combined forces with the regional institutes of hygiene to form a single unit, and are supported in their work by both the education and the health authorities. The professors of

¹ The aid given by the International Health Division of the Rockefeller Foundation during the period 1920 to 1936 inclusive for the establishment of the institutes and schools of hygiene referred to in this report amounts to \$5,366,981, and, for their development and maintenance, \$475,684.

hygiene are at the same time directors of the regional institutes, and the associate professors and assistants to the chair of hygiene at the university are heads of the sections of the institute. Besides giving post-graduate training, these institutes act as centres of health work in certain areas ; at Nancy, in the Department of Meurthe-et-Moselle ; at Cluj, at Bucharest and at Jassy in a group of provinces. The instruction in hygiene of medical students is given in the same institutes. Post-graduate training is very much facilitated by these arrangements, especially as regards practical work and studies of local health problems. In the case of the Nancy institute the health organisation in the Department extends to practically all fields of public health and provides unusual facilities for practical work. In the Roumanian institutes of hygiene, the field work at present is restricted to certain smaller areas, demonstration centres and suryeys. The staff of the Nancy institute is employed on a whole-time basis, that of the Roumanian institutes on a part-time.

The *third type* includes the schools at Warsaw, Budapest, Rome and Ankara. In these, the institutes of hygiene organise the public health courses by means of a department known as the school of public health. The staff of the institute provides the greater part of the instruction, and practical training is conducted in the laboratories of the different sections and in health centres and field demonstration areas organised by the institute. At Budapest, the school is only a function of the institute, having no offices, buildings or laboratories of its own. The institute in its turn is organised as a section of the Ministry of the Interior. At Warsaw and at Ankara, the schools are housed in separate buildings but form administrative units within the institutes of hygiene.

The *fourth type* is represented by the Zagreb and Athens schools, which are special institutions of the State health administration, directly under the authority of the Health Ministries. Both institutions (Zagreb and Athens) give courses in public health and carry out part of the programme of the State health administration—Zagreb in matters of health education, field surveys and sanitary engineering—Athens in anti-malaria work and sanitation. The training of physicians and of auxiliary public health personnel is not the principal task of the Zagreb school, which devotes more time and interest to the general improvement of village life and to

health education. The Athens school with its health centre serves as a model for the new type of health organisation which is now developing in Greece.

B. STUDENTS, TEACHERS AND COURSES.

The post-graduate training in public health carried out by these institutes and schools of hygiene is not of a uniform type. There are many differences as regards the duration of the course, the subjects taught, the recruiting of students and the status of the teachers.

The teaching is conducted by the university institutions or by the institutes and schools belonging to the health administrations. In the former, the training is organised by university professors whose main duties are scholastic in character, as at the London school, in the medical faculties of five French universities and in Roumania ; in the latter, this teaching is undertaken by the staff of the institutes, which is mainly concerned with routine and research laboratory work.

The London school is attended by students from all parts of the world. In the period 1930-1936, 1,060 students from 44 different countries followed its courses. The major part (528) came from the British Isles, 164 from India, 83 from Ceylon, 54 from the United States of America, 32 from Egypt, 29 from South Africa and the remainder from 21 European and Asiatic countries. The courses organised by the Forlanini Institute in Rome are also followed regularly by numbers of foreign students. The remaining institutes and schools are of a more national character, recruiting students, except in very rare cases, locally.

Regular courses have been given in London, in five French medical faculties, at Warsaw, at Budapest, in Roumanian institutes and at Athens. During the last eleven years, the Warsaw courses have had an average yearly attendance of 25 students. Since 1929/30, the public health course in London has been attended each year by 40-50 students, the course in tropical medicine by 100-140, that in bacteriology by 10-14 students, and that in epidemiology and vital statistics by 1-15 students. At Budapest, the course for district health officers and community doctors is attended by an average

of 25 students. From 1931/32, 9-27 students have graduated yearly at Athens. In Roumania, the number of students had decreased from 72 in 1933/34 to 44 in 1935/36, owing to the fact that the training is not compulsory. At Madrid, the maximum number attending has been 30.

Tuition and examination fees are payable by the students taking post-graduate training in London, in French faculties and at Budapest. In London, the fees are high but are considered by the students as a necessary investment for their careers ; in France, the tuition and examination fees average 600 francs, while, at Budapest, examination fees only are charged. At Warsaw, Budapest, Zagreb and Ankara the students are given facilities in the form of cheap board and lodging, leave from their posts with full salary, and allowances for travelling expenses.

The duration of the courses differs considerably. The courses for medical officers in Sofia and those for community doctors at Budapest last from six to eight weeks ; public health courses at Ankara last four months ; at Zagreb, Nancy, Montpellier, Lyons, Paris, Algiers and Warsaw six months ; at Budapest nine months ; at Bucharest, Jassy and Cluj from ten to eleven months ; in London and at Athens twelve months.

The programmes of the courses, even those of the same duration, differ widely, especially as regards the time given to the different subjects. The courses organised by the schools at Warsaw and at Zagreb may be taken as examples. The problems with which the physicians in public service are confronted are about the same in both countries. At Warsaw, the teaching consists of 335 hours of theoretical lectures and 436 hours of laboratory or field work ; at Zagreb 341 hours of lectures and seventy hours of practical training in laboratories and field surveys. The number of hours spent in sanitary engineering is practically the same ; in industrial hygiene the number of hours at Warsaw is five times greater than at Zagreb. Theoretical training at Budapest comprises 430 lectures and 129 hours of laboratory practice during a period of five months. The curriculum in Ankara comprises 414 hours, of which 108 hours are practical training.

The curricula of the Roumanian institutes differ too as regards hours of teaching, practical training and subjects taught. In French medical faculties, the courses also show differences. In

London and at Athens, the teaching lasts for an academic year, but there are great differences in the methods of teaching and in facilities for instruction. In those schools where the members of the teaching staff give whole-time service, instruction appears to be on a more satisfactory basis. University professors have obviously more freedom in the selection of the subjects to be taught and in the methods of teaching. In the majority of the institutes and schools, the staff, in addition to their administrative, technical and routine work, have also teaching responsibilities.

Short-term courses are held from time to time. At Warsaw, Zagreb and Belgrade, and in Roumania, special courses of varying duration are provided for school health officers.

Some of the schools organise courses for laymen. In London, the Ross Institute, which is incorporated in the school, gives courses on the control of malaria and on tropical hygiene for persons going to the tropics. In the Warsaw school, courses for students, social workers and teachers are held regularly. Beginning in 1934, short courses have been given in the Athens School of Hygiene to teachers of normal schools, in co-operation with the Ministry of Education. At Zagreb and Belgrade, there are systematic courses for peasants with lectures and practical work in hygiene, general education, agriculture and housekeeping.

As regards the training of auxiliary personnel, there are schools of nursing attached to the institutes and schools, as at Budapest and Zagreb, or special institutions for the training of nurses collaborating with the institutes in teaching and practical training, as at Rome, Warsaw, Prague, Cluj, Jassy, Bucharest and Athens. The courses for nurses are more uniform than those for doctors ; they average three years in length, and the diplomas given cover both general nursing and public health work. The demand for trained nurses is growing rapidly in all countries. Training for sanitary inspectors is conducted at the schools of Zagreb, Belgrade, Warsaw and Athens. The courses vary in length ; at Warsaw four months, at Athens eight months, at Zagreb and Belgrade one year.

Each school and institute has facilities in specially established demonstration areas, health centres, rural health services and laboratories for practical training. The museums also are of great help. The largest and best equipped museums are in London, at Rome and at Warsaw ; at Zagreb, Belgrade and Budapest the

museums are organised for the general public rather than for the students ; at Nancy, the museum is not large but is very satisfactorily arranged ; at Athens the museum is located in the auditorium and consists of important charts and models.

Students after graduation from the schools cannot expect immediate employment, except in cases (Yugoslavia, Bulgaria, Turkey and Greece) where the training is organised for physicians already in the health service. At Athens, the majority of the students of the school of hygiene have been Government officials who take the post-graduate training and return to their former positions. Practically all the British graduates from the London school enter one or other of the branches of the public health service ; in France, a certain percentage is still in medical practice ; in Poland, the graduates are employed in the majority of cases after a certain delay. There is undoubtedly a growing interest in post-graduate training in public health amongst physicians.

4. GENERAL OBSERVATIONS ON THE WORK OF THE INSTITUTES AND SCHOOLS.

More than a decade has passed since the first of the schools described in this study was established. Professor PRAUSNITZ' report describes the beginnings of their activities. During the past five years, many changes have occurred in the political and social life of the world and the institutes and schools have naturally been considerably influenced by the general trend of social and economic conditions.

The primary aim of the institutes and schools is to train physicians and auxiliary personnel for the recently organised services in public health, social insurance and social assistance, or to promote the improvement of existing services, as well as to carry out pure and applied research work. Originally certain of the institutes and schools were organised as branches of the national public health system with the object of carrying out a public health programme, especially as regards field work. A study of their development and activity during the last few years reveals that only in exceptional cases has there been stability ; in the majority of cases, too many

changes have occurred as regards organisation, programme and activities.

The majority of institutes and schools have succeeded only partially in carrying out their original programmes. Let us examine the reasons for this partial failure.

A. FULL-TIME SERVICE.

A full-time public health service has not been introduced in every country. In some, the law limits the requirement of full-time employment to certain appointments in the health services, but, in practice, the salaries paid the holders of these appointments do not ensure a reasonably comfortable livelihood—an essential factor in full-time employment. In reality, such full-time service is, in England, found only for the staff of the London School of Hygiene and for medical officers (and assistant medical officers) of health ; in France, for departmental inspectors ; in Hungary, for the staff of the institute and for medical officers in the Ministry, departments and districts ; in Yugoslavia, for the staffs of the school and institutes of hygiene, and of health centres ; in Turkey, for the staff of the Ministry, the institute and for medical officers of health. The salaries differ widely. Taking the cost of living into consideration, only the salaries of the staff in the public health services in England and those of high ranking officials in the health services of the other countries make adequate provision for a comfortable livelihood. In Poland, Czechoslovakia and Roumania, the majority of the medical officers earn additional incomes from other employment. Naturally, in these circumstances, they cannot devote themselves entirely to the carrying-out of their primary duties.

B. COMPULSORY TRAINING IN PUBLIC HEALTH.

Only in England, France, Hungary and Greece is a diploma or certificate in public health compulsory for applicants for posts in the public health services. In England, the diploma has long been obligatory, while, in France, Hungary and Greece, this requirement is of more recent date. In Poland, there is provision for the train-

ing of physicians who apply for positions in the district health service, but the authorities may still appoint a district medical officer who has not received a public health training. In Czechoslovakia, an examination known as the "physicate" (without any regular courses of training) is all that is required. In Yugoslavia, the provincial administrations are obliged to send district physicians to the school of hygiene for post-graduate training, but this provision has been enforced only in part. In Roumania, compulsory training was abandoned four years ago. In Turkey and Bulgaria, medical officers of state and local administrations are officially invited (*i.e.*, required) to attend short-term courses.

C. THE TRAINING IN HYGIENE OF MEDICAL STUDENTS AND GRADUATES.

In order to provide adequate health protection for all classes of the population, it is essential that physicians should receive proper training in modern hygiene. This need was evident in all the countries visited during the study tour. The rôle of the medical practitioner in public health is much more important than one would assume from the time devoted to the teaching of hygiene in medical faculties. The responsibilities of the private practitioner as regards the health services organised by the State and by local authorities and his relationship to social insurance institutions and other medico-social organisations require on his part a considerably greater knowledge than he now possesses concerning modern public health practice and medico-social problems. He should acquire this knowledge during his medical course. The lectures, demonstrations and practical work given by the staff of the Department of Hygiene of the university do not suffice; the spirit of preventive medicine should permeate the whole of the curriculum. While these principles are generally accepted, they are very rarely put into practice, with the result that medical graduates are not adequately prepared to meet the social and public health responsibilities with which they are confronted.

Before describing the post-graduate training, it is necessary briefly to review the present status of teaching in hygiene in medical schools and to see how the students are instructed and prepared

for their future work as medical practitioners in a highly organised society.

It is common knowledge that a graduate physician is less thoroughly prepared for preventive than for curative work. This has been one of the main reasons for the wide development of post-graduate training in recent years.

In *England*, hygiene is taught usually in the fifth year of the medical course. The year is divided into three terms (autumn, spring and summer). The lectures in hygiene are given as a rule in the summer term, for an average of thirty hours (0.8% of all hours). In Aberdeen, Glasgow, Edinburgh and St. Andrews, the total is fifty-five hours (1.4% of all hours). In general, the number of hours varies between twenty and sixty, of which five to ten are devoted to practical training and visits to health institutions. The subject is taught by special lecturers or professors, who are nearly always members of the public health service. All students receive courses of training in bacteriology and in infectious diseases.¹

In *French* medical faculties, hygiene is taught mainly in the fifth year of the course. The lectures (two to three hours weekly) include general hygiene and epidemiology. Social hygiene forms part of general hygiene. Practical training in laboratories is obligatory. In some faculties, there is a special chair of bacteriology. The examinations in hygiene are mainly oral and occasionally practical, including questions in infectious diseases, general hygiene and social hygiene.

In *Italy*, public health and health organisation are taught in the fifth year, three hours per week of lectures and two hours per week of practice in laboratories. The examination is oral.

In *Hungary*, the teaching of hygiene started at Budapest in 1874 in a modest institute of hygiene. At present, hygiene is taught in four medical faculties for five hours a week in the seventh or eighth semester. The subjects taught are : history of hygiene ; environmental hygiene ; nutrition ; social hygiene (tuberculosis, venereal diseases, alcoholism, cancer) ; maternal and child welfare,

¹ " Outlines of Medical Education ", by C. PRAUSNITZ ; *The Year-Book of Education*, 1935.

" Medical Education and the Reform of Medical Studies ", by E. BURNET ; *Quart. Bull. Health Org.*, 1933, 2, 620.

welfare of children of pre-school age, school hygiene, industrial hygiene, social insurance, vital statistics and epidemiology. At Budapest, there is an institute of bacteriology at the medical faculty.

The *Czechoslovak* medical curriculum includes the teaching of hygiene in the fifth year. At the Charles University, in Prague, a special chair of social medicine has been created ; the programme of teaching is spread over two semesters each comprising five hours per week ; two hours are devoted to theoretical lectures and three to visits to different institutions suitable for demonstration and practical training. In all, the yearly programme consists of forty-eight hours of lectures and seventy-two hours of practical work. The courses are not obligatory but give the students certain advantages in their career with social insurance institutions.

In *Poland*, general hygiene is taught in the fifth year and microbiology in the third. At Warsaw, teaching in hygiene comprises forty hours theory and twenty hours practical work in the fourth year. The professor of hygiene teaches social hygiene in the fifth (twenty hours) and sixth years (twenty hours), with thirty hours of demonstrations and visits.

The teaching in *Yugoslavia* varies in the different faculties. At Belgrade, there are a chair of bacteriology, a chair of general and special hygiene and a chair of infectious diseases. The number of hours of teaching varies. Bacteriology and infectious diseases are taught in the fifth and sixth semesters ; general and special hygiene and social medicine in the nine and tenth.

At *Zagreb*, there is a chair of hygiene with five hours weekly of teaching in the last semester. Field training of students, which was organised a few years ago, has been abolished. Under new regulations, teaching in hygiene is greatly extended, and includes compulsory courses and examinations in infectious diseases, bacteriology, general and special hygiene and social medicine.

In *Bucharest*, since 1935, medical teaching in hygiene has been compulsory during two terms, in the fifth (two hours weekly) and sixth (three hours weekly) years, and includes : prevention of infectious diseases, disinfection, personal hygiene, housing, nutrition,

water-supplies, sewage disposal, child hygiene, school hygiene, industrial hygiene and vital statistics. The students are obliged to present, before examination, a health survey of some village. Similar teaching is given by the faculty of *Jassy*. Practical laboratory work is compulsory for two hours a week in two terms. A significant innovation in regard to the teaching of public health to medical students has been introduced at the Medical Faculty of the University of *Cluj*. For the past ten years, this teaching has been given in the fifth and sixth years of medical training. It includes three hours of lectures and two hours of laboratory practice each week. Before graduation, each candidate must spend one month in the demonstration health district at *Gilan* and carry out practical field work under the guidance of the professors and health officers.

In the third year of medical studies at the University at *Sofia*, epidemiology, bacteriology, immunology, serodiagnosis and practical bacteriology are taught for five hours weekly, and in the fifth and sixth years, general hygiene, personal and social hygiene, epidemiology and health administration (twelve hours weekly in the winter and eleven hours weekly in the summer period).

At *Istanbul*, the medical faculty was reorganised four years ago. The medical courses last twelve terms, lectures in hygiene being given in the fifth, sixth and eighth terms ; in the fifth and sixth terms, general hygiene (three hours weekly) ; in the eighth term, social hygiene (three hours weekly), and practical laboratory work (two hours weekly) in the sixth term ; microbiology and epidemiology are taught in the fourth term (five hours weekly), in the fifth term (four hours weekly) and in the sixth terms (three hours of theory and two hours of practical work per week). The teaching is in German, but is translated by the assistant professors into Turkish ; examinations are also conducted with the help of an interpreter.

The institutes and schools of hygiene collaborate with the medical schools in teaching hygiene. The school in London is a university institution for post-graduate training, the institutes at Paris, Nancy, Montpellier, Lyons, Algiers, Bucharest, *Jassy* and *Cluj* are combined institutions and the university staff teaches in post-graduate courses and lectures to undergraduates.

D. THE RELATIONS BETWEEN SOCIAL INSURANCE INSTITUTIONS AND THE INSTITUTES AND SCHOOLS OF HYGIENE.

The number of physicians employed by the health insurance services is considerable.¹ In England and Wales, about 17,000 physicians work under the health insurance scheme. In Poland, of 12,000 physicians, 3,000 are employed by health insurance institutions ; in Czechoslovakia, of 11,000 physicians, 4,000 serve on a whole-time and 4,500 on a part-time basis in social insurance institutions ; the Hungarian health insurance system employs 3,309 physicians out of a total of 9,557. In Yugoslavia, about one-third and, in Roumania, about one-fifth of all physicians work for the insurance services. In Great Britain and France, the choice of physician is left to the insured and physicians are not appointed at fixed salaries. The Medical Association of France has adopted general rules concerning the methods of providing medical service. In Great Britain, the central authority, the Ministry of Health, supervises the operation of Health Insurance Institutions (in Scotland, the Department of Health for Scotland). In 1920, a special regional medical staff was organised for the supervision of medical benefit. Now there are some eighty whole-time regional medical officers, all of whom have had a considerable experience in the general practice of medicine as insurance practitioners.

In France, the law of 1930 provides for free choice of doctors and subsequent decrees assure the physician the maximum amount of freedom. In other countries, the social insurance services establish their own health institutions and employ a considerable number of physicians on a full-time or part-time basis, independently of the public health administration, which only occasionally collaborates.

¹ The average number of persons insured in the health insurance schemes in 1936 was (in millions) :

In Bulgaria	0.27	In Hungary	0.9
Great Britain	18.8	Italy	3.8
Czechoslovakia	3.2	Poland	1.9
France	8.7	Roumania	0.85
Greece	0.06	Spain	0.7
		Yugoslavia	0.73

These figures do not include members of families.

Recent publications of the head office of the health insurance societies in Prague¹ show to what extent independent health services have been organised in the past few years. In Italy, the tuberculosis insurance institutions are very numerous ; special attention has been paid to the establishment of sanatoria for the prevention and treatment of tuberculosis. The large scale of social insurance schemes and the number of the doctors they employ suggest that physicians serving under such schemes might play a large part in preventive medicine if they were given special training to this end.

The Sixth International Conference of the National Unions of Mutual Benefit Societies and Sickness Insurance Funds, held in Paris from September 27th to 30th, 1936, discussed the problem of the training of the physicians employed by health insurance institutions. The following conclusions were adopted :

(1) The medical student should receive systematic training in social insurance questions and in the duties of a social insurance physician ;

(2) In countries in which this teaching does not exist, special courses should be organised. The curriculum should comprise : social legislation, social diseases (tuberculosis, infant mortality, alcoholism, infectious diseases) ; industrial hygiene, occupational diseases, accidents, prevention of accidents ; the rôle of the physician in health insurance : economical prescribing of medicines, invalidity and the pathology and treatment of the more important diseases among workers.

The training should be mainly practical. It was proposed that the courses should be organised in collaboration with medical faculties and medical association.

The institutes and schools of hygiene have little to do with the training of social insurance physicians. The first attempt was made in Yugoslavia in 1931 under a special law prescribing the qualifications of medical officers and, in addition, requiring all physicians in social insurance institutions to take a three-month course in social medicine at the school of hygiene. Owing to financial difficulties, the courses have been temporarily suspended.

¹ " For Public Health ", Prague, September 1936.

In Czechoslovakia, the head insurance office and medical associations organise courses lasting three weeks. In Poland, special courses for health insurance physicians were given in 1937. In both cases, the staff of the institute of hygiene took part in this training. Special courses of instruction in tuberculosis, lasting two years, are given by the Forlanini Institute (tuberculosis insurance) at Rome.

The courses for post-graduate training in public health include in every institute and school the subject of social insurance. However, the amount of time devoted to this subject varies greatly.

5. CONCLUSIONS.

The schools and institutes of hygiene in Europe, although possessing certain common features, differ from one another in many respects. Their organisation has been influenced by the social, economic, educational and political conditions of the respective countries, so that there is no uniform type. Such uniformity, indeed, is neither possible nor desirable. It is all to the good that a school of hygiene should have a national character and that its activities should have a national character and that its activities should be directed towards the solution of national problems.

It may not, however, be inappropriate at the outset to point out that in many of the institutions visited, the conditions of service of the scientific staff were so unsatisfactory that the older members were obliged to seek extra work outside the institution in order to increase their earnings. The result is a dispersion of effort which is not in the interests of the schools. Any person who is regarded as fit to occupy a responsible post in an institution of this kind should receive an adequate living wage, as the success of a school depends much more on the quality of its staff than on the beauty of its premises. The conditions of service should be such as to attract the scholars most competent in their respective spheres of activity and to permit them to devote the whole of their time to teaching and research.

The same situation exists in the public health services of certain countries. The posts, whose holders are expected to devote the

whole of their time to their work, are occupied by officials who are obliged to seek other paid work in order adequately to support their families. As long as a public health service does not offer satisfactory conditions of employment, those wishing to enter it cannot be expected to follow courses at a school of hygiene, and yet it is admittedly desirable that such instruction should be made compulsory.

Each school, when circumstances permit, should enjoy a certain amount of financial autonomy ; an institution can always develop more freely when it is authorised to spend as it thinks fit the credits provided for its annual upkeep. Detailed control of the administration and of the budget of a school by a government department tends to have a harmful effect on the institution's activities.

In the conclusions to the present report we shall therefore consider certain particular questions of a practical nature concerning (a) the relations between the schools of hygiene and the respective health administrations ; (b) their relations with universities ; (c) the contribution of these institutions to the improvement of health in the country ; (d) liaison between the schools of the different countries.

(a) We have seen that relations between the directorate of a school of hygiene and the central health administration of the State vary greatly in different countries. Such schools in certain countries act as a technical organ directly connected with the activities of the Health Ministry or Health Department, while, in others, they possess the most complete autonomy, having only an indirect connection with the central public administration through their budget. Certain schools which, as we have seen, are closely dependent on the university, only receive a subsidy from, and are to a great extent independent of, the State. In this case, it becomes difficult to draw any conclusions on the value of the school as a public health institution except from the point of view of its indirect influence through the scientific and technical training of health officers. The Budapest Institute of Hygiene is perhaps the most characteristic example in Europe of a great public health institution which is, at the same time, a school of hygiene and directly dependent on the central Government as a technical organ of health adminis-

tration. Apart from a certain autonomy, chiefly in scientific matters, the Budapest institute is directly linked up with the Ministry's activities : as regards infectious diseases, epidemiology, medical statistics and measures for the prevention of endemic diseases and the organisation of rural health services, the Budapest Institute of Hygiene acts as a section of a Department of the Ministry. All the Health Ministry's activities in these branches are exercised through the institute. In such a case, the activities of the institution are more likely directly to influence the state of the public health than in the case of an institution functioning only as an educational centre.

The institutes of hygiene of Roumania are perhaps the most diametrically opposite in type. These institutions are the outcome of the universities' scientific activities and have dealt chiefly with certain special problems from epidemiological, prophylactic and other points of view. Their efficiency made possible, at a later date, their transformation into institutes of hygiene. They have assumed a specialised educational task, always connected with the teaching activities of the Faculty of Medicine through the Professor of Hygiene, and finally have become Government institutes of hygiene while retaining their scientific independence and their standing as university institutions.

Between these two types of schools, there are all the intermediate types, each adapted to the health organisation of its country, and moulded by the varying historical and political situations.

However, while noting these differences and once more emphasising the advisability of maintaining the specific national characteristics of each school, we should consider whether a certain co-ordination is not possible. The public administration must be able to form an accurate idea of the utility of such institutions and should be in no doubt as to the necessity of providing them with adequate funds, while respecting the teaching and scientific autonomy which are essential to technical efficiency. Public administrations, however, are not always easy to convince of the necessity of spending money on activities, which give an indirect return and which, in certain countries, are still considered in some quarters as a luxury.

It is therefore to be hoped that every effort will be made, by means of annual reports and the publication of special studies, to bring

the work of schools of hygiene to the notice of the health administrations, and of the general public, and to show the place these institutions can take and the part they can play.

The countries in which *sickness insurance* is highly developed are particularly interesting in this connection. Among the countries which we visited the most striking example in Europe is perhaps Czechoslovakia, which illustrates the necessity of determining the relations between the institute of hygiene, as an organ of the State, and the institutions created by the sickness insurance funds. There is still a lack of true co-operation, and consequently a delay in reaping the benefits which could be derived from an agreement between the insurance funds, whose economic basis is extraordinarily strong, and the institute of hygiene whose scientific and technical influence on the direction to be given to prophylactic work, on the establishment of dispensaries and sanatoria and on the study of some urgent problems of epidemiology might be of great advantage to the health of the population, both urban and rural.

In Italy, the National Institute of Social Welfare has allowed the fullest autonomy from the scientific point of view and as regards organisation, etc., to the technical directorate of the Forlanini Institute for the study of tuberculosis, so that it has become an agency for both educational and practical work which occupies an important place in the general health organisation of the State. By contributing to the training of specialised staff, it exercises educational functions similar to those of a school of hygiene (although in a narrower field) and nevertheless continues to rely *exclusively upon the economic resources of sickness insurance for its support.*

We have confined ourselves to recalling some examples of the differences which exist in this co-ordinated utilisation of a country's economic resources ; but they are no doubt sufficient to show that certain common principles ought perhaps to be laid down which might render the position of the different institutions somewhat more homogeneous in future.

(b) Relations with the university constitute, in our opinion, the second problem of real interest from the point of view of the scientific standing of the technical staff of institutes of hygiene. In our opinion, one of the causes of certain delays in the application

of major measures of public health in the community, and even of some reluctance on the part of the medical profession in certain European countries to accept and apply innovations in regard to public health, is that the students of the Faculties of Medicine do not always receive from the Professors of Hygiene of the Faculty instruction corresponding to the requirements of modern hygiene. The Faculties of Medicine are indeed professional schools whose aim is to prepare doctors for the exercise of their profession, but they have not yet fully adopted everywhere the modern conception of preventive and social medicine, and consequently they give the Professor of Hygiene too limited a programme and field of action. A better understanding between the Faculties of Medicine and the public health institutions of the State would be of mutual benefit.

The relations of the institutes of hygiene and schools of public health with the university need consideration from two points of view—namely, from that of the recruiting of the administrative and technical staffs of the institutes, and from that of the influence which the educational and practical activities of a school of public health should exercise on university circles.

(c) We expressed above the opinion that it would be desirable to bring the activities of institutes and schools of hygiene to the notice of health administrations and, if need be, of the general public. The manner in which this should be done must vary in different cases and may present some difficulty, particularly when the activities of a school of hygiene and of an institute of hygiene must be measured only by indirect results. There are a few schools, the most striking example of which is perhaps the school of Zagreb, which takes direct action by the application of measures of hygiene (provision of drinking-water conduits, construction of septic tanks, latrines, manure pits in rural districts, etc.) in the improvement of sanitary conditions. This is an exceptional case due to the circumstances in which the school was established, and to the fact that it receives support from the local as well as the central authorities. But it is not necessary to go as far as this type of direct action, which can, indeed, be left in the hands of the Government health organisation (provincial health inspectors, health officers, heads of districts, etc.) Even in schools of the university type which seem at first sight to be the furthest removed from the type of school

at Zagreb, there are examples of activities which, though less direct, achieve comparable results.

But we think that this is a question which should be thoroughly dealt with at special meetings of directors of schools of hygiene. It would be desirable to ascertain by what statistical, demographic, economic or other methods it is possible to demonstrate within a certain space of time, every year or every five years, the real output in the way of scientific educational activities and the results in certain cases of practical field work.

For the moment, we shall confine ourselves to suggesting that such exchanges of views should be arranged, and it is in this connection that we shall now consider the fourth question—namely, (d) liaison between the schools of different countries. This closer co-operation and mutual exchange of information might be established on the basis of the following measures :

(1) A regular exchange of information on the work in progress, and on the programmes of instruction adopted in the schools and institutes. The Health Section of the League of Nations might serve as an intermediary in this exchange and the *Bulletin of the Health Organisation* might include notes on the activities of the different schools. An annual report on its activities published by each school would be interesting.

(2) More frequent conferences, organised by the League of Nations and bringing together the directors and staffs of schools and institutes of hygiene. The questions to be discussed should be carefully selected, and the meetings should be held at a different place each time. These discussions might, from time to time, be followed by studies on the spot in the country visited.

(3) An occasional exchange of visits between the staffs of the schools. This exchange would permit of more satisfactory technical co-operation and the joint study of certain questions of general interest.

Annexes.

1. THE ANKARA INSTITUTE AND SCHOOL OF HYGIENE.

INTRODUCTION.

It is common knowledge that few countries have, in recent years, witnessed so many important changes as Turkey. Thus, its capital, on a site formerly occupied by a town of but a few thousand inhabitants, has now become a large modern city, embodying the most modern principles of hygiene and town planning. Not far from Ankara are the new settlements laid out to provide for the immigrants who are flowing into the country in a steady stream (99,709 families) in accordance with the Lausanne Peace Treaty.¹ These settlements satisfy all reasonable hygienic requirements; they have modern schools, some of them equipped in part as boarding-schools for poor children and with dispensaries at which the settlers receive medical care of every kind.

In modern Turkey, public health is a matter to which the Government is giving the closest attention; the work is carried out by a series of central and regional institutions comparable, in planning and organisation, with those of countries having long-standing traditions in this field.

¹ Between 1926 and 1936, 299,685 immigrants entered Turkey; 11,860 new houses were erected (houses for 6,750 families are now being built), each house comprising 2 rooms, hall, water-closet and stable. According to the fertility of the land, the families receive from 5 to 8 hectares and, in the first year, foodstuffs, seeds, implements, draught animals and fuel; artisans are supplied with the necessary credits. The cost of the new houses averages from £T350, to £T500, and total expenditure per immigrant family £T600 to £T750. The Ministry of Public Health and Social Assistance spent £T2,200,000 from June to the end of December 1936 on housing.

PUBLIC HEALTH DEVELOPMENTS IN RECENT YEARS.

The public health service of Turkey is controlled at the centre by the Ministry of Public Health and Social Assistance, established in 1920. For the last fourteen years, its head has been Dr. REFIK SAYDAM.

When this Ministry was established, Turkey had no modern public health service ; most health institutions were at Istanbul and the other large cities, whilst elsewhere there were but a few small dispensaries and private hospitals ; and there were only twenty-two dispensaries and 2,744 beds in the public hospitals.¹ The number of physicians outside the main cities and bigger towns was insignificant. Now, after some years of systematic work financed by adequate appropriations in State and regional budgets, Turkey possesses a very well equipped basic health organisation, capable of rapid expansion in all branches of modern public health work.

At Ankara, a building has been erected for the Ministry of Public Health and institutions are being set up which will act as research centres. It is with this object in view that the Institute and School of Hygiene were established at Ankara, as a first step, to be followed by the Central Hospital with 400 beds (which will soon be increased to 1,000) and the Institute for Maternal and Child Welfare, which will later be moved to a new building with 100 beds. There are also dispensaries for tuberculosis and venereal diseases directed by specialists. The capital city thus possesses institutions designed to provide not only medical care, but, with the Institute and School of Hygiene, practical and theoretical post-graduate training for public health officers. Not far from Ankara, in the new immigrant settlement at Etimesut, a rural health centre has been built with a few beds for maternity cases. In the same settlement, a school health centre is organised with all the necessary equipment for the regular work of a medical service.

But the activity of the Ministry is not limited to the capital and its vicinity. There are now 173 hospitals in Turkey, 127 of which belong to the State (Government, regional or municipal hospitals). In addition there are 285 dispensaries with beds (five to ten beds

¹ At present there are 14,468 beds.

each) and twenty-five without beds, all belonging to the State. Special attention has also been paid to maternal and child welfare, infectious disease control, malaria and syphilis. The Institute of Hygiene and regional laboratories have undertaken the study of contagious diseases and large numbers of persons have been vaccinated against typhoid. There are ninety medical specialists and 300 sanitary inspectors actively engaged in malaria control in twenty-four departments (*vilajetsa*), carrying out sanitary engineering work. At Adana, a special institute has been established, with the main object of organising anti-malaria work, of undertaking research with a view to solving the problems attendant upon this disease, and training the medical officers responsible for the control work.

The campaign against tuberculosis is now being organised ; a few dispensaries and sanatoria are being established.

The problem of medical care and the distribution of physicians throughout the country still presents many difficulties to the health administration ; at the moment, there are, in Turkey, not more than 3,200 doctors for a population of 16,200,000, and these are practising mostly in the larger cities (one thousand in Istanbul alone). The situation is much better, however, than it was a few years ago, for to-day almost every district has its medical officer ; but it is unlikely that a sufficient number of doctors will be available for at least twenty years. It is with these requirements in view that the medical school at Istanbul has been reorganised. In 1933, a number of German professors were invited to give courses of instruction at the school and they agreed to learn the Turkish language. Medical students in Istanbul now number 2,198 ; some will be army medical officers whilst the others will enter the public health service ; a very few are studying at their own expense, and these are mostly women. The Ministry has provided a special students' hostel for its scholarship holders of bursaries and is planning a new school of medicine at Ankara which will utilise such medical institutions as the Institute and School of Hygiene and the Central Hospital. This new medical school will be under the control of the Ministry of Public Health and Social Assistance.

In the central health institutions ten foreign specialists—mostly from Germany—have been engaged, but the number of Turkish specialists is growing daily and they fill the majority of responsible

posts. A few of these specialists have profited from the help given by the Rockefeller Foundation, which has sent Turkish physicians to be trained in foreign institutes, mostly in the United States.

PUBLIC HEALTH ORGANISATION.

The central authority in health matters is the Ministry of Public Health and Social Assistance which works in close touch with the Ministries of Education, Public Works and National Economy.

The total number of officials and employees of the Ministry is 4,210, of whom 1,243 are doctors. The central offices of the Ministry have a staff of 102 officials, including twenty-two doctors. The salaries of the medical staff vary from £T165 to £T500 per month.

The expenditure of the Ministry of Health has increased since 1932 as follows :

In 1932,	it was	2.07%	of the	general	expenditure ;
„ 1933,	„	2.46%	„	„	„
„ 1934,	„	2.57%	„	„	„
„ 1935,	„	2.47%	„	„	„
„ 1936,	„	3.87%	„	„	„

In addition to its ordinary budget, the Ministry has obtained large sums in the form of special appropriations.

The health officers of the State, provincial and municipal administrations are appointed by the Ministry and those connected with schools, means of communication and the administration of justice by the corresponding Ministries.

Turkey is divided into sixty-two provinces (*vilajetsa*) and 424 districts. There is a Director of Health and Social Assistance with an office in the capital of each province. In the capitals of the more important provinces, the Director has a medical officer as his deputy, and is, furthermore, advised by the health counsellors. These Directors are the senior health officials of the provinces, and in this capacity they act as health advisers to the Governors-General. They are responsible for all the health and social assistance work of the province. Each district has a Government medical officer and the necessary sanitary inspectors. The salaries of provincial and district health officers vary from £T84 to £T288 per month.

THE PREVENTION AND CONTROL OF SOCIAL DISEASES.

The treatment of *venereal diseases* is compulsory by law, and free of charge in hospitals, anti-venereal dispensaries, public health service polyclinics, and in districts having a resident health officer. In areas specially infected with syphilis, the Ministry provides a special anti-venereal travelling unit with a specialist in charge and health assistants as auxiliary staff. In such areas, the whole population, without exception, is examined by a specialist.

In *trachoma* infected regions, the Ministry appoints a commission to control the disease under the direction of a specialist. Twelve hospitals, each with ten to twenty beds, and a number of dispensaries have been organised in these districts. The commission is empowered to examine the inhabitants and to take all measures necessary for the control of trachoma. Special schools have been established for children suffering from trachoma.

As regards *tuberculosis*, dispensaries with an attached social service have been provided in a certain number of cities. Open tuberculosis is compulsorily notifiable. Under the special Law of 1921 and the Health Act, medical examination before marriage is obligatory. The examination is carried out free of charge and is concerned only with venereal disease, mental disorders, open tuberculosis and leprosy. The certificates of private physicians must be confirmed by the medical officer of health.

THE WORK OF THE CENTRAL HEALTH INSTITUTIONS.

Central Hospital.

The work of the various departments¹ of the hospital has grown considerably during the last six years. The following table shows the increase in the number of patients and consultations :

Year	Number of in-patients	Number of consultations
1930	2,421	24,011
1932	3,132	35,163
1935	6,692	71,460

¹ Medicine (76 beds), surgery (72 beds), gynæcology and obstetrics (27 beds), infectious diseases (68 beds), pediatrics (36 beds), neurology (17 beds), venereal diseases (20 beds), ophthalmology (22 beds), oto-rhinology (19 beds), urology (16 beds), radiology (10 beds), physiotherapy (12 beds), sick prisoners (5 beds).

Institute of Hygiene.

There is no doubt that the Institute of Hygiene, with the School of Hygiene, is the most important institution of the Ministry of Public Health at Ankara in all matters connected with research, field investigations and training of public health staff. The Law of May 24th, 1928, laid down the programme of this institution on the following lines : practical work in connection with public health questions ; preparation of sera, vaccines and other means required for diagnostic and for curative purposes ; testing of imported pharmaceutical products ; advice to public administrative bodies, local administrations and other institutions.

The Institute carries out all work for the State and local administrations free of charge. Patients and private institutions pay the fees laid down by the Ministry. The Government appoints the officials of the Institute and fixes their salaries ; the Minister of Health is empowered to engage foreign specialists.

The Institute started its work on a limited scale in 1932, but by 1935 it was in full operation. It is divided into two departments : the Department of Hygiene and the School of Hygiene. These departments are separately administered, but as far as teaching is concerned they form one unit. The Rockefeller Foundation gave \$80,000 for the scientific equipment of the Institute and \$200,000 for the building and fittings of the School—approximately one-third of the total expenditure of the latter.

The Director of the Institute is Professor GOTSCHLICH, his assistant is Professor SERVER KAMIL, who is the administrator of the Institute.

The Institute is divided into two sections : administration and technical services. The latter comprise bacteriology, chemistry, production and testing of sera and vaccines, biological research and production of organic preparations. The Director of the Institute is responsible for the general control of the work in the Institute, the distribution of staff, the initiation of new practical work and scientific research, as well as liaison with the other institutions ; he is at the same time the head of the bacteriological section. The Deputy-Director is responsible for administration, for the budget and for the control of the personnel ; he is also the chief adviser to the Director.

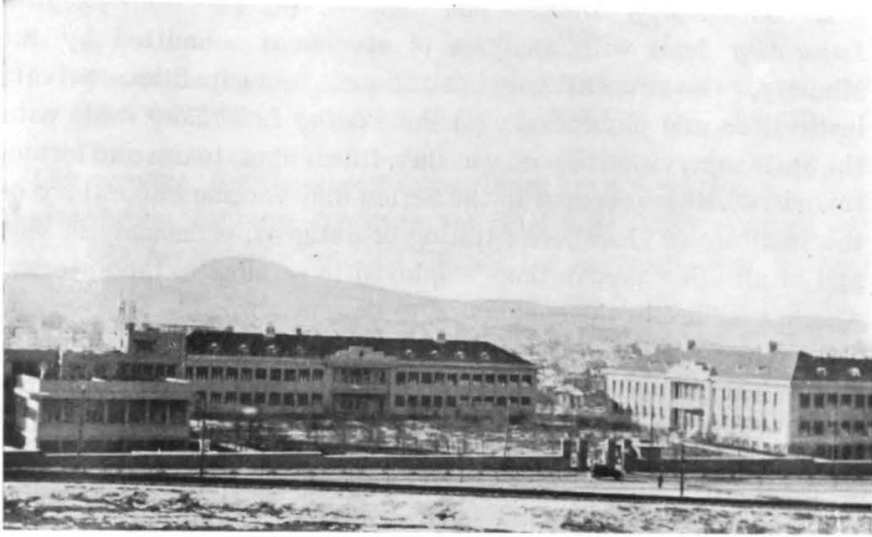


Figure 1.—GENERAL VIEW : INSTITUTE AND SCHOOL OF HYGIENE AT ANKARA.



Figure 2.—SCHOOL OF HYGIENE AT ANKARA : FRONT OF THE BUILDING.

240 SECOND REPORT ON CERTAIN EUROPEAN SCHOOLS

Section	Professor	Subject	Hours
Epidemiology (continued)	COLLINS and KAMIL IDIL	Measles, scarlet fever, diphtheria, smallpox, poliomyelitis, influenza, enteric fever, cerebro-spinal meningitis, coryza, food poisoning, yellow fever, intestinal parasites, malaria	20
	COLLINS and ZEKI NASIR	Morbidity and mortality statistics, statistical methods	22
Social hygiene	SERVER KAMIL	The child, the school, tuberculosis, trachoma, cancer, maternal and child welfare, mental hygiene.	17
	ASIM ARAR	Venereal diseases and sexual hygiene, alcoholism, drug addiction.	7
	CEMAL OR	Rural hygiene, visiting nurses..	5
Sanitary engineering	W. WRIGHT	Theoretical and practical laboratory work	72
Parasitology	MAHMUT SABIT	Theoretical and practical laboratory work	36
Bacteriology Serology	GOTSCHLICH BAECHER	} Theoretical and practical laboratory work	108
Public health administration	ASIM ARAR		
Clinics			26
Free study			26
Practical work			One month

The number of students who took the course in 1936 was twenty-two. It is expected that this number will increase considerably during the next few years.

Article 23 of Law No. 3017, of June 23rd, 1936, on the Organisation and Functions of the Ministry of Public Health and Social Assistance lays down the method of recruiting students as follows : " The School of Hygiene undertakes to organise special courses of post-graduate training in general and social hygiene, for doctors serving in the Public Health Services, the different municipal administrations and the larger industries ; and, in case of need, for sanitary inspectors and teachers of the Ministry of Public Instruction ; for inspectors in industry and agriculture ; for engineers or other officers who may be concerned with public health."

Students are granted scholarships to cover their travelling expenses and for their expenses in Ankara for the duration of the course. If they are employed in the State Health Services, they continue to receive their salaries during this period. At the end of the course, the doctors return to their original posts.

For purposes of practical training, the School of Hygiene collaborates with the Central Hospital in Ankara ; the Anti-Tuberculosis Dispensary ; the Dispensary for the Treatment of Venereal Diseases ; the Maternal and Child Welfare Centre ; and in connection with Rural Hygiene with the Etimesut Health Centre which serves the model village of Etimesut and other villages nearby. A new urban health centre will be established in the near future. The Rockefeller Foundation has already approved a grant of \$30,000 for a five-year programme, and the Government will contribute the same amount.

POST-GRADUATE TRAINING IN MALARIOLOGY.

By a special law, graduates in medicine since 1927 in Turkey who have entered Government service have been required to take a course in malariology in an institute appointed for the purpose by the Ministry of Public Health and Social Assistance. It is at the Institute of Malariology at Adana, established in 1928, that doctors complete their studies in malariology by following theoretical and practical courses. Doctors appointed to the anti-malaria service will, however, be given the option of taking this training in their own areas.

At the Adana Institute of Malariology the practical training lasts for three weeks, beginning in September of each year. The courses have been organised regularly during the past eight years. The syllabus comprises courses and lectures in parasitology, epidemiology, entomology, pathology and malaria control. The number of post-graduates who attended was as follows :

Year 1928	52 (34 physicians in military service)
1929	38 (23 physicians in military service)
1930	19
1931	17
1932	11

Year 1933	40 (22 physicians in military service)
1934	50 (27 physicians in military service)
1935	52 (27 physicians in military service)
1936	61 (33 physicians in military service).

MEDICAL TRAINING.

The Institute and the School of Hygiene do not collaborate with the university institutions. As already stated, the Istanbul Faculty of Medicine was organised four years ago. The medical studies occupy twelve semesters and the lectures in hygiene are given in the fifth, sixth and eighth semesters; in addition, in the sixth, there are two hours of practical laboratory work weekly. There is a special chair for microbiology and epidemiology; lectures are given in these subjects in the fourth and fifth semesters. The lectures are delivered in German and translated into Turkish; hence the courses actually last only half the time mentioned. Interpreters are also used at the examinations. The institutes of the Faculty of Medicine are housed in the buildings of the former Ministry of War, which were adapted for the purpose. There is a museum in the University Institute of Hygiene with exhibits of all kinds concerned with local health problems.

THE TRAINING OF AUXILIARY PERSONNEL.

Schools for auxiliary personnel are being established, and the Edirnekapu Health Centre has a practical training school for visiting nurses.

After the world war, the Red Crescent selected a number of young women and arranged for them to study in the Medical Faculty of the University, but this met with very limited success. The need for an independent institution was clear, and the Committee appointed a special Commission to study the programmes of American and European schools. As a result, a school was opened in February 1925 under the auspices of the Red Crescent Society.

Applicants for admission had to be in good health, unmarried, and between 18 and 30 years of age and to have had an elementary

education (five years at school). Thirty-two students registered in the first year.

The school gave a course lasting two years and three months, the first three months being a preparatory period devoted chiefly to domestic science. During the first year, anatomy and physiology, bacteriology, hygiene, chemistry and care of the sick were taught, and, in the second year, surgery, materia medica, obstetrics and pediatrics.

The administration of the school was under Dr. OMER LUFTI, Director of the Guraba Hospital, who was assisted by two German nurses, one for the school and the other in the hospital.

Students were required to sign a five-year contract to work wherever posted for duty (with pay, of course) after satisfactory completion of the course.

In May 1936, a foreign nurse was appointed as the Director of the school. At that time, one hundred students were attending the classes. Class rooms, study hall, library and offices and living-quarters were distributed among three adjacent buildings in the large garden.

The school continued under the direction of Dr. OMER LUFTI, who was at that time assisted by two Turkish nurses. The students received their practical training in Guraba Hospital (chiefly male patients), the Foundling's Home at the City Poor House and the Zeyneb Kamil Hospital (a fifty-bed obstetrical and gynæcological hospital in Scutari).

A new syllabus had been worked out some months previously and the length of the course increased to three years, whilst other arrangements remained unchanged. A part-time woman physician was employed for the supervision of the health of the students.

The school co-operates with the Medical Faculty as regards teaching staff. All teachers, save one, are from the medical school and have taken a great interest in the training of the students.

The problem of the right practical exercises from which students can acquire adequate experience of the work they will be called upon to do is a difficult one. For this reason, the school organises "model nursing services" at the Istanbul Health Centre which are run by school instructors and are fully equipped by the school. Such experience of public health nursing now forms an integral part of the basic programme and a knowledge of this branch will be required

of every student. Later it will form an optional subject in the second part of the third year for those particularly interested in it. The new programme has been organised so as to lay special stress on prophylaxis and public health throughout.

Conditions for entrance are now more exacting. Only students who have successfully completed a secondary school course were admitted this year. Candidates are given a thorough physical examination by the school physician, X-rayed and subjected to the necessary laboratory tests. Only girls of Turkish race are admitted.

A monthly allowance of £T5 has been given the students until now. Uniforms are provided by the school.

There has certainly been a great improvement in the type of student admitted to the school, in regard both to their school training and to their general cultural background. The fact that parents are invited to visit the school has stimulated interest and co-operation as well.

So far, 216 nurses have graduated from this school, including five who were trained at the American Hospital and took the examinations after a course of tests lasting three months, in order to have the right to be appointed to State institutions. Of this total, sixty-three are at Istanbul and twenty-five at Ankara, the others being distributed throughout the country.

An organisation has been formed under the Red Crescent which provides a home for the accommodation of nurses without an appointment and nurses on vacation at Istanbul. Sick nurses are also cared for. To this organisation nurses pay 5% of their salary. At present, this home is attached to the school and is under the direction of the school Director. In reality, the school pays for everything but the cost of food.

General Curriculum of the Nursing School at Istanbul.

I.

3 months : Preliminary period.

4 months : Practical training in the model medical and surgical teaching services.

II.

2 months : Theoretical teaching.

7 months : Practical work ; advanced medical and surgical work, dietetic cooking and communicable disease services. One month vacation included.

III.

- 1½ months : Theoretical training.
- 12 months : Practical work : obstetrical, pediatric, operating theatre, special services and public health. One month vacation included.

IV.

- 1½ months : Theoretical teaching.
- 5 months : Practical period : students may choose from among the following subjects—public health nursing, dietetic cooking, pediatrics, operating theatre, etc. Includes one month vacation.

All students are given the same work except in the last five months, when they may select the service in which they wish to acquire more experience.

Theoretical Curriculum.

First period (12 weeks) :

Anatomy and physiology	75 hours
Bacteriology	45
Chemistry and physics	45
Psychology and sociology	30
History of nursing	15
Ethics of nursing	15
Personal hygiene	15
Physical training	15
Nutrition and cookery	30
Nursing the sick (principles and practice of nursing)	90
Hospital housekeeping and organisation ...	} 15
Bandaging	
	_____ 390 hours

Second period (8 weeks) :

Introduction to medical science, including pathology	15 hours
Materia medica	30
Medical nursing	45
Surgical nursing	45
Care in cases of communicable disease	15
Dietetics or diet therapy	15
Advanced nursing, including massage	75
Physical training	15
	_____ 255 hours

Third period (6 weeks) :

Obstetrical nursing	45 hours
Nursing care of children	45
Operating-room technique	15
Nursing in special conditions such as gynæ- cology, genito-urinary diseases, eye, ear, nose and throat, skin, etc.	30
Public health nursing	45
Physical training	15
	195 hours

Fourth period (6 weeks) :

Social hygiene and preventive medicine: social legislation	30 hours
Professional problems	30
Survey of the status and aims of the nursing profession	30
Psychiatric nursing	15
Advanced nursing: first aid	30
Preparation for professional work	15
Special lectures: X-ray and radium, physio- therapy, metabolism, etc.	30
Physical training	15
	195 hours
Total	1,035 hours

The Training of Sanitary Inspectors.

Two schools give courses for the training of sanitary inspectors, one at Tschorpum (a boarding-school with a capacity for fifty students), and the other at Istanbul, accommodating fifty students. The two schools had together eighty-seven students in 1936. The curriculum is spread over a period of two years. The theoretical and practical training is given in hospitals and public health institutions; after graduation, the young sanitary inspectors are employed in health services for a minimum period of five years. At present, 1,538 graduates from these schools are in the service.

The Training of Midwives.

In order to qualify for practice, midwives must spend two years in the hospitals attached to the Faculty of Medicine at Istanbul

and one year in a maternal and child welfare centre. The requirement for admission to the school is graduation from a secondary school. The Ministry maintains an establishment for a certain number of boarded students. Those who are admitted to it are pledged to remain in the health service of the State, provinces, municipalities, districts or communes for a minimum period of three years. Under a new law, provision has been made for the training of midwives for service in villages, in this case, the period of training is shorter and the requisite standard of preliminary education is lower.

RESEARCH WORK.

The Ankara Institute and School of Hygiene, after a period of organisation, commenced its work in 1935. This work has been carried out under the direction of Professor GOTSCHLICH, the well-known bacteriologist, the results of whose research will probably be included later in scientific publications. The collaboration of Dr. COLLINS (Rockefeller Foundation) as Director and Organiser of the School has been greatly appreciated by Dr. KAMIL, Assistant Director, Dr. ZEKI BARKER, Professor SERVER KAMIL and others. The special Institute of Malariology at Adana has published a number of studies on the epidemiology and prophylaxis of malaria in Asiatic Turkey, which have contributed to our knowledge—still limited to certain regions, but already important—of local malaria problems.

2. THE ATHENS SCHOOL OF HYGIENE.

THE PRESENT HEALTH ORGANISATION IN GREECE.

In Greece, public health questions come under the Ministry of Health and Public Assistance, which is divided into three departments :

(1) Department of Public Assistance, dealing with the protection of abandoned children, orphans and the poor, public institutions and philanthropic organisations, pensions and assistance to war victims ;

(2) Department of Public Health, dealing with the prevention of infectious diseases, especially the control of malaria, tuberculosis and venereal diseases, maternal and child welfare, medical assistance to the poor, supervision of the medical profession and hospitals ;

(3) The Department of Public Relief, dealing with unemployment, housing accommodation for the poorer classes and the care of refugees.

The Minister is advised in health matters by a Supreme Health Council.

The budget of the Ministry for 1935/36 amounted to 733.2 million drachmas, of which sum 4.01 millions were spent for the Athens School of Hygiene, 11.02 millions for district (prefectural) health services, 10.28 millions for the control of infectious diseases, 10.9 millions for malaria control, 1.17 millions for the control of trachoma, 38.11 millions for the campaign against tuberculosis, 9.14 millions for the control of venereal diseases, 1.63 millions for maternal and child welfare and 27.57 millions for medical assistance, the largest amount—*i.e.*, 243.38 millions, being spent for pensions and assistance to war victims.

In the Department of Public Health, nine medical officials are employed with a monthly salary varying from 3,700 to 6,500 drachmas. In different medical institutions (mostly hospitals), 100 phy-

sicians are employed with salaries ranging from 2,760 to 6,500 drachmas per month, and 120 special staff at a daily wage varying from 25 to 250 drachmas.

A health centre (Departmental Health Organisation) is established in each prefecture and in the Port of Piræus. The centres are divided into grades A and B. The statutory staff of the grade A centres consists of a medical hygienist, a deputy, three practitioners, four visiting nurses and three sanitary inspectors. The B classes have only one hygienist and two sanitary inspectors. There are seven grade A and thirty-two grade B health centres. Altogether, forty-three medical hygienists, twenty-four practitioners, about ten visiting nurses and ninety-five sanitary inspectors work in these centres.

The municipalities are required by law to appoint a health officer. In cases where the health officer appointed does not possess adequate training in public health, the municipality is required to send him to the School of Hygiene for a special course. Seventy municipalities have gradually conformed to these requirements. Communes with an annual budget of over 400,000 drachmas are also obliged to appoint health officers under the same conditions. Of 5,578 communities, only sixty-six are in a position to provide the necessary funds for this purpose. The remaining communes make use of the services of local practitioners and pay only small fees. Many communes have no form of medical assistance.

In addition to the Health Department of the prefectures, under the charge of public health officers, there are special health institutions as follows : hygienic and bacteriological laboratories at Athens and Salonica, the Pasteur Institute at Athens, the Pathological and Anatomical Centre of the Ministry of Health, disinfecting stations at Athens, Salonica, Corfu and Samos, an anti-rabic vaccination laboratory with a hospital at Athens and infectious-disease hospitals at Athens and Salonica.

In 1937, a special tax was imposed on tobacco and correspondence. This is levied in the form of a social welfare stamp and the proceeds are to be used exclusively for social welfare and public health work, in addition to the credits already earmarked for those purposes. The tax is distinct from the general State budget and bears the name " Social Welfare Fund ". It is estimated that it will bring in 500 million drachmas a year.

The allocation of this fund has already begun ; various sums have been assigned with the object of increasing the number of beds in existing hospitals and sanatoria, establishing new hospitals and sanatoria and assisting various other agencies engaged in social welfare work. Moreover, a sum has been assigned for the erection of buildings for a State school of visiting and hospital nurses and for its working expenses. The buildings will be adjacent to those of the School of Hygiene. The school began work in temporary premises in December 1937.

Special committees, composed of professors of the School of Hygiene, senior officials of the Ministries and other persons, such as university professors, etc., have been appointed by the Ministry to determine the lines along which campaigns against tuberculosis, malaria, trachoma and other diseases may be organised within the framework of the Public Health Organisation.

As regards the programmes of tuberculosis and malaria control, Dr. PAPACOSTAS and Dr. LIVADAS, of the School of Hygiene, have respectively been appointed rapporteur of the committee concerned.

Furthermore, the execution of the malaria control scheme in the Department of Epirus, drawn up by Dr. LIVADAS and approved by the Supreme Health Council, has already been initiated and the necessary higher grade and subordinate personnel engaged. This personnel has been recruited from among former students at the School of Hygiene.

A committee, of which the Director of the School is a member, has also been formed to draw up a programme for the reorganisation of the outlying health services.

As the various committees have not yet completed their work, all the details of the general programme are not yet available. Nevertheless, this programme is known to comprise the establishment of a number of polyvalent health centres, and the inclusion, within the general framework of the health organisation, of all specialised work such as the anti-tuberculosis campaign, anti-malaria campaign, etc.

In the Ministry of Education, there is a special organisation : the School Medical Service—fifty-two school physicians and three school nurses. The Service is responsible for the regular medical inspection of schools and for the vaccination and revaccination of scholars and the protection of their health.

There are, in Greece, 6,500 physicians, of whom 1,800 reside in Athens-Piræus, with a population of slightly over 800,000.

COLLABORATION WITH THE LEAGUE OF NATIONS IN HEALTH MATTERS.

In October 1928, the Under-Secretary of State for Public Health of the Greek Government asked the League of Nations to collaborate in the reorganisation of the Hellenic Health Services. The invitation was accepted and it was decided to send a commission of experts to study the existing health organisation. The experts remained in Greece from January to April 1929, visiting different parts of the country and studying all the administrative problems involved. The Commission presented a report in April 1929.¹

The main conclusions reached were that the Public Health Service in Greece should be completely reorganised and that public health work should be entrusted to specially trained experts. To carry out this part of the programme, it was proposed to establish a new health centre and a school of hygiene. The basic organisation was to be the Athens Health Centre, which would form the nucleus of a permanent national public health service. It was proposed that the new health services should first be organised in six typical provincial territories (departments) with special health centres and should then be gradually extended ; and it was emphasised that, to ensure success, no political influence should be allowed to interfere with the service.

In 1929, by Law No. 4333, the School of Hygiene was established at Athens as part of the Central Health Organisation, under the name of the Athens Health Centre and School of Hygiene. The school was housed in modest premises. According to this law it was :

- (a) To direct, under the supervision of the Ministry, the public health work in the six selected areas, according to the programme proposed by the experts of the League of Nations ;
- (b) To train the necessary personnel for the new health services ;

¹ See League of Nations document C.162.M.63.1929.III.

(c) To act in an advisory capacity to the Central Health Administration in all matters regarding public health.

The law provided for the collaboration of the centre with the Athens Pasteur Institute, which was to become a research department of the centre.¹

Foreign experts were called in to direct the Athens Centre and the Divisions of Malariology and Sanitary Engineering.

This programme was only partly carried out. On the one hand, there were many difficulties to overcome in order to adapt the old health organisation to the new system, and, on the other hand, the economic depression adversely affected the development of the proposed health service.²

The Athens Centre and School of Hygiene began its work in 1931. This institution was placed directly under the Ministry of Health and consists of six divisions :

- (1) Public health and social medicine, including the School of Hygiene ;
- (2) Malariology ;
- (3) Sanitary engineering ;
- (4) Pharmacology and bio-chemistry ;
- (5) Research (Pasteur Institute) ;
- (6) School of Hygiene (this division co-operated with the direction of the School of Hygiene of the Ministry of Public Instruction).

By the Decree of March 5th, 1930, four prefectures were selected for the establishment of the new public health centres. Two years later, those centres were closed and the scheme proposed for the training of visiting nurses was abandoned. In January 1934, a new law was enacted providing for the establishment of public health centres in place of the health bureaux of the prefectures, and

¹ In practice, this collaboration continued for a short period only.

² Several years ago, Greece was confronted with the difficult problem of settling more than one million Greek immigrants from Asia Minor and other parts of neighbouring States. New settlements were established with remarkable success ; there were no epidemics and sanitary conditions were improved in many rural areas. This work was carried out by a Commission appointed by the League of Nations and the Greek Government. Under the auspices of the League of Nations a loan of £12 million was raised for this purpose.



Figure 3.—ATHENS SCHOOL OF HYGIENE : PART OF THE BUILDING.



Figure 4.—AMBELOKIPI HEALTH CENTRE (see page 258).

requiring medical officers of the prefectures to hold a diploma in hygiene.

In October 1935, a model health centre service for the practical training of students of the School of Hygiene was organised in newly constructed premises adjacent to the School in a district of Athens with 30,000 inhabitants.

Under a recently enacted law, every medical officer appointed to the State Public Health Service must hold a diploma in public health. The municipalities are obliged to give preference to graduates in public health when making appointments in their Public Health Services. A special law provides that no doctor in the navy can be promoted to the rank of colonel without a diploma in hygiene conferred by the School of Hygiene. Moreover, under a recently enacted law, army doctors, up to the rank of captain, are required to attend a post-graduate course in the School of Hygiene.

The School of Hygiene is empowered to confer diplomas :

- (a) In public health ;
- (b) In chemistry ;
- (c) In sanitary engineering, and
- (d) For sanitary inspectors and public health nurses.

Up to the present, the School has conferred diplomas only in hygiene and for sanitary inspectors.

THE SCHOOL OF HYGIENE.

I.

The relations of the School with the University were defined in a decree of March 1936. According to this decree, the Director of a division in the School may be appointed only on the recommendation of the School Council and with the approval of the Medical Faculty of the University. The Director of the School is elected by the School Council for a term of three years.

The head of each division, whose number has increased from six to nine, has been given the title of Professor. The divisions are the following :

- (1) Microbiology and serology (Dr. PAPAMARKU) ;
- (2) Epidemiology and statistics (Dr. G. ALIVIZATOS) ;

- (3) Public health (Dr. KYRIAZIDES) ;
- (4) Malariology and tropical diseases (Dr. Gr. LIVADAS) (Dr. BALFOUR, Technical Adviser) ;
- (5) Social hygiene (Dr. PAPACOSTAS) ;
- (6) Sanitary engineering (Chr. FLORAS, Engineer) ;
- (7) Bio-chemistry and nutritional hygiene (teaching in this course, for the academic year 1937, has been entrusted to Dr. S. GALANOS, Professor of Food Hygiene in the University of Athens) ;
- (8) School hygiene (Dr. LAMPADARIOS) ;
- (9) Meteorology and climatology in relation to public health (M. MARIOLOPOULOS).

Important work is carried out by the Divisions of Malariology and Sanitary Engineering. Two years ago, funds were provided by the Ministry for sanitary engineering work in different regions, mainly for the construction of model latrines, wells, sewers and piped water-supplies. The total appropriation for this purpose was five million drachmas. The Sanitary Engineering Division acts as an advisory department to the Ministry, the prefectures and the municipalities. The Division of Malariology directs and supervises all the Ministry's anti-malaria work. For purposes of demonstration and research, two regions were selected in 1930—one in the Peloponnesus and comprising four villages, with a population of 1,700 inhabitants, and the other in the City of Drama, with 30,000 inhabitants. These demonstrations have been extended to many other areas. The Ministry has recently decided to adopt a programme for the control of malaria under the direction of the Malaria Division of the School of Hygiene, assisted in this work by additional personnel and provided with the necessary anti-mosquito material. Costs will be divided between the Ministry, the municipalities and the rural districts. The Ministry is to spend four million drachmas a year. Of the major projects for land improvement and malaria control, the drainage of the Struma and Vardar valleys (over 6,050 million drachmas) should be mentioned.

II.

The School is financed out of the State budget. Since 1930, the Rockefeller Foundation has provided funds varying from \$15,000 to \$40,000 annually. These sums have been devoted to special

work undertaken by the Divisions of Malariology and of Sanitary Engineering.

The budget of the School decreased from 6,122,371 drachmas in 1931/32 to 3,032,296 drachmas in 1935/36. Of this sum, 2,126,500 drachmas are spent in salaries. Part of the decrease in the budget is accounted for by the fact that expenditure on all departmental (prefectural) health services is now met out of the regular budget of the Ministry.¹

III.

The teaching in the School is theoretical and practical, and includes laboratory practice and visits to health institutions, with practical training in the health centre attached to the School. The main building has a large laboratory and an auditorium ; in a temporary building, there are smaller laboratories for different divisions. The library contains 1,243 volumes and receives 32 periodicals regularly.

The course lasts for two semesters and is divided into two parts.

The first part covers a period of four and a-half months and includes the following subjects :

Bacteriology, bio-chemistry, sanitary engineering, meteorology and malariology ; field work for three weeks at malaria stations, followed by a forty-day summer recess.

The second part begins on September 1st and includes the following subjects :

Epidemiology and statistics, social hygiene, public hygiene, school hygiene, physiology, health survey (twelve days), practical training at the Ambelokipi Health Centre (twelve days), and a general examination for graduation.

Class and field work during the academic year 1936 was divided up as follows :

¹ The expenditure for Health and Social Welfare Services in the State budget amounted to 2.4% of the total expenditure in 1928/29, and 3.06% in 1934/35.

Subject	Lectures Hours	Laboratory Hours	Visits Hours	Field work
Bacteriology	63	80	—	—
Parasitology	26	40	—	—
Bio-chemistry	26	75	—	—
Physiology	10	—	—	—
Tuberculosis	5	24 (clinical)	—	—
Sanitary engineering	26	52	8	—
Meteorology	10	20	—	—
Social hygiene	40	40 (seminar)	58	—
Malariology and tropical di- seases.....	21	45	—	3 weeks
School hygiene	20	—	18	—
Epidemiology and statistics...	77	76	—	—
Public health	30	—	39	8 days
Health survey	—	—	—	2 weeks
Ambelokipi Health Centre ...	—	—	—	2 weeks
Total	354	452	123	8 weeks

The number of students varies between twenty and twenty-four. They are appointed from among physicians employed by the Ministry of Health, the Ministry of Education and the Ministry of the Army and Navy by competitive examination, and from among private physicians. The students continue to receive their salaries if they are employed in the public service.

During the first years of the School's work, graduates in public health were practically all appointed to posts in the central or local health organisations.

In 1932, there were twenty-one graduates (sixteen of them employed by the Ministry of Health and two by the Ministry of the Army and Navy); in 1933, eighteen graduates (eight employed by the Ministry of Health, six by the Ministry of the Army and Navy); in 1934, nine graduates (eight of them employed by the Ministry of Health); in 1935, twenty-six graduates (thirteen employed by the Ministry of Health, one by the Ministry of the Army and Navy, four by the Ministry of Education, four by a municipality, one from Cyprus); in 1936, twenty-two graduates (seventeen employed by the Ministry of Health, one by the Ministry of the Army and Navy, one from Cyprus). Between 1932 and 1936, nineteen failed to graduate.

The School also organises courses for sanitary inspectors. The annual curriculum, which lasts for eight months, is divided into

theoretical teaching, practice in the laboratory and in the field, and a special course in disinfection. Seventy students have graduated after taking this course and all of them were appointed to posts in the public health centres by the municipalities or communities.

All courses are given free of charge.

IV.

The staff of the School consists of six regular professors, three professors of the University (who are paid for their lectures), three sanitary engineers, four hygienist malariologists, two chemists, one statistician, one librarian, one assistant librarian, four laboratory assistants, twelve clerks, four manual labourers and eight other employees engaged from day to day.

With the grant from the Rockefeller Foundation, the Division of Malariology employs a specialist in entomology, three medically trained malariologists and a technician, with the necessary subordinate personnel ; the Division of Sanitary Engineering employs one sanitary engineer and three subordinates.

The basic salaries of the regular professors are higher than those of the other State employees. Their basic salary is 12,000 drachmas per month. Except in three cases, the regular professors hold other posts in Government or private services. According to the new regulations, the salary for additional employment cannot be higher than the salary for the main employment.

THE AMBELOKIPI HEALTH CENTRE.

The Ambelokipi Health Centre was organised for the practical training of the students of the School and to serve as a model local health service. An agreement was made between the School, the City of Athens and the Rockefeller Foundation for the maintenance of the centre for five years.¹ Several public and private health

¹ *Capital expenditure* was as follows :

Cost of building : 1.8 million drachmas provided from the funds of the School of Hygiene.

First year's budget (includes 500,000 drachmas capital expenditure for furniture and equipment) : Total, 1,400,000 drachmas (500,000 School of Hygiene, 500,000 City of Athens, 400,000 Rockefeller Foundation).

Second year's budget : 1,250,000 drachmas.

agencies are co-operating in the centre with a view to working out a general public health programme.

The personnel of the centre consists of a public health officer, an assistant health officer, a supervising public health nurse, five public health nurses and two sanitary inspectors, all on a full-time basis, and of five part-time physicians who are employed as specialists in the clinics of the centre, and a school physician.

The aim of the centre was to provide complete public health service for a part of the city, and to facilitate the practical training of the students of the School of Hygiene and of the recognised nursing schools. The first practical training of student health officers began in November 1936. The programme of the centre includes pre-natal work, maternity, child welfare, school hygiene, dentistry, control of communicable diseases (including tuberculosis and syphilis), sanitation, statistics, health education and propaganda. During the first fifteen months (October 1935-December 1936), 1,072 different families were registered at the clinics for regular health supervision, representing one-seventh of the entire population of the district.¹

For the education of nurses in public health, the centre collaborates closely with the Red Cross and Evangelismos schools of nursing. The programme of collaboration was first carried out in April 1936. The centre is responsible for public health teaching,

¹ During the same period, the attendance at these clinics was 9,453. The five public health nurses made 11,628 home visits. Four hundred and twenty-two infants were registered; they represent about 40% of the total number of infants under one year in the district. Of the pre-school children, 528 have been registered. Infants and pre-school children came for consultation 4,531 times, and to supervise them 7,675 home visits were made. Four hundred and sixty-five expectant mothers have been under the supervision of the centre; they represent about 45% of the total number of pre-natal cases of the district. They came for consultation 1,156 times and the public health nurses made 1,830 home visits to them. Three hundred and sixty-four persons registered at the TB clinic, with 941 attendances at the clinics, and 1,406 home visits. Two hundred and fifty-five persons registered at the syphilis clinic (1,643 treatments and 274 home visits). To control epidemic diseases, the centre has endeavoured to collaborate with the practitioners. In the diagnostic laboratory of the centre, 2,081 examinations were made during the period. The Health Centre, in collaboration with the Sanitary Engineering Division of the School, has made a survey of the water supply and sewage disposal in 4,957 houses of the district. The centre was also responsible for the mosquito control of the district, and five inspectors visited 2,143 homes for this purpose. A small campaign has been launched for building cheap hygienic privies and thirty-four were set up by the inhabitants.

both theoretical and practical. All the senior students must practise in the centre for from one to two months. For specialisation in public health nursing, a minimum period of six months is required.

In Athens, there are now two schools of nursing—the school of the Greek Red Cross, which opened thirteen years ago and is housed in the new hospital, and the school at the Evangelismos Hospital. In both, the course lasts three years. The programmes are similar, although the subjects and the number of hours of teaching vary somewhat. During the last six months of their three-year training, the students may specialise in any hospital service or in public health nursing. This programme was first applied during 1935/36. Since 1924, 120 nurses have graduated from the Red Cross (four of them specialised in public health nursing) and since 1931, forty-nine have graduated from the Evangelismos. It is expected that a State school for public health and hospital nurses will soon be established.

The curriculum of the Red Cross School of Nursing comprises :

First Year (Preparatory Period).

Subjects	Hours	Practical work and seminars	Total
		Hours	Hours
Anatomy and physiology	35	20	55
Bacteriology	15	10	25
Hygiene	25	—	25
Chemistry	25	10	35
Pathology	14	—	14
Dietetics : cooking for the sick	20	20	40
Art of nursing : theory and practice	30	70	100
Dressing of wounds	4	10	14
Upkeep of material	20	20	40
Massage	4	10	14
Medicaments and analyses	10	—	10
Psychology	12	—	12
Ethics of nursing	12	—	12
History of nursing	12	—	12
Physical education	—	20	20
Total, preparatory course			428

Subjects	Hours	Practical work and seminars	Total
		Hours	Hours
<i>First Year.</i>			
Pharmacology	30	10	40
Surgical diseases	16	—	16
Diseases of infants and children	16	10	26
Nursing of internal and surgical diseases ...	10	20	30
Total, first year			112
Grand total, first year			540
<i>Second Year.</i>			
Infectious diseases and disinfection	20	8	28
Communicable skin diseases	10	4	14
Gynæcology and obstetrics	20	10	30
Diseases of the ear, nose, throat	8	—	8
Diseases of the eyes	8	—	8
First aid	4	8	12
Psychiatrics and neurology	16	—	16
Tuberculosis and malaria	6	—	6
Professional problems	6	—	6
Advanced nursing	22	10	32
Total, second year			160
<i>Third year (subjects required of all students).</i>			
Physiology	8	—	8
Eugenics and health education	6	—	6
Social problems	10	—	10
Psychology of children and adults	16	—	16
Dietetics	6	4	10
Accounting : statistics	6	—	6
The rôle of the visiting nurse	6	—	6
Total, third year			62

During their training at the Ambelokipi Health Centre, the students receive theoretical and practical instruction in the following subjects :

	Hours	Practical work and seminars	Total
		Hours	Hours
Principles of public health administration ...	18	—	18
P. H. legislation : social service : sanitation ..	12	—	12
Hygiene and prophylaxis (maternity, infancy, syphilis, tuberculosis, trachoma)	14	—	14
Public health nursing	24	49	73
Visits to institutions	—	10	10
Total hours			127

RESEARCH WORK.

The scientific work of the Athens School of Hygiene is particularly worthy of note for the effort made there to study thoroughly endemic malaria in Greece and bring it under control.

The Department of Malariology of the school, under the direction of Mr. C. BALFOUR, with the assistance of the Rockefeller Foundation and the help of BARBER, RICE, SHANNON and the Greek malariologists, LIVADAS, DIMISSAS, SPHANGOS, MANDEKOS and others, has, during the last few years, published a series of studies on the biology of anopheles and on malaria epidemiology and prophylaxis. Among these studies, special mention should be made of the work of BARBER and RICE on methods for the dissection and permanent preparation of the salivary glands and stomachs of anopheles, this being of unquestionable general interest ; that of BARBER on the degeneration of sporozoites in infected anopheles, on egg-laying among the various species of anopheles, on polychromatophilia as an index of post-malarial anæmia, and on epidemiological variations of malaria in Eastern Macedonia and elsewhere ; SHANNON'S experiments on the influence of microclimatic factors on the life of the anopheles ; and the work of BALFOUR and his collaborators on methods for measuring endemic intensity and on the results of malaria observation over a period of six years in Greece ; and the entomological researches of PANDAZIS, carried out in part at the School of Hygiene, into the Greek *culicidæ*.

In connection with the Biochemistry and Nutritional Hygiene Department of the School, mention may be made of the investigations of JOACHIMOGLOU and KLISSIOUNIS into the morbid physiological results of coffee-drinking, and the work of ALIVIZATOS and ARVANITIS, carried out in part in the School of Hygiene Laboratory, on the standardisation of the examination of yoghurt.

Researches concerning vital statistics were carried out by VALAORAS in part in the Athens School of Hygiene ; they bore on the increase of the population of Greece as shown in a logistical curve.

The Social Hygiene Department has carried out investigations in the Ambelokipi area (Athens), which has a population of 25,000,

and in the industrial town of Eleusis ; it has studied the relations between the Government health services and those of municipalities and communes, and has prepared several draft sanitary laws, including one on hospital organisation in Greece in relation to the needs of rural populations.

3. THE BUDAPEST INSTITUTE OF HYGIENE.

INTRODUCTION.—HEALTH ORGANISATION.

Important changes have taken place during the last few years in the Public Health Administration of Hungary. Among others, the Ministry of Social Welfare has been abolished and the Ministry of the Interior has taken charge of the Public Health Service.

Beside the Minister and the political Secretaries of State, there are in the Ministry two permanent Secretaries of State ; one of these, Dr. Béla JOHAN, who was for some years Director of the Institute of Hygiene, directs the Department of Public Health.

The Ministry comprises the following Departments :

- (1) General Public Administration ;
- (2) Police ;
- (3) Social Welfare ;
- (4) Public Health.

The Public Health Department is divided into five sections : Public Health ; Health Administration ; Epidemiology and Social Hygiene ; Hospitals ; Child Welfare Service.

The Section of Epidemiology and Social Hygiene is housed in the building of the Institute of Hygiene and is under the Director of the Institute. The Director thus has charge of the activities of the Institute and, as chief of the appropriate section in the Ministry, draws up the public health programme and gives orders to local administrations in regard to its execution.

In the past, the Ministry had four inspectors for the supervision of district and municipal health officers. Each inspector was responsible for the supervision of the Public Health Services of six to eight counties and several cities. This system of inspection has been modified and five inspectors have been appointed to supervise sanitation work, child welfare services, the tuberculosis campaign, the epidemic disease control of rural hygiene.

The country is divided into twenty-five counties and eleven municipalities with the status of counties. There are 149 districts

and forty-six towns as administrative subdivisions of the counties. Under the terms of a special law, the medical officers of the counties, municipalities, districts and towns are appointed on a full-time basis by the Minister and work under the direction of the Sub-Prefect. In technical matters, however, they correspond directly with the Ministry. They are not allowed to engage in private practice. Every community with more than 5,000 inhabitants is required to employ a part-time physician, whose principal function is to treat the poor. Communities with fewer than 5,000 inhabitants are combined into rural health unit areas. The community and health unit physicians are appointed by the Minister, who pays a substantial sum out of his budget to the local authorities for the salaries of the medical staff. This sum amounted last year to 4½ million pengö.

A ten-year programme for the development of Rural Health Services (known as "Green Cross" services) has been adopted by the Ministry, and each year the necessary appropriations are provided by the State budget. According to this programme, about 140 district health centres and 800 smaller health centres will be gradually established, this involving a complete change in the present district and communal health services, which have been in operation since 1876. The district centres are to be public health institutions organised in several sections, fully equipped for treatment, diagnosis and field work, with specialists in charge of the different sections. They will supervise the rural health centres, which are to be much simpler. Each rural centre will take charge of an area comprising usually 6,000 to 8,000 inhabitants. In the larger villages, a special room for medical examinations will be provided; in the smaller villages, the premises of the village administration will be used for this purpose. A physician and public health nurse will visit the villages regularly. The expenses are to be divided as follows: the salary of the nurse is paid by the Ministry, which will also provide the material for health education; a certain sum is to be allocated in the budget of the Department for the maintenance of the health centre in villages. The village in its turn will provide a room for consultations and living-quarters for the public health nurse. The village will also be obliged to supply the means of communication for the doctor and the nurse and meet the cost of heating, lighting and cleaning the health centre premises.

In the first year of the activities of a rural centre, the State will pay about 50% of all expenses. Out of the Department's grant, the doctor will receive an honorarium for medical examinations, and the travelling and subsistence expenses of the nurse will be met when the distances she has to travel from the centre are considerable.

During the last three years, this organisation has been set up in 378 communes ; five district and 128 rural health centres, thirty-three communal health centres and 241 consultation rooms have been provided in this way. Twenty-seven medical, 137 communal physicians, ten tuberculosis specialists, six venereal disease specialists, fifteen dentists, ten dentists' assistants, 128 public health nurses and eleven sanitary inspectors are at present engaged in this work. These institutions ensure close collaboration between the Institute of Hygiene in Budapest and the private maternal and infant welfare organisation known as "Stephania".¹

The full-time medical officers of the counties, municipalities and districts are paid according to their position and length of service. They begin with a monthly basic salary of 204 pengő, which rises by automatic increments to 555 pengő. In addition, there is a special allowance which varies according to the size of the medical officer's family. Another allowance for living-quarters is provided. The Ministry collects the fees for the issue of various certificates and permits and distributes them among medical officers according to the size of their families.

Part-time physicians in rural services start with 141 pengő monthly, rising by automatic increments to a maximum of 232 pengő ; additional amounts are paid for living-quarters and by way of family allowance.

The salary of a nurse ranges from 120 to 232 pengő per month, plus dwelling allowance.

Of nine million inhabitants in Hungary, over three millions come under social insurance. Workmen's compensation funds in industry

¹ The activities of the newly organised Health Service have been very extensive. The reports for 1936 give a detailed account of them. Practically every young child and child of the pre-school and school age has been examined, and special efforts have been made in the field of tuberculosis control and in the treatment of trachoma and venereal diseases. The nurses have made 384,819 home visits to 289,693 families and given many lectures on hygiene.

and commerce and in agriculture have a membership of 1.7 million persons ; national health insurance covers 760,000 persons ; invalidity and old age insurance, widows' and orphans' pensions 350,000 persons, and other social insurance institutions about 120,000 persons.

The Social Insurance Law of 1928 prescribes that the Health Insurance Office should also organise and finance preventive health work. In pursuance of a decree of the Ministry of the Interior, issued in 1936, a special commission was appointed within the office to draw up a plan for the preventive medical work to be undertaken by the Health Insurance Office. This commission comprises twelve members, elected by the autonomous sections of the office for a period of five years, and includes, *ex officio*, the Director of the State Institute of Hygiene, the Chief of the Health Centre, a representative of the Ministry of Industry and the Director of the Health Insurance Office.

There were, in Hungary, at the end of 1936, 9,577 registered physicians, 242 employed by the State and municipalities, 1,105 by the communes and towns, 953 by the hospitals and 3,309 by social insurance. In Budapest, there is one physician to 257 persons and, in rural areas, one to 1,730.

THE INSTITUTE OF HYGIENE.

(Director : Professor J. TOMCSIK.)

The Institute has three main activities : the first is the post-graduate training in public health and the training of nurses ; and the second, laboratory work, which is divided into five sections : parasitology (Chief : Dr. G. K. MAKARA), bacteriology (Chief : Dr. S. LOVREKOVICH), serology (Chief : Dr. G. OLAH), chemistry (Chief : E. SCHULEK) and water testing (Chief : A. JENDRASSIK) ; while the third consists of practical field work (Chief : Dr. A. GAAL), epidemiology (Chief : Dr. A. PETRILLA), tuberculosis control (Chief : G. PETRANYI), the supervision of rural health services and sanitary engineering (Chief : E. A. VASS).

Activities.

The activities of the Institute have grown from year to year. Branch laboratories have been organised to improve the diagnostic work. Three of these are attached to the Institutes of Hygiene of the Universities. Some very important investigations have been initiated : the bacteriological laboratory has carried out a study of typhoid carriers in seven counties and two cities by examining all persons reported as typhoid cases after 1926. Altogether 126,000 persons have been examined and 677 typhoid carriers found. Vaccination against diphtheria has been made compulsory, and over one million children have already been vaccinated. The parasitological laboratory, with the help of the Higher School of Agriculture, has carried out studies on flies to determine the breeding places and the rôle of flies in epidemics. Field surveys in regard to malarial and intestinal parasites have been undertaken in certain districts. The chemical laboratory analyses, tests and registers drugs and patent medicines ; the laboratory for water analysis has examined 18,000 wells and regularly supervises public water supplies. The sanitary engineering section prepares designs of simple wells, which it distributes free of charge to villagers ; 300 to 400 wells have been constructed every year with the help of the Institute. Model plans for the improvement of rural housing, latrines and other sanitary installations are distributed. The serological laboratory prepares diphtheria anatoxin, undertakes the official testing of sera, and performs serological analyses, mainly Wassermann tests. Finally, the Institute carries out field work, maintains liaison with the regional authorities, and supervises the conduct of field surveys and field work generally.

The library of the Institute contains 10,285 volumes and receives 153 periodicals regularly, of which ninety are foreign.

Budget.

The expenditure of the Institute is covered by grants from the Treasury (82%), by fees for the analyses of drugs, patent medicines and water (10%), and by grants from the Rockefeller Foundation (at present 8%). The total expenditure amounted to 485,809 pengö in 1932/33 and 1,130,000 in 1936/37. Of this last sum, 268,059



Figure 5.—STATE INSTITUTE OF HYGIENE AT BUDAPEST : MAIN BUILDING.



Figure 6.—HEALTH CENTRE AT PÉCEL.

pengö were expended on salaries. The upward trend in the expenditure on sanitation, especially rural water supplies, is shown below :

Period	Expenditure Pengö
1932/33	5,000
1933/34	18,000
1935/36	155,148.09
1936/37	280,000 (were provided)
1937/38	330,000 (are provided)

As regards expenditure on rural health centres, the increase has also been considerable :

Period	Expenditure Pengö
1932/33	37,000
1935/36	147,000
1936/37	242,000
1937/38	364,200

The income of the Institute (from fees, etc.) increased from 35,000 pengö in 1932/33 to 140,000 pengö in 1936/37. A larger income is expected when the examination of cosmetics, which has been proposed, is made compulsory. The contribution of the Rockefeller Foundation decreased from 217,878 pengö in 1932 to less than half of this amount in 1936.

Staff.

The staff of the Institute is partly recruited from the University and partly trained in the Institute itself and abroad. The appointments are on a full-time basis ; the salaries paid are on the same scale as for medical officers, according to the provisions of the Civil Service Law.

Courses for Post-graduate Training in Public Health.

Course for Public Health Officers.

In the programme of this course, no essential changes have been made. The course must be taken by all physicians applying for positions as health officers. The first part consists of theoretical instruction for five months, comprising 430 hours of lectures and

visits to public health institutions, as well as laboratory practice. The second part of the course, lasting for four months, is devoted to practical work in public health institutions, in the City of Budapest and in rural areas (Public Health Demonstration Districts).

The subjects taught are as follows :

	Hours
Bacteriology, serology, parasitology, filterable viruses	38
Epidemiology	42
Air conditioning ; housing	13
Soil ; water ; sewage	21
Nutrition	20
Meat inspection	8
Physiology of work	5
Personal hygiene	4
Social hygiene	48
School hygiene	11
Mental hygiene	15
Industrial hygiene	10
Eugenics	4
Social insurance	10
Public health administration	110
Rural hygiene	10
Vital statistics	24
Miscellaneous subjects	57
Laboratory training :	
In bacteriology	26
In serology	24
In parasitology	9
In hygiene of water, food, air, soil	52
In vital statistics	18

Field training consists of :

	Weeks
Field work in rural health districts	5
In a city health department	4
In a hospital for infectious diseases	2
In the TB dispensary	1
In a venereal disease dispensary and trachoma hospital	1
In maternity and infant welfare clinics	1
In a hospital for mental diseases	1
In the Institute of Legal Medicine	1

The number of applicants for the course of public health training is from four to five times as large as the number admitted. The

average time which has elapsed between the obtaining of a medical degree and admission to the courses is seven years. The requirements for admission are :

- (1) The physician must have spent at least two years after graduation in the different wards of a hospital ;
- (2) Apart from the two years in a hospital, the applicant should have had the opportunity for at least three years of acquiring some experience of public health work (Institute of Hygiene, assistant to a public health officer, community physician).

No fee is charged for the course, but there is an examination fee of 150 pengö. Students attending the different post-graduate courses at the State Institute of Hygiene may obtain board and lodging at reasonable rates in the Physicians' Hostel, located in a special building attached to the Institute. There are forty rooms and a dining-room for the staff of the Institute and those attending the courses. Only a few fellowships have been granted by different organisations.

Of 221 graduates of the period 1928-1936, two are at present officers of the Ministry, six county health officers, ninety-seven district health officers, seventeen municipal health officers and twenty-seven communal physicians ; fifteen are working in the Institute of Hygiene and hospitals, forty-four are engaged in private practice and the rest hold appointments in the army or in other services.

The number of students attending the course for the post-graduate training of public health officers has been :

In 1928	24
1929	26
1930	27
1931	24
1932	26
1933	26
1934	26
1935	26
1936	28
Total	233

Course for Communal Physicians.

Four years ago, courses lasting six weeks were organised for communal physicians. Attendance was not compulsory. In 1936, however, the course was made compulsory for applicants for positions in the communal health service and for communal physicians appointed after July 1st, 1936.

The teaching is mainly theoretical, consisting of 135 lectures and ten laboratory demonstrations. The theoretical lectures are followed by visits to rural health centres and to other health institutions—an average of one visit a week. Eighty students were admitted to the school in 1936.

The course is divided as follows :

	Hours
Epidemiology	25
Infectious diseases	12
Diseases of infants	5
Rural environmental hygiene	15
Nutrition	14
Social hygiene	18
Rural health centres	18
Insurance of agricultural workers	4
County and village public health administration	20
Miscellaneous subjects	4

The duration of these courses will be increased in the near future.

Communal doctors are accepted for these courses only if they have done not less than two years work in different hospitals or in general private practice since obtaining their medical degree. It is desirable that the applicant should have had a general and not a specialised hospital training. No tuition fees are required from students : the examination fee amounts to 50 pengō. Board and lodging have been paid by the county administrations for twenty-two students and by the Institute for twenty students.

Communal physicians are allowed leave on full pay, but must arrange for another physician to carry on their work during their absence.

School of Nursing.

(Director : Alexander M. WACKER.)

Four groups have graduated since 1933, representing a total of ninety-eight students.

The opening of a new course is advertised in various journals and the daily Press. The number of applicants for admission is about 50% larger than the number admitted. Entrance requirements are : a secondary school certificate, good physique, and age 18 to 30 years. Students must pay 200 pengő for uniforms and personal equipment, and 60 pengő monthly for room and board ; half of the students are allowed a reduction of 50% in these expenses.¹

The curriculum of the Nursing School covers a period of thirty-two months and includes the following subjects :

(1) The preliminary course :

	Hours
Anatomy, including demonstrations	40
Physiology and pathology, including demonstrations.....	39
Chemistry, including laboratory	31
Bacteriology, including laboratory	39
Pharmacology	27
Personal hygiene	12
Hospital administration	6
Principles of nursing, including ethics	50
Nursing demonstrations	27
Medical diseases	35
Surgical diseases	35
Nursing practice	224
	565

Practice in cooking during twenty days.

¹ Beside the Nursing School in Budapest, there is a Nursing School in Debreczen which had twenty students in its first year. There is a disproportion between the number of nurses graduating yearly and the number of posts for nurses in new institutions according to the ten-year programme for rural health services.

(2) The Public Health course is divided into theoretical and practical training ; it includes lectures in :

	Hours
Public health and sanitation	35
Maternity welfare and obstetrics	63
Infectious diseases	22
Pediatrics	22
Ear, nose and throat diseases	6
Eye diseases	8
Physiotherapy	6
First-aid	10
Care of the healthy baby	20
Tuberculosis problem (diseases and care)	21
Skin and venereal diseases and care	23
Psychology and psychopathology	30
Mental hygiene	12
Statistics	14
Legal aspects of public health nursing and social work	25
Social and industrial problems	40
Principles and practice of public health nursing	36
Elements of farming	25
	418

So far as practical training is concerned, the School undertakes nursing responsibilities for certain wards in three hospitals in Budapest. These hospitals are :

	Beds
A medical ward (female) in the City Hospital, St. Stephan.....	48
A surgical ward (female) in the University Clinic	36
A surgical ward (male) in the University Clinic	34
A babies' ward in the University Children's Clinic	11

Students spend twenty-two weeks in medical and surgical wards and eight weeks in the babies' wards. In addition, they receive the following training :

- 3 weeks in the State Eye Hospital ;
- 4 weeks in the State Mental Hospital "Lipotmezo" ;
- 4 weeks in the Maternity Clinic (Health Centre) at Gödöllo, and in the maternity ward of the City Hospital ;
- 1 week in the Nose, Throat and Ear Out-Patients' Department of the City Hospital ;
- 2 weeks in the City Tuberculosis Dispensaries ;
- 10 weeks in the Stephania Association for Maternity and Child Welfare, and
- 8 weeks in the rural health districts of the Institute of Hygiene.

Teaching Staff.

The teaching staff for the courses for public health officers, for communal physicians and nurses, consists of ten university professors and fourteen members of the staff of the Institute and a varying number of specialists. The laboratory teaching is conducted under the direction of the heads of laboratories ; the director of the nursing school and five nurses take part in the teaching of the nursing course. The staff of the Institute, excluding the staff of the Nursing School, delivers about 560 lectures in all.

Special Courses in School Hygiene.

Part-time courses for school health officers and secondary-school teachers of hygiene have been held in the University Institute of Hygiene in Budapest since 1885. In 1933, both these courses were combined in a single course lasting for two and a-half months. The course is at present conducted by the University Institutes of Hygiene in Budapest and Pecs. The training comprises teaching in general hygiene (eight hours), social hygiene (fifteen hours), infectious diseases (thirty-eight hours), pedagogy (ten hours), demonstrations of school hygiene (two hours) and laboratory practice in the institutes (twelve hours). The courses are not held regularly every year.

RESEARCH WORK.

A perusal of the last two reports on the work of the Hungarian State Institute of Hygiene (year 1934, under the direction of Dr. JOHAN ; year 1935, under the direction of Dr. TOMCSIK) is sufficient to convey an idea of the scientific work of the technical staff of the Institute. The 1934 report summarises thirty-six publications, and the 1935 report fifty-seven.

The impulse given by JOHAN during the last few years to the study of rural hygiene problems has been followed up by his collaborators. BOROS studied the consumption of sugar in rural districts ; PETRES, the question of venereal disease in country districts ; STELLER, nursing in rural districts ; and GAAL the organisation of rural sanitation and assistance.

Mention should also be made of the work published by JENDRASSIK and his collaborators of the water and food analysis service on food-poisoning, drinking-water, and methods for the analysis of chemical elements dissolved in liquid foodstuffs.

In the matter of infectious diseases, the Budapest Institute has long been devoting special attention to diphtheria and typhoid fever.

In his works on diphtheria from the point of view of immunology, FARAGO made a study, in four districts, of 7,533 children from one to twelve years to whom the Schick test was applied; he found a maximum of 93.6% immunised after a single inoculation of 1 c.c. of anatoxin precipitated by alum. Marked differences were, however, noted among the groups examined.

Statistical studies on diphtheria were also carried out from 1927 to 1935 under FARAGO's direction. This series of investigations has made it possible to formulate theoretical and practical suggestions concerning the efficacy of immunisation from the epidemiological standpoint.

As regards typhoid fever, special mention should be made of the work of PETRILLA, head of the Epidemiological Department of the Institute. A study of 37,151 cases of typhoid notified in Hungary between 1931 and 1935 enabled him to establish facts of real epidemiological importance and to note clinical and statistical differences between cases treated in hospital and cases diagnosed and treated in the country.

Among work on parasitology may be mentioned in particular the researches of LÖRINCZ and his collaborators on intestinal protozoa and helminths in Hungary, with special reference to ankylostomiasis.

The enquiry conducted by the Parasitology Department (LÖRINCZ, MAKARA) on flies and manure, as planned by the Directors of Schools of Hygiene after the European Conference on Rural Hygiene of 1931, formed a remarkable contribution towards the knowledge and solution of this problem, and were duly appreciated at the meeting of entomologists held in London by the Health Organisation in 1934.

Studies in microbiology, more particularly pure bacteriology, and serology, were carried out chiefly by TOMCSIK, the present Director of the Institute, who has just published, in collaboration with LOVREKOVICS and LÖRINCZ, a "Treatise on Bacteriology, Immunology and Parasitology". TOMCSIK studied with BODON the biochemical

structure of *B. anthracis* from the point of view of nucleoproteins and polysaccharids ; he propounded the hypothesis of immunity against a partial capsule antigen, and attempted to produce a protective serum. GANDELLINI carried out experiments to determine the action of the bacteriophage on rabbits, carriers of Eberth's bacillus, inoculated by intravenous injection or directly into the gall-bladder. RAUSS and DOZOIS studied the relations between the velocity of electrophoretic migration and the virulence of diphtheria and paradiphtheria bacilli ; FARAGO, the dissociation of colonies of Fränkel-Welch bacilli ; LÖRINCZ, Schwartzman's and Arthus' phenomena from the histological standpoint ; and VASARHELYI, certain biological characteristics of *Sp. pallidum* and the cytochol test compared with serological tests for syphilis.

In the field of chemistry and pharmacology, remarkable work has been done by CLAUDE, on a new method for the determination of sulphides and halogens in organic analysis ; GERVAY, on the dissociation of acetyl-salicylic acid salts ; SCHULEK and GERVAY, on the determination of hexamethylenetetramine ; SZEGHÖ, SZLATINAY, SZONGOTT, VASTAGH and WOLDTADT on morphine, arsenobenzenes, digitalis, camphor, etc.

It will be seen, then, that the scientific activities of the Budapest Institute are mainly concerned with problems of epidemiology. In this connection, it may be noted that the medical statistics service and the records of notifiable infectious diseases in Hungary are entirely in the hands of Dr. PETRILLA, head of the Epidemiological Department, while the Institute itself acts as the central technical organ of the State in these matters.

4. LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE.

INTRODUCTION.

The first Medical Officer of Health in England was appointed in Liverpool in 1847, and a year later a similar appointment was made in the City of London. During the next twenty-five years, many other local authorities followed the lead given by these two cities, and finally in 1872 such appointments were made compulsory in all areas, although full-time service was not generally required. The Government undertook to pay 50% of the salaries of medical officers of health and their conditions of appointment and tenure of office were henceforth subject to its approval. A special post-graduate qualification in public health was instituted by Trinity College, Dublin, in 1870, and the first course of instruction was given in that medical school in the session 1870/71. Similar arrangements began to be made shortly afterwards in a number of other universities, and, in 1886, the Medical Act provided that every registered medical practitioner to whom a diploma in public health or its equivalent had been granted by any examining body in the United Kingdom was entitled to have this additional qualification registered in the Medical Register if such diploma appeared to the Privy Council or to the General Medical Council to deserve such recognition. The Local Government Act, 1888, required all persons appointed medical officers of health of counties or of areas with a population of 50,000 or more to be holders of a registered diploma in public health ; accordingly in 1889 the General Medical Council intimated that they would not consider such diplomas or degrees as deserving of recognition in the Medical Register unless they had been granted under such conditions of education and examination as would ensure, in the judgment of the Council, the possession of a distinctively high proficiency, scientific and practical, in all branches of study which concern the public health. The

Council then issued certain rules which they required to be observed in the conduct of the course of instruction and of the examinations.¹

In the early part of this century, practically all medical schools in Great Britain offered courses of training for the diploma in public health, and, by 1919, it became obvious that modern developments in public health were making it more and more difficult for any but the larger and better equipped schools to provide adequate instruction. Indeed, the Board of Studies in Hygiene of London University had called attention on several occasions from 1909 onwards to the need for "one London centre for post-graduate teaching in public health to replace the system whereby candidates for the D.P.H. worked at ten different centres and demanded part-time service from forty-four lecturers and demonstrators".

In 1921, the Minister of Health appointed a committee, under the chairmanship of the Earl of ATHLONE, "to investigate the needs of medical practitioners and other graduates for further education in medicine in London, and to submit proposals for a practicable scheme for meeting them". This committee reported in 1921, and one of its recommendations was that an institute of state medicine should be established by the University of London in which instruc-

¹ According to the curriculum, every candidate must attend, during not less than 280 hours (a) theoretical and practical instruction in bacteriology and parasitology (including immunology, serology and medical entomology in relation to public health); (b) theoretical and practical instruction in physiology and bio-chemistry in relation to public health; (c) instruction in the application of the principles of chemistry and physics to environmental and personal hygiene (including methods of examination and purification of water and sewage, the composition and various forms of adulteration of the more common foods, the nature (and methods of estimation) of pollution of the atmosphere, and methods of disinfection and disinfestation). The candidate must receive during not less than 160 hours, instruction in the following subjects: (a) epidemiology and vital statistics (including statistical methods); (b) the principles of hygiene and sanitation and public health; (c) public health law and administration (including social insurance, public medical services and hospital administration); (d) industrial hygiene and the welfare of industrial workers; (e) house planning and sanitary construction; (f) the principles of genetics; (g) mental hygiene. Attendance for three months at a recognised hospital for infectious diseases is required, and, during a period of not less than six months, students have to receive practical training in the duties, routine and special, of public health administration under the supervision of a medical officer of health, who shall certify that the candidate has received during not less than three hours on each of sixty working-days practical instruction in the duties, routine and special, of (a) maternity and infant welfare service; (b) health service for young children and children of school age; (c) venereal diseases service; (d) tuberculosis service; (e) industrial hygiene service; (f) hospital service; (g) inspection and control of food, including meat and milk; (h) arrangements for dealing with mental disorder and deficiencies.

tion should be given in public health, forensic medicine, industrial medicine and in medical ethics and economics. In 1922, the Rockefeller Foundation informed the Minister of Health that they were in agreement with a revised scheme which had been submitted to them for the creation of a school of hygiene ; and that they would be prepared to meet the cost of the site, building and equipment on the conditions that the school would eventually be associated with the University of London and that His Majesty's Government would undertake to provide an annual maintenance grant. In the end, the London School of Tropical Medicine, founded in 1899, was incorporated in the new school, which took as its title the London School of Hygiene and Tropical Medicine ; the Rockefeller Foundation contributed a sum of two million dollars, and His Majesty's Government promised an annual grant of £40,000. The new building was opened by His Royal Highness the Prince of Wales in July 1929, and all the medical schools in London ceased post-graduate public health teaching from that date.

The five provincial universities of Birmingham, Durham, Leeds, Liverpool and Manchester also offer courses of instruction and grant diplomas in public health ; between them they train about forty to fifty students a year. In London, the Royal Institute of Public Health provides instruction, on a part-time basis, for students proceeding to the Diploma in Public Health of the Examination Board of the Royal Colleges of Physicians and Surgeons and the Scottish and Irish universities have also courses for their own diplomas.

It is of interest that legislation in recent years (1) has required county councils to take such steps as may be necessary, whether by combination of districts or otherwise, to ensure that all district medical officers of health appointed in future shall be debarred from private practice and (2) has made the possession of a registered diploma in public health obligatory in the case of *all* persons appointed medical officers of health.

ORIGIN AND CONSTITUTION OF THE SCHOOL.

The London School of Hygiene and Tropical Medicine was established by Royal Charter in 1924, but it united with an older

institution, the London School of Tropical Medicine, which had been maintained under the auspices of the Seamen's Hospital Society since 1899.

The School is governed by a Court, which meets annually to receive a report on the year's work, and by a Board of Management which meets normally once a month. The Board of Management is advised by a Finance and General Purposes Committee, and, on academic matters such as the organisation of teaching and research, by a Council representative of the teaching staff of the School.



Figure 7.—LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE :
GENERAL VIEW.

The chief executive officer of the School is the Dean. He is *ex-officio* Chairman of the Council, and it is his duty to advise the Court and the Board of Management on all matters involving the policy, finance, government and administration of the School.

Two changes are to be noted in the last few years. First, the Director of the School, Sir Andrew BALFOUR, died in 1930. The post of Director was then replaced by that of Dean, and Professor JAMESON, who holds concurrently the Chair of Public Health, was appointed. Secondly, the Ross Institute was incorporated in the

School in January 1934. The Institute had been founded in July 1926, in honour of Sir Ronald Ross, and it concerns itself largely with furthering measures of hygiene in the tropics—particularly the control of malaria—in co-operation with industrial and commercial undertakings.

The Charter of the School was modified in 1934 to enable representation to be given to the Ross Institute on the Court of Governors and the Board of Management.

BUDGET OF THE SCHOOL.

The ordinary expenditure of the School is in the region of £65,000 annually. The chief sources of income are as follows :

	£
Parliamentary grant, transmitted through the Court of the University of London	40,000
Students' tuition fees	6,000
Dividends and endowments, including certain endowments appropriated to special purposes	7,000
Donations and subscriptions	11,000

Donations and subscriptions are received largely, though not exclusively, in respect of the School's work in tropical medicine and hygiene. They come from colonial Governments, from private individuals and from industrial undertakings, particularly those concerned in overseas industries such as planting and mining. Apart from its ordinary expenditure, the School spends annually large sums on research. Money for this work comes in part from invested trust funds but to a far greater extent from grants made by outside bodies in respect of particular pieces of research. Bodies to which the School is indebted for grants in aid of research include the Ministry of Health, Ministry of Agriculture, Medical Research Council, Agricultural Research Council, Milk Marketing Board, Imperial Chemical Industries, Ltd., and the Anglo-Iranian, the Asiatic and the Burma Oil Companies ; charitable trusts including the Leverhulme Trust, the Pilgrim Trustees and the Halley Stewart Trust.

Total expenditure was as follows :

	Total expenditure	General account, balance special funds
1930,31	£64,244 9s. 8d.	£55,753
1931,32	£63,665 6s. 1d.	£55,112
1932,33	£67,225 12s. 7d.	£58,404
1933,34	£70,278 7s. 9d.	£61,797
1934,35	£74,150 16s. 2d.	£65,002
1935,36	£82,644 7s. 11d.	£65,125

COURSE IN PUBLIC HEALTH.

The course is designed for qualified medical practitioners and it is intended to prepare them for the Diploma in Public Health of the University of London. A period of not less than two years must have elapsed from the date of the candidate's qualification in medicine before he may be granted the diploma, and the authorities of the School regard it as desirable that medical practitioners should have devoted not less than two years to obtaining experience in resident appointments in hospitals and in general practice before they enter upon the course in public health in the School.

The tuition fee for the course is 54 guineas and this covers the cost of tuition in the School, together with practical work and instruction in infectious disease and hospital management.

The course commences about the end of September and it lasts one academic year of nine months. The first term (October to December inclusive) is devoted to bacteriology, chemistry and physics, and parasitology as applied to public health, and to physiology. Candidates are examined on this syllabus at Part I of the University's D.P.H. examination in January. The second and the third terms of the year (January to June inclusive) are devoted to study of the theory and practice of public health administration, the principles of sanitary law, epidemiology and vital statistics, medical industrial psychology and domestic sanitary engineering. In addition, during these two terms, members of the class undertake district work under medical officers of health, and they receive a practical course of instruction in the work of a hospital for infectious diseases. Some forty visits are made to places of public health interest including water-works, sewage-works, refuse-disposal plants,

markets, food factories, offensive trades, slum areas, garden cities, special industrial processes, the Port of London, rural areas, maternity and child welfare organisations, special schools, tuberculosis institutions and venereal disease clinics. Part II of the University's D.P.H. examination, which covers the syllabuses of the second and third terms of the course, is held at the end of June.

PRACTICAL TRAINING IN PUBLIC HEALTH.

Practical training in the duties of a medical officer of health must, according to the Rules of the General Medical Council, be spread over a period of at least six months and must consist of not less than sixty attendances of three hours each. It was felt that no one area in London would provide students with sufficiently varied experience, so it was finally decided to select three districts—the Metropolitan Boroughs of St. Marylebone and of Kensington and the Borough of Willesden, situated on the immediate outskirts of the London County Council area. The respective medical officers—Dr. Charles PORTER, Dr. FENTON and Dr. George F. BUCHAN—are men of great experience both as teachers and as administrators.

The Borough of St. Marylebone is an administrative area in the west end of London. It has a population of 92,000 and consists partly of a high-class residential quarter of London and partly of shops, small manufactories and working-class houses. The Borough has a staff of one medical officer of health and three assistants, ten sanitary inspectors, eleven health visitors and other auxiliary personnel. The services administered include maternity and child welfare, the dispensary care of tuberculous persons, epidemiology, vaccination and sanitation. The London County Council is responsible within the borough for the school medical services, sanatoria for tuberculous persons and hospitals of all sorts. These London County Council services are also used for the instruction of students from the School.

The Municipal Borough of Willesden is situated in the county of Middlesex at a distance of about three miles from the School. It has a population of 188,000, mainly artisans and clerks. The district contains a number of factories and many small industries. The Borough undertakes all public health services save those dealing

with tuberculosis, venereal disease and the provision and maintenance of general hospitals, which are the concern of the Middlesex County Council. The staff consists of one medical officer of health, six whole-time assistant medical officers of health, four whole-time dentists and seven part-time specialists, forty-four health visitors, eleven sanitary inspectors, a large number of clerks, assistants for the provision of school meals and other auxiliary personnel in addition to the staffs at the isolation and maternity hospitals.¹

Consideration has been given to the possibility of establishing a special health demonstration area administered in conjunction with the School and so staffed as to permit of the carrying out of a large programme of teaching. In England, such a scheme presents rather peculiar difficulties. Every available district has a tradition of at least sixty years of more or less autonomous local government and is invariably jealous of its rights and privileges.

Moreover, in all populous areas, a reasonably complete public health service is available to which young men and women may be appointed as assistants working under supervision. The need therefore for providing a practical training of a kind likely to fit a student to take over immediately the duties of a medical officer of health is less than in certain continental countries. At the same time, there are great and admitted advantages in having attached to a school an area where special investigations may be undertaken and model arrangements may be demonstrated to groups of students.

¹ The Willesden Borough Council is composed of fifty-two members, popularly elected, and is the health and educational authority for the area. The health services controlled by the Council are provided out of local funds subsidised from the Imperial Exchequer. The health services for tuberculosis (sanatorium and dispensary treatment), venereal diseases, work under the Sale of Food and Drugs Acts, vaccination and the institutions of the Poor Law, are provided by the Middlesex County Council. The Borough Council is responsible for the maintenance of the Public Health Administration, Maternity and Child Welfare (fifty-six beds in Maternity Hospital), Municipal Hospital for Infectious Diseases (160 beds), school medical service, nutrition of school-children, special schools and housing. Three health centres are organised in the Borough, and 66% of all births take place in the hospital. A thousand school-children get daily breakfast and lunch. The total expenditure of the health department of the Municipal Borough for the present fiscal year is £139,228. Almost the same amount is spent on health services in the Borough by the Middlesex County Council.

COURSE IN TROPICAL MEDICINE AND HYGIENE.

The course is designed to prepare medical practitioners for the Diploma in Tropical Medicine and Hygiene of the conjoint examining board of the Royal College of Physicians of London and of the Royal College of Surgeons in England. The course of study is open to any qualified medical practitioner and the examination for the diploma is open to graduates of any medical school which has been approved for the purpose by the Conjoint Board. In addition, certain non-medical candidates, such as veterinary surgeons and sanitary inspectors, are admissible to certain parts of the course. The class includes officers, and persons selected for appointment as officers, in the Colonial Medical Service, but, in addition, students are drawn from a great many countries all over the world.

The tuition fee for the whole course is £40, or for Part I only, £25 and for Part II only, £15. Part I lasts twelve weeks and Part II nine weeks. Part I is repeated three times a year, commencing in September, January and April, and Part II is repeated twice, commencing in January and April.

Instruction in clinical tropical medicine is given by the honorary staff of the Hospital for Tropical Diseases (seventy-six beds) on two afternoons weekly throughout both parts of the course. The remaining syllabus of Part I includes medical zoology (protozoology, entomology and helminthology), elementary sanitation and personal hygiene in the tropics. The laboratory and theoretical instruction in helminthology, protozoology and medical entomology is concentrated into a separate month for each subject. The syllabus of Part II of the course includes, in addition to clinical tropical medicine, instruction in bacteriology in relation to tropical medicine and hygiene, medical statistics and racial hygiene in tropical countries and tropical hygiene. During Part II of the course, the class visits places of hygienic interest, including the Army School of Hygiene at Aldershot, water-works, sewage-disposal works, milk-plants, markets and slaughter-houses. The examination for the diploma is held in two parts: Part I includes medical zoology, principles of sanitation and personal hygiene; Part II includes medicine, surgery and clinical pathology in relation to tropical

diseases, bacteriology in relation to tropical medicine and hygiene, epidemiology, vital statistics, public medical services in the tropics and tropical hygiene.

COURSE IN BACTERIOLOGY.

The course is designed for medical practitioners, and other persons holding suitable qualifications in medicine, in science and in pharmacy, and it is intended to prepare them for the Post-graduate Diploma in Bacteriology of the University of London. No more than twelve students are admitted to the course in any year.

The tuition fee for the course is £47 15s. The course commences in early October and it lasts one academic year of nine months. The syllabus is designed to offer alternatives to students according to whether they are interested in the application of bacteriology to hygiene and medicine or to industry. Those who wish to study the application of bacteriology to hygiene and medicine must previously have obtained a medical or veterinary qualification or must have had some equivalent training. Those who wish to study bacteriology as applied to industry must previously have had an adequate training in chemistry. The course of study includes general bacteriological chemistry followed by micro-biological chemistry, general bacteriological technique, special bacteriological technique, mycology, bacteriology applied to hygiene and medicine, tissue reactions to bacteriological infections, filtrable viruses, and bibliographical methods. The examination for the diploma is held once in each year in July.

COURSE IN PSYCHOLOGY WITH SPECIAL REFERENCE TO INDUSTRY AND MEDICINE.

The course is designed for graduates of an approved university who have already some elementary knowledge of general psychology, and it is intended to prepare them for the Post-graduate Diploma in Psychology of the University of London.

The tuition fee for the course is 28 guineas per session. The course commences in October and, in the case of candidates who

already have an adequate knowledge of general psychology, it lasts one academic year. Candidates without sufficient previous knowledge of psychology may be required to devote two years to the course. Members of the class are required to attend lectures at University College and elsewhere on general psychology, on the technique of experimentation, on industrial psychology and on practical neurology. (The cost of these lectures is included in the composition fee of 28 guineas.) The School provides courses of instruction on the general principles of industrial psychology, mental hygiene, statistical methods and industrial conditions from the psychological standpoint. Arrangements are made to enable students to obtain practical experience of various industrial organisations.

The examination for the diploma consists of two parts which may be taken concurrently and it is held once in each year in July.

COURSE IN EPIDEMIOLOGY AND STATISTICAL METHODS.

A special short course of instruction in epidemiology, vital statistics and statistical methods is provided for suitably qualified persons. The tuition fee is 7 guineas. The course, which does not demand a student's whole time, lasts three months. Provided a sufficient number of students is forthcoming, it is repeated three times a year, commencing in October, January and April. The work consists of four or five lectures and six or seven hours of practical work each week.

COURSE ON MENTAL DEFICIENCY.

A part-time course on mental deficiency was held for the first time in March 1937 and will be repeated annually. The course lasts four weeks and the time-table is arranged so that the course may be taken by members of the public health class. It is open to a limited number of other persons, particularly assistant school medical officers employed by local authorities in London and the Home Counties. The work consists of a series of lectures together with demonstrations and practical work on the testing of children

for the detection of mental deficiency. The course is given in co-operation with the Central Association for Mental Welfare, and students who complete it satisfactorily are eligible for recognition by the Board of Education as certifying officers under the Mental Deficiency Acts.

COURSE IN APPLIED HELMINTHOLOGY.

A short course on applied helminthology (agricultural and veterinary) was held for the first time in July 1936. The course was given by Professor LEIPER with the assistance of staff of the Institute of Agricultural Parasitology. It was designed for members of the agricultural and veterinary services at home and overseas. It lasted three weeks, and the syllabus included theoretical and practical instruction on general helminthology and on helminthology of agricultural and veterinary importance.

COURSES FOR LAYMEN.

The Ross Institute holds in the School a course, designed for non-medical men and women, on the control of malaria. The course is held in June in each year and lasts a week. No tuition fee is charged. In December, a course is held on tropical hygiene for men and women about to proceed to the tropics for the first time. A tuition fee of 1 guinea is charged and instruction is given on the elements of hygiene, on diseases seen in the tropics, on water supplies and conservancy, on personal hygiene, on the prevention of malaria, and on the rôle of the administrator in the prevention of disease in the tropics.

STUDENTS.

Since 1929/30, 814 students have attended the courses in tropical medicine and hygiene, 219 in public health, eighty-one in bacteriology, sixty in epidemiology and vital statistics and six in psychology. Of these students, 164 came from India, eighty-three from Ceylon, 112 from elsewhere in the British Empire, fifty-four from the United

States of America, 118 from other parts of the world and the remainder from the British Isles.

A majority of the members of the D.P.H. class come to the School as independent students. The classes in Tropical Medicine and Hygiene include officers selected for appointment to the Colonial Medical Service, and these men are required to follow the course before taking up their appointments. Similarly, the class in bacteriology usually includes some students who have been required to follow the course as a necessary preparation for taking up some post.

A majority of the D.P.H. students pay their own tuition fees. Fees of officers of the Colonial Medical Service who attend the course in tropical medicine and hygiene are paid for them by the Government concerned. The course in tropical medicine and hygiene is frequently taken during their periods of leave by medical officers holding appointments overseas. Members of the D.P.H. class as a rule have to find a post after completing their course.

There are no arrangements for part-time study but both the D.P.H. and the D.T.M. and H. courses are divided into two parts and it is possible for a student to take Part I of the course and to return at a later date for Part II. This, for instance, makes it possible for a man to complete the course in tropical medicine and hygiene during two successive periods of leave.

Scholarships.

The following awards and scholarships are available :

The Fishmongers' Company Studentship, open to candidates of European descent, which carries remission of fees for the public health course.

The Wandsworth Scholarship, for research in tropical medicine. The emoluments amount to £350 per annum together with overseas pay and allowances when the scholar is abroad. The scholarship is tenable for two years and is renewable for one further year. The holder is normally required to undertake a piece of research overseas.

The Avebury Memorial Studentship, which is awarded from time to time in aid of research in entomology.

The Andrew Balfour Memorial Studentship, which carries remission of fees in Part II of the course in tropical medicine and hygiene and which is open to all fee-paying students who have completed Part I of the course.

Various prizes and awards on the results of the examinations for which the students in the School are prepared.

Subsequent Careers of Students.

Most of those who follow the course of instruction in public health hope to enter the public health service of Great Britain. During the past seven years, many have become assistant medical officers and some senior medical officers of health. Others are health officers in the Colonial Medical Service, in the dominions and in India, and a smaller number have been appointed medical inspectors of Government departments, medical officers to industrial firms or research workers in laboratories. A few enter general practice, where the training they have received in the School in preventive medicine should make them all the better practitioners. A fair proportion of the students are women and they usually become maternity and child welfare medical officers either at home or abroad.

Most of the students attending the course for the Diploma in Bacteriology already hold appointments from which they are released temporarily in order that they may study at the School. The majority of the medical members of this class undertake laboratory work abroad, but a few have obtained appointments in academic institutions. Practically all the chemists following the course seek a career in the research departments of industrial undertakings. Some of them already hold appointments, and others are selected by the School staff at the request of firms and are given a training in bacteriology, at the expense of the firms concerned, before proceeding to take up their appointments.

Students who join the School to study tropical medicine and hygiene undertake subsequently every form of medical work in the tropics—in the Colonial Medical Service, in the Indian Medical Service, in industry and in private practice. A good many members of this class come from various European countries and from the

United States of America and many of them are medical teachers in their own countries.

In Great Britain, every county and district medical officer of health is required by law to hold a registered diploma in public health or its equivalent. The course in public health in the School prepares students for the D.P.H. of the University of London or the D.P.H. of the Conjoint Examining Board, both of which are registrable diplomas in public health.

THE WHOLE-TIME STAFF OF THE SCHOOL.

DIVISION OF PUBLIC HEALTH.

Professor	1
Senior Lecturer	1
Divisional Assistant	1
Personal Assistant to Director	1
Clerk	1

Department of Medical Industrial Psychology.

Professor (half-time)	1
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Department of Industrial Physiology.

Reader	1
Lecturers	2
Demonstrator	1
Clerk	1
Senior Laboratory Assistant	1
Laboratory boy	1

DIVISION OF EPIDEMIOLOGY AND VITAL STATISTICS.

Professor	1
Reader	1
Lecturer	1
Clerk	1

DIVISION OF BIO-CHEMISTRY AND CHEMISTRY AS APPLIED TO HYGIENE.

Professor	1
Lecturer	1
Demonstrators	2
Clerk	1
Senior Laboratory Assistants	2
Laboratory boys	2

Department of Chemistry as applied to Hygiene.

Professor	1
Lecturer	1
Demonstrator	1
Clerk	1
Senior Laboratory Assistant	1
Laboratory boys	2

DIVISION OF BACTERIOLOGY AND IMMUNOLOGY.

Professors	2
Lecturers	2
Demonstrators	2
Clerk	1
Senior Laboratory Assistants	2
Junior Laboratory Assistants	3
Laboratory boys	15

Animal House.

Supervisor	1
Assistant Supervisor	1
Assistant	1
Junior Laboratory Assistant	1
Laboratory girls	4

DIVISION OF MEDICAL ZOOLOGY.

Clerks	2
Senior Laboratory Assistant	1
Junior Laboratory Assistant	1

Department of Helminthology.

Professor (also acts as Director of Institute of Agricultural Parasitology)	1
Research Fellow	1
Collector and Demonstrator	1
Senior Laboratory Assistant	1
Laboratory boy	1

Department of Protozoology.

Professor	1
Lecturer	1
Collector and Demonstrator	1
Junior Laboratory Assistants	2
Laboratory boy	1

Department of Entomology.

Professor	1
Reader	1
Collector and Demonstrator	1
Clerk	1
Senior Laboratory Assistant	1
Junior Laboratory Assistants	2
Laboratory boys	3

DIVISION OF CLINICAL TROPICAL MEDICINE.

Director (part-time)	1
Deputy Director (part-time)	1
Lecturers (part-time)	6
Demonstrator	1
Senior Laboratory Assistant	1

MALARIAL STUDIES.

Professor	1
Laboratory Assistant	1
Laboratory boy	1

STUDIES ON TROPICAL MYCOSES.

Director (part-time)	1
Senior Laboratory Assistant	1
Junior Laboratory Assistant	1

INSTITUTE OF AGRICULTURAL PARASITOLOGY.

Director (part-time, see Department of Helminthology)	1
Principal Research Assistants	2
Research Assistant	1
Field Officer	1
Investigation Officers	2
Clerk	1
Senior Laboratory Assistant	1
Laboratory Assistants	3
Farm staff	5

ROSS INSTITUTE.

Director	1
Deputy Director	1
Field Officer (part-time)	1
Secretary	1
Demonstrator	1
Clerks	4

ADMINISTRATION.

Dean (who also holds the Chair of Public Health)	1
Secretary	1
Accountant	1
Warden of Studies and Curator of the Museum	1
Organising Secretary (who also acts as Secretary to the Ross Institute)	1
Clerks	3
Storekeeper	1

The teaching staff is graded as follows :

Professors, with salaries ranging between £1,100 and £1,500 per annum ;

Readers, whose salaries are £900 to £1,000 per annum ;

Senior Lecturers : salaries £800 per annum ;

Lecturers : salaries £600 rising by increments to £750 per annum ;

Demonstrators : salaries £400 rising by increments of £25 to £500 per annum ;

Auxiliary laboratory staff from £1 per week for boys to £5 10s. for Senior Laboratory Assistants.

In addition to employing a whole-time staff, the School makes use of the services of a large number of visiting lecturers.

Professors and Readers are appointed by the Senate of the University. In making appointments, the Senate is advised by a Board of Advisors which includes representatives of the School, and " external experts "—that is, persons who do not hold a paid office in the University of London or in any institution connected with it. Other members of the graded staff of the School are appointed by the Board of Management of the School on the recommendation of an Appointments Committee which includes the head of the division and department most nearly concerned with the appointment under consideration. Vacancies on the teaching staff are normally advertised.

Generally speaking, members of the staff are appointed to hold their posts up to the age of 60, and their tenure may be renewed for a further five years—in the case of Professors and Readers, by the Senate of the University ; in the case of other members of the staff, by the Board of Management of the School.

ALLOCATION OF TIME.

Practically all the members of the teaching and scientific staff hold full-time appointments. It is impossible to state precisely how their time is allocated between teaching and research as it varies to some extent from division to division, but all members of the teaching staff are given adequate opportunities of carrying on research. They do not normally undertake activities apart from their teaching and research.

THE ACTIVITIES OF DIVISIONS.

Division of Bacteriology.

(Professor W. W. C. TOPLEY and Professor C. S. WILSON.)

The main lines of research at present in progress in the Division are :

An investigation, jointly with the Division of Bio-Chemistry, on the fractionation of bacterial cells. The object of the investigation is an endeavour to secure from bacteria chemical fractions which may have a high immunising value and which may at the same time be non-toxic.

Studies, jointly with the Division of Epidemiology and Vital Statistics, in experimental epidemiology. The work has been in progress over a period of years and the present experiments aim at testing the effect on the epidemic process of varying the closeness and continuity of the contact of mouse populations. The work is also being linked up with the study of the relationship of diet to resistance to infection.

Work on milk, including an investigation into methods for the bacteriological grading of raw and pasteurised milk.

Division of Bio-chemistry and Chemistry as applied to Hygiene.

(Professor RAISTRICK and Professor DELAFIELD.)

The research in the Division follows two main lines. The first consists of an investigation of the bio-chemistry of the lower fungi

and the results that are being obtained are of pharmacological and industrial interest. The second is the work undertaken jointly with the Division of Bacteriology on Immunological Chemistry. Other work in progress includes an investigation of the relations between anæmia and a deficient diet, work on the activated sludge process of sewage purification and, jointly with the Division of Bacteriology, work on the methylene-blue reduction test for the grading of milk.

Division of Clinical Tropical Medicine.

(Dr. G. Carmichael Low.)

Studies at present in progress include work on tropical sprue, on those diseases affecting the small intestine which present a sprue-like syndrome, on Weil's disease and on malarial hæmoglobinuria.

Division of Tropical Hygiene.

The Ross Institute constitutes this division and, since its incorporation in the School, the Institute has continued to devote its energies largely to the furtherance of measures of hygiene overseas. It maintains, for instance, a branch in India chiefly for the purpose of co-ordinating the control of malaria on tea estates in Assam. The overseas and advisory work of the Institute is supported by contributions from various sources, including industrial and commercial organisations.

Division of Epidemiology and Vital Statistics.

(Professor GREENWOOD.)

The salaries of a large proportion of the personnel of the Division are provided by the Medical Research Council and the Industrial Health Research Board, and much of the time of the staff is devoted to confidential statistical analyses for public departments. Other work includes a study of the changes in rates of mortality due to tuberculosis in adolescence, an analysis of age and sex incidence in epidemics of typhoid fever, an analysis of the sickness experience of certain classes of transport workers, the co-ordination and criticism of medical-statistical reports from tropical areas, an analysis of data relating to long-continued studies of experimental

carcinogenesis, a statistical analysis of the use of convalescent and of adult serum in the prophylaxis of measles planned by the London County Council Medical Department, a study of the evolution of rates of mortality in England and Wales, and studies, jointly with the Division of Bacteriology, in experimental epidemiology.

Division of Medical Zoology.

(PROFESSOR LEIPER.)

Department of Helminthology.

(PROFESSOR LEIPER.)

The Department undertakes investigations overseas and a member of the Department has recently been working in Assam and Malaya. Apart from this a great deal of research associated with the Department is carried out in the Institute of Agricultural Parasitology, which is dealt with separately below.

Department of Entomology.

(PROFESSOR BUXTON.)

Research is carried on both in the laboratory and overseas. Work at home includes studies on the effect of climate upon biting insects, on the hormones which control growth and metamorphosis in insects, on the larvicidal qualities of mineral oils and on the life history of the bed-bug. Recent work overseas includes an investigation of the distribution of *Glossina palpalis* in Uganda and a study of the distribution of *Anopheles funestus* in East Africa.

Department of Protozoology.

(PROFESSOR THOMSON.)

Research is being carried out on the phagocytosis of blood cells and malarial parasites by macrophages ; and on possible correlation between the severity of blood infection and its duration, the occurrence of relapses, and the incidence of residual brain infections in relapsing fever. Professor THOMSON is responsible for the management of the laboratory maintained by the Ministry of Health in connection with the treatment of certain mental disorders by induced malaria.

Division of Public Health.

(Professor W. W. JAMESON.)

Apart from research, the staff of the Division regard it as an important part of their duties to maintain close relations with Government Departments, with official bodies and with professional and voluntary organisations whose interests have a bearing on public health practice. Accordingly, a great deal of their time is devoted to work on committees instituted by such bodies.

Department of Industrial Physiology.

(Dr. CROWDEN.)

Work in progress includes studies in the early detection of deafness in school-children by means of the gramophone audiometer ; work on insulation against heat and cold by the use of metallic surfaces ; work on air-conditioning in its application to tropical hygiene and to the ventilation of shops and public buildings in this country ; studies in heating, lighting and ventilation ; work on the dust hazard and methods of dust extraction in industry ; and work on first-aid, particularly on methods of artificial respiration.

Department of Medical Industrial Psychology.

(Professor CULPIN.)

Much of the research work of the Department is undertaken on behalf of the Industrial Health Research Board. It includes studies on sickness absenteeism, and on the testing of fitness for various occupations.

Institute of Agricultural Parasitology.

(Professor LEIPER.)

Prior to 1925, accommodation was provided in the Department of Helminthology in the School for a small group of workers engaged on the investigation of helminthological problems in relation to agriculture. Since 1925, the work has been carried out at Winches Farm, St. Albans, under grants provided through the Ministry of

Agriculture. The staff consists of the Director and five research assistants, together with two associate research workers of the Agricultural Research Council. Investigations are in progress on the biology, prevention and treatment of helminth diseases of farm-stock, poultry and game, economic plants and insect pests. A journal of helminthology is issued quarterly.

LIBRARY AND MUSEUM.

The main library contains more than 23,000 bound volumes and some 27,000 pamphlets and receives 440 current periodicals. Most of the departments have their own small specialised collections of books, reprints and reports.

The museum is one of the main features of the School and occupies large halls on three of the floors. One hall contains a collection of graphic material representative of tropical medicine, another of public health and social services and a third of sanitary engineering.

THE ACTIVITIES OF THE STAFF OUTSIDE THE SCHOOL.

A large proportion of the staff working under Professor GREENWOOD's direction in the Division of Epidemiology is employed either by the Ministry or by the Medical Research Council. Other divisions, including those of Bacteriology and Protozoology, undertake work on behalf of the Ministry, and this includes work on the bacteriological grading of raw milk (on the basis of which an order has recently been issued prescribing a methylene-blue reduction test in place of the plate count for the grading of milk); an investigation of the naso-pharyngeal flora of the normal population; an analysis of epidemics in boarding schools; and the supervision of the laboratory maintained by the Ministry in connection with the treatment of certain mental disorders by means of induced malaria.

Members of the staff of the School serve on committees of the Medical Research Council; and a great many workers employed by the Council are accommodated in the School. The Council provides a part of the salary of the professor of medical industrial psychology and of the reader in epidemiology and vital statistics.

Certain others of its workers have academic status as teaching members of the staff while the remainder have the status of guest research workers. Apart from the Division of Epidemiology, which has been mentioned above, the Departments of Industrial Psychology and Industrial Physiology in particular are strengthened by workers in the service of the Medical Research Council.

Through the Institute and the Bureau of Agricultural Parasitology, the School has close relations with the Ministry of Agriculture and Fisheries, and with the Agricultural Research Council. The Professor of Helminthology in the School is Director of the Institute of Agricultural Parasitology, which is financed by grants from the Ministry of Agriculture.

The School maintains close relations with practically all the bodies representative of medical education and research and of public health activities in England and the colonies.

Members of the staff are not permitted to hold other salaried posts without the sanction of the Board of Management. Such sanction has been given in a small number of cases where the duties undertaken are likely to further the studies on which they are engaged in the School.

The Appointment and Work of Medical Officers of Health.

In England, the councils of counties, county boroughs, municipal boroughs, urban districts and rural districts are popularly elected bodies responsible through their public health committees for the sanitary and public medical services in their respective areas. Each of these councils must appoint a medical officer of health. In the larger and more populous areas, the medical officer of health and his assistants are invariably whole-time officers, but, in the smaller urban and rural districts, part-time service is still common. Recent legislation, however, has imposed on county councils the duty of making such arrangements, whether by combination of districts or otherwise, as will ensure that all medical officers of health appointed in the future will be debarred from private practice. The medical officer of health is an advisory and executive officer of his local authority and enjoys a considerable amount of freedom in the carrying out of his duties. All questions of policy and all decisions as to the taking of legal proceedings are, however, the function of

the local authority and not, in the first instance, of the medical officer of health. Medical officers of health are usually school medical officers as well ; and have charge of schemes for maternity and child welfare, tuberculosis and venereal disease, epidemiological services, hospitals, housing, general sanitation, etc. Vacant appointments in the office of medical officer of health must be advertised, and the candidate finally selected by the council concerned must be approved by the Ministry of Health. He is given security of tenure as he may not be dismissed by the local authority without the consent of the Ministry.

All whole-time medical officers of health and assistant medical officers are paid salaries in accordance with a scale agreed by the British Medical Association and the associations representative of local authorities. The minimum commencing salary of £800 a year is paid to the medical officer of health of an area with a population not exceeding 50,000 and the maximum commencing salary of £1,800 to the medical officer of health of an area with a population of 750,000 or more. Deputy medical officers of health receive salaries averaging 60% of those of their chiefs and in all cases provision is made for suitable increments. Assistant medical officers are paid salaries of from £500 to £700, with annual increments of £25.

Auxiliary Personnel in the Public Health Service.

Sanitary Inspectors.—Sanitary inspectors must have passed the examination of the Royal Sanitary Institute and Sanitary Inspectors Examination Joint Board. Candidates are admitted to the examination only if they have attained the age of 20 years and can produce evidence of a satisfactory general education. They must also have received theoretical training in a recognised institution, and practical training for at least one year in the public health department of a local authority. The subjects of examination are : Statutes and orders, inspection and administration, water, food, air, ventilation, heating and lighting, construction and sanitation of buildings, drainage, sewerage and sewage disposal, collection and disposal of refuse, prevention of infectious diseases, flies, pests and vermin, statistics and office routine. By the end of December 1936, 6,000 sanitary inspectors were at work.

Midwives.—The Midwives Act, 1936, requires each local supervising authority to secure the whole-time employment of a sufficient number of midwives for attendance upon women in their own homes, not only as midwives, but also as maternity nurses during child-birth and from time to time thereafter during a period of not less than ten days. The Act provides for the payment to local supervising authorities by the Exchequer of grants towards the estimated additional cost of the scheme. The course of training for midwives lasts twelve months (full time) in the case of trained nurses, and two years (full time) in the case of other women.

Health Visitors.—According to the rules of the Royal Sanitary Institute,¹ candidates for the examination must produce evidence of having completed a whole-time course of training approved by the Ministry of Health in public health work lasting for at least six months. Before taking part in such a course, the nurse must have completed a training course of three years in a hospital approved by the General Nursing Council. She must in addition have spent at least six months in a maternity hospital and have obtained a certificate of the Central Midwives Board. The subjects of examination are as follows: Elementary physiology and structure of the body; personal domestic hygiene, general hygiene and sanitation; infectious and communicable diseases; maternity, infant and child welfare; school medical service; sanitary law and government, elementary economics and social problems; the principal legal enactments and regulations.

In England and Wales, there were registered, in the period from September 1921 to December 1936, 106,652 health visitors, midwives and qualified nurses, of which 55,956 are estimated to be in active work.

¹ The Royal Sanitary Institute conducts examinations in sanitary science as applied to buildings and public works, in general hygiene and sanitation, in the inspection of meat and other foods, in tropical hygiene for sanitary inspectors, in smoke inspection, for sanitary inspectors for appointments outside England and Wales, in school hygiene, for the Nursery Nurses' certificate and for the certificates in advanced child study. With the approval of the Ministry of Health, this Institute also conducts the official examination for health visitors.

RESEARCH WORK.

The number of works published by the staff of the different sections of the London School is so large that it would be difficult to give an account of the School's scientific activity from the time of its foundation. These works are in any case so well known in scientific circles that they need not be enumerated here.

The following paper will therefore be limited to the scientific production of the London School during the academic year 1935/36, with the addition of some references to previous researches which show the continuity in the work done.

In the sphere of public health generally, the fifth edition (1936) has just been published of "A Synopsis of Hygiene", by JAMESON and PARKINSON, and also the second edition of CLAY's work "The Sanitary Inspector's Handbook".

The Tropical Medicine Section has recently devoted a great deal of its time to the pathogenic study of sprue and the forms of tropical anæmia connected with it. The writings of FAIRLEY, partly in collaboration with Colonel MACKIE, have been the chief contribution to the knowledge of these problems. Cases of Weil's disease (BROWN), and Nicolas-Favre's disease, have also been studied. Mention should be made of the publication by MANSON-BAHR of the tenth edition of his treatise "Manson's Tropical Diseases".

Professor LEIPER, head of the School's Helminthological Department, and also Director of the Institute of Agricultural Parasitology, has published, with the help of his collaborators, a series of scientific papers which entailed special technical work for keeping up the large quantities of live material, including numerous specimens of parasite-carrying invertebrates, needed for current researches. Most of these papers appear in the *Journal of Helminthology*, published by LEIPER for several years past.

The work of the Entomological Department, directed by Professor BUXTON, has been chiefly concerned during recent years with the study of insect physiology (influence of climatological factors on insects which are parasites upon man or animals, respiration of insects, etc.). We should here mention BUXTON's researches on *Pediculus hominipitidis* (1936), those of EVANS on the physiology of the *Lucilia sericata* in relation to temperature conditions, humidity,

etc. (1936), and the studies of WIGGLESWORTH on the regulation of respiration in *Xenopsylla cheopis* (1935), which are of real biological interest.

The scientific output of the Department of Protozoology, under the direction of Professor J. G. THOMSON, includes the researches of DAS GUPTA on *Trichomonas* and *Eutrichomastix* (1936), which must be considered as two different species, and those of ROBERTSON on the reticulocyte response in mice, rats, guinea-pigs and monkeys infected with *Treponema duttoni*, *T. gambiense*, and *P. Knowlesi* (1935), which represent an important contribution to the study of the reactions of the hæmatopoietic organs to infection with these protozoa. Professor THOMSON has continued his research into immunity and organic defences against malaria, particularly as regards the activity of the macrophages and leucocytes in general in the placenta of women infected with malaria, a problem of both theoretical and practical interest in connection with congenital malaria (1936). He has also written works on malaria in Nyasaland (1934), on the mechanism of the transmission of trypanosomiases and leishmanioses (1934), which continue a long record of studies in pure and applied protozoology.

The Bacteriology and Immunology Section, under the direction of Professors TOPLEY and WILSON, has been occupied chiefly in investigating the composition of the antigens of pathogenic micro-organisms. Its experiments, mainly concerned with *B. typhi murium* (TOPLEY and RAISTRICK, DELAFIELD, MARTIN, DELAFIELD and SMITH, CRUICKSHANK, STAMP, M. WATSON), have led to remarkable results in spite of the inherent defects of the method employed, which entails considerable technical and financial difficulties on account of the thousands of animals required. It has, however, been found possible to apply the same method to other pathogenic micro-organisms (*B. typhosum*, *B. Gaertneri*, *B. pertussis*, *V. cholerae*, etc.). The partial immunity which can be obtained by chemical means to isolated atoxic antigenic fractions of these bacilli has formed the starting-point of a long series of researches. This is a new development which may be of considerable importance for immunisation with non-toxic substances.

Other studies have been made under the direction of Professor WILSON, on milk bacteriology (1936) and particularly on the methylene-blue reduction test.

The Section of Bio-chemistry and Chemistry applied to hygiene, under the direction of Professor RAISTRICK, has continued its study on the bio-chemistry of mycetes. The work of ANDERSON, BIRKENSHAW, CLUTTERBUCK, HAWORTH, OXFORD, RAISTRICK, ROBINSON, STACEY, SMITH, etc., has dealt with different varieties of *Penicillium*, *Helminthosporium* and *Aspergillus*, and has led to the identification of certain products of the metabolism of these mycetes, such as penicillic acid, palitantin, geodin, erdin, byssochlamic acid, and terrestrin, which last, by its molecular structure, is related to ascorbic acid. These contributions form a body of doctrine on the bio-chemistry of micro-organisms which marks a new stage in the progress of our knowledge.

Mention must be made of the research work of DELAFIELD and his collaborators in the Department of Chemistry applied to hygiene, as well as that of WOOLDRIGE on the physico-chemical problems of respiration and on the activity of enzymes (1936).

The scientific production of the epidemiological and vital statistics Section is well known. The use of the most modern technical methods, and the great ability of the Director, Professor GREENWOOD, and his collaborators (G. EDGE, W. T. RUSSELL, W. J. MARTIN, A. B. HILL, J. O. IRWIN and others), have made it possible to assemble a vast amount of working-material and to publish papers, several of which have been epoch-making in the evolution of medical statistics and contemporary epidemiology. Among the latter (1936), are the researches into experimental epidemiology (GREENWOOD, HILL, BRADFORD, TOPLEY, WILSON (1936)); the study of absences through sickness and working-time lost among the working classes (GREENWOOD, SMITH, LEIPER (1936)); works on mathematical statistics and applied statistics by IRWIN, critical studies by EDGE on medical statistics, and researches by MARTIN into the decline of the birth-rate (1936).

The Department of Industrial Physiology, under Dr. CROWDEN, has published in recent years a series of researches into the influence of certain physical factors (temperature, light, dust, etc.) on health. We need only mention a recent monograph by BEDFORD on heating and ventilation from the point of view of industrial physiology (1936); and works by ANGUS and CROWDEN in the field of industrial hygiene.

On the subject of psychology applied to industry and labour, there are works by Professor Millais CULPIN on psychological disturb-

ances among industrial workers (1936) and by SMITH on the temperamental factor in industry.

The Ross Institute and Hospital for Tropical Diseases, annexed to the London School of Hygiene, continues its work under the direction of Sir Malcolm WATSON, particularly through scientific missions to tropical countries. RAMSAY, CHANDRA and LAMPRELL, for example, have lately investigated the anopheline fauna on tea estates in Bengal and Assam under the auspices of the Ross Institute, and many other investigators have been able to continue their work thanks to this institution.

Sir Rickard CHRISTOPHERS is the Professor in charge of a special department of experimental studies on malaria which have led to important results as regards the action of synthetic products, such as atebirin, on the organism as compared with that of quinine.

The School Library contained 23,128 volumes and 26,946 monographs and pamphlets in 1936 ; the Librarian, Mr. BARNARD, has published a study on the classification of medical libraries.

Finally, the Bureau of Hygiene and Tropical Diseases has its seat at the School of Hygiene, where it has published, for thirty-three years, the *Tropical Diseases Bulletin*, a series indispensable for any research in the field of tropical medicine.

5. SCHOOL OF HEALTH AND NATIONAL INSTITUTE OF HYGIENE, MADRID.

INTRODUCTION.

It was not until December 1936 that public health in Spain, which had previously fallen within the province of the Ministry of Labour and Social Assistance, was entrusted to a new Ministry of Public Health. The central health administration, which is under a Director-General, consists of four inspectors-general, the heads of the technical sections, provincial health inspectors and the port and frontier health staff. Though subordinate to the prefects for administrative purposes, the provincial health inspectors are responsible to the Directorate-General of Health for all technical questions ; they superintend the work of the municipal inspectors, who are selected from among the village doctors. The medical profession in Spain is so large that medical attendance is available at the rate of one doctor per 1,200 of the rural population.

The organisation of secondary health centres dates from 1932, and a short time ago there were some sixty-two secondary centres in full operation. The chief medical officers of these centres are selected from among the technical officials of the national medical corps, and are mostly students from the National School of Health, set up in 1931.

The national budget for public health, which was only 9,000,000 pesetas in 1930, amounted to 32,000,000 pesetas in 1933, when Dr. M. PASCUA was in charge of the Directorate-General of Health.

* * *

The *National Institute of Hygiene*, Madrid, is one of the oldest in Europe ; it was set up in 1899, and was then under the direction of the great histologist RAMON Y CAJAL. Its activities were at first confined to applied bacteriology and epidemiology and to the production of sera and vaccines for the State, but they steadily expanded ; in 1914, it was divided into six sections and, in 1924,

into eight. Down to 1931, the Institute provided courses for the training of doctors for administrative and technical careers in the national medical corps. These courses, which were optional, were attended by thirty or forty people every year.

In 1931, the *National School of Health* was set up under Professor PITTALUGA. It took over the organisation of the teaching work. The courses, previously optional, were made compulsory for candidates for official appointments; in accordance with the regulations, admissions, of which there were not more than thirty every year, were decided upon a theoretical and practical examination, after a preliminary selection on the basis of diplomas. An entrance fee of 300 pesetas was charged, and the course lasted eleven months, including practical work during three months in rural centres or in various towns, all travelling expenses being paid by the Government.

In 1934, the National School of Health and the Institute were combined into one institution known as the *National Institute of Health*, under Professor PITTALUGA. The Institute, which was housed in the old Moncloa building (now partly destroyed), consisted of two services, one for applied hygiene and the other for teaching. The first consisted of the following sections: (1) anti-rabies treatment; (2) anti-smallpox and ultravirus vaccination; (3) bacteriology; (4) parasitology; (5) the chemistry of diet; (6) serotherapy (preparation of therapeutical sera); (7) epidemiology (particularly that of typhoid fevers and water-borne diseases); (8) disinfection and delousing. The teaching provided by the second service embraced: (1) bacteriology and immunology; (2) parasitology and tropical diseases; (3) epidemiology; (4) medical statistics; (5) industrial hygiene and occupational diseases; (6) infant and school hygiene; (7) sanitary engineering; (8) health administration and legislation. A Health Museum, which provided a special course in health propaganda, was also attached to the Institute.

The Institute of Hygiene and the National School of Health were of great importance in Spain in training the health staff and in combating infectious diseases. This is the more noteworthy in that the budget of the two institutions was never very large (500,000 pesetas for the financial year 1935/36). In their respective spheres, the anti-smallpox and ultravirus vaccine section, under Dr. GALLARDO, the bacteriology section, and the parasitology

section—directed from 1924 to 1933 by Dr. DE BUEN, whose death was a great loss—have been extremely successful. In connection with this last-named section, mention should be made of the Malaria Research Centre at Naval Moral de la Mata (Province of Cáceres), organised by Dr. DE BUEN and his collaborators as a practical school of malariology, which till lately was frequented by malariologists and doctors from different countries attending courses organised by the Spanish Health Administration and especially by the Health Organisation of the League of Nations.

RESEARCH WORK.

The scientific work of the Madrid Institute has appeared in turn in three periodicals : the *Bulletin* of the Institute (1905-1919), directed by S. RAMON Y CAJAL ; the *Transactions of the National Institute of Hygiene* (1922-1930), directed by Professor TELLO ; the *Review of Public Health and Hygiene* (1931-1936), directed by Professor PITTALUGA. Important contributions will be found in the last of these on rabies, cholera, malaria, leishmaniasis, the epidemiology of infectious diseases, demography and health statistics, etc.

Among the investigations carried out in the most recent years (1934-1936), mention should be made of GALLARDO'S work on neurovaccine and its use by hypodermic injection ; MANZANETE'S work on the biology of *B. typhi* ; the work of CARRASCO, ALVARADO, PASTOR, PINOLES and OLMEDO on the chemical components of Spanish foods and their vitamin content (1934/35) ; and that of A. BOTELLO on iodine determination in biological products. In the field of parasitology, S. DE BUEN'S work on *Treponema hispanicum* in the *Ornithodoros erraticus* tick (1935) ; the work of M. BAEZA CUELLAR and J. DE CISNEROS on various problems of mycology, and that of M. BAEZA, on the treatment of thrush by thallium salts (1936) ; GIL COLLADO'S investigations into the behaviour of *Aedes stegomyia vittatus* in Spain (1935) ; ALDA CALLEJA'S study of Henry's seroflocculation in malaria ; that of MACIAS on a case of otomyiasis by *Wohlfahrtia magnifica* (1935) ; and that of PEREZ PARDO on BCG vaccination in Spain (97,000 doses in 1934 and 119,714 in 1935).

313 SECOND REPORT ON CERTAIN EUROPEAN SCHOOLS

A number of studies—among which should be mentioned the investigations of FORNIELES on carriers of pathogenic streptococci, carried out in the bacteriology department of the Institute—have been published in the collection of monographs of the Scientific Research Commission set up by PASCUA (1932-1936).

6. THE NANCY INSTITUTE OF HYGIENE.

INTRODUCTION.

During the past decade, the public health service in France has shown a twofold tendency towards expansion and unification which the creation in 1930 of the Ministry of Health has done much to promote. The social insurance services came into operation during this same period. The Ministry is advised in regard to certain matters by the Superior Health Council ; it is assisted by the services of the former Office national d'hygiène sociale, which are responsible for the technical study of the various health questions, propaganda, documentation and the organisation of health education.

Some attempt at decentralisation has also been made, by bringing the health services under the administrative machinery of the départements (ninety in all) ; the prefect of the département is advised by the Departmental Inspector of Health. Under the tuberculosis legislation of 1916 and 1919 public health agencies known as offices d'hygiène sociale have been established in the départements. In some cases, their activities are restricted to tuberculosis control, but, in others, they have been called upon to undertake the whole of the social hygiene work in co-operation with the departmental health administration. Whilst the scope of the public health work programme varies a great deal in different areas, a large number of departmental administrations have shown keen interest in this subject on the one hand by appointing special health officers in districts and, on the other hand, by organising health centres, of which the number is yearly increasing. Every city with more than 20,000 inhabitants is obliged to establish a health bureau, which deals mainly with sanitation and infectious disease control ; these bureaux are now developing social hygienic services as well. Furthermore, a Decree-law of October 30th, 1935, and public administrative regulations of April 17th, 1937, have made departmental health inspectorates compulsory and established a model set of rules governing the status of the officials concerned ; the latter (inspectors and deputy inspectors) must be recruited by competi-

tion and must be specialists in hygiene (holders of the Diploma of Public Health). Appointments are on a full-time basis and salaries have therefore to be adequate.

So far as the co-ordination of the different health and social welfare agencies is concerned, the necessity of close collaboration between the services concerned was recently stressed afresh in circulars issued by the Ministry ; and departmental commissions for health and social co-ordination were immediately constituted for this purpose.

There were 25,930 physicians in France by the end of 1936. Of this number, 165 were departmental health inspectors, 180 directors of municipal health bureaux employed and paid on a full-time basis ; sixty-six full-time and 500 part-time physicians in social hygiene dispensaries and thirty-five directors and forty-five deputy-directors of public tuberculosis sanatoria. The salaries of full-time medical officers of health vary from 45,000 to 55,000 francs per annum.

In recent years, the expenditure for health and social welfare in the State budget has shown a constant increase. Indeed, the proportion which this expenditure bore to the total State budget was 2.23% in 1930/31 and 6% in 1936/37.

INSTITUTE OF HYGIENE OF THE NANCY UNIVERSITY.

The development and work of the Nancy University Institute of Hygiene certainly afford one of the best illustrations of recent trends in health teaching and co-ordinated medical and social activities. The Institute, which is the seat of the Chair of Hygiene and Social Medicine, does not confine itself to university medical teaching and post-graduate training (public health diploma), but plays a vitally important part in every branch of health protection work in the département, indeed in the whole area. It also acts as the connecting link in an effectively devised scheme for the collaboration of the university, State, departmental, municipal and private institutions and endeavours to bring to bear all their facilities and resources in a spirit of real team work.

As early as 1920, the departmental Office d'hygiène sociale, originally with an anti-tuberculosis programme, was established for the département of Meurthe-et-Moselle, with Professor PARISOT

first as Secretary and later as President. He was also in charge of the tuberculosis clinic at the Villemin sanatorium hospital (a modern institution with 250 beds opened by the Nancy Hospitals Administrative Committee) and the Villemin anti-tuberculosis dispensary. The purpose was, on the one hand, to provide hospital treatment for tuberculosis patients and, on the other hand, to produce well-trained tuberculosis physicians, and by means of suitable teaching (theoretical and practical, medical and social) to secure their co-operation in anti-tuberculosis work. In 1920, no cases of tuberculosis were reported by the practitioners or sent to the special tuberculosis institutions. At present (and for several years now), at least 80% to 90% of all tuberculosis patients attending the dispensaries are sent there by their own physicians.

In the national course of its development, the Office d'hygiène sociale gradually extended the scope of its activities. The anti-tuberculosis work alone was not sufficient to make any appreciable improvement in the health conditions of the population ; field surveys were undertaken for the purpose of solving, on regional lines, the most important and urgent questions. In 1924, some new sections were added to the Office and, at the same time, the specialised dispensaries were replaced by polyvalent dispensaries. At present, the departmental Office d'hygiène has eleven special sections and thirty-two polyvalent dispensaries (sub-area health centres). These sections, which maintain close contact with one another, are as follows :

- Tuberculosis control ;
- Venereal disease control ;
- Maternity welfare ;
- Child welfare ;
- Mental hygiene ;
- Anti-cancer action ;
- Dental hygiene and prophylaxis ;
- University health work ;
- Workers' leisure and allotments ;
- Propaganda (anti-tuberculosis stamp, children's week, etc.).

Each of these main sections has a specialised central dispensary usually attached to the special hospital which is the headquarters of the special clinic of the Faculty of Medicine. The professor in charge of instruction is also the technical director of the special

section of the Office d'hygiène ; in this capacity, he supervises the work done by the polyvalent dispensaries of the département which are the sub-area health centres.¹ This service is entirely voluntary.

The total general expenditure of the Office amounted to 1,500,000 francs in 1936.² In 1935, in all branches of the office, 131,512 medical examinations and 66,237 social (home) visits were made.³ The population of the département is 550,000.

¹ The A. Pinard Departmental Maternity Clinic is the headquarters of the University Obstetrical Clinic. It has all modern facilities for maternal and infant welfare, and is able to provide the fullest training. In special cases, women can stay in the home three months before and three months after delivery. On an average there are 2,200 to 2,400 deliveries annually, representing 70% of all births in the town of Nancy. The out-patient activities consist of daily consultations for babies, for expectant mothers and gynaecological cases and for cases of syphilis under treatment. A school of midwifery with 243 beds is attached to the maternity home. Here sixty students attend courses.

The A. Fournier Central Dispensary, which organises and supervises the anti-venereal work, holds six morning and three evening consultations every week. The patients are examined and their clinical and social records kept. The origin of each venereal infection is carefully investigated. To facilitate this work, close collaboration is maintained between the municipality and the military authorities. Many patients are sent by private medical practitioners. A specialist physician is in charge of the control of hereditary syphilis. A special service for the treatment of gonorrhœa, a prison anti-venereal service and a dispensary for the treatment of university students are attached to the central dispensary. The anti-venereal work throughout the département is conducted by the polyvalent dispensaries. Hospital cases are accommodated in the A. Fournier Hospital.

The Dentistry Centre is housed in a new, very carefully equipped building. Here the training of dentists and physicians specialising in dental hygiene is, as well as polyclinical treatment of dental cases, specially provided for students of the different schools.

The University Centre of Preventive Medicine which was created in collaboration with the University and the departmental office d'hygiène sociale, supervises the health of the students. Each student is medically examined before entering the University and re-examined every year. Courses in health education are given and sick students treated. The staff consists of a principal doctor, who belongs to the teaching staff of the University, two assistant physicians and one public health nurse. Each student is obliged to pay an annual fee of ten francs.

² The funds are largely provided by the Ministry of Health, the département (out of local resources), social insurance and the municipalities.

³ For the same year the following figures show the activities in greater detail : in the dispensaries 54,364 consultations, 21,074 X-ray examinations, 3,879 bacteriological examinations and 23,466 prophylactic visits ; 23,140 patients under care by January 1st, 1936 ; 35,640 anti-venereal consultations and treatments with 23,838 sero-reactions ; 30,620 consultations and 42,861 home visits with 25,492 children under care by January 1st, 1936 ; 1,573 cancer consultations ; 1,866 university pupils examined at the University Health Centre ; 725 consultations in mental hygiene cases ; 7,316 dental cases treated ; 223,735 francs collected by selling anti-tuberculosis stamps.

Institute of Hygiene.

The Institute is housed in the building of the former Osiris Foundation Institute of Serotherapy. At the beginning, space was limited and equipment meagre. With the help of the Rockefeller Foundation (\$25,000) and a grant of 250,000 francs from the Ministry of Health, the building has been enlarged and new laboratories have been opened. The Institute has gradually developed into the "Regional Institute of Hygiene", and acted as the co-ordinating centre of the health activities of the département. The Office d'hygiène sociale is located in the Institute's premises.

The Institute is divided into :

- (1) A laboratory for bacteriological, chemical and cytological examinations of specimens sent in by health institutions and private practitioners ;¹
- (2) A laboratory for the control of the water-supply, foodstuffs and other articles in common use, and sewage disposal ;
- (3) Serum-prophylaxis (measles, etc.) ;
- (4) Statistics ;
- (5) Administration of the Office d'hygiène sociale ;
- (6) Museum.

The expenses of the Institute are covered by the contributions of the University, Ministry of Health, département, town and social insurance, and by fees for laboratory analyses.²

The Director of the Institute is Professor of Hygiene and Social Medicine in the University ; the associate professor is Deputy Director. A director of practical work and a laboratory assistant also belong to the teaching staff of the University ; one assistant, two female laboratory assistants, two secretaries and four auxiliary workers are also on the staff of the Institute.

Such collaboration with the University and the health authorities of the département makes it possible to organise the teaching of

¹ Number of examinations : 1927, 680 ; 1931, 6,764 ; 1935, 13,984.

	Francs
² Financial resources are derived from :	
Ministry of Education	181,850
Ministry of Health	45,000
Département (Meurthe-et-Moselle)	31,000
Municipalities	6,000
Social insurance	10,000
Laboratory analyses	25,000
Total	298,850

hygiene and social medicine for medical students and post-graduates in a single institution, which is itself in touch with all branches of public and social health activity in the city, in districts and in rural areas.

The medical student trained in this Institute is kept constantly in touch with practical health problems throughout his studies. He is familiarised with questions of social medicine and can thus more readily appreciate the rôle which he, as a physician, will be called upon to play in a health administration.

The main principles governing the teaching given to students on health and social medicine are :

- (1) For successful health work, the collaboration of private medical practitioners is necessary ;
- (2) Such collaboration must be suitably organised ;
- (3) It is essential that all persons working in the public health services should contribute effectively to the work ; they must therefore be well trained in both theory and practice ;
- (4) Special post-graduate courses are important for medical practitioners.

Four hours a week of instruction in hygiene is provided for medical students. In the fifth year of studies, the course is divided into two parts—theoretical and practical—and lasts from November to July. The theory comprises : *general hygiene* (health organisation of France from the legal, administrative and technical standpoints ; sanitary engineering, housing) ; *social hygiene* (medical statistics, preventive medicine) ; *social medicine* (health and social protection of labour, prevention of industrial accidents, occupational diseases, unemployment, social assistance and insurance, alcoholism, drug addiction) ; *international hygiene* (international health organisations) ; *epidemiology and infectious disease prevention*. Demonstrations are given of typical examples of applied hygiene (sanitation, water-supplies, sewage disposal, supervision of water-supplies), of examples of *applied epidemiology and social hygiene* (school hygiene, epidemics, tuberculosis, etc.). There are also exhibitions of charts and photographs, and films are shown.

Post-graduate training in public health (public health diploma) covers a period of six months, from January to the end of June,

every year.¹ The courses are attended by candidates for the public health diploma (physicians and students at the end of their medical studies). The public health diploma is conferred only on French doctors of medicine and foreign physicians with a doctor's degree recognised by the University of Nancy. The students may follow the course during their fifth year (sixteen places).

The subjects taught are as follows :

I. SPECIAL INSTRUCTION IN HYGIENE AND SOCIAL MEDICINE.

A. *Health Laws.*

General health organisation of France ; laws and regulations. Public health services ; departmental and communal organisations ; their operation. Part played by health officers and the medical profession respectively. Instruction in hygiene ; methods.

B. *Sanitary Engineering.*

The major questions of urban and rural hygiene. The housing problem. Town extension planning. Overcrowding and slums. How to combat insanitary conditions. The drinking-water problem. Water-supplies for built-up areas.

Methods of purifying water. Treatment of water. Inspection of water-supplies. Wastes ; sewage ; household refuse. Disposal and treatment.

C. *Nutritional Hygiene.*

Inspection of foodstuffs. Part played by medical and veterinary services and collaboration between them. Inspection of meat and milk. Adulteration of foodstuffs. Food poisoning.

D. *Epidemiology and Prophylaxis.*

General epidemiology. General methods of prophylaxis. Active immunisation. Passive immunisation ; seroprophylaxis.

Special prophylaxis of contagious diseases ; common diseases. Epidemic diseases in France.

Epidemic control ; parts played by health officials and medical practitioners.

E. *Social Hygiene and Preventive Medicine.*

Legal measures ; medico-social technical organisation. Conduct of the campaign against social scourges : Tuberculosis, syphilis, cancer. Campaign against alcoholism and narcotic-drug addiction.

The problem of the birth rate. Maternal welfare. Child welfare from birth to adolescence. Preventive examinations ; school hygiene and school medical inspection. Mental hygiene and rehabilitation of the mentally abnormal. Defective children, juvenile offenders, etc.

¹ As from 1938/39, this training will extend over eight months (from November to the end of June).

Organisation of leisure. Physical training. Medical supervision.

F. *Preventive Medicine.*

Assistance and hygiene ; the relations between them. Legal measures to safeguard the health of the individual at different ages and in varying social circumstances.

Social insurance. Industrial hygiene. Labour regulations as related to the protection of health. Health organisation in working-class centres. Protection of the worker in unhealthy occupations.

Industrial accidents. Occupational poisoning and diseases. Protection from poisonous gases.

G. *International Hygiene.*

International sanitary Conventions. International preventive action. Public and private international health organisations. Part played by the League of Nations Health Organisation.

II. SPECIAL INSTRUCTION IN BACTERIOLOGY, NUTRITIONAL CHEMISTRY AND PARASITOLOGY.

A. *Bacteriology.*

General methods of bacteriological diagnosis. Technique and sample-taking. Technique of the isolation and identification of the chief pathogenic microbes. Bacteriological examination of pus, sputum, faeces, urine. Serological examinations : Bordet-Wasserman, Kahn and Vernes tests. Bacteriological examination of water. Bacteriology of milk.

B. *Nutritional Chemistry.*

Determination of the food-intake and the nutritional balance. Cooking of foodstuffs. Study of various natural foodstuffs. Preservation of foodstuffs. Food-borne diseases. Chemical analysis of milk. The vitamins.

C. *Parasitology.*

Study of the chief parasites of man. Poisonous insects. Mushroom poisoning.

**III. PRACTICAL INSTRUCTION
(PRACTICAL WORK, PRACTICAL TRAINING, VISITS).**

A. *Practical Work.*

Practical work in bacteriology, chemistry and parasitology in accordance with the programme of special instruction.

B. *Practical Demonstrations.*

Practical demonstrations of applied hygiene, applied prophylaxis and applied social medicine. Survey of an insanitary building, a district, a commune.

- Scheme for a water-supply. Plan for the sanitation of a commune.
 - Epidemiological investigation and the measures to be taken during an epidemic.
 - Social investigation.
- C. *Practical Training.*
- In the office of the Departmental Health Inspector.
 - In the municipal health bureau.
 - In the school medical inspection service.
 - In health centres : maternal welfare ; child welfare ; campaign against syphilis, tuberculosis, cancer ; mental hygiene.
 - In the physical-training centre.
 - In the departmental social insurance service.
- D. *Visits to establishments to which the various parts of the instruction relate (slaughter-houses, industrial establishments, dairies, water-supply plants, household refuse plants, sanatorium, preventorium).*
- E. *Health Survey (epidemiology and social hygiene) to be carried out in a commune of the département and to be conducted in accordance with a given scheme.*

One of the main features of health training consists in field work and the carrying-out of a health survey of one of the communes of the département. Students are divided into groups and carry out this work during a period of three months ; for this purpose, they are introduced officially by the prefect to all the local authorities and institutions. Extensive surveys of health and social conditions in about 150 towns and villages have been made in this way, and valuable material has been collected relating to about 300,000 inhabitants.

The examinations consist of one paper containing four questions, laboratory tests and an oral examination ; and there is also a discussion on the health survey.

The number of candidates who have been awarded the public health diploma is as follows :

1926	2	1932	35
1927	2	1933	30
1928	4	1934	34
1929	13	1935	34
1930	16	1936	27
1931	22			
			Total.....		219

These graduates have formed an association ; the members meet regularly to discuss important public health subjects, and are in permanent contact with the Institute and the Office d'hygiène sociale. Similar associations have been established by the public health graduates of other universities. A medal has recently been struck by the Nancy Association as an award for specially distinguished work in public health. One-fifth of the graduates are private practitioners.¹

The total number of candidates for France who had received the public health diploma by the end of 1934 is distributed as follows :

From the University at Paris	511
From the University at Lyons	718
From the University at Montpellier	284
From the University at Nancy	219
From the University at Algiers	113

The fees collected from each student vary between 600 and 700 francs.

¹ The medical faculties of the universities in Paris, Lyons, Montpellier and Algiers also organise courses for post-graduate training in public health.

In Paris, in the academic year 1935/36, the course started at the beginning of March and ended in the middle of June. General hygiene, legislation, maritime health service, disease prevention, urban hygiene, rural hygiene, colonial hygiene and tropical epidemic diseases, nutritional hygiene, industrial hygiene, child hygiene and school health, social hygiene, statistics and epidemiological surveys were dealt with in a series of 180 lectures. Practical training consisted of a period in the Claude-Bernard Tuberculosis Hospital and of demonstrations on the work of the health services of départements and communes.

The faculty in Lyons began organising post-graduate training in 1905. In subsequent years, Professor Jules COURMONT (1865-1917) improved the training considerably. In 1910, a museum of hygiene was created which greatly facilitated the instruction. As early as 1914, courses were started consisting of 173 lectures on different subjects (applied hygiene with practical demonstrations, infectious diseases, housing hygiene, hydrogeology, water-supplies, social and industrial hygiene, nutrition, toxicology, school health, venereal diseases, tuberculosis and sanitary legislation). In 1930, the Institute of Hygiene and the Museum of Hygiene were housed in new university buildings, erected with the help of the Rockefeller Foundation. The Museum comprises twenty rooms. The curriculum of present post-graduate training in public health is spread over a period of six months (January-July) and comprises teaching in microbiology (two and a-half months) and in hygiene (three and a-half months) which includes practical training in laboratories, visits, field work, etc. The faculty in Lyons confers a public health diploma, a public health certificate and a certificate of public health studies.

The Training of Auxiliary Personnel.

Hospital and public health nurses are trained in eighty-five schools in France.¹ By 1933, 3,000 students had attended courses lasting three years. Unity in methods and training is secured by the Council of Nursing Schools and Schools for Social Workers, whilst the supervision and protection of graduated nurses is in the hands of the Nurses' Bureau, which has been working since 1925.

There is a certain number of special, mostly private, schools for the training of social workers, from which, on an average, 100 students graduate every year.

RESEARCH WORK.

Two considerations have always been borne in mind in planning the work of the Nancy Institute of Hygiene. The aim has been to do *scientific research work*, and also to make *practical application* of this work to the promotion of hygiene and health protection and to educational propaganda. As the Nancy Institute is a university institution, its scientific work is both didactic and technical, as will be realised in particular from the number of *theses* for the doctorate of medicine which have been prepared and edited in recent years under the general direction of Professor PARISOT. The scientific work of the Institute may be classified as follows :

(1) "The Best Methods of treating Manure-heaps to prevent the Hatching of Flies" has been the subject of the studies in sanitary engineering in both rural and urban areas. The European Conference on Rural Hygiene, held in 1931, recommended schools of hygiene to study this question. The results obtained at Nancy were reported upon by PARISOT and FERNIER (1934). This piece of work made an important contribution towards the solution of the problem, and was accompanied by bacteriological research into the infective capacity of *Musca domestica*, *Calliphora vomitoria* and *Tabanus bromius*.

¹ Twenty-eight belong to the hospitals, thirty-two to the Red Cross, twenty-one to private organisations, four to faculties of medicine.

In this connection, mention should be made of DEPARDIEU's thesis on " Le problème de l'eau potable dans le département de Meurthe-et-Moselle " (1934) ; the " Histoire d'un quartier insalubre de Nancy " by PARISOT and SALEUR (this refers to the St. Sébastien quarter, which the town of Nancy undertook to clean up in 1936 as a result of the energetic campaign that had been conducted, and the evidence of its insalubrity furnished by the two observers) ; and the thesis of DU CLOS (1934) on " L'amélioration des conditions sanitaires et sociales de la vie rurale et l'effort réalisé en Meurthe-et-Moselle ".

(2) From the epidemiological point of view, the main subject of study and research at the Nancy Institute has been the infectious diseases, the epidemiology of which has been modified in Lorraine in recent years—viz. :

(a) Enteric fever, which has been declining in the département during the past twenty years (PARISOT, *Revue d'hygiène*, 1934).

(b) The brucelloses, which have recently appeared in an epidemic form in Lorraine. They have been studied by PARISOT and ROBERT-LÉVY since 1931, and have formed the subject of many papers : " La fièvre ondulante dans la région lorraine " (1933) ; " La dangereuse extension des brucelloses en Lorraine " (1934) ; " Organisation d'un service d'épidémiologie des brucelloses en Meurthe-et-Moselle " (1935). These investigations, in which some assistance was given by the Montpellier Research Centre for Undulant Fever, have established a number of facts of undoubted epidemiological value, such as that the disease has been imported by sheep purchased in regions infected with animal diseases and taken to Lorraine, and that ovine brucella *melitensis* is spreading to cattle. They have also led to effective prophylaxis.

(c) Diphtheria, which is common in Lorraine, has been studied mainly in connection with preventive inoculation. This was begun at the Flavigny Preventorium of the Meurthe-et-Moselle Office d'hygiène sociale in 1928, and steadily improved in subsequent years. Thanks to collective controlled prophylaxis, this centre for delicate children is now quite safe. The need for collective controlled action was brought out in

several immunological studies by PARISOT and MELNOTTE (1935/36), and in MOUTON-CHAPAT's thesis (1935) : " La diphtérie et sa prophylaxie par la vaccination dans le département de Meurthe-et-Moselle ".

(3) Nutritional Hygiene : Since 1934, milk hygiene in Meurthe-et-Moselle formed the subject matter of many scientific papers by PARISOT, MELNOTTE and FERNIER and of a thesis by MARCHE : " Contribution à l'étude de la pasteurisation et du contrôle hygiénique des laits (1934/35) ".

Research has also been carried out into the bacteriology of eggs and ice-cream, on the identification of isolated *B. coli* in milk, on the frequency of tuberculous milk and on tuberculous infection in cattle.

(4) Tuberculosis is still the most dangerous social disease in both urban and rural areas in Lorraine. It has been dealt with in several papers based on the documents collected in the dispensaries of the Meurthe-et-Moselle Office d'hygiène sociale—viz., the theses by ROUSSEL on conjugal tuberculosis and of SALEUR on latent tuberculosis in childhood (1921/22) ; that of LEDUC on tuberculosis and alcoholism in Lorraine (1923/24) ; of GASTON-LÉVY on tuberculosis among the working-class population in towns (Nancy) (1927/28) ; of ROBERT-LÉVY on the Vernes-resorcin reaction during tuberculosis infection (1928/29) ; of DEBUCHY on the anti-tuberculosis campaign in rural areas (1932/33) ; and of SNEBERG on the incidence of tuberculosis infection in a large town observed over a period of twelve years (1920/32). Methodical studies have been conducted during the past ten years on tuberculosis infection in all classes and at all ages, by means of the tuberculin test.

Since PARISOT's comprehensive work on "The Organisation of Tuberculosis Control in the Département" was published in 1928, there has been a survey by PARISOT and SALEUR on " Five Years of BCG Anti-tuberculosis Vaccination in Meurthe-et-Moselle ". As early as 1931, 827 children treated by the digestive tract and 651 treated subcutaneously were under observation. Subsequently, the effects and results, both individual and family, of some thousands of inoculations were studied (1936).

(5) Apart from general memoranda, such as PARISOT's study on " The Development of Hygiene in France " (1933) and others,

the following studies have been conducted on social hygiene, statistics and demography :

(a) The demographic situation in the département—thesis by HAIMOVICI on the fall in the birth-rate, and infant morbidity and mortality in rural areas (1934/35) ; thesis by SCHMIDT on the child population of Nancy and its danger from infection (1935/36).

(b) Social medicine in general, particularly in industrial centres—thesis by CLAUDE (1935/36) on the development of health protection and social welfare in a recently industrialised city (Jœuf : Meurthe-et-Moselle) ; paper by CHAVAROT on variations in health and social conditions during the industrialisation of the Meurthe-et-Moselle salt-mine area (1936) ; thesis by COLCKER on the welfare of pregnant workwomen (1935).

(6) Finally, the present position as regards preventive medicine and its extension in the future was the subject of the “ Essay on University Hygiene ”, 1927/28, which led to the institution of the University Dispensary in 1933 ; it was also the subject of the theses by GIRY (1928/29) on maternity and infant welfare at ante-natal clinics and CLODOT (1933/34) on the protection of the health of schoolchildren.

Attention was drawn in the thesis by CHAVAROT (1935/36) to the part played by social insurance in preventive medicine. He concludes that the resources of insurance funds should be devoted to prevention. The operation of insurance funds in Meurthe-et-Moselle has been studied by MOYSE (thesis 1933/34), who has described the functions of technical medical supervision.

(7) The Nancy Institute of Hygiene was anxious to popularise the idea of hygienic training among the country dwellers. With this object in mind, it arranged for the prophylaxis of certain animal diseases and the diagnosis of certain veterinary ailments ; thus, over 2,000 sero-diagnoses of “ pullerose ” (a disease which attacks newly-hatched chickens) were carried out, and a minor centre of swine erysipelas was discovered.

Farmers who benefit from services of this kind realise their economic advantages, and in this way the confidence of the rural population is won and kept.

(8) To this list should be added the works of SPILLMANN and his collaborators on the prophylaxis of venereal disease in the département. They are based on epidemiological, microbiological and serological research covering a wider field than the general routine work of a dispensary, particularly in the case of syphilis, and relate, not only to the city of Nancy, but also to several other places in the département of Meurthe-et-Moselle.

7. THE PRAGUE INSTITUTE OF HYGIENE.

INTRODUCTION.

In the Republic of Czechoslovakia, public health work is not under the exclusive jurisdiction of the Ministry of Public Health and Physical Education. By no means unimportant public health activities are in the hands of the Ministry of Social Welfare, which controls the machinery of social insurance and industrial inspection and carries out a considerable part of the maternity and child welfare work. There are, in addition, a number of well-organised private institutions and societies engaged in public health work, such as the Red Cross Society, the Masaryk Anti-Tuberculosis League, child welfare societies, anti-venereal associations, etc. There are also a few private societies which are interested in rural health problems.¹

Social insurance exercises a very great influence on public health matters. The number of persons insured in all branches of social insurance is 3.3 millions, not including dependants of insured persons. The Central Social Insurance Institute has become an important financial organisation with a capital which, by the end of 1935, amounted to about 5,500 million Kč. During the ten years ending in 1935, the Central Social Insurance Institute approved large loans to local authorities for the improvement of general

¹ The Red Cross Society administers 478 different institutions : three sanatoria, three convalescent homes, 105 consultation centres for children, thirty consultation centres for adults and twenty-nine dental polyclinics for children, six tuberculosis dispensaries, five anti-venereal dispensaries, two dispensaries against alcoholism, four dental clinics, 288 first-aid stations and a great number of social relief institutions.

The Maternal and Child Welfare Union has 280 branches with 404 consultation centres, twenty-one homes for mothers, twenty-four children's nurseries, and a few maternity hospitals and homes. The union is a semi-official institution closely connected with the work of provincial and local administrations.

The Anti-Tuberculosis League has organised 300 branches and 129 tuberculosis dispensaries.

Fifteen different societies dealing with social welfare and public health questions are organised in the National Federation of Voluntary Agencies, which co-ordinates and unifies the activities of the separate societies and pays special attention to the technical improvement of the services.

health conditions : for instance, 122 million Kč. were granted for the construction of hospitals, 59 millions for the construction of homes for the aged, 36.3 millions for sewerage, 137.87 millions for water-supply and 667.99 millions for the construction of cheap dwellings. Similar loans have been granted by the General Pensions Institute, amounting at present to 4,000 million Kč. The Social Insurance organisation employs 8,500 physicians, of whom 4,000 are paid on a whole-time basis. Only 1,150 of them do not engage in private medical practice. The salaries and fees paid to physicians amount annually to 250 million Kč.

In the field of social welfare, new laws have been enacted modifying and improving the old system of social insurance. As a result of these, the number of insured persons has increased to such an extent that, in certain areas, it amounts to more than three-quarters of the population. In the field of public health, on the other hand, old laws are still in force. The Minister of Public Health and Physical Education, in a speech delivered to Parliament during the discussion of his budget, pointed out that the Austrian law of 1870 was still in force as a basic health law. " This law, " he added, " was probably very effective at the time it was enacted, but to-day it weighs like lead on our health organisation and on all other bodies engaged in public health work. In addition to this old Austrian law, a Hungarian Law of 1876 is still in force in the eastern parts of the country. This confusion should be cleared up as soon as possible and a new basic health law should be enacted."

THE PUBLIC HEALTH ORGANISATION.

The Ministry of Health and Physical Education was established in 1918, and, since then, no essential changes have occurred in the organisation. The Ministry is divided into five departments, which comprise seventeen different sections. The first department is concerned with infectious diseases and is in charge of the personnel of the health services, hospitals and pharmacies ; the second deals with general and environmental hygiene ; the third with social hygiene, social pathology and social therapy, the fourth with physical education and the fifth with legal, economic and technical matters in connection with health administration. The Secretariat

of the Ministry is responsible for the appointment of the staff and the drafting of regulations and Acts of Parliament.

The State Institute of Hygiene is placed under the Ministry of Health and is regarded as a technical organ of the Ministry.

The country is divided into four provinces (Sub-Carpathian Russia has a special autonomous status); in each provincial administration there is a chief medical officer, assisted by medical officers. The provinces are divided into 248 districts, each with an average of 60,000 inhabitants; the districts are subdivided into local sanitary areas. The larger municipalities are divided into sub-districts for health purposes. Only Prague, the capital city, has its own medical officers of health and school medical officers. These officers are appointed by the City, and are not State medical officers, as is the case in all the other cities. In the State, provincial, district and communal administrations, there are 2,450 medical officers; their salaries vary from 6,000 to 60,000 Kč. yearly. Only in exceptional cases are the medical officers appointed on a whole-time basis. There are 11,000 licensed physicians in Czechoslovakia. The total expenditure of the State administration has decreased considerably since 1928,¹ but the expenditure on health has increased. In 1926, it amounted to 1.52%, in 1928 to 1.78% and in 1935 to 2.24% of the general State expenditure. The expenditure on social welfare increased still more.

THE STATE INSTITUTE OF PUBLIC HEALTH.

Development and Organisation.

The main activity of the Institute is the study of various problems connected with infectious diseases and social hygiene; it mostly takes the form of work in the laboratories, the production of sera and vaccines and health education.

The Institute was founded by the State Institute of Public Health Act of October 12th, 1925²; its work was divided into two

¹ Grand total expenditure: in 1928, 11,454.1 million Kč.; in 1935, 9,386 million Kč.

² The Rockefeller Foundation contributed half of the total cost of the Institute (54 million Kč.).

main departments : sera and vaccines, and diagnosis. Some other departments, formerly operating in temporary quarters, have since been housed in a new central building, completed and equipped in 1930 and 1931. By the end of 1930, a department for the control of biological products was transferred to the new buildings. At first, this department examined only the products referred to it by the Departments of the Institute, but, since 1932, it has dealt with products submitted to it by private organisations or institutes as well.

The Department of Social Hygiene began regular work at the end of 1930 in the large new premises of the central building.

The Department of Health Education and Propaganda started work in 1931.

The Institute at present is divided into the following departments :

Serum and Vaccine Production.—Chief : Dr. FEIERABEND until July 1933, and, after his death, Dr. VANICEK.

Production of Smallpox Vaccine.—Chief : Dr. URBANAK.

Control of Biological Products.—Chief : Dr. SCHUBERT.

Microbiology.—Chief : Dr. DRBOHLAV.

Social Hygiene.—Chief : Until September 1935, Professor PELG, but, on his appointment as Professor of Social Medicine at Charles University in Prague, Dr. KLÍMA was appointed to the above post.

Health Education and Propaganda.—Chief : Dr. VOTAVA.

Three independent institutes are housed in the buildings of the State Institute of Public Health. These are :

The State Institute of Food Control at Charles University.—Chief : Dr. KLABZUBA.

State Institute of Food Control of the German University at Prague.—Chief : Dr. PLAHL.

Institute for the Control of Drugs at the Ministry of Public Health and Physical Education.—Chief : Professor SKARNITZL.

The research work of the Institute is under the control of the Scientific Board of Directors. The members of this Board are representatives of all the faculties of medicine in the country and of the Polytechnic School.¹

¹ The Director of the Institute and a representative of the Ministry of Public Health complete the list of its members. The Board holds meetings regularly every month.

The Library of the Institute consists of 13,526 volumes and receives 180 periodicals regularly.

Budget.

The Institute is maintained from the funds approved in the State budget. It derives an income from the sale of its products and from examination fees.¹ This income is paid into the Treasury.

An annual estimate of the expenditure of the Institute is included in the budget of the State as shown in the following table for the years 1931-1936 :

Year	For personnel Kč.	For materials Kč.	Total actual expenditure Kč.
1931	3,178,995	3,243,339	6,422,334
1932	3,359,536	3,099,284	6,458,820
1933	3,484,422	3,513,834	6,998,257
1934	3,261,621	3,433,647	6,695,268
1935	3,573,964	4,616,495	8,190,459
1936	3,702,847	4,633,866	8,336,713

The Staff of the Institute.

The staff of the Institute is divided into three categories according to the conditions of appointment : members of the permanent staff rank as State civil servants, members of the temporary staff are given contracts, and some workers are paid daily wages.

In 1929, the first legal classification of permanent posts was made ; as a result, nineteen posts were reserved for Doctors of Medicine. In the following years, all senior health officers were taken over as State civil servants. There are still persons in responsible positions in the Institute working for daily wages.

¹ The following table shows the revenue of the Institute for the period 1931 to 1936 :

Year	Actual Revenue Kč.	Estimates Kč.
1931	3,694,270	3,300,000
1932	4,240,932	3,898,000
1933	4,332,175	3,864,400
1934	6,003,212	3,898,500
1935	5,587,745	4,545,000
1936	5,336,985	4,810,000

The Institute employs as experts :

- Fourteen doctors of medicine ;
- Three doctors of veterinary medicine ;
- Seven doctors of natural science ;
- Three chemists ;
- One engineer.

Twelve of these are appointed State civil servants.

Post-graduate Training in Public Health.

The Institute has not organised systematic courses of training in public health for graduates. The staff of the Institute only occasionally takes part in teaching, in conferences outside the Institute and in short-term courses organised in various parts of the country by official bodies and by private societies.

At present, the examinations called "Physikat" (Diploma in Public Health) are the only obligatory requirement for physicians entering the public health service.

This examination was introduced under the Decree of the former Austrian Ministry of the Interior (No. 37, of 1873). The detailed requirements regarding the examination are contained in the Decree of the Ministry of the Interior No. 139, of 1873. The only modification since made is that introduced by the Decree of the Czechoslovak Government No. 571, of 1920, whereby the original scope of the examination was enlarged by the introduction of examinations in social medicine, epidemiology, bacteriology and serology.

In the original decree, no mention was made of courses for this examination. However, private courses were organised from the beginning at the different universities. The practice has been continued, and courses are now given in the four medical faculties (two at Prague, one at Brno, one at Bratislava) of Czechoslovakia.

The following are the subjects of the examination :

- | | |
|----------------------|--------------------------------|
| (a) Hygiene ; | (e) Chemistry ; |
| (b) Sanitary law ; | (f) Social medicine ; |
| (c) Legal medicine ; | (g) Epidemiology ; |
| (d) Pharmacognosy ; | (h) Bacteriology and serology. |

The decree contains no details regarding hygiene ; it only provides that two questions be set in that subject. The same applies to the health law. The law contains considerable detail with regard to the examination in pharmacognosy and in chemistry. In social medicine, the candidate is required to possess a knowledge of legal regulations regarding the campaigns against tuberculosis, alcoholism and venereal disease, child welfare, pre-natal care, mental hygiene, care of crippled, invalid and defective children, sickness, old-age and accident insurance, the legal stipulations regarding the protection of the working population, housing hygiene and nutrition. He must also have a general knowledge of epidemiology, the prevention and control of infectious disease, the applications of bacteriology, serology and the principles of immunology to medical practice.

The examiners are appointed annually by the Ministry of Health on the proposal of the provincial administration and in agreement with the Ministry of Public Instruction.

The examination just referred to is preceded by another written and a practical examination, held in the office of the provincial administration and in a general hospital and a chemical laboratory. This examination deals almost entirely with medical-legal matters.

A course, which 80% of the candidates attend, is organised by the professors and teachers of the Medical Faculty and lasts for twelve weeks. The subjects are as follows : general hygiene (theory and practice), fifty hours ; bacteriology and serology (theory and practice), thirty hours ; health laws, twenty hours ; medical statistics, ten hours ; social medicine, thirty hours ; and epidemiology, thirty hours.

Each candidate pays 3,000 Kč. in fees (including 250 Kč. for the examination fee).

*Post-graduate Training of Medical Officers
and Physicians of the Social Insurance Services.*

The Regulations for the employment of physicians in the Social Insurance Services give preference to candidates who have attended the lectures on social medicine at the Medical Faculty or special courses on social medicine organised or recommended by the Social Insurance Institute.

Since 1935, three short-term courses have been arranged by the Social Insurance Institute and by the Czechoslovak and German Societies of Physicians for candidates seeking appointment in the Social Insurance Services. The curriculum of such a course organised in February 1937 extended over a period of three weeks, and comprised the following subjects :

Social medicine	{	12 hours theoretical. 6 hours practical.
Organisation of social insurance	{	8 hours theoretical. 6 hours practical.
Organisation of the health activities of social insurance	{	10 hours theoretical. 6 hours practical.
Administration of the Social Insurance Institute	{	7½ hours theoretical. 5½ hours practical.
Treatment of patients in the social insurance institutions from the economic standpoint	{	19 hours theoretical.
Health activities of social insurance...	{	15 hours theoretical. 16 hours practical.
Organisation of physicians		4 hours theoretical.

Each of the thirty-five participants paid a fee of 400 Kč. for the course. The same course was repeated in May 1937.

Special Courses.

In recent years, special post-graduate courses have been arranged for health officers by the Institute of Public Health. The lecturers are university professors, health officers of the Ministry of Public Health and members of the staff of the Institute of Hygiene. The number of students averages from forty to eighty. The Institute has initiated several courses on preventive medicine in which members of the staff have taken part. The first course of this kind was held in January 1931, the last one in February 1936—a total of six courses altogether. The duration of such a course is on the average three days. The number of persons attending from all parts of the country has increased considerably. The first course was attended by twenty-six physicians only, the sixth by 250. Half

of the participants are private physicians, 30% health officers of the districts and communities, and 20% hospital physicians.¹

The two Institutes of Food Control (at the Institute of Hygiene) organise courses for market inspectors on the hygiene of food. Candidates for the post of market inspector are required by the local authorities to have followed these courses.

The Work of the Departments of the Institute.

The *Department of Serum and Vaccine Production* is at present the most important centre for the production of biological products in the country. It satisfies all requirements for sera and vaccines and exchanges these products with the Institutes in Warsaw and Zagreb. Over 1.5 million doses of smallpox vaccine are produced. The *Department of Microbiology and Serology* is divided into six special laboratories and deals with bacteriological examinations, sero-diagnosis of syphilis and other diseases, parasitological studies and examinations of intestinal parasites, and analyses of water. It collects cultures of micro-organisms and produces antigens and other material for sero-diagnostic purposes.

The *Department of Social Hygiene* has undertaken interesting field investigations in its special laboratories. The *Nutrition Laboratory* studies problems of nutrition for the whole of the country as well as for certain regions, consideration being given in the first

Period and place	Subject of course	Number present	Professional position of persons attending
November 23rd-December 3rd, 1931, Prague	Social insurance	45	Medical officers of social insurance
December 14th-17th, 1931, Prague	Control of venereal diseases	42	District and municipal health officers
January 14th-19th, 1933, Prague	Public health	40	District health officers
February 4th-6th, 1933, Košice	Control of typhoid	65	District and communal health officers
October 2nd-6th, 1933, Bratislava	Control of typhoid and trachoma	65	District and communal health officers
December 3rd-17th, 1934, Bratislava	Public health	17	Health officers
March 1936, four-day course in thirty-four places	Health and economic depression	1,300	State, municipal and communal health officers

place to the influence of the present economic depression. It also tests certain articles of food from the nutritional point of view. The *Biophysical Laboratory* studies conditions of labour, radiation of ultra-violet rays, atmospheric pollution, noise, etc. The *Laboratory of Statistics* receives notification of infectious diseases from the whole country and analyses the monthly, quarterly and annual rates. It studies the influences of the present economic situation on health conditions and has elaborated a programme of studies of health conditions among the unemployed. The *Laboratory of the Hygiene of Clothing* is at present studying the proper clothing of industrial workers and the use of working-gloves as a means of preventing accidents. The *Laboratory of Housing Hygiene* has prepared models of the most important types of certain sanitary units (privies, manure-pits, wells) and is working out a plan for a model rural dwelling, taking into consideration local needs and customs. For this purpose, the available vital statistical data of the towns as well as of the villages have been studied.

To bring the results of scientific work to the notice of the general public and to instruct the professional staff in health education is the task of the *Department for Health Education and Propaganda*. The State Institute of Public Health has delegated to this department the work of systematic post-graduate training of physicians and auxiliary health staff. As yet, however—for reasons outside the control of the Institute—this activity has not been begun except in so far as the above-mentioned short-term courses for state medical officers are concerned.

Much more progress has been made with the health education of the public. In this matter, the department is carrying out research work, and also acting as the executive centre for all the health education work in the State. It studies the health and social needs of the people and reaches all classes by its educational methods.

The department arranges exhibitions and lectures, and use is made of films, broadcasting, the Press, pamphlets and placards. This work extends to every part of the country. Up to the end of 1936, the department had prepared twenty-five sets of health exhibits. Several copies of these were made in different languages. During 1936, 141 exhibitions and 220 lectures were arranged. In the Institute, there is a Museum of Hygiene which is open to the

public. Here the exhibition material is changed and completed, and new material added.

MASARYK STATE SCHOOL OF PUBLIC HEALTH AND SOCIAL WORK.

This school, built in the grounds of the Institute of Public Health and equipped for 100 students, was opened in 1936. The monthly fee for board and lodging is 400 Kč., the annual tuition fee 400 Kč. However, the Ministry of Public Health and Physical Education provides scholarships for a certain number of students, and, in the case of others, it sanctions reductions in the fees. At present, two courses run simultaneously—a Czechoslovak course (thirty-six students) and a German course (fourteen students). The students come from all parts of the country. Candidates for admission must have passed the middle-school examination, unless they have had social training in another school of nursing or social work and, in addition, have done practical work for at least two years in connection with public health and social welfare. The age limits are 18 to 30 years.



Figure 8.—MASARYK STATE SCHOOL OF PUBLIC HEALTH AND SOCIAL WORK.

The teaching staff of the school is recruited mainly from university professors and lecturers and partly from experts in public health and social work.

The internal staff consists of the director and assistant director (both physicians) and seven instructors (four of them for public health teaching).

The administration of the school is entirely separate from that of the Institute ; it is under a board composed of the representatives of the Ministry of Health, and Social Welfare and of the Ministry of Public Instruction. The Ministry of Health is responsible for the administration of the school. The curriculum is as follows :

FIRST SEMESTER.

Theory.

(a)	Hours
Anatomy	33
Physiology	33
Hygiene and epidemiology	60
Technique of nursing :	
(a) Theory	55
(b) Practice	55
Public health and social work	30
Bacteriology and chemistry	33
Nutrition :	
(a) Theory	22
(b) Practical work : cooking	33
History and ethics of public health and social work.....	11
(b)	
Sociology	60
Social politics	40
(on account of technical difficulties temporarily changed to Social Insurance)	
Psychology	30
Pedagogics	30
Total	525
Weekly	35

SECOND SEMESTER.

The first period of practical training lasts from June 1st to July 15th and consists of practical nursing in the Král Vinohrady hospital. Students are

340 SECOND REPORT ON CERTAIN EUROPEAN SCHOOLS

divided into two groups, one of which takes this work in the morning, the other in the afternoon, changing their schedule weekly.

Summer vacation from July 15th to August 31st.

THIRD SEMESTER.

(From September 1st to January 15th.)

Theory.

	Hours
Internal diseases	33
First-aid and surgery	30
Pediatrics	30
Obstetrics	30
Infectious diseases	18
Mental hygiene	11
Dermatology and venereal diseases	11
Nose, ear, throat diseases	6
Ophthalmology	3
Oral hygiene	3
Remedies, prescriptions and their use	33
Dietetics :	
Theory	11
Dietetical cooking	22
Gymnastics and corrective exercises	22
Social medicine	37
Public health and social work	42
Social sciences	00
Social insurance	60
Public administration of health and social work	74
Civil law	60
Criminal law	40
Institutional and administration law	40
National economics	30
Administration of institutions and societies	20
<hr/>	
Total of required lectures	666
Weekly	35

FOURTH SEMESTER.

(From January 16th to October 20th, including vacation from July 15th to August 31st.)

(a) Practical training in the hospital from 7 a.m. to 1 p.m.

Students are divided into small groups working under the supervision of special instructors.

(b) In the afternoon :

(1) Three times weekly (one to two hours of lectures) :	Hours
Organisation of child welfare	25
Social science	97
Special lectures in the seminar period	54

(2) Twice weekly public and social work in connection with the cases in the hospital.

FIFTH SEMESTER.

(From October 21st to March 31st.)

Practical work in public health and social institutions and lectures on :

	Hours
(1) The anti-tuberculosis dispensary	10
(2) The children's dispensary	10
(3) The protection of child health	10
(4) Public health	24
(5) Child welfare	10
(6) Social and health education	30
(7) Journalism	12
(8) Handwork and special skilled work in children's institutions	30
(9) Special lectures on social science	20

SUMMARY.

	Public health Hours	Social sciences Hours
(1) Theoretical training	707	484
(2) Practical training in the hospital	176	
(3) Practical training in the health and social welfare institutions	54	102
	937	586

A somewhat full description of the above curriculum has been given, as the school is new and experimental in character and is trying to combine training in Public Health with training for social work.

There are seven schools for hospital nurses in Czechoslovakia with a curriculum extending over a period of two years ; the most important are the Czech and German schools at the General Hospital in Prague.¹

¹ The Red Cross Society organised in October 1935 a second Conference of Nursing Schools. Representatives of State and provincial administrations and of all nursing schools discussed the unification of curricula. However, no final decision was taken.

In all, there are about 9,000 nurses in the country, 1,500 of whom have graduated from nursing schools. Some 500 registered nurses are working in child welfare, tuberculosis and venereal disease centres.

RESEARCH WORK.

An account of the scientific research work undertaken at the Czechoslovak State Institute of Public Health has been published since 1930 in the Institute's *Transactions*. The whole series of this periodical constitutes an important source of epidemiological and statistical information. The editing of this publication is superintended by the members of the Institute's Technical Council, in particular by Dr. ROČEK, Professor of Hygiene in the Masaryk University at Brno. It gives, therefore, a direct picture of the scientific activity of the Institute.

In the field of infectious diseases, mention must be made of the fine work done by FEIERABEND—who, unfortunately, died in 1934—on diphtheria, tetanus and cerebro-spinal meningitis. His work on the epidemiology of diphtheria in Czechoslovakia, the study of strains of malignant diphtheria bacilli (1929), undertaken in collaboration with SCHUBERT and continued by SCHUBERT alone, and the publications on the preparation and standardisation of antitoxin and anatoxin (FEIERABEND, SCHUBERT, VANIČEK), represent an important increase in the knowledge of these problems.

In the matter of general epidemiology, PELC and his collaborators RÍPKOVÁ and ROZMARIČ published a detailed study (1934) on typhoid fever in the Malá Haná region (Jevíčko district). This study was carried out with the help of the Health Organisation as a result of the European Conference on Rural Hygiene at Geneva, and it has shown the importance of milk contamination and germ-carriers in connection with the dairy industry of the region.

DRBOHLAV studied (1935/36) the epidemiology of puerperal fever by bacteriological and serological methods, the importance of which he has stressed in a recently-published note (1937) on the detection of persons who may have caused cases of puerperal fever.

Malaria in Sub-Carpathian Russia was studied in 1932 by GABRIEL, with special reference to local anophelism; it was also the subject of an epidemiological enquiry published in 1936 by DRBOHLAV.

Pure bacteriological research has been undertaken by DRBOHLAV regarding *B. typhi*, and by JEGOROV and MAZEPOVÁ (1932) regarding the importance of the S,R and O forms of bacillus of the typhoid group in preparing diagnostic sera and antigens.

The workers of the Prague Institute have also devoted attention to serological problems. JEGOROV has studied the elimination of non-specificity in precipitating sera (1933) ; BOUČEK the lacto-gelification of the sera of immunised animals (1935), and BERGAUER, BOUČEK and PODROUŽEK several physico-chemical questions connected with sera (1934).

In the sphere of food and nutrition hygiene, PODZIMKOVÁ-RIEGLOVÁ has published experiments (1935) in estimating the activity of the antirachitic vitamin in relation to the international standard, and has attempted to express in terms of an international unit the activity of all preparations of irradiated ergosterol or cod-liver oil manufactured in Czechoslovakia. The same author has published a paper (1936) on the antiscorbutic principle in the cabbage.

In connection with social medicine, PELC and PODZIMKOVÁ-RIEGLOVÁ have published a large monograph (1934) on the food-consumption of a Slovak agricultural family as recorded during one year, and ČAKRTOVÁ, PELC and PODZIMKOVÁ-RIEGLOVÁ have published an attempt to devise a standard diet for a working-class family (1936).

We owe to KLÍMA, who has recently taken over the management of the Social Medicine Section of the Institute, a paper on the state of health of the population of Czechoslovakia during the year 1935, while KLÍMOVÁ-FÜGNEROVÁ has published a paper on the principles, methods and curricula of instruction in hygiene.

8. THE ROME INSTITUTE OF PUBLIC HEALTH.

INTRODUCTION.

The Italian public health organisation is too well known to call for the reproduction of what in any case would be an inadequate summary.¹ In recent years, moreover, several publications have appeared dealing with demographic data. The sources of statistical information and the technical perfection with which they are analysed and classified ensure a precise knowledge of fluctuations in the Italian population, more particularly as regards pathological and epidemiological factors and the influence exercised by State public health work and improved hygienic conditions.

The tradition of the Italian Institute of Statistics is maintained in the new Royal Italian Central Institute of Statistics, the organisation and modern equipment of which are models of their kind. The Institute employs a staff of about 600 and has a library of some 200,000 volumes. Medical statistics are in the hands of Professor DE BERARDINIS.

There is a very large number of doctors in Italy (35,600 for a population of 43 millions (1936), or almost one for 1,350 inhabitants), and public assistance through the old institution of " *medici condotti* " (9,390) is linked up with public health (some of these doctors act as " *medical officers of health* "). The whole system of central health administration thus operates through provincial health inspectors, who are under the direct authority of the prefect and, moreover, are appointed by and take their technical instructions from the General Health Department (Ministry of the Interior).

Before entering the State Service, communal health officers and officials of the State health administration have to pass a competitive examination. Grade-A officers are moreover required to hold a degree of Doctor of Medicine conferred by an Italian University or equivalent medical college. The Institute of Public Health,

¹ A full account was given in the publication : " *Les Services sanitaires et d'hygiène dans les régions rurales en Italie et la 'Bonifica Integrale'* ", 1931.

however, has not yet drawn up permanent regulations for post-graduate training, since the Institute has been open only a short time (1935), and the arrangements obviously involve a number of preliminary steps.

As regards social insurance, Italy has realised its great value in connection with maternity, invalidity and tuberculosis.

ROME INSTITUTE OF PUBLIC HEALTH.

(Director-General, Professor of Chemistry, D. MAROTTA.)

The building was begun in July 1931 and was opened on April 21st, 1934, in the presence of the head of the Government, accompanied by the Under-Secretary of State for the Interior, by His Excellency the Ambassador of the United States of America, and the representative of the Rockefeller Foundation in Italy. As a site for the Institute of Public Health, the State had at its disposal an area of 20,000 square metres next to the University Settlement. The State contributed 2 million lire for the initial works, together with an annual amount of 600,000 lire since 1933, specially earmarked for the Institute's technical equipment, plus the sums necessary for payment of staff and for the special radium equipment (the supply amounts to nearly 5 grammes). The Rockefeller Foundation contributed 12,500,000 lire for the building itself and 1,200,000 for certain special technical equipment. In pursuance of a Decree of January 1934, the Institute of Public Health was brought under the general Health Department of the Ministry of the Interior, and constituted the Centre for the research and experimental work of the Public Health Department and for specialised training of the personnel intended for the Italian Health Service. A law, dated May 27th, 1937, concerning the establishment of a post of Director of the Institute of Public Health, graded this post as that of a Director-General of the Ministry, and finally, a decree, dated July 1st, 1937, laying down regulations for the execution of the laws governing the Institute of Public Health, contains, in Articles 1 to 7, provisions concerning the Institute and its relations with the Ministry of the Interior ; and, in Articles 8 to 13 provisions concerning research and experimental work ; courses of instruction, and the methods to be followed ; whilst Articles 14 to 21 deal with staff

questions. The old scientific laboratories of the General Directorate of Health are now part of the Institute of Public Health. So far, however, no final regulations have been issued making attendance at one of the Institute's courses a necessary condition of admission to the Government Public Health Service.



Figure 9.—ROME INSTITUTE OF PUBLIC HEALTH.

Public health or medical officers not on the staff of Government, provincial or communal public health departments, will also be permitted to attend the training courses forming part of the Institute's curriculum on payment of a fee ; and scholarships for foreigners are provided.

As provided in the decree governing its operation, the Institute includes the following departments :

- (1) Micrography and bacteriology as applied to public health, including control of sera, vaccines and like products (Chief : Professor R. MAGGIORA-VERGANO) ;
- (2) Chemistry as applied to public health including testing of foodstuffs (Chief : the Director-General of the Institute) ;
- (3) Physical research as applied to public health, including a special department for testing physical therapy, X-ray and radium apparatus (Chief : Professor G. C. TRABACCHI) ;
- (4) Epidemiology and prophylaxis of malaria (Chief : Professor A. MISSIROLI) ;
- (5) Biology (tests and research on all public health matters relating to the use of organotherapeutic products, vitamins, etc.) (Chief : Professor M. CINGOLANI) ;

- (6) Sanitary engineering, mainly concerned with studies of the hygiene of the soil, water and housing (Chief : M. G. BIRELLI, Engineer) ;
- (7) Epidemiology in general and vital statistics ;
- (8) A general secretariat and a secretariat for the courses ;
- (9) The Library¹ (Chief : Dr. M. PANTALEONI) ;
- (10) The Museum.

Post-graduate training of the staff of Government, provincial, municipal or public administrative health services in general is provided for in the regulations dealing with the official work of the Institute ; but this fundamental teaching work has not yet actually been begun.

Lessons, have, however, already been given. Courses have been organised for veterinary surgeons and Red Cross nurses. The instructional material, the premises for the students' practical work and the technical education departments connected with the Institute have all been well arranged and made an excellent impression. Last year, a " refresher " course of lectures lasting one month was followed by twenty-three doctors, most of them already Government officials. So long as attendance at a training course for candidates desirous of entering the public health service is not made compulsory, this task of providing " refresher " courses for senior public health officers who are already in Government posts undoubtedly forms a valuable contribution by the Institute towards increasing departmental efficiency.

Although the decree founding the Institute was recently amended, more particularly as regards the Institute's independence and technical direction, the basic provisions remain in force. This decree, dated January 11th, 1934, enacts more particularly (Article 10) that : " The Sanitary Engineering Section shall make a technical study of proposals for works on which, under the existing laws, the opinion of the Higher Health Council is sought ; it shall arrange for the preparation of the technical material required for its own department and where necessary for other departments of the Institute ". The Sanitary Engineering Department of the Institute of Public Health thus supplies the Superior Health Council with expert technical advice on urban and rural sanitation

¹ The library of the Institute consists of 24,000 volumes and receives 353 periodicals (164 of them foreign).

works, water-supplies, housing-schemes, etc. It also prepares the technical material necessary for educational purposes for the Museum of Hygiene, etc., but it does not directly engage in sanitation work in urban or rural centres.

Nevertheless, Article 16 of the Royal Decree of January 11th, 1934, enacts that "with the prior authorisation of the Minister of the Interior, the Institute of Public Health may also undertake research work and surveys at the request of private administrations, associations and persons. A decree of the Minister of the Interior adopted jointly with the Minister of Finance shall fix the amounts to be paid to the public treasury in return for the sums expended". This provision has already led to close co-operation between the Institute of Public Health, as technical adviser, and certain private activities and undertakings, and in the opinion of the Institute this collaboration has, even in the field of rural life, given excellent results.

In Italy the production of sera and vaccines and of all biological preparations, though regulated by the Ministerial Circular of June 30th, 1933, is left to private industry. The National Health Institute officially supervises manufactured articles, both foreign and national, offered for sale, and even products (intended for free distribution or diagnostic or prophylactic purposes) made up and prepared in the various sections of the Institute, as, for example, the mixed Castellani : cholera + TAB vaccine, which was used in large quantities in East Africa.

INTERNATIONAL SCHOOL OF MALARIOLOGY.

The former *International School of Malariology*, now the "Ettore Marchiafava Institute of Malariology", under the direction of Professor BASTIANELLI, occupies a special and very modern building in the premises of the Policlinico Umberto I^o (it was opened in 1935). The staff includes Professor LEGA, assistant director, Professor RAFFAELE, entomologist, head of the Laboratory of Parasitology and Entomology, with Dr. SANDICCHI as assistant head, dealing more particularly with mosquito breeding, and Dr. CASINI in charge of the clinical department. There are also a librarian,

secretarial staff, and subordinate staff for the laboratories and clinics.

The *Clinic* is to be completed by a new ward with forty beds, which is not yet open. At present, it contains thirty-two beds for men and eight for women, all occupied. Most of the patients are Italians from the various malarial districts of the peninsula, and there are also some patients from Libya and East Africa. The length of the patient's stay depends on the development of the disease and also on teaching requirements, this being a small hospital for study and research serving solely the teaching purposes of the School of Malariology.

The school's *budget* has not yet been stabilised since it was installed in its new premises. Its resources include :

- (a) 500,000 lire from the Ministry for Foreign Affairs (the school is regarded as an international institution) ;
- (b) Subsidies of varying amounts from the Ministries of the Interior, Agriculture, etc. (annual grants) ;
- (c) Students' fees.

The students attending the malariological courses of the school belong to different groups ; they include scholarship-holders sent by Governments or foreign institutions, candidates for positions as heads of anti-malaria dispensaries and doctors preparing theses on malariological problems.

Since 1935, when the school was transferred to the new premises, various unsettling circumstances prevented the full development of its educational and scientific activities. In spite of this, twenty-five Italian and two foreign doctors took the course in 1935/36.

The National Institute of Public Health has also a special section of malariology, which gives annual courses of instruction. It is under the charge of Professor MISSIROLI, who works in close touch with the Rockefeller Foundation, represented by Dr. HACKETT. The scientific and practical work of investigation and prophylaxis done by this department is well known. Direct co-operation between the Institute's malariological section and the special School of Malariology under Professor BASTIANELLI will, it is anticipated, be arranged in the near future.

THE INSTITUTE OF TROPICAL AND SUB-TROPICAL DISEASES.

Another specially erected building beside the School of Malariology contains the *Institute of Tropical and Sub-tropical Diseases*. It is the university centre for the teaching of this subject in the Faculty of Medicine. The lectures which Professor CASTELLANI and his numerous colleagues give at this Institute are, therefore, partly ordinary faculty lectures for students engaged in their last year of clinical work, and also, and to a still greater degree, *post-graduate* courses for doctors from the colonies or sub-tropical countries, both Italian and foreign.

The clinical work of this Institute is a special feature, as it deals with cases from all parts of the world, more particularly in the field of dermatology.

THE INSTITUTE FORLANINI.

The Institute which bears the name of Forlanini and is intended for the study and treatment of tuberculous patients, merits special attention. Besides its function as a hospital and sanatorium (1,380 beds were occupied in December 1936) it is in the main a specialist school for Italian and foreign doctors engaged in the study of tuberculosis. From this point of view, it acts essentially as a public health school and is a part of the group of institutions which aim at improving the public health organisation of the country.

The Museum of Special and Pathological Anatomy, occupying an immense room on the first floor of the institute, contains an exceptionally fine collection of specimens and documents.

The "National Fascist Institute of Social Welfare" (Istituto nazionale fascista della Previdenza sociale) provides the financial basis for and organises the campaign against tuberculosis, more particularly the clinic and sanatorium which comprise the Institution founded at Rome.¹

¹ The work of the National Institute of Social Welfare is regulated by the Decree-Law of October 4th, 1935 (No. 1827). Article 3 enacts that "to achieve its purpose the Institute (Istituto nazionale fascista della Previdenza sociale) shall operate mainly in the field of compulsory insurance in respect of (a) inva-

In the year 1935/36, this programme gave highly satisfactory results.

In 1934 (the year covered by the last report published by the National Institute of Social Welfare), the following benefits were accorded in Italy in respect of tuberculosis :

	Days
Treatment given at home	3,944
Treatment given at dispensaries to 11,308 persons	1,871,819
Treatment given in institutions (sanatoria) to 47,132 persons	6,151,750
	Lire
Allowances paid to patients' families	4,204,871

Altogether 140,090,991 lire were spent on tuberculosis benefits.

The compulsory tuberculosis insurance scheme introduced in Italy by the Decree-Law of October 27th, 1927, and now regulated by the Decree-Law of October 4th, 1935, has, by a further Decree of March 16th, 1936, been extended to *settlers* and *share farmers*. This decision will increase by 587,000 the number of insured persons (at present estimated to be about 6,250,000) and will extend anti-tuberculosis protection to the 3,848,000 members of the families of these new insured persons. It will mean the installation of 3,800 new beds and will thus entail a further charge on the Institute of Social Welfare amounting to about 31 million lire per annum.

At the time of introduction of the insurance against tuberculosis, there were 27,400 deaths per annum from tuberculosis. In consequence, 85,000 to 100,000 patients might have been expected to require hospital or sanatorium treatment for an average of four months ; but by utilising the resources already existing in Italy it proved possible to reduce to 20,000 the places (or beds) to be provided.

lidity and old age, (b) tuberculosis, (c) unemployment, (d) maternity, (e) maritime workers, (f) certain classes of workers subject to special regulations".

For the time being, its activities are confined, in the sphere strictly connected with public health, to compulsory *tuberculosis* and *maternity* insurance.

Under Article 4, however, the Institute is fully empowered to set up and maintain *services* for medical or social relief, to take *any action necessary to reduce or forestall the insurance risks*, to initiate an effective campaign of *propaganda* and *popular education*, and to conclude *agreements with institutions for the relief, treatment or prevention of disease*.

The organisation comprises : (1) the Central Institute ; (2) the sanatoria in the various provinces.¹

The institute consists of a three-story central block for scientific and teaching work with a medical and surgical clinic containing seventy-five beds, research laboratories (bacteriological, histological, chemical, serological) and special clinics (thirty beds each) for pediatrics, orthopædics, midwifery and ear, nose and throat diseases. All this, together with the auxiliary services, the central office, the X-ray and physiotherapy departments and the large amphitheatre, constitutes a special school of tuberculosis, which, moreover, is linked up with the university teaching system through the Chair of Phthisiology in the Faculty of Medicine. A hostel for Italian and foreign medical students (with accommodation for seventy) is situated in one of the wings of the institute, together with the theatre and other services. On an open terrace on the top of the central block are sound-proofed houses for experimental animals. Next to the central block and in direct communication with the scientific departments are the four hospital sanatorium buildings, each with 250 beds (500 men, 500 women).

Methods that have been adopted to ensure the most rational economy in supplies, the mechanical distribution of food throughout the institution by means of small telepheric electrically driven conveyors, the details of ventilation, heating, lighting, refrigeration, etc., make this institute a model of its kind.

On a site near the central block, a school for nurses, with resident accommodation for 150, is now being built, and also a special hospital for pulmonary diseases of a non-tuberculous nature (100 beds for adults and forty for children).

¹ At the present time (1937), the sanatoria buildings planned in 1929 and under construction since that date by the Institute of Social Welfare as a result of the introduction of health insurance may be classified as follows :

- Twelve hospital sanatoria in operation, 3,450 beds ;
- Seventeen hospital sanatoria ready for opening, 5,278 beds ;
- Ten temporary buildings, 2,116 beds ;
- Sixteen hospitals and sanatoria under construction, 7,568 beds ;
- Ten hospitals and sanatoria planned, 2,228 beds.

It is expected that all these 20,640 beds, covering the whole of Italy, will be ready in 1939. The cost is estimated at 500 million lire, of which 300 millions have already been spent.

The Central Institute is engaged in training the staff of 400 specialists who will be required for these hospitals and sanatoria.

The whole building covers an area of 28,200 square metres, and there are 200,000 square metres reserved for gardens and parks for the patients.

At the new institute, the teaching programme includes three different courses : (1) a clinical course on tuberculosis and respiratory diseases, for students of the Faculty of Medicine (Professor MORELLI); (2) a *six-month* course of further study in physiology, the cost of which is borne by the " General Confederation of Italian Industry "; (3) a *two-year* course, which is the only means of obtaining the university degree of specialist and of securing a position as medical officer at a dispensary, hospital or sanatorium or at the Central Institute for the Study of Tuberculosis.¹

The following is the programme of instruction : (1) Clinic for tuberculosis and respiratory diseases (Professor MORELLI), (2) pseudo-tuberculous clinical syndromes (Professor OMODEI-ZORINI), (3) radiology of tuberculosis (Professor A. BUSI), (4) surgical tuberculosis (Professor ALESSANDRI), (5) pathological anatomy of tuberculosis (Professor OMODEI-ZORINI), (6) tuberculosis of the female genital organs and tuberculosis of gestation (Professor PESTALOZZA), (7) tuberculosis of children (Professor SPOLVERINI), (8) tuberculosis of the upper air passages (Professor BILANCIONI), (9) anti-tuberculosis social hygiene (Professor ILVENTO), (10) anti-tuberculosis legislation (Professor GIANNINI), (11) anti-tuberculosis prophylaxis and climatology (Professor BOCCHETTI), (12) sanatorium technique (Professor MENDES), (13) anti-tuberculosis dispensary technique (Professor BENEDETTI), (14) physiopathology of pulmonary tuberculosis (Professor MONALDI), (15) bacteriology and serology of tuberculosis (Professor DADDI).

Provision is thus made for at least six courses closely connected with public health and sanitary engineering. Medical officers acting as heads of dispensaries, including polyvalent dispensaries, under a health administration are advised for the purposes of their work to take the courses mentioned in 9, 10, 11, 12, 13 and 15 above. A detailed study of these subjects would give the specialist an equally essential knowledge of public health administration and of sanitary engineering and probably lead to an increasing number of *tuberculosis specialists engaging in preventive medical work as public health officials.*

¹ Between 1929 and 1936, these courses were attended, either voluntarily or as holders of Government scholarships, by twenty-five foreign doctors, including four Bulgarians, three Roumanians, two Austrians, one German, one Englishman, one Belgian, one Finn, one Pole, one Greek, one Swede and one Javanese.

Stress must therefore be laid on the teaching provided by the Institute. Even before the new building was opened, instruction in this subject was given, in 1929-1934, at the Porta Furba Sanatorium of the National Institute of Social Welfare to 1,170 medical students, of whom 285 received their degree after maintaining a thesis on some problem connected with tuberculosis.

Courses are given at the Littorio Hospital and at the Hospital for Infectious Diseases to doctors applying for posts in the Government Public Health Administration. These courses, however, and the attendance certificates issued only qualify students to compete for vacancies without conferring any right of appointment. Such courses are not compulsory.

At the large Policlinico Hospital, which combines all the university clinics and laboratories of the Rome Faculty of Medicine, and at the new institutes of the Rome Faculty of Medicine and of the University Settlement, there are several courses of instruction which increase the young doctor's knowledge of hygiene and public health; the Clinic for Contagious Diseases (Professor CARONIA), the Institute of Hygiene (Professor DE BLASI), the Institute of General and Experimental Pathology (Professor VERNONI), and the Institute for the Study of Cancer (Professor BASTIANELLI) may be mentioned in this connection. Except for the last-named, which forms part of the general organisation of public health, these institutions do not provide regular post-graduate training for public health officers.

RESEARCH WORK.

As the Public Health Institute at Rome was only inaugurated in 1935, this review of the research work carried out by the technical staff of its various departments will necessarily be brief. Among other activities, the Institute is carrying on the work of the old public health bacteriological laboratories which were run by the late Professor GOSIO.

In the field of infectious diseases, epidemiology and immunology, mention may be made of the work of PERGOLA on the influence of season and temperature on certain diseases (1936), and of ZANNELLI on methods of preparing sera for diagnosis (1935), and on culture media for the preparation of anti-typhoid vaccines (1936) and anti-typhoid agglutinins (1936).

Tuberculosis has been studied from the bacteriological and immunological standpoint by BABUDIERY (1936), and from the epidemiological standpoint by MAGGIORA-VERGANO (1936).

A large volume of 719 pages was published in 1936, under the auspices of the Institute, by PENSO and BERTOLINI, on "The Sanitary Inspection of Farmyard Stock".

In the field of parasitology, we may mention the research work of BABUDIERY on the biology of the acanthocephali; that of SALLA on a focus of intestinal bilharziosis in Eritrea (1936); that of PENSO on kala-azar in Italian Somaliland (1935), on the development-cycle of the oxyuris (1935), and on the presence of *Entamoeba dispar.* in Italy (1935); and that of CORRADETTI on the phlebotomi in a district where leishmaniasis is endemic (1936).

Continuing the long-established tradition of the Italian School, scientific research on malariology is being carried on at two centres—the malariology section of the Public Health Institute, under the direction of Professor MISSIROLI, and the Ettore Marchiafava Institute, under the direction of Professor BASTIANELLI.

Professor MISSIROLI's collaborators have added to our knowledge of parasite biology, the experimental transmission of malaria to man, and the varieties of anopheles in Italy. A large number of publications bear witness to the extensive researches into these questions made by the investigators, and even though we confine ourselves to works published by the Public Health Institute during the years 1935 and 1936, the contribution of Italian malariologists has been of the highest importance. In this connection, we would mention the close collaboration established during the ten years prior to the creation of the Public Health Institute at the Malaria Experimental Research Station between Italian malariologists, and the Rockefeller Foundation, represented by Dr. HACKETT.

In January 1937, Professor MISSIROLI brought out the first number of the *Rivista di Parasitologia*, which contains an important study by LA FACE on the anopheline fauna of the Italian colonies.

Problems of general pathology have been dealt with by BABUDIERY in his hæmatological research into the inducement of experimental scurvy in the guinea-pig (1935), and by GALAMINI in his study on the action of histamine and acetylcholine (1936).

Among the publications of the Section dealing with chemistry as applied to nutrition, mention should be made of the researches

of MAROTTA, DI STEFANO and VERCILLO on the action of the diastases in the maturation of flour (1935), and of VERCILLO on the determination of sugar in flour (1935) and on hydrolytic processes in sugar-formation (1936).

Several studies have been devoted to the drinking-water and mineral waters of Italy and her African colonies. For instance, TOFFOLI (1937) studied the thermal spring of Ali-Hasa in Eritrea and the water-supply of the colony generally ; and MAROTTA studied the mineral waters of Latium and the Abruzzi ; while DI STEFANO (1936) devoted himself to the determination of bromides in mineral waters containing chlorides and iodides.

On September 27th, 1935, Dr. RINALDI, well known for the astonishing results he obtained by a secret method for curing diseases of the joints, died tragically at Piazza. The following month, the Public Health Institute was requested to enquire into the identity of the drugs used and to reconstruct RINALDI's method. In 1936, the Director of the Institute, Professor MAROTTA, addressed a report to the Under-Secretary of State for the Interior, informing him that the researches had been completely successful. The report in question has been published by the Public Health Institute under the title : " The Drugs and Method employed by RINALDI for the Treatment of Arthritis ".

During the period 1929-1935, the " Forlanini " Institute for the Study and Treatment of Tuberculosis, at Rome, published 256 scientific works, exclusive of students' theses. They deal with the following questions : pleurolysis of the apical forms of tuberculosis and association of pneumothorax with unilateral phrenicotomy ; antigen action of the lipid fractions of Koch's bacillus ; part played by the bovine bacillus in human pulmonary tuberculosis (DADDI) ; intestinal and pneumo-peritoneal tuberculosis (MONALDI) ; pseudo-tubercular syndromes, pneumoconioses, etc. The collaborators of Professor MORELLI, Director of the Institute, and Professor OMODEI-ZORINI, Deputy-Director, devoted their main attention to the study of the problems of collapse-therapy on modern lines.

As the outcome of his researches at the Institute, Professor MONALDI published a treatise on " The Morbid Physiology of the Respiratory System in Pulmonary Tuberculosis " (1937). The author draws from his observations practical deductions for a new technique of thoracoplasty which would enable better functional

results to be obtained than those achieved by current practice, while the risk attaching to the operation is very slight.

MONALDI further makes a very detailed study of the regulation of breathing, thoracic and pulmonary equilibrium, pleural pressure, and the influence of breathing on pulmonary circulation and on the functions of the mediastinum. With the help of a new thoracic pneumograph, the author is able to transcribe simultaneously the movements of different points of the thorax, by which means he obtains characteristic curves for normal subjects and subjects suffering from various affections : these findings have been confirmed by radio-cinematographic observations of the thorax.

This treatise bears witness to the efforts made by the Italian School to place collapse-therapy on a sound scientific basis ; it is a testimony to the discovery of FORLANINI, the master of Italian phthisiology.

9. THE INSTITUTES OF HYGIENE IN ROUMANIA.

INTRODUCTION.

Health administration in Roumania is at present centralised in the Ministry of Public Health, which is also responsible for the administration of social welfare work. Prior to 1910, there was complete decentralisation in the field of public health. At that time, the first law providing for centralisation was drafted.

Immediately after the world war, a partial decentralisation again took place, the country being divided up into eleven health areas ; a local *health budget* was established for each department and municipality. This was the position until 1935, when all the local health budgets were taken over by the Ministry of Public Health and incorporated in a " Central Health Fund ".

In 1936/37, the budget of the Ministry amounted to 908 million lei provided out of Treasury funds ; it was made up as follows :

762 millions for public health and social welfare ;

104 millions for labour ;

42 millions for social insurance (this autonomous institution has a budget of 800 millions annually for the payment of personnel only).

The *Central Health Fund*, which is administered independently of the State Treasury by the Ministry of Public Health, is of considerable interest. The budget estimates of this autonomous administration amounted in 1936/37 to 762 million lei ; in fact, however, only 75% of this total was reached. The fund derives revenue from a State lottery for which the Ministry of Public Health has a monopoly, the fees collected by the hospitals for the treatment of patients, merchant shipping surtaxes, lottery taxes, 90% of the revenues from the Alcohol Monopoly, 70% of the yield of taxes on cosmetics and patent medicines, and taxes on mineral waters.

There are, in addition, seventy-one departmental health funds, twenty-one municipal health funds, appropriations earmarked for

medical purposes by the Autonomous Railway Board, the Post Office, the National Education Department, the Department of Justice, etc., to an aggregate amount of 1,000 million lei.

A Central Institute of Statistics, under the direction of Dr. MANUILA, a physician, was organised in 1928, with the assistance of the Rockefeller Foundation, as a Bureau of Vital Statistics, and attached to the Ministry of Public Health. Lately, this bureau has been merged with the State Statistics Service, to constitute the " Central State Statistical Institute ", and placed under the authority of the Ministry of the Interior. Within a very short time, the institute has been able to collect the requisite statistical data for the whole country and to work up this material by the most modern mechanical methods and with the help of a well-trained staff. The institute issues monthly reports showing the results of the statistical enquiries carried out some three to four months earlier. In this way, vital and medical statistical studies have been greatly facilitated, for it has to be borne in mind that the material is collected from health institutions scattered over a wide area.

The Royal " Prince Carol " Foundation, of which Professor GUSTI is Director-General, carries out important field studies into the condition of the peasants and the means of promoting their welfare.

At the end of 1936, there were 8,263 physicians in Roumania, 6,712 of whom were permanently resident in urban and 1,510 in rural areas ; 1,482 physicians attached to the urban area services and 1,510 working in rural areas are paid out of the State budget. The salaries vary from 5,750 to 19,900 lei per month.

The first attempt to consolidate the different public health laws inherited by Roumania after the war was made in 1930. The law then framed is known as Professor Moldovan's Law, after the Under-Secretary of State for Public Health. The aim was to establish a public health service on modern lines in administrative units, and especially in rural areas. According to this law, the physicians in the public administration were divided into five categories :

- (1) Public Health Officers of prefectures and districts ;
- (2) Public Health Officers of the Medical Assistance Service ;
- (3) Doctors in laboratories ;

- (4) Doctors of the communal health services ;
- (5) Doctors attached to courts of law.

The law provided that all physicians in charge of disinfection services, port health services, and of health administration in prefectures, districts and municipalities, as well as chief medical officers, social insurance inspectors, and the medical personnel of the Institute of Hygiene, must be specially trained in public health. The public health officers of prefectures and districts were to work on a full-time basis. By the same law, regional Institutes of Hygiene were established at Bucharest, Jassy and Cluj, to undertake research work and carry out the public health programme. In 1935, this law was amended, and the requirement that medical officers of health should hold a public health diploma was waived. According to the new Law of 1935, doctors in the public service must have taken a nine-month course of training—three months in obstetrics, three months in pediatrics and three months in infectious diseases.

The Law of 1930 provides that professors of hygiene of the medical faculties shall be directors of the regional institutes of hygiene ; assistant directors to be appointed on the recommendation of the directors. Each institute has a technical council, composed of specialists in surgery, internal medicine, venereal diseases, psychiatrics and child hygiene. The members of the council are appointed for a period of five years. The council may consult other experts. The duties of the institutes are defined by law as follows :

- (1) To advise public and private health and social welfare organisations in technical matters ;
- (2) To investigate, at the request of the authorities, sites for new buildings, etc., housing conditions, water supplies, sewerage systems and other sanitary matters ;
- (3) To take direct action in case of emergency or at the request of authorities whenever a situation arises calling for action on technical lines ;
- (4) To conduct health education ;
- (5) To carry out research work ;
- (6) To supervise private bacteriological and chemical laboratories.

The institutes are responsible for the technical direction and supervision of the infectious diseases hospitals, health centres and institutions for training auxiliary personnel. The personnel of the

institutes and organisations under their supervision are appointed on the recommendation of the directors. Directors and technical personnel may not practise medicine nor undertake any duties in connection with private laboratories.

THE INSTITUTE OF HYGIENE AT BUCHAREST.

(Director : F. D. MEZINCESCU.)

This Institute was established by a special law in 1927. Under the terms of this law, the Professor of Hygiene of the University is at the same time Director of the Institute.

The programme of the Institute is as follows :

- (a) To provide post-graduate training in public health ;
- (b) To provide courses in public health for medical students ;
- (c) To train the auxiliary personnel (public health nurses and sanitary inspectors).

By virtue of the Public Health Law of 1930, the Institute became the regional Institute of Hygiene. The Institute is provisionally housed in premises belonging to the Faculty of Medicine. The Rockefeller Foundation has made a grant of \$180,000 for a new building for the Institute, which is now under construction. The Ministry of Health pays the salaries of three chiefs of departments, two chiefs of laboratories, three assistants and three auxiliaries, to an aggregate amount of 1,126,200 lei. In the budget for 1936/37, 80,000 lei were appropriated for material. The University pays the salaries of the director, two assistants and three auxiliaries, and provides on an average 30,000 lei yearly for material.

In 1927, the Institute began to organise post-graduate courses in hygiene and preventive medicine for the physicians of the State Health Administration, school medical officers and private physicians. Last year, two courses were organised for public health officers (a) in hygiene and preventive medicine, with fourteen students (including eight in the State health service), and (b) in school hygiene, with twenty-nine students (including seven in the school health service).

The following table indicates the number of doctors attending these courses from 1927 to the present time :

Institute of Hygiene and Public Health, Bucharest.

Year	Number of doctors who attended the courses :						Total
	of preventive medicine			of school hygiene			
	Offi- cials	Private persons	Total	Offi- cials	Private persons	Total	
1927/28....	12	19	31	—	—	—	31
1928/29....	27	5	32	8	113	121	153
1929/30....	8	4	12	3	2	5	17
1930/31....	11	2	13	7	5	12	25
1931/32....	8	1	9	—	—	—	9
1932/33....	15	2	17	—	—	—	17
1933/34....	20	3	23	3	4	7	30
1934/35....	13	8	21	6	18	24	45
1935/36....	8	10	18	4	13	17	35
1936/37....	8	6	14	5	24	29	43
Total for 1927-1937			190			215	405

The Bucharest Institute is divided into the following departments :

(1) Department of epidemiology, bacteriology and parasitology ; this department carries out the study of infectious diseases and malaria and organises the control of malaria ;

(2) Department of chemistry (foods, drugs, nutrition, water supply, etc.) ;

(3) Department of social medicine (maternal and child welfare, school hygiene, social diseases, social assistance, anthropometry) ;

(4) Department of field activities (supervision and organisation of public health services in administrative units, courses in public health for physicians and auxiliary personnel, vital statistics, health education).

The library of the Institute contains 1,080 volumes and receives eight periodicals regularly.

There are two field stations attached to the Institute for practical training : the Malaria Station at Gurbanesti and an Urban Health Centre organised in the fourth administrative district of Bucharest.

THE INSTITUTE OF HYGIENE AT JASSY.

(Director : Professor Dr. Al. SLATINEANU ; Deputy Director : Professor Dr. J. BALTEANU ; Assistant Professor : Dr. J. ALEXA.)

The Institute of Hygiene at Jassy is attached to the Medical Faculty of the University and the Professor of Hygiene is the Director of the Institute. Two assistant professors and other assistants from the Medical Faculty are in charge of the different sections. The staff of the Institute consists of a director, one deputy director, two chiefs of departments, one chief of laboratory, four assistants, one malariologist, one epidemiologist and three auxiliary personnel. The activities of the Institute are research work, practical training and field work. The Institute has five departments :

- (1) Infectious diseases ;
- (2) Malaria ;
- (3) Therapeutics of malaria ;
- (4) Epidemiology and vital statistics ;
- (5) Regional laboratory.

The Institute gives courses in public health for doctors, public health nurses and sanitary inspectors. In the field of research work, the Institute carries out studies in malaria, pellagra, infectious diseases and tuberculosis, rural hygiene and experimental medicine. Of the field activities, the following are the most important : supervision of all public health services in the provinces of Moldavia, Bessarabia and Bukovina ; maternal and child welfare ; the study of malaria in special centres ; food control ; control of infectious diseases ; bacteriological investigations ; water-supply supervision.

The budget for the Institute is provided by the Ministry of Health. In 1931, the amount for salaries was 2,506,800 lei and for material 400,000 lei. In 1936, the amount for salaries was 1,429,000 lei and for material expenses 90,000 lei.

The curriculum for the training of doctors in the public health service covers a period of ten months and is divided up as follows :

	Hours of lectures	Hours of practical training
Bacteriology and immunology	15	20
Parasitology and entomology	5	10
Epidemiology	30	25
Infectious diseases	15	28
Public health organisation and health laws	10	2
Demography	15	20
Social hygiene, social pathology and social diseases	20	2
Child welfare	20	21
School hygiene	30	32
Industrial hygiene	20	9
Sanitary engineering	25	17
Venereal diseases	15	21
Tuberculosis	15	15
Nutrition	20	15
Mental hygiene	12	1
Applied psychology	20	10
Social insurance and occupational diseases	20	6
Heredity, eugenics	15	—
Laboratory practice	—	20

At the end of their post-graduate training, students must present a thesis dealing with some important subject relating to applied hygiene. The complete curriculum comprises 336 lectures, 142 hours of practical training, 339 hours of clinical demonstration, twenty-two days in the health demonstration areas and four months in the clinics. The number of students, according to years, is as follows :

1931-1932	28	
1932-1933	23	(one following the school health course)
1933-1934	29	(six following the school health course)
1934-1935	10	(four following the school health course)
1935-1936	12	
1936-1937	12	

THE INSTITUTE OF HYGIENE AT CLUJ.

(Director : Professor Dr. J. MOLDOVAN ; Deputy Director :
Professor Dr. M. ZOLOG.)

The Director of the Institute is Professor of Hygiene in the Medical Faculty of the University, and part of the Faculty personnel is

attached to the Institute. The Institute is not organised at present in special departments, but the personnel consists of :

- A specialist (physician) in rural, urban and school hygiene ;
 - A specialist (engineer) in sanitary engineering ;
 - A specialist (chemist) in food control ;
 - A specialist (physician) in industrial hygiene ;
 - A specialist (physician) in maternal and child hygiene ;
 - A specialist (physician) in vital statistics ;
 - A specialist (physician) in epidemiology
 - A specialist (physician) in social hygiene
 - A specialist (physician) in eugenics
- } These three are employed by the Medical Faculty.

The budget is provided by the Ministry of Health and, in 1932/33, amounted to 1,252,200 lei for salaries and 500,000 lei for material expenses. In 1936/37, the amount for salaries was 944,400 lei and for material 81,000 lei.

The library of the Institute contains 7,500 volumes and receives forty-two periodicals regularly.

The course in public health lasts for about eleven months (seven months for lectures, laboratory work and demonstrations and four months for field training). Lectures are given in the following subjects :

	Hours of lectures	Hours of training
Public health organisation	18	
Public health administration	8	24
School hygiene	16	8
Vital statistics	32	20
Epidemiology	48	34
Infectious diseases	20	14
Social hygiene	8	
Pre-natal hygiene and obstetrics		20
Oral hygiene	6	
Nose, throat and ear hygiene	6	
Food control and hygiene	16	16
Child hygiene	30	32
Industrial hygiene	32	28
Tuberculosis	10	28
Venereal diseases	16	20
Psychology	10	
Pedagogy	20	
Eugenics	10	
Social insurance	10	
Sanitary engineering	42	22

In all, there are 358 hours of theoretical training and 266 hours of laboratory work and demonstrations. The field training lasts for four months : one month in the tuberculosis service, one month in the children's clinic, one month in the infectious diseases hospital, and one month in the demonstration health district of Gilau.

The number of physicians who have graduated in public health from the courses is as follows :

1929	15	(only in school hygiene)
1929/30	16	
1930/31	13	
1931/32	8	
1932/33	11	
1933/34	20	
1934/35	11	
1935/36	17	

Refresher Courses at Cluj.

For the last three years, the Association of University Lecturers at Cluj has organised refresher courses for physicians under the auspices of the Medical Faculty. Lectures on public health problems are organised under the auspices of the Institute of Hygiene, particularly as regards epidemic disease control. The practical work carried out at the demonstration health district of Gilau is also under the Institute. The courses are not compulsory, but the Ministry assists the district and commune physicians by allowing special leave for two months for the purpose. Physicians attending number from twenty-five to forty.

* * *

Students following the courses in the Institutes at Bucharest, Jassy and Cluj have to pass an examination before an examining board of professors. The practical examination includes a thesis on some public health subject, usually consisting of a field survey of certain areas (Bucharest Institute).

The tuition fees vary. At Bucharest, no fees are charged ; at Jassy, the fees amount to 3,000 lei per course but are not usually collected. The directors, assistant directors and specialists of the

institutes do not engage in private practice ; a large percentage of them receive additional payments from other services.

THE " CANTACUZINO " INSTITUTE OF SERA AND VACCINES.

(Director : Professor C. JONESCU ; Deputy Director :
Professor Dr. M. CIUCA.)

The " Cantacuzino " Institute of Sera and Vaccines is obliged by law to organise courses for the post-graduate training of specialists in bacteriology, bio-chemistry, microbiology and experimental pathology.

Courses on microbiology have been given since 1927. They are attended on an average by thirty-five physicians each year, the curriculum extends over a period of from four to five months. Of the students, 25% are physicians employed in the State laboratories and in the army ; 30% are physicians in private laboratories ; and the rest are practitioners. Ninety-three bio-chemists graduated from special courses in bio-chemistry between 1926 and 1936.

The main work of the Institute consists in the preparation of sera, vaccines and other similar products necessary for the prevention and treatment of the most serious diseases prevalent in Roumania, in scientific research concerning these diseases ; in working out standard serological and microbiological methods, and in the control of bacteriological diagnostic work. Since vaccination against diphtheria is now obligatory, a new laboratory for the production of anti-diphtheritic vaccine is at present under construction in a special building of the laboratories for the production of BCG vaccine.

The Institute is divided into the following thirteen sections : production of antitoxic and antibacterial vaccines ; medical-biological and chemical laboratory ; veterinary pathology ; parasitology ; entomology ; malaria ; tuberculosis research ; cancer research ; control of drugs ; keeping of bacterial cultures ; sterilisation ; library ; administration.

The staff consists of forty-three experts (doctors in medicine, veterinary surgeons, doctors of natural science and pharmacy) and 114 auxiliary personnel. The salary of a chief of section

amounts to 75,000 lei, that of a chief of laboratory to 50,000 lei, and of an assistant to 25,000 lei per annum.¹

COURSES FOR CHILD WELFARE.

The Ministry of Public Health organises special courses for child welfare at Bucharest, Cluj and Jassy, the Institutes of Hygiene collaborating in the scheme. The staff of the institutes usually give lectures on pre-school and school hygiene and vaccination, and conduct the practical training of physicians in health demonstration areas. These courses are not compulsory. All rural physicians are, however, invited to attend, and they are expected to participate unless special reasons prevent them from doing so. The number of physicians attending each course varies between thirty and forty.

HEALTH CENTRES ATTACHED TO THE INSTITUTES.

Health centres were established for the field investigations and practical training of candidates for the position of medical officer of health.

The *Hospital and Malaria Station, Gurbanesti-Ilfov*, and the Health Centre at Bucharest are attached to the Institute of Hygiene at Bucharest. Beside malaria investigations and control, the Gurbanesti-Ilfov Station deals with problems of rural hygiene in general. Post-graduate students spend some time during the summer in rural areas studying malaria problems. The Health Centre at Bucharest was organised in 1935 with the help of the Rockefeller

¹ Sera and vaccines are supplied to health institutions free of charge. To army institutions, a discount of 50% is given for sera and 75% for typhoid and paratyphoid vaccines, while 70% discount is accorded to local insurance societies. The value of the products delivered in 1935 was 70 million lei; in the same year, approximately 90% of the analyses were made free of charge (total number of analyses 122,880).

In 1935/36, the Ministry paid for personnel 7.92 million and for material 7.2 million lei.

The library of the Institute is a very large one; it is the most important specialised library in the country (in 1935/36, it was consulted by 6,760 readers). "Archives roumaines de Pathologie expérimentale et de Microbiologie" is printed on behalf of the Institute; extensive contributions are also made to other important research publications.

The Institute collaborates with the Antituberculosis League, and prepares BCG vaccine in quantities which are increasing year by year. At Bucharest, 10,760 infants were vaccinated, 15,805 were kept under observation and 51,390 home visits were made by the BCG Social Service alone.



Figure 10.—BUCHAREST HEALTH CENTRE.

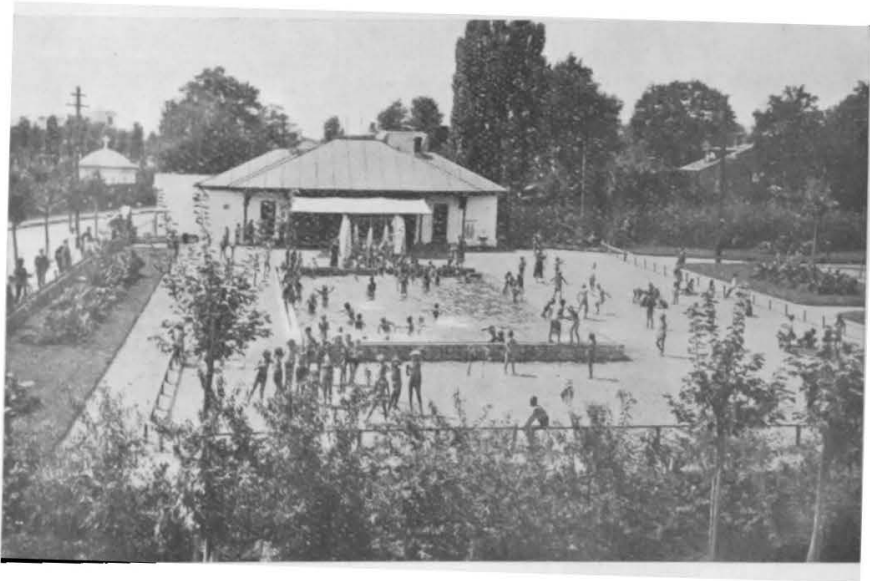


Figure 11.—BUCHAREST HEALTH CENTRE : PLAYGROUND.

Foundation. The urban and suburban area served by the centre has a population of about 60,000. During the first year of its operation, the centre took a census and studied a number of families from the social and health points of view. It was able to organise the following services : maternal and child welfare, school hygiene, distribution of milk, anti-tuberculosis and venereal disease consultations and treatment, health education, playgrounds, school baths, sanitation, home visits, etc. No fees are charged for the work performed by the centre.

The *Rural Health Centre at Tomesti* attached to the Institute of Hygiene at Jassy possesses a longer experience. It began work six years ago in a very modest building, which was subsequently renovated, enlarged and fully equipped. At present, it is a model centre for all branches of public health work. The population of



Figure 12.—TOMESTI RURAL HEALTH CENTRE.

this rural district numbers 32,000, in forty-four villages. The machinery of the centre has been greatly expanded and at present consists of one main centre and eleven sub-centres. The following figures illustrate the character of its work. In 1934, there were :

- 17,427 consultations ;
- 7,350 investigations dealing with elementary-school children ;
- 2,987 home visits ;

1,720 sanitary inspections ;
1,973 Wassermann tests ;
35,000 blood analyses in connection with the malaria campaign.

This centre has collected valuable records in regard to the social-economic conditions of villages and social diseases in rural areas and is doing admirable work in the control of malaria.

The Institute of Hygiene at Cluj directs and supervises the *health demonstration district of Gilau*, which was established in 1931 and serves as a centre for the practical training of health officers, nurses and students. The district comprises twenty-six villages with a total population of about 30,000, divided into four rural health areas. The villages are scattered over an area of 835 square kilometres ; two-thirds of the population live in compact villages and one-third in villages in a mountainous region. The main occupations are agriculture and forestry. The district has one full-time health officer, assisted by a head nurse, a sanitary inspector and a clerk, and three part-time physicians (specialists in tuberculosis, in puericulture and in dentistry). In each health area, a physician, aided by a public health nurse, deals with the health work. In the central village, a health centre has been constructed with rooms for the offices of the district health officer and nurses, four rooms for dispensaries, one room for X-ray work and a demonstration kitchen. In the health centres of each area, accommodation is provided, with a waiting-room, a consulting-room and living-quarters for the nurse. In one of these centres, there are living-quarters for the physician. The total expenditure for the demonstration district health services amounted to 2.09 million lei in 1931 and 1.32 million lei in 1936. During the first five years, the work was supported by the Rockefeller Foundation. The programme consists of maternal, infant and child-welfare work, prevention and treatment of tuberculosis and venereal diseases, control of infectious diseases, health education and sanitation.¹ Consultations

¹ In 1935, 21.6% and, in 1936, 19.6% of all pregnant women received medical advice and help ; in 1936, the centre took care of 52.1% of all children under 2 years of age, of 43.3% of pre-school children, and of 83.9% of children attending elementary schools. In the period from 1931 to 1936 inclusive, 5,697 persons were examined for tuberculosis and, among this number, 581 cases of tuberculosis were detected ; among 5,191 persons examined for venereal diseases, 828 new cases were discovered. In the period 1931-1936, there was a total of

are given free and the sanitation work is subsidised to the extent of 50% to 60%.

NURSING-SCHOOLS.

The first school of nurses in Roumania was founded in 1879, the training in this school being confined to the care of the sick. The present schools have been created since 1918. Professor MOLDOVAN, who was General Secretary of the Department of Health in the Transylvanian Provisional Government, created the first modern nursing-school at Cluj in 1919. At first, the training course lasted for one year only ; later, it was extended to eighteen months, and recently to three years. In all, 303 nurses have graduated from this school. The curriculum comprises, in the first year, a three-month preliminary course in practical nursing, the dressing of wounds and housekeeping, and 363 hours of theoretical lectures in the history and ethics of nursing, anatomy and physiology, personal and general hygiene, elementary bacteriology, general and applied chemistry, principles and technique of nursing, housekeeping, physical education, elementary pathology, surgery, internal and infectious diseases, pharmacology and nutrition. In the second year, there are 208 hours of lectures in epidemiology, child welfare, pediatrics, obstetrics and gynæcology, biology, psychology, dietetics, physical therapy, tuberculosis, venereal diseases and administration, with practical work in the hospitals and laboratory ; while, in the third year, 178 hours are devoted to theoretical training in public health, pre-school and school hygiene, industrial hygiene, mental hygiene, health administration, social problems, professional problems, sociology and statistics, with practical work in health centres and clinics.

At Jassy, there is a school for public health and hospital nurses with a training programme very similar to that of the school at Cluj. The training during the first two years is the same. In the

70,967 consultations (2% pre-natal, 15.7% infant, 9.2% pre-school, 14.6% school-children, 13.1% tuberculosis and 31% venereal disease cases). In the period 1934-1936, 5,400 children were vaccinated against diphtheria and scarlet fever. A great deal was done in housing ; dwellings were reconditioned, windows enlarged, wooden floors laid, privies and wells and a school bath constructed. The birth rate and death rate are decreasing (for the period 1931-1936, 29.3% and 18.7% respectively). There is evidence of a decreased death rate from infectious diseases in comparison with other parts of rural Roumania.

third year, however, candidates wishing to become public health nurses must be given practical training lasting from six to eight months in the health centres, while the candidates for hospital nursing require only two months of such training.

The schools at Cluj and Jassy are attached to the Institutes of Hygiene, and the staff of the latter devote a considerable amount of time to the necessary teaching.

The newly organised school at Bucharest is under the direct supervision of the Ministry of Public Health. With the assistance of the Rockefeller Foundation and the Ministry, the school will shortly be housed in new premises.

In the hospitals, there are a few private schools which have adopted a similar training programme.

Candidates desiring to enter any nursing school in Roumania must have successfully passed through a junior middle school and be between 18 and 30 years of age.

In all, there are 300 public health nurses, most of whom are working in Transylvania; only two-thirds of them have had adequate training. An Association of Public Health Nurses has been formed, with headquarters at Cluj, for the purpose of improving the working conditions of nurses and raising the standard of efficiency.

Nurses' salaries have been increased by 50%, beginning with the fiscal year 1937/38.

RESEARCH WORK.

The long tradition of scientific research which exists in Roumania has enabled the health institutes and the institutions engaged in the investigation of public health problems to continue and publish important work. Professor CANTACUZINO, the master of several generations of Roumanian scientists, greatly contributed to this effort.

The work we shall examine comes from :

- (1) The « Cantacuzino » Institute of Sera and Vaccines at Bucharest, directed from the beginning by Professor CANTACUZINO, and at the present time by Professor JONESCU-MIHAESTI and Professor CIUCA ;

(2) The Institute of Hygiene of Bucharest, under the direction of Professor MEZINCESCU ;

(3) The Institute of Hygiene of Jassy, formerly directed by Professor CIUCA, and, since 1935, by Professor SLATINEANU and Professor BALTEANU ;

(4) The Institute of Hygiene of Cluj, under the direction of Professor MOLDOVAN.

(1) The Cantacuzino Institute has made a noteworthy contribution to research in applied biology (especially bacteriology and serology). In a pamphlet published in 1932, which summarises the history of the Institute, a list of 518 publications bears witness to its scientific activity (1902 to 1932). We shall only examine the work carried out during the last five years (1932 to 1936). What characterises this production is the close connection that has always been maintained at the Cantacuzino Institute between the study of practical problems of immediate importance (epidemics, applied hygiene, serology) and that of general biological questions. Many of the Institute's publications are the outcome of the direct action of its late chief and his collaborators in the campaign against infectious diseases in Roumania ; but other work is also being carried on : ætiological research, the study of viruses, investigations into the chemical and physico-chemical nature of serological reactions, and work in experimental medicine, pure cytology and biochemistry, some of it of outstanding importance in the history of science during recent years.

The Cantacuzino Institute maintains a close connection with the other university institutions in Roumania (Jassy, Cluj), and should be considered as the institution which is the focusing-point at Bucharest of all the specialised scientific activity of epidemiologists, bacteriologists and hygienists. The recent creation of the special Institute of Hygiene and its forthcoming installation in the new building designed for it at Bucharest will perhaps involve a change of venue for part of this scientific activity ; but, in view of the close agreement existing between the new Institute of Hygiene and the Cantacuzino Institute, this arrangement cannot but lead to useful results in the direction of specialising research.

The 311 sets of work published from 1932 to the end of 1936 can be grouped roughly into ten research series.

The first series includes research into the problems of immunity, which have always engaged the attention of Professor CANTACUZINO and his collaborators. The research of G. and A. MAGHERU into the rapidity of fixation during immunisation ; the work of COMBIESCU, TZETZU and POPESCU on the bacteriophage ; the study of associated vaccinations, by SUHATEANU, ALBESCU, and TARCOVEANU ; the experiments of BRAUNER on the part played by the red corpuscles in immunity ; the fine research of JONESCU-MIHAESTI and his collaborators into the modifications in the protein equilibrium of the blood-serum in horses undergoing immunisation ; the quite recent investigations of COMBIESCU, ISTRATI and others into the action of staphylococcus antitoxin in experimental infection ; and those of HORTOPAN and CIULIN and of ALBESCU into scarlet-fever vaccination have established facts of great interest.

The second series of research concerns infectious diseases, especially scarlet fever, diphtheria, typhus and cerebro-spinal meningitis. We should mention the studies of boutonneuse fever transmitted by dog-ticks by COMBIESCU, ZOTTA and others ; the work carried out from the epidemiological, diagnostic and experimental points of view by JONESCU-MIHAESTI and his collaborators on Nicolas-Favre's disease (1932 to 1935) ; the work on the experimental transmission of leprosy by CANTACUZINO and LONGHIN, with demonstration of an invisible phase in Hansen's bacillus (1932) ; and the quite recent contribution (1936) of CIUCA, BALTEANU and CONSTANTINESCU to the epidemiological study of typhus, demonstrating the cat's receptivity to the virus and the existence of an inapparent spontaneous infection.

Malaria has been studied from the epidemiological and entomological points of view by ZOTTA and his collaborators, and from the therapeutic point of view by CIUCA, BALLIF and others ; this work represents an important contribution to our knowledge of the evolution of the disease in relation to the biology of the parasite in the blood and organs, and of the action of synthetic drugs and quinine.

The third series (pure bacteriology and research on filter-passing viruses) includes the work of BOIVIN and MESROBEANU on the chemical composition of bacteria (1932) and on the action of the electrolytes on the equilibrium of the phosphorus compounds in the bacterial cell (1933) ; the recent research of BOIVIN and his

collaborators into the extraction of the complex antigenic polysaccharid enclosed in Aertrycke's bacillus (1934) ; the work of COMBIESCU on the dissociation of a strain of anthrax bacillus ; and that of DAMBOVICEANU and SORU on the *in vitro* action of the bacteriophage on the properties of cholera vibrio.

Among the most recent work may be mentioned that of BOIVIN and MESROBEANU on the composition of the residual antigens and the total antigens in Aertrycke's and Gärtner's bacilli ; the work of PETROVANU on Twort's phenomenon and the reduction of methylene blue in transmissible lysis ; the work of MAGHERU, BOIVIN and others on *B. coli* endotoxin ; that of PARASCHIVESCU on the total somatic antigen enclosed in *micrococcus prodigiosus* (1936), and that of CIUREA on the action of the sodium and calcium ions on the respiratory intensity of *B. coli*. We may also mention the thesis of MESROBEANU on the carbohydrate and fat antigens of bacteria ; the contribution of DAMBOVICEANU and ROTH to the study of the metabolism of bacteria in vaccinated and exhausted media ; the study of CORALIA AGAPI on the hæmolytic streptococcus isolated from scarlet-fever cases ; and the research of ROSCA into the cell-structure of bacteria.

A long series of experiments (the fourth) was devoted to tuberculosis, the biology of Koch's bacillus, and methods and technique of BCG vaccination (the application of which in Roumania is at the present time certainly among the most extensive in the world). About a hundred studies have been carried out and published on these subjects by the Cantacuzino Institute. Those of NASTA and his collaborators are well known.

Among the works on serology (fifth series) are the researches of SIEGLER and SORU on the physicochemical action of certain metals on human sera, under various pathological conditions (1933) ; the tests performed by CANTACUZINO and his collaborators on the sera of invertebrates (1934) ; and the work by Gaté-Papacostas on formol-gelification in canine filariasis (POPESCU, 1933) ; on Henry's reaction in malaria (BADENSKI, DIVOL and others) ; on the serological diagnosis of dourine (ZAHARIA FILIP, 1933 ; JONESCU, 1935) ; on the Weil-Felix reaction (COMBIESCU, 1934) ; and on Kopaczewski's reaction (CAPPON, 1935).

The sixth series of work was devoted to cytology and general biology, under the direct inspiration of Professor CANTACUZINO.

It comprised studies on the alterations in the ganglionic cells of the spinal cord in cases of inanition and in some cases of experimental avitaminosis (NICOLAU, 1933) ; on the biological modifications in the epithelial tissues cultivated *in vitro* (CRACIUN, 1933) ; on the medulla of the rabbit subjected to action from a distance (BRAUNER and SORU, 1933) ; on the expulsion of the cell nucleolus in certain pathological conditions (JONESCU-MIHAESTI and BADENSKI, 1933) ; and on the histology of Schwannomata (TUPA, 1935).

We shall group into a seventh series the work on hæmatology and hæmopathology—that of NASTA, TOCILESCU and BACANU on corpuscular sedimentation and the leucocyte formula in tuberculosis (1933) ; the thesis of SOFRONIE JOAN ELENA on the platelet variations in infectious diseases in relation to the time of coagulation (1933-1936) ; research by POPESCU into eosinophilia and Arneht counts in canine filariasis (1933, 1935) ; CRACIUN's work on reticulo-endotheliomata and reticulo-sarcomata (1933-1934), and especially the paper by CRACIUN, PAPAZOL and URSU on an experimental reticulosis by X-rays and leucocyte trialism ; and lastly the research of BRAUNER and SORU on the reduction potential of normal and pathological blood (1934).

Grouping the work on experimental medicine and pathological physiology in the eighth series, we may mention CRACIUN's research on the development of cancer grafts under the influence of metabolic and hormonal factors (1932) ; the experimental transmission to the monkey of a disseminated human encephalomyelitis by JONESCU-MIHAESTI (1932) ; the production of an acute pseudo-tabetic syndrome following experimental inoculation with a filtrate of Nicolas Favre's *lymphogranuloma inguinale* by JONESCU-MIHAESTI (1932) ; the work of MAGHERU and others on the action of tar on immunity reactions (1932-1933) ; BONCIU's contribution to the histo-pathogenic study of chronic gastro-duodenal ulcers (1933) ; the experimental research into typhus fever in the dog and the spermophile, by COMBIESCU and others, and into the permeability of the placenta to the same virus (1933) ; V. BOTEZ' work on experimental diphtheria in *spermophilus citillus* ; the histo-pathological studies on experimental poliomyelitis of the monkey, by TUPA (1934) ; and the research of BONCIU and CONSTANTINESCU into changes in the internal organs in burns (1935).

A ninth series may be mentioned—that of biochemical and chemical research, which includes work on carbohydrates considered in relation to the biology of bacteria (MARBE, BOVIN and others, 1935) and on the chemical composition of bacteria generally (BORVIN, BARBER and CIUREA, 1932-1935) ; also the research of SORU into the deshydrogenase of the S and R forms of *B. coli*, and that of CIUREA on the action of the sodium and calcium ions on the respiratory intensity of *B. coli* (1936).

The tenth series of research, dealing with entomology and parasitology, comprises chiefly the work of ZOTTA and his pupils on the Roumanian anopheles ; his well-known study of malaria in the Danube Delta (1932) ; a contribution to the study of intestinal parasitism in Roumania (ZOTTA, RADACOVICI, JORDAN and MADORE, 1934) ; research into the malaria of monkeys (*P. knowlesi*) and its transmission to man ; and the previously mentioned work of CIUCA and his collaborators on immunity and the treatment of malaria.

(2) The Institute of Hygiene of Bucharest has published a series of papers dealing with :

(a) Malaria : Dr. LAZAR, in his thesis (1933), has studied the diagnosis and symptomatology of chronic malaria ; while Professor MEZINCESCU, with F. PETER and D. CORNELSON, has studied the results of treating parasite-carriers and clinical cases with atebirin and plasmoquine in a village in the Mostistea valley (1933) ; he has also carried out, with D. CORNELSON, detailed experiments on the efficacy of atebirin and quinine in the prophylactic treatment of malaria (1935-1937).

(b) Rural hygiene : Research work by TATARANU on infection by Bang's bacillus on a farm (1932) ; by OLINESCU and BUSILA on paratyphoid B infections in rural malaria districts (1933) ; and by RASMERITA on manure in rural hygiene (1935).

(c) Child, school and industrial hygiene : The work of RASMERITA and others on workers' nutrition, the atmospheric conditions in work premises ; and child labour.

(d) Tuberculosis among craftsmen at Bucharest (OLINESCU and BUSILA, 1933) ; in the country (TATARANU and GONTEA, 1933) ; and in the universities (work of OLINESCU and his collaborators on the clinical, bacteriological and radiological control of students of

the Faculties of Medicine and Pharmacy at Bucharest, and of the High School of Physical Education, etc. (1934).

(e) Biological chemistry and morbid physiology (work of MEZINCESCU and his collaborators on the part played by amino acids in the endogenous nitrogen expenditure, on the biochemistry of certain micro-organisms, on technical problems affecting the determination of the non-protein nitrogen in the tissues, and others).

(3) The Institute of Hygiene of Jassy affords a remarkable example of intense production by a group of scientists who have for a long time been working with a common aim in a provincial district relatively poor in economic resources. It is to a large extent the work of Professor M. CIUCA, formerly Professor of Hygiene at Jassy, now at Bucharest, which has been taken up and carried on by his collaborators in the Jassy Faculty, Professors SLATINEANU, BALTEANU, BALLIF, ALEXA and others.

The bibliography, which includes 130 publications since 1930, will permit us to follow developments in the problems of applied biology on which the research at the Institute has hinged. Experimental malaria (immunity in malaria, clinical and parasite cycles, species and strains of parasites, comparative efficacy of different treatments) is one of the problems studied at Jassy under the direction of Professor CIUCA, with the co-operation of Professor BALLIF, Director of the Mental Hospital and holder of the chair of psychiatrics at Jassy, and of CHELARESCU. The contribution of the Jassy School in this field may nowadays be asserted to rank among the most important in Europe. A score of papers have been published on this subject by CIUCA, BALLIF, BALTEANU, CHELARESCU, etc. The careful observation of 2,681 artificially infected patients, some of whom have been followed up for 9 years, has made it possible for scientists at the Socola Malariological Station (to which the Rockefeller Foundation has lent its support), near Jassy, to reach interesting conclusions. As Professor CIUCA says in his paper on immunity in malaria (1935): "This institution may claim some of the credit for placing the study of the problem of immunity in experimental human malaria on a sound experimental basis."

Since 1925, the Socola and Tomesti malaria observation and experimental study stations and the Izolarea Hospital have been

engaged, under the auspices of the Health Organisation, on research into the comparative efficacy of anti-malaria products—secondary cinchona alkaloids, total cinchona alkaloids, synthetic products, etc. The results of this research have been discussed in the Malaria Commission and embodied in its reports on the therapeutics of malaria. This work has been carried out by M. CIUCA, BALTEANU, IRIMESCU, E. MANOLIU-ALEXA, CONSTANTINESCU, M. FRANKE, CHELARESCU, AGAPI and MICU.

Scarlet fever, which holds an important place in morbidity and mortality in Roumania, has also formed the subject-matter of a research series based on the work of Professor CANTACUZINO and carried out by CIUCA, BALTEANU, TUDORANU, E. MANOLIU-ALEXA, GHIORGHIU, TOMA, M. FRANKE, C. AGAPI and CRACIUNESCU. The problems studied by these workers are connected with the diagnostic value of the Dick test, the rôle of the hæmolytic streptococcus in scarlet fever, the interpretation of the blanching phenomenon, and the treatment of scarlet fever by a convalescent serum. For two years, GORDON and JANNEY, of the Rockefeller Foundation, in co-operation with C. AGAPI and E. MANOLIU-BALTEANU, have been carrying out a study on hæmolytic streptococcus isolated from scarlet-fever patients. There are also studies by BALTEANU and ALEXA (1930) on the changes in the humoral fluids in scarlet fever and on the acid-base equilibrium and by SLATINEANU, BALTEANU and their collaborators (1935), on the part played by sodium chloride in certain cases of scarlet-fever anuria.

A certain number of papers were devoted to pellagra ; in particular, the research of CIUCA, SLATINEANU, BALTEANU, ALEXA and others on the metabolism of pellagra patients (1934), and the study of the alimentation of peasants in the pellagra area of Moldavia (1935) by AYKROYD, ALEXA and NITZULESCU, which brought weight deficiencies of vitamin B₂, of calcium, of biologically adequate proteins and of protective foods (milk, green vegetables) contrasting with an excess of corn.

Lastly, reference should be made to papers on various aspects of the tuberculosis problem and to a series of biochemical and experimental researches on typhus fever which helped to show the existence of the unapparent disease as a human reservoir of infection (CIUCA, BALTEANU and CONSTANTINESCU, 1935).

(4) The Institute of Hygiene of Cluj has published, since 1930, about a hundred papers devoted partly to questions of health technique and practical hygiene, partly to pure scientific research. During 1932, it published, under the direction of Professor MOLDOVAN, monthly instructions and information on health technique, epidemiology and prophylaxis, which make up an important collection of 742 pages.

From 1932 to the end of 1936, the scientific activity of the Institute may be summarised as follows :

In the matter of health legislation and organisation, Professor MOLDOVAN has advocated in numerous publications the 1930 Health Law, which embodies the principles of preventive medicine, and so meets the real needs of the population. M. ZOLOG showed by his studies of the model health district of Gilau, which is under the supervision of the Institute of Hygiene, the superiority of a health organisation based on preventive medicine.

The control of arsenobenzenes and their action on the human and animal organisms were studied by M. ZOLOG and O. COMSIA (1935/36) in papers on the part played by the reticulo-endothelial system in the chemo-therapeutic mechanism of the arsenobenzenes and on the value of the international method of evaluating the toxicity of the arsenobenzenes.

In the matter of infectious diseases, we should mention the research of T. TURCU and E. MORARIU into the *B. abortus* undulant fever (1932-1934) ; that of T. TURCU into diphtheria and scarlet-fever vaccination (1933-1935) ; and that of J. MOLDOVAN into the tuberculosis bacillus and the pneumotropism of acid-fast bacilli (1936).

L. PRODAN studied cadmium poisoning and several other questions of occupational and industrial hygiene.

The statistical works published by P. RAMNEANTZU (1934-1936) deal with the demographic situation in Roumania (especially in the provinces of Transylvania and the Banat), movements of the population, depopulation factors in certain regions, infant mortality, etc.

Lastly, in the sphere of national biology, general race-improvement, eugenics and anthropology, J. MOLDOVAN, O. COMSIA and J. FĂCĂOARU have published numerous studies.

10. THE INSTITUTE OF PUBLIC HEALTH IN SOFIA.

The central authority in public health is the Ministry of the Interior and Public Health, its department of health being organised on the following plan : Hygiene and social medicine, hospitals and institutions dealing with the treatment of patients, infectious diseases and vital statistics, pharmacies and control of drugs, institute and school of public health. The country is divided into seven departments and eighty-four districts, each with a medical officer of health.

The health work is helped forward by 2,719 physicians, 1,361 feldschers, 955 midwives, 919 sanitary inspectors, 425 hospital and eighty public health nurses. In the central administration forty-six health officers are employed, in the departmental services seven, in the districts eighty-four, in rural communes 500, in the cities 143. As regards physicians generally, 579 work in rural areas, 2,140 in the cities ; altogether 1,505 are employed in the public services.

Compulsory Government insurance covers the risk of accidents, occupational diseases, sickness, maternity, invalidity and old age. The number of insured persons (excluding members of families) was 251,268 in 1933/34. Out of a total Social Insurance Fund expenditure of 84 million leva in 1933/34, 35.6 million leva were spent on cash benefits, medical assistance in sickness and maternity insurance.

The Institute of Public Health was housed for some years in provisional premises. Its total expenditure was, in 1932/33, 3.69 million leva and, in 1937, the estimates amounted to 6.38 million leva. There are three departments in the institute :

(1) Department of Microbiology : It produces sera and vaccines which are generally given free of charge to public health institutions. It also controls and standardises the diagnostic methods for the country as a whole.

(2) Department of Chemistry : It examines the foodstuffs, drugs, pharmaceutical preparations and waters, and makes chemical analyses in connection with judicial proceedings.

(3) Department of Hygiene : It is concerned with the study of hygiene and health education.

Beside this institute, there are in the country six laboratories similarly organised but mainly for diagnostic purposes ; the laboratories in Trnovo and Varna produce anti-rabic vaccine.

A School of Public Health attached to the Institute of Public Health organises courses for physicians and auxiliary personnel.

While the Institute was housed in provisional quarters, its activities were much restricted. A new building has been constructed and equipped with the aid of a grant of 19 million leva from the Rockefeller Foundation. The State contributions amount to over 20 million leva.



Figure 13.—FRONT VIEW OF THE INSTITUTE OF PUBLIC HEALTH AT SOFIA.

The records of the Institute's work during the last three years show a considerable increase in all departments. Between 1934 and 1936, the number of bacteriological examinations increased from 7,900 to 23,500 ; and the number of serological examinations from 9,800 to 19,800 ; the production of sera and vaccines is sufficient to meet the full requirements of the country.

Courses in Public Health.—Paragraph 221 of the Health Law of 1929 provides that all communal, district, departmental or school physicians must have spent at least one year in a clinic or in a first-class Government hospital after completing their medical studies. Permanent appointments can be obtained only by physicians who have attended a special course in the Institute of Public Health and who have passed the examinations in health legislation, health administration, epidemiology, general hygiene, forensic medicine and psychiatry. This applies also to the physicians who have been in the service less than five years. The length of these courses is not determined by law but can be altered by decision of the Health Department of the Ministry and on the advice of the Higher Medical Council.

The courses started in 1929/30. Forty physicians attended the first course. In 1932, another course was held for country physicians with the same number attending them. In 1936, a course was held for thirty-seven physicians in communal and city service.

Physicians attending these courses pay no fees and receive their salary and travelling expenses to Sofia and back. For practical instruction, the Institute uses the city health centre in Sofia which was established in 1931 ; recently, the village health centre in Golemo Komarje, established in 1933, has been used for the practical training of health visitors and nurses.

The Institute also arranges special courses ; in 1934 and 1935 it organised six-week courses of bacteriology for country physicians. Ten country physicians attended each course. In 1936, with the help of the Institute, two courses of malariology were held at Burgas and were attended by seventy county and communal physicians.

The course for physicians given in 1936, comprised lectures on general hygiene, social hygiene, epidemiology, medical statistics, alcoholism, child welfare, trachoma, tuberculosis, malaria, health propaganda, school hygiene, microbiology, health co-operatives, health laws, health administration, sanitary engineering, forensic medicine and psychiatry (128 hours of theoretical instruction and forty hours of practical training). The lecturers were university professors and specialists from the Department of Health and from the Institute of Public Health.

RESEARCH WORK.

As the Sofia Institute of Hygiene has only quite lately been established, the scientific research carried out by its staff covers a period too brief to allow of the publication of results. Mention should, however, be made of the work of Dr. KOJUHAROFF, the Director of the Institute, on "Methods for the Bacteriological Analysis of Drinking-water" (1936). As for malaria, its epidemiology has been studied by MARKOFF, who recently published a paper on "Malaria in Bulgaria during the Last Fifteen Years". This contains interesting details of the efforts made and the results secured in that country, together with a tribute to the valuable collaboration of COLLINS, of the Rockefeller Foundation, in this field.

11. THE WARSAW STATE INSTITUTE OF HYGIENE.

INTRODUCTION.

The health administration of Poland was for several years controlled by a Ministry of Health, which was later abolished. At present, the Ministry of Social Assistance and the Ministries of the Interior and Education are responsible for the health services.

The Ministry of Social Assistance is divided into the Department of Public Health and that of Labour and Social Welfare. The Ministry of the Interior deals with the specifically hygienic aspects of matters of sanitary engineering. The Ministry of Education has charge of medical education, of school hygiene, and, in part, of physical education, which is now concentrated in the newly established Central Institute for Physical Education.¹

The health services of the railways are under the Ministry of Communications.

For administrative purposes, Poland is divided into seventeen provinces (województwa). Warsaw, the capital, has the status of a province. The provincial administrations maintain departments corresponding to the Ministries of the Central Government. A province comprises a population of about 2 millions. The provinces are divided into 241 rural and twenty-one urban districts, each with a population of from 25,000 to 125,000. Districts are subdivided into communes. For the purpose of the health services, the communes have been combined into 735 health areas. In the rural parts of Poland, 235 special health centres have been organised.²

¹ The Central Institute for Physical Education, situated in grounds covering seventy-three hectares, was opened in 1930 in a large building, comprising lecture rooms, laboratories for practical work, medical examination rooms, physical training equipment, a dormitory, a dining-room and a library. The Institute gives training to physical education instructors and teachers, mainly for schools and the army, examines and improves methods of physical training and undertakes research work. For these purposes, the Institute maintains special departments of anatomy, anthropology, applied physiology, physics and chemistry, psychotechnics and a cardiographical laboratory. The course lasts two years for both men and women students. It comprises 3,070 hours of actual work. Hygiene is taught in the third and fourth terms, ninety-four hours being devoted to this subject. The Director of the State Institute of Hygiene is on the teaching staff.

² The centres are housed mostly in new buildings, and serve as model hygiene and preventive medicine institutions. Five hundred doctors, 402 nurses and ninety sanitary inspectors work in the centres.

The Department of Health in the Ministry of Social Assistance comprises five sections, concerned with : (1) legal questions, drafts of laws, regulations ; (2) the supervision of preventive health work ; (3) the supervision of the institutions which provide for medical treatment ; (4) the supervision of pharmacies, control of drugs and pharmaceutical preparations ; and (5) the technical services of the health administration.

The Minister is advised by a Central Council of Health ; the Institute of Hygiene, with its regional branches, is a technical organ of the Ministry.

There are 12,600 physicians in Poland, of whom twenty are employed in the Central Health Administration of the Ministry and 264 in the Provincial and District Health Services as medical officers of health. The physicians of the districts and the communal health officers are appointed by the local authorities.

Medical officers of health in the State service receive salaries varying between 300 and 700 zloty a month, and are considered as full-time officials ; in reality, however, the majority of them have subsidiary employment.

About 15% of the total population is insured against sickness, accidents and invalidity ; 3,600 physicians are employed by the Social Insurance system, with fixed salaries ranging from 350 to 750 zloty a month. Part-time physicians are paid on an hourly basis—*i.e.*, 85-150 zloty a month for one hour of work a day.¹

More than 2,000 physicians live in Warsaw. In rural areas, the proportion is one physician to 6,000-7,000 inhabitants.²

¹ Special courses in social medicine have recently been organised by the Ministry of Social Welfare and the Social Insurance Board in collaboration with the Faculties of Medicine. The courses were held at Warsaw, Krakow, Lwow, Poznan and Wilno. The first course was organised in Warsaw, starting on January 18th, 1937, with an attendance of fifty students, the majority of whom were physicians belonging to social insurance institutions. The course consisted of lectures, visits to health institutions and factories and a seminar in the final stages of the course. The lectures were given in the evening three times weekly. The following subjects were treated :

- Social insurance—forty-five lectures ;
- Industrial hygiene—nine lectures ;
- Social hygiene and public health—nine lectures ;
- Organisation of medical care—seven lectures ;
- Legal responsibilities of physician—seven lectures.

² A detailed description of the organisation of the Health Administration is given in the publication : " L'Hygiène publique en Pologne ", edited in 1933 on behalf of the Health Organisation of the League of Nations.

By the Decree of January 16th, 1925, medical officers of the State Health Service must have completed one year of special training—*i.e.*, six months in the health administration and a course to six months of public health training given by the School of Hygiene. On the completion of this training, they are required to pass an examination in the following subjects :

- (1) General knowledge of constitutional and health laws ;
- (2) State and local administration ;
- (3) General knowledge in the practice of administration ;
- (4) Health administration ;
- (5) Hygiene, epidemiology and vital statistics ;
- (6) Forensic medicine ;
- (7) Forensic psychiatry.

These requirements are not strictly observed, and the Government may appoint medical officers who have not had the above training.

The economic crisis has made its effects felt on the State finances, and, since 1930/31, budget receipts have declined steadily. There has been drastic retrenchment mainly by cuts in salaries and pensions and the reduction of expenditure on new constructions and material. The total expenditure fell from 2,992.7 million zloty in 1929/30 to 2,168.4 million zloty in 1935/36 (estimates). Correspondingly, the expenditure for health was reduced from 14.3 to 11.4 million zloty, the proportion which it bears to total expenditure being brought down from 2.1% to 1.87%.¹ Local administrations, especially in the provinces and municipalities, spend a considerable amount on health services,² but the economic crisis has affected them also.

POSITION OF THE INSTITUTE OF HYGIENE IN THE HEALTH ADMINISTRATION : RECENT DEVELOPMENTS.

The State Institute of Hygiene acts as a technical organ of the Department of Public Health of the Ministry of Social Assistance,

¹ Economic Intelligence Service ; League of Nations.

² Autonomous urban administrations with a population of 8.6 millions have spent 36.4 million zloty for health work, and the rural administrations with a population of 23.2 millions, 16.4 million zloty. The bulk of this money was spent on hospital maintenance (accounts for 1932/33). The estimates for 1936/37 show only slight differences.

and provides Public Health training for State employed health officials. It is entrusted, by order of the Ministry of Social Welfare, with the supervision of the municipal bacteriological laboratories as well as the control of foodstuffs.

In 1930, Dr. Gustav SZULC was appointed Director of the Institute of Hygiene.

In 1933, a special service for the control of hormone preparations and for the biological examination of pharmaceutical products was organised and a laboratory for the analysis of mineral waters was established in the department of chemistry.

In 1935, four State institutes for the control of foodstuffs, which were formerly independent, became parts of the Institute of Hygiene.

In 1936, a Department of Hydrology was established in the Institute, to control water supplies throughout Poland. The branch institutes of Poznan, Lwow, Wilno, Krakow, Lodz, Lublin and Gdynia have already similar services.

The Ministry of Social Assistance has appointed seven specialists in epidemiology who co-operate with the State Institute of Hygiene and branch institutes and with the provincial health authorities in the control of epidemic diseases.

In 1935, an Institute of Mental Hygiene was established with the aid of the Rockefeller Foundation, for the purpose of centralising and directing research, teaching and education in the matter of mental hygiene, as well as for the organisation and management of a model clinic and a dispensary for neuropathic children.

TEACHING STAFF OF THE INSTITUTE.

Owing to budgetary difficulties in 1931, a reduction in the teaching staff of the State Institute of Hygiene became necessary. This reduction was not very great, however, and, taking all the departments of the Institute of Hygiene together and excepting persons working on a daily basis, the present staff comprises 312 persons. Of this number, 176 are specialists and senior officials, and 136 auxiliary employees, clerks, laboratory assistants. The senior staff consists of thirty-nine doctors, forty-two chemists, five pharmacists, two veterinary surgeons, fifteen bacteriologists and seventy-six officials.

The staff of the Institute is not on a full-time basis. The chiefs of departments are paid 800-1,000 zloty per month ; the others, an average of 300-400 zloty a month.

BUDGET OF THE INSTITUTE.

The expenditure of the State Institute of Hygiene is met out of Treasury Funds. The Department for the Production of Sera and Vaccines is self-supporting, meeting its expenses from the sale of its biological products. During the years 1932-1934, the State Institute of Hygiene received a subsidy from the Rockefeller Foundation which enabled it to extend its activities in spite of budgetary difficulties arising out of the economic crisis.

Amounts spent by the Institute of Hygiene.
(In zloty.)

Year	Expenditure met from Treasury Funds			Expenditure of the self-supporting Department for the Production of Sera and Vaccines		
	Personnel	Material	Total	Personnel	Material	Total
1931/32.....	506,864	264,392	771,256	351,862	709,609	1,061,471
1932/33.....	402,482	241,840	644,322	341,314	717,226	1,058,540
1933/34.....	675,201	343,982	1,019,183	365,861	544,015	909,876
1934/35.....	595,142	326,160	921,302	359,329	715,965	1,075,294
1935/36.....	580,058	309,058	889,462	356,898	683,872	1,040,770
1936/37 ¹	618,710	322,630	941,340	417,490	758,610	1,176,100
1937/38 ²	741,320	400,400	1,141,720	420,700	898,900	1,319,600 ²

¹ Estimated expenditure.

² In addition to the Department for the Production of Sera and Vaccines, there are also the following self-supporting activities :

1. *The Analytical Laboratory of the Institute, whose expenditure and estimates are as follows :* (In zloty.)

Year	Personnel	Material	Total
1933/34	77,067	38,099	115,166
1934/35	99,354	61,887	161,241
1935/36	137,126	78,672	215,798
1936/37*	155,500	59,300	214,800
1937/38*	287,400	59,700	347,100

2. *The Institute of Mental Hygiene :*

1936/37*	55,200	25,300	80,500
1937/38*	55,000	30,900	85,900

3. *Living-quarters for the Students :*

1935/36	21,489	17,738	39,227
1936/37*	17,600	24,400	42,000
1937/38*	19,500	28,000	47,500

* Estimated expenditure.

ORGANISATION AND ACTIVITIES OF THE INSTITUTE.

The Institute is divided into six Departments :

- (1) Bacteriology and Experimental Medicine (Director : Professor Dr. L. HIRSZFELD) ;
- (2) Chemistry (Director : Dr. M. DOMINIKIEWICZ) ;
- (3) Sera and Vaccines (Director : Dr. J. CELAREK) ;
- (4) Public Health Instruction (School of Hygiene) (Director : Dr. W. CHODZKO) ;
- (5) Control of Food (Director : Dr. S. KRAUZE) ;
- (6) Hydrology (Director : Eng. M. A. SZNIOBIS).

The Institute has nine branches—in Lublin, Lwow, Gdynia, Lodz, Krakow, Poznan, Torun, Vilna and Katowice.

The work of the Department of Bacteriology and Experimental Medicine has greatly expanded in the last few years. In 1925, the Institute of Hygiene examined 44,664 specimens and in 1935, 394,355. Of these, examinations for typhoid fever account for 30.3% ; those for typhus 6.3%, and those for diphtheria 3%. The serodiagnosis of syphilis also occupies an important place. The control of sera is conducted by the same department, and, in 1935, 1,614 preparations were examined. It also carried out vaccinations against diphtheria : 170,474 children under 15 have been vaccinated since this measure was first applied. The Department endeavours to promote co-operation with the district officers for the control of epidemic diseases. The Wassermann Laboratory of this Department prepared 70 litres of antigen in 1935. It is also responsible for the supervision of the disinfection and disinfestation services.

The Chemical Department examines the pharmaceutical preparations. In all, 1,887 specimens were examined in 1935.

The Department for the Production of Sera and Vaccines and Biological Products increased its production in 1935 ; it prepared, as regards sera :

- 309 million units of diphtheria antitoxin ;
- 193 million units of tetanus antitoxin ;
- 257 litres of antimeningococcus ;
- 471 litres of antistreptococcus ;

and, as regards vaccines :

650,129 doses of typhoid fever vaccine ;
 400 litres of diphtheria anatoxin ;
 538 litres of diphtheria and scarlet-fever anatoxin ;
 1,641,000 doses of vaccine lymph.

The insulin requirements of Poland are met in full by the Institute ; in 1935, 17,039,400 units were produced for the requirements of the country and for sale abroad (in 1934 : 8,846,800 units).

DEPARTMENT OF INSTRUCTION IN HYGIENE : SCHOOL OF HYGIENE.

Though it began work in 1924, the School of Hygiene was not officially inaugurated until April 1926. The staff of the School numbers thirty-seven, including an auxiliary personnel of eleven. Instruction is provided for :

(1) Candidates for posts in the Public Health Services : The duration of the course is six months, from October 1st to March 31st.

(2) Candidates for the post of sanitary inspector : The duration of the course is four months, from the middle of January to the middle of May.

In addition, the School organises special courses for doctors, teachers, labour inspectors, engineers, social workers, physical training instructors or supervisors.

The number of students taking the six-month public health course of training varies from twenty to thirty.¹ Those already occupying posts are seconded with pay during the period of training ; others receive grants from the Ministry of Social Assistance (250 zloty per month) ; and some study at their own expense. With few exceptions, all those who have followed the course of training have been given posts either in the Government or the Municipal Health Services.

The Institute pays over to the School 42,000 zloty annually for the organisation of courses. Lecturers (including members of the

¹ Each year there is an average of seventy candidates for the post-graduate course in public health, but not more than thirty are admitted.

staff of the Institute) are paid 10 zloty per hour of theoretical and 8 zloty per hour of practical teaching.

A six-month course of training is required of all candidates for posts in the State Health Service. This stipulation does not, as a rule, extend to municipal doctors, though there are some municipalities which either require from candidates the certificate in question or send their doctors to follow the course. A certificate is granted at the end of the course, but no scientific degree.

Organisation of the School of Hygiene.

The School of Hygiene has the following sections :

(1) *Statistics, Epidemiology and Social Hygiene* : Director, Dr. KACPRZAK.

This section collects and collates the statistical material on infectious diseases (fifty cities report directly to the section), and demographical material in general ; it also carries out studies concerning population problems in various countries. In the field of rural hygiene, it works out methods of health education and studies the possibilities of improving rural housing.

(2) *Industrial Hygiene* : Director, Dr. B. NOWAKOWSKI.

This well equipped section undertakes special studies in regard to poisoning in industry, ventilation, heating, lighting and other subjects relating to industrial hygiene. It proposes to the Ministry and other authorities schemes for the organisation of industrial hygiene services and draft regulations for the protection of the workers' health in industrial enterprises.

(3) *Biochemistry and Nutritional* : Director, Dr. G. SZULC (who is also the Director of the Institute of Hygiene).

This section examines vitamin preparations, biological products, and tests the value of different foods, nutritional questions being studied in relation to local needs. Four special laboratories are attached to the section : (a) Biochemistry, (b) Histology, (c) Biology and (d) Pharmacology.

(4) *Institute of Mental Hygiene* : Director, Dr. K. DABROWSKI.

(5) *Museum*, (6) *Library* and (7) *Living-quarters for students*.

The museum provides an excellent opportunity for studying practical public health problems in general and those of Poland in particular. The material is very well presented and special attention is paid to rural hygiene. The Library contains 2,750 volumes, and 7,773 publications, and receives 235 periodicals. In the living-quarters, the students can have full board and lodging for from 3 to 3.50 zloty per day.



Figure 14.—SCHOOL OF HYGIENE : INSTITUTE OF MENTAL HYGIENE.



Figure 15.—“AMELIA” HEALTH CENTRE AT WARSAW.

In 1936, the Sanitary Engineering Section of the School became the Department of Hydrology of the Institute of Hygiene.

From 1924 to the end of 1936, 134 courses were organised, with 6,851 students, of whom 1,970 were doctors.¹

¹ These courses consisted of :

A. *Basic Courses :*

1. Six-month course for district health officers. Eleven such courses have already been given to 260 students.
2. Four-month course for sanitary inspectors (nine courses to 325 students).

B. *Permanent Courses :*

1. Three-week course for medical directors of Centres (eight courses to 219 students).
2. One-week courses for trachoma doctors (ten courses to 522 students).
3. Three-week courses for elementary school teachers (fifteen courses to 1,357 students).
4. One-week courses for social workers for the campaign against alcoholism (ten courses to 2,004 students).

C. *Special Courses :*

1. Supplementary courses for district physicians already in the service.
2. For school physicians.
3. For doctors supervising athletic training.
4. For doctors employed by the Health Insurance system.
5. Preventive medicine for medical practitioners.
6. Courses of specialised medicine for general practitioners.
7. Tropical medicine and hygiene for doctors.
8. Eugenics for doctors.
9. Health education for doctors.
10. Schick test technique for medical practitioners.
11. Bacteriology and hygiene for military doctors.
12. Special instruction for doctors engaged in the campaign against typhus.
13. Course for medical students in charge of the supervision of sanitary conditions in vacation camps.
14. For district engineers.
15. For labour inspectors.
16. For secondary-school teachers.
17. For teachers in agricultural schools.
18. For physical education teachers.
19. Statistics.
20. Nutritional chemistry.
21. Health legislation for judges and lawyers.
22. For anti-tuberculosis visiting nurses.
23. For nurses of the rural health service.
24. For nurses in children's nurseries.
25. For nurses of the mental hygiene service.
26. Advanced courses for midwives.
27. Courses for social welfare workers.
28. Courses for women social welfare workers.
29. For welfare nurses of sports associations for the working classes.

In all, 2,839 persons have attended these courses.

Curriculum of the Course for Public Health Officers.

The course is limited to twenty-four regular students ; two or three special students may be admitted above that number in all the branches of the course except that of forensic medicine. All students must be holders of medical degrees and must have a licence to practise medicine.

The course begins on October 1st and ends on March 31st.

Subject	Number of hours		
	Lectures	Laboratory or field work	Total
<i>Section I :</i>			
Bacteriology and immunology (including medical zoology)	49	28	77
<i>viz :</i>			
Bacteriology, immunology	30	24	54
Smallpox vaccination	3	—	3
Anti-rabic vaccination	2	—	2
Serum and vaccine production	2	—	2
Medical zoology	10	4	14
Parasitic fungi	2	—	2
<i>Section II :</i>			
Epidemiology and vital statistics	56	76	132
<i>viz :</i>			
Epidemiology and sanitary statistics.	30	34	64
Methods of statistical investigation and registration	6	—	6
Disinfection	8	—	8
Training in the acute contagious diseases hospital	12	42	54

Subject	Number of hours		
	Lectures	Laboratory or field work	Total
<i>Section III :</i>			
Sanitary engineering	45	14	59
viz :			
Water-supply	19	8	27
Sewage disposal	12	6	18
City planning	4	—	4
Garbage disposal and city cleaning ..	4	—	4
Hygiene of dwellings and institutions.	6	—	6
<i>Section IV :</i>			
Industrial hygiene and physiology	30	24	54
viz :			
Physiology of work	4	2	6
Ventilation and heating	6	1	7
Light	4	1	5
Occupational diseases	8	—	8
Industrial safety and protection of labour	8	—	8
Practical training in factory inspection	—	20	20

Sections I-IV are covered in three months—*i.e.*, October 1st to December 22nd. One day weekly is devoted to field work in epidemiology for case investigations under the direction of city health officers : the cases are discussed at the seminar held in the afternoon of the same day.

Subject	Number of hours		
	Lectures	Laboratory or field work	Total
<i>Section V :</i>			
Physiology and hygiene of nutrition...	18	18	36
viz :			
Nutrition, its physiology and chemistry	10	18	28
Control of foodstuffs	6	—	6
Organisation of drug control	2	—	2

Practical work on the control of foodstuffs is done once a week during January.

Subject	Number of hours		
	Lectures	Laboratory or field work	Total
<i>Section VI :</i>			
Social hygiene (public health) and health administration	86	172	258
1. Tuberculosis (social pathology and prevention)	6	—	6
2. Venereal diseases (including occupational skin diseases)	6	—	6
3. Ophthalmology	4	—	4
4. Cancer	2	—	2
5. Mental hygiene	4	—	4
6. Alcoholism	2	—	2
7. Maternal and infant welfare	8	—	8
8. Eugenics	2	—	2
9. Public health nursing	2	—	2
10. School hygiene and health education	6	—	6
Basic State administrative laws ..	16	—	16
Health legislation	12	—	12
Social insurances	4	—	4
Public health administration	8	—	8
Current problems of public health administration	4	—	4
Field training in health work	—	108	—
Field training in social hygiene work	—	40	—
Seminar in health administration.	—	24	—
<i>Section VII :</i>			
Forensic medicine	35	104	139
Forensic medicine	23	92	115
Psychiatry	12	12	24
<i>Section VIII :</i>			
Gas defence (toxicology of poison gases, first aid in gas poisoning)	16	—	16
Total number of hours	335	436	771

Curriculum of the Course for Sanitary Inspectors.

Subject	Number of hours		
	Lectures, demonstra- tions	Practical training, exercises, field work	Total
<i>Section I.—Generalities :</i>			
1. Physics	30	—	30
2. Chemistry	20	20	40
3. Anatomy and physiology	10	2	12
4. General and personal hygiene	36	—	36
5. Organisation of government and communal authorities	14	—	14
6. First aid in urgent cases	6	—	6
7. Anti-gas aid	9	—	9
8. Post-mortems	2	2	4
Total	127	24	151
<i>Section II.—Control of Diseases :</i>			
1. Statistics and information about Poland	10	6	16
2. Bacteriology	12	—	12
3. Acute and chronic contagious disea- ses	28	—	28
4. Health legislation	6	—	6
5. Disinfection, disinsectisation, derati- sation	20	20	40
Total	76	26	102
<i>Section III.—Sanitary Engineering :</i>			
1. Drawing and reading of plans	—	16	16
2. Municipal and rural sanitation, water- supply and sewage disposal	36	20	56
3. Local water-supply and water main systems	4	2	6
4. City cleaning and garbage disposal ..	4	2	6
5. Building	6	2	8
6. Housing and hygiene of public utility buildings	10	4	14
7. Heating and ventilation	4	—	4
Total	64	46	110

Subject	Number of hours		
	Lectures, demonstrations	Practical training, exercises, field work	Total
<i>Section IV.—Hygiene of Food :</i>			
1. Food control, inspection of sanitary production, transport and handling of food. Visiting manufactory plants, warehouses and retail shops	42	42	84
Total	42	42	84
<i>Section V.—Field Work :</i>			
1. Organisation and activity of Public Health Service	4	6	10
2. Registration and record-keeping in Sanitary Service Office	4	2	6
3. Exercises in public health survey and sanitation planning and preparing of reports	—	30	30
4. Field work in town and village	2	24	26
5. Ethics in the sanitary inspector's work	2	—	2
Total	12	62	74
Summary of hours	321	200	521

PRACTICAL TRAINING IN PUBLIC HEALTH.

The Health Centre at Mokotow (Director : Dr. E. S. STYPULKOWSKI) was established for this purpose in 1925. The initial capital outlay was met by the Rockefeller Foundation, and, for the operating expenses, the Foundation assisted during a period of five years, with an annual grant of \$10,500. At present, the expenditure is covered by the contribution of the Warsaw municipality, Ministry of Social Assistance and the Social Insurance system. The Centre became a model centre for all other health centres in the country, and at present is one of nine centres of the Warsaw Municipal Health Service.

The Mokotow Centre is composed of three departments : (1) office of the medical health officers of the sixteenth, twentieth and twenty-first police districts of the city ; (2) dispensaries, and (3) public assistance.

For successful social work, it was indispensable to co-operate with other services. For this purpose, a commission was organised representing the State and municipal health services, the social insurance system and the School of Nurses. This commission administers and directs the activities of the Centre and has its own budget.

The staff consists of the Director of the Centre, a Deputy Director, two sanitary inspectors, sixteen part-time physician-specialists, one head nurse, ten visiting nurses, three school nurses, two instructors for the practical training of nursing students, four laboratory technicians, one clerk, seven servants, three clerks to deal with patients not admitted to the sanatorium. The public assistance section comprises one physician for the treatment of the poor, one secretary, one nurse, three social service workers and one servant.

The activities of the Centre cover a wide range of subjects. Complete records have been made of 10,000 families and these constitute very valuable material for the study of the social-economic and health conditions in the area (which has at present a population of about 100,000). Some 25% of the population avails itself of the facilities of the Centre. Important field surveys, in which the students always participate, have been carried out.

POST-GRADUATE COURSES FOR DISTRICT MEDICAL OFFICERS AT ANNUAL CONFERENCES.

During the last ten years, annual meetings of district physicians have been held in Poland. In each province, in accordance with arrangements made by the Ministry of Social Assistance, a three-day meeting is convened each year under the direction of the Medical Officer of Health of the province. This meeting is attended by the physicians of districts and communes and by representatives of administrations whose work has a bearing on that of the Health Service. During the last few years, the Institute of Hygiene has participated in these meetings by preparing reports on current

problems. Usually two or three members of the Institute's staff (the chief of the local Institute of Hygiene and representatives of the Central Institute of Hygiene), as well as the Health Service Inspector of the Ministry of Social Welfare (after approval by the head of the Health Services), prepare the programme of the meeting in advance and draw up a list of the subjects to be discussed. Most of these subjects concern the most widely prevalent epidemic diseases in the province.

Reports, followed by a discussion, are presented on the following subjects : nutrition, water, refuse removal, tuberculosis control, rabies, goitre, etc., and outside experts are called in for special subjects. The discussions are followed by demonstrations and visits to installations of special interest from a health point of view. The meeting is held each year in different localities of the province. A meeting of provincial Directors of Public Health is also held annually in Warsaw, for which the State Institute of Hygiene prepares reports on current problems, which serve as a basis for discussion.

This system has given excellent results and ensures effective collaboration between the district medical officers and the Institute and School of Hygiene.

TRAINING OF THE AUXILIARY PUBLIC HEALTH SERVICE PERSONNEL.

The School of Hygiene gives the theoretical and practical training for sanitary inspectors, and higher grade training for nurses, midwives, disinfectors, etc.

As provided by the Law on Nursing of February 21st, 1935,¹ the nursing schools are separate institutions under the supervision of the Ministry of Social Assistance. There are at present five nursing schools—one at Poznan, one at Krakow and three at Warsaw.

The Warsaw School of Nursing (Director : Miss S. SZLENKIER) was established in October 1921, with the help of the State and City

¹ The law provides training for a minimum of two and a-half years in premises suitable for teaching purposes. Living-quarters must be attached to each school. The Director must be a qualified nurse and must serve on a whole-time basis. The council of the school is composed of physicians and nurses. The conditions for admission to the course of training are higher middle school education, age from 18 to 30 and good health.

Health Departments, the University of Warsaw and the American and Polish Red Cross. In 1929, a new building was constructed thanks to contributions from the State and the Rockefeller Foundation. The number of students averages 150. There are twenty-two nurses who act as full-time teachers and thirty-one part-time teachers (physicians, social workers, etc.). Theoretical instruction is spread over three periods (giving a total of 845 hours during eight months) and practical training over a period of twenty months. Tuition fees have been reduced, the rates now ranging from 80 to 120 zloty a month. The total expenditure of the school in 1935 was 238,000 zloty. The Ministry of Social Assistance contributed 60,000 zloty in 1935, the Municipality of Warsaw 15,000 zloty and the social insurance system 3,000 zloty.

In all, 406 students have graduated from the school ; 50% of them are now in the public health services, 25% in hospitals, 12.5% in nursing schools, 12.5% not employed.

The number of registered certificated nurses in Poland is 1,200. Their salaries vary from 250 to 450 zloty per month.

RESEARCH WORK.

Although the Warsaw Institute and School of Hygiene have been engaged in research for many years and have produced important works, we shall here mention only the researches carried out and published between 1934 and 1936.

In the field of serology, mention should be made of the works of Z. AMZELOWNA on " The Serological Differentiation of the Salmonella Group " and on " The Bordet-Wassermann Test in Malaria " (1936), and of BURON on " The Thermic Amplitude of Isoagglutinative Sera ". Professor L. HIRSZFELD, head of the Bacteriology and Experimental Medicine Section, has published a paper on " Sero-diagnosis in Blood-transfusion " (1935), in which he describes the present state of our knowledge regarding the non-specificity of the Bordet-Wassermann test ; he points out that whereas formerly the test was usually carried out on patients with suspicious clinical symptoms, it is now frequently employed on healthy subjects

(donors of blood for transfusions), and it has been observed that certain individuals who have no sign of syphilis nevertheless have a positive Wassermann reaction.

The study of blood-groups and constitutional serology on the lines indicated by HIRSZFELD for this branch of biology has been pursued for years at the Warsaw Institute. We would mention the following works : HIRSZFELD on " The Application of Blood-groups to Criminology ", and on " The Hereditary Determinism of the Mother's Blood-group " (1936) ; HIRSZFELD and LEWINSKI on " The Determination of Blood-groups from Bloodstains in Criminology " (1936).

Infectious diseases in general, and some of them in particular, have been studied by the technical staff of the Institute. We will merely mention the works of AMZEL, EPSTEIN and FEJGIN on " The Presence of the Bacteriophage during the Dysentery Epidemic at Krzemienec (Poland) " ; of MORZYCKI and ZABLOCKI on " The Antigen Properties of *B. typhosus* " and on " Dysentery Anatoxin obtained by Means of Repeated Congelation " (1936) ; of J. SZPEROWNA on " The Isolation of *B. typhosus* and *B. paratyphosus* from Water " (1935), and on " The Action of Sodium Tetrathionate on the Development of *B. typhosus* and *paratyphosus* " (1936) ; and of ZABLOCKI and MORZYCKI on " Typhoid Endotoxin obtained by Means of Repeated Congelation, and its Chemical Properties ". The numerous works on *diphtheria* are particularly noteworthy. " The Virulence of the Strains of *B. diphtheriæ* of the *gravis* and *mitis* Types " (GOLIBORSKA, 1936) ; " The Immunisation of Infants against Diphtheria " (JAKOBRIEWICZ) and " The Influence of Age and Constitutional Factors on the Immunisation of Children against Diphtheria " (JAKOBRIEWICZ and ZAJDEL, 1936) ; " Local and General Reactions after the Injection of Diphtheria Anatoxin precipitated by Alum " (1936) ; " The Course of Diphtheria in Children vaccinated with Diphtheria Anatoxin " (MAZUREK and SZENAJCH, 1936) ; and " Bacteriæmia in Diphtheria " (SEYDEL, 1936), have been studied by Professor HIRSZFELD's collaborators, who also investigated other questions connected with diphtheria and methods of vaccination against diphtheria. We may refer to a number of studies by Professor HIRSZFELD on " The Laws of the Propagation of Diphtheria and Other Diseases of Children " (1936).

Dr. L. ANIGSTEIN, head of the Department of Parasitology, has published a report on a medical enquiry in Liberia entrusted to him by the Liberian Government.

Typhus fever, which still constitutes an important problem in Poland, has been studied from various angles. ANIGSTEIN dealt with "Experiments in Vaccination against Typhus Fever with Live Virus" (1936); HIRSZFELD and his collaborators with "Specific and Non-specific Reactions in Typhus Fever, Cancer and Tuberculosis" (1935).

Various problems relating to cancer, constitution and heredity have been tackled. "The Factors promoting the Growth of Neoplasms" and "FREUND-KAMINER's Theory relating to the Diagnosis of Cancer" have been studied by DMOCHOWSKI (1936); "The Serological Properties of Fibrin obtained from Normal and Cancerous Subjects" by POLLAK (1936); and questions of pathological heredity by HIRSZFELD and H. HIRSZFELDOWA.

SZCZYGIEL studied the effects of infra-red rays on the growth of rats fed on a diet deficient in vitamin A. Indeed, the Warsaw Institute of Hygiene has a long tradition of research work on vitamins; we need only refer to the work of FUNK (1913-1918) a former head of department in the Institute.

Dr. SPORZYNSKI, of the Anti-Smallpox Vaccination Department of the Institute, published a note on the work done by him in regard to the culture of the vaccinal virus on the allantochoridian membrane of the chicken embryo.

The Director of the School, Dr. SZULC, who has devoted particular attention to physical training, has made a special study of the metabolism of growth in connection with what he describes as "the disaster of endemic goitre in Polish territory". In a report specially devoted to the educative work of army doctors, he examines the question of eugenics and the influence of the physical education of the young on racial characteristics and national demography.

We must also mention the report by the Director of the Mokotow Health Centre, Dr. S. STYPULKOWSKI, on the nine years' work of the Centre. This document does not merely consist of statistical and demographic data, but takes stock, in the light of many years of experience, of the results that can be achieved by such an institution when it is directly connected with a school of hygiene. For the first five years, the Mokotow Centre received financial assistance

from the Rockefeller Foundation. The Warsaw municipality has since organised nine other similar centres in the city.

Reference should also be made to the scientific publications and contributions of the Central Institute of Physical Training, although this is an autonomous institution which is connected only indirectly with the Warsaw Institute and School of Hygiene so far as concerns the teaching of methods of physical training. Dr. SZULC, Director of the School of Hygiene, is also a professor at the Institute of Physical Training. The work of the laboratories dealing with anatomy and the mechanism of movement, anthropology and physiology at this admirable Institute, which has been in existence since 1930, has contributed substantially to the study of problems connected with muscular effort, fatigue and human biotypology as applied to sport.

12. THE YUGOSLAV INSTITUTES OF HYGIENE AND THE SCHOOL OF PUBLIC HEALTH.

INTRODUCTION.

In the course of the past fifteen years, the public health service in Yugoslavia has been completely reorganised. There is at present a network of public health institutions of various kinds all over the country. By the end of 1935, there were ten institutes of hygiene, a school of public health, forty-eight district health centres, 120 rural health centres and many special centres—making up a total of 290. The staff of the Institutes of Hygiene and of the School of Public Health, the directors and the heads of the departments of the health centres are employed on a full-time basis.

The central authority in public health matters is the Ministry of Social Welfare and Public Health. It comprises three departments—general administration, social welfare and public health. The country is divided into nine provinces (banovinas) with local administrations, including, in every case, a department of social welfare and public health. In the districts and in municipalities, the medical officers of health are not employed on a full-time basis. The districts are divided for health purposes into special areas and, in many of them, special communal doctors have been appointed.

The Central Institute of Hygiene at Belgrade and the School of Public Health at Zagreb, both technical departments of the Ministry for applied hygiene, research work and field activities are directly under the orders of the Ministry of Social Welfare and Public Health. In each province, there is an Institute of Hygiene with departments of : (a) bacteriology and epidemiology ; (b) chemistry ; (c) sanitary engineering and (d) social medicine. The Institute of Hygiene directs the public health work in the districts and communes, undertakes field activities and carries out studies. The secondary health centres comprise laboratories, policlinics and departments dealing with maternal and child welfare, school hygiene, school baths, the venereal disease dispensaries, tuberculosis and health education. In the rural areas, primary health centres have been

established with policlinics, health exhibitions, and public baths. These health institutions undertake curative as well as preventive work. In matters of hygiene and social medicine, the district health officers and communal physicians act under the direction of the provincial institute of hygiene and the district health centres.

While this gradual development of the public health services in Yugoslavia was taking place, health co-operative societies were organised in two provinces in particular. There are at present over a hundred such societies with a total membership of about 50,000. Their programme is to arouse public interest in and secure public support for health work in rural areas. These societies established health centres similar to the State centres, which provide with consultations and treatment. This co-operative movement is supported by special grants from the State budget. The Institutes of Hygiene collaborate closely with the societies, supplying them with sera and vaccines, and the material for health education, and helping them in sanitary engineering work.

Since 1931/32, the budgets of almost all the Ministries have been reduced. The Ministry of Social Welfare was united with the Ministry of Health in 1930/31. In 1933/34, the expenditure of the new Ministry amounted only to 65.9% of the expenditure of both Ministries in 1930/31. The budgets of the public health institutions organised during the past fifteen years suffered severely, being reduced in some cases to 50% of the 1929/30 figure. The social and health services received 2.5% of the total State budget in 1928/29, and 1.83% in 1936/37.

At the end of 1935, there were 5,130 physicians on the register. The number engaged solely in private practice is comparatively small.¹ According to the Chamber of Physicians (at Zagreb), of 1,165 physicians registered with this chamber, 708 are connected more or less closely with a public health institution.

Only 3.9% (family members not included) of the Yugoslav population is insured against sickness, accidents and invalidity. In 1934, the expenditure for sickness insurance amounted to 296

¹ Thirty-three are employed by the provincial administrations, 401 as district health officers, 313 by the Institute of Hygiene and health centres, 364 by the State hospitals, 1,197 by the local authorities (communes and health districts).

million dinars ; almost half of which was spent on maternity, treatment and health institutions and salaries of physicians and auxiliary personnel in the health services. The social insurance maintains 130 general polyclinics, fourteen children's polyclinics, twelve baths and physical therapy services, twenty-six sanatoria and hospitals with 1,305 beds ; it employs 1,686 physicians, 266 of them as permanent staff.

The salaries of medical officers range from 1,116 to 4,720 dinars a month. The staff of the Institutes of Hygiene, of the Public Health School and the medical officers of the district health centres give full-time service and receive on that account an additional salary of from 900-1,400 dinars a month. Social insurance physicians are paid 2,000 to 5,000 dinars a month.

THE ZAGREB SCHOOL OF PUBLIC HEALTH

The School was opened in 1927, and is now the central national institution in the matter of health education. Until 1930, the School was a part of the Institute of Hygiene, which was divided into several departments—namely : administration, bacteriology and epidemiology, preparation of biological products, chemistry, anti-rabic vaccination, production of vaccine lymph, infectious diseases hospital, parasitology, sanitary engineering and social medicine. In 1930, the School was separated by special decree from the Institute of Hygiene and divided into departments for field surveys, health education, sanitary engineering and the preparation of biological products. In the same year, the School of Nursing was placed under the administrative control of the School. The budget of the School, after approval by the Ministry, was embodied in the State budget and the School was permitted to retain the income of its different departments for its own purposes. A sum was appropriated out of the State budget to meet the deficit. This was intended to make the School more independent and to facilitate its work and development. For this reason also, the department for the preparation of biological products became a part of the School.

The School is, moreover, in close touch with the provincial Institute of Hygiene, to which a tuberculosis dispensary and school

policlinics for middle school students are attached. The Institute of Hygiene at Zagreb has three departments : bacteriology and epidemiology (Dr. ČERNOZUBOV, assisted by Dr. FILIPOVIĆ) ; chemistry (Dr. ROGINA, chemist) ; and the hospital for infectious diseases (Dr. PETRIĆ and Dr. MIHALJEVIĆ). The departments of the Institute are used for practical training and other duties devolving upon the School of Public Health, and the staff of the Institute of Hygiene assists in the courses organised by the School. The library of the School contains 8,500 volumes and receives seventy-two periodicals regularly, of which fifty-three are foreign.

Duties and Work of the Various Departments of the School.

The Field Survey Department (Dr. RASUHIN and Dr. MIKIĆ) is concerned with studies on social-economic conditions, vital statistics, locally prevalent diseases, housing, nutrition and other factors in the national life affecting public health.

The Department for Health Education (Dr. PREBEG, assisted by Dr. CHLOUPEK) organises lectures, produces material required for health education and training in public health, prints pamphlets, prepares posters for propaganda, makes films, publishes periodicals and organises health museums and travelling exhibitions. It supervises the work of physicians and health workers in health propaganda matters. The section has distributed in the past five years 1,200,000 books, pamphlets, posters and magazines. It has also been very active in the production and reproduction of educational films. In the same period, 447 films have been produced, twenty-five of them being original films. In the province of Sava¹ alone during this period, 20,470 health lectures were delivered to 2,335,000 persons. The propaganda section lends films and cinematographic apparatus (3,486,000 metres of film and 1,736 cinema projectors have been lent). A large health exhibition was shown to 612,746 visitors, and a small travelling exhibition to 724,448 visitors.

The Department of Sanitary Engineering (M. PETRIK, engineer) makes plans for wells, latrines, water-supplies and dwellings and

¹ Population of the province 2.7 millions.

maintains a laboratory for water analyses. It also carries on practical field work. The department organised two special courses for sanitary engineers which were attended by thirty-two persons. The practical and theoretical teaching was spread over two months. The subjects taught in the first course were the principles of geology and hydrogeology, epidemiology, housing hygiene, laws concerned with sanitary engineering, examination of water, water-supply, sewage disposal, heating and ventilation, malaria and village schools. The subjects of the second course were colloids, capillarity, the air, elements of statics, principles of modern architecture, ventilation, artificial ventilation in factories, natural and artificial light, industrial hygiene, noise abatement and building materials.

From 1930 to 1935, the department provided the plans for 2,453 sanitary installations (of these, 14.84% related to water supply, 36.92% to sewage disposal, 0.94% to health centres and public baths, 47.30% to dwelling houses and rural settlements). Between 1923 and the end of 1935, the department spent a little over 37 million dinars on sanitary engineering (12 million was contributed by the State, 14 million by the provinces and 2,200,000 by communes, whilst 9,400,000 came from private sources). Under a special law for village sanitation, a State fund was created for sanitary engineering work in rural areas. This law was in full operation only for a short time, owing to the lack of funds due to the economic crisis. However, some of the provincial administrations, especially that in Zagreb, created provincial funds for the promotion of hygiene in villages, and recently several village communities appropriated smaller amounts of money for similar purposes. Rural communities and peasants can thus obtain loans without interest—in the majority of cases up to 50% of the total amount necessary to carry out certain sanitary engineering projects. In this way, large sums have been devoted to the laying-out of water-supply systems. In addition to these funds, the School of Public Health obtained from the Ministry of Social Welfare and Public Health a great deal of iron piping suitable for water supplies. This represents a very important part of the help given by the School towards the sanitation of villages. In some cases, the iron pipes were handed over without charge : in other cases, a long-term loan was arranged without interest. All this work helps to inculcate an understanding of hygiene among the population.

The staff of the School Sanitary Engineering Department act as advisers to the State, provincial and municipal administrations in all matters of sanitary engineering.

The *Biological Products Department* (Dr. KRALJEVIĆ, assisted by Dr. BANIĆ and Dr. PERŠIĆ) is not only engaged in production, but conducts studies into serology and immunology and collaborates closely with similar departments of the Institutes of Public Health in Prague and Warsaw, exchanging products with them.

During the past two years, the School has begun to produce insulin (Dr. VRHOVAC) and arsenobenzene preparations (Dr. ORLIĆ and Dr. VULETIĆ).

Courses organised by the School.

The School organises post-graduate training in public health for physicians, courses for auxiliary personnel in the public health services and special classes for the health education of peasants, teachers and social workers.

The Courses for the Post-graduate Training of Physicians.

The courses for physicians are as follows :

- (1) Course for public health officers ;
- (2) Course for school health officers ;
- (3) Course in social medicine for the health officers employed by the social insurance institutions ;
- (4) Course for medical probationers.

Six courses in public health for district and municipal health officers have been organised since 1930 with a total of sixty-six students. At present, a diploma in public health is not required for a medical officer of health.¹ The provincial administrations

¹ It must be borne in mind that, in Yugoslavia, the officers in the Institute of Hygiene, the School of Hygiene, district health centres, health stations and school policlinics are specialists in hygiene and allied subjects. They constitute about 30% of all physicians employed in the public health service. The civil service law provides that the first three-year period after appointment shall be considered temporary. A permanent appointment can be obtained only on the termination of this period and after the civil servant passes a special examination. The physicians in the public service are examined by a special commission, consisting of university professors and members of the staff of the Institute of Hygiene in the following subjects : health administration and legislation, epidemiology, general hygiene, social medicine and legal medicine.

There are no compulsory courses leading up to this examination. There are two examining commissions, one at Belgrade at the Institute of Hygiene and one at Zagreb at the School of Public Health.

are, however, obliged to send the district health officers for post-graduate training in public health, and to provide the necessary funds for their maintenance. The economic crisis seriously reduced the funds available for the post-graduate training of medical officers and the number of students has been greatly restricted. Whilst attending instruction at the School of Public Health, medical officers continue to receive their salaries, and after graduation they return to their former positions. The training in public health comprises 341 hours of theoretical teaching, fifty-nine hours of practical teaching and 128 hours of clinical training. The course lasts for six months. The subjects taught during the period 1935/36 were :

Hygiene : General and personal hygiene, disinfection and disinfestation, chemistry, bacteriology, production of sera and vaccines (ten hours of theoretical, twenty-nine hours of practical training).

Epidemiology and Control of Infectious Diseases : Epidemiology, diagnosis and treatment of infectious diseases (forty-four hours of lectures).

Sanitary Engineering : Sanitation of towns and villages, hygienic condition of school buildings, factories, houses ; baths, drinking-water (forty-eight hours of lectures and three days of excursions) ;

Social Medicine : Social pathology and social therapy, maternal, infant, child welfare, school hygiene, school clinics, school dental clinics, mental hygiene, intelligence tests, nutrition, tuberculosis, venereal diseases, malaria, trachoma, goitre, malignant tumours, alcoholism, industrial hygiene and occupational diseases, social insurance, protection of the poor, invalids, blind, deaf and dumb and insane, vital statistics, health propaganda (165 hours of lectures and thirty hours of practical work).

Pathology : (ten-hour practical course).

Forensic Medicine and Toxicology : (ten hours of lectures, six hours of practical work).

Forensic Psychiatry : (ten hours of lectures).

Health Laws and Administration : Administration, international health work, professional medical associations (sixteen hours).

Miscellaneous : History of medicine, economics, laws governing population, eugenics, certain legal questions, medical ethics (forty-eight hours).

The staff consisted of nine university professors, nine specialists from other educational institutions, and seventeen members of the staff of the School of Public Health and the Institute of Hygiene.

The teaching and practical work last for about six hours a day. Three days of the week are spent in the lecture-rooms and in practical training in laboratories, and three days in the clinics. The students must visit the rural districts and make surveys for a minimum of fourteen days during their six-month course.

Only two courses have been organised for school medical officers (thirty-three attended, mainly medical officers of the school polyclinics and municipalities). This course lasted for three months and comprised the following subjects : school hygiene, school premises and equipment (fifty-three hours) ; hygiene of students and teachers (twelve hours) ; diseases and hygiene of the pre-school age (six hours) ; diseases of the school age (forty hours) ; infectious diseases (thirty hours) ; physical training (six hours) ; statistics, biometry (six hours) ; laws governing school hygiene and school hygiene institutions (sixteen hours) ; 169 hours of theoretical and eighteen hours of practical training. All of the students received their salaries and their travelling expenses during the course.

After graduation, physicians in Yugoslavia must spend one year in practical training—that is to say, six months in curative and six months in preventive medicine. If they are subject to obligatory military service, nine months of this service are counted as practical medical training. In this case, they are required only to do one month of work in preventive medicine and two months in obstetrics.

Altogether, 193 graduates have been given practical training in the School of Hygiene.¹ Whilst taking this course of practical training, the doctors are not paid, but, in exceptional cases, some of them, obtain a grant from the Ministry, provinces, or the Chamber of Physicians.² The training is divided into theoretical and practical courses, and the graduates are occupied on an average for six hours a day.

The period devoted to the study of preventive medicine must be spent in the School of Public Health or one of the Institutes of Hygiene and is divided as follows :

- (1) Two months in the hospital for infectious diseases, with practical training in epidemiology and pathology.

¹ The Institutes of Hygiene are authorised to give the same practical training.

² In 1935, in the School of Public Health, thirty-three doctors took post-graduate training, twenty of them spent six months on practical training in preventive medicine, and thirteen only one month.

- (2) One month in maternity and infant welfare work and health work for children of school age ;
- (3) A fortnight in a tuberculosis dispensary with practical work, including visits to the home with a health visitor ;
- (4) A fortnight in a venereal diseases dispensary ;
- (5) Ten days in an out-patients' department (ambulatorium) or a trachoma clinic ;
- (6) During the remaining period (seven weeks) the doctors work in the bacteriological, malarial and epidemiological laboratories, in the rural sanitation department, in the anti-rabies laboratory and in the department for the preparation of vaccines and sera. Lastly, they spend three or four days at a health insurance office.

The period set aside for preventive medicine is devoted in the main to practical work. The students attend short lectures dealing with the chief problems in the various branches which they are studying. After completing his studies in preventive medicine, each student receives a certificate of attendance, indicating that he has completed the period of training in preventive medicine. Unless a doctor holds this certificate, he is not authorised to practise.

The law provides for three-month courses in social medicine for the social insurance officers and physicians. The application of this law was postponed owing to the financial difficulties of the social insurance institutions.

The Training of Sanitary Inspectors.

The course for sanitary inspectors lasts for one year. Candidates (age 18 to 28) must have attended four classes¹ of junior middle school. Many of the students have senior middle school training. After graduation, the sanitary inspectors are engaged in food control and disinfection, unless they are employed as assistants in laboratories. Sixty-four have graduated from two courses. Students must defray all the expenses for their training, but in exceptional cases they receive grants from provincial and municipal administrations. The first three months of this course consist of preparatory training ; thereafter, the students are examined and only those who pass are allowed to continue their training.

¹ Recently changed to six classes of a middle school.

The curriculum for the preparatory course is as follows :

		Hours
<i>Biology</i> :	theoretical	30
	practical	20
<i>Anatomy and physiology</i> :	theoretical	50
	practical	30
<i>Physics</i> :	theoretical	20
	practical	30
<i>Chemistry</i> :	theoretical	20
	practical	100

The curriculum for the remaining nine¹ months comprises the following subjects :

		Hours
<i>Food chemistry</i> :	theoretical	30
	practical	150
<i>Public health laws</i> :	theoretical	30
<i>Languages</i> :	theoretical	60
<i>Hygiene</i> :	theoretical	60
	practical	40
<i>Bacteriology</i> :	theoretical	60
	practical	140
<i>Epidemiology</i> :	theoretical	60
	practical	60
<i>Disinfection</i> :	theoretical	30
	practical	17
<i>Public health administration</i> :	theoretical	20
	practical	60
<i>Sanitary engineering</i> :	theoretical	30
	practical	50

In all, 1,197 hours (500 theoretical and 697 practical) training.

The Peasant Classes.

The first peasant class was opened in 1928, and, in the past six years, nine courses for men peasants and eight courses for women have been held. By the end of 1936, 632 peasants had received public health training (336 men peasants and 296 women). The

¹ Now changed to fifteen months.

purpose of these courses is not only to train the peasants in public health but also to prepare them to collaborate in carrying out a programme of field health work and of general improvement in rural areas. The number of peasants who put down their names for these courses is much greater than the school is able to accept. They stay in special living-quarters prepared for them by the School, and fees are charged—600 dinars for men, 400 dinars for women. These amounts do not cover the expenses of the course, but the provinces and co-operative societies give grants, and the School of Public Health makes itself responsible for all other charges. The course lasts five months (996 hours) for men, and three months (627) for women. In addition to the training in public health, the students also receive a general grounding in history, geography, economics and agriculture. The teachers are members of the staff of the Public Health School and other educational institutions. After undergoing an examination, the peasants return to their homes ; almost all of them become most efficient and enthusiastic collaborators with the School of Public Health in sanitary engineering, health education and the general improvement of village life.

In collaboration with the co-operative societies, the School organises from time to time special courses of hygiene for the workers in these societies. The training in these courses lasts from two to two and a-half months. The number attending averages twenty-eight.

In the villages, short courses in housekeeping, with some lessons on public health, are organised for peasant women. The teaching is mostly practical and spread over four weeks, with one week in the classroom and three weeks in the peasant homes. The course is given only in the autumn and winter (October to March). The demand for the courses comes from the villagers themselves. Those attending are mostly married women. Up till now, thirty courses have been given every year with an average attendance of fifteen at each. In the past ten years, 3,217 peasant women have successfully passed through these classes. The villagers are obliged to supply the necessary implements for the practical training, and to provide the nurse in charge with free board and lodging. The other expenses are paid by the School of Public Health. In 1935, the School spent on each course an average of 1,000 dinars, and the women attending a similar amount.

The School of Nursing at Zagreb.

The School of Nursing (Director : Miss D. ZELENJAK) was organised in 1931 and subsequently attached to the School of Public Health. In all, 482 students have attended the School (240 belonging to various religious orders). Since 1921, 212 students have passed their examination in public health (twenty-four belonging to various religious orders).

In the preparatory period lasting three months,¹ the subjects taught are biology, physics, chemistry, anatomy, physiology, ethics, personal hygiene, nursing, domestic economy, cooking.

In the first year : theoretical teaching in internal medicine, surgery, first-aid, neurology, pharmacology, and practice in the nursing of patients in hospital for internal and surgical diseases, diet.

In the second year : hygiene of childhood and children's diseases, obstetrics, infectious diseases, bacteriology, venereal diseases, ophthalmology, and practice in nursing healthy and sick children, maternity cases and persons suffering from infectious diseases.

In the third year : epidemiology, social medicine, health legislation and administration, pedagogy and psychology, nursing, practice in social medical work of nurses and hospital administration.

The course lasts for three years. Candidates for entrance must have passed successfully through a junior middle school. For purposes of appointment in the public health service, the diploma in public health nursing is equivalent to the middle school certificate.

The Budget.

In 1930, the School of Public Health was made financially autonomous, and its funds were provided by the Ministry by means of a special grant included annually in the State budget. The income

¹ Recently, the legal provisions for the training of nurses have been changed. The preparatory period will last for five months. After five semesters of successful studies, the students will be divided into two classes, one for the training of public health nurses and the other for the training of hospital nurses.

of the School was very large—in 1932/33, 2,424,964 dinars, and, in 1936/37, 3,880,000 dinars. To cover deficits in running expenses in the same period, the School received grants of 1½ million dinars and 1,191,583 dinars out of the State budget. In 1936/37, the School ceased to be financially autonomous, any income earned by it being paid into the State Treasury, and all funds are now provided by the State. The budget has decreased considerably during the last four years. With regard to some of its activities, the school is in touch with the Provincial Institute of Hygiene, whose budget has also been considerably reduced. The total budget of the Institute in 1932/33 was 8,280,118 dinars, and, in 1936/37, 7,437,323 dinars. As a result, the field work of the Institute has been greatly restricted.

The Staff.

The staff of the School is appointed according to the civil service law and consists of 153 persons : thirteen physicians, twelve sanitary engineers, two veterinary surgeons, thirty-seven public health nurses and sanitary inspectors, one expert in cinematography and eighty-seven auxiliary personnel. The physicians, sanitary engineers, chemists and veterinary surgeons are employed on a full-time basis. They receive the same salaries as those paid to State employees of the same rank, and also an allowance for full-time service. Additional employment is strictly prohibited.

THE CENTRAL INSTITUTE OF HYGIENE AT BELGRADE.

The Central Institute of Hygiene at Belgrade, which is under the direct control of the Ministry of Social Welfare and Public Health, has been directed by Dr. IVANIĆ since 1926.

The Institute was created in 1926 by the amalgamation of three previously independent institutions—viz., the Bacteriological Station, founded in 1922, the Laboratory of Tropical Diseases (1922) and the Institute of Social Medicine (1923). It now occupies a new building specially constructed for the purpose in 1926. This building also houses the following sections and services :

- (1) Bacteriology and epidemiology (Dr. KALIĆ) ;
- (2) Biology and immunology (Dr. KUŠIĆ) ;

- (3) Social medicine (Dr. KONSTANTINOVIĆ), together with services concerned with biometry, vital statistics, propaganda ;
- (4) Applied chemistry (Dr. KOSTIĆ, chemical engineer), together with services concerned with water examination, analysis of food products, drugs, etc. ;
- (5) Parasitology, medical zoology and botany (Dr. VUKASOVIĆ, naturalist) ;
- (6) Sanitary engineering (M. TOMAŠEVIĆ, engineer) ;
- (7) Applied hygiene (Dr. STAMBUK) ;
- (8) Infectious diseases (this section is represented by the Hospital for Infectious Diseases, of which Dr. RANKOVIĆ is head).



Figure 16.—FRONT VIEW OF THE CENTRAL INSTITUTE OF HYGIENE AT BELGRADE.

In addition, there are a large number of institutions under the direct control of the Institute, particularly two anti-tuberculosis dispensaries, an anti-venereal dispensary, three school policlinics and a Maternal and Child Welfare Institute. The Institute is also in touch with several institutions set up by the municipal health organisation or by private bodies, such as the Association of Serbian Mothers, the Mothers' Union, etc. Although the medical officers of the services created by private societies of this kind are appointed by those responsible for the administration of the institutions concerned, there is nevertheless an official connection between them

and the Institute. The latter supplies experts for certain services and exercises indirect supervision over the technical activities of the institutions, which distribute milk, food, etc. (There are eight different institutions of this type in and around the town.)

There has been very little change in the internal organisation of the Institute since 1930. It is governed by the Law of December 21st, 1929, but certain services, such as the new section of applied hygiene and the section responsible for the preparation of sera and biological products, were not started until 1931-1933. An inter-ministerial commission appointed by decree on September 1st, 1931, which is still in existence, ensures co-operation between the Institute and the social welfare and educational bodies attached to other Ministries. The Library of the Institute contains 6,500 volumes.

With regard to education and propaganda, special mention should be made of the *department of social medicine* : The activities of this department include :

(1) Field investigations and studies of social pathology, ætiology and therapy, and biometry.

(2) The collection and analysis of vital statistics and other statistical material connected with the public health services and hospitals. Up to 1934, statistical data were published in the revue of the Central Institute of Hygiene : "Socialno-medicinski pregled". Data for the years 1935 and 1936 were published in 1937 in the first of the annual public health reports.

(3) The training of physicians, of medical officers and of the auxiliary staff ; this forms part of a programme similar to that described in the chapter on the School of Public Health in Zagreb.

(4) Special courses for peasants ; courses for teachers.

(5) The publication of popular books, pamphlets and posters, and the distribution of this material. The Institute is publishing a series of pamphlets "Zdrav dom" ("Healthy Homes") ; ninety-two pamphlets have been issued, dealing with various health problems. Each pamphlet is issued in at least 8,000 copies.¹

(6) Permanent health exhibition.

In this connection, special attention is paid to national nutrition and to sanitary engineering, models, pictures and graphs concerning which are exhibited

¹ As regards propaganda material, the Institute has distributed :

	Books	Copies of the pamphlet "Zdrav dom"	Posters
In 1930	13,304	131,532	34,396
1931	23,008	24,000	14,414
1932	5,905	58,752	11,904
1933	2,586	33,725	14,828
1934	2,197	34,837	1,695

in special laboratories of the institution. The exhibition is organised by a special board consisting of delegates of the Institute, the Union of Co-operatives and the Public Health Association. The Hygiene Exhibition organised in Belgrade in 1933 was visited by more than 100,000 persons.

(7) Broadcasting from Radio-Belgrade ; twenty-minute lectures are given weekly, and a special talk for peasants is broadcast on the last Sunday of each month.

The Department of Sanitary Engineering carries out field work in rural sanitation.

Between 1927 and 1936, the cost of these activities amounted to 27.52 million dinars (66% of this was paid by the State Treasury, 17% came out of provincial funds and 17% was paid by communes, co-operative societies, and private organisations).

Altogether 998 sanitary installations have been built ; 38% of the money went to water supply, 32% to rural settlements, 9% to public baths and hygienic privies, 6% to health centres and summer resorts and 15% to other objects.

In addition to this work, the Department is preparing standard plans for health centres, schools, sewage-disposal work in villages, model peasant-dwellings, etc. This involves a great deal of propaganda work. These plans are distributed free to all persons interested.

Courses.

The Belgrade Institute carries on the following educational activities : (1) a six-month course for medical probationers. There are nearly a hundred students every year from all parts of the country ; (2) a course for school doctors ; (3) a course for tuberculosis specialists, intended for doctors in dispensaries, etc. ; (4) the Director of the Institute and some heads of section (bacteriology, parasitology, mycology, etc.) also give special courses for which only an attendance certificate is issued, the number of students taking these courses is small ; (5) a course for auxiliary staff (sanitary inspectors, laboratory assistants, disinfectors). One hundred and two students attended during two courses.

The Institute also has courses of special training for teachers and medical students. Two of these were for field-workers ; there are also courses in social medicine for nurses.

Courses for peasants have been given since 1928. During the past three years, they have been held in connection with the Union of Health Co-operatives and the Public Health Association. They are not all of the same type. At first, they were held in Belgrade and lasted for three months. Since 1932, they have been shorter, lasting only one month. Lectures are also arranged for in the villages twice or three times weekly throughout the winter. Lecturers are sent from the Institute, and there is a permanent nurse in each village.

By 1933, the courses in the Institute had been attended by 360 persons. In the villages, there were six courses attended by 273 men and 430 women. During her visits, the nurse encourages the villagers to attend these courses, and this has proved very effective in spreading knowledge in rural homes. Courses for women paid special attention to teaching of mother-craft. Since 1934, only two courses, each lasting six weeks, have been held at the Institute in connection with the Union of Health Co-operatives ; fifty-eight pupils attended. Three-month courses in housekeeping for peasant girls are given in the villages. Two instructors for each course are sent from the Institute. By the end of 1936, fifty-four courses, attended by 1,094 peasant girls, had been given.

The collaboration between the Institute and the Union of Health Co-operatives is very close. The Institute helps this movement in different ways ; it organises courses for the staff and workers of the co-operatives, conducts field surveys, distributes plans for sanitary engineering projects, gives sera and vaccines and material for health propaganda free of charge, pays the salaries of certain members of the staff and provides teaching staff for different courses.

Hospital for Infectious Diseases.

The Hospital has been in existence since 1928. It has accommodation for three hundred patients, but more beds can be made available by temporary arrangements during epidemics.

The Institute of Hygiene, which is in the neighbourhood, carries out the necessary bacteriological, serological and chemical examinations on the patients in the hospital.

Because of its close relations with the Institute of Hygiene on the one hand and the Faculty of Medicine on the other, this hospital

may be regarded as forming part of the public health organisation and as assisting in its educational activities for the public health training of students in the Faculty of Medicine, or of doctors who finish their training at the Institute of Hygiene.

The Budget.

The budget of the Institute for the year 1936/37 amounted to 12,000,000 dinars. For the financial year 1937/38, this amount has been increased by over one million dinars. Owing to its administrative autonomy, the Institute has some latitude in spending its funds. The receipts from the preparation of sera and biological products (vaccines, etc.) amount to approximately 1,000,000 dinars per annum and must be handed over to the State Treasury.

SCHOOLS OF NURSES.

The Belgrade School of Nurses is directed by Mlle. GAVRILOVIĆ. At the end of 1936, there were seventy-three students (twenty-one in their first year, twenty-four in their second year and twenty-eight in their third year). There were fourteen scholarship-holders and the remaining students paid an average of 400 to 800 dinars a month.

The School received financial assistance in the beginning from the Red Cross Society, from the American Child Welfare Mission and from the Ministry of Health. Construction and equipment cost a little over 4 million dinars.

The object of the School is to train a specialised staff of nurses for both hospital and social medical work. It is run by a Committee consisting of representatives of the Ministry of Social Welfare and Public Health, the Red Cross and different humanitarian societies and health institutions.

At present, the cost of maintaining the School and the building is shared equally by the Red Cross and the Ministry. The School has received assistance from the Rockefeller Foundation, which has provided it with a fully equipped model kitchen and the material for practical training. The Foundation has also granted

scholarships for additional training abroad. The Red Cross Society offers two scholarships to students of the School for additional training.

The expenditure as shown in the School's budget amounts roughly to 1,200,000 dinars for about eighty students.

At first, a two-and-a-half-year course of training was provided, but this was soon found to be inadequate. The period of training was therefore extended to four years, but was afterwards reduced to three. Up to the present, five groups in all have completed their studies—that is to say, forty-nine students under the first scheme and forty-one under the second.

The School is under the control of the Ministry of Social Welfare and Public Health, and the examination for the certificate is equivalent in standard to that of the middle-school leaving examination.

* * *

Attached to the Institutes of Hygiene at Ljubljana and Skoplje, there are nursing schools, which provide training along the same lines as in the schools at Belgrade and Zagreb according to the provisions of the law on vocational schools for the auxiliary personnel in the health services.

The School at Ljubljana started by giving one-year courses, mainly for the training of nurses to be employed in the child welfare institutions ; later, the course was prolonged to two years, and, after the coming-into-force of the above-mentioned law, to three years. Altogether 141 nurses have passed through this School ; in 1936/37 the number of students was twenty-seven.

The School at Skoplje has been faced with many difficulties ; the number of students is comparatively small.

RESEARCH WORK.

Although the Zagreb School of Hygiene is chiefly remarkable for its direct and practical contribution towards sanitation and public health propaganda, it has not therefore neglected scientific research.

The papers—numbering 182—published under its auspices during the last few years may be grouped as follows :

First, technical papers on questions of sanitary engineering, urban and rural sanitation, etc., have been composed under the direction of PETRIK, engineer and head of section. These form a series of publications, used for instructional purposes, in which the practical solutions proposed or adopted for certain problems—drinking-water supplies, in particular—are invariably based on a previous scientific study of the various factors.

There have also been a number of special epidemiological enquiries into certain diseases, and researches on the infectious diseases prevalent in the country. Mention may be made of ČERNOZUBOV'S study of the epidemiology of scarlet fever (epidemic of 1928-1930) and the same author's works on active immunisation against typhoid fever and dysentery (1935) ; those of ROGINA on post-vaccinal encephalitis ; TRAUSMILLER'S research on malaria and the means of combating it in certain sections of the population on the Adriatic coast (1932 and 1935) ; and an important enquiry carried out by MALOJČIĆ into tuberculosis in the Sava rural district 9,087 persons examined (1936).

In the field of chemical and pharmacological research, IVEKOVIĆ has investigated some of the physico-chemical problems connected with drinking-water whilst ROGINA has given attention to the question of citric acid in milk (1935).

Researches on microbiology and serology include those of VARIČAK on the *cytology* of ascomycetes (1932-1935), and of LAZAREVIĆ and BANIĆ on *viperidæ* venom and its neutralisation by homologous or heterologous sera.

The purely statistical studies and studies of applied or vital medical statistics carried out by Dr. MIKIĆ, head of section, represent a real contribution to our knowledge of biological phenomena among the Slovene population, of infant morbidity and mortality in the city of Zagreb (1936), and even of certain biometric problems.

In the field of pure and applied entomology, the researches of BARANOFF on the *Simulidæ* and on the biology of *Simulium columbacense* and the causes of its periodic invasions of Serbia, and his works on the classification and biological characteristics of diptera (1929-1936), rank as classics.



Members of the various departments of the Central Institute of Hygiene at Belgrade have published numerous papers.

As regards epidemiology, bacteriology and serology in relation to infectious diseases in Yugoslavia, especially in Old Serbia, mention should be made of studies by ALBERTI-ŠAMIĆ on diphtheria and the Schick test (1932); ILIĆ on venereal diseases, with a note on the cutaneous localisation of Nicolas-Favre's disease (1936); ST. IVANIĆ on diphtheria and on the technique of isolating intestinal pathogenic bacteria (1933); KALIĆ on the Vi-antigen of *B. typhosus* (1936); KOROSTOVEC on salmonellosis generally (1934-1936); VRAČEVIĆ on tuberculosis; and RISTIĆ on anthrax.

In protozoology, M. IVANIĆ has for many years (1924-1936) been pursuing his investigations, which he has summarised in over eighty articles; the latest relate to the nuclear division of *P. vivax*, and especially the pre-mitotic phenomena of the parasite, and to the morphology and biology of *Arcella*, *Chilodon*, *Vampirellidicum*, *Blastocystis hominis* and to the growth and reproduction of amoebæ. He is now investigating the *Babesia*, as regards both their cell-structure and their reproduction in the cells of the vertebrate host.

In mycology, MILOŠEVIĆ has published nearly fifty articles and notes (1934-1936), dealing in particular with the dermatophytes, of which the Belgrade Institute has a remarkable collection.

The pure and applied entomological research of VUKASOVIĆ, bearing more particularly on insects parasitic on plants and on a number of questions connected with the biology of insect parasites, is also well known.

In physiology and anthropometry, MALEŠ and his collaborators have published, in various foreign reviews, interesting papers on thermo-regulation, basal metabolism, anthropometry applied to the rural population in Serbia and the Dinaric race (1930-1936).

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METHODS OF ASSAYING THE CONTENT
OF MORPHINE IN OPIUM
AND OF COCAINE IN RAW COCAINE
AND IN COCA LEAVES.

INTRODUCTION.

I.

In 1930, the Advisory Committee on Traffic in Opium and Other Dangerous Drugs asked the Health Committee to work out a method of assaying the content of morphine in opium which would meet the practical requirements of a system of control over the manufacture of morphine.¹ The Health Committee decided to entrust the study of this question to a Committee of Experts. Since its appointment, the latter has held seven meetings (Geneva, 1931 ; The Hague, 1932 ; Zürich, 1933 ; Berne, 1934 ; Copenhagen, 1935 ; The Hague, 1936 ; London, 1937).² Under the chairmanship of Professor L. VAN ITALLIE (Netherlands), the following experts participated in the work of the Committee : Professor H. BAGGESGAARD-RASMUSSEN (Denmark), Professor R. EDER (Switzerland), Professor A. GORIS (France), Professor E. KNAFFL-LENZ (Austria),

¹ See, in this connection, the *Quarterly Bulletin of the Health Organisation*, 4, 1935, page 809.

² See reports : documents C.H.975, C.H.1089, C.H.1125, C.H.1174, C.H.1224, C.H.1260, C.H.1283.

Professor Charles LA WALL (U.S.A.) (replaced in 1935 by Dr. Herbert J. WOLLNER and succeeded in 1937 by Professor Lyndon F. SMALL), Professor C. MANNICH (Germany),¹ Mr. J. R. NICHOLLS (United Kingdom), Professor Kotaro NISHIZAKI (Japan) (replaced in 1935 by Professor J. ASAHINA and succeeded in 1937 by Dr. Yutaka KINUGASA).

At its first meeting, the Committee of Experts resolved to extend its enquiries to methods of assaying the cocaine content of coca leaves and raw cocaine. For this part of its work, the Committee co-opted Dr. A. W. K. DE JONG (Netherlands).

II.

Research into *methods of assaying the content of morphine in opium* was carried on from 1931 to 1933 in the laboratories of members of the Committee. During that period, the Committee studied the method of the British Pharmacopœia of 1914, that of the Netherlands Pharmacopœia of 1926, the new method proposed for the fifth edition of the Swiss Pharmacopœia, and a series of other processes, including methods worked out by its members.²

After many tests, the Committee chose a method similar to that in the British Pharmacopœia. In 1933, it recommended the Health Committee to adopt this method. It was subsequently submitted to all Governments, which were requested to send in their observations.

The Governments of the following countries stated that they had already adopted, or were willing to adopt, the method advo-

¹ Professor MANNICH ceased to participate in the work of the Committee when Germany withdrew from the League of Nations.

² See : N. RUSTING : " Ueber die quantitative Bestimmung des Morphins im Opium ". *Archiv der Pharmazie*, 1931, 609, and 1932, 323.

E. KNAFFL-LENZ : " Ueber Morphinbestimmungsmethoden im Rohopium ". *Pharmazeutische Monatshefte*, 1932, 82.

R. EDER and W. STUCKI : " Ueber eine neue Methode zur Bestimmung des Morphins im Opium ". *Pharmaceutica Acta Helvetiæ*, 1932, 259.

A. GORIS and J. FOURMONT : " Aperçus critiques sur le dosage de la morphine dans l'opium par le procédé à la chaux ". *Bulletin des sciences pharmacologiques*, 1932, 337.

H. BAGGESGAARD-RASMUSSEN, K. A. JACKEROTT and J. C. JESPERSEN : " Morfinbestemmelse i Opium efter Kalkmetoden ". *Dansk Tidsskrift for Farmaci*, 1934, 185 and 206.

H. BAGGESGAARD and F. REIMERS : " Die Löslichkeit des Morphins in verschiedenen Lösungsmitteln ". *Archiv der Pharmazie*, 1935, 129.

cated by the Committee: Australia, Chile, Czechoslovakia, Denmark, Egypt, Iran, Latvia, Poland, Portugal, Sweden and Switzerland. So far, it has been introduced into the pharmacopœiæ of Denmark, France and Switzerland.

The Governments of the following countries made reservations or offered criticisms with regard to the proposed method: Austria, Bulgaria, Germany, Italy, Netherlands, Turkey, Union of Soviet Socialist Republics, United States of America.¹

At its 1935 meeting, the Committee of Experts took note of these observations. None of its members, however, was able to suggest another method likely to yield more accurate results than that which it had advocated. The Committee surveyed the results of the research work it had carried out since 1933, which had dealt mainly with the method described in the United States Pharmacopœia of 1926 and the alternative form of that method given in the eleventh edition of the United States Pharmacopœia, but also with other methods.² It found that those methods gave no more accurate results than the method it recommended.

The Committee subsequently carried out further comparative research into the methods prescribed by the United States Pharmacopœia and the Japanese Pharmacopœia, and into new methods and modifications proposed by its members. In spite of the large number of processes thus tested, the Committee, at its last meeting (1937), was obliged to adhere to its opinion that, in the present state of chemical knowledge, and notwithstanding such defects as may attach to it, the prescribed method presents certain advantages over others so far known. In particular, the Committee noted that the range of dispersion of the findings of the individual analyst is narrow, and that the concordance of the results obtained by different analysts is relatively good.³ On the other hand, the Committee is not unaware of certain imperfections in the method, particularly in connection with the morphine extraction, the purity

¹ See documents O.C.1512(a) and 1512(b).

² BUCHBINDER: *Journal of the Americ. Pharmaceut. Ass.*, 1917, 6, 618.

C. MANNICH: "Eine neue Methode z. Bestimmung des Morphins insbesondere im Opium". *Arch. d. Pharmaz.*, 1935, 97.

³ See, e.g., H. BAGGESGAARD-RASMUSSEN, K. A. JACKEROTT and J. C. JESPERSEN: "Quantitative Bestimmung von Morphin. Morphinbestimmung in Opium nach der Kalkmethode". *Pharmaceutica Acta Helvetica*, 1936, 307, and *Bulletin of the Health Organisation*, 1935, 4, p. 839.

of the precipitated morphine and the correction factor. Notwithstanding the progress made in these various directions by the methods worked out by its members, the Committee felt that these had not yet reached a stage at which it could cease to recommend its own method as the best.

Nevertheless, the Committee remains convinced of the importance of continued efforts to perfect or even improve upon the proposed method. The work of its members in this sphere¹ will doubtless be supplemented by the investigations of other scientists and official laboratories in various countries. As it is impossible at present to tell how long it will be before the object of all these efforts is achieved, the Health Committee has decided to publish the method recommended by the Committee, with all the latter's reservations.

The method of assaying morphine content given below is therefore the method laid before Governments in 1934. The description of this method of analysis proper is preceded by a description of the manner in which samples should be taken for purposes of analysis. This method of sampling was devised by the Committee of Experts on the basis of the information furnished by the Governments of manufacturing countries.² Its practical utility has yet to be established.

III.

As regards *methods of assaying cocaine content*, exhaustive investigations have been carried out ever since the Committee was set up, and the results have been examined at its various meetings as and when they became available.³ The Committee—at its last meeting (1937)—finally established the methods of sampling and analysis of both coca leaves and crude cocaine. It therefore regards its work in this sphere as completed. The method adopted is also set forth hereunder.

¹ See: H. BAGGESGAARD and J. C. JESPERSEN: "Kvantitativ Bestemmelse af Morfin". *Dansk Tidsskrift f. Farmaci*, 1937, 278.

R. EDER and E. WAECKERLIN: "The Determination of Morphine in Opium". *Quarterly Journal of Pharmacy and Pharmacology*, 1937, 680.

E. KNAFFL-LENZ: "Ueber die Bestimmung des Morphins im Rohopium". *Pharm. Monatshefte*, 1937, 17.

² See document C.H.1219.

³ See the reports on the meetings referred to above.

DETERMINATION OF THE MORPHINE CONTENT OF OPIUM.

The determination of the morphine content of opium comprises two stages :

- A. The taking of samples for analysis.
- B. The determination of the morphine content by analysis of the samples.

A. METHOD OF TAKING SAMPLES.

The object is to obtain from a given quantity of opium for analysis a sample that shall be as near the average as possible.

I. *Maximum Amount of Opium from which an Average Sample should be obtained.*

It is desirable that the amount of opium from which average samples are to be obtained should not exceed 20 chests (about 3,000 lb.). Larger quantities should therefore be divided into parts of not more than 20 chests each, an average sample being taken from each part.

II. *Determination of the Net Weight of the Lot of Opium from which an Average Sample is to be taken.*

The contents of each chest are weighed separately (to the nearest 100 grammes) and the amounts recorded.

III. *Taking of Samples from a Lot of not more than Twenty Chests of Opium.*

- (1) Opium must be taken from each chest.
- (2) A chest contains a varying number of cakes, usually ranging from 40 to 160 according to origin. Moreover, the cakes may be fairly similar or they may vary in shape, size, consistency, appearance and homogeneity.

If the cakes in a consignment are similar in composition, it is sufficient to take a sample from every third, fifth or even tenth cake, according to the degree of similarity.

If the cakes are not similar, opium must be taken from each individual cake. This procedure must also be applied if the quantity of opium to be tested consists of only a few chests (1 to 3), and this even if the opium cakes are similar.

(3) *Method of taking a sample from a single opium cake.*—In taking samples, the following points should be borne in mind :

(a) The homogeneity of the opium cakes at the time of their preparation.

In many cases, the opium is made homogeneous when the cakes are prepared, while, in other cases, this is not done.

(b) The shape of the cakes.

Cakes may be more or less regular (spherical, cylindrical, ellipsoid or brick-shaped) or irregular in shape.

(c) The degree of humidity or of dryness of the opium cakes at the time when the sample is taken.

Opium cakes may retain their original degree of humidity in special circumstances, for instance, if they are packed on manufacture in hermetically sealed tins.

Opium cakes stored in the open gradually dry from the outside to the centre. This process may or may not be uniform over the whole surface. In consequence of this drying, the outer layers which have lost their moisture attain a higher morphine content than the inner parts.

The following cases must therefore be considered when samples are taken :

(1) An opium cake which was made homogeneous at the time of preparation and which has retained its moisture content during storage (*e.g.*, by being packed in a hermetically sealed tin).

In this case the sample will be taken in the following manner : a slice will be cut from the outside to the centre of the opium cake, representing approximately 2.5% of the volume of the cake.

(2) An opium cake of regular shape which was made homogeneous at the time of preparation and which has dried evenly during storage.

The sample should include the various parts of the cake in the same proportions as the cake itself.

This is done by taking the sample as follows :

If the opium cake is *spherical*, the correct way to test the average composition is to take a wedge-shaped piece bounded by two planes which intersect along the diameter of the sphere (the shape of a section of an orange) or a pyramid or cone, the base plane of which lies on the outer surface of the cake and its apex at the centre of the cake (see Fig. 1).

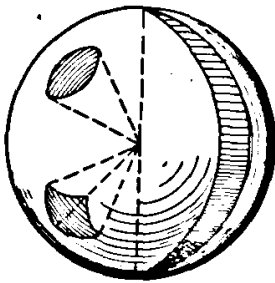


Fig 1

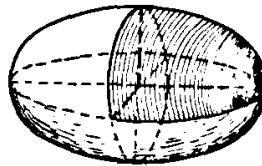


Fig.3

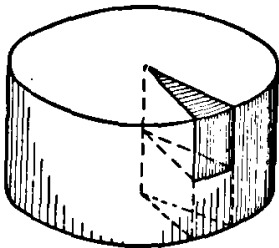


Fig. 2

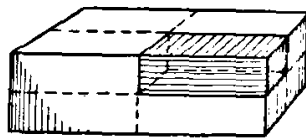


Fig.4

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If the opium cake is *cylindrical* in shape, a true sample will consist of half of a wedge formed by two planes which intersect along the axis of the cylinder (see Fig. 2).

If the cake is *ellipsoidal* or *brick-shaped*, the correct way to take a piece for testing is to cut out an eighth part of the ellipsoid or brick along the three symmetrical planes passing through the three main axes (see Figs. 3 and 4).

The weight of opium cakes of different origins usually varies between 1 lb. (*e.g.*, Iranian opium) and 4 lb. (*e.g.*, Turkish opium).

It should be sufficient to take the following quantities from a single *ball-shaped* or *cylindrical cake* :

From 4-lb. cakes, about 50 grammes each = about 2.5% ;

From 1-lb. cakes, about 11 grammes each = about 2.5%.¹

In the case of *ellipsoidal* or *brick-shaped cakes*, the average sample amounts to one-eighth, or 12.5% of the cake.²

(3) An irregularly shaped opium cake which was made homogeneous at the time of preparation and which has dried evenly ;

An opium cake which was made homogeneous at the time of preparation, but which has not dried evenly ;

An opium cake which was not made homogeneous at the time of preparation :

In all these cases samples should be taken from the various parts of the cake so that all parts may be represented in their proper proportion in the sample, which should amount to at least 10% of the whole cake.

During the process of sampling, which may take several hours, each piece removed is immediately placed in a container which can be tightly closed so as prevent it from drying or absorbing moisture.

¹ By this method, in a chest containing about 160 English pounds of opium :

If a part is taken from each cake, a sample of about 1,800 grammes (maximum quantity) will be obtained ;

If only one out of every 10 cakes is sampled, the total sample will weigh about 180 grammes (minimum quantity).

A consignment of 20 chests of opium will thus give a sample with a total weight ranging from about 36 kilogrammes (maximum quantity) to 3.6 kilogrammes (minimum quantity) according to the number of cakes from which samples are taken.

² The sampling of one cake in five will give, for a chest of opium weighing 160 English pounds, a sample of a total weight of about 1.8 kilogrammes. Thus, for 20 chests of opium, the sample obtained would be about 36 kilogrammes.

In the case of cakes which are not similar and which have to be sampled separately, the total quantity taken from 20 chests would be about 180 kilogrammes. The resulting inconvenience may be avoided by preparing average samples for a limited number of chests, say for a group of four chests, and then taking another average sample from the first five samples.

IV. *Homogeneisation of Samples.*

The samples taken from a given lot of opium should be thoroughly mixed.

Naturally, only samples representing approximately the same proportion of the weight of the opium cakes will be mixed. Thus, samples representing 2.5% (equal to one-fortieth) of a cake should not be mixed with samples representing 12.5% (equal to one-eighth) of a cake.

Hard opium should be powdered, passed completely through a sieve with a maximum mesh of 0.30 mm. and then mixed.

Soft opium should be kneaded together, preferably in special machines for kneading and mixing, until the mixture is homogeneous.

In carrying out these operations, care should be taken to avoid loss of moisture through heat (*e.g.*, through the working of machines), and also absorption of moisture from the air.

V. *Samples for determining the Morphine Content.*

When the opium has been made homogeneous in the manner above described, 30 to 50 grammes are taken and placed immediately in a wide-necked flask closed by a cork or ground-glass stopper sealed with sealing-wax and stamped. The label should be placed inside the flask to obviate any risk of loss or fraud.

It is advisable, in order to deal with any subsequent complaints, for control tests, etc., to keep in reserve other flasks similarly filled with 30 to 50 grammes of homogeneous opium.

Flasks are kept hermetically sealed until used for assay.

B. METHOD OF DETERMINING THE MORPHINE CONTENT.

The test falls into three parts :

- (1) Determination of loss of weight on drying at 103°-105° (moisture) ;
- (2) Determination of the quantity of extractives which dissolve in water in the presence of calcium hydroxide under the conditions of the test ;
- (3) Determination of the morphine content.

Determination of Loss of Weight on Drying (Moisture).

One gramme of opium (weighed to within 0.1 milligramme) is weighed in a weighing-glass with a ground-glass stopper, dried for two hours at 103°-105°, and re-weighed ; the drying process is continued until the loss of weight after drying for an hour no longer exceeds 0.005 gramme. The loss of weight is computed in terms of a percentage of the analysed opium. In the formulæ given below, this percentage loss of weight is represented by F.

In the case of soft opium, the weighed mass should be rubbed up with a little water and dried in a thin layer.

Determination of Content of Extractives and of Morphine.

Four grammes of opium (weighed to within 5 milligrammes) is rubbed up in a mortar with 1 gramme of calcium hydroxide and 10 c.c. of water until it forms a homogeneous mixture ; it is then stirred up with a further 10 c.c. of water and allowed to stand for fifteen minutes, during which it is frequently stirred. The mixture is washed out with a little water into a small weighed flask and water is added to make the weight up to 45 grammes (weighed to within 0.1 gramme). The flask is closed and vigorously and continuously shaken for half an hour, and the contents then passed through a glass suction filter (Schott und Gen. No. 3G3, or any other make of the same porosity and of suitable size), the minimum suction being applied at first. The filtrate is used partly for the determination of extractives and partly for that of morphine content.

A. Determination of Content of Extractives.

Three grammes of the filtrate (weighed to within 0.1 gramme) is evaporated on a water-bath and dried at 103°-105° until the loss of weight after one hour's drying does not exceed 0.003 gramme.

From the weight of the residue (M gramme), the content of extractives in the extract (E) from 100 grammes of opium is calculated according to the following formula :

$$E = \frac{(1000 + F) M}{3 - M}$$

where M = weight in grammes of the residue from 3 grammes of filtrate

F = percentage of moisture in the opium.

B. *Determination of Morphine Content.*

Twenty-five grammes of the filtrate (weighed to within 0.1 gramme) is weighed into an Erlenmeyer flask of 50 c.c. capacity or into some other suitable container, and 2.5 c.c. of alcohol (90% by volume) and 12.5 c.c. of ether are added. The flask is then closed and swirled round, after which 1 gramme of ammonium chloride is added and the flask shaken vigorously for five minutes, and again on frequent occasions for half an hour. The mixture is allowed to stand overnight in the closed flask. The deposited morphine is brought into suspension by vigorous shaking and the contents of the flask are poured out as completely as possible into a glass suction filter (Schott und Gen. No. 3G4, or any other make of the same porosity and of suitable size), care being taken not to wet the upper portion of the filter. The fluid is then completely filtered off by the application of slight suction. The flask is washed out by shaking up 3 c.c. of ether in it and pouring this into the glass suction filter without applying suction. The filter is inclined and turned round so as to rinse it and the fluid is then completely sucked through. The rinsing of the flask and filter is repeated with 3 c.c. of saturated aqueous solution of morphine until the filtrate ceases to react when tested for chloride.

The flask, in which some traces of morphine may be left, and the glass suction filter which contains most of the morphine, are then dried at 103°-105° for half an hour.

After cooling, the upper portion of the filter is lightly smeared round inside, to a depth of about 0.5 centimetre, with vaseline, and fixed with a stopper into a suction bottle of 300 c.c. capacity.

In the flask, 10 c.c. of methyl alcohol are warmed up so as to dissolve the last adhering morphine crystals. The warm solution is poured into the glass suction filter without applying any suction, the main mass of morphine is dissolved by imparting a swirling motion to the filter, and suction is then applied. The process is repeated twice with 10 c.c. of methyl alcohol on each occasion. After this, any remaining morphine deposit in the glass suction

filter (or in the lower end of its tube) is washed through into the suction bottle with a further 10 c.c. of warm methyl alcohol delivered from a small wash-bottle. Any impurities in the morphine remain on the filter-plate.

Care should be taken to verify that the filtrate is absolutely clear. If any morphine has crystallised out, it should be brought into solution by gently warming the mixture. Five to ten drops of methyl red solution are then added, and the titre is adjusted to a faint orange colour with 0.1 normal hydrochloric or sulphuric acid. It is then diluted with 120 c.c. of fresh boiled and re-cooled water, which turns the colour of the liquid back to yellow, and the titre is adjusted again with 0.1 normal acid until it begins to turn red.

The morphine content is calculated according to the following formula :

$$(a) \text{ as a percentage of the dried opium} \\ \frac{(1000 + E + F) (A + 1) 0.114}{100 - F}$$

$$(b) \text{ as a percentage of the original opium} \\ \frac{(1000 + E + F) (A + 1) 0.114}{100}$$

E being the percentage of extractives calculated on the original opium ;

F the percentage of moisture in the original opium, and

A the number of c.c. of 0.1 normal acid used in adjusting the titre.

In these formulæ, a correction of + 1 c.c. of 0.1 normal acid, equivalent to + 0.0285 gramme of morphine, is introduced to allow for the morphine which has not separated out.

Reagents.

Calcium hydroxide (Ca(OH)₂. Mol. wt. 74.09)

Is prepared from lime of marble and contains at least 85% Ca(OH)₂.

Before being tested and used, calcium hydroxide should be rubbed through a sieve of not more than 0.3 millimetre mesh.

About 0.4 gramme calcium hydroxide (weighed to within 1 milligramme) is mixed with 20 c.c. neutral glycerine in a graduated flask of 500 c.c. capacity. The mixture is diluted with about 400 c.c. of fresh boiled and re-cooled water, well shaken and allowed to stand for half an hour, during which time the contents of the flask are frequently vigorously shaken. The mixture is then diluted to 500 c.c. with similar water, well shaken and quickly filtered through a large folded filter ; 50 c.c. of the filtrate is taken, five drops of methyl red solution are added, and the titre is adjusted with 0.1 normal acid to the point at which the colour turns red. For this purpose, not less than 9.2 c.c. and not more than 10.8 c.c. of 0.1 normal acid should be used.

1 c.c. 0.1 normal acid = 0.0037 gramme $\text{Ca}(\text{OH})_2$.

Calcium hydroxide should not contain more than traces of magnesium.

Alcohol ($\text{C}_2\text{H}_5\text{OH}$. Mol. wt. 46.05)

90% by volume = 85.7% by weight.

$$D \frac{15}{15} = 0.8343. \quad D \frac{15^\circ}{4^\circ} = 0.8335.$$

Ether ($(\text{C}_2\text{H}_5)_2\text{O}$. Mol. wt. 74.08)

$$D \frac{15}{15} = 0.72. \quad \text{Boiling-point } 760 \text{ mm. } 34^\circ\text{-}35^\circ.$$

Limit Test for Peroxide.—10 c.c. of ether is repeatedly shaken up with 1 c.c. of freshly prepared (10%) potassium iodide solution in a completely full glass-stoppered vessel of 12-15 c.c. capacity and kept in darkness. Neither the ether nor the potassium iodide solution shall become coloured within an hour.

Ammonium Chloride (NH_4Cl . Mol. wt. 53.5).

Pharmacopœia standard.

Saturated Aqueous Solution of Morphine.

Finely powdered morphine is added to a quantity of distilled water insufficient for its dissolution and heated to 80° for an hour,

being frequently shaken. The solution is then allowed to cool and shall be kept for twenty-four hours before use, being frequently shaken during that time.

The solution is shaken with a few drops of chloroform, and is kept with the excess morphine remaining in it. It shall be well shaken and filtered before use.

Methyl Alcohol (CH_3OH . Mol. wt. 32.03)

$D \frac{15^\circ}{15^\circ} = 0.798$. Boiling-point 760 milligrammes $64^\circ\text{--}65^\circ$.

Methyl Red.

Dissolve, while warming slightly, 0.05 gramme of dimethyl-aminoazobenzene — o — carbolic acid ($(\text{CH}_3)_2\text{N} - \text{C}_6\text{H}_4 - \text{N} = \text{N} - \text{C}_6\text{H}_4 - \text{COOH}$) in 75 c.c. alcohol (95% by volume) and complete with water up to a volume of 100 c.c.

0.1 Normal Hydrochloric or Sulphuric Acid.

The factor is determined as follows : 0.5 gramme (weighed to within 1 milligramme) of chemically pure sodium borate is dissolved in 25 c.c. of warm water in an Erlenmeyer flask of 125 c.c. capacity.

It is then cooled, five drops of methyl red solution are added and the titre is adjusted with 0.1 normal acid until the colour is just red.

As a control, 50 c.c. of water with the same quantity of indicator and a few drops of 0.1 normal hydrochloric or sulphuric acid can be used.

1 gramme sodium borate requires 52.43 c.c. of 0.1 normal acid.

$$\text{Factor} = \frac{52.43 \times \text{weight in grammes of sodium borate}}{\text{quantity in c.c. of acid used}}$$

Sodium Borate, chemically pure ($\text{Na}_2\text{B}_4\text{O}_7 \cdot 10\text{H}_2\text{O}$. Mol. wt. 381.4).

Chemically pure sodium borate can be prepared as follows : 100 grammes of borax is dissolved in 400 grammes of boiling water

and filtered. The clear filtrate is carefully cooled to 50°, so that no crystals separate out. Then it is well shaken up, so that crystallisation may begin. If the solution is now frequently stirred, chemically pure sodium borate is deposited, which should be filtered off, washed and dried in air.

Three grammes of sodium borate, when carefully heated to redness, loses from 1.415 to 1.418 grammes of its weight.

DETERMINATION OF THE ECGONINE-ALKALOIDS CONTENT OF RAW COCAINE AND OF COCA LEAVES.

A. SAMPLING OF RAW COCAINE.

From each chest of raw cocaine, parts are taken of several parcels and these parts are divided into small pieces.

From these pieces, several smaller quantities are mixed and the whole is brought to a coarse powder. This powder is well mixed and parts of it are filled into well closed glass containers.

The quantities taken must at least be 1% of the content of the chest.

B. ANALYSIS OF RAW COCAINE.

I. *Determination of Moisture.*

Weigh accurately in a glass-stoppered weighing tube about 1 gramme of raw cocaine. Dry in a vacuum desiccator containing sulphuric acid until the loss in weight is not more than 1 milligramme in 24 hours. Calculate the moisture as a percentage of the raw cocaine.

II. *Determination of Ecgonine.*

Weigh accurately in a small flask about 0.5 gramme of raw cocaine and dissolve it in 15 c.c. of 2 N hydrochloric acid. Add some small pieces of pumice and boil the solution for 5 hours, using a reflux condenser.

Cool the liquid in ice or allow to cool slowly for not less than 2 hours and filter it through a small plug of cotton wool into a 25 c.c. measuring flask. Wash the flask and the cotton wool several times with small quantities of 2 N hydrochloric acid until the filtrate measures 25 c.c. at 20° C. Mix the solution to homogeneity and measure the optical rotation for sodium light at a temperature of 20° C. in a 2-decimetre tube, using a polarimeter accurate to within 0.02°.

The ecgonine as a percentage of the raw cocaine is given by the formula :

$$\text{Ecgonine} = \frac{a \times 25}{2 \times 57} \times \frac{100}{w} = \frac{21.929 a}{p}, \text{ or practically } \frac{22 a}{w}$$

Where a = the optical rotation in degrees ;

w = weight of raw cocaine ;

+ 57° = the specific rotatory power of ecgonine.

Cocaine = Ecgonine \times 1.64.

Express the result in terms of cocaine as a percentage of the original and of the dried raw cocaine.

III. *Determination for Control of the Acids combined with the Alkaloids.*

As a check on the content of ecgonine, the combined acids (benzoic, cinnamic, truxillic) may be determined. The result obtained by titration of the acids should agree substantially with that obtained polarimetrically.

Weigh accurately in a small flask about 0.5 gramme of raw cocaine and dissolve it in 5 c.c. of acetone and 5 c.c. of 2 N sodium hydroxide solution. Add some small pieces of pumice and boil the solution for 15 minutes, using a reflux condenser.

Disconnect the flask and evaporate the acetone on a water-bath. Cool the liquid and transfer it to a separator, rinsing the flask with about 15 c.c. of water. Add 10 c.c. of 2 N hydrochloric acid and shake the liquid vigorously for one minute with 30 c.c. of a mixture of two parts by volume of ether and one part of light

petroleum (boiling-point 40° to 60° C.). Allow the mixture to separate and remove the ether layer.¹ Extract the acid liquid in a similar manner successively with two further quantities of 30 c.c. of the mixture of ether and light petroleum.

Dry the ethereal extracts with 1 gramme of anhydrous sodium sulphate and filter into a flask ; wash the filter with a small quantity of the solvent. Evaporate the solvent at a temperature of about 30° C. using reduced pressure and blowing a current of air over the surface.² Dissolve the residue in 5 c.c. alcohol (95% by volume) previously neutralised to phenolphthalein and titrate the solution with N/10 solution of sodium or potassium hydroxide, using 2 drops of a 1% solution of phenolphthalein as indicator.

$$\begin{aligned} 1 \text{ c.c. N/10 alkali solution} &= 0.0185 \text{ gramme ecgonine} \\ &= 0.0303 \text{ gramme cocaine.} \end{aligned}$$

C. SAMPLING OF COCA LEAVES.

Samples of coca leaves taken for analysis should amount to :

0.5%	for quantities below 500 kilogrammes,
0.25% „ „	between 500 and 1,000 kilogrammes,
0.15% „ „	above 1,000 kilogrammes,

¹ It is convenient to use a separator consisting of a cylindrical tube through the cork of which two tubes are passed, one bent at its lower end and acting as a siphon so as to remove the ether layer.

The attached figure (Fig. 5) makes it unnecessary to explain the working of this fitment.

Each extraction will be followed by washing with ether (two washings with about 5 c.c. in each case after the first extraction, one washing after each subsequent extraction).

The tube can be placed in a low-speed centrifuge to hasten the separation of the ether layer.

² It is convenient to close the flask with a stopper fitted with two tubes, one of which is connected to a pump the other being a capillary tube open to the air and adjusted so that it is a few centimetres above the surface of the ether. The flask is partly immersed in a water bath at 30° C. A slight vacuum (about 400 millimetres) ensures rapid evaporation of the ether.

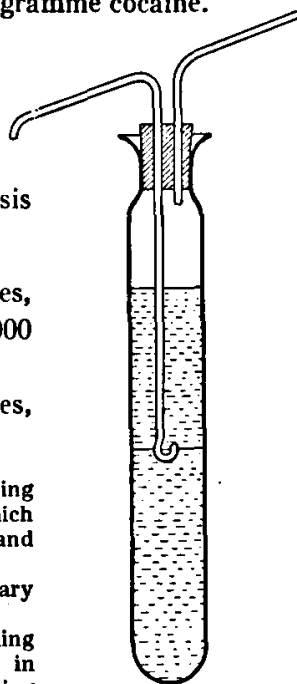


Fig. 5.

provided that the quantity taken shall in no case be less than 2 kilogrammes.

For the taking of these samples, recourse may be had with advantage to sampling irons of different sizes (as used in Amsterdam) which yield samples of 40 to 50 grammes in the case of the smaller irons, and of 140 to 150 grammes in that of the larger irons.

If the coca leaf is put up in compressed bales, samples may be taken with a 5-centimetre diameter mechanical borer, which should be driven in laterally to the centre, about half way along the bale (usual depth reached 15 to 20 centimetres).

If the coca is in the form of whole leaves, which are sometimes used for cocaine extraction, the leaves should be ground up and mixed before a sample of the above-mentioned proportions is taken.

Samples taken should be carefully mixed and parts should be placed in a stoppered bottle for despatch to the laboratory.

D. ANALYSIS OF COCA LEAVES.

I. *Preparation of the Sample.*

(a) If the sample will pass through a sieve of 2-millimetre mesh (Amsterdam condition) it shall be used as received.

(b) If not, it shall be ground until it will pass through such a sieve.

II. *Determination of Moisture.*

Weigh accurately in a glass-stoppered weighing tube about 2 grammes of the sample. Dry at a temperature of 103°-105° C. for 4 hours, cool in a desiccator containing sulphuric acid and weigh.

Continue the drying for half an hour and repeat if necessary until the loss in weight between successive weighings is not more than 5 milligrammes. Calculate the moisture as a percentage of the coca leaves.

III. *Determination of Ether-soluble Ecgonine Alkaloids.*

Mix in a mortar¹ till the mixture is homogeneous 20 grammes of the sample with 20 c.c. of 2 N solution of sodium carbonate and allow to stand for half an hour, stirring from time to time. Transfer the mixture to a suitable apparatus for continuous extraction under a reflux condenser. Drench immediately with ether; extract in such a manner that the ether runs in an almost continuous stream out of the condenser. Continue the extraction for several hours, and allow to stand overnight, the powder being completely covered with ether; resume the extraction on the following day until a total extraction of 8 hours is reached. Transfer the ethereal extract to a separator, rinsing the flask with ether and adding the rinsings to the extraction ether contained in the separator. Shake the ethereal solution vigorously for one minute with 20 c.c. of N/10 solution of hydrochloric acid. Allow the mixture to separate and run off the lower layer, filtering the liquid through a small plug of cotton wool. Extract the ethereal solution in a similar manner successively with two further quantities of 15 and 10 c.c. of N/10 solution of hydrochloric acid. Add to the acid liquid which is placed in a separator, 30 c.c. of a mixture of two parts by volume of ether and one part of light petroleum (boiling-point 40° to 60° C.). Add 1 gramme of sodium bicarbonate in several portions. Shake vigorously for one minute, allow to separate and remove the ether layer.² Continue the extraction of the watery liquid successively with three further quantities of 30 c.c. of a similar mixture of ether and light petroleum.

Dry the ethereal solutions with 1 gramme of anhydrous sodium sulphate, filter through a small plug of cotton wool into a tared flask, wash the sodium sulphate adhering to the filter with a mixture of the two solvents, and evaporate the latter. Dissolve the residue in 5 c.c. of neutral alcohol (95% by volume), add 2 drops of a solution of methyl red (0.05%) and titrate with N/10 solution of hydrochloric or sulphuric acid until a faint orange colour is produced. Then add 50 c.c. of freshly boiled and cooled water and continue the titration until the solution turns red.

¹ It is advisable to admix the sodium carbonate solution gradually in quantities of about 2 c.c.

² It is convenient to use the technique described on pages 444-445.

$$\begin{aligned} 1 \text{ c.c. N/10 acid solution} &= 0.0185 \text{ gramme of ecgonine} \\ &= 0.0303 \text{ gramme of cocaine.} \end{aligned}$$

Express the result in terms of cocaine as a percentage of the original and of the dried leaves.

IV. *Determination for Control of the Acid combined with the Alkaloids.*

As a check on the titration of the ecgonine alkaloids, the combined acids (benzoic, cinnamic, truxillic) may be determined. The result obtained by titration of the acids should agree substantially with that obtained by titration of the alkaloids.

Add to the solution from the titration of the alkaloids 5 c.c. of 2 N sodium hydroxide solution. Add some small pieces of pumice and boil the solution until the liquid is reduced to about 10 c.c. and then continue boiling for 5 minutes, using a reflux condenser to prevent evaporation of the liquid. Cool the liquid and transfer it to a separator, rinsing the flask with about 15 c.c. of water. Add 10 c.c. of 2 N hydrochloric acid and shake the liquid vigorously for one minute with 30 c.c. of a mixture of two parts by volume of ether and one part of light petroleum (boiling range 40°-60° C.). Allow the mixture to separate and remove the ether layer.¹ Continue extraction of the acid liquid in a similar way successively with two further quantities of 30 c.c. of the mixture of ether and light petroleum. Dry the ethereal solutions by adding 1 gramme of anhydrous sodium sulphate, filter the ethereal solutions into a conical flask and wash the filter with a small quantity of the solvent. Evaporate the solvent at a temperature of about 30° C. using reduced pressure and blowing a current of air over the surface.² Dissolve the residue in 5 c.c. of alcohol (95% by volume) previously neutralised to phenolphthalein and titrate the solution with N/10 solution of sodium or potassium hydroxide, using two drops of a 1% solution of phenolphthalein as indicator.

$$\begin{aligned} 1 \text{ c.c. N/10 alkali solution} &= 0.0185 \text{ gramme ecgonine} \\ &= 0.0303 \text{ gramme cocaine.} \end{aligned}$$

¹ See footnote 1, page 445.

² It is convenient to use the technique described on pages 444-445.

REAGENTS REQUIRED FOR THE ESTIMATION OF THE ECGONINE-
ALKALOIDS CONTENT OF RAW COCAINE AND COCA LEAVES.

- 2 N hydrochloric acid.
- 0.1 N hydrochloric acid.
- 2 N sodium hydroxide solution.
- 0.1 N sodium hydroxide solution.
- 2 N sodium carbonate solution.

Phenolphthalein.

A solution of 1 gramme phenolphthalein in 100 c.c. alcohol (95% by volume).

Methyl Red.

Dissolve, while warming slightly, 0.05 gramme of dimethyl-aminoazobenzene — o — carboic acid ((CH₃)₂N — C₆H₄ — N = N — C₆H₄ — COOH) in 75 c.c. alcohol (95% by volume) and complete with water up to a volume of 100 c.c.

Ether.

Diethyl-ether (C₂H₅)₂O, alcohol free, specific gravity (15°/15°) not more than 0.720. Boiling range 34°-35.5°. Must comply with the test for purity in the pharmacopœiæ.

Light Petroleum.

A colourless, very volatile, highly inflammable liquid, obtained from petroleum, consisting of a mixture of the lower members of the paraffin hydrocarbons, and complying with the following definitions : Specific gravity (15°/15°) 0.65-0.67. Boiling range 40°-60°.

Alcohol.

Containing approximately 95% (v/v 15°) or 92.4% w/w of ethyl alcohol. Specific gravity (15°/15°) 0.816.

Acetone.

Dimethyl ketone (CH₃)₂CO, specific gravity (15°/15°) 0.80.

Sodium Sulphate, Anhydrous.

The salt of the formula $\text{Na}_2\text{SO}_4, \text{H}_2\text{O}$.

Test for neutrality. Dissolve 0.5 gramme in 10 c.c. of water, add 5 drops of blue bromothymol solution (B.P.). A green colour but not a yellow or a blue colour must be produced.

Pumice.

The particles of commercial pumice, powdered and sifted, which pass a sieve of 1-millimetre mesh and are retained by a sieve of 0.25-millimetre mesh.

**SENSITIVENESS AND SPECIFICITY
OF A BORDET-WASSERMANN
REACTION (MORCH)
AND KAHN'S STANDARD REACTION**

By

P. KRAG,

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Since the autumn of 1930, when the League of Nations' Third Laboratory Conference on the Sero-diagnosis of Syphilis was held at Montevideo, a number of experiments have been performed with a new Wassermann antigen at the State Serum Institute in Copenhagen.

In the years 1924 to 1930, the former head of the sero-diagnostic department, the late J. R. MØRCH, had worked out a Bordet-Wassermann-modification (hereinafter called WR) having a marked degree of sensitiveness and specificity. During a period of several years, the sero-diagnostic department tested this new modification comparatively with the Bordet-Wassermann method as formerly used (THOMSEN-BOAS human-heart extract (WaR H-H), and the Kahn reaction with standard extract (KR)).

In order to check the findings obtained with samples examined in the department, MØRCH (1) followed up 55,000 cases from the years 1934-1935. The result was as follows as regards blood samples:

The sensitiveness of WR and KR was the same, whereas the sensitiveness of WaR H-H was only one-third as great;

The unspecificity (false positive reactions expressed as a percentage of the negative control material) was about 1‰ for KR and only 0.5‰ for the Wassermann methods.

MØRCH also asserted that the sensitivity of WR and KR depends on the kind of material to be tested: KR is specially sensitive in the

case of previously treated syphilis, whereas WR is markedly sensitive to fresh syphilis.

Similar tests were made with cerebro-spinal fluids, and showed WaR H-H to be slightly sensitive and KR to be better though less sensitive than WR.

As for specificity : there were no unspecific reactions with the Wassermann methods, and some with KR, often with atypical flocculation.

Since 1934, Mørch's Wassermann modification (called WR) has been constantly used, all samples sent in being tested by WR and by Kahn's standard reaction (KR). In addition, about 12% of the samples were examined with the following reactions :

- Presumptive Kahn reaction (PK) ;
- Müller's *Ballung* (conglomeration) reaction (MB) ;
- Meinicke's *Klärung* (clarification) reaction (MK).

This more comprehensive test is recommended alike for the verification of re-tests in serological diagnosis of new cases, and for the demonstration of weak reactions (fresh cases, treatment control, etc.).

TECHNICAL DATA.

Description of Mørch's Bordet-Wassermann Modification (WR).

The antigen is an optimally cholesterinised alcoholic extract of dried calf's heart previously extracted with acetone. For use, the extract is diluted with salt solution in two stages :

- (1) 1 c.c. antigen + 1.1 c.c. (or thereabouts) of salt solution as with the Kahn antigen ;
- (2) Dilute again rapidly with salt solution to a total volume of 150 c.c. (or thereabouts) ;

the degree of dilution at both stages being titrated for each new antigen by comparison with earlier preparations.

The constant specificity and sensitiveness of the antigen are ensured by a long series of double tests, clinical information as to any divergent results being sought whenever a new portion of the antigen is brought into use.

Daily Routine Work.

The constancy of the sensitiveness in daily routine work is secured by :

- (1) Careful complement titration ;
- (2) Daily testing of six control sera.

Sera are always titrated with a dilution series extending to the level of a negative reaction.

Technique.

Serum doses : 0.025 c.c.—1/3 0.025 c.c.—1/9 0.025 c.c., etc.

Antigen dilution : 0.20 c.c.

Complement dilution : 0.10 c.c. of a solution of 1 in 18 to 1 in 33 (the concentration depending on the day's titration).

Fixation : 45 minutes at room temperature + 45 minutes at 37° C.

Blood : 0.20 c.c. of a 2½% sheep's blood corpuscle suspension with three times the titre dose of amboceptor.

Hæmolysis : 1 hour at 37°.

Standing time : 15-16 hours (overnight) in ice-box (+ 4°).

Reading : By hæmolysis percentage scale, ranging from 0 to 100% hæmolysis.

Converting hæmolysis percentages by slide rule into degrees of strength, (2) we obtain a logarithmic value of the titre of the sample, the degree of strength being indicated as the value of n (in the formula $a = 0.025 \cdot 3^{-n/3}$), where a is the quantity of serum which just causes the weakest complement fixation reaction (60.100). The reaction 10 60 100 is strength 3, and 0 10 60 100 is strength 6.

Kahn's standard reaction (KR) is carried out with standard extract from the University of Michigan ; titration is also carried to the end point in KR, but, as in WR, we have used a falling series of doses obtained by successive divisions by 3—i.e., 0.15—0.05—1/3 0.05, and so on.

The result is read according to the degree of flocculation as described by Kahn, but the titration is indicated in degrees of strength

as in WR. The relation between Kahn's units and our degrees of strength will be seen from the following :

10 units	correspond to	strength	3 ;
20	„	„	„ 5 ;
40	„	„	„ 7 ;
60	„	„	„ 8 ;

and so on, the decimals being rounded off.

The three more sensitive precipitation tests are carried out according to the three authors' own descriptions, though the Meinicke reaction is performed as M K R II, with both *Klärung* (clarification) reading and the centrifuging method.

* * *

Three years having passed since Mørch's exposition, I considered it of interest to undertake a similar examination of routine work material, partly in order to verify the results of 1935/1936, partly in order to probe further into the sensitiveness and specificity of the tests.

As this department has a file of all syphilitics examined since 1920 (3), (4), it has been possible by reference to this file, to get particulars of medical history and clinical facts relating to a large number of cases.

The material comprises all samples examined in the course of the first quarter of 1937. Since January 1st, 1937, in all cases in which a serological reaction was detected for the first time, I have procured particulars of the clinical diagnosis, and any evidence pointing to syphilis that is afforded by examination findings, medical history and temperature records.

A total of 26,028 blood samples came in during the first quarter :

A.

Of these, 5,239 were control-tests of syphilitics under treatment, or latent or cured cases :

5,135 of these samples were tested by both Mørch's Bordet-Wassermann modification (WR) and Kahn's reaction (KR) ;
 3,216 were negative to both methods ;
 1,919 yielded a positive reaction to one or both tests. Sub classification of these 1,919 by strengths according to the

findings of the WR and KR tests gave the following totals for the various strengths (Table I) :

Table I.

Strength	WR	KR
0	315	114
1	346	525
2	165	285
3	160	229
4	205	153
5	143	161
6	118	123
7	157	79
8	136	82
9	68	49
10	39	49
11	19	22
12	10	23
>12	38	25
	1,919	1,919

Observations.

- (1) WR positive 1,604 times, KR positive 1,805 times.
- (2) Strengths 1, 2 and 3 show a considerable preponderance of KR :

$$\text{KR : } 525 + 285 + 229 = 1,039$$

$$\text{WR : } 346 + 165 + 160 = 671, \text{ or } 368 \text{ more KR than WR.}$$

- (3) The higher strengths 4-9 show a corresponding preponderance of WR (180 more than KR).

- (4) The number of samples yielding respectively concordant and divergent WR and KR findings was :

	$\cong 1$		$\cong 3$	
	Number of cases	Percentage	Number of cases	Percentage
WR<KR	681	35.5	215	23.6
WR=KR	429	22.4	230	25.3
WR>KR	809	42.1	464	51.1

Conclusion.

A simple count is misleading.

WR is more sensitive generally, but KR has one sphere (strengths 1, 2 and 3) in which it is superior to WR.

B.

In the same period there were examined 20,789 patients who were not in the file prior to December 1st, 1936 :

19,405 were negative ;

585 had a sero-reaction for the first time (799 tests, representing re-tests, too little serum, reaction unreadable, old syphilis hitherto not on file are not included in the calculation).

The 585 new sero-reactions were :

122 of fresh syphilis ;

114 of old syphilis (tertiary, vascular, cerebral) or congenital ;

41 of old syphilis verified by the medical history ;

201 of " observation for latent syphilis ", there being no clinical-anamnestic indications of syphilis ;

107 doubtful reactions (negative WR and KR, but 1, 2 or 3 of the sensitive precipitation reactions positive).

Sensitiveness.

The sensitiveness of WR and KR in the three groups of newly-diagnosed syphilis was very uniform, as evidenced by practically the same number of reactions (Table II) ; throughout, however, WR tended to react more strongly than KR. In the case of fresh syphilis especially, the sensitiveness of WR was pronounced : $WR > KR$ in 55% of the cases and $WR < KR$ in 15%.

Table II.—Number of Positives.

	Fresh syphilis		Mixed clinical old syphilis		Syphilis verified by med. history		Exclusive sero-diagnosis obs. for <i>Syph. latens</i>		
	WR	KR	WR	KR	WR	KR	WR	KR	
All strengths	104	105	105	112	39	40	108	180	
Strength 3 and over ...	102	97	99	95	36	35	69	63	
	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	
All strengths	WR < KR ..	18	15	31	27	12	29	112	56
	WR = KR ..	37	30	29	25.5	7	17	29	14.5
	WR > KR ..	67	55	54	47.5	22	54	59	29.5

Specificity.

201 cases without other supporting diagnostic evidence of syphilis among about 20,000 examinations represent about 1% ; the error of the methods therefore lies below this figure, for serological observations of 149 of the cases showed that 74 displayed a spontaneous decrease of the original reaction in from one to three weeks, whereas 75 were constant.

These 74 cases are definitely wrong diagnoses.

From records of the findings it is seen that :

WR was temporarily positive 22 times ; percentage of error 0.1 ;

KR was temporarily positive 65 times ; percentage of error 0.3 ;

there being 52 instances in which KR yielded a transient value of 1, whilst the corresponding figure for WR is 11. This low specificity of KR = 1 should be borne in mind having regard to the high degree of sensitiveness manifested in the examination of old, treated syphilis, for unspecific reactions in syphilitics doubtless occur from time to time.

If only the strong reactions are taken into account, we find that WR and KR are the same :

At strengths ≥ 3 , incorrect reactions were 9 WR and 8 KR—*i.e.*, percentage error approximately 0.05 (in five of the cases both WR and KR were ≥ 3 , so that there was a possibility of a serious error (0.025%)).

It being usual in Denmark to take samples of blood from all patients admitted to medical departments whatever their disease, and send them in for a syphilis sero-diagnostic test, we have thus a large and varied mass of control material including many cases of febrile pulmonary affections, cancer and inflammations of the internal female genitalia.

This, of course, burdens our control material, but, on the other hand, it has provided valuable information as to the frequency of transient sero-reactions (5), especially in the case of the affections referred to above.

Guided by this experience, we always request an observation period of four to six weeks for the diagnosis of syphilis on a purely serological basis.

WR and KR are very nearly equal in sensitiveness and specificity. As a rule, WR will be somewhat stronger (*i.e.*, more sensitive) than KR, except when applied to old, treated syphilis, which yields KR strengths of 1 and 2 in a large number of cases.

In the lower range of strengths, the specificity of WR is better than that of KR.

In the higher range of strengths, the specificity of both tests is equal.

A similar survey of the sensitiveness and specificity of the sensitive precipitation reactions (PK, MB and MK) will be published later, together with a more complete account of the results discussed above.

* * *

A compilation has also been made of the results of the testing of 1,664 spinal fluids by MØRCH'S Bordet-Wassermann modification (WR), MÜLLER'S *Ballung* (conglomeration) reaction (MB) and MEINICKE'S *Klärung* (clarification) reaction (MK). Of these fluids, 1,506 were negative to all three tests; the remaining 158 are distributed in the following:

	≧ 3 strong	= 2 weak	= 1 doubtful	None
WR	123	11	14	10
Müller conglomeration	104	29	13	12
Meinicke clarification	116	21	19	2

which means that the three methods give the same total of reactions, taking the weak and strong groups together—*viz.*, 134, 133 and 137 respectively.

Conclusion.

As a test for cerebro-spinal fluid, WR is quite equal to the precipitation test. The specificity cannot be calculated from this material since the majority of samples are sent in from syphilitics or cases suspected of syphilis; the number of samples from non-syphilitics is so low that the information concerning non-specific reactions (possibly one such reaction) in this material is valueless.

SUMMARY.

At the League of Nations' Laboratory Conferences—1928 in Copenhagen and 1930 in Montevideo—it was agreed that :

“ The best of the precipitation tests were demonstrated to be superior as regards sensitiveness and equal as regards specificity to the B.-W. reaction and its modifications.”

The investigation of WR (MØRCH's Bordet-Wassermann modification) and KR (KAHN's standard reaction) which has been described above, appears to show that we now have complement-fixation tests that are equal to the KAHN test in respect both of sensitiveness and of specificity, though each of these two kinds of tests has certain advantages and certain defects.

Other institutes having had the same experience, it would accordingly seem advisable when the opportunity arises at a new laboratory conference to compare the more recent modifications of complement fixation with the precipitation tests—those already examined as well as those which have appeared since.

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**REPORT BY THE
TECHNICAL COMMISSION ON NUTRITION
ON THE WORK OF ITS THIRD SESSION**
Held in London from November 15th to 20th, 1937.

CONTENTS.

	Page
<i>Introduction</i>	431
I. CONSIDERATION OF THE AVAILABLE KNOWLEDGE REGARDING CERTAIN SPECIFIC PROBLEMS OF THE SCIENCE OF NUTRITION :	
A. Mineral Requirements	470
B. Vitamin Requirements	472
C. Proteins	476
D. Fats	478
E. Nutritional Requirements during the First Year of Life	479
II. THE NUTRITIVE VALUE OF MILK	483
III. NUTRITION SURVEYS	486
A. Studies of Food Consumption	486
B. Methods of Assessing the State of Nutrition in Infants and Adolescents	496
IV. NUTRITION PROBLEMS OF THE FAR EAST	499
V. STUDIES ON NUTRITION IN CHILE	502

INTRODUCTION.

It will be remembered that the two previous sessions of the Technical Commission on Nutrition were held in November 1935 and June 1936. The Commission had been asked to define, in accordance with modern concepts of physiology, the principles of nutrition best suited to ensure the fullest development and the maintenance of the organism. This work culminated in the "Report on the Physiological Bases of Nutrition", published in the September 1936 issue of the Bulletin of the Health Organisation.

That report ended with a list of ten questions, into which the Commission felt that further investigations were required. Some referred to a number of issues in dietetics which are still obscure; others related to the technique of dietary surveys and to suitable methods of assessing the nutritional state of the organism and at the same time detecting any deficiencies of diet. These ten questions are given below, as arranged in order of priority:

- A. Assessment of the state of nutrition in children and adolescents.*
- B. Nutritive food requirements during the first year of life.*
- C. Minimum vitamin and mineral requirements.*
- D. Minimum fat requirements.*
- E. The nutritive and "supplementary" values of the different protein-containing foods, to determine to what extent and in what forms animal protein is necessary for growth and health.*
- F. The relative nutritive value of different cereals according to the degree of milling.*
- G. The extent to which the increasing consumption of sugar is detrimental to health.*
- H. Influence of climate on food requirements.*
- I. The extent to which diets in common use fall below the standards recommended in this report.*
- J. The optimum amounts of milk required at different ages.*

The Commission's report was forwarded to learned societies and scientific institutions in various countries, in order to obtain their views and induce them to take a share in the investigations listed above.¹ Most of these institutions accordingly set up commissions and sub-commissions, each with its own rapporteur, and divided among them the problems recommended for further study according to the relative importance of such problems within the national sphere and to the work already undertaken by the health services and national laboratories.

It is clear that the Technical Commission could not contemplate the simultaneous systematic investigation of all ten questions. Accordingly, attention was concentrated, in 1936, on the first two problems, which were considered of quite special importance—namely :

- A. *Assessment of the state of nutrition in children and adolescents.*
- B. *Nutritive food requirements during the first year of life.*

In December 1936, a meeting was held of the rapporteurs of the various commissions and sub-commissions to which these two problems had been referred by the learned societies and scientific institutions

¹ Those institutions fall into three categories :

1. Academies of medicine, academies of science and scientific commissions :

United States of America : National Academy of Science and United States Nutrition Institute.

Belgium : Royal Academy of Medicine.

United Kingdom : Medical Research Council.

France : Academy of Medicine.

Italy : National Research Council.

Netherlands : Academy of Science.

Spain : Madrid Academy of Medicine.

Union of Soviet Socialist Republics : Scientific Research Council.

2. Commissions whose competence covers nutritional problems :

Australia : Advisory Committee on Nutrition.

United Kingdom : Advisory Committee on Nutrition, responsible to the Ministry of Health and the Secretary of State for Scotland.

Denmark : Advisory Committee on Nutrition.

Norway : Norwegian Committee on Nutrition.

Turkey : National Committee on Nutrition.

3. National councils specially set up for the study of nutritional problems and for co-operation with the League of Nations :

France : National Committee for the Study of the Problem of Nutrition.

Sweden : Royal Committee on Nutrition.

of different countries. On the first problem, that of the assessment of the state of nutrition in infants and adolescents, the group of experts presided over by Professor LAUGIER (France) submitted a report¹ recommending three types of survey : the first, which is of a general character, is designed to afford a ready idea of the state of nutrition of large numbers of children ; the second and third types, covering a much smaller number of subjects, involve more thorough and more elaborate scientific investigation, somatometric, clinical and physiological tests to detect at the earliest possible moment the first signs of malnutrition attributable to a deficiency, however slight, in the diet.

On the second problem, that of nutritive requirements during the first year of life, a group of experts, of which the chairman was Professor GORTER (Netherlands), drew up a report² which includes a number of recommendations bearing upon the diet of the infant. The experts endeavoured to express their views in the simplest language, so as to make them readily accessible to all medical or social organisations that might be interested. They themselves also suggested that further enquiries should be undertaken into the following three questions :

1. Has the daily administration of more than 750 c.c. of cow's milk to children between six months and one year any unfavourable influence on the nutritive exchanges and, in particular, on the absorption of calcium and iron ?

2. What are the differences between the action of an artificial preparation of an irradiated sterol and that of irradiated milk, when quantities containing the same number of international units of vitamin D are administered ?

3. Is it desirable to provide systematic preventive treatment against anæmia for all children between four months and one year by the administration of an iron salt ?

The study of questions A and B, which headed the Technical Commission's programme of work, had thus led to the submission of conclusions jointly prepared by the appropriate national rapporteurs. Their reports were included in the agenda of the third session of the Technical Commission on Nutrition, for which a number of notes dealing with question A had also been received. Those notes related

¹ *Bulletin of the Health Organisation*, 1937, 6, 129.

² *Ibid.*, 291.

particularly to pre-deficiency tests and to the results of various enquiries designed to ascertain the state of nutrition of various population-groups. In the following report, the Technical Commission has dealt, under III, B, with methods of assessing the nutritional state of children and adolescents, and under I, E, with nutritional requirements during the first year of life.

The following three questions were problems of a scientific character which fell exactly within the scope of the Commission's first report—namely :

- C. Minimum vitamin and mineral requirements ;
- D. Minimum fat requirements ;
- E. The nutritive and supplementary values of the different protein-containing foods.

The Commission had asked a number of its members to prepare a report upon each of these problems. At its meeting¹ in November 1936, it examined the conclusions of the rapporteurs so appointed, and,

¹ The following members attended this meeting :

- Sir Edward MELLANBY, K.C.B., Secretary-General of the Medical Research Council, London (*Chairman*) ;
- Dr. E. P. CATHCART, Professor of Physiology, Glasgow University ;
- Dr. L. S. FRIDERICIA, Professor of Hygiene at the Copenhagen University ;
- Professor Axel HÖJER, General Director of the Public Health Services, Stockholm ;
- Dr. André MAYER, Professor of Physiological Chemistry at the Collège de France, Paris ;
- Dr. E. V. McCOLLUM, Professor of Biochemistry, Johns Hopkins University, Baltimore ;
- Sir John Boyd ORR, Director of the Imperial Bureau of Animal Nutrition, Rowett Institute, Aberdeen ;
- Professor W. H. SEBRELL, Chief of the Department of Nutrition, National Institute of Hygiene, Washington ;
- Professor Mary SWARZ ROSE, Department of Nutrition, Columbia University, New York.

Technical secretaries of the Commission :

- Miss Harriette CHICK, Lister Institute of Preventive Medicine, London ;
- Dr. E. J. BIGWOOD, Professor at the Université Libre, Brussels.

The following also attended the meeting :

- Miss H. STRIEBELING, Bureau of Home Economics, Department of Agriculture, Washington ;
- Professor A. G. VAN VEEN, Head of Chemical Department, Medical Laboratory, Batavia.

in the first four chapters of its own report, made a brief survey of the present state of our knowledge concerning human requirements of inorganic substances, vitamins, proteins and fats. It will be seen that the Commission proposes the following four new subjects for investigation:

- (1) Factors influencing the utilisation of calcium and phosphorus ;
- (2) Determination in man, by biological tests, of the assimilable proportion of iron contained in various foods ;
- (3) Determination of the amounts of iron required by adults of both sexes, with special reference to women during menstruation, pregnancy and lactation ;
- (4) Assimilation of iron by children at various ages, when the diet given is one in which the assimilable proportion of the iron content has been ascertained in advance.

The last of the questions included in the list which we have quoted at the beginning of this introduction—that of the optimum amounts of milk required at different ages—was also a scientific problem, and was referred by the Commission for investigation to one of its members.

In this connection, the Health Committee, in the second half of 1936, organised a special enquiry into the questions of hygiene involved in the production, transport and distribution of milk. That enquiry culminated in a report laying down a number of principles, the observance of which would be desirable in the interests of the production and distribution of pure milk.¹

The Technical Commission was thus called upon to examine the milk problem as a whole. As regards the place which milk should occupy in a balanced diet, by reason of its special properties, it will be remembered that the Commission had already fully defined its position in its "Report on the Physiological Bases of Nutrition". In the report which follows, the Commission has endeavoured to show, under II, why, in the light of recent scientific research, milk constitutes a food of outstanding value, especially during the period of growth. The Commission also lays stress on the importance of eliminating the noxious properties of milk as a possible vehicle for bacterial infection. Finally, it shows how skim-milk can be turned to good account.

¹ See *Bulletin of the Health Organisation*, 1937, 6, 371.

The Health Organisation is thus now in possession of a comprehensive body of information on the value of milk as a protective food, on the means of deriving the maximum advantage from it, and on the conditions to be observed in order that the production, preservation and distribution of milk may answer the demands of modern scientific knowledge.

Of the ten questions included in the Technical Commission's programme, the above are those which were dealt with at its session in November 1937.

Four questions remain :

F. The relative nutritive value of different cereals according to the degree of milling.

G. The extent to which the increasing consumption of sugar is detrimental to health.

H. Influence of climate on food requirements.

I. The extent to which diets in common use fall below the standards recommended in the report on the Physiological Bases of Nutrition.

Problems F and G will appear in the programme of future work of the Commission, together with the various questions relating to human requirements of inorganic substances, the study of which has now been proposed by the Technical Commission.

The two remaining problems call for certain comments.

Influence of Climate on Food Requirements (H).—The agenda of the Intergovernmental Conference of Far Eastern Countries on Rural Hygiene (Java, August 1937) included the question of nutrition in the Far East. The Conference devoted Chapter IV of its report¹ to this question. The last Assembly of the League of Nations, acting upon a recommendation submitted by the General-Advisory Health Council (May 1937), also asked that the Technical Commission should undertake a study of the diet of the populations of Asia and of tropical countries generally.

It follows that the Commission's activities will be more and more directed towards countries outside Europe, and particularly towards

¹ Published in September 1937 as document A.19.1937.

tropical and sub-tropical countries. The Technical Commission has already undertaken an examination of the recommendations of the Java Conference, and, under IV in the report which follows, it submits a preliminary programme of studies to be carried out under its auspices, principally in the Far East. In preparing this programme, it has had the assistance of Professor A. G. VAN VEEN, head of Chemical Department of the Batavia Medical Laboratory and joint-rapporteur on nutrition to the Java Conference. The examination of this draft programme is to be continued at the Commission's next session.

The Extent to which Diets in Common Use fall below the Standards recommended in the Report on the Physiological Bases of Nutrition (I).—A beginning has already been made with the study of this question. In order to give a sufficiently accurate answer, it is essential to carry out dietary surveys to elicit fuller information as to actual diets in urban and rural districts. If, however, the results of such surveys are to be comparable, there must be previous agreement as to the method used.

The Technical Commission had, in fact, been asked to examine methods for carrying out dietary surveys, and under III, A and B, of the following report deals with that question : III, A, is concerned with the technique of surveys to determine the real consumption of foodstuffs, while III, B, to which reference has already been made, embodies the Commission's views on methods of assessing the nutritional state of children and adolescents.

A survey of the actual diets of urban and rural populations will, therefore, be in the forefront of the programme of work for 1938.

A meeting of directors of European Institutes and Schools of Hygiene, held in Geneva at the end of November 1937, made use of the general directions laid down by the Technical Commission for guidance in preparing a programme of studies to be carried out in rural areas. These studies would fall into three categories :

- (a) Quantitative studies for the determination of nutritional requirements ;
- (b) Quantitative studies for the detection of any deficiency in the diet of certain specified communities ;
- (c) Qualitative studies to serve as a basis for the elaboration of a nutrition policy.

Each of these three kinds of survey answers a practical purpose. The various countries will be guided in their choice by the work that has already been done in this field, by the problems to be solved, and the staff and resources available.

The National Committees on Nutrition and the Institutes and Schools of Hygiene of Belgium, Czechoslovakia, Finland, France, Hungary, Poland, Roumania, Sweden and Yugoslavia have intimated their intention of undertaking enquiries of this kind. Czechoslovakia, Hungary and Yugoslavia have already taken practical steps to this end. In January 1938, Dr. H. K. STIEBELING, Senior Food Economist of the Department of Agriculture at Washington, visited those three countries on behalf of the Health Organisation in order to assist the appropriate authorities in the organisation and co-ordination of the enquiries contemplated.

The last chapter of the Technical Commission's report deals with studies of nutrition in Chile.

It will be remembered that the Chilian Government asked for the help of the League of Nations in order to study the state of nutrition of the population, and that Professor E. BURNET (France) and Professor C. DRAGONI (Italy) went to Chile in 1935 on a study mission.

In June 1936, the Commission heard a statement from Professor BURNET and Professor DRAGONI on the purpose, method and conclusions of their investigation. At the request of the Chilian authorities, the Commission drew up a series of recommendations as to the measures to be contemplated in order both to improve national nutritional standards, and to provide for the continuation of the enquiries. Those recommendations were published in the Bulletin of the Health Organisation.¹

Since then, the Chilian Minister of Health, taking advantage of the Technical Commission's offer, has forwarded a number of official documents on the measures taken by the Chilian authorities to make good such deficiencies as had been revealed, and to co-ordinate further investigations. The Commission has examined this plan of action with great interest, and has replied to the Minister's communication.

¹ *Bulletin of the Health Organisation, 1936, 5, 424.*

The foregoing is a very brief summary of the work done by the Technical Commission on Nutrition since 1936, and of its programme of future work.

The Health Committee examined this programme on February 9th, 1938, and took the opportunity to pay a tribute to the perseverance of the Commission and to the success which had attended the execution of its programme. It also expressed its gratitude to the learned societies, national committees and scientists who had come forward to help the Commission.

The Health Committee attaches special importance to the investigations proposed by the Commission among the peoples of Asia and of tropical countries generally. Preparations are being made for the organisation and co-ordination of studies in the Far East, with the assistance of scientific institutions.

The Committee is also giving careful attention to the investigations into the actual nutrition of the rural communities which are being undertaken in Europe with the co-operation of the Institutes and Schools of Hygiene. These enquiries will furnish a technical basis for the work of the European Conference on Rural Life, which is to meet in July 1939.

In this connection, the Committee has decided to supplement these enquiries by a series of comparative studies on the composition of bread. The various kinds of bread consumed even in any single country—and, a fortiori, in different countries—often have little in common but their name, and show wide variations in nutritive value. In view of the part which bread plays in the diet of the rural population, these enquiries might prove quite valueless unless a preliminary study of the composition of the bread had been carried out.

The Health Committee has also decided to undertake enquiries into the effect of outbreaks of foot-and-mouth disease on rural economy, and particularly on the production, distribution and consumption of milk.

Lastly, it considers that the time has come to embody in a general report, and to translate into terms of practical application, the Technical Commission's recommendations concerning the bases of a rational diet.

I. CONSIDERATION OF THE AVAILABLE KNOWLEDGE REGARDING CERTAIN SPECIFIC PROBLEMS OF THE SCIENCE OF NUTRITION.

A. MINERAL REQUIREMENTS.

The knowledge available at the present time upon mineral requirements is imperfect, and the recommendations contained in the following paragraphs must be regarded as approximate and provisional.

(a) CALCIUM.

With present food habits, there is a grave risk of calcium deficiency in the diet. Although the efficient utilisation of calcium is closely related to adequate supplies of phosphorus and vitamin D, the reserves in the body will not be at their optima unless ample calcium is available for storage.

The results of numerous metabolic studies agree in indicating the *minimum requirement* of the adult for the *maintenance of calcium equilibrium* at about 0.5 gramme calcium daily. As a margin of safety, it is recommended that this intake should be increased by about 50%, say to 0.75 gramme daily, for a man of 70 kilogrammes body-weight, and in the case of the pregnant and lactating woman to about 1.5 grammes daily. Apart from breast-fed babies, the allowance of calcium for growing children should be about 1 gramme daily.

(b) PHOSPHORUS.

The adult requirement of phosphorus, which amounts to about 1 gramme daily, is usually provided by ordinary diets, owing to the wide distribution of this element in foods. Utilisation of phosphorus may be impaired, however, unless the supply of calcium is also adequate. This fact is of special significance in childhood when food must provide the amount needed for the formation of bony tissues.

(c) CALCIUM AND PHOSPHORUS.

The Commission again calls attention to the unique value of milk in all forms as a source of readily available calcium along with an abundance of phosphorus, and also to the importance of cheese, which may be regarded as a valuable dietary source of these elements.

The utilisation of both calcium and phosphorus is greatly enhanced in the presence of an abundant supply of vitamin D, as provided either in the diet or by sunshine.

In cases where cereals form a major source of the energy supply, especial emphasis should be laid upon liberal supplies of calcium and of vitamin D to correct any tendency of cereals to interfere with the storage of calcium and phosphorus in the body. The assimilation of calcium and phosphorus appears to be assisted by the presence of fat in the diet when the latter consists largely of cereals.

Problem recommended for Further Study :

Factors influencing the utilisation of calcium and phosphorus.

(d) IRON.

In view of the fact that in some foods part of the iron may not be absorbed, liberal standards should be set as guides to dietary practice. The value of lightly milled cereals is emphasised in this connection both because the outer layers of the grain contain considerable iron of easy utilisation and because these foods are relatively cheap.

A consensus of expert opinion at the present time would place the average requirement of the adult man for iron at about 10 milligrammes daily. The requirement of women of child-bearing age is higher, owing to the demands of menstruation, pregnancy and lactation.

Infants and children need to be safeguarded against nutritional anæmia by the use of suitable diets. Since this usually can be achieved by means of foods rich in iron, there is generally no need for iron medication.

Problems recommended for Further Study :

Determination in man, by biological tests, of the assimilable proportion of iron contained in various foods ;

Determination of the amounts of iron required by adults of both sexes, with special reference to women during menstruation, pregnancy and lactation ;

Assimilation of iron by children at various ages, when the diet given is one in which the assimilable proportion of the iron has been ascertained in advance.

(e) IODINE.

Iodine is an essential nutrient and the daily requirement of man appears to be less than one-tenth of a milligramme.

Iodine deficiency is generally conceded to be the chief dietary factor associated with endemic simple goitre. Since in some regions the amounts of iodine contained in the local water and locally grown foods are too low to prevent the occurrence of goitre, it is necessary that an extra supply be provided for the entire population of such districts.

The provision of iodine, in amount not exceeding 1 milligramme per week per person, has been strikingly successful in the prevention of goitre in such areas. Experience in the United States of America, Austria, Roumania, Switzerland and other countries has established the effectiveness of iodised salt for this purpose.

B. VITAMIN REQUIREMENTS.

Advance in our knowledge of man's requirements for each of the several vitamins is conditioned by the development of accepted techniques for the experimental determination of the minimum quantities needed to prevent the least impairment of function or structure, characteristic of a deficiency and of the quantities above which further dietary additions do not enhance the well-being of the body.

This work requires, on the one hand, extensive knowledge of the physiological action of the several vitamins and of the factors affecting their absorption and utilisation. On the other hand, it requires numerous and exact estimations of the vitamin content of food as eaten.

As yet there do not exist in the various countries comprehensive tables giving universally applicable figures of the average content of the various vitamins in different foods. Such tables should indicate the variability in vitamin content of each important food, as produced in different seasons and in different regions, and as affected by storage and by methods of preparation for consumption. One reason why such tables as exist are not satisfactory for international use is that the biological vitamin estimations made upon the various articles of food have too often been based upon the degree of response of the experimental animal, which is an exceedingly variable criterion, and have not been conducted in direct comparison with international standards, because the latter have been so recently established.

In all biological assays for vitamin potency, it is essential that simultaneous tests be made on stable materials employed as standards of comparison for the different vitamins. Such are (1) the official international standards adopted by the Vitamin Standardisation Conferences of the League of Nations, and distributed to all countries on behalf of the League, or (2) any subsidiary standard which has been compared with the latter by biological tests. Owing to the recent adoption of this principle, the figures published for the vitamin potency of any one food are frequently not comparable with those obtained in other laboratories or at different times.

For all the above reasons, the existing data on vitamin requirements are difficult to apply and also to establish, and all figures contained in this section are to be regarded as approximate and provisional.

(a) VITAMIN A.

The figures suggested at the present time by different investigators for the requirement of the *adult* for vitamin A vary from 1,400 to 3,000 international units daily, the difference being partly accounted for by differences in the vitamin A content assigned to common foods by different workers, and partly by the fact that no accepted technique for experimental determination of vitamin A

requirement has been developed and applied. It is probable that 2,000-4,000 international units daily may be regarded as a safe allowance. Such a supply is afforded by a daily intake, for example, of 500 millilitres of whole fluid milk, 1 egg, 25 grammes butter and a medium-sized serving of a green leafy vegetable.

The allowance for *pregnant and lactating women* should be greater than for other adults.

The requirements of *infants and all growing children* for vitamin A (and other vitamins) are relatively greater than for adults. The vitamin A requirements of infants may be met by the inclusion in the diet of a comparatively small amount of some substance rich in vitamin A, such as fish-liver oils.

(b) VITAMIN B₁.

As a result of considerable experience, an allowance of 10 international units per 100 calories of food-intake seems to be adequate. This allowance would place at 300 international units the daily requirement for an adult of 70 kilogrammes body-weight receiving a diet of 3,000 calories.

The above estimate has been confirmed by consideration of the vitamin B₁ content of a large number of diets which protected human beings from vitamin B₁ deficiency, in contrast to others which did not provide such protection.

The requirements of animals for vitamin B₁ have been shown experimentally to be greatly increased during pregnancy and lactation. Pending direct evidence, it is recommended that the diets of *pregnant and lactating women* should contain 2 to 3 times the minimum allowance for the adult in general. The quantities of vitamin B₁ recommended above would probably be contained in ordinary mixed diets when lightly milled cereals are a staple of the diet, or when milk, fruits and vegetables are freely used and highly milled cereals and sugars are not allowed to displace protective foods.

The requirements of the *infant* for vitamin B₁ would appear to be met by about 10-15 international units per 100 calories of food-intake. An allowance of 200-250 international units daily is probably sufficient for *nursery school-children*.

(c) VITAMIN B₂.

Vitamin B₂, previously used to signify the heat-stable portion of the water-soluble vitamin B complex, is now known to be multiple in nature and to include riboflavin, lactoflavin, the pellagra-preventive substance, and other factors the physiological and nutritional significance of which is at present obscure.

Any one of the following foods in the quantity indicated furnishes an adequate amount of the pellagra-preventive vitamin for the daily needs of an adult :

	Grammes
Dried yeast	30
Wheat germ (fat free)	150
Salmon ¹	170
Lean beef	200
Green peas ¹	450
Turnip greens ¹	480
Kale ¹	530
Juice from tomatoes ¹	1,200
Milk, fluid	1,200

(d) VITAMIN C OR ASCORBIC ACID.

The adult's requirement of ascorbic acid is no doubt covered by about 30 milligrammes daily, which has been shown to be a curative dose for adults suffering from scurvy.

There is evidence that the requirement of vitamin C is increased in, and following, febrile conditions.

In the case of *children*, special attention should be given to an abundant supply of vitamin C. *Artificially-fed infants* should receive a daily ration of 10-30 millilitres of orange or tomato juice (or the equivalent, in vitamin C potency, of other fruit or vegetable juices). This allowance provides 5-15 milligrammes of ascorbic acid, or 100-300 international units of vitamin C.

Cow's milk cannot be relied upon as a source of vitamin C for the infant. The heating required to make milk a safe food for infants reduces its relatively low initial content of vitamin C. The anti-scorbutic value of milk is also quickly reduced when bottled milk is exposed to light.

¹ Figures based on tests made on canned products.

(e) VITAMIN D.

The dietary requirement of vitamin D, both for adults and children, depends on the amount of sunshine enjoyed, as well as on the quantities of calcium and phosphorus in the diet. *Abundant supplies of vitamin D are especially needed by pregnant and lactating women.*

Adequate provision of vitamin D is also specially important in the case of *infants and children*. To protect infants from rickets, 150 international units daily have been found necessary. In order to promote full growth and vigour, a daily allowance of 400-500 international units is recommended. In temperate climates, in winter, when the supply of sunshine is meagre, this requirement is conveniently met by a small daily ration of cod-liver oil or other fish-liver oil.

C. PROTEINS.

Proteins yield upon digestion twenty-two relatively simple substances known as amino acids ; during metabolism, these are recombined in new patterns to form the proteins required for the body's growth and maintenance.

· BIOLOGICAL VALUE OF DIFFERENT PROTEINS.

There are certain amino acids which the body is incapable of synthesising and which must be supplied by food. Certain proteins do not contain one or other of these amino acids and they are not present in the same proportion in all proteins which do contain them. The proteins may have therefore very different " biological values " for nutrition.

Rations containing proteins of high biological value can be fed at lower levels than those containing proteins of lower biological value and yet give equal results in growth and maintenance. The economic value of knowledge of this kind derives from the fact that the protein-rich foods are more costly than the fats and carbohydrates, and proteins of high biological value more expensive than those of low value.

SUPPLEMENTARY ACTION OF PROTEINS.

The nutritive value of one and the same protein may also differ according to the combination with other proteins in which it is taken. Milk proteins are not only themselves of high biological value, but they have a high supplementary value for cereal proteins, enhancing the nutritive value of the latter so that they are much better utilised than when fed alone. In general, the supplementary value of one kind of vegetable protein for another is less than is that of the proteins of milk, meat or eggs for vegetable protein. Vegetable or cereal proteins are therefore more advantageously utilised if animal proteins are taken with them. The proteins of highest supplementary value are those of milk and eggs.

Extensive studies of the supplementary relations existing between the proteins contained in different feeding-stuffs have been made by agricultural scientists. The results of such studies have great economic value, as indicating the best mixture of proteins for promoting the growth of farm animals, for milk production in cows, for growth of wool in sheep, etc.

PROTEIN REQUIREMENT.

There has been much discussion of the question of the quantity of protein that should be supplied in the diet of man. Experiments on man and animals and observations of the dietary habits and the health and physique of different races indicate that a liberal allowance of protein is highly desirable during growth. They show also that, in the adult, health is enhanced by a protein allowance above the minimum amount which will just cover the daily nitrogen expenditure involved in the wear and tear of tissues in the processes of life and work. *The protein intake from a mixed diet which has been found consistent with prolonged maintenance of health in the adult is about one gramme daily per kilogramme of body-weight.*

The *pregnant woman* requires somewhat more protein than the non-pregnant woman. The demand for protein is relatively much greater in the lactating woman, since the milk proteins which she produces are formed from the food proteins of her diet.

D. FATS.

By the fat content of a food should be understood the content of esters of fatty acids, saturated or not, of phosphorus compounds of such fatty acids, and of substances known as lipoids, which are soluble in certain specific solvents, whether contained in the adipose tissues or not.

FAT REQUIREMENT.

The minimum quantity of fat or fatty substances which should be present in the diet is not known. Just as the minimum requirement of proteins depends on the nature of constituent amino acids, so also the minimum requirement of fat doubtless depends on the degree to which the constituent fatty acids are, or are not, indispensable. It will also depend upon the extent to which fat is absorbed from the intestine, and possibly also upon the presence of some other substances in the food, notably of certain mineral elements. The minimum quantity of fat cannot therefore be established in absolute terms.

A consideration of dietary habits shows that the consumption of fats and fatty substances varies greatly according to country and climate. It is very low in certain tropical countries and in the Far East. It is very high in certain northern countries, for example, among the Esquimaux. In countries with a temperate climate, in Western Europe and in the United States, the fat-intake cannot be very high without leading to digestive troubles and instinctive distaste. It cannot, on the other hand, be very low without leading to under-nutrition since the result is likely to be an inadequate energy intake.

In the countries of Western Europe and in the United States, feasible dietary limits might be defined as approximately 80-125 grammes of fat for a varied diet of 3,000 calories.

DIETARY VALUE OF FATS.

Fats are the most concentrated energy-bearing foods in the dietary and their inclusion in a diet makes it possible to provide

sufficient calories without increasing the bulk of the food to a degree which taxes the capacity of the digestive tract. People who are restricted to diets very low in fat frequently complain that they become hungry soon after a meal. A certain amount of fat seems necessary to ensure satisfactory digestion and absorption of some other nutrients.

In addition to their importance as foods of high calorie-value and their property of giving a sense of well-being which diets poor in fats fail to provide, certain fats are of extreme dietary importance as carriers of the fat-soluble vitamins A, D and E. Some yellow vegetable oils contain carotene, the provitamin A, rather than vitamin A itself. Carotene is converted in the body into vitamin A.

Many vegetable oils contain vitamin E, but none are known to contain vitamin D. The fats of milk carry both carotene and vitamin A. The degree of yellowness of milk, butter or cream does not serve as an indicator of their total vitamin A values, since the vitamin itself is colourless or only faintly yellow.

Vitamin D is found in abundance in fish-liver oils, which, however, differ greatly in their value. Cod-liver oil of average grade contains, per gramme, about 100 international units of vitamin D and 600 international units of vitamin A ; halibut-liver oil is about 100 times as rich as cod-liver oil in vitamin A and is also much richer in vitamin D. Certain species of percomorph fish-liver oils contain as much as 35,000 to 100,000 international units of vitamin D per gramme.

E. NUTRITIONAL REQUIREMENTS DURING THE FIRST YEAR OF LIFE.

The Commission considered the recommendations submitted by the experts who met at the request of the Health Committee in December 1936, to consult on the nutritional requirements during the first year of life.¹

The Commission generally endorses these recommendations which, in its opinion and in the light of present physiological know-

¹ *Bulletin of the Health Organisation*, 1937, 6, 291.

ledge, appear adequately to meet the requirements of infants. On various points, however, the Commission wishes to record the following observations.¹

(a) VITAMIN REQUIREMENTS.

Vitamins A, C and D : Artificially-fed infants should receive a ration of fruit juice from the second week of life to provide extra vitamins C and D, and also a small dose of fish-liver oil, gradually increasing with the age of the infant, to provide extra vitamins A and D.

(b) IRON.

Attention is called to the great value of egg-yolk as a source of iron for young infants. It is recommended, however, that yolk only should be given to infants under six months of age.

(c) CEREALS AND VEGETABLES.

The Commission would draw attention to the following statement in its former report:²

“ The practice of giving cereal foods before the age of six months is not advised ; after this age, the use of potatoes, suitably prepared, is advocated, as a partial or complete substitute for cereals. ”

(d) MEAT, SOUPS.

Liver, well cooked and finely chopped, may be recommended in addition to the lean meat and white fish mentioned in the experts' report.

¹ Professor BIGWOOD, who took part in the meeting of experts, was unable to agree with the conclusions of the Commission given in paragraphs (a), (b) and (c).

² *Bulletin of the Health Organisation*, 1936, 5, 412.

(e) NUTRITIVE REQUIREMENTS OF PREMATURE CHILDREN.

The Commission would recommend the administration to premature infants of additional quantities of vitamins A and C, as well as of vitamin D. Standardised vitamin concentrates may be given under medical supervision where natural products, such as cod-liver oil, are not tolerated.

(f) MILK.

Where raw milk is used, or pasteurisation is not effective, the Commission emphasises the need for heating the milk in the home. The milk should be brought to the boiling-point and subsequently cooled as quickly as possible, since the nutritive value may be seriously affected by prolonged heating and by the unavoidable oxidation which takes place.

(g) MILK MANIPULATION.

In addition to commenting on the report of the group of experts, the Commission feels bound to publish a note of caution in regard to the harmful effects of certain manipulations of milk for infant feeding, more especially the addition of sugar in large amounts, a practice still prevalent in many quarters. For example, a formula sometimes used for the nourishment of infants during the first five to six weeks provides a diet consisting of equal parts of milk and water, with 7% of added sugar. A prescription of 500 grammes of milk (325 calories) plus 500 grammes of water, plus 70 grammes of sugar (280 calories) constitutes a mixture having a total content of 605 calories, of which 46% is provided by the sugar, an energy-bearing food without any protective value. It is believed that the younger the infant the more important it is that the diet should provide a high proportion of protective food ingredients. The above formula appears dangerous as tending to reduce greatly the mineral, protein and vitamin content of the diet. For example, the initial vitamin B₁ content of milk is relatively small, and if, as experimental evidence indicates, its function is to aid appetite, digestion and carbohydrate metabolism, the amount in the mixture described

would appear to be entirely inadequate, particularly in view of the large amount of added sugar. The above is only one of many instances of altering the nutritive balance of the constituents of milk by manipulation with resultant decrease in protective substances.

It should be emphasised that when combinations of milk products are being planned for infant feeding, the precise nutritive value of the final mixtures should be carefully considered in the light of modern knowledge of nutrition.

II. THE NUTRITIVE VALUE OF MILK.

The emphasis placed upon the unique qualities of milk as a prominent constituent of the diet is based chiefly upon experience of two kinds :

(a) In countries where a satisfactory supply of milk is not available, the period following weaning is one of great hazard for children. The young child cannot be safely transferred from a diet of breast milk, even if supplemented by other foods, to one consisting of the foods of vegetable and animal origin upon which the adult may maintain fairly good health. It has been the habit under such circumstances to prolong the breast feeding of children beyond infancy as a measure of safety. Even a small supplement of milk will afford great protection to infants when placed by necessity on the adult type of diet. When weaned from breast feeding to a regime in which a liberal allowance of cow's milk is supplemented with other foods suitable for the very young, infants will continue to develop uninterruptedly. In the critical post-weaning period, there is no effective substitute for milk.

(b) Investigators in nutrition are familiar with the striking benefits which experimental animals derive when diets of many kinds, even those which contain a wide variety of cereals, fruits, vegetables and meats, are supplemented with a liberal amount of milk. Great improvements in general condition and growth, in success in rearing of young and in retention of full vigour in adult life, are the results of liberal milk-intake. Farm experience fully bears out the importance of liberally supplementing the rations of calves, pigs, colts and poultry with skim-milk. After young animals reach the stage of maturity when they can eat grass or leafy vegetables in considerable amounts, it is possible to maintain a good state of nutrition without a milk supplement, but even then they fare much better if milk is given. The effects observed upon various species of animals which, like man, require a mixed diet, are so

striking that those who have witnessed them have become greatly impressed with the importance of increasing the human consumption of milk as a health measure.

There is not, as many assert, a limited, variously estimated, quota of milk which will yield the maximum benefit in the diet. In practice almost any diet can be considerably improved by the liberal addition of milk.

PASTEURISATION OF MILK.

The experience of health officials shows that certain diseases are frequently milk-borne. Effective pasteurisation of milk makes it safe for human consumption, but this can be expected only where effective supervision is exercised by the health authorities. In districts where pasteurisation is not practicable, the housewife should be urged to bring to the boiling-temperature the milk that is consumed in the home. No milk should be drunk without this precaution.

SEPARATED AND SKIM-MILK.

The manufacture of cream and butter results in the production of a large amount of separated and skim-milk which could with advantage be used for human consumption. Since the fat content forms the basis of the price paid for milk, skim-milk is a cheap food. It is not nearly so palatable a beverage as whole milk, and does not, therefore, find consumer demand. Since the price at which it can be sold does not make its distribution in the fluid state profitable, skim-milk is used at present for the manufacture of casein and for conversion into skim-milk powder. The latter is used as a nutritious addition in the making of bread, and in animal feeding, where it competes with semi-solid and dried butter-milk and with whey powder.

Skim-milk powder keeps indefinitely in a proper container and could advantageously be used as a human food to a greater extent than is now customary. There are many ways in which it can be employed in cookery. As much as 12% can be used in making wheat bread. While skim-milk is lacking in the nutrients contained

in butter fat, it is still a valuable food for supplying mineral salts, water-soluble vitamins and proteins. The proteins are not only of high nutritive value in themselves, but have a high supplemental value which leads to the better utilisation of proteins from vegetable foods.

Skim-milk, however, should not be given to infants and children as a complete substitute for full milk because the milk fat which carries vitamin A is not found in the skim-milk.

III. NUTRITION SURVEYS.

The Commission emphasises the value of making parallel studies of food consumption and of the nutritional state upon the same human subjects. Heretofore, these two lines of investigation have often been conducted independently. Useful as each is by itself, the value of both types of study is greatly enhanced when they form the two parts of a single enquiry.

For trustworthy comparisons of results from studies made in different countries or by different investigations, it is necessary that the methods employed be as uniform as possible with respect to essential features. It is with this end in view that the Commission is presenting the following suggestions and recommendations.

A. STUDIES OF FOOD CONSUMPTION.

All quantitative studies of food consumption should be conducted as precisely as circumstances permit and cover as many individuals and as long a period as is feasible. On the basis of the size of the personal unit involved, four types of study may be described :

NATION-WIDE (FIRST TYPE).

The object is to determine what are the food supplies of a given country, what foods—of what kinds and in what quantities—are available in the country, as month by month or year by year.

In general, the method consists in determining first the *total available quantities of food products* from statistics of production, imports and exports. Allowance also has to be made for the changes in stocks in hand at the beginning and close of the period of enquiry as shown by inventories. To obtain an estimate of amounts available for human nutrition, the total figures must be further corrected to allow for quantities needed for seed purposes,

for the feeding of animals, and for the use of certain products in industry, such as the industrial utilisation of fats or of casein.

An analysis of the resulting data is useful to a government in framing its nutrition policy, particularly with regard to practical measures affecting the quantity and quality of food materials. These studies are also useful in following the trends of the dietary habits of a country. In addition, some evidence as to the effects of diet on health may be derived from comparisons on international lines of the relationship in which the food-consumption figures of different countries stand to other national statistical data (*e.g.*, somatometric tests, morbidity rates, infant and maternal death rates, etc.).

Nation-wide studies of this type furnish the basis for only very rough estimates of possible defects in national diets. They give only a general average of *per caput* consumption and cannot show differences in consumption among different persons or groups of persons. These differences become more markedly apparent as the scope of the survey is narrowed from the nation to the community and from the community to the individual. Information on the actual diets consumed must be sought through more intensive studies on individuals or social groups; such are the studies of the second, third, or fourth type, described below.

Results of studies of the first type rarely show a satisfactory degree of concordance with those of other types of dietary enquiries. To a certain extent, this is to be expected, in view of the differences in the method and scope of the investigations. Many of the estimates involved in nation-wide studies are difficult to make and to interpret with accuracy. The Commission is of the opinion that effort should be directed towards arriving at a better assessment of the degree of error involved in these estimates.

COMMUNITY OR INSTITUTION (SECOND TYPE).

These include studies of the food supply of isolated communities having traditional food habits (army or navy), or of institutional groups (large residential schools, homes for children, homes for the aged, and public institutions, including prisons). The food consumption of such different groups may be very different within one and

the same country, and, if observed in given social groups over long periods in conjunction with periodic assessment of the physical condition of the persons concerned, will throw light on the effects of dietary habits on nutritional status.

The technique of such surveys is similar to that of family surveys (see below).

FAMILY (THIRD TYPE).

There are in common use two methods for conducting such enquiries :

(a) *The Weighing Method.*

This is the method usually employed. It consists of taking an inventory, by weight, of food on hand at the beginning and end of the period of study, and of securing records of the weight of each kind of food obtained by the family during the course of the study, together with daily records of the inedible refuse and of the edible food not consumed by the family—*e.g.*, garbage, food for pets or chickens, etc. This work is done by, or under the close supervision of, a trained investigator.

(b) *The Account-book Method.*

In this method, day-by-day record of food brought into the kitchen is kept by the housewife and combined with inventories at the beginning and end of the period. A special account-book should be provided, in which the housewife should make these entries in accordance with the instructions she receives. This method calls for constant supervision on the part of the investigators, and the keeping of a check upon the care with which the housewife plays her part.

* * *

The weighing method is the more accurate, but it is more laborious. Care must be taken to ensure that the weighing is carried out with accuracy in accordance with a technique with which the investigator is thoroughly familiar.

In certain countries, the view is held that if a very strict check is kept upon the accuracy of account-book entries, trustworthy results can be obtained.

In either method, a distinction can be made between family surveys in which the food consumption of the family is measured in the aggregate, and others in which the investigation bears, in addition, upon the distribution of food among the various members of the family.

In the interest of adequate interpretation of results, it is essential that the families be classified into *homogeneous groups*. Among others, the following factors may influence food consumption, and should be considered in such classification :

(a) Geographical location, considering climate, plains, mountains, sea-coasts, latitude and altitude of the area, proximity to food markets, kind of farm production, actual or possible utilisation of land ;

(b) Urbanisation: whether the area is a rural or urban one, distinguishing between different degrees of urbanisation and general hygienic conditions ;

(c) Occupation of the head and other wage-earning members of the family (note should be made if work is largely seasonal) ;

(d) Composition of the family, number of persons of different age and sex ;

(e) Family income (in money and kind) or the money value of the food consumed by the household. It should be observed, however, that this factor may operate in different ways according to the country considered ;

(f) Racial background, wherever this factor plays an important part (*e.g.*, white and black races in certain parts of the United States of America).

INDIVIDUAL (FOURTH TYPE).

These studies require the weighing of the portion of all foods consumed by each individual under enquiry ; and data on the composition of prepared food dishes is also essential. These may be secured by chemical analysis or by a quantitative study of the

proportion in which natural products (ingredients) appear in each prepared dish.

In every type of dietary study, care must be taken that the food consumption during the period of observation shall conform to the usual pattern, but especial care must be taken in studies of individual consumption to prevent the psychological element from biasing the results.

Mention may also be made of enquiries carried out by the distribution of questionnaires to be filled in by the persons under enquiry. Although such data give a general and approximate impression of certain food habits, it is obvious that they cannot yield sufficiently accurate information to enable the exact physiological characteristics of a diet to be judged.

SOME RECOMMENDATIONS REGARDING METHODS TO BE EMPLOYED IN MAKING DIETARY SURVEYS.

Collection of Data.

(a) The services of thoroughly *competent investigators* are absolutely necessary for the conduct of quantitative dietary studies. While it is not absolutely necessary that they be college or university graduates, they should understand thoroughly the *purpose* of the study and the *requirements* of quantitative procedures. For instance, when the weighing method is used, they should be familiar with the use of scales and know the absolute and relative errors involved in weighing procedures. There should be a period of apprenticeship during which the director of an investigation should give the field agents any special technical training which they may need.

Technical competence is not the only requirement which investigators must meet. They must also possess the *gifts of personality* needed in order to *gain the confidence, goodwill, and co-operation of families*.

(b) *Printed forms and instructions* should be provided for the guidance of investigators. These should contain a suitable list of the foodstuffs to be considered, and specific directions on points such as the recording of quantity, quality, price, mode of preparation, and the utilisation or otherwise of cooking-water.

It is suggested that each country which is planning dietary surveys should send specimens of the instructions and forms in use to the Health Section of the League.

(c) *The period of investigation* will vary according to the technique adopted. Investigations by weighing should be continued for a week at least ; the account-keeping method allows of longer periods of observation—say, one month. Certain authorities hold that the period of one week in the inventory-weighing method may be insufficient, in view of unforeseen developments that may occur in the course of the enquiry ; nevertheless, one week is the period usually advocated in studies by this method.

It is recommended that all enquiries be repeated three or four times during the course of the year, in order that seasonal variations may be brought to light. These variations are not of equal importance in all circumstances.

Analysis of Data.

(a) The *results* of studies of food consumption should be reported both in terms of articles of food and in terms of calories and of the several nutrients, such as protein, calcium, iron, vitamins A, B, C, etc.

(b) In each country, there should be compiled suitable *tables of food composition* in terms of calories, proteins, fats, carbohydrates, various mineral elements and vitamins. Standard methods for making the necessary estimates should be adopted in all countries. Food composition tables should include information upon the approximate number of analyses on which the averages are based, the range of values commonly encountered, the influence of season and of the various methods of cooking upon average values.

More information than is now available is desirable concerning coefficients of intestinal utilisation and the factors influencing them.

(c) *Scales of relative requirements or of consumption coefficients* are intended exclusively for use in investigations which bear on the aggregate food consumption of a family or other group that is heterogeneous with respect to requirements, rather than on that of individuals.

When studies are concerned with groups which are not homogeneous with respect to factors influencing food requirement, such as age, sex, body-size and build and physical activity, investigators

will find it necessary to resort to some device for comparing the consumption requirements of different persons or groups of persons. This is usually done by determining the number of "units" to which each group is equivalent in so far as food requirements are concerned.

In the past, this equivalence has usually been computed on the basis of the relative energy requirements of the different individuals comprising the group. For such calculations, scales of equivalents have been drawn up in which the "adult man's requirement" for calories has generally been taken as the unit, and those of the adult woman and of children of different sexes and ages are expressed as fractions of this unit. Many such scales have been published and have been widely used. An example is that given in the report of the Expert Committee convened by the Health Organisation of the League in 1932.¹

The Commission considered that this question should be scrutinised more closely, inasmuch as the energy requirements of the "adult man" vary widely according to his occupation, size and activity (*e.g.*, from 2,400 calories daily for the sedentary man to 4,000 calories and over for the man performing heavy muscular work). In the Commission's previous report, the conception of "man value" was therefore abandoned, and the unit adopted for expressing the calorie needs of different individuals was a definite number of calories—*i.e.*, 2,400 calories, the daily allowance appropriate for a sedentary man. This report also suggested definite allowances for energy content of "basic" diets for various categories of individuals, but deliberately did not include in these allowances any supplements for work or muscular activity. Regarding the latter, the report stated :

" The following supplements for muscular activity should be added to the basic requirements :

- " Light work : up to 75 calories per hour of work.
- " Moderate : 75 to 150 calories per hour of work.
- " Hard work : 150 to 300 calories per hour of work.
- " Very hard work : 300 calories and upwards per hour of work.

¹ *Quart. Bull. Health Org.*, 1932, 1, 480.

“ The muscular activities characteristic of every healthy child and adolescent necessitate additions to the basic requirements. It is suggested that the activities of children of both sexes from 5 to 11 years be considered equivalent to light work, of boys from 11 to 15 years as moderate work, and of girls from 11 to 15 upwards as light work.”

It is obvious that the appraisal of the muscular activity of a given individual, as well as of the energy supplements involved, is but approximate at best. It is impossible to suggest a single set of figures which are internationally applicable, since the energy requirements of men, of women and of children of different ages differ greatly from country to country, and even within one and the same country, owing to such factors as differences in the length of the working day, differences in the intensity of activity, in average body size, in climate, etc. Therefore the Commission makes no attempt to suggest single figures for the total energy requirements of each category of individuals.

Since, however, such figures are needed in connection with dietary surveys for constructing scales of relative requirements, the energy supplements required in addition to the basic allowances should be noted by the nutrition experts responsible for the dietary surveys. When the total energy requirements have thus been determined, scales of relative requirements can easily be developed, using as unity either 2,400 calories, the allowance for a sedentary man, or 3,000 calories, the allowance for a moderately active man.

The following schedule may be of use in drawing up such scales. Column 1 contains the Commission's allowances for energy requirements in average basic diets. Columns 2 and 3 provide space for the investigator's entry of the average number of hours during which the subjects are especially active, and the average number of calories per hour needed to support this activity. In column 4 can be entered the total daily allowances. In column 5 or 6, the totals given in column 4 should be expressed as decimal fractions of the two values of unity—*i.e.*, 2,400 or 3,000 calories, respectively.

The decimal coefficient which is to be given in one of these two columns expresses the relation of the total ration (column 4) to the value of unity chosen.

Scales based on either value of unity may be used in appraising the calorie value of diets, provided that the value of unity and the scale used are stated along with the results.

Schedules for recording Relative Energy Allowances.

Individual	Energy allowance for basic diets (without work) in net calories	Supplementary allowance for special activity		Total energy allowance in net calories ¹	Scale of relative allowances ²	
		Number of hours of special activity	Number of calories per hour of activity		Total, 2,400 = 1.00	Total, 3,000 = 1.00
	1	2	3	4	5	6
Men (20 to 59 years) :						
Sedentary	2,400					
Light work	2,400					
Moderate work	2,400					
Hard work	2,400					
Very hard work	2,400					
60 years and over	2,400					
Women :						
Ordinary life	2,400					
Housework	2,400					
Pregnant + housework ..	2,400					
Nursing + housework ...	3,000					
Boys :						
Between 15 and 19 years .	2,400					
" 12 " 15 " "	2,400					
" 11 " 12 " "	2,160					
" 9 " 11 " "	1,920					
" 7 " 9 " "	1,680					
" 5 " 7 " "	1,440					
Girls :						
Between 15 and 19 years .	2,400					
" 12 " 15 " "	2,400					
" 11 " 12 " "	2,160					
" 9 " 11 " "	1,920					
" 7 " 9 " "	1,680					
" 5 " 7 " "	1,440					
Children :						
Between 3 and 5 years .	1,200					
" 2 " 3 " "	1,000					
" 1 " 2 " "	840					
Under 1 year ³						

¹ Computed to nearest 100.

² Computed to nearest 0.05.

³ To be computed on basis of weight.

In order to illustrate the way in which the scales should be computed, the Commission cites the following arbitrary example :

Individual	Energy allowance for basic diets (without work) in net calories	Supplementary allowance for special activity		Total energy allowances in net calories ¹	Scale of relative allowances ²	
		Number of hours of special activity	Number of calories per hour of activity		Total, 2,400 = 1.00	Total, 3,000 = 1.00
	1	2	3	4	5	6
<i>man</i> , weighing about 70 kg., aged 20 to 59 years :						
Sedentary	2,400	0	—	2,400	1.00	0.80
Light work	2,400	8	35	2,700	1.15	0.90
Moderate work	2,400	8	75	3,000	1.25	1.00
Hard work	2,400	8	150	3,600	1.50	1.20
Very hard work	2,400	7	300	4,500	1.90	1.50

¹ Computed to nearest 100.

² Computed to nearest 0.05.

It must be clearly understood that the above scales refer to calories only and are not valid for the separate constituents of the diet such as protein, minerals or vitamins. Before internationally accepted scales can be prepared for each of these components, further work must be conducted in the various countries to determine more precisely the requirements for these several nutrients of individuals of different ages and living under different circumstances. It is recommended that, in the meanwhile, the amounts of the nutrients supplied in the diet be expressed in terms of intake *per caput*. If, in addition, the results are stated in terms of scales that may be devised by an individual investigator, the scales used and the value of the unit adopted should be given.

Classification of Foodstuffs.

The Commission recommends that reports of dietary studies should contain full details regarding consumption of, and expenditure on, the different articles of food. This precaution will enable the data to serve as a basis for further research in the field of nutrition as well as for economic and social purposes. Since, however, abridgment is often necessary, it is desirable to draw up a uniform

classification of foods to be adopted in the various countries. Such classification may be designed to serve, as far as possible, the needs of statisticians in the construction of cost-of-food indices, as well as those of nutrition workers in appraising the physiological value of diets.

Having regard to the great differences which exist between various countries as regards the types of food consumed, it is proposed that each country interested in this question should send the Health Section of the League specimens of the classification which it considers appropriate. It will then be possible to explore the prospect of drawing up a common table for all countries.

It is also suggested that for most foods, especially, but not exclusively, those belonging to the vegetable kingdom, the scientific (Latin) name of the variety or species concerned should be given, since without this the products are difficult to identify. Further, the part of the animal or plant which is used for food should always be noted.

B. METHODS OF ASSESSING THE STATE OF NUTRITION IN INFANTS AND ADOLESCENTS.

The Commission considered the report of the group of experts appointed to study methods of assessing the state of nutrition in infants and adolescents. Three types of enquiries were outlined by the experts.¹

Type 1 is for use in extensive demographic surveys or in the first rough classification of a very large number of subjects. Information is secured for each individual as to age, sex, physical appearance (slender, medium or stocky type), height (and possibly sitting height) and weight. It is recommended that the weighing and measuring be repeated at fairly frequent intervals. In addition, each child is given a simple elementary clinical examination, especially with regard to the colour, firmness and elasticity of the skin, the state of the teeth, the conditions of the subcutaneous fat layer, the state of the muscles, and any signs of abnormal fatigue.

¹ *Bull. Health Org.*, 1937, 6, 137.

All children whose nutrition appears to be defective should also receive a medical examination, and should become subject to a medical-social enquiry, dealing especially with diet.

Type 2 is designed for more thorough and more scientific but still partial investigations, and includes, on a smaller number of subjects than considered in studies of *Type 1*, all of the tests of the first type, together with enquiry into the child's food intake, an enquiry into the economic and social status of his family, a thorough medical examination of the child and as many of the following tests as facilities permit : additional somatometric data (*e.g.*, bisacromial breadth, the breadth of the pelvis, chest girth, etc.) ; photography ; special tests, particularly those presumed to be related to latent or unapparent " pre-deficiencies " of nutrition, such as measurement of hæmoglobin ; tests for adaptation of visual acuity in semi-darkness—vitamin A ; determination of ascorbic acid content of blood and urine, or X-ray examination of wrist of infants.

Type 3, which is of a bio-typological nature, includes all of the tests of *Type 1* coupled with as many measures as possible of morphological characteristics and biological functions amenable to mensuration. Such enquiries should include somatometric measurements ; physiological measurements bearing on the muscular, respiratory, circulatory, digestive, nervous, endocrine and urinary systems ; psychological tests ; complete medical and psychiatric examinations ; dietary studies ; and studies of the child's progress in school-work.

The Commission recommends that enquiries conducted in the future should be more especially those of *Types 2* and *3*, having regard to the great importance of improving our knowledge of physiological tests capable of detecting conditions of unapparent dietary pre-deficiency at an early stage. With this object in view, these tests should be used in surveys, even though, for the time being, their interpretation may present great difficulty.

In extensive surveys of *Type 1*, in order to assist the interpretation of the summary clinical examination employed in this type of investigation, there should be at least a brief enquiry into the consumption of certain foods—for instance, the daily intake of milk and other protective foods. It should be understood that this

would not involve a complete dietary study, but would aim at obtaining some rough but useful guidance as to the general character of the diet. This should be of value in correlating the general clinical impression with any evidence of dietary adequacy or inadequacy that may be revealed.

The Commission also recommends that methods be worked out which would be applicable to children of pre-school age.

Finally, it is desirable, in enquiries and studies undertaken for the purposes of assessing the state of nutrition of children, to bear in mind the possible connection between defective nutrition and many abnormal conditions of ill-defined cause. Examples are the following : deformation of the bones, naso-pharyngeal troubles, septic sinuses, adenoids, enlarged and infected tonsils ; discharging ears ; also susceptibility to broncho-pneumonia and rheumatic fever.

The structure of the teeth, as indicated by the texture and pigmentation of the enamel, should also be taken into consideration as a reflection of previous nutrition.

IV. NUTRITION PROBLEMS OF THE FAR EAST.

The Commission considered and generally approved the technical report on nutrition and the recommendations on this subject submitted by the *Intergovernmental Conference of Far-Eastern Countries on Rural Hygiene*, held at Bandoeng, in August 1937.¹

The Commission recognises that when a population must be sustained in geographical areas in which economic, climatic and soil conditions do not permit of the supply or local production of foods adequate for the maintenance of optimal nutrition, the first efforts can only be directed towards alleviating as quickly as possible the most outstanding nutritional defects. The programme which is adopted must nevertheless contemplate future steady progress in the direction of achieving step by step higher planes of nutritional adequacy of food supply.

1. RESEARCH WORK.

Among the nutrition problems of importance to the Far East, the Commission recommends further research on the following (it is understood that this is only a first selection, which will be amplified later in consultation with nutrition workers in the East) :

A. *Problems to be studied in the Far East.*²

1. The composition of foodstuffs peculiar to the Far East.
2. Dietary surveys.
3. Dietary standards.
4. Assessment of the state of nutrition.

¹ *Vide* report of the Conference, document A.19.1937, section IV, page 65.

² These items are reproduced from the research plans outlined in the Conference's report.

- B. *Problems on which Workers in the Far East specially desire Collaboration with Other Investigators under the Auspices of the Commission.*

The Commission requests the Health Section to establish contact with nutrition research workers in the Far East with a view to submitting an annotated list of possible studies at its next session.

This list might include the methods to be employed in nutrition surveys. In this connection, the Bandoeng Conference specifically mentioned the problem of consumption units.

- C. *Problems previously noted for Study by the Commission which might also be investigated in the Far East.*

Assessment of the nutritional state of children (A).

Minimum vitamin and mineral requirements (C).

Minimum fat requirements (D).

The nutritive and "supplementary" values of the different protein-containing foods to determine to what extent and in what forms animal protein is necessary for growth and health (E).

The relative nutritive value of different cereals according to the degree of milling (F).

Influence of climate on food requirements (H).

The extent to which diets in common use fall below the standards recommended in the Commission's report on the Physiological Bases of Nutrition (I).

2. CO-ORDINATION OF WORK IN THE FAR EAST AND LIAISON WITH THE TECHNICAL COMMISSION.

A. In order effectively to link the general activities of the Commission with the investigations carried out by various nutrition workers and institutions in the Far East, it is important, in the first place, that the workers and institutions be duly co-ordinated. To this end, the Commission proposes :

1. That a centre be established in the Far East to effect this co-ordination and at the same time to help in maintaining liaison with the Commission. It would be the function of this centre to

collect and make available full particulars of the work which is proceeding in the Far East, and to distribute to all workers in that part of the world information as to the progress which is being made elsewhere.

It is suggested that, if this were acceptable to the authorities concerned, the centre might appropriately be established at Coonoor.

2. That meetings of Far-Eastern nutrition research workers be held from time to time as the progress of the work may require.

B. In order to provide for liaison with the Commission, the Commission proposes further :

3. That two members from the Far East be appointed to sit on the Commission.

4. That a member of the Commission be selected to visit nutrition workers and institutions in the Far East and to represent the Commission at such meetings of Far-Eastern workers as may be held.

These arrangements would help to keep workers of the Far East in touch with the developments that are taking place elsewhere, and would at the same time enable the Commission to include the consideration of Far-Eastern nutritional problems within the range of its activities.

The machinery set up should, moreover, enable the research work outlined to be satisfactorily prosecuted, and the programme itself to be revised and amplified as circumstances may require.

Finally, as a general principle, the Commission is of opinion that any material made available by other organisations engaged in the study of nutrition problems should be considered and collated with its own findings.

V. STUDIES ON NUTRITION IN CHILE.

The Commission has taken note of the report¹ of Professor Burnet and Professor Dragoni on the enquiry which they have conducted on the nutrition conditions in Chile and the recommendations made by them to the Chilian authorities, together with the Governmental decrees and documents kindly communicated¹ by Dr. Cruz Coke, the Chilian Minister of Public Health.

The Commission considered these texts with interest. It should not be overlooked that some time must elapse before the measures outlined can be fully carried into effect, so that results can only be secured as time goes on. This is therefore a long-term policy, the developments of which will have to be carefully watched by the Chilian Government, not only to ensure its adequate enforcement, but in order to judge of its results and make any needful adjustments. In this connection, the Commission attaches special importance to the creation of a National Nutrition Committee, as evidence of the Chilian Government's intention to carry through the scheme which has been planned and to develop it on rational lines.

The Commission is gratified to note that the Government of Chile recognises the importance of the problems involved in the nutrition of the people, and proposes to take concerted action to deal with them. It wishes again to record its readiness to assist in every way.

¹ *Bull. Health Org.*, 1937, 6, 299.

INVESTIGATIONS ON UNDULANT FEVER IN FRANCE¹

by

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Investigations here discussed were begun in 1931, and a preliminary report and several articles dealing with special observations have been published in French journals. Since these publications, our data have been amplified, and we now propose to present what we consider to be the salient features brought out in these studies. In one of the articles (1) referred to above, a review of the literature on the epidemiology of undulant fever in France was given and need not be repeated here. Since the appearance of this paper, only one publication (PARISOT and LÉVY (2)) has been made which embraced a careful study of a considerable number of cases. The survey of these authors was made in the province of Lorraine and, considering the peculiarities of this region, their findings were in accord with our observations and require no special discussion; nor is it within the scope of this paper to digest the voluminous literature on similar studies in other countries.

To understand fundamentally the epidemiology of an infectious disease, it is essential to know, not only the manner, or manners, of excretion of the infectious agent, the persistence of the excretion, and the route, or routes, by which the infection enters the body of new hosts, but also the frequency of occurrence of these factors.

A cursory view of brucellosis will serve to indicate that it is subject to an exceedingly complex epidemiology. It has been shown that the organism may be excreted through the milk, the urine, and abortion products and subsequent vaginal discharges. Circumstantial evidence also points to "manure" as being a source of danger.

¹ From the Centre de Recherches sur la Fièvre ondulante, Institut Bouisson-Bertrand, Montpellier. These investigations were made possible by a grant from the International Health Division of the Rockefeller Foundation.

Not only may the disease be contracted by ingestion, but also the offending organism possesses the ability to enter the body easily through the skin or mucosa of the nose and eye. Add to this the fact that the organism may infect a wide range of domestic animals—there are at least three varieties of *Brucella* possessing certain differences in their pathogenic selectivity—and the problem assumes formidable proportions. Not only may it be difficult to trace the source and manner of infection in an individual case, but the dominant epidemiology may vary markedly in accordance with the importance of the rôle of these numerous factors.

Thus the source and manner of infection in different countries or communities may show wide divergencies, and the mistake is frequently made of drawing analogies without due consideration of the prevailing circumstances and conditions. Hence, it should be borne in mind that these studies deal with the disease as it occurs in France : the inferences which may have been drawn need not necessarily apply elsewhere.

TECHNICAL METHODS.

While no new principles were developed, it is appropriate for the evaluation of our results to describe briefly the procedures followed in testing for the allergic and serological reactions and in the isolation and identification of *Brucella*.

Agglutination Reaction.

Although a variety of strains and preparations were tried, the adopted standard antigen¹ consisted of a heat-killed suspension of a single strain (S-6)² in 0.9% saline solution with 0.2% formalin subsequently added as a preservative. Preparation is as follows : the surface growth, after incubation on liver infusion agar (pH 7) for seventy-two hours, is carefully washed off with a small quantity of sterile 0.9% saline solution, filtered through gauze, and heated at 58° to 60° C. for one hour. After testing for sterility, salt solution is added until the density is equal to a 1 to 1,000 suspension of fullers' earth, and, finally, 0.2% of formalin is added. Such a preparation may be kept for four to five months at room temperature.

¹ This antigen was supplied to all diagnostic laboratories in France, upon request.

² This strain is a *suis* type isolated by TRAUM, sent by MEYER to the Lister Institute, and is listed in the National Collection of Type Cultures as Number 900.

For testing human sera, the standard antigen is mixed with an equal volume of the serum dilutions, thus giving a density equal to a 1 to 2,000 suspension of fullers' earth in the final test-tubes. With goat, sheep, and cow sera, a 50% concentration of the antigen is employed, so that the final test suspension is equal in density to 1 to 4,000 fullers' earth.

Serum dilutions are made by placing 0.2 c.c. of serum with 0.8 c.c. of salt solution in the first tube and 0.5 c.c. of salt solution in the succeeding tubes. With the rheometre syringe gauged to deliver 0.5 c.c., the serum and salt solution are thoroughly mixed in the first tube and 0.5 c.c. carried to the second, where the mixing process is repeated, and so on to the end of the series; 0.5 c.c. of antigen is then added to each tube, thus giving final dilutions of 1/10, 1/20, 1/40, etc., to 1/1,280. In routine tests, it was not the custom to carry the dilutions beyond 1/1,280.

The tube racks are then placed in an incubator at 37° C. and the readings are made at the end of twenty-four hours. Readings are recorded as —, ±, +, ++, and +++ . A tube was not regarded as positive unless the agglutination was approximately 75% complete (++) , and a serum was not recorded as giving a positive reaction unless there was a ++ or +++ reaction in a 1/80 dilution, or above.

The zone phenomenon was not infrequently encountered, and may extend beyond the 1/80 or 1/160 dilution; therefore, it is important to carry dilutions to at least 1/320. Also in bloods of some goats, and especially of sheep, this inhibiting action may completely suppress agglutination. It was later found that this inhibiting effect could be largely controlled by making the serum dilutions in 5% instead of 0.9% saline solution.

Complement Fixation Reaction.

This test was not used as a routine procedure, but a series of some 2,000 blood samples, mostly from goats and sheep, were tested for comparison with the agglutination and allergic reactions. In the beginning, a solution of *Brucella* protein was used as antigen, but it was later found that the above-described antigen used for agglutination gave satisfactory results, although the spread between the fixing and anticomplementary point was not so great as with the protein solution. In view of the simplicity of the preparation, the suspension was finally chosen as the antigen for routine use. The tests were set up as follows:

Anticomplementary Control.

				Antigen	Controls	
Back row :						
Test serum	0.05	Salt	0.3	0.2		
Salt	0.4	Complement	0.2	0.2		
Complement	0.2	Antigen	0.1	0.2		
Front row :						
Test serum ...	0.05	0.025	0.0125	0.0062	0.0031	0.0015
Salt	0.4	0.4	0.4	0.4	0.4	0.4
Complement .	0.2	0.2	0.2	0.2	0.2	0.2
Antigen	0.1	0.1	0.1	0.1	0.1	0.1

The rabbit-sheep-guinea-pig hæmolytic system was used. After incubation for one hour at 37° C., 0.4 c.c. of an equal mixture of hæmolysin (two units) and red-blood cells were added to each tube, and the final reading was made after incubation for a second hour.

A serum was not recorded as definitely positive unless there was better than 75% fixation in the third tube (0.0125 c.c. of serum), although we believe that complete fixation in the first two tubes may be regarded as highly suspicious.

Allergic Reaction.

Preliminary trials were made upon guinea-pigs with a number of antigens, including the filtrate of an old broth culture (melitin or brucellin), suspensions of the whole bacterial cell, soluble cell products and several precipitates or fractions of soluble cell substances. The saline soluble substances of the entire cell gave the best and most uniform results, and this preparation was adopted and routinely employed in work with animals.

It is prepared by washing off the surface growth of a seventy-two-hour agar culture with 0.9% saline solution. The suspension is then heated to between 58° and 60° C. for one hour, and the bacterial cells are precipitated by centrifuging and washed a second time. The packed cells are then dried in vacuum and ground forty-eight hours in a ball mill. The resulting white powder is then dissolved in a slightly alkalisied (pH 8) sterile saline solution and passed through a Chamberland filter (L. 4). The clear filtrate is standardised according to the nitrogen content. For animals, a solution containing 1 centigramme per 100 c.c. is employed, and as 0.1 c.c. is injected intradermally for the test, the amount of nitrogen in the test dose is 0.01 milligramme.

If this preparation is used upon humans, it should be diluted 200 times; otherwise severe reactions may be encountered. It was also found that a "nucleo-protein" gave satisfactory results with humans, and the reactions were less severe. This antigen is prepared from the solution described above by precipitating in the cold with N/10 acetic acid and redissolving the precipitate in a slightly alkalisied saline solution. It is then standardised, so that a test dose of 0.1 c.c. contains 0.008 milligramme of nitrogen.

As above stated, the test is made by injecting 0.1 c.c. intradermally. A positive reaction is manifested by an œdematous swelling which reaches its maximum between twenty-four and forty-eight hours. It is preferable to make two readings, one at the end of twenty-four hours and a second at the end of forty-eight hours. If only one reading is made in animals, it is best to make it thirty-six hours after the injection. In large animals, the injection is made in the caudal fold, about 2 inches from the base of the tail. The extent of the reaction is determined by comparing the thickness of the fold on the injected side with the opposite uninjected fold. An increase in thickness on the injected side of 1 to 2 millimetres is recorded as a \pm reaction, 3 to 4 as +, 5 to 7 as ++, 8 to 12 as +++, and 13 or more as ++++. While normal animals will usually show no reaction, or only a slight thickening of 1 to 2 millimetres, the result is not regarded as being definitely positive unless there is a thickening of 5 millimetres (+ +) or above, although a + reaction may be looked upon with suspicion.

The test is performed in guinea-pigs by giving the injection in a shaved portion of the abdominal skin. In heavily infected guinea-pigs, a central hæmorrhagic, or occasionally a necrotic, area may develop. In goats and sheep, necrosis never occurs, and the reaction rapidly subsides and rarely leaves any traces after a few days.

In our experience, the antigen above described is preferable to the other preparations tested, in that it may be accurately standardised ; it does not produce pseudo or false reactions, and a positive reaction develops rapidly and soon disappears. The filtrate of old broth cultures (melitin or brucellin) are difficult to standardise and may, presumably because of peptones, etc., in the broth, produce pseudo or false reactions. The objections to a salt suspension of *Brucella* cells are that the reaction is frequently slow in developing ; that retarded false reactions may occasionally occur in normal animals ; and that agglutinins are developed which not infrequently in normal animals will reach a diagnostic titre even after one intradermal test.

The significance and value of the intradermal reaction in relation to other diagnostic procedures will be discussed later.

Cultural Methods.

The liver infusion described by STAFSETH and HUDDLESON was used as a basis for all media. For ordinary cultivation, either in broth or upon agar, the medium was adjusted to a pH of 7, and when there was any uncertainty as to the type of strain, duplicate cultures were made, one set being incubated in free air and the other in an atmosphere of 10% CO₂.

Hæmoculture.

First, a description of the procedure which was most commonly employed will be given. Later, certain modifications which may be more suitable for laboratories doing only a limited number of blood cultures will be indicated.

Our attention was called to a vacuum-tube sold on the market under the trade-name of " Venule ", which was found very convenient for taking blood from both man and animals. For practical considerations, it is highly desirable to be able to perform, not only a blood culture, but an agglutination and complement fixation test from the same specimen. Therefore, after having tried out the effect of sodium citrate on these reactions and having found that it had no influence, we had a quantity of 10% sodium-citrate solution placed in the venules which, when filled with blood, would give a final dilution of 0.5%. This was done for the purpose of preventing coagulation and thus facilitating the handling of the blood sample for culture. Venules having a capacity of 15 c.c. are preferable.

Upon receipt at the laboratory, the blood samples taken in this manner are handled as follows. A sterile gauze saturated with alcohol is placed about the rubber stopper of the Venule and the stopper removed. The blood is then withdrawn by a sterile 10 c.c. pipette and 4 to 5 c.c. is passed into each of two test-tubes of 22-millimetre diameter containing 30 c.c. of beef liver infusion bouillon. The remaining quantity of citrated blood is centrifuged for precipitation

of the red blood cells, and the plasma is withdrawn and used for the agglutination or complement fixation tests.

One of the culture tubes is incubated in free air, the second in a jar with an atmosphere containing 10% CO_2 . For the sake of economy, the ordinary fruit-jar with rubber-washer seal and clamp top is utilised. It is necessary, however, to have a hole (1 centimetre in diameter) drilled in the cover of the jar. Into this aperture is inserted a tightly fitting rubber stopper, through which passes a glass tube. To the outer end of the glass tube is attached a small piece (approximately 5 centimetres in length) of heavy-wall rubber tubing. The cultures to be incubated in CO_2 atmosphere are placed in the jar, and the cover is tightly fixed by the metal clamp. To avoid leakage, it is advisable to smear previously both sides of the rubber washer with Vaseline. The atmospheric pressure is then reduced in the jar by attaching the rubber tube to a vacuum-pump with a manometer. When the manometer registers a reduction of 10% atmospheric pressure (70 millimetres of mercury), the rubber tubing attached to the jar is closed with a Mohr's clamp and detached from the vacuum-pump. The tubing is then connected with a Kipp apparatus in which CO_2 is generated, and the Mohr's clamp is opened, allowing the 10% vacuum to be replaced by CO_2 . The Mohr's clamp is then finally closed and the jar is placed in an incubator at 37° C. (see Fig. 4, page 545).

The moisture which inevitably occurs in a closed jar is conducive to the growth of moulds. This can be largely avoided by first flaming the cotton plugs of the tubes, using only previously sterilised jars, and by pouring a small quantity of a 5% solution of "Sunoxol" on a pledget of cotton in the bottom of the jar.

Transplants are made from both broth cultures at ten-day intervals by removing 0.25 to 0.5 c.c. of the broth with a sterile pipette and inoculating on an agar slant. Naturally, the transplants made from the broth cultures in CO_2 are likewise incubated in a CO_2 atmosphere. If the transplants show no growth, a second transplant is made at the end of twenty days and a third at the end of thirty days, at which time it is the custom to discard the broth cultures.

A Gram's stain is made of any growth appearing upon the transplants, and if the organism resembles *Brucella*, it is then tested against a known agglutinating serum. Macroscopic slide agglutination is used as a preliminary test.

An analysis of records of more than 1,400 human blood cultures performed by this technique shows that only 8% were contaminated after incubation for thirty days. On the other hand, it has been our experience that the majority of specimens received from physicians, taken with a syringe, were contaminated.

As stated above, we have found no objection to the use of citrated blood in the performance of the agglutination test. If the blood is not taken in citrate, it is very awkward to make a culture from the clot, and its manipulation will greatly increase the chances of contamination. Furthermore, it is not feasible to divide the clot and make duplicate cultures, which is necessary if all types of *Brucella* are to be obtained. Thus if citrated blood is not used, and it is desired to perform the blood culture at the laboratory, as well as the agglutination reaction, it is virtually necessary to take two samples, a procedure to which there are obvious objections.

As there is some inconvenience in using a jar for a single culture in laboratories where blood cultures for *Brucella* are made infrequently, the same results may be obtained by employing an especially moulded test-tube, the lip of which is so constructed that a heavy rubber cap, such as is in common use for nursing bottles, will fit snugly. These tubes containing bouillon are prepared for culturing as described above. After the introduction of the blood, the cotton plug is flamed and pushed in so as not to extend above the lip, and the rubber cap is fitted over the mouth of the tube to be incubated under an increased concentration of CO_2 . The amount of CO_2 required to make approximately 10% of the volume of the tube is then introduced by inserting a hypodermic needle connected with a 10-c.c. syringe having a two-way attachment. One attachment leads to a Kipp apparatus, in which CO_2 is generated, and the other to the hypodermic needle. These attachments are made with rubber tubing and a T-shaped glass tube. The rubber tube to which the hypodermic needle is attached is closed by a Mohr's clamp and the connection to the Kipp apparatus is opened. The required amount of CO_2 is then drawn into the syringe, the connection to the Kipp apparatus closed, the needle thrust through the rubber cap on the culture tube, the connection to it opened and the CO_2 injected. The needle is then withdrawn. The elasticity of the rubber is effective in sealing the hole made by the puncture. Transplants on agar made from the CO_2 culture are treated in a similar manner.

There is another method which permits the making of cultures in the field, or at the bedside, with a minimum risk of contamination. In this procedure a special culture bottle, similar to the one described by McCARTNEY (3), with a metal cap and a heavy rubber washer is used (see Fig. 3, page 544). A hole approximately 0.5 centimetre in diameter is made in the centre of the metal cap, which permits the insertion of the needle through the heavy rubber washer for the inoculation of the blood. In order to have a sterile surface through which to make the inoculation, the metal cap is covered with "Viscap". The Viscap cover is peeled off just before making the inoculations. In the process of sterilisation by autoclave, the Viscap contracts and makes a snugly fitting cover. With this procedure, it is not necessary to use citrate, as the blood for culture is introduced immediately into the bouillon and a sufficient amount is saved for the agglutination test.

Either a syringe or a venule may be used for withdrawing the blood. If the latter is employed, it is necessary to create a partial vacuum in the bottles in order to withdraw the blood from the venule. This is accomplished before final sterilisation by placing the bottles containing the media in a water-bath, bringing them to boiling temperature and capping while hot.

Two bottles are inoculated from each specimen of blood. When they arrive at the laboratory, they are handled in a manner similar to that described for the tubes with rubber caps. That is to say, the required amount of CO_2 is injected into one through the rubber washer, under sterile conditions. The cap is removed from the bottle to be inoculated in free air and replaced by a sterile cotton plug. This method has a theoretical advantage of placing the blood immediately in culture media, which by some investigators has been

claimed to be important. However, we have repeatedly succeeded in isolating *Brucella* from samples of citrated blood which were not cultured for three, four, or even six days after being taken. In fact, in most instances our specimens have not been introduced into culture media until twenty-four hours, or longer, after withdrawal. While it is possible that a higher percentage of positive cultures might have been secured if the blood samples had been immediately introduced into bouillon, and placed in an incubator, it will be observed from a succeeding table that cultures were obtained from over half of the specimens of human blood which produced agglutination in diagnostic dilutions. .

Some strains of *Brucella* grow very slowly or, it is probably more correct to say, are very slow in starting to grow. Analysis of 305 positive blood cultures from man, from which transplants were made at ten-day intervals, showed that 70% were positive at the end of the first ten days, and an additional 24% at the end of twenty days; 6% were not positive until on the third transplant or after incubation for thirty days. In other words, if these cultures had been discarded after incubation for ten days, 30% would have been missed, and if they had been discarded after twenty days, 6% would have been missed. Indeed, we had one culture negative up to and including the fifth week, but the transplant made in the sixth week was positive. Hæmocultures should, therefore, be held for thirty days, or longer, before being rejected as negative.

Isolation of Brucella from Milk.

Both direct culture upon agar plates and guinea-pig inoculation were used. If the milk could be cultured within twenty-four hours after it was taken, direct culture was employed and was found to compare favourably with guinea-pig inoculation, although a slightly higher percentage of positives was obtained by the latter procedure.

The cultures were made by centrifuging at low speed a small quantity of milk and inoculating one drop of the cream upon an agar plate. The drop of cream was then spread evenly over the plate by means of a bent glass rod. Suspicious colonies were picked on the third and sixth day of incubation and verified microscopically and by slide agglutination.

In most instances, cultures were made on plates of plain liver infusion agar and also on this medium containing 1/300,000 gentian violet, as recommended by HUDDLESON. It was found that the gentian violet will inhibit the growth of most contaminating bacteria and will not, as a rule, prevent the development of *Brucella*. It therefore ordinarily facilitates the picking of *Brucella* colonies. However, it was discovered that some *melitensis* strains were very sensitive to this dye and refused to grow in a 1/300,000 concentration. Consequently, if gentian violet is used in culturing *Brucella*, particularly of the *melitensis* type, it is believed advisable to make also a duplicate culture on plain agar. If the milk is taken with the usual precautions and cultured within twenty-four hours, only a few samples will show excessive contamination, and plain agar alone will give quite satisfactory results. Indeed, it was exceedingly rare to find the gentian-violet plate positive when the plain agar plate was negative.

If the specimens are shipped some distance and not kept cold, direct culture was found to be of limited value, and in such instances guinea-pig inoculation

was employed. When it was expected that the samples would be in transit in excess of twenty-four hours, the boric-acid method of preservation suggested by TRAUM (4) was used.

Guinea pigs were inoculated subcutaneously with 1 c.c. of cream obtained either by allowing the specimen to stand in the refrigerator overnight, or by centrifuging at low speed,

Recognition of Infection and Isolation of Brucella in Guinea-pigs.

It was the custom to wait one month after inoculation to test for infection. At this time, blood was withdrawn from the heart for culture and agglutination. Also an intradermal test was performed. The procedure was again repeated after two weeks. Two months after inoculation, all animals were sacrificed and duplicate cultures on agar plates and broth were made from all organs and enlarged lymph nodes.

Both the intradermal and the agglutination reactions were found to be quite reliable indicators of infection. Occasionally, an infected animal failed to react to one of these tests, but very rarely to both. The agglutination reaction was found to be slightly more consistent than the intradermal test.

Blood culture during the course of infection proved to be a simple and reasonably trustworthy method of isolating *Brucella*.

In a few guinea-pigs inoculated with cow's milk, positive agglutination and intradermal reactions were found at the end of one month. Two weeks later, these reactions had diminished and the blood and organ cultures were negative. The question arises as to whether these guinea-pigs had been infected and had recovered within this period.

The intradermal test is of particular value in indicating infection following vaccination. Vaccination with a dead culture will stimulate agglutinins, but, in guinea-pigs, will not produce allergic sensitivity.

EXPERIENCE WITH DIAGNOSTIC METHODS.

Blood Culture and Agglutination.

It may be of interest, particularly to those engaged in laboratory diagnosis, to record the results of blood culture in relation to the agglutination titre of the same specimen.

In Table 1 is shown the result of culture of 1,412 human blood specimens classified in respect to agglutination. These specimens were taken either by the epidemiologist or sent to the laboratory by practising physicians. Presumably, they came from persons suspected of having undulant fever. It is probable, however, that most, if not all, of the specimens which were negative to both the

agglutination reaction and blood culture came from patients suffering from some other disease. It should also be stated that these represent the results on a single specimen. Naturally, if repeated specimens had been taken and the positive results recorded according to case, the percentage of positives would have been much higher.

It will be noted that the percentage of positive hæmocultures augments in keeping with the agglutination titre, until it reaches 1/160. After this dilution, there is no significant difference. Among the specimens which agglutinated in 1/80 or above, 55.5% gave a positive hæmoculture. Of the strains isolated, 95% classified as the *melitensis* variety, the remainder as *abortus*.

We know of no comparable statistics, but we have the impression that investigators working in countries where the *abortus* variety prevails have not been so successful in recovering the organism from the blood. Perhaps the percentage of positive cultures may be influenced by the fact that we were dealing principally with the *melitensis* variety; yet the proportion of *abortus* obtained corresponds to about what would be expected from the epidemiological data.

Brucella were isolated from thirty-nine specimens which failed to agglutinate, or agglutinated in titres of less than 1/80. An analysis of thirty of these cases, concerning which information was obtainable on the onset of the disease as manifested by clinical symptoms, gave the following results :

Number of cases	Period between onset of symptoms and withdrawal of blood specimen
1	3 days
1	8 days
1	19 days
15	1 to 2 months
7	2 to 3 months
5	More than 3 months

It seems evident that the failure of the serum to produce agglutination, or its ability to do so only in very low titres, was not due, except in two or three instances, to the specimen's being taken too early in the disease. Indeed, in most instances clinical manifestations had been in progress for a considerable period.

Beyond the date of onset, accurate clinical data were usually not obtainable, but it is of interest to note that in at least eight of the cases the symptoms were mild and the disease was of a chronic

nature, frequently manifested by arthritis, with little or no temperature.

There are a number of explanations that might be offered for the failure of these sera to agglutinate properly.

1. We have observed in a few cases which were followed through the course of the disease that the agglutination titre may vary considerably from time to time, and as the disease becomes less active the titre tends to fall. For example, in one case, during the active febrile period, the serum agglutinated in a dilution of 1/640. Three months later, during which time the patient was practically free from all symptoms, the agglutination titre had fallen to 1/80, yet the blood culture was still positive. It is therefore possible that, in some of these cases, the specimens were taken following a latent period during which the agglutinins had largely disappeared. The chronic nature of a considerable proportion of the cases would suggest this explanation.

2. There is also the possibility that some individuals, as we have occasionally observed among experimentally infected guinea-pigs, and even more frequently among sheep, do not respond to infection by the production of agglutinins. Indeed, in four of the thirty cases analysed, a second specimen was taken at from a week to three weeks following the first, and the second specimen showed little change in titre, in no instance reaching as high as 1/80.

3. There is another factor which cannot be overlooked but requires further investigation to determine its importance—*i.e.*, the possible existence of an anti-agglutinating action of the serum. We have demonstrated that this may frequently occur in sheep's blood if the reaction is performed with the usual technique and dilutions made in a physiological salt solution. Although the increase of salt concentration seems to have little effect upon the agglutinating titre of human bloods, it is nevertheless conceivable that, in some instances, the serum may have an anti-agglutinating action which will mask the presence of agglutinins. This was suggested in one case which was followed through the attack. In this instance, agglutinins were not manifest in diagnostic titre until three weeks after the onset of the symptoms, and two weeks after the blood culture was positive. Later, however, the agglutination titre rose rapidly, reaching 1/1,280. However, on one occasion during the acute stage, the serum failed to produce significant agglutination up to, and including, a dilution of 1/640. A week later, the serum agglutinated completely up to a 1/640 dilution. We think it not improbable that, on the occasion when agglutination failed to occur in a significant amount, there may have been present some inhibitory action similar to the prozone phenomenon which masked the agglutinins.

4. In all the thirty-nine cases failing to agglutinate above a dilution of 1/40, the *Brucella* strains isolated classified as the *melitensis* variety. We were using as antigen a *suis* strain. It may therefore be inferred that agglutinins were produced, but were of specific nature and failed to act upon the antigen employed. We doubt, however, if this is a legitimate explanation, for among

a certain number of the cases under discussion, as well as a large number of other specimens, a *melitensis* antigen was employed ; indeed, in some instances, a homologous strain. Yet we never encountered a serum which agglutinated *melitensis* and at the same time failed to agglutinate our standard antigen.

5. The question may also arise as to whether the infecting organism may not have been of the " para " type (which, in our opinion, is synonymous with a " rough " strain). We doubt, however, if this explanation is valid, as all the thirty-nine strains agglutinated well with an " S " antiserum, which would not have been the case had they been of the rough, or para, type. Furthermore, the thermo-agglutination was determined on twenty-seven of the strains, and only one of them showed a slight agglutination after heating for a period of two hours at a temperature of boiling water.

While we consider the agglutination reaction as being the most practicable and valuable laboratory method of recognising undulant fever, it must be borne in mind that it is not infallible and that the blood from some active cases may fail to agglutinate. Such phenomena have been encountered by others (GILBERT and DACEY (5)).

In order to determine the specificity of agglutination, or rather its association with clinical manifestations, we tested 927 samples taken from patients in the wards and out-patient department of the Montpellier General Hospital, which were sent in for the Wassermann test. This hospital draws patients from an area where *melitensis* infection is endemic and not infrequent. Among the specimens tested, nine, or 1%, agglutinated in dilutions of 1/80, or above. Seven of these patients were later found to be actually suffering from typical attacks of undulant fever, and the remaining two had, or had recently had, symptoms that were highly suspicious. There were also nine samples which agglutinated in 1/20 or 1/40. Accurate histories were obtainable from five patients. Two had suffered within the year with febrile attacks of short duration, but no suspicious history was elicited from the remaining three. The blood of thirty individuals agglutinated in a dilution of 1/10, but no effort was made to check their symptoms.

In routine blood cultures from goats and sheep, the organism was recovered from only 18% and 15%, respectively, from the specimens which gave a positive agglutination. As might be expected, the presence of the organisms in the circulating blood seems to depend largely upon the stage of the disease. In experimentally, or acutely, infected sheep and goats, *Brucella* can in most instances be isolated from the blood. This was the case in our

experimentally infected sheep, although the organism existed in the blood over relatively short periods (maximum, two months).

In a recently infected flock of 142 goats, 58% of those which gave positive agglutination reactions also gave positive blood cultures, and, while the number of positive blood cultures in the flock constantly diminished, there were three animals from which positive cultures were consistently obtained at two-month intervals during a period of eight months. Though the blood culture cannot be recommended as a routine measure, and is of little value in chronic infections, it is usually positive in the acute stages of the disease and is therefore useful in indicating recent and acute infections.

Allergic Reaction.

The mass of our data relates to experiments on guinea-pigs, goats, and sheep. Observations on some 2,500 guinea-pigs used for diagnostic and experimental purposes showed that, as a rule, the intradermal test correlated very well with the serological reactions and the existence of infections as determined by cultural methods. However, exceptions were encountered, and a small percentage of guinea-pigs infected failed to give an allergic reaction. On the other hand, a few animals that were apparently not infected gave a positive reaction. Repetition of the test on such guinea-pigs was frequently negative. It is possible that such false reactions may result from an extraneous local infection introduced in process of making the injections.

While, as stated above, the intradermal and agglutination tests correlate to high degree, the former has missed a few more animals proved to be infected than the latter. Also, the intradermal test gave a slight excess of false positives. In other words, in our hands the agglutination reaction was more reliable in detecting infection in guinea-pigs.

We realise the danger of reasoning by analogy and of inferring that other animals react in the same manner. But these observations have been mentioned because by autopsying the guinea-pig it is possible to establish, with a high degree of certitude, the existence or non-existence of the infection.

It is the general experience that human cases of brucellosis develop an intradermal reaction rather early in the disease, but, in some instances—and we have encountered one—it may be considerably

delayed. Our data on humans are rather limited and apply mostly to patients who have recovered. We have used the reaction principally for the purpose of identifying past or inapparent infections in the course of epidemiological investigations. Two hundred persons in villages where the disease was prevalent (*melitensis* type) were tested, and sixty, or 30%, reacted. Among these there were sixteen who gave a history of having had undulant fever, and all of them were definitely sensitive. The intradermal reaction is useful, therefore, as a method of retrospective diagnosis. But it would be a mistake, as further exemplified by observations on experimental sheep, to infer that it necessarily indicates an existing infection. It would be more correct to say it signifies either a present or a past infection.

Complement Fixation.

The complement fixation reaction was used largely in a comparative study on blood samples from goats and sheep. The results will be discussed in the following paragraph.

Comparison of Agglutination, Complement Fixation, and Intradermal Reactions.

The most extensive study on the comparative value of the agglutination, complement fixation, and intradermal reactions was made upon a recently infected flock of goats. Approximately 50% of the animals in this flock had aborted within two months preceding the beginning of the tests. Thereafter, examinations were made each two months until the flock had been surveyed five times. Each examination consisted of an intradermal, an agglutination, and a complement fixation test and cultures of the blood, and of the milk when it was available. The results of the five examinations have been combined in Table 2. Animals from which *Brucella* were cultured from either the blood or milk on the same or preceding examination are listed as bacteriologically positive, and it is believed may be regarded as actively infected. We shall not discuss this table in detail, but merely point out that, while a greater number of animals reacted as "positive" or "doubtful" to the intradermal test, this test was not so successful in identifying the known infected

animals as were the agglutination, and particularly the complement fixation, reactions.

Similar results were obtained in the survey of several flocks of sheep in which it was found that, as a rule, more animals reacted to the intradermal test than were positive to either the agglutination or complement fixation tests ; the latter reactions, however, were more trustworthy in selecting the animals that were proved to be infected through culture of the blood, milk, and vaginal discharges. Where the disease had been recently introduced in a flock, the correlation of the three tests was very close, but if the infection was of some standing and was no longer active (as manifested by the absence or infrequency of abortions and the failure to recover the organism from the blood and milk), the number of animals reacting to the intradermal test was far in excess of the serological reactors.

Yet the intradermal reaction appears to be quite specific in indicating past or present infection, as no reactions were obtained in over two hundred sheep coming from four different flocks which, according to the best information obtainable, had never been subjected to *Brucella* infection. The rapidity with which the test may be performed makes it adaptable to extensive surveys, and it is of undoubted value in determining whether or not a flock is, or has been, infected.

CLINICAL ASPECTS OF UNDULANT FEVER.

Though clinical manifestations of undulant fever received only minor consideration, certain data were collected on the cases visited in the course of the epidemiological studies.

The frequency and severity of the most important symptoms in 333 cases are reflected in Figure 1. These findings correspond closely to those of HARDY (6), although perspiration, chills, and constipation were somewhat more frequent in our series. These minor differences may be due to the personal factor in recording symptoms rather than to any essential variation of the disease. However, HARDY's cases were infections with the porcine and bovine varieties of *Brucella*, while ours were predominantly *melitensis* infections. Thus, of the 143 strains isolated from the 333 cases,

135 strains, or 94.4%, were classified as the *melitensis* type. The remaining eight, or 5.6%, behaved as the *abortus* variety.

The chief complaints, or combinations of symptoms which were responsible for putting the patients in bed, are listed in the order of frequency :

	Number	Percentage
Asthenia	121	38.1
Pain (muscular, articular, headache, etc.)	54	17.0
Asthenia, with headache or other pain	30	9.4
Headache	29	9.1
Asthenia, with chills or fever	25	7.9
Pains, with chills or fever	24	7.5
Fever	15	4.7
Chills	7	2.2
Angina	6	1.9
Bronchitis or other pulmonary symptoms	5	1.6
Orchitis	2	0.6
	<hr/>	<hr/>
	318	100

It may be of interest to practising physicians to note the errors of their colleagues in making initial diagnoses based solely upon clinical manifestations. In only 232 of the 322 cases (72%) were clinical diagnoses made. In the remaining ninety cases, the physician was too cautious or wary to venture an opinion. The diagnoses on the 232 cases, arranged in order of frequency, were as follows :

	Number of cases	Percentage
Undulant fever	89	38.4
Grippe	71	30.6
Bronchitis	10	8.2
Pneumonia or pleurisy	6	
Pulmonary tuberculosis	3	
Typhoid or paratyphoid	16	6.9
Articular rheumatism	6	2.6
" Courbature "	5	2.2
Malaria	4	1.7
Angina	4	1.7
Fever, undetermined origin	4	1.7
Sciatica	3	1.3
Renal congestion	2	0.9
Meningitis	2	0.9
Orchitis	2	0.9
Diphtheria	1	0.4
Intercostal neuralgia	1	0.4
Menopause	1	0.4
Neurasthenia	1	0.4
Gall stones	1	0.4
	<hr/>	<hr/>
	232	100

While undulant fever heads the list, it will be noted that only slightly better than one-third of the cases were recognised before the laboratory settled the issue. It is not surprising from the symptom complex and the frequency, or almost universal presence, of what is commonly called grippe, or influenza, that 30.6% were thus diagnosed. The group next in importance, comprising 8.2%, includes bronchial or pulmonary infections (this group being followed by typhoid or paratyphoid—6.9%). The list illustrates the variety of conditions which undulant fever may simulate in its initial stages. No doubt, if malaria were a common disease in France, chronic forms would frequently be confused with undulant fever.

It is not the province of this paper to go into detailed description of the character of the particular symptoms, but merely to show their frequency and the order of appearance. It may, however, be of help to vivify our statistics by indicating what the physician is likely to find if called to see a bedridden case of undulant fever. He would certainly find the individual suffering from asthenia and fever. The chances are approximately nine to one that he would have had chills and profuse perspiration. It is almost equally certain that he would have lost his appetite, and the probabilities are four to one he would be constipated and have difficulty in sleeping. It is more than probable he would complain of muscular and articular pains, and it is not unlikely he would be nervous—either irritable or depressed.

In taking the history of initial symptoms, it would be almost certain that the onset was manifested by general fatigue, probably accompanied by chills, loss of appetite, perspiration, fever, insomnia, headache, or muscular and articular pains, and that the patient had gone to bed because of weakness which was probably accompanied by headache, muscular or articular pains, or chills and fever.

Careful questioning would, in most instances, reveal that, for a few days to several weeks preceding the development of definite symptoms of illness, the patient had been feeling "out of sorts" and tired easily on physical exertion. We suggest these frequently prolonged prodromal symptoms may be helpful in distinguishing undulant fever from grippe, the malady with which it is most commonly confused.

It may be added that *in France the chances are better than eight to one the patient would have had direct contact with goats, sheep, or cows.*

The errors in diagnosis which have been made when only clinical manifestations were relied upon as a basis clearly illustrate the desirability of the physician's having recourse to the laboratory when in doubt. Indeed, it would be a sensible procedure to take a specimen of blood for laboratory diagnosis in all cases of suspected gripe of protracted nature and to look with suspicion upon any form of continued fever of an undetermined origin.

Finally, we wish to say that, in our opinion, the text-book practice of classifying undulant fever into several categories, according to the severity or predominance of certain symptoms, may be misleading. While the disease may vary widely in its manifestations, it does not fall naturally into clear-cut clinical categories, and any such classification is largely arbitrary and artificial. In any event, the physician will do well to wait until a case has run its course before assigning it to a special type. We have seen cases which commenced as "mild", or "ambulatory", and then suddenly became "severe", and others which at the onset would be regarded as very severe, but in which rapid and complete recovery ensued after a few weeks. While the ultimate prognosis is generally favourable, the wise physician will certainly avoid committing himself on the duration of the case or the course the disease is likely to pursue.

EPIDEMIOLOGY.

General Environmental Features and the Distribution of Undulant Fever.

It will be appropriate, first, to describe briefly the dispersion of domestic animals, the customs of the people in relation to them, and the regional occurrence of undulant fever in France.

As France is, for the most part, a country of agricultural and animal husbandry, domestic animals such as cattle, horses, sheep, goats, and hogs are rather widely distributed. As the farms are usually small, the herds and flocks are not large. There are, however, certain regional exceptions to these general statements. In the tier of departments bordering upon, or near, the Mediterranean, cattle are scarce, and most of the domestic animals consist of sheep and goats. These departments are included in the sections of the

country which subsequently will be referred to as "south-east" and "south-west". While sheep and goats are frequently as numerous in the departments to the north, there prevails in the south-east and south-west the custom known as "*transhumance*", which consists of gathering together flocks of sheep in the lowlands adjacent to the sea and transporting or herding them to high mountain pastures during the summer. These assembled flocks may number several thousand animals. In the fall, they are redistributed to their respective owners. Also, in villages situated in the mountain valleys, there is customarily a village shepherd who is responsible for grazing all the sheep and goats of the village. Consequently, there is a daily intermingling of all the small flocks of each village. The communal shepherd and the practice of *transhumance* are almost unique to this region, although they are encountered to some extent in the regions designated as "east".

It is generally stated that, in France, milk is used largely for cooking and with coffee, and that in either case it is ordinarily brought to a temperature approaching the boiling-point before it is consumed. While there are exceptions to this rule, raw milk is not frequently partaken of in France as compared with Germany, England, Holland, the Scandinavian countries, and the United States, nor is fresh unfermented cheese extensively eaten.

On the other hand, the contact of the rural population with their domestic animals is exceedingly intimate. On the smaller farms, the stable is commonly part of the house, and on approach one may be confused in distinguishing the door which leads to the human habitation from the one which opens into the animal quarters. Even on the larger farms, the buildings, including the residence, are habitually constructed in the form of a quadrangle, and the enclosed space constitutes what may be termed the barnyard, where animals circulate and pass to and from pasture.

Owing to the great laxity in reporting communicable diseases, it is impossible to know the number of cases of undulant fever which actually occur. Estimates between 2,000 and 4,000 per year have been made. However, from various sources of information, including diagnostic laboratories, it is possible to form a fairly accurate idea of its relative prevalence in the different parts of the country. For purposes of description, we shall use the six classical

divisions of France which are designated as " north ", " centre ", " west ", " east ", " south-east ", and " south-west ". Though a few cases of undulant fever have been diagnosed in many of the departments of the north, the centre, and the west, the disease is comparatively rare, and occurs in these regions only in the form of isolated and widely separated cases. In contrast, it is endemic and frequent in the south-east and south-west, and here and there may reach epidemic proportions over a period of a year or so. In the east, it occurs largely in sporadic form, but in some areas, epidemic foci have developed. This distribution of the disease in man will be subsequently referred to in connection with the type of *Brucella* concerned.

Another feature of its distribution, which applies to the country as a whole, is that it affects almost exclusively the rural populations. When cases develop in larger towns or cities, they occur almost invariably in persons who have been associated with the transportation or the slaughtering of animals, particularly sheep or goats. Also a few infections in villages and towns have been observed which were apparently due to the consumption of fresh goat's cheese.

Classification of Brucella Strains.

During the course of these studies, 817 *Brucella* strains were isolated from man and animals, and fifty-two of animal origin were kindly furnished by Doctor RINJARD, of the State Veterinary Laboratory, at Alfort. The methods of classification employed were those advocated by HUDDLESON (7), and consisted of the determination of the bacteriostatic action of thionin and basic fuchsin, the production of H_2S and CO_2 requirements on primary culture. It was found that the discoloration of fuchsin was also helpful in eliminating *melitensis*,¹ as none of this variety possessed this quality.

Of the 869 strains examined, 843, or 97%, fell clearly into one of two types—namely, *melitensis* or *abortus*; that is, they either grew well on both thionin and fuchsin media and produced no H_2S what-

¹ There exist some differences in opinion as to the exact terminology that should be applied to the *Brucella* group, depending upon whether the different types are regarded as true species or merely varieties of the same species. In this paper, the terms *melitensis*, *abortus*, and *suis* will be used to designate respectively the caprine, bovine, and swine types, without prejudice as to whether they represent species or varieties.

ever, or only a slight amount within the first twenty-four hours (*melitensis*); or they were inhibited by thionin and produced H₂S in fair to considerable quantities for two or more days (*abortus*). None having the characteristics of *suis* were encountered.

Of the twenty-six atypical strains, there were sixteen which failed to produce H₂S, or only a trace, during the first twenty-four hours, but in other respects behaved as *abortus*. Seven strains, though producing H₂S beyond twenty-four hours and when first isolated preferring CO₂ for active growth, were not inhibited by either thionin or fuchsin. Three seemed to be equally sensitive to both dyes, and therefore could not be classified by this method. As all these twenty-six strains came from cows, or from persons who had been infected by cows, they have been tentatively classified as *abortus*.

Although it was found that, with few exceptions, *Brucella* strains could be classified by these methods, it is of paramount importance to the epidemiologist to know to what extent disease-producing tendencies and host-selectivity coincide with these cultural types. We know of no better way to determine this than by observing the behaviour of the respective types under natural environment. As in all instances we knew the host and geographical origin of the strains examined, and for most possessed accurate information on the circumstances surrounding infection, it is worth while to examine this question in the light of these facts.

It will be noted from Table 3 (1) that the strains classed as *melitensis* predominate in the regions where undulant fever is frequent and endemic, and *abortus* where it is rare and sporadic; and (2) that the strains of animal origin reacting as *abortus* were, with one exception, recovered from cows and horses, while the strains from goats and all save one from sheep were culturally *melitensis*.

Epidemiological investigations indicated that all the human strains typing as *abortus* were traceable to infection from cows, and in every case where the human infection appeared to be traceable to sheep or goats the strain isolated was typed as *melitensis*.

These main features correspond to what one would expect from the usually accepted attributes of the two types—i.e., *melitensis* is found exclusively in infections of goats and, with one exception, in infection of sheep, and in the localities where this type occurs undulant fever is frequent. The *abortus* is associated with infection

of cows and horses, and in the region where it predominates human infections are rare.

The exceptions to these general rules of host and geographical distribution are perhaps still more enlightening. Six of the seven *melitensis* strains coming from the north were recovered from personnel of the Paris abattoir, who were engaged in slaughtering or handling sheep. As sheep are received in this abattoir from all parts of France, these cases, strictly speaking, can scarcely be considered as of indigenous origin. The seventh strain of *melitensis* from the north was recovered from a ewe in a large flock of 350 sheep which had been purchased from a stock-dealer. Beyond this, the origin of the sheep could not be definitely traced, but it is not unlikely that some of the animals came from the east, where in certain localities *melitensis* infection had been demonstrated. The specimen of milk from which the culture was obtained was received from the departmental veterinarian, and when the identification was made, the health officer was advised to be on the look-out for human cases. True to our prediction, it was found that three cases of undulant fever had developed in the family of the owner of the flock, thus giving additional proof of the correctness of the identification. The two strains identified as *melitensis* from the centre and west came from departments bordering on the east and south-east and probably represented spillovers, or extensions from the latter regions, where this type of *Brucella* is frequent. The single sheep strain identified as *abortus* was obtained through Dr. RINJARD, and, while exact information relative to the source of infection is lacking, it came from a region where *abortus* infection among cows is known to be prevalent, and it is not improbable that the infection was of bovine origin.

The number (64) of strains recovered from cows and classed as *melitensis* is rather startling and, if judged on the basis of host alone, the accuracy of identification might be questioned. However, epidemiological considerations give support to the view that their cultural character reflects their true pathogenic nature. In the first place, these *melitensis* strains were found only in the *melitensis* zone. Furthermore, *melitensis* infection was known to exist in the particular community from which they came, and with few exceptions there was direct contact of the cows with infected sheep or goats. Finally, in every instance where *melitensis* was recovered

from a cow, there were associated cases of undulant fever. On the other hand, *abortus* infection of cows is widespread, yet the number of secondary human infections is comparatively small.

A striking difference between the *abortus* and *melitensis* infections of man was that the former were scattered and isolated and the latter tended to be bunched, and several cases in one family were common.

Field Studies.

Attention was first focused upon the personal investigation of cases reported from all parts of the country, but it soon became evident that, in the majority of instances, it was impossible to determine definitely the source or manner of infection. That is, it was common to find that the person had had contact with several species of domestic animals and had sometimes consumed milk or fresh cheese from more than one source. Also, laboratory examinations of blood and milk specimens from suspected animals sometimes failed to clarify the situation.

It was therefore decided to select certain communes where the disease was particularly prevalent and survey the entire population, with the object of ascertaining any differences in the habits and environments of the persons who had contracted undulant fever and those who had escaped. The questionnaire and the methods employed were presented in detail in a progress report (1). It will suffice to state here that, for each person then residing in the community under survey, a record was made by means of a house-to-house canvass. This record included the housing conditions, sanitary arrangements, water supply, kind and number of domestic animals the distance between the stable and the dwelling the general cleanliness of the stables and premises, the history of abortion among the animals, the personal habits of the individuals with regard to contact with animals, handling of manure, and consumption of raw milk and raw-milk products. A careful history was also taken of previous illnesses, and from persons ill or recently ill with symptoms suggestive of undulant fever specimens of blood were taken for culture and agglutination tests.

While the particular communes were selected for survey because the disease was then active, it was found upon investigation that, in some instances, it had existed for several years, although the

great majority of cases had occurred within the last two to three years. For purposes of analysis, it was necessary to decide whether a person had had the disease or not. The accuracy of retrospective diagnoses based upon clinical manifestations may be questioned, but we believe the error was not great, as the local physicians, as well as the people, had become thoroughly familiar with the usual symptoms. This was evidenced by the correctness of the diagnoses on the active cases. As additional confirmation, 200 intradermal tests were performed, and it was found that all persons who had been diagnosed as having had undulant fever gave a positive reaction to *Brucella* protein. There were also a number who gave no convincing history of having had the disease, but who reacted positively. While no doubt some persons who had mild or sub-clinical infections were placed in the negative group, we feel that, with very few, if any, exceptions, the ones who were diagnosed as positive on a clinical basis actually had had the disease. Thus, if errors were made, they tended to be on the conservative side.

These surveys, involving a population of 4,315, among whom 496 cases of undulant fever were diagnosed, were made in the south-west of France, and all the strains isolated from both man and animals were classified as *melitensis*. Sheep and goats were the predominating domestic animals and, according to epidemiological and laboratory evidence, constituted the principal, if not the sole, reservoir of infection. Perhaps the most impressive information gleaned from this particular study bore upon the habits and circumstances which contribute to human infection.

As the object of this paper is to condense and summarise what we regard to be the most important and significant features of our field studies, we shall present only a selected number of tables. In some of the tables, we shall also make use of data collected in the course of investigation of 466 cases occurring in various parts of France.

Seasonal Distribution.

The percentage distribution by months of 810 cases occurring in various parts of the country, and in which the date of onset of symptoms could be more or less accurately determined, is plotted in Figure 2.

It will be observed that there is a marked seasonal variation. The lowest number of cases occurs during the summer and early fall months, followed by a gradual rise, reaching a peak in March.

During the six months from December to May inclusive, 78% occur, and 50% in the three months of February, March and April. The significance of this seasonal distribution and its relation to the period of parturition and abortion among certain domestic animals will be discussed later. Irrespective of the animal source of infection, more cases occur in winter and spring than in the other seasons, but the spring incidence is most marked among cases attributable to goats and sheep.

Age and Sex Distribution.

The distribution and attack rates according to age and sex of cases encountered in the communal surveys are shown in Table 4. These data correspond very closely to the distribution of 466 cases reported in various parts of the country, except that, in the latter, the ratio of males to females was somewhat higher (three to one). Of 496 cases discovered in the communal surveys, 67.9% occurred among males and 32.1% among females. It is believed this discrepancy can be accounted for by the intensity of the infection in the communes surveyed and by the women of the families assuming the duties of men as they fell ill.

It will be noted that relatively few clinical cases occur below the age of 15 years. In the older age-groups, the differences are not so marked, yet the highest rate is found in the age-group of 30 to 49 years.

Below the age of puberty, there is little difference between the two sexes, but thereafter the infection rates among males are from two to four and a-half times as high as among females. For the entire group, the attack rate is slightly more than twice that for females. Nor do differences in exposure in the age-group of 15 and above account for the significantly higher rate in males. It will be shown later that, in these communes, contact with sheep and goats and handling of their excreta constituted the principal means of infection and, while the males were thus somewhat more exposed, the attack rate among the females who were similarly exposed was only about half that of the males. This, coupled with the lack of significant difference between the two sexes below the age of 15,

strongly suggests that, after puberty, females are relatively resistant to clinical attacks of undulant fever.

It likewise appears that children enjoy a certain immunity, at least to manifest attacks, as in these villages the stable was, as a rule, virtually a part of the house, and apparently the exposure of the children was as great as that of the adults.

Animal Reservoirs and Sources of Human Infection.

In the communes where the entire population was surveyed, sheep and goats were the predominating domestic animals and, as above indicated, all evidence pointed to them as the principal, if not the sole, reservoirs of the disease. The relation of undulant fever to the presence and number of these animals and the history of abortion among them is clearly illustrated in Tables 5, 6 and 7. In these and other tables compiled from the communal surveys, sheep and goats have been grouped together, because both species were proved to be infected, and, as they were usually mixed, it was not feasible to treat them separately. We shall subsequently refer to these tables in discussing the manner of transmission.

An analysis of the 466 cases individually investigated gives a more comprehensive picture, as these were located in various parts of the country, including northern and eastern sections. These were investigated as they came to our attention through official reports and other sources. The correctness of the diagnoses was confirmed in all by the agglutination reaction, or blood culture, or both. Likewise, blood and, when obtainable, milk were taken for examination from all, or a representative number, of the suspected animals. In Table 8 are listed the possible, or what were regarded as the most probable, origins of infection. The placing of a case in one of the columns, under "goats", "sheep", "cows", etc., means that no other source of infection was suspected. However, it was common to find that there had been contact with, or milk had been consumed from, more than one species of animal from which the disease might have been contracted. The most usual combination of sources was goats and sheep, followed by goats, or sheep, and cows.

According to this analysis, goats and sheep, either separately or in combination, account for 45.5% of the cases; cows alone, for 15%; and cows, in combination with either goats or sheep, for an

additional 25.8%. This gives us a total of 86.3%, which we believe can be attributed definitely to these three species of animals. It is probable that they were responsible also for the majority of cases placed in the "miscellaneous and doubtful" group.

Two cases were attributed to handling of a colt which died shortly after birth, and in four instances the only elicited means of infection was contact with a human case. In the miscellaneous and doubtful category were placed 12½%, which includes eight laboratory infections. A certain number of persons denied having had contact with animals, or having consumed any raw milk or raw-milk products. In other words, no sources could be found for their infection. However, with one exception, these cases occurred in regions where undulant fever of the *melitensis* type was frequent.

The rôle of the hog as a source of infection was kept in mind from the beginning of the studies, but, with the exception of one commune where there appeared to be some relation between undulant fever and contact with this animal, nothing was discovered to incriminate it. In that commune, the hogs under suspicion had been slaughtered and no laboratory tests could be made upon them. As *melitensis* was the only type isolated in this commune, an attempt was made to test the susceptibility of hogs to this type. Eight young hogs were employed. In two, a broth culture was rubbed upon abraded skin, two received 50 c.c. of broth culture on two successive days in food mash, and four were fed with naturally infected goat's milk for a period of four months. None of them developed a positive agglutination or intradermal reaction, nor could *Brucella* be isolated at autopsy. Enquiries at several large abattoirs failed to elicit a history of undulant fever from any of the personnel engaged in slaughtering of hogs, while the disease was common among the butchers of sheep and goats. And, as before stated, no strain among the 869 examined possessed the cultural characteristics of the *suis* type.

While chickens are ubiquitous throughout rural France, there was no reason to suspect them of having anything to do with harbouring or transmitting the disease, but to determine their susceptibility to *melitensis* we examined the blood of fifty chickens that were daily receiving milk from infected goats. Only one gave an agglutination reaction in 1/40 dilution, but it was also found that agglutination in this titre is occasionally produced by blood from chickens

that have in no way been exposed. Furthermore, neither massive doses given experimentally in the food nor a million *Brucella* injected subcutaneously produced the infection in hens. A dose of one hundred million *Brucella* given subcutaneously did produce a transient infection with positive blood culture.

Two naturally infected rabbits were discovered, but these rabbits had been allowed to run in a barn where a number of sheep and goats had recently aborted, and were therefore unusually exposed. There is every reason to suppose that the rabbits, as well as the associated human case, were secondarily infected from the sheep and goats.

While dogs have been accused of passively or actively transmitting the infection to other animals and to man, we could find no proof for this accusation. It is true that families with sheep or goats usually have dogs, but there are also families, with dogs, who have no sheep or goats; and where the disease is introduced, it follows the sheep and goats and not the dogs.

Undoubtedly some unusual sources and manners of infection escape detection, and when discovered attract attention simply because they are unusual. But it is well to remember that the epidemiologist is, or should be, primarily concerned with averages and frequencies and not with rarities and exceptions. If the most common reservoirs of disease can be located and the methods of infection can be controlled, the transient and unusual may be neglected, as they are probably secondary to, and dependent upon, the former. Thus, we are convinced that if *melitensis* infection could be eliminated primarily in goats and sheep, and secondarily in cows, the problem would be solved.

In view of the predominating importance of sheep, goats and cows as sources of the infection in man, a further word about the distribution of the disease among them is not out of place. Brucellosis of sheep and goats is limited largely to the south-east and south-west, with some scattered foci in the east. It will be recalled that it is in these regions that the *melitensis* type is found, and human infections are most frequent. Northward, and as cattle become more numerous, contagious abortion among them increases. The number of human infections is in direct ratio to the presence of *melitensis*, and in the regions where this type is not found, human infections are sporadic and rare, although it is here that abortion among cows is most common. However, when cows become

infected with *melitensis*, they appear to equal, if not to exceed, goats or sheep in producing human infections. Nor is the *melitensis* infection in cows merely a transient disease. Like *abortus*, the organism tends to localise and persist in the udder. In five of nine cows examined a year and a-half to two years after the infection was first recognised, the organism was still being excreted in the milk and still preserved the cultural characteristics of *melitensis*. It is estimated that not less than two-thirds of the human cases originating from cows are of this type.

Some epidemiological and laboratory studies of brucellosis in sheep suggest that sheep (8) tend to recover from the infection; that both sheep and goats are most dangerous in transmitting the disease during, or shortly following, abortion; and that the disease among them is closely allied to the practice of *transhumance*.

Manner of Human Infection.

It was found that, in the process of acid fermentation of milk in the preparation of cheese, *Brucella* were destroyed and that they could not be recovered from rennet-prepared cheese after it had been permitted to age for a period of two weeks or longer. That aged cheese is not dangerous is further indicated by the fact that a well-known cheese is prepared from sheep's milk, which from time to time is certainly contaminated with *melitensis*, yet no case of undulant fever has ever been traced to eating this cheese. Consequently, in the tables to be discussed, only raw milk and relatively fresh unfermented cheese have been regarded as likely conveyors of infection.

In the horizontal columns of Table 8, the cases individually investigated have been classified according to the probable route, or manner, of infection. While the largest number risked the possibility of infection through both consumption and contact, the number that had contact alone was more than five times as great as the number who were exposed through consumption alone. In this table, we are confronted with the impossibility of determining the relative danger of these two routes, as we do not know the frequency of the exposure among people in general. However, data collected in the communal surveys help in answering this question.

In Table 9, a comparison is made from the survey data of the frequency of consumption of raw milk and fresh cheese in the group that had had undulant fever and in the group that had escaped. Similar comparisons are shown in regard to habitual contact with sheep or goats and handling of their excreta. The percentage of persons consuming raw milk and fresh cheese in the two groups is virtually the same for those who had and had not contracted the disease, the slight differences which occur being well within the error of chance selection. But the proportion of individuals having habitual contact with sheep and goats is very significantly higher in the group that contracted the disease than in the group that escaped. This likewise applies to handling manure. In addition, of the fever victims, there were less than 3% of the milk and fresh cheese consumers who did not have contact with the animals or their excreta, while more than 50% of those in contact with the animals or excreta denied having consumed raw milk or fresh cheese.

There was also a great deal of circumstantial evidence indicating that infection through contact is much more frequent than infection through food. For example, in these communes, there was usually a large town or trading centre with few sheep and goats, where the people generally purchased their milk and cheese from the surrounding hamlets in which most of the sheep and goats were kept. The number of infections within the towns was very low, and most of the cases occurred in the hamlets among the people who had direct contact with animals. Also in one community investigated, it was attested by all that for more than a year, as a result of advice from the local physician, the milk had been boiled before consumption and before preparing cheese, yet the epidemic had continued unabated.

It was not practicable to distinguish between the dangers of contact or the handling of manure, as most of the persons who performed this work also had direct contact with animals. We have observed, however, a few cases in which there was no contact with animals where the disease was apparently contracted through manure-handling. Yet from such observations it is not justifiable to conclude that *fæces*, *per se*, carry the infection, as manure would naturally contain, not only the urine, but, above all if there had been an abortion, the aborted products and the vaginal discharges following abortion.

It is clear (Tables 5, 6 and 7) that there is a relation between the incidence of undulant fever and the number of animals retained by the family. Indeed, most of the cases of the disease which occurred in families that did not possess sheep or goats were in persons having contact with such animals off the premises. There are probably several reasons why the incidence of undulant fever increases with the number of animals. First, the exposure is greater; secondly, the greater the number of animals, the greater is the chance that some of them will abort if infected; and, thirdly, the larger flocks are more subject to infection, for, if a family has one or two goats only, the chances are that they will be kept entirely on the premises, but if a larger number is owned, it is the custom to send them out to pasture in charge of the communal shepherd, where they mingle with other goats and sheep of the village. Thus the opportunity of acquiring the disease is greatly increased.

As might be expected, there was found to be a correlation between the incidence of undulant fever and the history of abortion among the retained goats and sheep (Table 6). In fact, we believe it not improbable that some abortions may have occurred in the group in which no such history was elicited, as this event may be overlooked in goats and sheep.

That both the size of the flocks and abortions influence the incidence of undulant fever is shown in Table 7. The influence of abortions is further suggested by Figure 2, as most of the cases occur during the period when sheep and goats are pregnant.

Sanitary Conditions as Factors in Distribution.

Besides investigating the personal habits relating to consumption of milk or fresh cheese and contacts with animals, an attempt was made in the communal surveys to determine the influence of the sanitary environment, such as water supply, disposal of excreta, the general cleanliness of the stables and dwellings, etc. It should be stated that, in the localities surveyed, the general sanitary conditions were of a low order, particularly in the small villages or hamlets, and consequently opportunity was not afforded to study wide variations in environment.

These communes usually comprised a number of hamlets and a somewhat larger village or trading centre. The water supplies of the hamlets were commonly subject to contamination, and toilet

facilities were non-existent or very primitive. In the larger villages, the water supplies were better constructed, and other sanitary arrangements were on a somewhat higher level. As the incidence of undulant fever was much greater in the hamlets, there was found to be a correlation between undulant fever and the poor quality of the water, the lack of toilet facilities, and the piling of manure. But most of the goats and sheep were also retained in the hamlets, and when correction for their presence was made, the above correlations disappeared. We therefore believe the correlations with water supplies and other sanitary conditions were merely partial and unrelated to cause.¹

DISCUSSION.

These studies afforded an opportunity to observe the behaviour of the *abortus* and *melitensis* types of brucellosis and have confirmed the opinion that the latter is much more infectious for man. They have also shown that the epidemiological patterns displayed by the two types are quite different. Human infections of the *abortus* type are usually single and sporadic, while the *melitensis* is characterised by producing epidemic outbreaks in which multiple cases in one family are frequent.

Though the possibility of man's becoming infected with the *abortus* type should not be ignored, in France this variety is comparatively of greater importance in causing economic losses sustained through the abortion of cows, and, for this reason, is primarily a veterinary problem.

On the other hand, the presence of *melitensis* constitutes a real threat to human health and deserves consideration from this aspect alone.

The danger of contracting the disease through contact with infected animals is well known, but we suspect that, in the minds

¹ Stress is laid on this point, because we have been quoted as demonstrating in a previous article (TAYLOR and HAZEMANN (1)) that undulant fever was transmitted through water. This was not our interpretation of the data presented (see page 510, above citation). We would not go so far as to say the disease may not be transmitted by water; indeed, in several cases, individually investigated, infection by this means was suspected. But we believe it to be comparatively rare and of relatively little importance.

of many health officers, the epidemiology of undulant fever is still too closely associated with the consumption of raw milk. In this connection, it is well to remember that the often cited classical example of the dramatic reduction of undulant fever among British marines stationed at Malta, following the withdrawal of fresh goat's milk from their diet, occurred in a group of men in which the only opportunity of infection was from milk. Had they been equally exposed through contact with goats, we imagine the results would have been quite different.

Our observations indicate that in France contact infection is much more frequent than infection through consumption of raw milk and raw-milk products. This excessive proportion of contact infections is no doubt influenced by the custom, particularly in cities, of boiling milk before it is used. Yet in localities where opportunities for infection by both means were co-existent, it was found that the hazard of becoming infected through contact was definitely greater than through the consumption of raw milk. This finding is in accord with the experimental infection of animals.

It was also shown that the incidence of undulant fever correlated with the parturition period of goats and sheep. Our bacteriological studies on the excretion of the organism by these animals further confirm the view that the danger of the disease being transmitted by them during abortions, and shortly thereafter, is far greater than at any other time.

An additional reason for recognising the importance of contact infection is that it presents quite a different control problem. Through boiling or pasteurisation, transmission of the disease by milk may be arrested. But for those whose occupations bring them into contact with animals, or their carcasses, no such simple means of prevention is at hand. Our unsuccessful attempts to protect animals by killed vaccines and the occurrence of seven cases of undulant fever among the personnel associated with this investigation, all of whom had received prophylactic vaccination, leaves us with little faith in protecting man by this measure.

We believe the greatest hope lies in the control of the disease in animals. Perhaps a more thorough understanding of the manner of spread of the infection among them would suggest a practicable means of breaking the chain of transmission.

Some success has been reported with the use of living attenuated vaccines in preventing open infection of the *abortus* type in cows, but, in the case of the *melitensis* variety, the field requires further exploration.

In that the mass behaviour of a disease is dependent upon the factors related to its spread, it naturally follows that the greater the number of such factors, the greater will be the possibility of divergence in its mass behaviour. In undulant fever, we are dealing with a malady singularly susceptible to a varied epidemiology and we may expect such variation with changes in the animal reservoirs, the types of *Brucella* concerned, and the personal habits of the people. In interpreting the data presented in this report, it is therefore well to remember that they reflect the characteristics of the disease as manifested under the conditions prevailing in France.

SUMMARY AND CONCLUSIONS.

1. In the study of 869 *Brucella* strains isolated from man and animals in France, it was found that 97% could be definitely classified by the production of H₂S and the bacteriostatic action of thionin and basic fuchsin. Judged by the behaviour of the strains under natural conditions, such classifications appear to give valuable information upon their pathogenic attributes.

All of the classified strains fell into one of two types—*i.e.*, *Br. melitensis* and *Br. abortus*; no *suis* variety was encountered. Of the 507 strains isolated from man, 477, or 94%, were classified as *Br. melitensis*.

2. The *melitensis* type of infection is a definite hazard to human health and deserves consideration from this aspect alone.

In France, the *abortus* type is relatively unimportant as a cause of undulant fever and is essentially an economic and veterinary problem.

3. Cases of undulant fever of the *melitensis* type are usually multiple and tend to occur in localised epidemic outbreaks, while those of *abortus* variety are almost invariably sporadic and isolated.

4. There is a marked seasonal variation in undulant fever which reaches a peak in the early spring. This corresponds to the period of abortion and parturition among domestic animals, particularly sheep and goats.

5. There is a significant age and sex distribution. Clinical cases of undulant fever are rare in individuals below the age of 15 and are from two to three times as frequent in males as in females. These differences in age and sex incidence may be partly explained by difference in contact exposure, but our data suggest that children, and females after the age of puberty, enjoy a certain resistance to the infection, or at least to clinical manifestations of the disease.

6. Goats, sheep and cows constitute the main animal reservoirs. Infections in goats and sheep are almost always of the *melitensis* type. Cows are the principal hosts of the *abortus* variety, but in certain regions are not infrequently infected with *melitensis*.

7. Undulant fever occurs principally among the rural population and in persons whose occupations bring them in contact with these animals or their carcasses.

8. Our studies indicate that the risk of infection through contact with animals is definitely greater than through the consumption of raw milk or fresh cheese.

9. In the transmission of this disease, sanitary conditions and environment are of limited significance. The danger of infection is dependent largely upon the personal habits of the individual in regard to contact with infected animals and, to a lesser degree, upon the consumption of raw milk and fresh cheese.

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Table 1.

COMPARISON OF AGGLUTINATION REACTION AND HEMOCULTURE OF HUMAN BLOODS RECEIVED FOR DIAGNOSIS.¹

Agglutination		Hæmoculture positive	
Reaction	Number	Number	Percentage
Negative	569	11	1.9
Positive 1/10	29	4	13.8
Positive 1/20	41	9	22.0
Positive 1/40	47	15	31.9
Positive 1/80	90	41	45.6
Positive 1/160	117	67	57.3
Positive 1/320	145	80	55.2
Positive 1/640	145	82	56.6
Positive 1/1,280	229	133	58.1
Total	1,412	442	31.3

¹ Contaminated specimens not included. Within a period of one month, 8.3% were contaminated. Specimens agglutinating 1/80 or higher gave 55.5% positive blood cultures.

Figure 1.

FREQUENCY OF OCCURRENCE OF VARIOUS SYMPTOMS
(MILD AND MARKED) (333 CASES).
(In percentage)

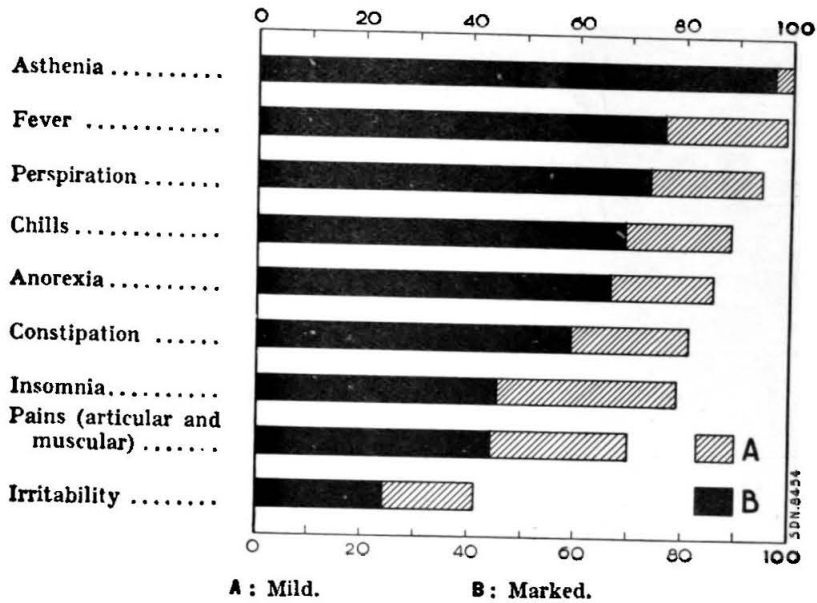


Table 2.

COMPARISON OF INTRADERMAL, AGGLUTINATION,
AND COMPLEMENT FIXATION REACTIONS IN A FLOCK OF INFECTED GOATS.

Degree of reaction	Intradermal			Agglutination			Complement fixation		
	Total number	Bacteriologically positive		Total number	Bacteriologically positive		Total number	Bacteriologically positive	
		Number	Percentage		Number	Percentage		Number	Percentage
Negative	153	14	9.2	173	16	9.3	216	9	4.2
Doubtful	219	56	25.6	160	15	9.4	150	26	17.3
Positive	266	126	47.4	302	165	54.6	267	161	60.3
Total	638	196		635	196		633	196	

Note.—“ Bacteriologically positive ” indicates that *Brucella* were isolated from either the blood or milk at the same time as the intradermal, agglutination, and complement fixation tests were performed, or at the preceding examination made two months previously.

540 INVESTIGATIONS ON UNDULANT FEVER IN FRANCE

The degrees of reaction signify :

- | | | |
|--------------|---|---|
| Negative... | } | - or \pm Intradermal ; |
| | | No agglutination or agglutination in 1/10 dilution only ; |
| | | No complement fixation. or fixation with 0.05 c.c. of serum only. |
| Doubtful .. | } | + intradermal ; |
| | | Agglutination in 1/20 or 1/40 dilution ; |
| | | Complement fixation with 0.025 c.c. of serum. |
| Positive ... | } | ++, +++, or ++++ intradermal reaction ; |
| | | Agglutination in 1/80 dilution, or above ; |
| | | Complement fixation with 0.0125 c.c. of serum, or less. |

Figure 2.

SEASONAL DISTRIBUTION OF UNDULANT FEVER (810 CASES).

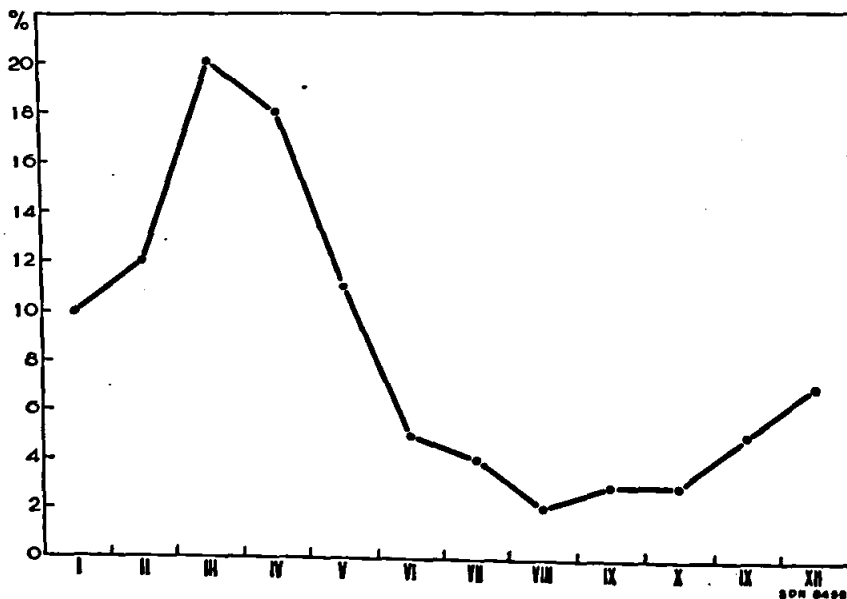


Table 3.

DISTRIBUTION OF BRUCELLA STRAINS (MELITENSIS AND ABORTUS)
ACCORDING TO HOST AND GEOGRAPHICAL DIVISION.

Geographical division	Human		Animal										Total		Undulant fever
			Cow		Goat		Sheep		Horse		Rabbit				
	M	A	M	A	M	A	M	A	M	A	M	A	M	A	
North	6	2	0	32	0	0	1	1	0	6	0	0	7	41	Rare, sporadic.
Centre	1	1	0	16	0	0	0	0	0	3	0	0	1	20	Rare, sporadic.
West	0	1	0	10	1	0	0	0	0	0	0	0	1	11	Rare, sporadic.
East	57	22	31	44	1	0	9	0	0	4	0	0	98	70	Frequent, epidemic foci.
South-east ..	119	1	32	15	18	0	3	0	0	0	2	0	174	16	Prevalent, endemic.
South-west .	294	3	1	6	94	0	32	0	0	0	0	0	421	9	Prevalent, endemic.
Total	477	30	64	123	114	0	45	1	0	13	2	0	702	167	

" M " = *Melitensis*.
" A " = *Abortus*.

Table 4.

ATTACK RATE OF UNDULANT FEVER ACCORDING TO AGE AND SEX.
(Taken from surveys of communes.)

Age-group	Sex	Population	Undulant fever	
			Number	Percentage
Under 15	M	554	13	2.3
	F	463	13	2.8
	Total	1,017	26	2.6
15-29	M	426	98	23.0
	F	411	22	5.4
	Total	837	120	14.3
30-49	M	462	117	25.3
	F	560	69	12.3
	Total	1,022	186	18.2
50 +	M	727	109	15.0
	F	711	55	7.7
	Total	1,438	164	11.4
All ages	M	2,169	337	15.5
	F	2,145	159	7.4
	Total	4,314	496	11.5

Table 5.

ATTACK RATE OF UNDULANT FEVER IN RELATION TO THE NUMBER OF SHEEP OR GOATS ON THE PREMISES.¹

Number of sheep or goats on premises	Number of persons involved	Cases of undulant fever	
		Number	Percentage
None	659	17	2.6
1-11	1,254	129	10.3
12 +	1,384	324	23.4
Total	3,297	470	14.3

¹ Persons under 15 years not included.

Table 6.

ATTACK RATE OF UNDULANT FEVER IN RELATION TO THE HISTORY OF ABORTION AMONG SHEEP OR GOATS ON THE PREMISES.¹

Abortions	Number of persons involved	Cases of undulant fever	
		Number	Percentage
Minus	1,758	150	8.5
Plus	880	303	34.4
Total	2,638	453	17.2

¹ Persons under 15 years not included.

Table 7.

ATTACK RATE OF UNDULANT FEVER IN RELATION TO THE NUMBER OF SHEEP OR GOATS ON THE PREMISES AND HISTORY OF ABORTION AMONG THEM.¹

Number of sheep or goats on premises	Abortions	Number of persons involved	Undulant fever	
			Number	Percentage
None	—	659	17	2.6
1-11	—	1,028	64	6.2
12 +	—	730	86	11.8
1-11	+	226	65	28.8
12 +	+	654	238	36.4
Total		3,297	470	14.3

¹ Persons under 15 years not included.

Table 8.

PROBABLE SOURCE AND MANNER OF INFECTION IN CASES OF UNDULANT FEVER INDIVIDUALLY INVESTIGATED (466 cases).

Manner of infection	Source								Total	Percentage
	Goats	Sheep	Cows	Goats and sheep	Goats or sheep and cows	Horses	Miscellaneous and doubtful	Contact with U.F.		
Consumption ¹ alone..	7	4	4	7	8	0	7	0	37	7.9
Consumption ¹ and contacts	22	10	50	69	73	0	15	0	239	51.3
Contacts alone	13	32	16	48	39	2	36	4	190	40.8
Total	42	46	70	124	120	2	58	4	466	100
Percentage	9.0	9.9	15.0	26.6	25.8	0.4	12.5	0.9	100.1	

¹ Consuming of raw milk or fresh cheese.

Table 9.

COMPARISON OF CERTAIN HABITS OF 470 PERSONS WHO CONTRACTED UNDULANT FEVER WITH THOSE OF 2,827 WHO ESCAPE). (Communal surveys).¹

Manner of exposure (goats and/or sheep)	Males		Females		Both sexes	
	U.F.+	U.F.—	U.F.+	U.F.—	U.F.+	U.F.—
Consuming milk	81	285	43	416	124	701
No consumption	243	1,006	103	1,120	346	2,126
Percentage consuming milk.	25.0	22.1	29.5	27.1	26.4	24.8
Consuming fresh cheese ...	128	550	60	657	188	1,207
No consumption	196	741	86	879	282	1,620
Percentage consuming fresh cheese	39.5	42.6	41.1	42.8	40.0	42.7
Habitual contact	294	836	132	905	426	1,741 ²
No habitual contact	30	455	14	631	44	1,086
Percentage having habitual contact	90.7	64.8	90.4	58.9	90.6	61.6
Handling manure	303	883	39	230	342	1,113 ²
No handling	21	408	107	1,306	128	1,714
Percentage handling manure	93.5	68.4	26.7	15.0	72.8	39.4

¹ Persons under 15 years not included.

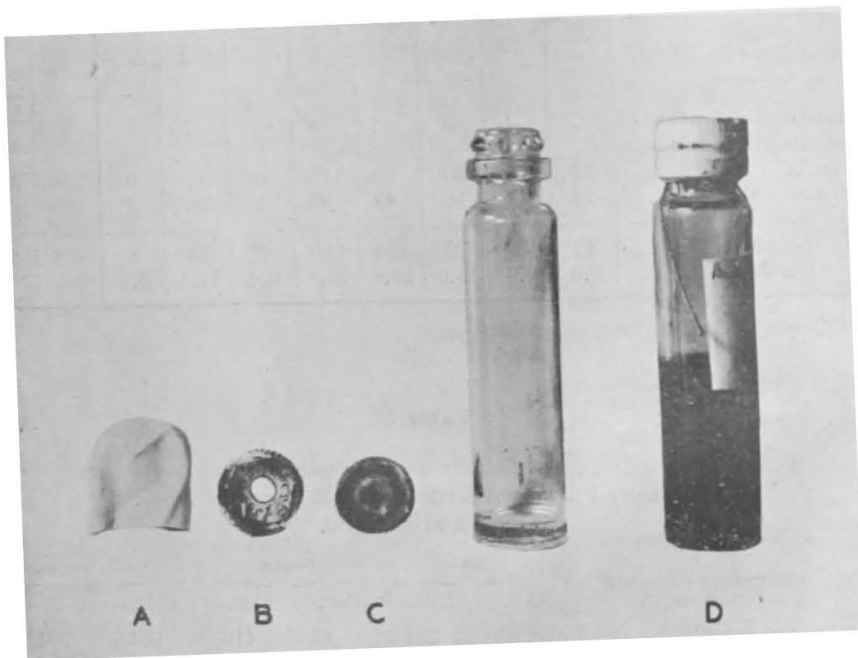
U.F. + indicates number of persons who had contracted undulant fever.

U.F. — indicates number of persons who had not contracted undulant fever.

² χ^2 (Chi square) of difference between U.F. + and U.F. — group greater than 150.

Figure 3.

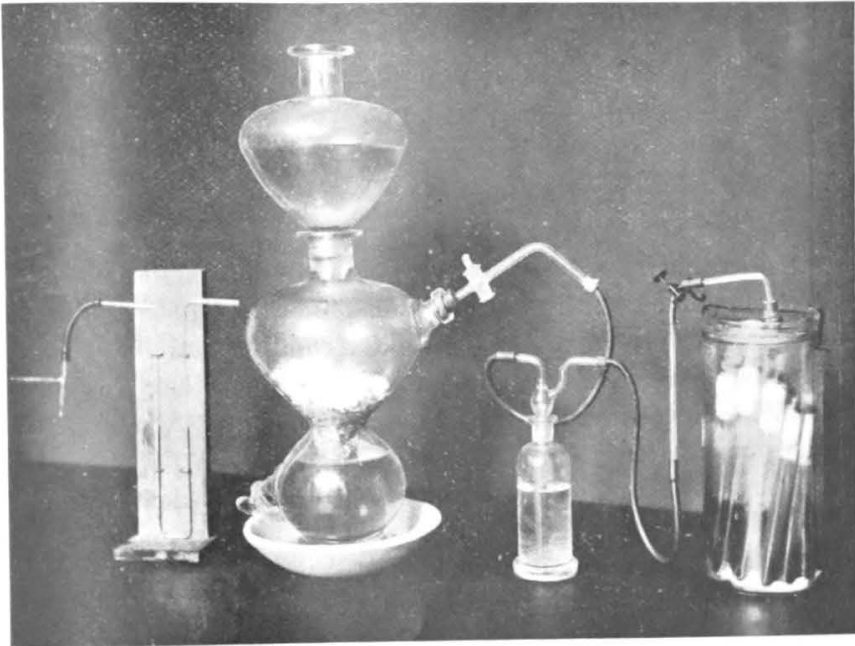
BOTTLE USED FOR BLOOD CULTURE.



- A. "Viscap" cover.
- B. Metal cap.
- C. Rubber washer which fits into metal cap.
- D. Assembled bottle after sterilisation containing media. The string is for the purpose of removing the "Viscap" cover.

Figure 4.

APPARATUS EMPLOYED FOR CULTURE IN CO₂.



THE SIGNIFICANCE OF CODEINE AS A HABIT-FORMING DRUG

by

P. WOLFF.

Attention has been increasingly directed during the last decade or so to alkaloids which are capable of producing habituation and addiction. The international Conventions and the activities of the League of Nations Health and Opium Sections and their Advisory Committees have played their part in bringing home to wider circles of the public the *social*, as distinct from the medical, significance of these narcotic drugs—a term which it may be convenient to adopt for the sake of brevity, even though it is not strictly applicable to all the substances in question.

Generally speaking, it is true to say that the various international Conventions concluded from 1912 onwards have laid a broad foundation for the restrictive measures that may be required to deal with the problem in its various phases, from the growing of poppy to the individual consumption of opiates. Though the difficult question of raw materials will call for further agreements, these Conventions have already made it possible to lay hands upon some part of the illicit traffic and production. Anyone at all conversant with what has been done up to date and with the difficulties which are continually arising will exercise caution and guard against hasty generalisations. This remark would seem to be all the more pertinent at this point in that the obstacles to effective repressive and regulative action are not, primarily, technical and professional, but arise out of administrative and economic considerations. The stabilisation of Government authority in many countries which are still suffering

severely from the scourge of narcotics is essential to clear up the position and ensure effective control.

War and conditions approximating to a state of war have always done the health of populations grave injury ; during the world war, for instance, even neutral countries were involved, in varying degrees, in the evils of addiction and in the illicit drug traffic. This is still fresh in our memories, as witness the penetrating study of H. W. MAIER, the well-known Zurich psychiatrist, on cocaine addiction.

From the point of view of science and medical practice, the question of the narcotic properties of the various opiates used for therapeutic purposes seems to have been settled. Recently, however, in view more particularly of certain communications from Canada, the question of how to classify *codeine* has been raised afresh.

That question had already been discussed at great length in the course of various international negotiations. At the Hague Conference in 1912, codeine was included in the first draft ; it was eventually deleted at the request of the German delegation ; nevertheless, the British delegate asked that it should be made clear that this did not imply that codeine addiction was unknown (83). Eventually, it was found impossible to reach unanimous agreement on this point.

In 1931, the subject was again exhaustively debated at Geneva. It will be remembered that, under the terms of the international Conventions and hence under the national laws of the individual countries, all substances capable of producing addiction are subject to strict control, which extends even to the stage at which the therapeutic dose is administered to the sick. Other compounds, which are not themselves habit-forming but which may serve as the initial material for the production of chemical substances of that nature, are subject to like measures of control, which, logically, do not extend into the field of medical activity. The latter group of substances includes more particularly *codeine*, which is far and away the most widely used opiate¹ after morphine. Now codeine can

¹ It is calculated that the quantity of codeine consumed in civilised countries for therapeutic purposes is about three times that of morphine. Further, the Supervisory Body set up under the 1931 Convention makes it a rule, when establishing estimates of codeine requirements, to take from two to three times the quantity of morphine required for consumption.

be employed, for example, as the initial material for the manufacture of dihydrocodeinone (dicodide), dihydrohydroxycodone (eucodal) and dihydromorphine (paramorphane)—three regular habit-forming drugs.

The four experts (W. E. DIXON, E. VON KNAFFL-LENZ, M. TIFFENEAU and the author of the present article), appointed by the Council of the League of Nations before the Conference for the Limitation of the Manufacture of Narcotic Drugs in 1931, gave it as their considered view that codeine itself is practically harmless from the point of view of producing drug addiction. This opinion was reached on the basis of published scientific papers and of observations relating to the use, during several decades, of doses of codeine ranging up to very large quantities. On these same grounds, the medical prescription of codeine instead of morphine, etc., is recommended and explicitly encouraged by public authorities and scientific bodies. When formulating their opinion, the experts only had in mind, of course, administration *per os*.

In the meantime, however, observations in Canada, to which further reference will be made hereafter, have shown that *parenteral* administration is also within the bounds of possibility ; this admittedly creates quite a different situation, which calls for a further detailed and, if possible, comprehensive study of the whole problem of codeine.

In discussing the question whether, from the point of view of drug addiction, codeine should be regarded as more dangerous than had been thought and possibly as necessitating stricter control than in the past, the following points call for consideration :

- (1) Is there such a thing as a genuine codeine addiction ?
- (2) If it does exist, is it such as to constitute a menace to public health ?

The criteria applicable to the recognition of true addiction have been frequently defined and need not be discussed here again in detail. All that need be said is that the principal characteristics must be present—namely : the development of addiction, the absolute need for increasing the dose, fixation upon the drug and typical abstinence symptoms, etc. The substance must be capable of producing *primary addiction* : that presupposes, in our view, obser-

vations concerning a sufficient number of indubitable codeine addicts not previously addicted to morphine, heroin or other drugs for whom codeine was the first substance causing the drug habit.

Opium and all its known habit-forming derivatives fulfil these conditions, even when administered in accordance with therapeutic requirements. They are all true narcotics.

At the same time, though the criterion afforded would be less conclusive, it would be a matter of some importance if it were found that a substance—in the present instance, codeine—possessed only the property of producing *secondary addiction*. By this term we mean that the substance alone would enable morphine addicts to satisfy their craving or to eke out their store of morphine by means of codeine in lieu of morphine. Withdrawal symptoms, for instance—which would serve as a test—would not appear in such secondary cases, because the desire for morphine would be satisfied by codeine.

It they did occur, however, in a secondary case of this kind when the patient—for example, a former morphine addict who had changed over to codeine—was deprived of the drug, then theoretically it would still be an open question whether the symptoms were merely (or mainly) those of morphine deprivation, held in check up till then by the “substitute” codeine, or, on the other hand, produced by the lack of codeine itself. The qualification “theoretically” was made advisedly, since such a retarded elimination of morphine does not seem very probable, in the present state of our knowledge. It would be desirable to clear up this point by chemical analytical methods; it does not appear to have been settled yet, although morphine withdrawal cures have often been carried out by administering codeine.

If only a secondary effect, produced by codeine, occurs, the problem will be far more complex.

The stipulation that conclusions should be derivable from unmistakable primary cases appears still more imperative if account is taken of the chemical properties of codeine and morphine and the results of the comparative experiments performed on animals with these two drugs taken as prototypes. Considering the properties of codeine, should it really be classified with the other substances of the morphine series which are known to be genuine

habit-forming drugs ? We shall confine ourselves to the following observations on this point :

It is known that there are fundamental differences between morphine and codeine—the methylation of the phenol hydroxyl group effects a far-reaching modification of the latter. Codeine may, it is true, have a certain sedative effect on human beings, in therapeutic doses ; but even large doses produce no real narcosis ; furthermore, it is less capable of diminishing the sensation of pain, etc. In the few observed cases of idiosyncrasy, only restlessness, slight muscular contractions and mydriasis (45) are observed. The higher centres are not affected at all.¹

On normal animals, the effect of codeine is different from that of morphine even, and so is the mode of elimination. Morphine introduced subcutaneously is, for the most part, at least, eliminated with the fæces, whereas codeine is eliminated chiefly in the urine. TAUBER was the first to contribute clear experimental data on this point. A difference in the physical properties due to methylation is given as an explanation. Heroin, like codeine, also passes, for the most part, through the kidneys (39) ; it therefore appears that the mode of elimination of morphine derivatives depends on the position of the OH groups. This analogy, however, extends only to elimination—the pharmacological behaviour of heroin and codeine is entirely different.

It is known that, when addiction occurs, the organism has first to *adjust itself* to some extent to the chemical decomposition of the substance administered ; the latter is only eliminated during the initial doses—later, it is reduced to very little or nothing. Classical research work has shown that this is the case with morphine and heroin, for instance. *This affords, perhaps, a sign of addiction that may be detected by chemical means.*²

¹ MAYOR (44) at one time carried out a thorough comparative test.

² Recent research, carried out by PLANT and PIERCE, W. A. WOLFF, and associates, KEESER, and associates, etc., would, however, appear to show that the addicted organism does not possess an increased capacity to decompose morphine, etc. This is only mentioned in passing, without going into details. On the other hand, there is certain more recent work—for instance, that of HOTTA—which does not reject the idea of an increased decomposition of the morphine ; we leave aside the various theories concerning the formation of drug habits which have recently been put forward on the basis of other experimental observations.

On the other hand, in experiments with animals, one may say that codeine is eliminated *in toto* ; so that elimination gives no indication of the addiction.

In spite of all the research work which has been done, our knowledge is still extremely incomplete with regard to what may be called the *dynamism of addiction*, so far as both the living organism and the habit-forming substance are concerned. We do not yet know *what* acts on the organism when morphine, heroin and the like are administered. We do not know whether an organism which is already accustomed to drugs reacts in a different fashion from one which is not,¹ or whether it possesses other new possibilities of decomposing—*e.g.*, demethylating, or transforming codeine. Nor are we yet in a position to say what the substance really is which produces what we describe as the morphine effect, etc. It is quite within the bounds of possibility that the active principle of morphine is not the whole molecule but an intermediate product (77, 78, 79)—which might perhaps explain the relatively stronger effect of certain esters. If such an intermediate product exists, the habituated organism might perhaps also produce it from codeine—more successfully than the attempts made in laboratories to regenerate morphine from codeine, which did not succeed (66), because the alkyn groups are apparently much more strongly held than, for example, acetyl groups in heroin.

The indestructibility of codeine in the organism has, however, only been established in animals not previously used to opiates, nor has there been any research into the elimination of codeine in cases which are described in medical literature as codeine addicts. None of the work hitherto published contains any reference whatever to this matter ; which it seems essential to elucidate before the question of the part played by codeine as a narcotic drug can be cleared up as a whole. There is thus a considerable gap in the evidence needed for exact demonstration ; this should be constantly borne in mind in connection with the clinical data given below. Indeed, it is not impossible that the organism might “ learn ” to liberate, through an alteration of the codeine molecule, habit-forming elements, such as the hydroxyl, which are precluded from exercising their effects so long as they are held behind the methyl

¹ *Cf.* in this connection the observations regarding cross tolerance.

barrier. The organism which is, or has been, accustomed to genuine habit-forming opiates (this condition is essential) would thus have *acquired* the capacity to split off the methyl radical and to liberate from codeine either morphine or the (hypothetical) intermediate or decomposition product which acts as a habit-forming substance in the intermediate metabolism.¹ Such an explanation would also make clear why the *secondary* character of codeine addiction would be less helpful in settling the fundamental issue involved than evidence of *primary* addiction. The above are, however, pure hypotheses ; but it may perhaps be permissible to mention them. They bear upon the ultimate aims of pharmacological research—namely, such questions as why any substance acts in a particular way and not otherwise. In such young sciences as physiological chemistry and pharmacology, ultimate problems are, understandably enough, still unsolved.

Some light may, in time, be thrown on the problem of the dynamism of drugs by the large-scale American research work which has been going on for some years in order to produce new compounds of phenanthrene and decomposition—derivatives of morphine—and study them through pharmacological and clinical investigations (85).

But until our ideas on this subject are based on more substantial evidence, the indestructibility of codeine in the organism may be accepted as the reason why no real addiction is induced in animal experiments (BOUMA). Some years ago (1923), GUNN, in a critical survey, reached the conclusion that, in an animal, codeine habituation and tolerance could be produced but rarely, and with great difficulty. Experiments undertaken since that date have, as a matter of fact, strengthened this negative view.

These general remarks may serve as an introduction to the detailed information given below regarding experimental attempts to produce codeine habituation in animals. These observations provide a crowded and variegated picture, still full of contradictions and overlappings ; but they do not—for the time being at all events—warrant any such reliable conclusions as pharmacological research may legitimately be expected to afford in the end. For, after all,

¹ If this view is correct, codeine should, on principle, not be given to morphine addicts undergoing a cure.

such research should provide some sort of solid foundation for clinical work which frequently requires an experimental basis when it is concerned with addicts' own statements or with findings derived from them.

Experiments on Animals.

In judging of the action of opiates on man, the limitations attaching to *conclusions based on experiments with animals* must be clearly understood ; otherwise, misunderstandings will constantly occur. When assessing the value of pharmacological tests, care should be taken not to go to either extreme. Animal experiments are essential, however, before it is possible to proceed to " pharmacology applied to living human beings ". Only a human being can provide a complete picture of the effect of opiates. In animals, the euphoric and, indeed, the whole of the mental aspects of the effect of the drug can either not be established at all, or can be determined only in part.¹

It should not be forgotten that, in the past, animal experiments led to the assertion that certain substances of the morphine group are not habit-forming, whereas later clinical experiments or more extensive administration has shown these same substances to possess typical properties of genuine narcotics. On the other hand, experienced research workers know that some effects on particular organic functions may be demonstrated in certain specially suitable animal species. Pharmacological literature abounds in examples of this. EDDY, for instance, recently described the practical possibilities of such tests (19). It is the comparative examination of different animal species that enables progress to be made in this field. Rats and dogs can doubtless be used for investigations into habit-formation and addiction, but the best animal for the purpose is the monkey.

On the other hand, as has already been pointed out, undue importance should not be attached to animal experiments. The

¹ In some instances, allowance should perhaps also be made for exaggerated or false interpretation by the person conducting the experiment. The part played by the unconscious in all subjective findings whenever it is sought or desired to the will or desire to make some special observation—in this particular case, the mental effect on the animal—should not be forgotten.

results of experiments on one kind of animal must not be regarded as certainly valid for other animal species, still less transposable from terms of animals into terms of human beings. If reliance had been placed solely on the old experiments (*cf.* W. v. SCHROEDER), the indisputable therapeutic value of codeine might perhaps never have been discovered. In experiments with dogs, for instance, the narcotic effects of codeine often appear to be slight and are disguised by agitation, contractions and tetanic symptoms, which predominate, and give an apparently characteristic picture. The quantitative factor also frequently plays a decisive part in the reactions observed in many test animals.

Heroin furnishes a similar example when administered to rabbits. It produces tetanus-like symptoms (similar to those produced by codeine) ; and it acts in the same way, though perhaps not to the same degree, in dogs (39). In any case, the quantitative factor frequently plays a decisive part in the reactions observed in many test animals. It should also be emphasised that animals of the same species have individuality. Their resistance to poisons may differ, and their sensitiveness to morphine, etc., may vary considerably (32). Great caution is therefore necessary in drawing conclusions from limited numbers of animals. The deterioration in the general condition, the cachexia which often occurs in animals after prolonged administration of drugs of the morphine series must also be taken into consideration. In most cases, the cachexia is more severe than the usual somatic effects in addicts.

With these considerations by way of preface, a brief summary is given below of some of the observations carried out on various species of animals :¹

The weight curve of white rats is not disturbed by the administration of codeine over a long period, but is very considerably modified by morphine and sometimes also by heroin. For various reasons, however, SOLLMANN'S experiments do not appear to be conclusive—there is no evidence to prove that the weight curve is a reliable test of habituation ; no deprivation symptoms appeared in any of the animals to whose food these various drugs of the opium group, including morphine and heroin, were added. On the other hand,

¹ We would draw the reader's attention to the experiments made on tissue cultures (pigmented epithelium cells of the iris, SANJÔ ; and fibroblasts, SEMURA), which lie outside the scope of the present study.

HIMMELSBACH (30) demonstrated marked codeine addiction in the rat by the appearance of an increase in tolerance and deprivation symptoms (irritability before injections being interpreted in that sense).

FURU was able to produce codeine habit in rabbits, though with greater difficulty than in monkeys and dogs, the reason adduced being a different distribution of co-efficient as between the brain and the blood.¹

BOUMA detected no codeine habituation in dogs and hence no corresponding power to decompose codeine ; instead of chronic narcotic poisoning, there was rather an increase in sensitiveness—according to TATUM, SEEVERS and COLLINS, codeine produces a “ false tolerance ” (which is not permanent), whereas BONSMANN found no evidence of habituation. In a recent communication, however, OKAMOTO and FURU announced that they had succeeded in inducing codeine habituation in dogs, this being accompanied by a reduction in the efficient of distribution between brain and blood ; no details of these experiments are given.

Generally speaking, the reaction of monkeys to opiates shows considerable similarity to that of human beings ; this is proved by the various observations published by KOLB and DUMEZ ; TATUM, SEEVERS and COLLINS ; YOKOTA ; AKAMATSU ; OKAMOTO, among others, and, more recently SEEVERS (61), on the effect of addiction and deprivation upon weight, general condition, etc. In the special case of codeine, conditions for experiments on monkeys are, as a matter of fact, favourable, since, like the lower animals, they develop, after the administration of codeine, transient symptoms of irritation which are absent in man ; contractions are commonly observed, whereas morphine and heroin have a soothing effect (34). There is thus no complete analogy between monkeys and human beings in their reactions to codeine. The occurrence of contractions precludes the administration of doses comparable in point of clinical efficacy to those employed for human beings (five to eight times the morphine dose would be the right amount) (62). Codeine habituation can, however, be induced in monkeys ; this is borne out, for

¹ The question of distribution co-efficients has been more exhaustively studied by HARA, among others. He found, too, that the sensitiveness of the various animal species, assessed in terms of the quantity of codeine per kilogramme body-weight, is not constant, the affinity of codeine for the tissue of the central nervous system varying also. These experiments do not, however, relate specifically to addiction.

instance, by KOLB and DUMEZ, and by SEEVERS (60), NISHIDA, OKAMOTO, and FURU. Deprivation symptoms were only observed in certain cases and were very much slighter than those produced by morphine and heroin ; generally speaking, the results obtained are unsatisfactory, owing to the convulsive action (62). According to the extensive observations of KOLB and DUMEZ, codeine (administered subcutaneously) produced more marked habituation effects in some cases than morphine or heroin—the animals appeared to age rapidly, there was a marked deterioration of the general condition, even after the administration of far more smaller doses than in the case of the other two narcotics ; necrosis of the ear-tips appeared earlier and was more pronounced. On the other hand, menstruation continued with codeine, whereas during the morphine and heroin experiments on monkeys, it was immediately inhibited (61).

After a time, some of the monkeys were able to tolerate doses which should, in themselves, have been fatal—110 milligrammes produced less serious symptoms at that stage than 10 milligrammes at the beginning of the experiment (34). But this increased tolerance for toxic doses is still not conclusive evidence of that state of dependence upon the drug for the maintenance of well-being and vitality which is commonly observed in addiction. On the contrary, notwithstanding increased tolerance, the monkeys appeared to be poisoned and their powers of resistance declined rapidly, more rapidly, at all events, than in experiments with other narcotics of the opium group. Tolerance and addiction are not always concomitant or virtually identical or necessarily successive conditions. The contradictory findings recorded and the varying reactions of individual monkeys would appear to justify the conclusion that the general symptoms of habituation following on the administration of codeine are very slight, compared, at all events, with morphine and heroin (34). It is, however, impossible, as has been said, to arrive at any definite conclusion.

For the purposes of our clinical enquiry, special importance attaches to observations relating to *cross tolerance* :

It is an established fact of experience that alcoholics, for instance, offer increased resistance to the narcotic effects of ether. This reduction of sensitiveness is termed *cross tolerance*—*i.e.*, the

transfer of tolerance from one substance to the action of another substance in the same individual. The cause of these phenomena is unknown. In the example just referred to, however, the increased combustion of alcohol in the addict offers no explanation ; for ether is not oxidised in the organism, but is eliminated without having undergone any change. How far the pharmacological and chemical similarity between the two substances is a contributory factor is not yet clear. Cross tolerance can also be assumed to exist, for example, between chloroform and chloral.

This phenomenon does not appear to be a general one ; for example, rats inured to alcohol behave towards morphine in exactly the same way as non-alcoholised rats (73) ; in this case, therefore, cross tolerance does not occur.

So far as codeine is concerned, observations on animals have yielded the following information ;

The brain substance of morphine-habituated rabbits will decompose heroin to some extent, but not codeine (one experiment each). Similarly, a morphine-habituated pigeon reacted with normal sensitiveness to a lethal dose of codeine, which was therefore not decomposed in the tissue like morphine (6).

On the other hand, codeine behaves substantially like morphine in the morphine-habituated rat ; the rat is at once " inured " and " sensitised " to codeine, " inured " in the sense that—as with prolonged administration of morphine—narcosis no longer occurs, and " sensitised " in the sense that certain symptoms of excitement appear, as after prolonged administration of morphine, though more transient and less marked (32). In rats habituated to morphine, therefore, codeine may be said to be interchangeable with morphine.

Both codeine and morphine lower the activity of the respiratory centre and in the dog, for example, cause a disturbance of equilibrium. The effects on the respiratory centre (panting for a certain time), on the equilibrium (swaying) and on peristalsis (increased defæcation), which codeine produces in the non-habituated dog, do not occur in a morphine-addicted animal when the same minimum effective doses of codeine are administered. If the quantity of codeine is slightly increased, these three symptoms become more accentuated in the normal dog, but in the morphine-habituated dog only a slight transient disturbance of equilibrium is noted. Con-

siderably larger doses of codeine produce in the normal dog a distinct stimulation, followed by marked depression, of the respiratory centre, increased disturbance of the equilibrium and extraordinary sensitiveness of the spinal cord. In contrast to this, a morphine-habituated dog, which has received equal doses of codeine, shows no signs of any action on the respiratory centre, and but a slight disturbance of equilibrium, while the whole effect of the codeine is of shorter duration. Extreme sensitiveness of the spinal cord is observed only after the administration of very large doses (46).

There exists, therefore, in morphine-habituated dogs a definite tolerance for codeine. The conclusions of DOWNS and EDDY also confirm the fact that in such animals tolerance of large doses of codeine is distinctly increased.

On the other hand, there is one known case of cross tolerance in a dog in which primary tolerance of codeine had been induced : with small doses of morphine, which would have produced narcosis in an animal not previously treated, only a slight impairment of function was noted, accompanied, however, by excitement or increased irritability (69). From this (single) experiment, the conclusion has been drawn that the "codeine dog" develops increased tolerance of the narcotic action of morphine (*i.e.*, less effect), but that this is accompanied by an increased sensitiveness to the stimulating effect of the morphine.¹

In dogs, there is also cross tolerance between morphine and heroin (18, 46) and, in the group of purine derivatives, between the diuretic action of caffeine and that of theobromine and theophylline (47).

In the monkey, however, no cross tolerance of codeine could be found (34); in one morphine-habituated animal, this drug, for example, was quite easily and successfully replaced by heroin; codeine, on the other hand, produced a very different state of affairs: the general condition became unsatisfactory and other deprivation symptoms appeared. (A month later, the animal's condition was once more satisfactory.) It was impossible to substitute codeine for morphine in this case.

¹ OKAMOTO also reports that morphine tolerance is increased in codeine-habituated animals and that a modification of the morphine distribution in the body is also found, as happens in the case of codeine—but the species of animal is not stated.

Conversely, codeine-habituated monkeys tolerated quantities of morphine (and also of heroin) which would ordinarily have been fatal without exhibiting any special symptoms.

As regards habit-producing effects, then, codeine cannot be ranked on a par with morphine or heroin. Our knowledge on the subject is still, however, very far from complete. Yet notwithstanding much conflict of evidence, these brief notes on animal experiments would appear to demonstrate with sufficient certainty that primary and secondary codeine habituation are not of equal significance.

Observations on Man.

From a clinical standpoint, the question of the *secondary effects* of a substance to be tested for habit-forming properties would appear to claim special consideration, since these effects are easier to analyse in human beings, for such substances can clearly not be tested for their primary effects on healthy individuals.

The primary clinical observations occasionally carried out with new opium derivatives whose habit-forming properties have not yet been established—*e.g.*, post-operative use for a short period in place of morphine—usually tell us little or nothing; for, luckily, even morphine, when administered for a very short time in such therapeutic doses, does not produce addiction—otherwise, the use of morphine would impose an almost unbearable moral burden on the doctor.

Now after brief observations such as these, otherwise excellent and reliable clinics publish first clinical findings to the effect that this or that new drug has not produced craving or euphoria (or but the slightest symptom of the latter), and the drug is then labelled harmless and put on the market; its use becomes widespread; and then the real trouble begins.

It is essential, therefore, when animal experiments have yielded results within their own limitation, that the first decisive clinical test should be carried out on addicts—under unexceptionable test conditions; this, at all events, is the best attainable method.

Codeine per os.

It may be mentioned, incidentally, that many well-known textbooks on pharmacology and therapeutics regard codeine as non-

habit-forming. Many research workers have expressed themselves in the same sense. A few pronouncements may be mentioned :

In 1921, the Committee on Narcotic Drugs of the American Medical Association adopted the attitude that codeine rarely, if ever, leads to the development of addiction. It was therefore in favour of the medical prescription of codeine in place of other drugs (4).

In 1922, WATSON put the question : " Is codeine a habit-forming drug ? " Taking 117,000 prescriptions in 57 North-American towns and 28 States in the year 1907/08, he found that codeine ranked seventh, and therefore occupied an important place ; nevertheless, on the strength of 700 replies (to 12,500 questionnaires) from the doctors of Maryland, including the State and private institutes for mental and nervous diseases, prisons, etc., he reaches the conclusion that : " No case of codeine habit had ever been seen in Maryland ". He elicited similar opinions from particularly experienced doctors, etc.

In the course of an investigation conducted by TERRY and Cox in six different districts of the United States in 1923/24, it was found that the vast majority of doctors consulted, some of whom prescribed codeine in large quantities, knew of no cases of codeine addiction. Even when 10 grains of codeine were administered daily for sixteen weeks, there were no after-effects. Only two exceptions were observed ; they are described below. Moreover, the general consumption of codeine had greatly increased on account of the growing reluctance of the doctors to prescribe other opiates.

The Narcotic Drug Conference which was officially convened at Washington in 1930 was also of opinion that the habit-forming qualities of codeine are doubtful or practically non-existent,¹ but that a morphine addict can possibly satisfy his craving with codeine (48).

TATUM and SEEVERS observe that codeine addiction is rare and only a few authentic cases are known.

An investigation by the author (76) also led to the result that " no real addiction from codeine is to be feared ".

ZURUKZOGLU does not mention a single case in Switzerland.

No observations appear to have been made in children (CHIARI).

¹ Only one adverse vote.

Reports have frequently been made regarding cases in which codeine has been used for a number of years without any signs of addiction (see 78). One of the older statements on this subject is that by LÖWENMEYER (1890), who points out that aged chronic asthmatics received codeine for a long period without contracting addiction ; one of the most recent reports is that by GABRIEL and KRATZMANN :

A Customs official suffering from a violent cough with severe bronchitis took 0.03 gramme of codeine two or three times a day for ten years without increasing the dose; but an increase took place immediately when, on medical advice, he took dicodide instead of codeine ; he increased the dose from 3 tablets a day—*i.e.*, 21 tablets per week to 40 and even 70 per week and, according to his statements, even considerably more.

*What published cases can be regarded as cases of codeine addiction ?*¹ A summary published in 1930 (77) states that, according to communications from all over the world, extremely few such cases have been recorded.

It is a striking fact that most statements are very vague and indefinite. Such statements can therefore scarcely be used for an analysis designed to clear up the facts.

L. LEWIN (40), it is true, speaks of codeine addiction, but without giving definite details. Later, he described a case (also without definite details) of a patient who took up to 3 grammes of codeine per day (41) ; no clinical data warranting any definite conclusions are given.

SOLLMANN speaks of " only three cases² in medical literature, and these were so mild that they could be treated by withdrawal for a few days without leading to clear withdrawal symptoms ; the patients took 2 grammes per day ".

LAMBERT found among 1,593 drug addicts 17 " who had the codeine habit " (36). There are no further details. Elsewhere, he states that, of 1,700 addicts, 10 were codeine addicts (37, 38) ; here, also, no details are given.

Statements are thus frequently made in general terms whose value cannot be assessed and which may therefore be ignored ;

¹ It is assumed that codeine is administered *per os*, even if this is not expressly stated. Injection was unusual until quite recently.

² It is impossible to state whether or not these are the same cases as those published in other papers.

for instance, there is a " statistical " statement by A. PILCZ regarding one or possibly two cases ; in the first place, it is by no means certain that the patients really took codeine and, in the second place, the author, according to his own reply to an enquiry, was unable to furnish the observations relating to these cases.¹ The same reservations apply to a statement by H. W. WILLIAMS to the effect that when an addict cannot procure either morphine or heroin, he can satisfy his craving with large doses of codeine and avoid the worst withdrawal suffering ; yet the same author had stated a few lines earlier that codeine addiction was practically unknown.

PELZ describes a case (doubtful, moreover) of a seriously affected man ; BASTEDO mentions two cases regarding which no details are known ; JOEL, in spite of his wide experience in this field, only mentions a single case incidentally and without giving clinical data. HEIMANN-HATRY gives an account of a woman who forged a prescription in order to obtain codeine. No details are known. Whether these observations include any primary cases cannot be ascertained, in view of the lack of sufficient data.

W. L. TREADWAY, in giving a careful analysis of 1,660 cases of drug addicts, only records a single case of codeine addiction.

A doctor in El Paso (Texas) asserted, according to TERRY and COX, that after codeine had been administered over a considerable period to tuberculosis patients, its withdrawal was followed by sleepless nights and other symptoms which he regarded as mild withdrawal symptoms. No details are, however, given. One case is described in greater detail in the same report :

A man of 37 years had been addicted to the use of codeine for about twelve years ; apart from a short period in which he supplemented the quantities of codeine by morphine, he never (according to his own statements) took other opiates, not even before he began to take codeine. His average daily dose amounted to about 11 grains. The withdrawal is said to have been in no way different from that of morphine addiction ; the tendency to relapse was also the same.

A case which is scarcely known and has, at any rate, never been quoted, is mentioned by FOLEY :

A woman of 35, who, for twenty years, had suffered from attacks of asthma, coinciding with menstruation, took in 1930, on account of an alleged ner-

¹ Personal communication.

vous breakdown, a daily dose of 2 tablets containing 0.25 grain hyoscine, morphine and cactoid—that is to say, very small quantities of morphine; during menstruation, she increased the dose to 6 tablets. Later, the attacks of asthma became more frequent; they could only be relieved by these tablets; sometimes the woman simulated an attack, in order to obtain the drug. Occasionally, slight withdrawal symptoms were observable; the patient lost 20 lb. in weight in five months. There were curious abscesses on the thighs; according to FOLEY's report (statements by the patient), the drug was taken exclusively *per os*.

The patient was then transferred to codeine, which was entirely suppressed after one month. After two months, there was a relapse; the patient began with 2 grains daily *per os*; after two and a half months, the dose was doubled; then slow withdrawal within one week; apart from abdominal symptoms, there were few withdrawal troubles. Relapse after a week, when more abscesses (1) appeared; again withdrawal during one week. Presumably, no serious supervision was exercised, in order to ascertain whether the patient was really free from codeine. In any case, according to her husband's statement, about six months later she took 200 to 300 0.5-grain tablets (that is to say, about 9.75 grammes) per week or about 1.4 grammes per day! The patient was greatly emaciated and had lost a further 15 lb. in weight, appeared to be melancholy and had already made two attempts at suicide. She was transferred to a psychiatric institution.

This case is of interest because, after *oral* doses, first of relatively small quantities of morphine and then of fairly considerable doses of codeine, serious symptoms were observable. It is assumed that the doctor was not deceived by the patient; the abscesses, the origin of which is unexplained, and in particular their repeated appearance, are a suspicious circumstance.

Perhaps the case described by MENNINGER-LERCHENTHAL (44(a)) is also a primary one; the person in question became "very lively" through use of codeine. Later on, he took to dicodide instead and developed the symptoms of real dicodide addiction.

The latest case, described by CHODZKO (a woman, who was a former morphine addict, took increasing doses of codeine up to 1.2 grammes daily *per os*; typical withdrawal symptoms, etc.), is a secondary case. It is the only case reported from Poland, in spite of the fact that the medical prescription of codeine is very widespread in that country.

¹ *Cactus grandiflora* preparation; these products are considered as mild heart remedies in the case of nervous troubles, but have been almost entirely abandoned.

Apart from the above-mentioned case at El Paso, the following further six cases may be regarded as *primary* cases (it being always tacitly assumed that the patients' statements—which cannot be proved—regarding their previous history are correct) :

SOLLIER, in the course of more than twenty years, only observed a single case of codeine addiction among more than 400 alkaloid addicts :

A doctor of 72 years of age took codeine *per os* for more than six years on account of alleged rheumatic pains ; he began with 0.25 to 0.4 gramme daily, and ultimately reached 2 grammes daily, taken in tea. He never used any other opiates, narcotics or analgesics ; according to the anamnesis, it was therefore a primary case. As soon as he tried to reduce the doses, the pains increased. (SOLLIER regards this as a withdrawal symptom.) Moreover, he suffered from sleeplessness and loss of appetite. The withdrawal lasted eight days ; the symptoms were similar to those of morphine addicts, but were less intensive. After six weeks, he was discharged in excellent health.

ROGUES DE FURSAC and MONESTIER observed a girl of 29 with circular insanity, depressive rather than maniacal in character, and suffering from asthma ; in 1916, she was treated for an attack of asthma beginning with a solution which contained about 0.03 gramme of codeine per tablespoon, and also, *inter alia*, potassium iodide. She soon felt a sensation of euphoria (1), which is described in detail. In view of this euphoric effect, she subsequently took the solution even without having an attack of asthma. The dose was not increased, at any rate not more than to 1½ tablespoons, which were taken at fairly long intervals. From 1921 onwards, she used the solution practically for all troubles and conditions. At the end of 1922, during an attack of bronchitis, she began to take it daily and regarded the solution as a "pick-me-up" ; the euphoric effect decreased and the doses were increased up to 1 to 1.25 grammes per day, always in the same solution. The iodine content was then diminished on account of an iodine acne, and was subsequently omitted altogether. The following observation is of importance : during the use of codeine, the previous extreme depression diminished, the patient became somewhat indifferent and often irascible. Then loss of appetite, emaciation, constipation, amenorrhœa, etc., occurred ; these are typical withdrawal symptoms which were completely removed by a few tablespoonfuls of the solution. Gradual withdrawal in ten days ; from 0.08 gramme withdrawal symptoms occurred but were less marked than in the case of morphine addicts.¹

H. SCHWARZ has described three cases of genuine primary codeine addiction observed at the Berlin University Psychiatric Clinic ; there was a

¹ These two cases have been described in somewhat greater detail because they are fairly important and are not easily accessible in medical literature.

touch of euphoria, an increase in tolerance, craving for codeine, etc. ; the daily dose of codeine amounted to as much as 3 grammes. There were genuine medium to severe withdrawal symptoms. The treatment was relatively simple. Withdrawal symptoms were observed for three to eight days ; it was, however, considered necessary to place the patients in a suitable establishment.

SLIGHT treated a woman whom he calls a " psychopath " who admitted taking about 30 grains daily *per os* ; a primary case it would seem, but based solely upon the patient's own statements. Some of the symptoms described may be regarded as withdrawal symptoms.

Thus, in fact, the number of known cases of primary codeine addiction is only seven. It is, however, remarkable that, in view of the widespread practice of prescribing codeine, the number should be so small. The cases of secondary codeine addiction which can be identified from the more or less definite data available are also extremely few in number.

Moreover, even according to the latest publications in American medical literature, codeine does not produce addiction as easily as morphine ; it is expressly stated that codeine addiction is rare and is generally easy to remove (86). In view of the statements quoted above regarding the *possibility* of creating addiction by the oral administration of codeine, this attitude appears to be of importance.

The lengths to which what might almost be called the state of confusion has gone is clear from a recent question and the reply to it in the *Journal of the American Medical Association* (86) :

A lady of 78 was given for one or two years a dose of 1 to 2 grains of codeine *per os* in the evening as a soporific, after luminal had become ineffective ; she had chronic hypertension and had had three strokes ; she had been under observation by the same doctor for fifteen years. Her will, which had been made six months before her death, was contested on the grounds that she had constantly taken a habit-forming drug—namely, codeine—and had been under its influence, that this drug was contra-indicated in a case of hypertension, etc. These charges were rejected and rightly so. The mere fact that the doses did not require to be increased over a period of one to two years proves that there was no addiction in the proper sense of the word. There is no evidence to show that the mental faculties are influenced by this form of codeine treatment.

One more point may be mentioned : At times doses of codeine which originally had a good effect subsequently cause nausea and even vomiting. This may indicate that a certain tolerance has

developed. If so, however, only certain centres should be affected and, for instance, not the vomiting centre (16). This should be viewed in the same light as the well-known *partial habituation* obtained in certain animals which are given heroin. Dogs thus easily become inured to the narcotic effect, but not to the exciting (convulsive) effect, etc. Moreover, certain experimental evidence tends to confirm this view in the case of codeine, though the author (BOUMA) has not paid any particular attention to this matter ; whilst the dose remains the same or increases but slightly, an initially well-marked narcotic effect gradually decreases, etc. If there had been no habituation to the narcotic components, BOUMA would undoubtedly have observed the conflict between narcosis and excitement as described by VON SCHROEDER in experiments with higher doses.

In view of the observations made up to date, the first of the two questions raised at the beginning of this report—namely, whether the administration of codeine *per os* results in genuine addiction—could not be answered in the negative ; there are, however, no sufficiently conclusive findings to justify an affirmative reply. The second question, however, as to whether, if such cases exist, they represent a danger to the public health can be already answered in the negative. In view of the vast and justified extension of codeine consumption in the world for several decades, these few primary and secondary cases together *cannot be regarded as a danger to public health*.

Parenteral Administration of Codeine.

In the past, there was never any serious question of the parenteral—*i.e.*, subcutaneous or even intravenous—administration of codeine, and so very little information is available on this point.

Some clinical experiments have been made with codeine and other substances of the opium group on healthy men (SEEVERS and PFEIFFER). The result was that, unlike morphine, dilaudide and heroin, codeine usually gave no narcotic effect when administered subcutaneously, and indeed even intravenously. Previously, MACHT had given himself subcutaneous or intramuscular injections of 20 to 25 milligrammes of codeine phosphate, but these did not lead to any result which would have any bearing on the subject under discussion.

Only one case of investigations on addicts taking codeine by injection is described by TERRY and COX, 1927 :

A woman of 44 had injected codeine subcutaneously for about seven years—in the first year, 1 grain a day ; in the fourth and fifth years, 2 grains, and in the seventh year, 4 grains. The withdrawal symptoms are said to have been the same as in the case of morphine, together with the tendency to relapse. No further details are known.

Recently, the position has completely changed : at the end of 1934, for the first time, statements were made at the session of the Advisory Committee on opium and other dangerous drugs to the effect that addicts were carrying out subcutaneous or intravenous injections of codeine, with the result sought.

The Canadian member of the Committee, Colonel C. H. L. SHARMAN, drew attention to the enormous increase in the consumption of codeine in his country, as shown by the following official Canadian figures :

Imports of Codeine into Canada.

Year	Free alkaloid and salts together	Free alkaloid alone
	Kg.	Kg.
1926	311 (89)	
1927	265	
1928	388	
1929	724	
1930	682	
1931	628	
1932	671	483 (92)
1933	1,040	749
1934		821
1935		1,011 (97)
1936		665 (97)

A comparison of the *estimated consumption* of codeine in Anglo-Saxon countries¹ in 1935 gives the following result (84) :

	Consumption per million inhabitants
	Kg.
Canada	109
United States of America	33
United Kingdom	11
Australia	4

¹ For purposes of comparison, the figures of other Anglo-Saxon countries are given, on account of the similarity of their therapeutic practice in general.

The following table gives the consumption in 1935 per million inhabitants in the countries with the highest figures :

Country	Population (in millions)	Estimates of	
		Consumption for medical purposes Kg.	Consumption per million inhabitants Kg.
Canada	10.590	1,153	109
France	41.860	4,500	107
Austria	6.740	500	74
Belgium	8.213	425	52
Czechoslovakia	14.925	700	47
Germany	65.050	3,000	46
Hungary	8.784	363	41
Netherlands	8.183	320	39
Sweden	6.190	217	35
United States of America..	125.200	3,689	29

On the other hand, the imports of morphine into Canada have decreased considerably during the same period ; in thirteen years, they fell to a-sixth (91). This is due to the fact that the Canadian Government very rightly encouraged the medical practitioners to prescribe codeine, as far as possible, instead of morphine.¹ Under the international Conventions, moreover, the control over morphine was considerably tightened ; it therefore became more and more difficult for addicts to obtain their drugs legally (and presumably illegally as well). These figures, showing the great rise in imports of codeine and the drop in imports of morphine, are of great interest, not only from the fiscal, but also from the medical and social, point of view. They show, in particular, that " something is wrong ". The explanation was soon found. Since about the end of 1933, a considerable number of addicts have been turning to codeine because they could not obtain other opiates. And now comes the fact which is essentially a new development. These Canadian addicts *inject* codeine subcutaneously or even intravenously,² sometimes in the

¹ This is entirely in accordance with the view which generally prevails. It will be seen, for instance, from the latest summary of the Opium Section (95), that the production of codeine in 1935 increased by 15% as compared with 1934, while exports increased by 46% (while, for instance, the figures for heroin—*i.e.*, the licit consumption—dropped considerably). The total consumption of codeine in the world is, moreover, estimated in the same document at 19,357 kilogrammes in 1935.

² A Government report from Hong-Kong (89) also shows the increased interest which is taken in codeine in " illicit " quarters. In the Far East, a hard struggle is being carried on against heroin pills, which are sold under the name

most primitive manner ; they pierce the skin with a thick safety-pin at a place which is free from large blood-vessels, and then introduce the codeine solution with a glass dropper. (This method is also known, for instance, to Egyptian heroin addicts ; in that country, it contributes to the spread of malaria !) In the underworld, these intravenous injections are said to be very popular.

Some of the cases which have become known may be mentioned. One addict is said to have taken 0.9 gramme of codeine daily by intravenous injections ; in other cases, figures of, for instance, 60 to 70 grains are mentioned ; indeed, one former morphine and heroin addict took as much as 80 grammes by intravenous injection (65, 91).

All the experience gained so far shows clearly that the addicts only take codeine as a substitute or " carry-over ", and that they would immediately return to morphine, etc., if they could obtain it. The administration of codeine is not so pleasant for the addicts ; larger volumes are required for injection than morphine and particularly than heroin (weak solubility, milder effect of codeine), and the price is higher (28).

The official Canadian reports state that, as far back as May 1935, thirty-four cases were treated in the hospitals of one province of Canada (91). That same year, SLIGHT published observations of two cases, which were both secondary.

The general symptoms would not appear to be essentially different from those usually observed. There are certain interesting accessory effects : they may produce hard globular swellings under the skin, which continue for a long time ; in " competent " quarters this phenomenon is known as " cement arm " and it is stated that " it turns into lumps of cement " (90).

The withdrawal symptoms are similar to those in the case of morphine addicts—*i.e.*, nausea, vomiting, restlessness, sleeplessness, perspiration, gastric troubles, convulsive pains, craving for codeine, etc.

" Red pills ", " Golden pills ", etc., and which, moreover, contain considerable quantities of caffeine (attention has already been drawn to the considerable imports of caffeine into China). One typical seized consignment was found to contain not heroin but codeine, mixed with caffeine. It is significant that the owner of this material preferred not to come forward, and no further details are available.

In another case, 7,500 pills were discovered, containing codeine instead of heroin ; they were undoubtedly intended to be *smoked*, like heroin pills (91).

Let us try and go a little more closely into this question. HIMMELSBACH made the following systematic investigation (28). Seven carefully observed and controlled morphine addicts were transferred to codeine ; at first, they were given four subcutaneous injections per day with quantities of morphine which just satisfied their craving ; on successive days, these injections were replaced one by one with codeine, also administered subcutaneously, so that only codeine was given after the fourth day. During the transition period, all seven persons showed mild withdrawal symptoms—which were somewhat stronger in three cases—until the doses were correspondingly adjusted ; these symptoms then disappeared. It was possible to maintain the addiction completely in all cases by suitable quantities of codeine. After sudden withdrawal, mild deprivation symptoms occurred in the first thirty hours and were then followed by serious symptoms for four or five days. The result was the same as in the case of morphine, except that the severe symptoms were delayed. The doses of codeine were 3.8 to 8 times as large as the morphine doses, the average being 5 times.¹

These investigations led to two conclusions. The symptoms after the complete withdrawal of *parenterally* administered codeine do not differ greatly from the usual withdrawal symptoms ; *injected codeine can undoubtedly maintain an addiction and, in this manner, a morphine addict can satisfy his craving with codeine.*

The euphoric qualities of codeine are less strongly marked than those of morphine. In the observations carried out by HIMMELSBACH, however, particularly sensitive persons experienced a euphoric effect even after one injection of codeine (29). SEEVERS and PFEIFFER failed, however, to observe such an effect in non-addicts.

In May 1935, Stuart J. FULLER reported to the Advisory Committee on opium and other dangerous drugs on eighteen further important cases collected by W. L. TREADWAY. (These codeine addicts included two doctors and a former nurse.) Two of these cases were undergoing a non-institutional course of morphine withdrawal treatment by the subcutaneous injection of codeine

¹ It is, moreover, a remarkable fact that, in these observations and in the clinical experiments, there is never any mention of the occurrence of hypersensitiveness of the skin (pruritus, erythema, exanthem) such as has been described in a few rare cases after the administration of codeine *per os* (SCHEER and KEIL ; HADEN).

and had become habituated to the latter. Others injected codeine subcutaneously, because they could no longer obtain morphine.

Now, are these eighteen cases primary or secondary addictions? According to the classification made by Dr. TREADWAY himself, eight may be regarded as primary cases (of which three relapsed after withdrawal); for nothing is known of any previous addiction. Some must be regarded as iatrogenous; according to the particulars available, codeine was injected subcutaneously, for instance, on account of spinal disease or post-operative pains; the persons in question then continued to take the injections.

In the *secondary* cases, the existence of cross tolerance may perhaps be assumed.

To sum up, the following conclusions may be reached. The *parenteral* administration of codeine has brought about a new state of affairs. Until further observations have been made, the following attitude would seem to be indicated.

It seems possible for a genuine primary codeine addiction to occur, even in persons who were not previously addicted to drugs.

In order to create this addiction, *very large doses*, administered parenterally, are necessary.

Genuine tolerance and withdrawal symptoms occur, though possibly of a milder kind than in the case of morphine.

What, then, is to be thought of recent communications from undeniably reliable sources? It has already been pointed out that the method of administration, unlike those used for decades, was parenteral, with all the differences that implies in the matter of resorption, intermediate action, etc. Now experience has shown that it is impossible to compare the effects of codeine administered *per os* and by injection (which is not true of morphine).

The new vogue of codeine *injections* undoubtedly represents a social danger which it is essential to overcome. We use the word "vogue" advisedly, since former codeine addicts, after being cured, have themselves related their experiences and impressions in the Canadian daily Press and demanded strong action on the part of the authorities.

As things are at present, it may be said that there is not—or, at all events, that there is not yet—any *general* social danger. This new evil can assuredly be put down effectively by means of national legislation, without any need to set in motion the elaborate machin-

ery of international regulation. In any case, there is room for doubt whether a sufficient degree of international agreement could be reached to permit of the conclusion of a convention. In the United States, for example, under existing legislation, which goes further than the international Conventions, codeine is much more strictly controlled than in most other countries (91). It is true that the country is already suffering from codeine smuggling, which developed in a very short time across the Canadian border and has grown alarmingly. Co-operation between the two countries is, however, so close that preventive measures can no doubt be readily devised, and, indeed, a beginning has already been made in this direction.

In Canada, various measures are already in force and are proving successful. Certain provinces have introduced stricter control ; a voluntary agreement between the authorities and the wholesale dealers enables a check to be kept on the purchases of retailers and appears to yield excellent results (88). According to the latest returns, sales of codeine in the first six months of 1936 had already fallen to just under half the sales in the corresponding period of 1935 (96), while codeine imports into Canada fell by approximately a third from 1935 to 1936 (compare the figures above, pages 567-568).

In the meantime, the import-certificate system has been extended to all outgoing consignments of codeine (and dionine) tablets from the United Kingdom to Canada. Since codeine has been less easily obtainable, however, a certain "demand" has developed among Canadian addicts for capsules which, in addition to acetyl-salicylic acid, phenacetine and caffeine, also contain 0.5 grain of codeine. Addicts buy these capsules in large quantities and extract the codeine by dissolving them in water (93). Experiments conducted on behalf of the Canadian Government have shown, however, that only 52% of the codeine can be recovered in this way (94), and it is obvious that the addicts will not have at their disposal such well-equipped laboratories as the Government. The yield of this elaborate method of obtaining small quantities of codeine (which, in any case, has not the same dynamic action as heroin, for example) is so small, and its cost so great, that it cannot be regarded as a social danger.

It should therefore be enough if the States affected should, for instance, strictly prohibit the sale of codeine, either pure or in tablets, and permit only certain clearly defined preparations from which the extraction of codeine would be either quite impossible or too

difficult to be worth attempting. This would be all the easier as the prescription of small quantities of codeine in tablets containing no other active substance is not common medical practice in Anglo-Saxon countries. On the other hand, doctors in the Central European States, for example, who are familiar with the excellent and harmless effects of small codeine tablets containing no other active substance, should not be compelled or influenced to abandon the use of an excellent remedy. No such restrictions should be placed on the prescription of codeine as on that of morphine and habit-forming substances.¹

On the other hand, it is essential that there should be strict control of the manufacture, import and export of codeine and also of all wholesale trade in the drug², if only because it can be used for the preparation of acedicone and dicodide. This would also react favourably upon the new situation described above. It is, further, necessary to provide that codeine and its salts should be supplied to individual purchasers, only on production of a medical prescription, and, *further, that the regulations should be so strictly enforced that, without a written prescription, the drug should really be unobtainable.*

It is in this way that action could be taken to cope with the new situation, which has arisen out of the misuse of codeine injections. As has been repeatedly pointed out, the problem is one of isolated cases and of heavy doses, the addiction is so far confined to relatively limited areas, and it has proved possible to deal with it effectively.

At the same time, there would appear to be no justification for any attempt to establish an analogy between codeine and certain more recent derivatives of the same family and of chemical substances in regard to which even international action was taken

¹ To avoid misunderstanding, it should, however, be pointed out that many really habit-forming drugs which may, chemically speaking, be regarded as codeine derivatives—*e.g.*, acedicone, dicodide and eucodal—are properly subject to very strict regulations, both internationally and by the laws of the various countries, even in the matter of medical prescription. These substances, however, have no bearing on the question of codeine addiction, which is the subject of this paper.

² This is, indeed, provided for in Article 13, paragraph 2(a), of the Geneva Convention of 1931, as provided in Articles 6 and 7 of the Geneva Convention of February 19th, 1935. There is also a very thorough system of control over the international trade in codeine; this does not, however, fall within the scope of the present study.

immediately their habit-forming properties had been demonstrated by a few cases of addiction. For a conclusive argument against such action is to be found in the millions of cases in which codeine is prescribed as a matter of current practice. Numbers tell; and, as E. W. ADAMS has well remarked: "We must not, however, lose our sense of proportion".

Further light should be thrown on the subject by the results of the investigations which the Health Section of the League of Nations has set on foot in various countries on the subject "Can codeine cause addiction?" On April 13th, 1937, for example, the French Academy of Medicine, in Paris, set up a commission of seven members (87), over a hundred years after the appointment of the commission appointed on February 24th, 1834, to make a thorough study of the physiological and therapeutic effects of codeine.

Every prescription of a therapeutic agent is, in the last analysis, always a fresh experiment. It has long been known that the individual reaction differs and that the mental factor often plays an important part, even in the case of substances producing a simple effect, and all the more so in the case of opiates. But even the individual reaction may change in a manner which cannot be foreseen. Many examples have been furnished recently, the most striking being perhaps the unexpected and unpredictable occurrence of agranulocytosis in persons who have, in some cases for many years, taken amidopyrine, for instance, without trouble.

According to the above considerations, the question *whether the medical use of codeine is a social danger may be answered in the negative*. The medical practitioner should not be alarmed at the facts set forth above, and should not allow himself to be deterred from prescribing codeine freely in the usual small therapeutic doses.¹ He is still as justified as ever in regarding codeine as a good remedy without any dangerous accessory effects. If possible—and it certainly is possible—he must have at least *one* opiate which he can prescribe without the restrictions which are necessary in the case of others.

In the case of persons who have formerly been addicted to morphine or other drugs, or persons who are constitutionally predisposed to

¹ The Canadian authorities themselves express the same view (84).

addiction, the doctor should, no doubt, avoid codeine, as far as possible, or, if that is impossible, keep a careful watch upon the quantities. If at any time he has among his patients one of those extremely rare cases in which the prolonged prescription of codeine causes a tendency towards increased doses, he will always have time to change the treatment, considering the slowness with which the habit develops.

Lastly, it should be borne in mind that persons having a special mental predisposition thereto may develop a certain addiction with much more harmless remedies, such as analgesics. Quite recently, reports have been published on such cases in increasing numbers. It may be wondered whether all these are really cases of addiction, or whether the growing amount of discussion of genuine drug addiction has not led doctors to argue by analogy. Investigations on a broad clinical basis would be necessary before such habits could be definitely recognised as "habituation" and "addiction".

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INSOLATION AND NATURAL AND ARTIFICIAL LIGHTING IN RELATION TO HOUSING AND TOWN-PLANNING.

Reports by the Housing Commission on the Hygiene of Environmental Conditions in Dwellings and on Noise in relation to Housing were published in 1937 (see Bulletin of the Health Organisation, Vol. VI, page 505).

In accordance with the programme of work of the Commission, a meeting of experts¹ on Insolation and Lighting was held on June 27th-29th, 1938. The report of this meeting is reproduced below.

¹ The following attended the meeting :

Dr. W. MÖRIKOFER, *Chairman*, Director of the Physico-Meteorological Observatory, Davos ;

Mr. H. BUCKLEY, *Honorary Secretary* of the National Illumination Committee of Great Britain ; Member of the Photometry Department, National Physical Laboratory, Teddington ;

Professor A. GIGON, *Director* of the Polyclinic of the University of Basle ;

Dr. J. E. IVES, *Member* of the Committee on the Hygiene of Housing of the American Public Health Association, Washington, D.C. ;

M. H. VAN DER KAA, *Inspector-General* of Public Health, The Hague ;

Professor V. KRCH, of the Technical School, Prague ;

Dr. R. J. LYTHER, *Reader* in the Physiology of Sense Organs, University of London ;

Professor A. MISSENERD, of the " École nationale supérieure des Beaux-Arts ", and of the " École supérieure des Travaux publics ", Paris ;

Mr. C. J. MORREAU, *Member* of the Illumination Research Committee of the Department of Scientific and Industrial Research (London), *Member* of the Science Standing Committee of the Royal Institute of British Architects, Guildford ;

Dr. Brunon NOWAKOWSKI, *Professor* of Public Health at the University of Wilno ;

M. Thadée NOWAKOWSKI, *Architect*, *Director* of the Building Committee of the City of Warsaw ;

Dr. J. PARISOT, *President* of the Health Committee, *President* of the Housing Commission of the Health Organisation, *Professor* of Public Health and Social Medicine at the University of Nancy ;

M. G. W. PLEIJEL, *Architect*, Stockholm.

Dr. L. CAROZZI, of the International Labour Office, also attended the meeting.

Technical Secretariat :

Dr. O. OLSEN, *Member* of the Health Section of the League of Nations Secretariat, Geneva.

I. INTRODUCTION.

1. During recent years, public opinion in all countries has taken an increasing interest in questions of insolation and illumination, particularly in relation to housing and town-planning. The towns of to-day have been seriously criticised because they deprive their inhabitants of the sun, light and air which modern hygiene has shown to be of great importance for health and physical and mental fitness. It has therefore been realised that architectural and town-planning methods should make proper allowance for the requirements of hygiene in these particulars. In all countries, moreover, there has been a spontaneous awakening of the masses of the people to the desirability of sun and light, which architecture and town-planning should also take into account.

2. The problem of insolation and illumination in its bearing on housing and town-planning is highly complex. Its solution requires close co-operation between specialists of various kinds : it is for the physiologist, the hygienist, the clinical physician and the ophthalmologist to define human requirements in the matter of sun and light, while the responsibility for providing environmental conditions in keeping with the requirements thus laid down lies with the architect, the engineer and the town-planning expert. To determine the various radiation factors in man's environment, the co-operation of the physicist and the climatologist is also essential.

II. GENERAL OBSERVATIONS.

CLIMATOLOGY OF RADIATION FROM THE SUN AND THE SKY.

3. Natural radiation reaches the earth in two ways : the direct solar radiation (insolation) and the diffuse radiation of the sky (including clouds). The combination of the two is the total radiation. The two radiations include different spectral regions : the visible light, the ultra-violet and the infra-red radiation.

In the earth's atmosphere, the rays of the sun are modified by scattering and diffusion (by air molecules and suspended matter) and absorption (by water vapour, gas and suspended absorbent matter). These modifications differ according to the spectral character of the radiation.

It has thus been recognised that the diffuse radiation of the sky is of great importance. Though this form of radiation is less intense than that of direct solar radiation, it has the advantage of being active throughout the day in bad, as well as in fine, weather, so that its cumulative effect is no less great than that of direct solar radiation.

The diffusion of radiation in the atmosphere is much more marked where the short wave-lengths are concerned. This is why the amount of diffuse sky radiation reaches high values in the case of the ultra-violet component. It may be said that in Europe, for example, and also in the tropics, the diffuse ultra-violet radiation is much more intense than the direct solar ultra-violet radiation during the greater part of the year.

4. Thanks to the research carried out during the past few decades, our knowledge of the properties of these radiations has made great progress. A considerable amount of climatological data has been collected, but it is far from being complete as yet for many countries and for many purposes.

5. In the vast majority of cases, the measurement of radiation has been carried out in observatories situated on the outskirts of towns or in the mountains. The climatology of radiation within towns still awaits fuller investigation.

The loss of light and radiation through smoke is, for example, as high as from 10% to 30% in certain towns (New York, Pittsburgh, Paris, Vienna, Saarbruck, Königsberg). Furthermore, it has been shown that in Berlin solar radiation is decreased by about 20%, whereas the diffuse radiation of the sky, particularly the ultra-violet, is the same in town and country, whether the sky be clear or overcast.

It should, however, be borne in mind that these results, which ought to be confirmed in other places and under different conditions, were obtained in the open, or even on the top of buildings. Total and ultra-violet radiation are much reduced in streets and courts and inside buildings.

6. It is therefore essential that the available data regarding radiation should be amplified by research conducted on appropriate lines both for various countries as a whole and especially for towns, the climatology of which determines the living conditions of their population. Such research concerned with the various parts of the spectrum in different latitudes and in different seasons should deal, not only with direct solar radiation, but also with the diffuse radiation from the sky, and the reflected radiation from the surroundings in clear, cloudy and overcast weather.

EFFECTS OF THE RADIATION FROM THE SUN AND THE SKY.

7. The physical, chemical and biological effects of the radiation from the sun and sky vary considerably with its spectral character. In connection with housing, the following effects must be taken into consideration :

- (a) The thermal effects ;
- (b) The visual effects ;
- (c) The physiological and psychological effects ;
- (d) The effects on bacteria.

8. The thermal effects of the radiation from the sun and sky exert considerable influence on the heat exchanges of the human body. They also influence the heat conditions in buildings and dwellings (see the report on the Hygiene of Environmental Conditions in the Dwelling—Temperature, Purity, Humidity, Movement of the Air and Temperature of the Surroundings¹).

9. The important biological effects of the radiation of the sun and the sky are becoming increasingly recognised. The experience of both medicine and hygiene has demonstrated the curative and preventive properties of light in regard to a wide range of diseases, and particularly rickets and certain forms of tuberculosis. It has shown the effect of radiations of different spectral character on metabolism, the endocrine glands, the nervous system and the constitution in general.

The formation of D vitamins in the skin by ultra-violet radiation (natural and artificial) may be regarded as generally recognised.

¹ *Bull. Health Org.*, 1937, 6, 518.

As regards the visible and infra-red radiations, research has shown that they exert a specific biological action in addition to their visual and thermal effects.

Modern hygiene therefore tends increasingly to regard light as one of the essential factors in health and fitness, and its value is shown by its influence on the mental no less than on the physical state.

10. The bactericidal action of light is due chiefly to certain parts of the ultra-violet spectrum. The importance of this action as exerted by solar radiation in the home is open to question because the quantity of active radiation which may reach the inside of a dwelling is small. Other effects on bacteria, both favourable and unfavourable, are produced by other spectral components of the natural radiation.

III. INSOLATION IN ITS BEARINGS ON HOUSING AND TOWN-PLANNING.

SPECIFICATION OF PHYSIOLOGICAL REQUIREMENTS.

11. In the present state of scientific knowledge, it is impossible to define accurately the quantity and quality of solar radiation which is necessary for perfect health. Although we have fairly reliable information regarding the daily doses of ultra-violet radiation capable of preventing and curing rickets in children, we are still ignorant as to the requirements for other purposes.

In view of the beneficial effects of sunlight on health, the hygienist is, however, justified in asking that, as far as possible, a certain amount of insolation should be available in every room. Nevertheless, at the moment, it would appear that the admission or exclusion, according to climatic conditions, of solar radiation in our dwellings is primarily governed by subjective considerations based on the sensations of comfort and well-being.

12. From the point of view of comfort as of physical and mental well-being, it is obvious that in tropical countries the individual usually requires protection against an excess of thermal radiation

from the sun, while in cold climates he should be enabled to secure the greatest possible amount of radiation from both the sun and the sky. In temperate climates, it may be desirable to secure the maximum amount of insolation during the winter and to exclude part of the solar radiation during the summer (for instance, the afternoon summer sunshine in bedrooms).

METHODS OF MEASURING INSOLATION.

13. Architects and town-planning specialists have a variety of methods at their disposal for determining the insolation of façades, the interior of dwellings and streets, both existing and projected. By these methods, for example, the duration of possible insolation or the volume of solar radiation received by a wall surface or a dwelling with a given obstruction or fenestration can be determined for the various latitudes and solar elevations. They also make it possible to determine the orientation, fenestration and spacing (height of buildings, width of streets and courts) necessary to ensure the desired insolation of a building or dwelling as well as of the various individual rooms.

The methods in question employ :

- (a) Graphs ;
- (b) Instruments.

14. The methods based on the use of graphs have recently been developed by numerous studies carried out in Germany, the United Kingdom, the United States of America, the Netherlands, Poland and Sweden (see in this connection the methods worked out by ATKINSON, FÄNGE, FREESE, HOEPFNER, VAN DER KAA *et al.*, KÜTTNER, LANGEN, LOVÉN, MOLESWORTH, T. NOWAKOWSKI, NEUMANN, PLEIJEL, the Royal Institute of British Architects, SCHMITT, and WALDRAM).

15. The following instruments are used :

- (a) The sunshine gauge (WALDRAM) ;
- (b) The heliodon (DUFTON and BECKETT) and similar instruments (BENNDORF and PRAUSNITZ) ;
- (c) The pinhole camera (BECKETT and DUFTON, PLEIJEL).

The sunshine gauge enables periods of insolation to be determined *in situ* by interposing a transparent sun-path diagram between the eye of the observer and the image of a window seen by reflection in a horizon mirror.

The heliodon makes it possible to study and record the insolation of projected buildings by means of models representing, for example, the exterior walls of a house, a window or a street. By means of an electric lamp acting as an artificial sun, the height of the sun can be accurately reproduced for every day of the year and every hour of the day.

The pinhole camera enables the period of insolation to be determined in existing buildings by photographs of the visible sky superimposed with sun-path diagrams.

16. It is unnecessary to dwell here on the various instruments used by climatologists, engineers and biologists for measuring the thermal radiation of the sun and the sky, whether in general or for each spectral region (pyrheliometer, actinometer, pyranometer, spectral pyranometer). As regards photometers, it should be pointed out that the instruments using photo-chemical processes are, as a rule, not sufficiently accurate. Photo-electric photometers, especially those for the measurement of ultra-violet radiation, can only give relative results unless they have been standardised in order to obtain comparable results.

ORIENTATION OF BUILDINGS.

17. The orientation of buildings, in order to secure the proper amount of sunlight or shade, has given rise to controversy in many countries. In any attempt to decide the matter, allowance must be made for various factors—latitude and the paths of the sun in the different seasons of the year and also the slope of the ground, the character of the skyline, the arrangement of the rooms of the house and the uses to which they are destined. Local conditions, such as prevailing winds and rainfall, as well as probable daily duration and times of sunshine, must also be taken into consideration.

The problem is relatively simple for single houses, but it becomes more complicated in connection with semi-detached houses or rows

of houses and blocks with regular or irregular frontages, with or without verandahs, balconies or gardens.

The problem of the orientation of streets is very similar.

18. These problems are too complex for it to be possible to recommend any one solution. The above-mentioned methods of measuring insolation, however, give architects, town-planners and legislators the means of dealing with the many questions which must be solved if dwellings are to receive any desired amount of insolation.

FENESTRATION.

19. It should be borne in mind that ultra-violet radiation having a pronounced biological action is, to a large extent, excluded by the glass commonly used for windows.

20. Certain investigations in Central Europe showed that, in rooms under favourable conditions, the ultra-violet radiation received from sun and sky in half an hour, at a distance of one metre from an open window, was equivalent to that received in the open air in five minutes. These observations indicate that the amount of ultra-violet radiation entering our homes is relatively small, even when the windows are open.

21. On the other hand, it should also be pointed out that appreciable quantities of diffuse ultra-violet sky radiation may enter open windows with a northern aspect (northern hemisphere).

22. With the usual arrangement of windows in rooms, the use of special glass transparent to ultra-violet radiation enables ultra-violet radiation in therapeutically active quantities to be obtained only in immediate proximity to the windows or in the direct rays of the sun. In consequence, the use of special glass in rooms whose windows are small or seriously obstructed can scarcely be justified.

23. The results of the experiments hitherto carried out do not, however, permit of any exact reply to the important question which arises in this connection—namely, what are the biological effects of ultra-violet radiation when it is received in small quantities over a long period, as it would be, for example, in the average home when

the windows are open or when the window-panes are transparent to ultra-violet radiation ?

Further research will therefore be necessary to elucidate the matter.

24. It is important to note that the specific biological effects of visible and infra-red radiations (see paragraph 9) will be exerted through ordinary window-glass.

Here, again, further research is desirable.

25. Suitable fenestration to secure any desired insolation inside dwellings under various conditions may be determined by the methods enumerated in paragraphs 13, 14 and 15.

In calculating the dimensions of windows, the architect is also obliged to make allowance for several important factors, more particularly :

- (a) The cost of windows of every type ;
- (b) The low heat insulating power of glass and the consequent effect on the heat exchanges of the human body and on the heating and cooling of dwellings ;
- (c) The hothouse effect produced by window-panes through conversion of solar radiation into heat and its accumulation inside the dwelling.

26. Owing to the restrictions which architects must lay upon themselves in planning the dimensions of windows and also to the fact that windows are usually vertical, the usual methods of fenestration do not, as a rule, enable more than a comparatively small proportion of the radiation from sun and sky to reach the inside of our dwellings.

Interesting attempts have been made in connection with schools, solaria and hospitals to adjust the insolation admitted to the interior. Modern technicians and architects may therefore ultimately succeed in working out more satisfactory window arrangements for dwelling-houses than those at present in use.

27. Experiments have also been carried out with a view to excluding part of the thermal radiation of the sun by the use of glass which combines reduced transmission in the infra-red portion of the spectrum with high transmission in the visible portion. Here, too, further experiments are desirable with a view to ascertaining

whether such glasses may be recommended for use under certain conditions—for example, in the tropics.

BUILDING METHODS AND MATERIALS.

28. The amount of solar energy reaching the inside dwellings through the walls, window-panes and roofs depends upon the angle of incidence of the direct solar insolation and the properties of the materials, as regards reflection, absorption, heat capacity and heat transmission, and also the structural dimensions. Its calculation is therefore difficult.

In several countries, a number of different methods of approximate calculation have, however, been worked out and are of great assistance to heating and ventilating engineers. These methods should be improved and simplified.

29. The effect of solar radiation on heating, cooling and ventilating may indeed be considerable, and research on the subject has been carried out in a number of countries, especially France, Germany, the United Kingdom and the United States of America. Certain experiments carried out in the United Kingdom, for example, showed that during the winter—October to April—the heating required in premises facing north was 17% greater than that in premises facing south. The thermal effects of solar radiation should therefore also be considered from the economic standpoint, particularly in connection with low-cost housing.

30. Considerable research has already been carried out on building methods and materials in relation to solar radiation, with the object, first, of securing a better utilisation of the thermal radiation from the sun for heating purposes and, secondly, of protecting buildings and individual dwellings against such radiation in hot weather and in the tropics. It is desirable that such research should be carried further.

OPEN SPACES, SWIMMING-POOLS, PLAYING-FIELDS.

31. As only small quantities of solar radiation penetrate indoors, it is all the more necessary that, in all climates, the greatest possible

facilities should be afforded for open-air activities and pastimes. It is therefore essential that those responsible for town-planning should provide the necessary space in the shape of gardens, recreation grounds and playing-fields, swimming-pools, etc.

32. Such spaces should obviously be so arranged as to afford sunlight and shade as required and according to local conditions. But when, as in certain cases, the objects in view include the provision of the maximum amount of ultra-violet radiation, the town-planning specialist must have regard, not only to direct solar radiation, but also to the diffused radiation of the sky, particularly in countries in which sunshine is infrequent. The action of such radiation is in proportion to the visible expanse of sky ; hence the value of roof-terraces and roof-gardens.

33. It is important from the public health point of view that the peoples of all countries should be educated to the increased adoption of open-air habits and pursuits. Latterly, appreciation of the stimulating action of sunlight has grown rapidly. Certain medical experiments would appear to show that, even in tropical countries, sun-bathing might be a means of assisting acclimatisation.

A detailed dosage system has been drawn up for the heliotherapy of certain diseases. In view of the dangers of over-exposure, certain rules must likewise be followed in the matter of sun-bathing by normal, or apparently normal, individuals. It is therefore essential that suitable instructions should be issued to the public and that the supervisory or teaching staff (swimming-baths, gymnasium, etc.) should be adequately qualified.

IV. NATURAL AND ARTIFICIAL LIGHTING.

THE VISUAL EFFICIENCY AND ILLUMINATION.

34. Visual efficiency is influenced by a large variety of physical, physiological and psychological factors. Its definition and measurement are as difficult as those of physical and mental fitness in general.

35. Experiments carried out in recent years in many countries have helped to elucidate the relationship between visual efficiency

and illumination. In particular, the influence of the intensity and uniformity of light, glare, and contrasts and shadows have been investigated.

36. Since the end of last century, there has been much discussion regarding the intensity of illumination at which visual acuity is highest. Certain investigators have put this intensity as low as 10 lux¹ (for black on white); others have estimated it as being as high as 80,000 lux. These divergences are possibly due to differences in the methods of experimentation and in the interpretation of results. Since visual sensation increases much less rapidly than the illumination, it is desirable that experimental results should, in general, be represented on a logarithmic scale.

37. According to recent experiments, visual acuity (for black on white) improves up to at least 12,000 lux. Acuity, rapidity of vision, perception of colours, etc., probably go on increasing at a diminishing rate up to illuminations of the order of 100,000 lux. In laboratory experiments, an upper limit of the illumination corresponding to maximum visual acuity has not so far been reached. It may, however, be observed that particularly fine work (such as embroidery) is sometimes done in full sunlight (approximately 100,000 lux).

38. This progressive improvement in visual acuity, which is directly related to the illumination of the area of work, is also dependent to a large extent upon that of the surroundings. In this connection, the state of adaptation of the eye is of great importance.

Visual acuity increases progressively as the illumination of the surroundings is brought up to the same value of slightly (about a tenth) below that of the area of work itself. If the illumination of the surroundings exceeds this value, the acuity rapidly decreases.

39. Specialists in the various countries are generally of the opinion that a moderate degree of uniformity of illumination over working areas is desirable. Deep shadows within the working area result in decreased visual acuity.

¹ Values of illumination in lux may be converted to values in foot-candles by division by 10.76, or with sufficient accuracy by division by 10.

40. The effects of glare have also been carefully investigated. This question, too, is highly complex. In general, glare produces a lowering of visual efficiency and, in addition, sensations of discomfort. In certain cases, glare may neutralise all the advantages of increased illumination.

STANDARDS OF NATURAL AND ARTIFICIAL ILLUMINATION.

41. Apart from the physiological advantages already mentioned above, the best form of lighting is that which is afforded by daylight. The aim should therefore be to obtain this natural illumination inside dwellings, and it will, in general, be preferable to artificial lighting. The optimum daylight in a room will obviously be obtained when as large an area as possible of the room receives direct light from the sky. It should be the aim of architects to achieve this.

42. The minimum standards of natural illumination are very difficult to define.

In England, positions in rooms where the direct daylight factor is less than 0.2% are regarded as definitely insufficiently illuminated for ordinary purposes. The 0.2% iso-daylight factor-line approximates to the no sky-line in rooms which are faced with a regular obstruction of 30° or more.

In certain other countries, this minimum is regarded as too low. For instance, the Committee on the Hygiene of Housing of the American Public Health Association recommends a minimum natural illumination of 60 lux.

43. It is generally recognised that, in so far as natural illumination is concerned, those parts of dwellings which do not receive direct light from the sky are not, in general, adequately illuminated for the performance of ordinary visual tasks, such as reading.

44. As regards adequate artificial illumination, the practical solution of the problem is essentially economic and technical in character. With the improvement in economic conditions and the technical progress which have marked the last few decades, the public has grown more exacting, and illumination standards in the various countries have steadily risen.

45. There has been a great deal of research in various countries on the influence of illumination on the output of certain industrial and other workers. Furthermore, as a result of the work of the International Commission on Illumination, various national lighting commissions, associations of illuminating engineers, etc., lighting codes have been drawn up in a large number of countries. The standards recommended in the various codes and guides for use in factories, schools, etc., are based upon the results of practical experience and research.

46. Lighting in the home is designed, on the one hand, to achieve a purely psychological effect, that of producing a feeling of well-being and comfort and, on the other hand, to facilitate various activities—*e.g.*, domestic work, art work, reading and writing, children's homework, sewing, mending, etc.

The standards laid down in various codes and guides in the United Kingdom, Germany and the United States, for example, fall within the following limits :

	Lux
(a) <i>Minimum values :</i>	
1. Writing and reading	25-50
2. Sewing, drawing, embroidery	80-150
(b) <i>Values recommended :</i>	
1. Writing and reading	50-1,000
2. Sewing, drawing, embroidery	100-5,000

47. From this, it will be seen that the figures given, particularly in the recommended values, show wide variations. These are due—at least in part—to the tendency towards a continual increase in the intensity of artificial lighting, which had already been mentioned above. In certain countries, the recommended standards are not generally accepted.

Distinctions are made in certain cases between natural and artificial lighting, but the values laid down in the codes usually hold good for both natural and artificial lighting.

48. Certain recommendations of the Lighting Service Bureaux and the associations of illuminating engineers in certain countries deal with lighting in the home.

The following table gives as an example the values recommended as adequate by the Illuminating Engineering Society of Great Britain.

	Lux
Reading, casual	50-100
Reading, sustained	80-150
Sewing	150-250
Students' homework	80-150
Table-games	50-100
Work-benches	80-150
Bedrooms :	
Beds and mirrors (special lighting).	
General	30-50
Bathrooms :	
General	50-100
Mirrors (special lighting).	
Nurseries	50-100
Kitchens :	
Cookers, sinks and tables	50-100
Corridors and stairways	20-40

The above recommendations can be taken as representing reasonable average standards which may be taken for guidance. Although not attainable in some countries, owing to material conditions and the state of technical development, they are probably exceeded in others by large groups of the population.

49. Attention should be drawn to the necessity of avoiding glare (filaments of lamps, small highly luminous sources of light and brilliant surfaces), objectionable shadows and the presence of too violent brightness contrasts in the field of view. Furthermore, the illumination of rooms, passages and stairways should be reasonably uniform, and the latter should present sufficient contrast between treads and risers to minimise the risk of accidents.

DEFECTIVE VISION AND ILLUMINATION.

50. In considering desirable values of illumination, account must be taken of the wide prevalence of defective vision. According to certain studies, visual acuity decreases by 50% in the forty years after adolescence. Even in childhood, defects of sight are fairly frequent. English reports quote 8% as the number defective among elementary-school pupils.

The wide prevalence of defective eyesight is important, because, according to American research, persons with reduced visual acuity

appear to require higher illumination than do normal individuals. On the other hand, the question arises as to how far it is possible to prevent abnormalities of the eye by the use of adequate illumination. This question has been studied, though not solved, in connection with the development of myopia. The majority of studies hitherto carried out on the effects of illumination on the visual functions deal primarily with the efficiency of the latter and the subjective sensation of comfort produced. It is therefore highly desirable that our hitherto somewhat limited knowledge of the effects of illumination on the prevalence of defects and diseases of the eye should be increased.

METHODS OF DETERMINING ILLUMINATION.

51. As in the case of insolation, engineers, architects, town-planning specialists and hygienists have at their disposal a whole series of methods for measuring illumination in connection with the many problems with which they are concerned.

METHODS OF MEASURING ARTIFICIAL ILLUMINATION.

52. It is not necessary to dwell here on the various photometric methods for the measurement of artificial illumination. Such processes have been brought to a high degree of precision. Portable photometers, in particular those in which the photo-electric cell emission or rectifier type is utilised, enable the illuminating engineer and hygienist to study problems of artificial illumination with sufficient accuracy.

MEASUREMENT OF NATURAL ILLUMINATION.

53. Numerous methods have been specially devised for the purpose of determining natural illumination. Some of these methods are purely photometric ; others determine the " daylight factor " ; and some ascertain the solid angle subtended by the visible sky (WEBER).

54. Owing to the variations in natural illumination from day to day, and even from minute to minute, the practice has arisen of expressing the internal natural illumination at a given point in a room as a fraction of the external diffuse illumination. This ratio, which is called the "daylight factor", has been found to remain substantially constant in moderately dull weather. Methods based on the determination of the daylight factor, which have been in use in England since the end of the last century, are being introduced to an increasing extent in other countries.

55. Many methods of determining the daylight factor in rooms and models have been devised. These methods can be grouped as follows :

- (a) Photometric ;
- (b) Mathematical and graphical ;
- (c) Optical and photographic.

56. In the photometric methods, use is made of :

- (i) Simultaneous observation by means of two photometers, one inside the room and the other on the roof ;
- (ii) Comparative photometers, allowing of a simultaneous comparison between the illumination of a point in the interior and the portion of sky visible from it. In this connection, mention may be made of the instruments of WEBER, THORNER and BARNARD.

57. The mathematical and graphical methods are based for the most part on the use of "daylight factor diagrams" (WALDRAM, PLEIER), on which the outlines of the portion of sky visible through the window are traced. The "iso-daylight factor-lines" may then be plotted and are of great value in connection with building-plans and for determining desirable fenestration and desirable spacing between buildings.

58. In the optical and photographic methods, the photographs or images of the portion of sky are superimposed on daylight-factor diagrams (*cf.* the instruments of SWARBRICK, BECKETT and DUFTON, PLEIER and WALDRAM).

WALDRAM'S "daylight-factor gauge" is very simple and convenient for measuring natural illumination in existing premises, because it enables the daylight factor to be determined *in situ*.

The no sky-line (the line behind which no sky is visible at table height) may rapidly be determined by direct observation or by the help of a mirror.

FENESTRATION AND SPACING OF BUILDINGS IN RELATION TO NATURAL ILLUMINATION.

59. Attention has already been drawn to the complicated nature of the question of fenestration in the chapter on insolation. When drawing up building-plans, preparing town-planning schemes, or defining the principles governing fenestration, height of buildings and space between them, architects, town-planning specialists and legislators must bear in mind the fact that light, not only enables one to see, but is also indispensable in view of its biological and psychological effects.

60. As regards natural illumination, the methods of measurement mentioned above enable architects to plan their buildings for any degree of natural illumination desired. Town-planners and legislators are also able, through such methods, to decide how buildings must be spaced so as to ensure that, with the fenestration adopted, the desired natural illumination of the dwellings shall be obtained. In view of the complicated nature of the question, it is impossible to put forward any general solution, and each case should be dealt with on its merits.

61. In addition, detailed studies have been carried out in some countries, in particular the United States and Germany, which have made it possible to determine the dimensions of the windows under certain conditions from the direct readings of tables and diagrams.

62. Certain simple rules have also been given for determining the size of the windows according to the area of the rooms. Indications of the proportions which should exist between the size of the windows and the area of the rooms vary considerably, however. Rules of this kind have been objected to on the grounds that they

do not take possible obstructions into account and that they ignore the shape and position of the window and the shape of the room. Although such rules may be very useful in certain cases, it is apparently impossible to apply them generally without making corrections for external obstructions, their reflecting power, and height and width of the windows. In any case, the area referred to should be that of the clear glass area of the window.

63. It should be remembered that windows may absorb a not unimportant quantity of radiation, according to their construction and according to the optical qualities, thickness and the state of cleanliness of the panes. Reflected light, though it cannot provide adequate illumination by itself, plays an important part : the use of light colours, which have a high reflective power, for decorations and finishes is particularly desirable both for psychological reasons and in order to improve the uniformity of illumination, both natural and artificial.

ARTIFICIAL-LIGHTING FITTINGS.

64. An enterprising industry has placed on the market in different countries a large number of fittings, but their value has not always been proved as far as their effect on the visual functions is concerned. A detailed study of this subject should be undertaken by illuminating engineers in collaboration with hygienists and ophthalmologists, so as to define, on a scientific basis, the purposes for which these various lighting appliances can be recommended.

V. CONCLUDING REMARKS.

65. The results of the large amount of research work carried out in various countries into sunshine and light and its importance to mankind, considered from the climatological, biological and physiological standpoints, provide a reliable scientific basis for the work of engineers, architects and town-planners. These also have a large choice of methods of measurement which have been worked out in detail and enable them to ensure the desired conditions of sunlight and illumination for their projects.

New architectural designs and town-planning schemes have already been adopted in various countries, bringing sun and light to city dwellers who had hitherto been deprived of them. The work which has been done cannot fail to have a beneficial effect on the physical and psychological condition of the populations concerned.

66. Such efforts must, however, be continued if a general solution is to be found for what is one of the most important social problems of our time.

Further research work is essential, so as to fill the gaps in our scientific and technical knowledge. It is to be hoped that the many different specialists interested in these problems will undertake the studies advocated in this report, in close collaboration with each other, and as part of the activities of the various national committees.

An exchange of information on the various aspects of the problems is also essential. The collection by the national committees of fundamental data regarding insolation and illumination which can be used for the design of dwellings is also recommended. It should be pointed out in this connection that standard forms are available for surveys of the insolation and of the natural and artificial illumination of dwellings.

67. In addition to the studies already mentioned, it may be appropriate to indicate the value of a study by the Health Organisation of the hygiene of clothing on the same lines as its present study of the hygiene of housing.

68. It is also desirable that, for purposes of propaganda and education, the Sub-Committee's report should be made known as widely as possible. It should be communicated, in particular, to the faculties of the universities, the schools of hygiene, the technical schools and the various professional groups concerned, especially to those among whose members are architects, engineers, town-planning specialists, physicians and hygienists.

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**REPORT OF THE GROUP OF EXPERTS
OF THE
COMMISSION ON PHYSICAL EDUCATION**
(Geneva, July 6th-8th, 1938)

INTRODUCTION

1. When determining its programme of work for the years 1937, 1938 and 1939, the Health Committee of the League of Nations decided to include the question of physical education.

The Committee felt that its work in this field could only be successfully pursued by appointing a Commission to formulate the scientific bases of rational physical education adapted to different ages.

Before setting up this Commission, the Committee thought it advisable to convene a group of experts, in order to obtain their advice as to the orientation of the investigations and the choice of subjects. The group of experts met at Geneva on May 28th and 29th, 1937.

2. Subsequently, the Health Committee, at its session in November 1937, decided that the terms of reference of the Commission on Physical Fitness should be to define the physiological bases of

rational physical education adapted to different ages. The Commission should be guided as far as possible by the conclusions of the consultation of experts held at Geneva in May 1937.¹

3. The Committee also recommended that National Committees on Physical Education should be instituted, the International Commission being composed of representatives of the National Committees. It appointed Professor H. Laugier (France) Chairman and Professor J. Dill (United States of America), Professor E. Hansen (Denmark), Professor B. A. McSwiney (United Kingdom) and Dr. C. Wroczynski (Poland) Rapporteurs of the Commission.

4. With a view to examining the possibilities of a practical application of the conclusions of the experts, Professors E. Hansen and B. A. McSwiney carried out a study tour in several European countries. The results of their studies are to be found in their report.²

5. Following an exchange of views between the Chairman and Professor Hansen, the latter agreed to prepare a memorandum on the questions which should be discussed by the Commission at its next meeting. It appeared that the following items should be placed on the agenda of this meeting :

(a) Discussion of the results of research work so far carried out in relation to the physiological effects of physical exercise. Definition of the conclusions which can be drawn from these results with a view to formulating the physiological bases of rational physical education.¹

(b) Preparation of a programme of studies to supplement the results of research work so far carried out.¹

(c) Establishment of a list of somatometric measurements and functional tests which should be universally recommended as descriptive of physical fitness and form.¹

¹ See document C.H./Educ. Phys./1.

² Document C.H.1314.

6. A meeting of the Rapporteurs of the Commission on Physical Education was held in Geneva on July 6th-8th, to discuss these questions. The following attended the meeting :

Chairman :

Dr. H. LAUGIER, Professeur de physiologie à la Sorbonne, Paris.

Members :

Colonel A. BAUER, Président de l'Association nationale suisse de l'Éducation physique, Berne.

Dr. J. DILL, Professor of Industrial Physiology, Fatigue Laboratory, Harvard University, Boston.

Professor E. HANSEN, Director of the Institute for the Theoretical Study of Gymnastics, Copenhagen.

Dr. B. A. McSWINEY, Professor of Physiology, Sherrington School of Physiology, St. Thomas Hospital, London.

Dr. C. WROCZYNSKI, School Medical Inspector at the Ministry of Education, Warsaw.

REPORT

A. GENERAL RECOMMENDATIONS

The subject of physical education is one which still calls for a great deal of research. The scientific evidence available so far is meagre and the recommendations which can be made in the present state of knowledge are limited.

Nevertheless, it appears possible to put forward the following recommendations :

1. The term " physical education " must be understood to include all forms of physical exercises.
2. Physical education should be developed in such a manner as to make it interesting for the individual.
3. The subject of physical education cannot be developed independently but must be considered in association with nutrition.
4. The aim of physical education should be not to develop " champions " but to benefit the whole community.
5. Routine physical exercises should be taken in moderation, so as to bring about a sense of well-being.

6. It is desirable that physical education should be undertaken under medical supervision.

7. No one should engage in strenuous training and competitive exercises without a medical examination. This precaution is particularly important for adolescents and for individuals over 30 years of age.

8. Strenuous exercise should be avoided during menstruation.

9. It is inadvisable to allow strenuous competitions between subjects of widely different categories (especially children and adults).

10. It is suggested that physical exercises should be spread over the week and not concentrated on one day.

11. It is suggested that severe exercise should be avoided shortly before and two hours after meals.

12. The evidence available shows that one of the best periods for physical exercise (physical education lessons) is in the middle of the morning, and two or three hours after the midday meal.

13. It is desirable that corrective exercise classes should be developed.

B. PROGRAMME OF LABORATORY RESEARCH

The Committee suggested that investigations should be carried out under the following headings :

1. Physiological research :

(a) Effects of physical exercise on the physiological functions of the body ;

(b) Specific effects of different types of exercise upon physiological functions at different ages.

2. Anthropometrical investigations :

The study of the characteristics of athletic types with regard to different countries.

3. Psychological investigations :

The relation of intellectual development and physical development.

1. PHYSIOLOGICAL RESEARCH

The Committee suggested that the investigations of the effects of physical exercise and the study of specific effects of different types of exercise at different ages on physiological functions should be considered under the following headings :

- (1) Locomotor mechanisms ;
- (2) Cardio-vascular mechanisms ;
- (3) Blood ;
- (4) Respiratory mechanisms ;
- (5) Digestive mechanisms ;
- (6) Metabolism ;
- (7) Excretory mechanisms ;
- (8) Hormonal mechanisms ;
- (9) Nutrition.

• It was also pointed out that, not only the immediate effects, but also the permanent effects should be studied, and that attention should be paid to the temporal incidence (meal-times, etc.), and to constitutional type and sex and also to climatic conditions.

(1) *Locomotor Mechanisms.*

- (a) Action potentials from individual muscle fibres.
- (b) The study of co-ordination and economy of movement of muscle groups, including the recording of movements by cinematographic photography, cyclographic recording and metabolic measurements.
- (c) Study of movements of joints.
- (d) Investigation on isolated muscles and muscle fibres.

(2) *Cardio-vascular Mechanisms.*

- (a) Studies on heart output :
 - (i) Heart rate ;
 - (ii) Minute volume.

- (b) Size of heart.
- (c) Blood pressure.
- (d) Elasticity of arteries.
- (e) Peripheral circulation.

(3) *Blood.*

- (a) Morphological studies.
- (b) Physical and chemical characteristics.
- (c) Volume.

(4) *Respiratory Mechanisms.*

- (a) Lung volume.
- (b) Ventilation.
- (c) Interchange of gases.
- (d) Energy exchanges.

(5) *Digestive Mechanisms.*

- (a) Motility.
- (b) Secretion of juices.
- (c) Absorption.

(6) *Metabolism.*

- (a) Blood sugar regulation.
- (b) Protein.
- (c) Fat.
- (d) Temperature regulation.
- (e) Capacity for oxygen supply.

(7) *Excretory Mechanisms.*

- (a) Kidney and bladder.
- (b) Sweat glands.
- (c) Large intestine.

(8) *Hormonal Mechanisms.*

Attention should be paid to the hormonal mechanisms, with special reference to the female subject.

(9) *Nutrition.*

In studying the effect of exercise upon physiological functions, it is important to take into account the state of nutrition.

Explanatory Notes regarding Physiological Research.

Heart Output.—The validity of present methods, particularly as applied to young subjects, should be investigated. The output in relation to various sports, to the state of the cardio-vascular system and to age should be studied.

Heart Rate.—Aside from observations on the heart rate while the above measurements are being made, interesting questions are :

How does the acceleration of the pulse vary with respect to training ?

What is the relation between “warming up” and the heart rate and heart output ?

Blood Pressure.—Various methods have been used to measure the blood pressure. As the criteria employed vary with each method, it is difficult to compare the results obtained by different workers. It should be pointed out that, during work and immediately after work, the difference between the lateral pressure with a free flow and the occlusion pressure is very marked. Measurements obtained using the occlusion pressure, under these conditions, do not give a true account of the pressure of blood in the arteries. It is important that simple methods should be developed for measuring the lateral pressure with a free flow of blood.

Elasticity of Arteries.—Information on the state of elasticity or extensibility of arteries may be obtained from measurements of the pulse-wave velocity.

Previous investigations have shown that individuals may be grouped into three classes.

- (a) Individuals with “hyper extensible” arteries ;
- (b) Individuals with “average extensible” arteries ;
- (c) Individuals with “hypo extensible” arteries.

The extensibility of arteries decreases with age. The relationship of the extensibility of arteries with blood pressure is important.

The *capacity for supplying oxygen* in severe exercise, measured in litres of oxygen per minute, is an excellent measure of cardiovascular fitness. The extent to which this function may improve with training, the variation in relation to various forms of sport, the dependence on age and sex and the degree to which it is influenced by the nutritional state are important questions.

Blood sugar regulation should be investigated along the following lines :

Does the regulatory efficiency vary with the age and state of training ?

How is it influenced by diet ?

What need exists for extra supply of sugar in various forms of sport ?

Blood volume and *sweating* are interdependent. All body fluids are reduced in volume by sweating. The capacity for work is thereby reduced and an eventual breakdown may occur. The supply of salt in palatable form (as in bouillon) may be advisable in such sports as tennis and football when played in hot weather. This question calls for careful examination.

Lung Volume.—Measurements of the size of the thorax do not afford accurate information of the pulmonary ventilation. Information of pulmonary ventilation can only be obtained by specific measurements (tidal air, vital capacity, etc.).

Investigations have shown that there is no strict relationship between the shape of the thorax and the vital capacity. Further, a large thorax does not necessarily indicate ability to perform severe exercise efficiently.

Motility and Secretions of the Digestive Organs.—Investigations have shown that exercise may interfere with the movements and secretions of the stomach, etc.

Further observations are necessary, not only to establish the exact effects of exercise on the digestive organs, but also to determine the optimum times for exercise with relation to meals.

Metabolism.—Further investigation, as outlined by Christensen, Krogh and Lindhard¹ are desirable.

¹ "Investigations on Heavy Muscular Work", *Quart. Bull. Health Org.*, 1934, 3, 388.

Kidneys.—Investigators have shown that during severe exercise the secretion of urine is inhibited. Further investigations of the effects of exercise on the function of the kidneys are desirable.

2. ANTHROPOMETRICAL INVESTIGATIONS

The Committee suggested that the following points should be studied :

- (a) The relationship between :
 - (i) The values of various somatic measurements and the standard of attainment in various sports ;
 - (ii) Between characteristic ratios of such values and the standard of attainment in various sports ;
- (b) The effect produced, in the course of growth, by the various methods of physical education and sports upon the values of somatic measurements and their ratios.

3. PSYCHOLOGICAL INVESTIGATIONS

The Committee considered that the following points should be studied :

- (a) The elementary psycho-physiological factors involved in the practice of various sports (time of reaction, attention, dispersion of attention, visual memory, auditory memory, precision and rapidity of movement, judgment of distance, quickness of eye, emotional excitability, self-control) ;
- (b) The effect of physical education and various sports on the measurable psycho-physiological factors.

C. DOCUMENTARY STUDIES

The Committee agreed that information should be collected on the following points :

- (a) The nature of the physical exercises, of the methods of training and of the types of sport in use in various countries according to sex and age ;
- (b) The number of hours devoted to physical education in different countries at various educational stages ;

- (c) Programmes of teaching for physical training instructors (programmes of work of various physical education institutes) ;
- (d) The rôle of the physician (sports doctor) and of the medical officer in relation to physical education ;
- (e) The award of badges for proficiency in physical exercise.

D

The Committee also agreed that evidence should be obtained of the best manner of utilising leisure hours during the day and weekly rest-days and, in particular, the part played by physical education.

E. TECHNICAL INTERCHANGE OF RESEARCH WORKERS AND THE PROVISION OF FUNDS FOR STUDIES OF THE PHYSIOLOGICAL BASES OF PHYSICAL EDUCATION

It was recommended that information should be obtained from national organisations and institutes of the facilities available for visiting research workers.

It is also desirable that the national and international organisations dealing with medical problems should set aside funds for the study of the physiological bases of physical education and for the technical interchange of research workers in this field.

F. MEDICAL EXAMINATION OF THOSE TAKING PART IN PHYSICAL EDUCATION

The Committee agreed that a medical examination form should be drawn up, so that the examination used for those taking part in physical education would be similar in different countries.

The following form was adopted, and it was agreed that it should be circulated to the Health Administrations National Committees and to individuals suggested by members of the Committee for comments and observations.

MEDICAL EXAMINATION FORM¹

Surname	Christian names
Address	Place and date of birth
School	Class Place in class
Club or organisation	
Occupation	Occupation of parent
Nationality	
Colouring	{ hair
	{ eyes
	{ skin
Past history	Measles
	Pertussis
	Mumps
	Chicken-pox
	Scarlet fever
	Typhoid fever
	Diphtheria
	Malaria
	Smallpox
	Pneumonia
	Pleurisy
	Rheumatism
	Tonsillitis
	Tuberculosis
	Influenza
	Otitis media
	Venereal diseases
	Chorea
	Convulsions (epilepsy)
Operations	
Injuries	
History of physical education	
.....	
.....	
<i>Physical examination :</i>	Stout : Medium : Slender
Appearance	{ tall
	{ medium
	{ short
Teeth	{ number missing
	{ number with caries
	{ number of bites

¹ It is contemplated that such a form would be set out in such a way as to provide for the recording of findings of successive examinations.

REPORT OF THE GROUP OF EXPERTS

Height (without shoes)	{	standing—cm.
		sitting ¹ —cm.
Weight (without clothes)		kg.
Chest girth	{	inspiration—cm.
		expiration—cm.
Adipose tissue	{	subject obese
		fat
		medium
		thin
Muscular development	{	marked
		medium
		poor
Skeleton :	{	erect
Posture		stooped
		any special characteristics observed..

Special characteristics of :

- (1) Spinal column
- (2) Chest and shoulder blades
- (3) Limbs
- (4) Feet

Thyroid : normal..... enlarged

Tonsils Adenoids

Mouth breathing

Other remarks

Lungs : Clinical examination

X-ray examination

Heart :

Rate	{	regular
		irregular
		etc.

Transverse diameter

Auscultation	{	Percussion
		X-rays

Peripheral circulation :

Arteries Veins Capillaries

Abdomen

Sense organs :

Eyes : R..... L..... Corrected to : R..... L.....

Wears glasses since constantly, reading, distance.

Colour vision

Hearing R L

¹ Height from crown of head to plane of seat, the back being vertical—the seat being set at such a height that the femur is horizontal.

Nervous system	}	phlegmatic
		stable
		excitable
Reflexes	}	knee jerks
		ocular (light and accommodation)
		other
Menstruation	}	regular
		irregular

Special examinations :

Vital capacity Breath holding secs.

Exercise test :

15 complete knee bendings in
15 secs., after sitting at rest
for 15 mins.

Heart rate :

Sitting at rest
Standing at rest

Sitting after exercise :

After 20-30 secs.
After 2½ mins.
After 4½ mins.

Blood pressure :¹

Auscultory or oscillatory method.	<i>Systolic</i>	<i>Diastolic</i>
Sitting at rest :		
Before exercise
Sitting after exercise :		
After 1 min.
After 3 mins.
After 5 mins.

Urine :

Protein
Sugar

Recommended for physical exercise :

(a) Without restrictions

(b) With restrictions

(c) For corrective purposes

Unfit for exercise until

¹ Underline method used.

**REPORT ON THE WORK OF
THE HEALTH ORGANISATION
BETWEEN JUNE 1937 AND MAY 1938,
AND ON ITS 1938 PROGRAMME**

INTRODUCTION

According to its Statute—which is similar to that governing the various technical organisations of the League of Nations—the Health Organisation includes a General Conference of a consultative character, the General Advisory Health Council, which meets once a year.

The duties in this connection have been confined to the Permanent Committee of the Office internationale d'Hygiène publique, set up by the Rome International Agreement of December 9th, 1907. For this purpose, the Permanent Committee organises an Annual Assembly at which States Members of the League of Nations which do not participate in the Office may be represented.

At this Annual Assembly, the Health Committee of the League of Nations presents “the report on the work of the Health Organisation during the past year and a statement on its programme for the following year”.

The report presented by the Health Committee during the Annual Assembly of May 19th and 20th, 1938, is given below ; it is proposed to publish these reports each year, so that readers may obtain a general view of the work carried out by the Health Organisation of the League of Nations.

I. RURAL HYGIENE

1. INTER-GOVERNMENTAL CONFERENCE OF FAR-EASTERN COUNTRIES ON RURAL HYGIENE (Bandoeng, August 3rd-13th, 1937)

Following upon the European Conference on Rural Hygiene of 1931, a number of delegations asked the League of Nations to call together a similar conference in the Far East. Thanks to the kindness of the Netherlands Government, the Conference was held at Bandoeng (Java) under the presidency of Dr. OFFRINGA, Director-General of Health Services in the Netherlands Indies. The Governments of the following countries were represented : British North Borneo, Burma, Ceylon, China, Fiji and the South Pacific Islands, Hong-Kong, India, French Indo-China, Japan, Malaya, the Netherlands Indies, the Philippines and Siam. In addition, observers were sent by the following : the Netherlands Indies Civil Service, the Colonial Institute of the Amsterdam Royal Association, the Rockefeller Foundation, the Central Statistical Bureau at Batavia, the Far-Eastern Association for Tropical Medicine, the International Institute of Agriculture and the League of Red Cross Societies.

The delegations were composed in such manner as to secure representations for all the various branches concerned with rural hygiene : health administration, local government, medicine, agriculture, rural reconstruction, education, co-operation, etc. The agenda dealt with the organisation of medical and health services, rural reconstruction, sanitation and sanitary engineering, nutrition and measures for combating certain diseases (malaria, plague, ankylostomiasis, tuberculosis, pneumonia, yaws and leprosy) in rural districts.

Five Committees were set up to deal with the various questions enumerated above. The report of the Conference¹ is similarly divided into five chapters, which record the work and findings of the several committees.

(a) *Medical and Health Services.*—On this subject, two theses confronted each other : the unitary and the dual.

¹ Document A.19.1937.III.

In the first case, medical care and health work are carried out by the same staff ; in the second case, there are parallel and distinct services. The Conference concluded that, where a country possesses the necessary resources, it is preferable for it to maintain separate services, and to provide a central directing and co-ordinating body. If, however, resources do not permit of separation, the unitary system should be used. In this connection, the Conference put forward a number of recommendations dealing with the training of the technical staff.

Members of the First Committee, who were mostly Directors of Health Services, laid stress on the difficulties encountered in obtaining a clear idea of the circumstances in which health services have to carry out their work in the various countries. Statistical material is incomplete, and certain data are entirely lacking. Hence, one of the main recommendations of the Conference urges the selection of certain areas for detailed surveys of the various factors affecting the health situation. A scheme for such a survey is given in an appendix to the report of the Conference. Under this scheme, the Health Organisation of the League of Nations is responsible for collecting and distributing the relevant documentary material and for maintaining contact with the investigating countries throughout, in order to secure the maximum degree of uniformity. This task will be carried out in the ordinary course through the Eastern Bureau at Singapore.

(b) *Rural Reconstruction*.—The discussions threw into relief the importance and urgency of rural reconstruction as a primary responsibility of every Government. In this connection, it is necessary that the development of villages and groups of villages should be along comprehensive and effective lines. Close attention was given to the most suitable method to be applied for this purpose. The Conference laid stress on the necessity for securing the willing acceptance of improvement plans by the rural population, rather than having these imposed through administrative channels.

Other recommendations of the Conference dealt with the important function of education, especially in agricultural

matters, and with the need for land reform and the methods to be employed to carry it out. The Conference, realising the increasing importance of the rôle which must be played by women in rural reconstruction, urged that everything should be done to ensure that women shall be given every opportunity to develop their activities in this important field. The Conference found that a number of countries possess experimental centres for rural reconstruction, and that these have worked out results which have proved applicable to other regions. It accordingly invited the Health Organisation to collect and make available information on these experiments, particularly by means of collective study tours.

(c) *Sanitation and Sanitary Engineering.*—Under this heading, the Conference adopted a series of proposals of which two deserve special mention : the first is concerned with the setting-up of local committees for small-village planning ; the other lays stress on the need for developing experimental research into measures of fly control, under the auspices of the Health Organisation.

(d) *Nutrition.*—The report deals with the nutritive value of foodstuffs consumed in the East, with the surveys to be carried out there, and with the dietary standards to be applied in that part of the world. The technical report has been referred to the Technical Commission on Nutrition for examination.

The recommendations of the Conference emphasise the importance of diet in relation to health problems in the East. Even more than in other parts of the world, the physical condition and general health of the individual are impaired by under-nourishment and malnutrition. To remedy this situation, the Conference urges that *National Nutrition Committees* should be established in each country and that they should include representatives of the public health, medical, educational, agricultural, animal husbandry and fisheries departments. In addition, there should be a central research institute in each country, specialising in nutrition, and a similarly specialised technical personnel, whose functions would be to promote the practical application of modern nutritional science. Close

collaboration, both national and international, should be maintained between research laboratories and the other institutions concerned. Accordingly, the Conference urges that the fullest co-ordination should be established under the ægis of the League of Nations.¹

(e) *Measures against Certain Diseases in Rural Areas.*— The last chapter of the report of the Conference contains a series of practical recommendations designed to assist Governments in their efforts to control malaria, yaws, ankylostomiasis, leprosy and mental diseases. As regards tuberculosis, pneumonia and plague, the Conference confined itself to emphasising the need for pursuing research work, and urged that national plans to combat those diseases should be forwarded to the Eastern Bureau at Singapore, so that information might usefully be exchanged between the various countries. Tuberculosis, for instance, is one of the scourges of the Far East concerning which little is yet known. As the financial means at the disposal of Governments are generally limited, tuberculosis control plans are necessarily simple and adapted to local circumstances. As regards malaria, the Conference emphasised the value of close collaboration between malariologists in the East and the appropriate commission of the Health Organisation. To this end, it suggested a series of measures, including the institution of special courses for anti-malaria engineers following the same lines as the existing International Course in Malariology. It is indeed essential to guard against the inordinate spread of malaria, which occurs when construction work is undertaken without regard to the necessary precautions.

Such, briefly, is the record of the Conference. Emphasis should be laid on the profound influence exerted by the Conference in awakening public opinion, in drawing attention to the urgency and complexity of the questions included on its agenda, and in encouraging co-operation on the part of all those who, in various capacities, will be called upon to contribute to the practical application of its

¹ This question will be discussed in the chapter dealing with nutrition.

recommendations. The Conference relied largely for this purpose upon the help of the Health Organisation. The Health Committee, with the approval of the Council, has accordingly made the necessary arrangements to lend its assistance in this field.

2. INTER-GOVERNMENTAL CONFERENCE OF AMERICAN COUNTRIES ON RURAL HYGIENE

During the 1936 Assembly, fifteen delegations, mostly from Latin America, expressed the hope that a Conference on Rural Hygiene would be organised for the continent of America. The Mexican Government having intimated that it would be pleased to see the meeting take place in Mexico City, and the Council having accepted this suggestion, the Conference will take place in Mexico City from November 10th-20th next.

The technical preparation of the Conference was entrusted by the last Assembly to a Committee, which included a representative of the International Labour Office. Last December, the Committee visited Mexico City and Washington in order to draw up, in full agreement with the Mexican Government and the Director of the Pan-American Sanitary Bureau, the agenda of the future Conference, to which all the countries of America were invited. The agenda which emerged from these consultations comprises the following five chapters :

- I. *Organisation of Rural Medical and Health Services :*
 1. Curative medicine in rural areas.
 2. Preventive medicine in rural areas.
 3. Health insurance and medical assistance in rural areas.

- II. *Selected Problems of Disease in the Rural Environment.*
 1. Malaria.
 2. Tuberculosis.
 3. Pneumonia.
 4. Helminthiasis.
 5. Typhoid and paratyphoid fevers.
 6. The dysenteries.
 7. Leprosy.
 8. Venereal diseases.
 9. Alcoholism.

III. *Medical and Health Survey of a Rural Region :*

1. The aims and utility of a survey.
2. Methods of conducting a survey.

IV. *Nutrition in Rural Districts.*

V. *Conditions of Rural Life :*

1. Housing.
2. Rural sanitation.
3. Rural betterment.

The omission from this agenda of any of the great pestilential diseases, some of which are characteristic of rural districts, is due to a desire to avoid as far as possible dealing with the same subjects as the tenth Pan-American Sanitary Conference which will be held in Bogotá next September. Each item on the agenda will be dealt with by a rapporteur of acknowledged scientific authority.

The Mexican Government has left no stone unturned to ensure the success of the future Conference ; for its technical preparation, it has set up a Committee which includes senior officials of the public health service, and it has also been kind enough to grant every material facility.

The Health Committee suggested to the Council that the President of the Conference should be Dr. Leonides ANDREU ALMAZAN, Director of the Mexican Department of Public Health.

3. EUROPEAN CONFERENCE ON RURAL LIFE

The 1931 European Conference on Rural Hygiene came to the conclusion that it would be advisable to call together a new Conference after a lapse of five years " to examine the results achieved and to adapt its recommendations to current problems and to the progress of public health technique ". It also asked the Health Organisation to arrange for the study of various problems of which it drew up a list.¹

Thus, in 1931, the Health Organisation found itself entrusted with a definite task—that of directing technical studies and preparing for a future Conference. The periodical reports on its work show

¹ See " Triennial Plan of Work of the Health Committee ", document C.219. M.159.III.1937, pages 9 and 10.

that, apart from the conferences just mentioned, the Health Organisation has organised and co-ordinated the research which various institutes and schools of hygiene in Europe were kind enough to undertake. The research may be classified as follows :

(a) *Sanitation* : Water supplies, analysis and testing of sewage, treatment of garbage and manure, prevention of fly-breeding, etc.

(b) *Prevention of the most serious diseases in country districts* : Tuberculosis, typhoid, undulant fever, etc.

(c) *Medical and sanitary assistance* : Cost and efficiency of various types of health services : maternity and child welfare, training of technical personnel of health services, etc.

(d) *Medico-social protection of rural populations* : Nutrition, housing, rural planning, etc.

The essential fact that emerges from this very cursory review is that an attempt has been made to carry out a systematic survey of rural life and of the factors which exercise an influence on the health of rural communities. Methodical efforts were directed, first, towards problems of general health ; secondly, to measures for the prevention of diseases which constitute a particularly serious problem in rural regions, and, thirdly, to the necessity of endowing rural districts with medical equipment for the protection of health. Lastly, the Health Organisation had to consider the material living conditions which constitute the basis of rural reconstruction : nutrition, housing and physical training.

The foregoing considerations explain the Health Committee's desire to extend the scope of the new Conference, which was agreed on in principle as far back as 1931. It realised that it was impossible to dissociate the health, economic and social aspects of rural reconstruction. That is why it came to the conclusion that, at the new Conference, " rural hygiene questions must be placed in their general setting—namely, that of rural life—while account must be taken of the factors of all kinds which come into play ”.

The 1937 Assembly endorsed the Health Committee's conclusions by deciding to convene, in 1939, a European Conference on Rural Life.¹

¹ Document A.48.1937, page 4.

A Preparatory Committee was set up to determine the field of action and the agenda of the Conference. The Health Committee proposed that the following questions should be singled out :

- Enteric fever ;
- Brucellosis ;
- The incidence of tuberculosis and methods of tuberculosis control ;
- Health indices ;
- Nutrition ;
- Housing.

4. SIXTH MEETING OF DIRECTORS OF INSTITUTES AND SCHOOLS OF HYGIENE IN EUROPE (November 22nd-27th, 1937)

It will be remembered that the chief object of these meetings is to examine the work carried on by the institutes and schools under the ægis of the Health Organisation, and their programme of activity for the future. These studies are now taking the form of technical preparation for the work of the future European Conference on Rural Life. That is why the institutes in question have drawn up a programme of work dealing with the questions set out above. The programme includes research work, to be continued or initiated, not only in the laboratory, but also and above all in the field, dealing with the health and economic factors influencing the incidence of enteric fever, the brucelloses and tuberculosis, the determination of their comparative importance and the framing of a plan of campaign adapted to the conditions of rural life, taking into consideration the financial consequences of such a step. In the sphere of nutrition, there are to be surveys for the determination of the actual food consumption of certain specified communities and the bringing to light of possible cases of malnutrition.

5. EUROPEAN RURAL HOUSING EXHIBITION (June 17th-November 25th, 1937)

The Health Organisation had the good fortune, thanks to the generosity of the French Government, to have at its disposal last

year a pavilion in the Exposition internationale des Arts et Techniques de la Vie moderne. Under its ægis, thirteen European countries,¹ the Institute of Public Health at Rome, the Hygiene and Water Board and the Milk Committee presented exhibits in connection with the modern hygiene of housing and rural environment. The Health Organisation also exhibited a series of graphs, descriptive tables and publications relating to its activities in the sphere of rural hygiene.

The national stands included panoramas of model villages, scale models of rural dwellings, maps and tables to demonstrate the basic principles underlying modern rural community planning. Other similar illustrations concerned public services, such as drinking-water supplies, dairies, co-operatives, slaughter-houses, schools, hospitals, etc. The French exhibit showed in particular the results of an enquiry carried out by the Ministries of Agriculture and Public Health into rural housing. The results of this enquiry were subsequently published.² Greece presented exhibits showing the work accomplished by the American Near East Foundation in collaboration with the Ministry of Health. The Netherlands exhibit gave a special place to the draining of the Zuyder Zee.

II. TECHNICAL WORK

1. BIOLOGICAL STANDARDISATION

In the person of Dr. Claus JENSEN, who died in January last, the Health Organisation has lost a collaborator of outstanding scientific eminence and devotion to his profession. As head of the Biological Standards Department set up at the Copenhagen Serotherapeutic Institute under the auspices of the League, he was in charge of the preparation, preservation and distribution of the twelve standard sera so far adopted for international use. The ability with which he carried out this difficult task, the value of his experimental work

¹ Belgium, Bulgaria, Czechoslovakia, Denmark, France, Greece, Hungary, Lithuania, Luxemburg, the Netherlands, Roumania, Sweden and Yugoslavia.

² " L'habitation en France : Rapport de la Commission technique de l'Habitation du Ministère de la Santé publique." Imprimerie Nationale, 1937.

on the assay of diphtheria antitoxins by the cutaneous method, and the interest attaching to his recent studies of poliomyelitis and the assay of convalescents' serum had won for him a scientific reputation going far beyond the bounds of his own country. The Health Organisation could not fail to pay a tribute to the memory of a deeply regretted collaborator.

This year again experimental work has been concentrated on the questions put down for study by the Inter-Governmental Conference on Biological Standardisation of 1935.

Although still incomplete, the comparative assays of five tetanus antitoxins carried out in five laboratories according to a pre-arranged scheme already warrant certain conclusions: where the standard method and the same test toxin are used, the resulting assays do not vary by more than 10%. But variations are more considerable where different methods and toxins are employed.

The problem is therefore to determine the causes to which may be ascribed the differences revealed as between the various toxins. In the first place, it will be necessary, as a basis for the measurement of toxins, to ascertain whether the slant of the neutralisation curve always remains the same and, further, whether a given strain always yields the same type of toxin. This problem is now being investigated.

The possibility of standardising the European anti-viper serum is to be investigated by the Copenhagen Institute. Recent publications show that three varieties of the European viper (*V. aspis*, *ammodytes* and *berus*) secrete venoms of very similar antigenic potency. Standardisation should therefore bear in the first place upon the venoms of those three varieties.

The Copenhagen and Zagreb institutes, having now agreed upon the principle which is to underlie the assay, will shortly proceed to a comparative examination of the anti-viper sera supplied by four European laboratories.

Last year, Professor FORSSMANN, of Lund, pointed out that only the anti-toxic potency of the staphylococcus antitoxin selected in 1934 as an international standard had been standardised, and not its anti-bacterial potency. Experimental work published by a number of institutes has shown that staphylococcus toxin can be split up into a series of fractional toxins possessing differing properties. While the α fraction, which the international standard

serum neutralises, exerts a strong necrotic and hæmolytic action, the γ fraction, which Professor FORSSMANN appears to have used, has a much less marked necrotic effect. In order to obtain an assay in terms of the standard serum, a toxin must be used of which the various properties are accurately known, and the attention of the institutes concerned should be drawn to this point.

As in each previous year, the Copenhagen Institute has verified the titre of national standards of diphtheria antitoxin against the international standard in its keeping. In two cases, variations in potency amounting to 5% have been brought to light.

In connection with gas-gangrene antitoxins, the objections raised against the basic principle upon which the assay rests by Professor M. WEINBERG have not been overlooked. If it should prove a fact that, in order to obtain valuable results, it is necessary, as Professor WEINBERG urges, to employ, not only the same standard serum, but also the same sample of toxin, this would be a finding of considerable importance, the more so since it might prove to be a general rule applicable to all the antitoxic sera. For this reason, and with Professor WEINBERG'S consent, comparative assays, undertaken by way of counter-check, of the *B. perfringens* antitoxin have been entrusted to laboratories in four different countries.

In the light of the striking results obtained in treating pneumonia with a serum of the homologous type, the Copenhagen Institute has undertaken the preparation of the whole range of sera, both agglutinating and therapeutic, corresponding to the thirty-two types of pneumococci so far identified. This will make possible both a rapid diagnosis of the type concerned, and homologous serotherapy.

The question which now arises is whether, in addition to the international standards previously adopted for sera of types I and II, it would not be desirable to provide further standards corresponding to the other types of pneumococci, or at any rate those types which are most frequently encountered.

This is one of the questions which the serologist members of the Permanent Commission on Biological Standardisation will have to examine at their next meeting, which it is proposed to hold at the end of September.

Before leaving the field of serology, it should be added that a report on the assay of anti-anthrax serum has been prepared by the Bucharest Institute, while the work in progress at Copenhagen with

a view to laying down a standard of purified tuberculin is nearing completion.

As regards *vitamins*, it has been expected that a new Standardisation Conference would be able to meet this year. Recently acquired experimental data have, however, opened up new avenues and it would be a definite gain if this Conference were postponed until 1939.

In the case of vitamin A, for example, there is every ground for believing that, within the next six months, a pure stable preparation will be available which could with advantage be substituted for the present international standard consisting of β -carotene. Similarly, in the case of vitamin D, the recently isolated substance known as vitamin D₃ appears to be identical with the active principle contained in cod liver oil. Should this prove to be the case, the new substance would make a more suitable standard of the antirachitic vitamin than does irradiated ergosterol. Here again, however, the conclusion of the clinical tests on man and on animals must be awaited. Finally, it is possible that, within the next twelve months, our knowledge of vitamins B₂ and E may have reached a stage at which standardisation will become possible.

At the moment, the standard which most requires improvement is that of vitamin B₁, of which the stock is now practically exhausted. Since synthetically prepared crystallised preparations of vitamin B₁ are now available, it would be of advantage to replace the present international standard, which is an impure product, by pure vitamin. The Director of the Hampstead Institute has been able to collect a stock of 50 grammes of crystallised vitamin B₁ and has submitted samples to a large number of European and American laboratories with the request that they should define the international unit of vitamin B₁—which has remained unchanged—in terms of the pure substance. If the results of those assays agree, the change over to the new standard preparation might be carried out without delay by agreement between the experts who took part in the last vitamin conference.

The problem of the standardisation of *hormones* is to be further considered by a conference which is to meet in Geneva in August next; this conference will not consider merely, as on previous occasions, the sex hormones, but will pay special attention to the anterior lobe pituitary hormones.

With a view to drawing up the agenda of the Conference, and obtaining adequate stocks of the hormones likely to be standardised, the Hampstead Institute has circulated two memoranda, together with a questionnaire, to some eighty scientists. From the large number of replies received, it would appear that the standardisation of the gonadotrophic hormone of human urine of pregnancy and of the thyrotrophic, gonadotrophic and lactogenic hormones of the anterior lobe of the pituitary gland is considered highly desirable and technically feasible.

It should be remembered in this connection that the Hampstead Institute had met with considerable difficulty in bringing together an adequate stock of crystallised progesterone, the substance which was to constitute the international standard of the progestational hormone of the *corpus luteum*, in accordance with the decision of the 1935 Conference.

Now, in October last, two samples of progesterone offered by German factories were added to a sample prepared at Hampstead, giving a total quantity which, however, amounted to less than 3 grammes. In view of the small quantity available, there was no alternative but to supply the standard preparation in ampoules of 20 milligrammes, instead of 100 milligrammes as recommended by the 1935 Conference. Moreover, the standard progesterone is not crystallised in the form of needles, as had been anticipated at the time of its adoption, but is present in the more stable form of prismatic crystals.

Finally, it may be mentioned that a further number of countries have officially set up national distribution centres within the meaning given to the term by the resolutions of the 1935 Inter-Governmental Conference for Biological Standardisation. They are : Chile, France, Japan, Roumania and the Union of Soviet Socialist Republics.

In Chile, in addition, the use of international standards has been made compulsory by a decree of the General Directorate of Health.

Mention should be made in this place of the attempts made to *standardise the agglutination reactions* used in the diagnosis of salmonellosis and brucellosis.

In connection with the Widal test, a further number of assays were carried out in 1935/36 at the Bucharest, Copenhagen, Oxford

and Warsaw institutes, in order to ascertain whether, owing to the variety of methods employed, considerable errors might not arise and whether the test could be rendered more accurate by using standard suspensions such as those prepared by the pathological laboratory of the University of Oxford.

The results of those assays, which are set out in a report by Dr. A. FELIX and Dr. A. D. GARDNER,¹ did not show complete concordance, and pointed to the need for further research in this field; a meeting of experts was held in London in November 1937, in order to lay down the main lines of such research.

After setting out in detail the technique recommended by them for the Widal test—a technique based upon the use of separate suspensions for the measurement of O and H agglutinations—the experts recommend the creation of an international centre which would distribute to authorised national centres standard sera, standard suspensions and typical cultures, in order that the results obtained by the Widal test might be rendered more uniform and comparable.

To improve the diagnosis of brucellosis by agglutination tests, the experts lay stress on the advantages which, here again, would attend the creation of an international centre to distribute standard sera, typical cultures and standard suspensions.

Finally, reiterating a proposal put before the International Microbiological Association in 1937, the experts expressed the wish that an international centre should be set up, preferably at the Copenhagen Institute, for the identification of salmonella strains.

These various proposals have been referred to the Permanent Commission on Biological Standardisation for study.

2. MALARIA

I. *Three-year Plan of Work.*

In laying down its three-year plan of work, the Health Committee confined itself to a few general indications as to the investigations to be carried out into malaria, and decided to consult the Malaria Commission on the exact terms of the programme of investigations to be laid down.

¹ "The Serum Diagnosis of Enteric Fever." *Bull. Health Org.*, 1937, 6, 223.

This consultation took place in October 1937, and the Committee was thus able at the beginning of November to submit to the Council its plan of work on malaria.

1. The first section constitutes a *programme of research* into :

(a) *Malaria Immunity*.—The collaboration initiated in 1933 between the Horton laboratory and a number of Roumanian centres is to be continued ; it has already resulted in the collection of important data on questions of immunity in relation to various species and strains of parasites.

The Commission also recommends that therapeutic and prophylactic experiments should be undertaken, in order to determine how drugs act upon the processes of immunisation or premunisation of the organism against various species of parasites.

(b) *Drug Prophylaxis*.—Experiments are to be undertaken to confirm and to define the prophylactic action of bi-weekly doses of 0.02 grm. of atebtrin. On a more general plane, an effort will also be made, having regard to the toxicity and the cost of the drug, to determine how far the prophylactic dose may be reduced once the optimum degree of concentration in the blood has been secured.

(c) *The Bionomics of Anophelines*.—Investigations are to aim, on the one hand, at measuring the longevity of malaria-carrying species of anophelines and, on the other hand, at ascertaining the geographic distribution of the various forms assumed by given species, as well as their biology, their relationship to malaria, etc.

(d) *Insecticidal Spraying*.—The value of this method in destroying adult mosquitoes is to be investigated ; this will necessarily involve consideration of the habits of vector anophelines.

(e) *Naturalistic Methods of Malaria Control*—namely, the methods adopted by man to modify one or more of the natural factors, dependent upon physical, chemical and biological conditions, which render water malariogenic, so as to prevent mosquito-breeding, to destroy larvæ or even to divert adult mosquitoes from man to animals. It will be necessary to

stimulate scientific advance by collecting the existing information and by publishing a critical study of what is being done along these lines. The task has been entrusted to Dr. L. W. HACKETT, with the collaboration of a worker from the East.

(f) Finally, the Commission will continue to follow the question of *malaria in deltas, and that of the connection between housing and malaria.*

2. The Council has approved the Health Committee's proposal that the Governments concerned should be consulted as to the desirability of convening an inter-governmental conference on anti-malaria drugs ; the agenda of such a conference might usefully include the present level of production of such drugs, the probability or possibility of increasing production in the future, prices and methods of distribution.

3. The Health Committee is contemplating undertaking a study of the results of anti-malarial measures and, more particularly, anti-larval measures in the Mediterranean Basin. Such a study might be used as a basis for the preparation of a new general report on the principles of malaria control.

4. The Health Committee has requested Sir Rickard CHRISTOPHERS and Professor L. W. HACKETT, Professor W. SCHUEFFNER and Professor E. SERGENT to prepare a draft report on the standardising of terms used in malariology.

II. *Fourth General Report of the Malaria Commission.*

It will be recalled that the Malaria Commission, in 1935 and 1936, carried out a series of experiments in treatment and prophylaxis, in order to compare the efficacy of synthetic drugs with that of quinine. The programme of these experiments, which was identical in the various countries, had been carefully drawn up in advance and involved the use of the same drugs, doses and methods of administration and observation. The experiments covered a total of 12,288 subjects. They were carried out in Algeria, Italy, the Federated Malay States, Roumania and the Union of Soviet Socialist Republics, under the direction of Professor E. SERGENT, Professor G. BASTIANELLI, Professor N. KINGSBURY, Professor M.

CIUCA and Professor P. SERGUEFF. On the basis of the results of those experiments and of the existing literature, the Commission drew up and has just published its fourth general report.¹ The report, which represents the unanimous opinion of the Commission, was prepared by a drafting Committee consisting of Professor E. SERGENT, Colonel J. A. SINTON, Dr. C. BALFOUR and Professor G. PITTALUGA. The annexes include an account of the experiments, a bibliographical digest and the text of the comments on the report submitted by various members of the Malaria Commission.

As regards *individual treatment*, the scheme followed consisted of 1 gm. of quinine per diem for seven days, or 0.30 gm. of atebtrin per diem also for seven days (adult doses).

The action of the two drugs on acute clinical symptoms appears to be equally rapid in the case of benign tertian, but is slower in the case of malignant tertian, the various strains sometimes showing considerable deficiencies as regards their reaction to the drug. Splenomegaly appears to yield more readily to quinine than to atebtrin. But the reduction is more lasting when it has been obtained by means of the latter drug and where the population is exposed to frequent re-infection. The influence of atebtrin in preventing relapses is more marked than that of quinine, especially in the case of benign tertian and of certain strains of malignant tertian.

There is no good reason to suppose that quinine treatment can retard the immunisation process, with the doses and methods adopted in these experiments; the action of atebtrin on that process has, on the other hand, not yet been completely clarified.

Plasmoquine should never be used alone; in combination with quinine or atebtrin, it has a marked action in preventing relapses, especially of benign tertian, while small doses of 0.02 gm. per diem appear to be readily tolerated. No ill-effects need be feared from the simultaneous use of quinine and plasmoquine, but if it is desired to use atebtrin and plasmoquine, it appears to be preferable not to administer the latter drug until the atebtrin treatment has been completed.

As regards *collective treatment*, atebtrin used in daily doses of 0.30 gm. (for adults) for five or seven days has the same effect as

¹ "The Treatment of Malaria: Fourth General Report of the Malaria Commission." *Bull. Health Org.*, 1937, 6, 895.

quinine given in doses of 1-1.30 grm. per diem for five, seven or a greater number of days. Apart from the financial considerations, there are no grounds for preferring one drug to the other. The conduct of collective treatment will depend upon the intensity of the endemic condition.

Collective treatment with quinine or atebtrin can be usefully accompanied or followed by treatment with plasmoquine, as this will tend to reduce the number of gametocytes and the risk of relapses.

There are, however, vast malarial regions, especially in the tropics, where collective treatment of this type cannot be carried out. In such cases, an effective and rapid treatment of clinical cases must be provided for and organised, in order to reduce morbidity, mortality and physical incapacity. Since medical supervision is often difficult, if not impossible, cinchona alkaloids appear to be indicated in such cases.

No method of *collective drug prophylaxis* will yield good results unless applied to disciplined groups of population placed under strict supervision. In this connection, the report recommends the use of daily doses of quinine (0.40 grm. throughout the period during which malaria is transmissible, and even for a few weeks thereafter) or of bi-weekly doses of atebtrin (from 0.20 to 0.40 grm. weekly) under certain conditions. The daily dose of 0.05 grm. of atebtrin suggested for prophylactic purposes proved inadequate. The harmlessness of quinine permits its administration by subordinate personnel without permanent medical control, but such control is essential in the case of atebtrin.

The use of plasmoquine for purposes of collective prophylaxis would only be justified in the case of a well-disciplined population for which medical assistance was constantly available, and with the particular object of preventing the transmission of the infection to the anopheles. The question of the dosage and method of administration of atebtrin and plasmoquine to children cannot be looked upon as definitely settled as yet.

Up to the present, experience has shown that *eradication by means of drugs* is, in practice, not to be hoped for. Apart from the impossibility of reaching all inhabitants in good time, it has proved impossible to kill all the parasites in every single carrier.

3. OPIUM

I. *Application of Articles 8 and 10 of the 1925 Geneva Convention and Article 11 of the Convention for the Limitation of Manufacture.*

(a) In accordance with the procedure laid down in the Conventions, the Health Committee submitted to the Office international d'Hygiène publique a request by the Advisory Committee on the Traffic in Opium that a new substance—desomorphine—should be placed under control (April 1937).

(b) In October 1935, the Health Committee had adopted a resolution to the effect that *preparations made from tincture or extract of Indian hemp* should be brought within the scope of the international Conventions. However, some Governments only accepted the resolution with certain reservations. The Committee accordingly considered that these reservations should be examined, in order if possible to restate its former decision in fuller and more detailed form and to secure the unanimous approval of the contracting parties. It therefore laid the reservations before the Permanent Committee of the Office (October 1937).

II. *Codeinism.*

As the Governments of Canada and the United States of America had drawn attention to certain cases of codeinism discovered in their territory in recent years, the Health Committee was requested, at the suggestion of those two countries, to include the problem of codeinism in its work. For this purpose, it consulted certain scientific institutions and psychiatric and pharmacological experts. It is also engaged on the preparation of a report based on a critical analysis of all that has been published on the question up to the present.¹ The results of this work will be placed at the disposal of the Advisory Committee on Traffic in Opium.

III. *Determination of the Morphine Content of Opium and the Cocaine Content of Coca Leaves.*

In 1930, the Health Committee was invited to have a standard method worked out for the determination of the morphine content

¹ See P. WOLFF : The Significance of Codeine as a Habit-forming Drug. *Bull. Health Org.*, 1938, 7, 546.

of raw opium, with a view to this method being adopted for the practical control of the manufacture of morphine. After study extending over three years, an expert Committee succeeded in establishing a procedure which is now known as the "international method". Since that time, the experts have carried on their work with a view to eliminating certain defects inherent in this method of assay, at the same time comparing it with other methods. They have also done similar work with regard to the cocaine content of coca leaves.

In October 1937, they placed on record the fact that methods of cocaine assay are now definitely fixed for both coca leaves and raw cocaine. So far as the morphine assay is concerned, they came to the conclusion that the international method,¹ notwithstanding such defects as may still attach to it, presents certain advantages over others so far known.

4. NUTRITION

The Technical Commission on Nutrition held its third session² in November 1937.

1. At its first two sessions, the Commission endeavoured to define, in the light of modern conceptions of physiology, what principles of nutrition would most suitably ensure the rational development and optimum maintenance of the organism. The result of its work was the "General Report on the Physiological Bases of Nutrition"³ published in September 1936.

At the end of the report, there appears a list of ten questions which the Commission recommended for further study :

- A. Assessment of the nutritional state of children.
- B. Nutritive food requirements during the first year of life.
- C. Minimum vitamin and mineral requirements.

¹ "Methods of assaying the Content of Morphine in Opium and of Cocaine in Raw Cocaine and in Coca Leaves." *Bull. Health Org.*, 1938, 7, 429.

² "Report by the Technical Commission on Nutrition on the Work of its Third Session." *Bull. Health Org.*, 1938, 7, 460.

³ "Report on the Physiological Bases of Nutrition." *Quart. Bull. Health Org.*, 1936, 5, 391.

D. Minimum fat requirements.

E. The nutritive and "supplementary" values of the different protein-containing foods, to determine to what extent and in what forms animal protein is necessary for growth and health.

F. The relative nutritive value of different cereals according to the degree of milling.

G. The extent to which the increasing consumption of sugar is detrimental to health.

H. Influence of climate on food requirements.

I. The extent to which diets in common use fall below the standards recommended in the report.

J. The optimum amount of milk required at different ages.

The Commission's report was communicated to the learned societies and scientific institutions of several countries with a view to securing their observations and their co-operation in the aforesaid studies.

2. The Technical Commission could obviously not hope to make a systematic frontal attack on all ten questions. It therefore concentrated its attention in 1936 and 1937 on the first five and the last.

(a) *Assessment of the Nutritional State of Children.*—In December 1936, a meeting was held of rapporteurs of the various Commissions working on this question on behalf of the learned societies and scientific institutions mentioned above. In their report,¹ they recommended three kinds of enquiries. The first of these is a general one and its object is to enable the state of nutrition of large numbers of children to be assessed; the two other types provide for more detailed and more elaborately scientific investigations on far fewer subjects—they involve somatometric, clinical and physiological tests, designed to detect the first signs of malnutrition at the earliest possible moment.

¹ "Report on the Work of the Group of Experts appointed to study Methods of assessing the State of Nutrition in Infants and Adolescents". *Bull. Health Org.*, 1937, 6, 129.

(b) *Nutritive Food Requirements during the First Year of Life.*—A similar method was employed in the study of this question. The rapporteurs also met in December 1936 and drew up a memorandum¹ containing recommendations on the diet suitable for infants.

The study of questions A and B thus led to the statement of conclusions by the national rapporteurs concerned. The Technical Commission at its session in November 1937 made various technical observations on these findings. It specially emphasised the need for continuing work on tests for pre-deficiency by the practical application of tests in as many instances as possible.

(c) *Minimum Vitamin and Mineral Requirements : Minimum Fat Requirements ; the Nutritive and Supplementary Values of the Different Protein-containing Foods.*—These three questions involved scientific problems falling within the exact scope of the Commission's first report. When the Commission met last November, it made a careful review of present-day knowledge of these questions and embodied its findings in the first four chapters of its new report. It came to the conclusion that it was essential to carry on the study of the factors influencing the utilisation of calcium and phosphorus, the proportion of assimilable iron in the various foodstuffs, the quantities of iron necessary for adults of both sexes (especially for women during pregnancy and lactation) and on the assimilation of iron by children.

(d) *Milk.*—At its November meeting, the Commission also reviewed the question of milk.

In the second half of 1936, the Health Committee had organised a special enquiry into the hygienic problems involved in the production and distribution of milk.² In addition, the Technical Commission had asked one of its members to submit a report on the *optimum amounts of milk required at different ages* (Question J).

Thus, the Technical Committee had to examine the whole of the milk question. In its " Report on the Physiological Bases of Nutrition ", the Commission has already fully defined its attitude to the question of the place which milk, on account of its special qualities, should occupy in a rational diet. Last November it endeavoured

¹ " The Nutritive Requirements during the First Year of Life." *Bull. Health Org.*, 1937, 6, 291.

² See " The Milk Problem ". *Bull. Health Org.*, 1937, 6, 371.

to show, in the light of recent research, why milk is a foodstuff of such paramount importance, especially during the period of growth. It also emphasised the necessity of eliminating the dangers of milk as a vehicle for bacterial infection. Lastly, it pointed out how skimmed milk might be turned to account.

3. The report of the Commission¹ contains its conclusions on the first five and the last of the questions on its programme of work ; the other four will be dealt with in subsequent studies.

Some remarks, however, should be made on questions H and I.

H. *Influence of Climate on Food Requirements.*

The Inter-Governmental Conference of Far-Eastern Countries on Rural Hygiene included the question of nutrition in the Far East on its agenda. The Technical Commission is also to undertake a study of nutrition amongst the peoples of Asia and tropical countries in general, in accordance with the desire expressed last year by the General Advisory Health Council.

The programme of subsequent work must therefore pay ever-increasing attention to countries in tropical and subtropical parts of the world. In November 1937, the Commission took note of the report of the Conference and drew up a preliminary programme of work to be carried out chiefly in the Far East. It will give this programme further consideration at its next session.

I. *The Extent to which Diets in Common Use fall below the Standards recommended in the Report.*

The study of this question has already been begun. To answer it with any degree of accuracy, it is essential to carry out dietary surveys with the object of gaining a clearer insight into actual nutritional conditions in urban and rural districts. If, however, the results of such surveys are to be comparable, there must first be agreement as to the method to be followed.

That is why, last November, the Commission set forth its conclusions as to the technical methods of carrying out investigations for the purpose of estimating actual consumption of foodstuffs.

¹ See " Report by the Technical Commission on Nutrition on the Work of its Third Session ". *Bull. Health Org.*, 1938, 7, 460.

A study of the food intake of urban and rural populations will therefore play a prominent part in the programme of work for 1938.

At their meeting in November 1937, the directors of the institutes and schools of hygiene in Europe made use of the general indications laid down for guidance by the Technical Commission to draw up the programme of the investigations they have agreed to undertake in the rural districts of their own countries. These investigations fall into three categories :

- (a) Quantitative studies for the determination of food requirements ;
- (b) Quantitative studies for the detection of any insufficiency in the diet of certain specified communities ;
- (c) Qualitative studies to serve as a basis for the elaboration of a nutritional policy.

So far, the National Nutrition Committees and the institutes and schools of hygiene in Belgium, Czechoslovakia, Finland, France, Hungary, Poland, Roumania, Sweden and Yugoslavia have intimated their intention to continue or to undertake enquiries of this kind. Czechoslovakia, Hungary and Yugoslavia have already made arrangements for the purpose. In January 1938, Miss H. K. STIEBELING, of the Department of Agriculture at Washington, visited these three countries on behalf of the Health Organisation, in order to assist the competent authorities in the organisation and co-ordination of the contemplated enquiries.

4. The last chapter of the Technical Commission's report deals with studies of *nutrition in Chile*.

It will be remembered that the Government of Chile had asked for the help of the League of Nations in order to study the state of nutrition of the lower and middle classes, and that Professor BURNET (France) and Professor DRAGONI (Italy) had visited Chile in 1935 on a study mission.

In June 1936, following the report drawn up by these experts, the Technical Commission drew up for the Chilean authorities, and at their own request, a series of recommendations as to the measures to be contemplated in order to improve conditions of national nutrition and to provide for the continuation of the enquiries.

Since that time, the Minister of Public Health of Chile has communicated the text of several decrees promulgated by the authorities of his country with the object of remedying the deficiencies which had been noticed and, in addition, the steps taken towards the co-ordination of subsequent studies. The Commission examined this plan of campaign with the greatest interest.

5. The foregoing is a very short summary of the present and future work of the Technical Commission on nutrition.

The Health Committee, when taking note of the report, emphasised the importance which it attached to the proposed study of nutrition in Asia and in tropical countries. Various measures are under consideration for the organisation and co-ordination of such work in the Far East.

The Committee is also giving careful attention to the investigations into the actual nutrition of rural communities, which are being undertaken in Europe with the co-operation of the institutes and schools of hygiene. These enquiries will furnish a technical basis for the work of the European Conference on Rural Life.

In this connection, the Committee has also decided to supplement these enquiries by comparative studies of the composition of bread. The various kinds of bread consumed, even in any single country, and *a fortiori* in different countries, often have, indeed, nothing in common but their name. Their nutritive value is therefore not comparable. In view of the part which bread plays in the diet of the rural population, the findings of these enquiries might prove quite valueless unless a preliminary study of the composition of the bread had been carried out.

The Health Committee has also decided to undertake work on the effect of foot-and-mouth-disease epidemics on rural economics and, in particular, on the production, distribution and consumption of milk.

Lastly, it considers that the time has come to embody in a general report the Technical's Commission's recommendations concerning the basis of a rational diet, projecting them on to the plane of practical application.

5. HOUSING

In August 1937, the Housing Commission published a first report on the hygiene of environmental conditions and noise and housing.¹

These two questions stood first on the programme of research drawn up by the Commission at the end of 1935, which covers the manifold problems involved by the hygiene of buildings and dwellings and of national, urban and rural planning; so that, when it has studied the various points by stages, the Commission hopes to be able to submit a series of conclusions on the subject of healthy urban and rural housing and healthy town and country areas.

The investigations are being conducted through the agency of the national committees which, at the Health Committee's request, have been set up in various countries.² The Housing Commission itself is merely a body representative of those national committees, being composed of their delegates. The status of the committees varies in different countries, but, whether they are official or unofficial, they are representative of all the persons and institutions in any way interested in the hygiene of housing.

In the national field, these bodies provide the necessary co-ordination, and endeavour to secure the practical application of technical progress in this direction. In the international sphere, they afford the most extensive and rational method of co-operation, the necessary liaison being provided by the Housing Commission. It would therefore be a good thing if similar bodies could be formed in countries where they do not as yet exist.

The Commission laid particular stress on the desirability of extending this form of co-operation to tropical countries, owing to the special problems involved in housing in those countries, and because housing is a very important factor in acclimatisation.

* * *

To revert to the two subjects dealt with by the Commission :

1. *The Hygiene of Environmental Conditions.*—The primary object of housing is to protect the individual from climatic discom-

¹ "The Hygiene of Housing." *Bull. Health Org.*, 1937, 6, 505.

² The United Kingdom, Czechoslovakia, France, the Netherlands, Poland, Sweden and the United States of America.

forts. The environmental conditions it provides must therefore be such as to ensure the maintenance of thermal equilibrium in the human body, and, from a more general standpoint, promote physical and mental fitness and a feeling of well-being.

The principal environmental factors are the temperature, humidity and movement of the air and the radiant temperature of the surroundings (walls, ceiling, flooring, windows, etc.).

Obviously, the optimum environmental conditions regulating the thermal exchanges of the human body must vary according to climate and the season. Different standards must therefore be established for each region:

The Commission's report accordingly aims at presenting a survey of the systems and processes available for heating, cooling, ventilating and conditioning the air, in the light of economic and physiological necessities and the circumstances peculiar to the climate in different parts of the world.

2. *Noise-abatement.*—A wide variety of processes is in existence for protecting a dwelling from noise, both external and internal, both air-borne and structure-borne. The Commission studies these processes and classifies them according to cost. Here, as in the case of environmental conditions, it is possible to establish, in the light of the experience of several countries, standards of noise which are considered desirable in flats and other residences, and also to define certain principles which should be observed to ensure that such standards of noise are not exceeded. Nevertheless, further research will be necessary with a view to the final determination of the standards in question.

The report contains a list of technical questions which are to be further investigated under the supervision of the national committees.

6. PHYSICAL FITNESS .

1. In placing on its programme the question of physical fitness, the Health Committee had in view investigations similar to those it is conducting in the sphere of housing and nutrition—that is to say, the defining of the physiological bases of rational physical training adapted to different ages. It consulted certain experts as to the selection of subjects for study and as to the lines on which these studies should be conducted (May 1937).

2. The experts emphasised the necessity for standardising methods for the objective appraisal of the effects of physical culture on the human body, from the somatic as well as from the psychological standpoint.

So far as methods of physical education are concerned, the experts considered that the primary object was that their application should be judiciously measured. The commission to be appointed should therefore attempt to determine the minimum amount of physical training required to ensure the normal health of the individual, as well as the maximum amount compatible with hard intellectual work.

In this connection, the experts drew attention to the disadvantages and dangers (physical, intellectual and psychological) of certain competitions calling for very intensive and exaggerated training. The important thing was not to produce champions, but to develop the physical fitness of the people along rational lines.

In order to achieve this object, the scientific bases of physical training must be determined. Although mass investigations carried out in certain countries by standardised methods may afford valuable scientific data, the experts pointed out the importance of research work in elucidating the complex problem of physical education.

As there are a great many institutions dealing with the different aspects—social, medical, educational—it would be desirable to set up national committees to co-ordinate the studies to be undertaken.

3. After the meeting, Dr. McSWINEY, Professor of Physiology at St. Thomas' Hospital, London, and Professor HANSEN, Director of the Physiological Institute, Copenhagen University, were requested to carry out a study tour which took them to Copenhagen, Lund, Amsterdam, The Hague, Paris, Warsaw, Rome, Vienna and Prague. The purpose of the tour was to supplement the recommendations adopted by the experts in May 1937 and to study the possibility of carrying those recommendations into effect in different countries.

4. Lastly, in order to complete this exploratory stage, the Committee requested Dr. WROCZYNSKI, Chief Medical Adviser to the Ministry of National Education, Warsaw, to draw up a report on the various factors influencing the maintenance of physical well-being.

This report¹ first examines the harmful aspects of our civilisation and the physical condition of the present generation. It then goes on to explore the relationship between physical condition and medical science, heredity and constitution.

The following part is devoted to an exhaustive examination of the methods of assessing physique, with special reference to anthropometric measures and medico-physiological methods. Lastly, an attempt is made to determine the various physical exercises suitable for children, for girls during puberty and adolescence and for adults.

In his conclusions, Dr. WROCZYNSKI shows that, considering the progress of civilisation, the physical defects of the population are still too numerous and too serious. In order to remedy this state of affairs, the life of the child must be completely changed; his conditions of life require to be rigidly controlled. He must have a suitable diet, sufficient sleep, freedom of movement, hygienic housing, sun, air and space. Up to the present, methods and systems of physical education have not produced any clearly demonstrable effect on the health of the masses, doubtless because the present state of our knowledge is not as yet sufficient to enable us to base them on accurate scientific data. Inordinate athletic ambitions are particularly harmful, and it is much to be deplored that the practice of sport should degenerate in this way.

5. The Health Committee then decided (February 1938) to go into the substance of this question and to apply the method which has proved so effective in the sphere of nutrition and housing—namely, to encourage the setting-up of national committees in different countries, whose representatives will form a commission on physical fitness.

7. ENQUIRY INTO THE RESULTS OF THE RADIOLOGICAL TREATMENT OF CANCER OF THE *Cervix Uteri*

This enquiry was organised in 1929 for the purpose of following up the results of the radiological treatment of cancer of the *cervix uteri* for at least five years after the last treatment.

¹ Dr. C. WROCZYNSKI: "Physique and Health." *Bull. Health Org.*, 1937, 6, 551.

The first report was issued in July 1937 (document C.H.1225). It is entitled "Annual Report on the Results of Radiotherapy in Cancer of the Uterine Cervix", and describes the clinical condition in 1936 of cases treated in 1930. This first report is naturally somewhat tentative, and the Committee in charge of the enquiry¹ intentionally confined it to data furnished by six clinics.

The second annual report is in course of preparation. It will take account of the experience acquired as a result of the publication of the first report and will cover more clinics.²

The main object of the Committee in charge of the enquiry is to provide a uniform statistical presentation of the results, so that conclusions may subsequently be reached as to the value of the different methods of treatment. To enable clinicians to classify the different varieties and stages of cancer of the *cervix uteri* according to the same standards, the Committee has prepared a pamphlet illustrating the main anatomico-clinical varieties of this type of neoplasm. This document, entitled "Atlas illustrating the Division of Cancer of the Uterine Cervix into Four Stages",³ was published in March 1938 and has been sent to all gynæcological and radiological clinics which may be able to assist in the enquiry.

8. TEACHING OF HYGIENE

In 1924, the Health Committee set up a Commission on Education in Hygiene and Preventive Medicine under the chairmanship

¹ Professor HEYMAN (Sweden), Professor LACASSAGNE (France) and Colonel SMALLMAN (United Kingdom).

² This report includes statements of results obtained in 1931 and previous years (collated in 1937).

The following clinics have contributed to the report :

- (a) Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York ;
- (b) Women's Hospital of the State of New York ;
- (c) Centre des Tumeurs de l'Université de Bruxelles ;
- (d) The Liverpool Radium Institute ;
- (e) The " Marie Curie " Hospital, London ;
- (f) Radium Centre for Carcinoma of the Uterus, London County Council ;
- (g) L'Institut du Cancer, Paris ;
- (h) L'Institut du Radium de l'Université de Paris ;
- (i) Radiumhemmet, Stockholm.

³ Document C.H. /Cancer /67.

of the late Professor Léon BERNARD. The work of this Commission led to the publication, in 1930, of a report drawn up by Professor Carl PRAUSNITZ on the methods of teaching hygiene and on the institutions concerned in Germany, the United Kingdom, Czechoslovakia, France, Hungary, Poland and Yugoslavia.

In 1936, the Health Committee decided that the methods of instruction and the syllabus of these institutions should be studied for the purpose of bringing Professor PRAUSNITZ's report up to date. This task was entrusted to Professor W. W. JAMESON, Dean of the London School of Hygiene and Tropical Medicine, Professor G. PITTALUGA, former Director of the Madrid School of Hygiene, and Dr. A. STAMPAR, former Director of the Zagreb School of Hygiene.

Professor PRAUSNITZ's report dealt with newly established institutions. The new report¹ had to record changes during the past five years, particularly under the influence of the economic depression. These changes have affected the activities of the institutions themselves and their organic relations with the health administrations. For this reason, the report deals mainly with the factors influencing the development and work of the institutes and schools of hygiene. These factors are connected chiefly with the social and economic background of the country, local tradition and, to some extent, the influence exercised by the Health Organisation and the International Health Division of the Rockefeller Foundation. The report then gives a full description of the way in which schools of hygiene are organised, and makes general observations about the work of these schools (full-time health service, training of health staff, training in hygiene of medical students and graduates; relations between National Health Insurance institutions and the institutes and schools of hygiene). The institutes considered are those of the United Kingdom, Bulgaria, Czechoslovakia, France, Greece, Hungary, Italy, Poland, Roumania, Spain, Turkey and Yugoslavia.

Another report contains the recommendations² made by the directors of these institutes and schools with regard to the

¹ "Second General Report on Certain European Schools and Institutes of Hygiene." *Bull. Health Org.*, 1938, 7, 191.

² "Report on the Meeting of Directors of Institutes and Schools of Hygiene." *Bull. Health Org.*, 1938, 7, 169.

organisation and resources of the institutions, the various types, and their fundamental task—to promote the teaching of hygiene and to interest students in this subject.

Here it is necessary, not only to provide special teaching for future health officers, but also to give appropriate instruction to medical students who, as the practitioners of the future, will be responsible for the collaboration of the medical profession in health work and social insurance. This collaboration, which is essential everywhere, is of particular importance in rural areas, and special measures should be taken to attract and retain there a sufficient number of medical men.

The institutions in question should not only devote attention to teaching and research but should also endeavour to help in public health work and support educative propaganda.

Experience shows that practical courses of field work are an essential part of the training of health officers. They might be given in the health services, in the public health and social welfare agencies (health centres, public health clinics, etc., in rural areas, in towns and in industrial districts). It is therefore essential that the teaching staffs of institutes and schools of hygiene should be in direct touch, in one way or another, with the health services and the organisations engaged in health and social work. Whilst there are good reasons for the existence of the different types of institutes, which are designed to meet national requirements, it is highly desirable that both their special work and their syllabuses should be co-ordinated on international lines. Such co-ordination could be effected with the greatest advantage when the syllabuses are being drawn up. These should take account both of the developments of new methods and means of health protection and social welfare work and of the needs of the populations concerned.

They should be suited to the requirements of the various categories of personnel, and adapted to the circumstances arising out of the introduction of new measures of public assistance, social insurance, occupational welfare, etc.

Research should cover both independent research work of a purely scientific character and research work relating to the everyday problems of public health. One of the main tasks of institutes and schools of hygiene must be kept in mind—the collaboration they can and should furnish in the form of advice to, or work for,

health authorities and social insurance, assistance and welfare agencies.

One matter which calls for attention is the education of the public both by the schools acting either by themselves or in association with public authorities or private organisations.

Attention has already been drawn to the importance, from the international standpoint, of maintaining relations between the various institutes and schools. It would seem desirable that, on the one hand, there should be permanent liaison between them and, on the other, that regular meetings of their directors should be held under the auspices of the Health Organisation. It would be very useful if the Health Section would act as a centre for the receipt and distribution of documentary material, so that the different institutions might pool their experience.

This collaboration would be usefully strengthened, not only by the direct exchange of publications and scientific papers between the institutes themselves, but also by an interchange of professors.

The publication of a periodical concerning institutes and schools of hygiene might also be contemplated.

Lastly, the supervision of the health of students was discussed, and the Director of the Health Section was asked to collect information on this subject through the medium of a questionnaire addressed to the universities in the various countries. It would also be desirable to ascertain whether any teaching on individual and community hygiene is given to students who do not propose to enter the medical or allied professions.

9. MATERNAL AND INFANT WELFARE

The question of maternal mortality and morbidity being one of the items on the Health Committee's programme of work, it organised last year a collective study tour, which took place in August and September 1937.

Its object was to prepare a report dealing, on the one hand, with the organisation of maternal welfare services, and, on the other hand, with the causes of maternal mortality and morbidity.

The following experts took part in this study tour : Dr. Barbara MAC EWEN, who was responsible for the local enquiries into maternal

mortality undertaken on behalf of the Ministry of Health of the United Kingdom ; Dr. Gabrielle HENRY, of the Inter-departmental Social Insurance Fund of Seine and Seine-et-Oise ; Dr. Tibor PIEĽEK, Inspector of Child Welfare in Hungary ; and Dr. A. STAMPAR, expert attached to the Health Section.

The above experts shared between them the task of visiting the following countries : Austria, Czechoslovakia, Denmark, England and Scotland, Finland, France, Italy, Poland, Sweden, the Union of Soviet Socialist Republics and Yugoslavia. In each country, they carried out their investigations according to a programme laid down by the national administration.

Dr. G. HENRY is at present engaged on preparing the report, which, after a general descriptive section, enumerates the various economic and social factors influencing, in each of the countries visited, maternal and child welfare.

III. EPIDEMIOLOGICAL INTELLIGENCE SERVICE

There is no need to describe in detail here the organisation and working of the Epidemiological Intelligence Service, of which national health authorities have, throughout the last seventeen years, been both the suppliers of material and the recipients of information.

All these authorities receive both the annual and monthly *Epidemiological Reports* and the *Weekly Epidemiological Record*. In addition, some of them exchange weekly information by telegraph or radio with the Singapore Bureau, which is the Section's Eastern branch.

We shall merely refer here to a few notable events and to the changes introduced during the past year in the working of the Service and in its publications.

1. *Singapore Bureau*.—In addition to its normal work, intensified by reason of the military operations in the Far East and the resultant epidemiological repercussions, the Eastern Bureau has, in accordance with the decisions of its Advisory Council, carried out investigations into current health problems such as the prevention of

epidemics of smallpox on board ship and the prevention of the transmission of cholera by aircraft. It has also collaborated with health administrations in the East in work undertaken by the latter as a result of the decisions of the Bandoeng Rural Hygiene Conference, especially in connection with health surveys, whether general or confined to certain diseases such as tuberculosis.

New or increased financial subsidies to the Singapore Bureau (from Australia, Burma, French Indo-China and New Zealand) have brought evidence of the interest taken by numerous countries in the Bureau's work.

Efforts have been undertaken to diminish the expense incurred by the Bureau in cabling its epidemiological bulletin every week to a number of health administrations who, for technical reasons, are unable to pick up the broadcast of the bulletin, which is transmitted by nine wireless stations in the East, regularly and free of charge.

In conjunction with the Transit Section of the Secretariat, an enquiry is at present being made among those health administrations (Aden, South Africa, Australia, Egypt, Iran, Seychelles, Somaliland and the Anglo-Egyptian Sudan) to determine whether they would be able to pick up a new broadcast transmission by directional short waves, from the League's own Radio-Nations station at Geneva.

2. No appreciable change has taken place in the work of the Geneva Epidemiological Intelligence Service ; nevertheless, certain alterations in the form of its publications deserve mention.

A return to monthly issues of the *Epidemiological Report*, inaugurated in 1937, led to the abandonment, in April 1938, of the regular publication in the *Weekly Epidemiological Record*—in the uncoordinated form in which they are received—of certain data on pestilential diseases which are not transmitted telegraphically.

These fragmentary data have now been replaced by notes on current epidemics of special importance, or on recent developments in connection with certain contagious diseases in one or more regions of the world.

In this way, the reader is spared the difficulty he might otherwise have experienced in judging whether the facts reported are normal or exceptional.

On the other hand, complete statistical series are to be found in the tables contained in the *Monthly Epidemiological Report*, while reference can be made to recent information contained in the weekly *Record* by means of an index which is now kept constantly up to date. This new method of presentation ensures that no duplication subsists as between the various epidemiological publications.

Attention should also be drawn to certain changes made in the *Annual Epidemiological Report*, such as : international tables of specific mortality by age and sex, and of standardised mortality rates ; tables of recent mortality figures classified according to the different causes of death enumerated in the abridged international list.

As the staff of the Epidemiological Intelligence Service has had to give up a considerable proportion of its time to the preparation of the forthcoming revision of nomenclatures of diseases, the preparation of purely epidemiological studies has necessarily been hampered. The following studies are, however, at present in course of preparation : Brucellosis in France,¹ spirochetosis ictero-hæmorrhagica, and, in addition, a number of statistical and epidemiological articles on tuberculosis, typhoid fever, brucellosis and general mortality in rural districts.

3. *Fifth Decennial Revision of the Nomenclature of Diseases.*—It will be recalled that, in 1929, the fourth decennial revision of the international lists of diseases was prepared by a Mixed Commission set up for the purpose by the International Statistical Institute and the Health Organisation of the League.

The valuable technical work done by this Mixed Commission led to a strong recommendation by the Fourth International Revision Conference, in the Protocol attached to the Nomenclatures Convention of October 16th, 1929, that the same body should remain in charge of the technical preparation of subsequent decennial revisions.

¹ R. M. TAYLOR, M. LISBONNE, L. F. VIDAL & R. H. HAZEMANN : " Investigations on Undulant Fever in France ". *Bull. Health Org.*, 1938, 7, 503.

The Mixed Commission has accordingly been reconstituted and slightly enlarged, with the following membership :

Members appointed by the International Statistical Institute :

Dr. L. DE BERARDINIS, Head of the Vital Statistics Department of the Central Statistical Institute of the Kingdom of Italy ;

Dr. A. BOHAC, Vice-President of the Czechoslovak Statistical Office ;

M. BRUSCHWEILER, Director of the Swiss Federal Statistics Bureau ;

Dr. BURGDÖRFER, Director of the Reich Statistical Bureau ;

M. M. HUBER, Honorary Director of the French *Statistique générale* and Vice-President of the International Statistical Institute ;

Dr. N. M. JOSEPHUS JITTA, President of the Netherlands Health Council.

Members appointed by the League Health Organisation :

Mlle Julie BACKER, Head of the Norwegian Bureau for Vital Statistics ;

Professor HAVEN EMERSON, President of the Nomenclatures Committee of the American Public Health Association ;

Dr. KACPRZAK, Head of the Polish Service of Health Statistics ;

Dr. S. MANUILA, Director of the Roumanian Central Statistical Institute.

Sir Percival VIVIAN, Registrar-General for England ;

One representative of the Health Statistics Services of the Union of Soviet Socialist Republics (not yet appointed).

As in the past, the French Government has consulted the Governments of the other countries as to their wishes in the matter of nomenclatures, and the French *Statistique générale* has acted as a clearing-house and as an agent for transmitting suggestions originating in the various countries to the Secretariat of the Mixed Commission. Twenty-three countries have forwarded suggestions—namely: Australia, Austria, Belgium, Brazil, Canada, Chile, Curaçao, Czechoslovakia, Denmark, the Dominican Republic, the United Kingdom, Estonia, Germany, Hungary, Italy, Japan, Mexico, the Netherlands, New Zealand, Norway, Sweden, Turkey and the United States of America.

Twelve further countries (Bulgaria, Egypt, Ireland, Latvia, Lithuania, Luxemburg, Panama, Poland, Portugal, San Salvador, Switzerland and Yugoslavia) have indicated that they have no proposals to submit for amending the existing nomenclature.

The revision proposals, collated by the Mixed Commission's Secretariat and analysed in a general report drawn up on behalf of the Commission by M. Michel HUBER, Vice-President of the International Statistical Institute, and by Dr. BIRAUD, of the Health Section, deal, *inter alia*, with the following points: detailed, intermediary and abridged lists of causes of death; lists of causes of infant mortality and morbidity; form of death certificates and rules for the statistical allocation of deaths due to concurrent causes; age-groups in published statistics.

Apart from the work of detail involved in bringing the existing nomenclatures up to date in the light of present medical knowledge, the proposals submitted deal particularly with the rearrangement of the following groups:

- (a) Infectious and parasitic diseases, on an ætiological basis;
- (b) Deaths due to cancer;
- (c) Deaths in childbed, with the object of excluding deaths due to sequelæ of abortion;
- (d) Deaths due to digestive disorders in children;
- (e) Deaths due to accidents.

The Mixed Commission will meet in Paris from May 2nd to May 5th and, in the light of the documentation received, will prepare drafts of new nomenclatures for submission to the fifth International Revision Conference, convened, through the agency of the French Government, for October 3rd next in Paris.

The revised nomenclatures are to come into force on January 1st, 1940.

IV. ANTI-EPIDEMIC ACTION IN CHINA

1. In September last, the Chinese Government informed the League Council that it would not be practicable to carry out the normal programme of technical collaboration between the League

and China in matters of general reconstruction, as originally proposed for the year 1938, and requested that technical assistance should be given to Government departments in the prevention and control of epidemics and the general relief of the civilian population and refugees.¹

Accordingly, the League Assembly, considering the possibilities of the spread of epidemic disease, not only within Chinese territory, but also across frontiers and overseas, voted in October last a maximum, non-recurrent appropriation of two million Swiss francs for the execution of an anti-epidemic campaign, adapted, as regards geographical area and methods of action, to the needs of the situation. Acting on instructions received from the Council, a special sub-committee of the Health Committee drew up a technical scheme, based on the following principles :²

(a) The appropriation of two million francs should not entail, directly or indirectly, expenditure in excess of this sum ; consequently, a reserve of 350,000 francs was provided for ;

(b) The Chinese authorities themselves would assume responsibility for the execution of the plan, which has as its sole object the reinforcement of the technical collaboration already existing in view of the unexpected and exceptional circumstances, or, in other words, to advise and support the competent Chinese technical services ;

(c) Epidemiological and medical officers and organisers of wide experience, grouped in three units, and provided with adequate sanitary material, should be sent without delay, organised with sufficient elasticity and mobility to meet the circumstances ;

(d) Action cannot be based solely on prophylactic intervention ; provision must be made for the isolation of infectious cases, their observation and facilities for accurate diagnosis ;

(e) In addition, therefore, to the despatch of mobile units, adequately staffed and provided with the necessary technical equipment and emergency supplies, there should be created a general sanitary and medical stock, on which the units would

¹ See document A.73.1937 (October 1st).

² See document C.524.M.363.1937.X.

draw, and additional supplies be taken for organising out of local resources the means for isolation and observation of the sick ;

(f) On the termination of the scheme, the material and equipment placed at the experts' disposal would become the absolute property of the Chinese Government, without implying any direct or indirect League responsibility for the future ;

(g) It is essential to establish in China an Epidemic Commission, consisting of the head of the Chinese Health Administration, of the Technical Adviser of the League of Nations to that Administration, and of the three Epidemic Commissioners. This Commission would ensure the necessary co-ordination between the component elements of the Health Mission of the League as well as between the three Commissioners, the Chinese Administration and the League's Technical Adviser, and would report periodically to the League Secretariat.

2. The epidemic situation in China at the time of the above decision is outlined in document C.H.1264, dated October 11th, 1937 ; while conditions at the beginning of the year are set out in document C.H.1313, dated January 26th, 1938.

Plague, typhus and smallpox in the north-west, cholera and dysentery in the centre and south-west, seem to have made their appearance in isolated foci earlier than usual.

3. The three units reached Hong-Kong early in 1938, and are at present stationed in three widely separated regions. Each unit is now supplied with its operating material and the necessary touring cars and light lorries. The general stock was due to arrive at Hong-Kong in April.

Unit No. 1.—The staff of this unit, headed by Dr. MOOSER (Swiss), Professor of Hygiene and Bacteriology at Zurich University, whose studies in typhus in Mexico are well known, includes Dr. JETTMAR (Austrian), Assistant Professor at the University of Vienna, who, for many years, studied plague in various parts of China ; Dr. H. WINZELER (Swiss), former Assistant at the Medical and Surgical Clinic and at the Institute of Hygiene, Zurich, and Medical Officer to the International Himalaya Expedition ; M. E. ETTER (Swiss), engineer, who was in charge of railway construction and supervision

of personnel in Persia. M. LANDAUER, Sanitary Engineer (Austrian), who was already in China, has been attached to this unit. Their headquarters are in Sianfu, the capital of Shensi, with a Production Laboratory at Lanchow (capital of Kansu) and branches at Tungkwan (Honan) and Yen-an (Shensi).

Unit No. 2 (Central China Epidemic Prevention Unit).—Led by Dr. R. C. ROBERTSON (British), Director of the Division of Pathology at the Henry Lester Institute, Shanghai, the staff of this unit consists of Dr. HAWES, former Assistant at the Aldershot Military Hospital for Infectious Diseases; Dr. POLLITZER (Austrian), who has dealt with plague and cholera epidemics in China for many years. Dr. ROBERTSON is also being assisted by Chinese medical officers from the Lester Institute at Shanghai. Their headquarters are at Changsha (capital of Hunan), with branches at Hankow (Hupeh), Changteh (Hunan) and Nanchang (Kiangsi).

Unit No. 3.—Under the leadership of Médecin-Général Dr. A. LASNET, this unit includes Dr. LAIGRET, of the Institut Pasteur at Tunis; Dr. P. DOROLLE, Director of the Hanoi Municipal Health Service; and Dr. MAUCLAIRE, as administrator to the unit. Dr. OU LI-KOU, of the Chinese Health Administration, is also assisting Dr. LASNET. The headquarters of the unit is at Nanning (Kwangsi), with branches at Nianing (production laboratory) and at Canton.

4. All three units are incorporated in the Chinese Health Administration, with a Chinese Health Commissioner attached as Government delegate to each, ensuring liaison with the provincial authorities. In addition to its foreign staff, each unit has engaged a Chinese operating staff, nominated by the Chinese authorities, composed of medical officers, technicians, sanitary inspectors, clerical staff and chauffeurs.

5. In the three areas, the Chinese Government has set up an anti-epidemic organisation composed of numerous sanitary units, staffed by personnel from the Chinese public health service, the Chinese Red Cross and officers of the Army Medical Corps placed at the disposal of the provincial authorities. The existing production and diagnostic laboratories are being utilised in this action, reinforced in many instances by the technical staff and the sanitary material

of the units. Whenever practicable, full use is being made of existing isolation hospitals, rural health centres and provincial as well as prefectural health units of all types.

The general principle governing the action of the three Commissioners is to utilise their relatively brief stay in China to strengthen the National Health Administration in its various branches and to reinforce its capacity to meet the present emergency and the impending extension of epidemics.

6. All three units have started the production of anti-cholera vaccines, units 1 and 3 of smallpox lymph, unit 3 the anti-typhus vaccine of the Laigret type. Unit 1 is equipped for the production of the Weigl type of typhus vaccine. Large stocks of smallpox lymph, both ordinary and dried, have been purchased out of the League credit and are being used on a large scale by the Commissioners, utilising the full machinery described above for the purpose.

Camps containing thousands of refugees represent a special care, particularly for units 1 and 2 ; the former having in particular to provide, or improvise, emergency and delousing stations. Isolation hospitals and isolation facilities are being rapidly co-ordinated or organised in all three areas.

Local medical missionary hospitals, International Red Cross missions and the International Refugee Relief Committee are in close co-operation with the League units : in certain cases, these organisations are carrying out medical relief and sometimes isolation of infectious cases among the refugees under the care of the units, while the latter's foreign technical staff advise the missions and take care of anti-epidemic organisation in the camps. Labour camps in cities and working in the field in all three areas are also under the surveillance of the units.

7. Unit 1 has already had to deal with outbreaks of typhus, and its Swiss sanitary engineer contracted this disease, but fortunately is now on the way to recovery.

Unit 2 has, since February, had to cope with several outbreaks of cholera and is already facing serious malaria problems.

Unit 3 is energetically preparing for epidemics of acute intestinal disease as well as with malaria, which is particularly apprehended in the area covered by its activities.

8. The Epidemic Commission has held two meetings, in order to discuss the location of the units, the principles and methods of the field work, and to consider the epidemic situation, the question of handling supplies, and finance matters.

The Chinese Government has placed a lump sum of 160,000 Chinese dollars at the disposal of the Epidemic Commission as a special epidemic grant.

The Lord Mayor's China Appeal Fund in London has provided supplies at the discretion of the Epidemic Commissioner of the Central China Epidemic Prevention Unit. It is hoped similar facilities may be provided in the two other areas.

The Danish Government and Danish Red Cross have offered large supplies of diphtheria and tetanus anti-toxin. The Netherlands and Netherlands East Indies Governments have each opened a credit of 25,000 florins for the purpose of assisting the anti-epidemic work in China ; and the French Government's Bill, providing 4 million francs to reinforce the action of the League epidemic units, has been voted by the Chamber of Deputies and awaits the vote of the Senate.

The British and French shipping companies are giving special facilities for the shipping of supplies.

Certain supplies can still be purchased in Hong-Kong and even locally at some of the larger towns in the three areas. Foodstuffs, milk, dried milk, vitamins are badly needed, also medical hospital stores of all kinds and hospital equipment.

TECHNICAL COMMISSION ON NUTRITION

REPORT BY A SPECIAL COMMITTEE WHICH MET IN GENEVA
FROM AUGUST 22ND TO 24TH, 1938.

On the invitation of the Health Committee, a Sub-Committee of the Technical Commission was convened under the Chairmanship of Sir Edward MELLANBY, F.R.S., Secretary-General of the Medical Research Council, London, with the participation of :

Dr. W. R. AYKROYD, Director of the Nutrition Research Laboratories, Coonoor, India ;

Dr. Ed. J. BIGWOOD, Professor of Physiology at the University of Brussels :

Dr. Lela E. BOOHER, Chief of the Foods and Nutrition Division, Bureau of Home Economics, U.S. Department of Agriculture, Washington ;

Dr. H. CHICK, Head of the Division of Nutrition, Lister Institute, London ;

Dr. L. S. FRIDERICIA, Professor of Hygiene at the University of Copenhagen ;

Dr. A. MAYER, Professor at the Collège de France, Paris ;

Sir J. Boyd ORR, F.R.S., Director of the Rowett Institute of Animal Nutrition, Aberdeen ;

Observer :

Dr. W. Ph. KENNEDY, Professor of Physiology, Royal College of Medicine, Baghdad.

* * *

INTRODUCTION

The activity of the Technical Commission is centring this year upon some of the questions included in its original programme of work¹—namely :

F. The relative nutritive value of different cereals according to the degree of milling.

H. Influence of climate on food requirements.

¹ For further reference to the Commission's programme of work, see the introduction to the report on its third session : *Bulletin of the Health Organisation*, 1938, 7, 461.

I. The extent to which diets in common use fall below the standards recommended in the Report on the Physiological Bases of Nutrition.

All these problems are interdependent.

1. In the report on its November session, the Commission dealt with nutrition surveys in some detail. As bread plays a prominent part in the nutrition of many groups of population, particularly in rural areas, and since the preliminary study carried out by Miss Hazel STIEBELING showed how greatly the composition of bread varied, not only in the rural regions of Europe from country to country, but even within the same region, a special study on the composition and preparation of bread was considered indispensable by the Health Committee, in order to permit useful comparisons to be drawn from the surveys carried out in different countries.

Such an investigation is at present being conducted in a number of European countries by Miss E. J. McDUGALL, D.Sc., formerly of the Imperial Bureau of Animal Nutrition, Rowett Institute, Aberdeen, and of the Basle Institute of Physiology.

The Sub-Committee noted with interest the progress report of Miss McDUGALL and will consider the question again in its various aspects at a subsequent meeting, in the light of the full report and other information.

2. The conclusions and recommendations presented by the Technical Commission in its different reports have been based mainly on the findings of research carried out in Europe and the United States. The Commission last autumn considered the report and recommendations regarding nutrition made by the Inter-Governmental Conference of Far-Eastern Countries on Rural Hygiene, held in Bandoeng in August 1937, and made a series of recommendations for the co-ordination of such work in the Far East as well as for providing liaison with the Technical Commission—this in pursuance of the Assembly's resolution in 1937 adopted on the recommendation of the League's General Advisory Health Council, covering all geographic areas in which economic, climatic and soil conditions did not permit of the supply or local production of foods adequate for the maintenance of optimal nutrition, particularly in many areas where the density of the population was considerable.

3. The " influence of climate on food requirements " is clearly a problem for inclusion in the above studies.

The Sub-Committee expressed the opinion that the collaboration of experts should be obtained in the analysis of existing literature on the influence of climatic factors on the physiology of nutrition. It requested its Chairman to suggest to the Health Committee the names of suitable experts for this purpose.

The presence at the meeting of Dr. W. R. ΑΥΚΡΟΥΔ, Director of the Nutrition Research Laboratories at Coonoor, enabled the Sub-Committee to learn of the arrangements now being negotiated with the competent authorities in India, whereby these laboratories might act as a centre of liaison both between Far-Eastern countries and with the Technical Commission itself.

4. The Health Committee requested an advisory opinion concerning the feeling of refugees in countries where whole groups of the population are threatened with acute malnutrition, or with actual famine, under the critical conditions of the day. The Sub-Committee's advice on this subject is incorporated in its report.

5. The agenda of the meeting thus included :

1. Guiding principles for the study of diets and nutrition of populations.

2. Nutrition work in the Far East, tropical countries and colonial territories :

(a) The problem of dietary standards considered in relation to the standards drawn up by the Technical Commission ;

(b) Research work on nutrition in the Far East, carried out in accordance with the programme of studies recommended by the Technical Commission ;

(c) Collaboration of the Coonoor laboratories in the work of the Technical Commission ;

(d) Influence of climate on food requirements.

3. Advisory opinion for the Health Committee regarding the feeding of refugees.

4. Studies on cereals and bread.

5. Co-operation with National Nutrition Committees.

* * *

I. GUIDING PRINCIPLES FOR THE STUDY OF THE DIETS AND NUTRITION OF POPULATIONS

At its November session, the Technical Commission had already emphasised the value of making preliminary studies on the food consumption and on the nutritional state of the same human subjects, these two lines of investigation having often been conducted independently. The Commission presented a number of suggestions and recommendations with a view to facilitating trustworthy comparison of the results of such studies made in different countries.¹ Four types of study on food consumption were considered in some detail—nation-wide (first type) ; community or institution (second type) ; family (third type) ; and individual (fourth type). Indications were given as to collection and analysis of data, schedules for recording relative energy allowances and classification of foodstuffs. The Commission further took note of the three types of enquiry outlined by the experts for the assessment of the state of nutrition of infants and adolescents. The recommendations of the autumn session were made available for a Conference of Directors of Institutes and Schools of Hygiene of different European countries convened in Geneva later in the same month (November 1937) to consider, *inter alia*, a preparatory study which the several institutes were to undertake in advance, and for the benefit, of the proposed European Conference on Rural Life, to be held in July 1939. A further memorandum, adapted more particularly to the rural areas of certain European countries, was drawn up by that Conference, under the guidance of Professor FRIDERICIA and Dr. Hazel STIEBELING.

The first meeting of representatives of National Nutrition Committees, held in 1937, recommended that the League Secretariat and the International Labour Office should arrange for the preparation of a comprehensive " Guide-book " for nutrition surveys in regard to (a) food consumption and state of nutrition and (b) social and economic aspects. Professor Ed. J. BIGWOOD presented to the meeting of the Sub-Committee a draft of this " Guide-book ",

¹ See *Bulletin of the Health Organisation*, 1938, 7, 486.

dealing with questions under (a). After detailed consideration of this draft, it was recommended for the use of the National Nutrition Committees and other central national institutions in charge of nutritional surveys. It was recognised that the " Guide " would be found useful both in European and American countries and, with necessary adaptations, in Far-Eastern and tropical regions.

The final text of Professor BIGWOOD'S " Guide " will be published shortly and will be laid before the second periodic Conference of representatives of National Nutrition Committees, meeting in October 1938.

In the meantime, the Secretariat, through the good offices of the members of the Technical Commission on Nutrition and otherwise, has collected data on the state of nutrition of populations in rural regions of Europe, to form preparatory documentation for the 1939 Rural Life Conference. It was recognised that intensive investigations in many countries likely to take part in that Conference would be of great value, particularly if dietary surveys and the assessment of the state of nutrition were combined with data on the general conditions of public health. If such investigations were undertaken by some of the competent national institutions, members of the Technical Commission would be glad to place their experience at the disposal of investigators, and the Sub-Committee would be prepared to suggest to the Health Committee the name of one of its members for consultation with the participating institutes as to methods of study to be adopted. The Sub-Committee felt such study would constitute an important contribution to general knowledge and would therefore prove particularly useful to all countries interested in improving the nutritional standards of their populations.

II. NUTRITION WORK IN THE FAR EAST, TROPICAL COUNTRIES AND COLONIAL TERRITORIES

A. DIETARY STANDARDS

The Sub-Committee considers that, in general, the dietary requirements of the populations of Eastern and tropical countries are not essentially different from those of the races of Western civilisation. Further comparative studies of physiological differences

due to race and climate, and their possible bearing on food requirements, are indeed desirable, and it is recommended that the existing data be collated and a report prepared upon the subject. At the same time, however, it appears unlikely that such a study will disclose any such differences of racial physiology in this respect as will seriously modify the approach to the practical problems of nutrition in tropical countries.

The standards drawn up by the Technical Commission on Nutrition, considered in their physiological sense, are universally applicable and can be expressed in terms of the dietary habits of the various peoples. They represent the ultimate goal to be aimed at in all countries. At the present time, however, the diets of the vast majority of the populations of Eastern and tropical countries are grossly deficient when judged by these standards, which are obviously out of immediate reach. In these circumstances, it becomes necessary to set up some attainable goal for purposes of practical nutrition work. Recommendations for improvement must be so adjusted as to raise the existing level of diets to a degree which is not beyond the bounds of practical possibility and which, at all events, makes it less remote from the optimum standard.

B. RESEARCH WORK ON NUTRITION IN THE FAR EAST

(1) *Study.*

In the investigation and attack of the problem, it is first of all necessary to :

- (a) Investigate the nutritive value of local foodstuffs ;
- (b) Carry out surveys of the diet of population groups ; and
- (c) Study the state of nutrition and the incidence of diseases directly or indirectly due to dietary deficiencies.

Methods which may be followed in such investigations have been outlined in the Report of the Intergovernmental Conference of Far-Eastern Countries on Rural Hygiene (see document A.19.1937.3). The technique of dietary surveys is fully dealt with in Professor Bigwood's " Guide ", to which reference has been made above.

With regard to (a), institutions concerned with nutrition research which are fully equipped to carry out work of this nature have been

established in certain countries. Elsewhere, no such institutions exist, and other arrangements are necessary. In the case of colonial territories lacking complete facilities, advantage can be taken of laboratories in the home countries for the chemical analysis and biological assay of foodstuffs.

With regard to (b), the data obtained in dietary surveys should be calculated, not only in terms of food factors (calories, proteins, minerals, etc.), but also in terms of actual foodstuffs. Knowledge of the approximate quantities of the various foodstuffs composing the diets will be found of great value in defining the best line of advance in planning educational action, in demonstrating the agricultural developments necessary to improve nutrition, and generally in framing satisfactory nutrition policies.

With regard to (c), it is suggested that, when a virgin area is being studied, a rough investigation of the incidence of gross malnutrition and deficiency diseases in hospitals and dispensaries should be carried out as a first measure.

As the enquiry proceeds, the investigations should not be limited to pathological conditions which are a direct manifestation of deficient diet, but extended to cover the relation between malnutrition and the occurrence and severity of protozoal and entozoal diseases, such as ankylostomiasis, bilharzia, helminthiasis, malaria, etc. The possible rôle of defective diet in the incidence and spread of leprosy should likewise be kept in view.

(2) *Action.*

(a) Such investigations will serve to define the problem. The action called for may be of various kinds. For example, it may consist in encouraging the use of under-milled rice in place of highly-milled rice, in attempting to popularise red palm-oil as a source of vitamin A, in taking steps to remedy mineral deficiencies, or in many other measures demanded by local circumstances.

(b) *Feeding experiments.*—Feeding experiments on groups may be of great value in that they provide a striking object lesson of the effects of improved diet and may also serve to bring to light any inadequacies in the local diets.

Experiments of this nature on infants and children are specially to be recommended, in that these age-groups should be given

first consideration when attempts are being made to combat malnutrition.

Other groups which might suitably be the subjects of feeding experiments are expectant and nursing mothers, organised labour groups of various kinds, inmates of institutions, bodies of recruits, etc. While it is, of course, desirable that experiments of this kind should be carried out, using scientific methods (*e.g.*, control groups, statistical analysis, etc.), nevertheless information obtained by rough-and-ready methods of assessment may be of considerable value. In industrial groups, an improved state of nutrition may be reflected in an increased output of work.

(c) *The value of limited data in the present circumstances.*—It is advisable that the study of the problem of nutrition should be undertaken by experienced workers along scientific lines, as indicated above. Nevertheless, it must be emphasised that valuable contributions can be made by local medical officers who are prepared to devote attention to the subject. In existing circumstances, even limited data can often be used as a basis of practical action. Every encouragement should be given to medical officers and other competent workers in tropical and Eastern countries to make observations on their local problems in the field of nutrition.

(d) *Agriculture.*—Planned developments in agriculture are necessary to bring about the improvements in diet which investigation shows to be desirable. The agricultural situation in the various countries requires close examination from this standpoint, with the object of formulating an agricultural policy which will relate production to the nutritional requirements of the consumer. In some countries, largely concerned with the raising of cash crops for export, it may be necessary to adjust production to enable the population to grow locally various foodstuffs—*e.g.*, vegetables—of which they stand in need.

(e) *Fisheries.*—In coastal and other areas, the encouragement and development of fisheries may be an important means of raising the standard of nutrition. The Report of the Intergovernmental Conference on Far-Eastern Countries on Rural Hygiene points out that “ fish is a good supplement to diets largely composed of rice, supplying good protein and sometimes vitamin A. *Small* fish which are entirely consumed are a rich source of calcium and other

inorganic elements." Sea fish is a good source of iodine and may thus be of value in the prevention of goitre. Administrative authorities should pay special attention to methods of improving the supply and distribution of fish.

(f) *The distribution of vitamins in pure or concentrated form.*—In general, it should be the aim of nutrition policy to rely on natural foodstuffs and, as far as possible, on locally produced foodstuffs, for the improvement of diet. Circumstances may, however, arise in which certain groups may benefit from the distribution of vitamins in pure and concentrated form, provided these can be obtained cheaply in large quantities.

(g) *Yeast.*—Yeast is rich in nitrogenous elements and in the B group of vitamins; it is of particular value in correcting deficiencies in the diets of tropical and Eastern peoples, which are usually largely composed of cereals. Methods by which yeast rich in water-soluble vitamins can be produced cheaply on a large scale in such countries should be investigated. This question should be studied by research institutes in Europe and elsewhere which are already concerned with problems of fermentation.

(h) *Mineral elements.*—Similarly, mineral deficiencies can often be made good by natural foodstuffs. Nevertheless, the expedient of supplementing diets by mineral elements as such should be borne in mind. Calcium salts, iron, iodine, etc., can be supplied cheaply to school-children and other groups suffering from a deficiency of these elements. Such a measure may be financially feasible when expense forbids the supplying of milk or other valuable foods. For example, it has been shown that one of the most important defects of the poor rice-eater's diet is a deficiency of calcium. In such circumstances, the regular provision of a calcium salt will do something to raise standards of nutrition. The same measure may be effective in the case of peoples living on other staples—*e.g.*, tapioca—which are deficient in calcium.

While it may in certain circumstances be expedient to correct deficiencies by means of pure vitamins, mineral elements, or yeast, the fact that it is usually preferable to aim at the improvement of diets by suitable combinations of ordinary foodstuffs may again be emphasised.

(i) *Education.*—It is important that in each country all classes of the population should be given simple instruction in the ways and means of improving their diet. All public health and educational services and other agencies may be used for this purpose. Administrative and medical officers in tropical countries should be familiar with the problems of nutrition, and for this purpose it is essential that the subject be included in their training curriculum before appointment. It is also essential that agricultural officers should have a knowledge of the practical problems of human nutrition. This would enable those in authority to develop nutrition policies, educate the people on sound lines, deal effectively with nutrition problems as they arise, and, in general, keep their administrative practice abreast of advancing scientific knowledge.

C. COLLABORATION OF THE COONOR LABORATORIES IN THE WORK OF THE TECHNICAL COMMISSION

At its third session, November 1937, the Technical Commission proposed that a centre should be established in the Far East, in order that the Commission might be kept in touch with Far-Eastern activities. The Sub-Committee is glad to learn that an arrangement is now being negotiated with the competent authorities whereby the Coonor Laboratories, India, may act as a centre of liaison both between Far-Eastern countries and with the Technical Commission itself. The Sub-Committee hopes that these negotiations will reach a satisfactory conclusion.

III. ADVISORY OPINION FOR THE HEALTH COMMITTEE REGARDING THE FEEDING OF REFUGEES

The attention of the Sub-Committee was drawn to the fact that even in Europe there are, at the present time, circumstances so critical as to result in a severe shortage of foodstuffs, so that the nutrition problem has in this case become one of taking emergency measures against famine.

The Technical Commission on Nutrition has hitherto attempted the task of establishing the dietary standard which will ensure an

optimum degree of nutrition. It was hoped that in all countries there would follow a steady advance towards that goal. It is therefore deplorable and disheartening that, under present world conditions, members of the Commission should be confronted with the duty of advising expedients for alleviating sheer famine, and should be driven to devise emergency diets which are remote from the ideal.

The Sub-Committee recognises that the approach to the problem of famine relief must largely depend on local circumstances. The relation between the available funds and the numbers to be fed, the facilities for the transport and storage of food, the supply of fuel, and many other factors, must influence the measures to be taken. The situation may be so desperate that it is necessary to aim at the bare minimum that will maintain life at all, and in such circumstances the question of the relative superiority of this or that type of food may scarcely arise. Nevertheless, it should be recognised that diets of an extreme simplicity and cheapness can be devised which will maintain life and avoid severe malnutrition. The Sub-Committee feels that it can assist those concerned with famine relief by drawing up dietary schedules of this nature. The suggestions put forward may serve as a guide to organisations occupied with the problem in the field, in that they will roughly show how far present methods are on the right lines and indicate a plan of action which may be followed in so far as circumstances permit.

The diets put forward in the following schedule to meet famine conditions, while extremely simple and inexpensive, are nevertheless not grossly inadequate from a physiological point of view. They provide a basis which can be modified according to local circumstances. Great stress is laid on the supplements of cod-liver oil, yeast, and salt mixture ; these supply essential constituents in which extremely simplified diets, containing a small variety of foodstuffs, are often deficient.

SUGGESTED EMERGENCY DIETS FOR FAMINE RELIEF

Scheme 1.—Where a Sufficient Supply of Dried Skimmed-milk Powder¹ is available.

<i>Growing children</i>		<i>Notes</i>
Whole wheat	5 parts	These relative proportions of wheat to skimmed-milk powder to be maintained, although the amounts given will depend on the supplies available. To provide a diet of 2,000 calories for an adult would require about 500 g. of wheat and about 45 g. of skimmed milk powder.
Skimmed-milk powder	1 part	
Cod-liver oil	5 g. daily	
Salt (sodium chloride)	5 g. daily	
<i>Adults</i>		
Whole wheat	12 parts	These relative proportions of wheat to skimmed-milk powder to be maintained, although the amounts given will depend on the supplies available. To provide a diet of 2,000 calories for an adult would require about 500 g. of wheat and about 45 g. of skimmed milk powder.
Skimmed-milk powder	1 part	
Cod-liver oil	2 g. daily	
Salt	8 g. daily	

Scheme 2.—Where the Supply of Skimmed-milk Powder must be limited to Young Children.

<i>Growing children</i>		<i>Notes</i>
Whole wheat	8 parts	In the children's diet, the proportion of wheat to skimmed-milk to be maintained, the amounts given to depend on the supplies available.
Skimmed-milk powder	1 part	
Brewer's dried yeast	5 to 10 g. daily ²	
Cod-liver oil	2 to 5 g. daily ²	
Salt mixture (containing 4 parts sodium chloride to 1 part calcium carbonate)....		
	5 g. daily	
<i>Adults</i>		
Whole wheat alone.		
Brewer's dried yeast	10 g. daily	
Cod-liver oil	2 g. daily	
Salt mixture	10 g. daily	

1. *Provision of Anti-scorbutic Vitamin.*—The above diets provide no anti-scorbutic vitamin; this essential principle must be obtained from local supplies: from citrus fruits (oranges, lemons), if available, from potatoes, cabbage or other vegetables, even from sprouted grains or infusions of non-poisonous green leaves. Half an orange or lemon twice weekly will supply the requisite amount of anti-scorbutic principle.

2. *Infants.*—Infants under 6 months of age should be fed on whole milk if possible (reconstituted from dried or condensed milk when necessary) plus a

¹ NOTE.—*Condensed Milk:* If condensed skimmed-milk is used in the above diets in place of dried skimmed-milk powder, the above proportions must be suitably adjusted to provide the equivalent amount of milk solids.

² According to age.

small daily ration of 2 to 5 g. of cod-liver oil. If necessary, skimmed-milk powder may be substituted. In this case, the supplement of cod-liver oil is of special importance. The daily ration of anti-scorbutic material is also essential for the young infant ; 5 g. (or 1 teaspoonful) of fresh fruit juice (preferably orange or lemon) is a suitable daily dose.

3. *Fat.*—The above diets contain no significant amount of fat. It is desirable to add fat in such quantities as are available.

4. *Meat, Dried Legumes and Cereals*, other than wheat, if available, can be substituted in the above diets for an equivalent amount of wheat.

5. *Supplements of Cocoa and Sugar*, though not essential, are desirable, particularly in the case of children, as greatly increasing the palatability of such monotonous diets as the above.

SOME PRELIMINARY REMARKS ON THE QUESTION OF THE STANDARDISATION OF SMALLPOX VACCINE

By

J. ORSKOV, M.D.

(Staten Serum Institut, Copenhagen).

In a general way, it may be said to-day that it is possible to produce a standard vaccine, a vaccine with constant qualitative and quantitative properties. The relative constancy of such a vaccine could probably be realised by means of one of the different drying methods.

The practical aim such a standard vaccine should have is to help us in estimating the value of a given smallpox vaccine when used in practical prophylactic work. As regards the question of value, there are three main problems which interest us :

- (1) What is the percentage of takes when a given technique is used ?
- (2) What are the local and the general clinical reactions ?
- (3) What is the duration of the immunity obtained ?

Suppose we have produced a dermovaccine from a calf, tested it *ad mod. GROTH* intracutaneously on rabbits and found a titre, for instance, of 1 : 16,000 on the third day after inoculation, and suppose it gives nearly 100% of takes in children and discreet local and moderate general reactions with the technique which we use, experience has shown that another vaccine with the same previous history will give the same clinical results, if it has the same titre when tested intracutaneously in rabbits. The standard vaccine has a value here because rabbits, even of the same age and breed

and litter, can be rather different in their reaction to vaccine. (But already here we meet a difficulty, as I do not think there is any place where a dried vaccine has been tested for constancy over a long enough period, and the vaccines which, for instance, are frozen down change their virulence slowly during storage.) And experience has shown us, too, that a vaccine with another previous history may have the same titre, but be essentially different from the standard vaccine when the final test is made on a child. So we know enough to say that only vaccines of very nearly the same origin can be compared directly, and this is due to the qualitative differences vaccines exhibit according to the different ways in which they have been produced. A few illustrations may be given.

It is a well-known fact that a dermovaccine from a calf can be made much more virulent by passing through the skin of a rabbit, a procedure very much used in practical work. If we now compare such a calf-vaccine which has recently passed through a rabbit and a vaccine which has been passed for generations from calf to calf, they may have the same titre when tested intracutaneously on rabbits, but be rather different as to percentage of takes in children and also as to clinical reactions. Another of my own experiments showed the following : a smallpox vaccine produced from the infected livers of quite small rabbits had a very high titre when tested *ad mod.* GROTH, 1 : 1,000,000, but only gave 10% takes when tried cutaneously on children with a material diluted only 1 : 4. Some experiments of LEDINGHAM & McLEAN showed something similar. By cultivating a vaccine intracutaneously on rabbits, they could make the intracutaneous material more and more quantitatively virulent when tested intracutaneously, but the ability to infect the rabbits cutaneously was at the same time diminished.

Finally, I have been able to confirm the findings of LEVADITI, who showed that a non-encephalitogenic vaccine acquired the qualities of a neuropilic vaccine by passing through the chorioalantoid membrane of an egg. The above-mentioned liver vaccine never causes any clinically visible disease when injected intracerebrally into a rabbit, but if the vaccine passes through a chorioalantoid membrane it kills the rabbits inside 5 to 6 days, just like a neuropilic vaccine.

These examples must suffice to show that it will be necessary to have different standards for comparisons of vaccines of different origin.

As to which of the existing titration methods is to be preferred in a particular case, this will depend on the task to be performed. The intracutaneous rabbit test *ad mod.* GROTH is a very valuable one, but in special cases GUÉRIN's method, or one of the cornea methods, will be preferable. The assay on the chorioalantoid membrane can only be made with bacteriologically sterile material. The counting of elementary bodies in purified suspensions is difficult, and will at best only give us information as to the number of bodies, and cannot tell us whether they are active or non-active.

If we now ask what practical use we can make of a standardisation of a given vaccine, apart from showing another vaccine to be too weak for practical use, the standardisation will in most cases have only a very limited value. Suppose we find that a given vaccine has a titre five times higher than a standard vaccine which in practical work is found to be of a suitable strength using a given technique, we cannot always conclude that the vaccine can be diluted five times and give results in conformity with the standard vaccine, because the concentration of the vaccine material plays a great rôle, quite apart from the fact that most smallpox vaccines become less stable the more they are diluted. Experience has recently shown us that a dermo-calf vaccine which has a titre five times higher than the one necessary for an efficient vaccine will, with the technique we use, give results which are not clinically distinguishable from those attained with the standard vaccine. With vaccines produced in other ways and applied differently, the experience will probably be different.

Expressed quite shortly, my view on the question of the possibilities of smallpox vaccine standardisation in practical work is :

- (1) It is probably possible to produce a standard vaccine which is stable enough for practical use ;
 - (2) Only vaccines with very nearly the same previous history will be comparable ;
 - (3) The practical value of a standard vaccine will, for the present, in most cases be limited to determining a vaccine as being too weak for practical use.
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Authors are alone responsible for views expressed in signed articles.

I

REPORT ON THE MEETING OF SEROLOGISTS
OF THE PERMANENT COMMISSION
ON BIOLOGICAL STANDARDISATION¹

(Paris, October 19th to 22nd, 1938)

TRIBUTE TO THE MEMORY OF DR. CLAUS JENSEN

Since its last session, the Commission has suffered a grievous loss through the death, in January 1938, of Dr. Claus JENSEN. Claus JENSEN, who had been in charge of the Biological Standards Depart-

¹ The following were present :

- Dr. Th. MADSEN, Director of the State Serum Institute, Copenhagen
(Chairman) ; ~
Dr. Percival HARTLEY, Director of the Department of Biological Standards,
National Institute for Medical Research, Hampstead, London ;
Professor L. HIRSZFELD, Director of the Department of Bacteriology and
Experimental Medicine of the State Institute of Hygiene, Warsaw ;
Professor C. IONESCO-MIHAIESTI, Director of the Sera and Vaccine Institute
" Dr. I. Cantacuzino ", Bucharest ;
Professor Louis MARTIN, Director of the Pasteur Institute, Paris ;
Professor A. SORDELLI, Director of the Bacteriological Institute of the
National Department of Health, Buenos Aires.

Experts :

- Dr. E. GRASSET, the South African Institute for Medical Research, Johan-
nesburg ;
Dr. Johs. IPSEN, the State Serum Institute, Copenhagen ;

ment of the State Serum Institute of Copenhagen from the beginning, had displayed a high sense of professional duty and outstanding scientific ability. He was responsible for the preparation, preservation and distribution of the international standard sera, and applied himself with admirable efficiency to the discharge of these delicate functions. He strove unremittingly to improve methods of serum standardisation, as witness his notable piece of research work on the assay of diphtheria antitoxin by the intradermal route—a method whose possibilities he foresaw—and his investigations into poliomyelitis and the assay of convalescents' serum. The Permanent Commission on Biological Standardisation wishes to pay a last tribute to one of its most devoted collaborators.

1. TETANUS ANTITOXIN

The plan of work adopted by the Commission at Copenhagen in 1934,¹ and thereafter somewhat expanded, has been carried out in five laboratories. The relevant documentary material is appended (Annex 1).

As Dr. P. HARTLEY explained to the Commission, the research work conducted in the five laboratories as well as the observations of Miss M. LLEWELLYN SMITH (see Annexes 1 *a* and 1 *c*) have shown that the variations observed in the assays are due, not to any inherent lack of precision in the methods employed, but to qualitative differences alike in the toxins and in the antitoxins. Of the various factors which are apt to affect the precision of the assay, the toxin is the most important.

Dr. F. KAUFFMANN, the State Serum Institute, Copenhagen ;
 Professor E. LECLAINCHE, Director of the Office international des Épizooties, Paris (attended the meeting on October 21st) ;
 Dr. Margaret LLEWELLYN SMITH, the National Institute for Medical Research, Hampstead, London ;
 Professor M. WEINBERG, Pasteur Institute, Paris ;
 Mr. P. BRUCE WHITE, the National Institute for Medical Research, Hampstead, London.

Secretariat :

Dr. R. GAUTIER, Secretary to the Permanent Commission on Biological Standardisation.

¹ See *Quart. Bull. Health Org.*, 1935, 4, 8.

This being the case, two problems, one scientific and the other administrative, arise for consideration.

The solution of the scientific problem will call for further investigations into the nature and interaction of the reagents employed in titration.

The administrative aspect of the question was studied in the United Kingdom under the auspices of a committee presided over by Dr. HARTLEY and working under the Pharmacopœia Commission ; five tetanus antitoxins were sent to four British laboratories, which assayed them by their own routine methods. Twenty assays were thus made of each of these five antitoxins, ten different toxins being used ; at the same time, a considerable measure of variation was introduced in respect of the other factors likely to influence the result of the test (see Annex 1 e).

A statistical analysis of the results showed that in 99% of assays the range of variation lay between 73.5% and 136% of the true value. Consequently, even in the case of assays carried out under such widely different conditions—which, incidentally, reflect those of routine work—this range is not so great as to invalidate the administrative control of tetanus antitoxin by the methods at present employed. On the contrary, since the variation of titre to be expected is now known, control is facilitated, for any antitoxin with a titre between the given limits can be regarded as acceptable.

It should be noted that, as the Chairman pointed out, the range of variation found in the United Kingdom is of the same order of magnitude as that calculated by Dr. JOHNS. IPSEN (71%-141%) from the findings of the five laboratories which took part in the comparative assays under the Copenhagen plan (Annex 1 a).

In this connection, Professor C. IONESCU-MIHAIESTI referred to the experiments conducted at the Cantacuzène Institute by Dr. CONDREA with the object of replacing the *in vivo* assay by an *in vitro* method, using the flocculation of mixtures as indicator of neutralisation.

The flocculation method as currently used in certain laboratories for the assay of diphtheria antitoxin and toxoid is not applicable to the assay of tetanus antitoxin. The causes of error are thought to reside in the antigenic structure of the tetanus bacillus itself and in the presence of flagellar and somatic antigenic components in the toxin filtrates. To obviate these drawbacks, Dr. CONDREA has

ment of the State Serum Institute of Copenhagen from the beginning, had displayed a high sense of professional duty and outstanding scientific ability. He was responsible for the preparation, preservation and distribution of the international standard sera, and applied himself with admirable efficiency to the discharge of these delicate functions. He strove unremittingly to improve methods of serum standardisation, as witness his notable piece of research work on the assay of diphtheria antitoxin by the intradermal route—a method whose possibilities he foresaw—and his investigations into poliomyelitis and the assay of convalescents' serum. The Permanent Commission on Biological Standardisation wishes to pay a last tribute to one of its most devoted collaborators.

1. TETANUS ANTITOXIN

The plan of work adopted by the Commission at Copenhagen in 1934,¹ and thereafter somewhat expanded, has been carried out in five laboratories. The relevant documentary material is appended (Annex 1).

As Dr. P. HARTLEY explained to the Commission, the research work conducted in the five laboratories as well as the observations of Miss M. LLEWELLYN SMITH (see Annexes 1 *a* and 1 *c*) have shown that the variations observed in the assays are due, not to any inherent lack of precision in the methods employed, but to qualitative differences alike in the toxins and in the antitoxins. Of the various factors which are apt to affect the precision of the assay, the toxin is the most important.

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prepared toxins from aflagellate strains devoid of the somatic polysaccharide. These toxins consist of protein solutions, and are obtained by precipitation with ammonium sulphate.

Dr. Louis MARTIN considered that the lack of concordance nowadays observable in the assays of tetanus antitoxins was due to the fact that the toxins and antitoxins employed were much more active than they used to be. The documentary material collected showed that the method of preparing and preserving the toxin affected the result of the assay. This raised the question of the preparation of a standard test toxin which could be distributed to all laboratories by the Copenhagen Institute.

Dr. IPSEN said that the Copenhagen Institute would first of all like to ascertain whether, when toxins prepared from the same strain by the same method were used, the variations in titre were smaller than those observed when toxins prepared by different methods were employed. It would accordingly like to receive, from the various laboratories, tetanus toxins prepared by a specified method from a strain supplied ; it would use those toxins to assay antitoxins which had been credited with different qualities on the strength of previous tests.

Professor A. SORDELLI was of opinion that considerable importance should be attached, not only to the nature of the toxin, but also to the level at which the assay was performed.

Account must further be taken of the fact that the antitoxic values of the various antitetanus sera as assessed by the present-day method of assay ($L+ /5$ toxin-level) did not always coincide with their experimentally determined prophylactic or therapeutic values ; if, for example, the serum was injected intravenously and an appropriate dose of toxin was administered subcutaneously after one, two, five, or even twenty-four hours, then, if the level of assay laid down in the Rosenau and Copenhagen methods was adopted, one unit of the less avid serum might prove four times as active as one unit of the more avid serum.

The results of the assay of various tetanus antitoxins against different toxins can, moreover, be seen in Annex 1 *b*. In these circumstances, it might well be wondered how far the antitoxic unitage given on the ampoules really indicated the therapeutic or protective action which the serum was capable of exerting. It was true, however, that, since the sera supplied for use at the

present time consisted of mixtures of antitoxins some of greater and some of lesser avidity, the question was not one of practical moment.

The CHAIRMAN observed that Professor SORDELLI's views were corroborated by the conclusions which Dr. RASCH, the statistician of the Copenhagen Institute, and Dr. IPSEN had been able to draw from the extensive records of assay findings available in the Biological Standards Department. These investigations had shown the need for further research into the relationship between the level of the test and the results yielded.

To facilitate the study of this question—the importance of which was recognised by all the members of the Commission—Professor SORDELLI submitted an explanatory note and plan of research which appear in Annex 1 *f*.

In the course of the meeting, the representatives of the Buenos Aires, Copenhagen and Hampstead Institutes agreed to carry out tests to ascertain whether neutralisation of the toxin at the L+ /5 level really reflects the protective action of the sera as it can be experimentally determined, or whether the use of some other level of assay would furnish a more adequate criterion. Six sera will be selected, three of which yield readily dissociable, and three less readily dissociable combinations with toxin, and their antitoxic action will be determined on the guinea-pig by the American method. The quality of each of these sera will be ascertained by determining the dilution ratio and assaying at two different levels. For the assessment of the protective action, the method proposed by Professor SORDELLI will be adopted.

“ The Commission, after reviewing the results of the investigations carried out in accordance with the plan drawn up in 1934, and extended at an informal conference held at Copenhagen in 1936, has concluded that the discrepancies observed in the titration of tetanus antitoxin in different laboratories are intrinsic to the reagents and are in no way due to lack of precision of the methods employed.

“ The investigations have shown that tetanus antitoxin can be assayed with a high degree of precision, the standard deviation being of the order of 5%. The factor which exerts the greatest influence on the precision of the assay is the toxin used, the species of animal, the route of injection, the time of

contact of the mixture being of minor significance in affecting the precision of the assay.

“ When the same samples of tetanus antitoxin are assayed in different laboratories, however, the variation in the results obtained are considerably larger than can be reasonably ascribed to the errors inherent in the methods of assay adopted ; they are due to qualitative differences in tetanus toxins and antitoxins.

“ In view of the fact that the discrepancies referred to may have an important bearing on the administrative control of tetanus antitoxin exercised in different countries, the Commission took notice of the result of an investigation carried out with the object of determining the extent of the variation to be expected in the assay of tetanus antitoxins as carried out under present conditions of standardisation. In these investigations, no attempt was made to restrict, but rather to encourage the widest variations in reagents and techniques. The results of twenty different assays of five different tetanus antitoxins carried out in nine different laboratories, in which ten toxins, four different routes of injection, two species of animals, three different standards of reference and several different end-points were employed, were submitted to the Commission. The analysis of the results showed that the variation to be expected in 99% of assays even under such widely different conditions is between 73.5% and 136% of the true value. Administrative control can therefore be adjusted in accordance with these data.

“ The causes of these differences are still unknown, and the Commission accordingly decided that further investigation into the nature and properties of the reagents used, their mode of preparation and interaction should be undertaken, in order to obtain potency values of samples of tetanus antitoxins representing more accurately their clinical value.

“ So far as the investigations into the part played by the toxins are concerned, the Copenhagen Institute will ask various laboratories to prepare, from a strain supplied by it and by a specified method, toxins which it will use to assay tetanus antitoxins which have been shown by previous tests to possess different qualities.”

2. ANTI-SNAKE VENOM SERA

The research into anti-viper serum standardisation which the Commission decided to undertake in 1935, limiting the field of investigation to the sera against the venom of European viperidæ, has been carried out by the Copenhagen and Zagreb Institutes, working in close collaboration. As the outcome of these investigations (see Annex 2), a method of assay has been worked out. It has also been shown that anti-viper serum should be standardised in relation to the venom of *V. aspis* and *V. ammodytes*, and that a standard serum would have to be established and a standard venom used for each of these species.

For some years past, Dr. E. GRASSET has assayed the polyvalent anti-viper and anti-cobra serum supplied by the South African Institute for Medical Research against the monovalent anti-*Bitis arietans* and anti-*Cobra flava* standard sera. These sera were dried and then kept in the ice-box and protected from the light ; and their neutralising properties have remained unchanged for three years.

The differences observed in the various samples of venom obtained from the same species, which are sometimes considerable, led Dr. GRASSET to prepare standard venoms for *Bitis arietans* and *Cobra flava*, each consisting of a mixture of several hundred samples of venom taken at different times of the year from specimens coming from different regions ; these venoms have been dried, and are kept in the dark in closed vessels.

The experiments made with a view to the determination of the test dose have shown that, in order to eliminate individual differences between animals, at least 2.5 lethal doses are required, especially in the case of viper venom.

It is also well to make certain of using a sufficient number of animals per dose (six in the case of mice), especially if a proportion of 50% of survivals is taken as a criterion.

Shock phenomena, sometimes followed by death may be observed, especially in rabbits, immediately after an intravenous injection of sub-lethal doses of *Bitis* venom or mixtures of venom and serum. The frequency of such reactions may be reduced by increasing the volume injected and injecting very slowly. Such early deaths are apt to hamper the interpretation of the results of the assay unless

a sufficiently large number of animals is used. In order, therefore, to reduce the cost of the test and to save venom and serum, Dr. GRASSET, after using rabbits for several years, now assays on mice. He took as the unit of anti-*Bitis* potency the quantity of a monovalent serum selected as a standard, which, when mixed with four to five lethal doses of *Bitis* venom, protects 50% of the mice injected. The anti-cobra unit was determined by a similar method.

When the assay is performed with the same sample of venom, the results more or less agree ; but if other venoms obtained from the same zoological species are used, the differences in the determination of the test dose may be as high as 20%.

These experiments, and others carried out at the request of the South African Government Biological Control Laboratory show that it is necessary to use not only monovalent standard sera but also standard venoms, if the assay of anti-snake-venom sera is to be performed under the best possible conditions of accuracy.

Dr. IPSEN was also in favour of the use of a standard venom, arguing that if all experimenters used the same venom for assay purposes, it would be possible to express the potency of a serum in terms of the number of milligrammes of venom neutralised. In this way, the use of the vaguer criterion of lethal doses neutralised, as a means of expressing the strength, could be avoided. In the opinion of Professor SORDELLI, the anti-venom sera used against the bites of South American ophidians do not lend themselves to standardisation. In the case of *Bothrops alternata*, for instance, the antitoxic strength of the sera of various horses showed considerable variations when tested against the venom of different specimens of this species.¹

The experiments described in Annex 2 merely confirmed Dr. P. HARTLEY in his opinion that anti-snake-venom sera do not lend themselves to international standardisation, owing to the variability of all the different factors which influence the assay, particularly the venom. When, in analogous cases, measures of administrative control had had to be taken in the United Kingdom, the practice of laying down minimum requirements had been followed. This system might perhaps be applied in the case of anti-viper serum.

¹ See A. SORDELLI and G. PACELLA : " Consideraciones sobre la valoración del suero antiofídico ", *Rev. Soc. Argentina de Biol.*, 1927, 3, 472.

The CHAIRMAN pointed out, first, that this practice would not do away with the necessity of assessing the potency of the sera, and, secondly, that the degree of precision of the assays carried out at Copenhagen, Johannesburg and Zagreb was quite adequate. The main difficulty, at the moment, was how to accumulate a stock of venom possessing the necessary qualities.

“ The Commission,

“ After taking note of the results of the work on anti-viper-venom serum now proceeding at the Copenhagen and Zagreb Institutes ;

“ Recommends that the investigations which are being carried out with a view to the standardisation of the anti-venom sera should be continued with the collaboration of any other Institutes interested in this problem.”

3. ANTI-PNEUMOCOCCUS SERUM

A. ADVISABILITY OR OTHERWISE OF ADOPTING INTERNATIONAL STANDARDS FOR SERA OTHER THAN TYPES I AND II

In 1934, the Commission adopted international standards and units for anti-pneumococcus sera, types I and II. Since that time, considerable progress has been made in the serotherapy of pneumonia. Thirty-two types of pneumococcus have been identified, with the result that the type of causal agent can now be rapidly determined and the homologous serum administered. In the United States, standard sera have been placed at the disposal of the Committee which is dealing with the standardisation of anti-pneumococcus sera of types V, VII and VIII. The CHAIRMAN therefore asked whether the Commission considered that international standards ought to be adopted for the sera corresponding to those three types ; the method of specific protein determination advocated by GOODNER, HORSFALL and DUBOS might perhaps enable titration to be effected by chemical means.

Dr. HARTLEY said that the international standards for types I and II and the American standards for types V, VII and VIII all consisted of horse anti-sera ; but a movement was now on foot

among clinicians in favour of the therapeutic use of rabbit serum. It had to be considered whether such a serum could be assayed in relation to a standard horse serum ? Up to the present, sera for types of pneumococcus other than I and II had not been prepared in the United Kingdom. If, however, this should be done, considering the striking results obtained from their clinical use, standards would be necessary for their assay. In such a case, the standards in force in the United States for sera of types V, VII and VIII might, he thought, be adopted for national use. The method of chemical titration was very attractive, and it was to be hoped that it would eventually supplant the biological method ; but it might not be applicable to a serum that had been dried and then redissolved.

Dr. Louis MARTIN had been greatly struck by the progress made in the United States in the serotherapy of pneumonia ; the diagnosis centres set up for that purpose could determine the type of pathogenic agent in a few minutes, thus enabling treatment with the appropriate rabbit anti-serum to be begun without delay. That was an example which many European countries might follow ; at the present time, Denmark alone possessed an organised service, covering the whole country, for the identification of the type of agent and the administration of the appropriate serum.

“ In view of the rapid developments in the therapy of pneumococcus infections in man, in the production of specific anti-sera prepared in different species of animals, and in the methods of assay of the anti-sera, the Commission decided that, for the present, international standards for types of anti-pneumococcus serum other than types I and II should not be provided.”

B. REPLENISHMENT OF STOCKS OF ANTI-PNEUMOCOCCUS STANDARD SERUM FOR TYPES I AND II : MEASURES TAKEN FOR THIS PURPOSE

The demand having been much greater than had been foreseen, it became obvious by the end of 1935 that the stocks of standard anti-pneumococcus sera, types I and II, would soon need to be replenished. By agreement between Sir Henry DALE and Dr. MADSEN, Dr. HARTLEY was entrusted with the task of establishing a new international standard for sera of these two types.

For the purpose of determining the potency ratio between the present international standard and the new standard, solutions of both were sent for comparative assay to Dr. H. J. PARISH and Miss A. M. BROWN, of the Wellcome Physiological Laboratories, Beckenham ; to Dr. G. F. PETRIE, of the Lister Institute, Elstree ; and to Dr. WILSON SMITH, of the National Institute for Medical Research, Hampstead.

The results of their assays were submitted to Dr. J. W. TREVAN, of the Wellcome Physiological Laboratories, Beckenham, and to Dr. J. O. IRWIN, of the Department of Epidemiology and Vital Statistics of the London School of Hygiene and Tropical Medicine, for statistical analysis. They found that the titre of the new serum could be expressed by the weighted average of the results of all the assays ; that this means in practice that the new unit might be assigned a slightly different potency than the unit as at present defined.

The members of the Commission unanimously expressed their gratitude to Dr. HARTLEY and his collaborators for this fine piece of work.

As Professor A. SORDELLI observed, the titres obtained by the different laboratories vary considerably according to the method of assay employed ; the adoption of an average value would therefore be nothing more than a compromise.

Moreover, as Dr. HARTLEY pointed out, the stocks of the present standard of type I anti-pneumococcus serum held by the Copenhagen Institute will be sufficient, with proper economy, for another two or three years. In those circumstances, it might perhaps be advisable for the Commission, while duly noting that a new standard serum is available in case of need, to postpone the final adoption of that standard until later. In the meantime, work on the determination of the titre of this new standard in terms of the present standard could continue ; it would be helpful if the Washington Institute would be good enough to compare the new standard serum with the American national standard, and state whether the approximate titre of 1,000 units per c.c. provisionally assigned to this new preparation was, in its opinion, adequate.

“ In 1935, it was reported to the Commission that the quantities of the international standards for anti-pneumo-

coccus serum, type I and type II, available for international use were being depleted more rapidly than had been anticipated, and, consequently, the question of their replacement by other dry, stable preparations, assayed in terms of the present international standards, would have to be considered at an early date.

“ In accordance with arrangements made between the State Serum Institute, Copenhagen, and the National Institute for Medical Research, Hampstead, it was agreed, in 1935, that the latter Institute should provide adequate amounts of dry, stable preparations of these respective anti-sera with a view to their eventual adoption as international standards, when the supplies of the present standards are exhausted.

“ The Commission took notice that, in regard to the replacement of the present international standard for anti-pneumococcus serum, type I, the National Institute for Medical Research, Hampstead, had prepared a large quantity of a dry, stable preparation, and that a provisional estimate of the weight of this new preparation equivalent to one international unit had been made in three laboratories in England and at the State Serum Institute, Copenhagen.

“ The Commission recommended that a further study of the results of the comparative assays already obtained should be undertaken and, if possible, an estimate of the relative potencies of the two type I preparations should be made by the application of other methods of comparison.

“ It was reported to the Commission that, by the exercise of due economy, the quantities of the international standard for anti-pneumococcus serum, types I and II, still available are sufficient for international requirements for almost two years, and, accordingly it was recommended that decisions regarding the suitability of the new dry, stable preparation for use as a second international standard and, if deemed suitable, its evaluation in terms of the present international standard should be postponed.”

4. GAS-GANGRENE ANTITOXINS

(a) *Perfringens Antitoxin.*

During the past few years, Professor M. WEINBERG, of the Pasteur Institute, Paris, has published three articles¹ criticising the method adopted for assaying perfringens A antitoxin. His argument was based on the fact that considerable discrepancies have been observed in the relative titres of perfringens A antitoxin when different toxins are used for assaying these antitoxins on the mouse. This was a criticism levelled at the whole principle of the standardisation of antitoxins, and as such it could not be ignored by the Commission, especially since it was supported by the work of S. E. STEWART and J. M. CLAMPIT. The Commission was therefore very interested to hear Professor WEINBERG's account of the result of his investigations proceeding from the observation made a few years ago that the same vibriion septique antitoxin, when assayed against two toxins, was found to possess different antitoxin titres (see Annex 3 d).

The result of the assay of a specific serum—and particularly of perfringens A antitoxin—depends on three factors: the serum, the toxin and the test animal. This last-named factor hardly affects the issue if a sufficient number of mice are used for the experiment and the injections are made intravenously.

On the other hand, in Professor WEINBERG's opinion, great importance is attached to the antigenic make-up of the sample of toxin used, and to the quality of the standard serum, the specific antibody content of which may vary widely. It follows from this that, if comparable data regarding the assay of perfringens A antitoxin are to be obtained in all laboratories, the same standard serum and the same sample of toxin should be used.

Pending the discovery of a strain producing all the toxic antigens proper to *B. perfringens* A, the logical procedure, in preparing a toxin for the assay of perfringens antitoxins, would be to mix two or more toxins which, taken together, would constitute a standard test toxin.

¹ WEINBERG and GUILLAUMIE: "Titres apparents et titres réels des sérums antitoxiques", *C. R. Soc. Biol.*, 1936, 123, 661; "Titration des sérums antitoxiques", *C. R. Acad. Sc.*, 1927, 204, 1012, *C. R. Soc. Biol.*, 1937, 126, 657.

The antitoxin which is to serve as a standard should be prepared with this standard toxin, for it should contain antibodies which will neutralise all the antigens contained in the latter.

Every laboratory investigating gas-gangrene antitoxins should endeavour to prepare a standard toxin and a perfringens A antitoxin which is very rich in the principal antibodies. These standard toxins and antitoxins might be sent to all laboratories for comparative tests.

The main object of research should be to establish the curative titre of the serum, for this is what matters to the medical man. Moreover, it is highly probable that this curative titre will only coincide with the antitoxic titre in the case of sera prepared by means of bacilli whose action is exerted mainly through a highly potent exotoxin such, for instance, as *B. tetani* and *B. botulinus*.

Professor L. HIRSZFELD had been able to demonstrate that most strains of *B. perfringens* which are pathogenic to man and animals destroy the specific blood-group substances.

As regards their biochemical, hæmolytic or toxic action, there is no difference between strains which destroy the specific blood-groups substances and those which do not.

The ferments which break down these specific substances are secreted in the culture media, but are non-filterable; they are specifically neutralised by the immune sera.

Future investigations will show whether the principle of the neutralisation of these ferments can serve as a basis for a new method of assaying the serum, and whether the presence of antiferments is of therapeutic value.

Professor SORDELLI noted that Professor WEINBERG's research work on the assessment of the antitoxic potency of perfringens antitoxin had been beset by difficulties as great as those encountered in the case of tetanus antitoxin, if indeed they were not greater. At the same time, the comparative assays of three perfringens A antitoxins carried out in three laboratories with different toxins, had not produced discrepancies as great as those recorded by Professor WEINBERG. It would therefore be of vital importance for Professor WEINBERG to supply to the Copenhagen Institute, samples of the toxins with which the said discrepancies were obtained, in order that comparative tests might be undertaken in the laboratories of various countries. The criticisms he had advanced were

directed against a method of assay which had been internationally adopted, the investigations on the bases of which any modification of that method might ultimately be effected should hence also be carried out on international lines.

In reply to the CHAIRMAN's request for samples of his toxins and standard serum for purpose of comparative tests, Professor WEINBERG said that he would willingly hold at the disposal of his colleagues the standard antitoxin prepared in his laboratory and the samples of toxin he had in reserve. He observed, however, that he did not regard this antitoxin as constituting the final standard.

When his laboratory had prepared a perfringens A antitoxin with a standard toxin containing an abundance of all the antigens, or, at all events, the principal harmful substances of *B. perfringens A*, such a preparation could then really be regarded as a standard antitoxin.

It should not be forgotten, however, that each horse reacted differently to the injection of each of the perfringens A antigens. For the successful preparation of a good standard antitoxin, it would therefore be necessary to immunise a complete batch of horses with the standard toxin and then proceed to a comparative examination of the resultant sera with a view to selecting the best.

In these circumstances, he suggested that the comparative assays should be carried out in relation to the international standard antitoxin, with a single test-toxin, which the Copenhagen Institute might be asked to prepare. It was essential, if the titres obtained were to be comparable, that the assays should be performed in all countries, not only in relation to one standard serum, but with a single sample of toxin.

For some years, Dr. HARTLEY had been testing the commercial preparations of perfringens antitoxin placed on the British market, using for the purpose the international standard antitoxin prepared by the Hampstead Institute, and had experienced no difficulties. This international standard was now being criticised; in order to judge of the value of the criticisms, it would be necessary to make sure that all the assays were made on a common basis—i.e., that the potency of the international standard and of the various national standards was identical. He would therefore like to have samples of the national standard sera for purposes of comparison.

Professor WEINBERG said that, in France, the national standard was used only in laboratory research; the whole of the output of

perfringens antitoxin was assayed in terms of the international standard.

“ Taking into consideration the interesting observations brought forward by Professor WEINBERG, the Commission is of opinion that the Biological Standards Department, Copenhagen, should be requested to prepare a convenient amount of a perfringens toxin, which could be distributed to interested laboratories for the purpose of carrying out further investigations into problems relating to the determination of the potency of perfringens antitoxins.

“ It takes note of the comparative research work which is proceeding in various institutes on the question of the use of a single sample of toxin.”

(b) *Cl. Sordelli*.

Annex 3 contains Dr. G. W. McCoy's proposal for the establishment of an international standard for gas-gangrene antitoxin (*Sordelli*) and the results of the assays by the Copenhagen Institute of the dried serum prepared by the National Institute of Health, Washington.

Professor SORDELLI considered that this question was mainly of interest to the American continent, partly because a far larger number of cases of infection with the bacillus described by him had been reported in America than in Europe, and partly because *Sordelli* antitoxin was exported by the United States.

Professor WEINBERG said he had a stock of dried *Sordelli* antitoxin which he would gladly place at the Commission's disposal ; the reason he had not as yet adopted any standard for this serum was because he knew of only two cases of infection due to *Cl. sordelli*.

“ The Commission decides to adopt as the international standard for gas-gangrene antitoxin (*Sordelli*) the dried serum prepared by the National Institute of Health at Washington, the unit of activity to be defined only when comparative assays have been carried out.

“ Provisionally, this unit might, however, be regarded as equivalent to 0.06668 milligramme of this dried serum. Before the final adoption, samples of different *Sordelli*

antitoxins should be assayed against the proposed standard by means of two or more toxins, and using the mice intravenous method proposed in Annex 3 b.

“ Various institutes should be invited to take part in these comparative assays, the results of which should show, first, whether the unit is of the same magnitude as those of the antitoxins corresponding to the other organisms of the gas-gangrene group and, secondly, whether the assay is affected by the toxin used.”

(c) *Vibrion Septique Antitoxin.*

Endorsing the proposal to increase the concentration in international units of the *vibrion septique* antitoxin issued by the Copenhagen Institute for international use (see Annex 3 b),

“ The Commission requests the Biological Standards Department of Copenhagen to prepare the solutions of the international *vibrion septique* antitoxin standard in future in such a way that they contain fifty international units per c.c.”

5. ANTI-ANTHRAX SERUM

In pursuance of the recommendation made by the Inter-Governmental Conference on Biological Standardisation, the Commission decided, in 1935, to resume work on the standardisation of anti-anthrax serum. Communications on the matter from the Cantacuzène Institute, Bucharest, and the Szeged Institute of Hygiene, will be found in Annex 4.

Professor C. IONESCU-MIHAIESTI had endeavoured to define the part played by the capsular antigen of *B. anthracis* in the immunisation process, in accordance with the research programme drawn up by him in agreement with Professor TOMCSIK. His investigations showed that, while this antigen played an important part in anthrax immunity, the somatic antigen was at least equally important. The sera possessing the highest protective power proved to be those with the highest content of antibodies neutralising those two antigens.

In order to secure more definite data in this connection, two sera were to be studied, one with a high content of capsular antigen and

the other with a high content of somatic antigen ; he would be glad to obtain the assistance of other institutes in this work.

The CHAIRMAN wished to take the opportunity of thanking Professor IONESCU-MIHAIESTI for the very generous hospitality afforded by the Roumanian Government and the Cantacuzène Institute to the mission which, in June 1938, visited the national centres established in Eastern Europe for the distribution of the international biological standards.

The question of the possibility of obtaining the assistance of institutes of veterinary medicine in assaying the anti-anthrax serum having been raised, Professor LECLAINCHE pointed out that the therapeutic use of anti-anthrax serum was confined to the rare cases of anthrax which developed slowly. From the preventive standpoint, the serum was sometimes used to induce a state of immunity rapidly in animals when an anthrax focus was discovered. From the veterinary standpoint, anti-anthrax vaccine was much more important than the serum.

Professor SORDELLI, who prepared the anti-anthrax serum at the Buenos Aires Institute, signified his readiness to take part in investigations with a view to improving the assay of this serum, while Dr. Louis MARTIN thought that Dr. BOCQUET, of the Pasteur Institute, Paris, would be willing to collaborate.

" The Commission, having before it the results of the research work conducted at the Bucharest Institute on the assay of anti-anthrax serum, is happy to note that this work can be continued on wider co-operative lines, thanks to the participation of the Pasteur Institute, Paris, and the Bacteriological Institute, Buenos Aires."

6. ANTI-TYPHOID SERUM

Thanks to the kindness of the author, Dr. A. FELIX, the Commission was able to acquaint itself, before publication, with his report on the standardisation of anti-typhoid serum. Commenting on this report, Dr. GRASSET expressed concurrence in the author's views. His own research into the preparation and therapeutic use

of anti-typhoid serum¹ showed that a serum having the maximum O and Vi antibody titre would be the most effective in treating typhoid fever, whatever the antigenic characteristics of the bacillus responsible for the infection.

The clinical tests carried out at Johannesburg in 1937/38 with an anti-typhoid serum having a high Vi and O antibody titre appeared to confirm the experimental results, but a final opinion on the value of this new type of serum must be deferred until it had been administered in a larger number of cases.

The question of the therapeutic action of anti-typhoid serum having been raised by Professor SORDELLI, Dr. GRASSET said that a pure anti-O serum prepared by means of endotoxoid had been used in South Africa in about 3,500 cases of typhoid fever; it had reduced the fatality rate from 20% to 10%; if it was administered during the first twelve days of the disease, the rate fell to 3%. The new anti-Vi and O serum which was being tried, not only reduced the fatality rate in the same proportion, but also appeared to have a more marked effect on temperature in the early stages of the disease and to be more effective in preventing complications.

Professor HIRSZFELD confirmed the therapeutic action of anti-typhoid serum. In forty cases of typhoid fever treated at Warsaw by intramuscular injection of serum obtained by immunisation with formol endotoxin, a rapid fall in temperature had been noted, sometimes after the second injection. The favourable action of the serum on the general course of the disease was very marked, especially in regard to inflammatory complications of the respiratory organs. The serum had not, however, conferred any immunity, since it had not prevented the reappearance of the disease.

Dr. KAUFMANN thought that it would be possible to standardise anti-typhoid serum by the method proposed by Dr. FELIX.

Dr. HARTLEY said that the stock of anti-typhoid serum prepared by Dr. FELIX and dried at the Hampstead Institute had been sufficient for 250 ampoules, which could be distributed to workers desirous of making comparative assays.

“ The Commission is of opinion that the report of Dr. A. FELIX on the standardisation of anti-typhoid serum, which

¹ “ The Preparation and Comparison of Different Types of Anti-typhoid Sera (Agglutinins, Mouse Protection and Preliminary Trials) ”, *Br. Jl. of Exp. Path.*, 1937, XVII, 460.

was communicated to it and has just been published in the *Journal of Hygiene*, 1938, Vol. 38, page 750, should be taken as the basis of an international comparative investigation, and that the anti-typhoid serum prepared by the Lister Institute and dried by Dr. HARTLEY should be used for this purpose.

“ Samples of this serum and also of the cultures which Dr. FELIX is ready to supply should be distributed to the following workers and institutes :

- “ 1. Lister Institute of Preventive Medicine, London ;
- “ 2. National Institute for Medical Research, Hampstead, London ;
- “ 3. State Serum Institute, Copenhagen ;
- “ 4. Cantacuzène Serum and Vaccine Institute, Bucharest ;
- “ 5. Mr. S. D. BEARD, Lederle Laboratories, New York ;
- “ 6. Dr. DUJARRIC DE LA RIVIÈRE, Pasteur Institute, Paris ;
- “ 7. Dr. Carlos GARCÉS BAEZA, Bacteriological Institute of Chile, Santiago de Chile ;
- “ 8. Dr. E. GRASSET, South African Institute for Medical Research, Johannesburg ;
- “ 9. Professor L. HIRSZFELD, Director of the Department of Bacteriology and Experimental Medicine of the State Institute of Hygiene, Warsaw ;
- “ 10. Professor A. SORDELLI, Director of the Bacteriological Institute of the National Health Department, Buenos Aires.”

7. STAPHYLOCOCCUS ANTITOXIN

In 1934, the Commission adopted as the international standard for staphylococcus antitoxin a dry, stable preparation made by the National Institute for Medical Research, Hampstead.

During the past four years, the stock of this standard, which is kept at the Copenhagen and Hampstead Institutes, had been depleted more quickly than had been foreseen, and it was now becoming necessary to replenish it.

Sir Henry DALE and Dr. MADSEN agreed to ask Dr. HARTLEY (who consented) to prepare the new standard; to this end, Dr. HARTLEY, in collaboration with Miss LLEWELLYN SMITH, carefully examined five staphylococcus antitoxins of varying origin. A description of the research work undertaken with a view to the preparation of this new standard and its assay in terms of the present international standard is given in Annex 5.

The CHAIRMAN referred to the criticism of the international standard serum made by Professor FORSSMANN, of Lund, which might be summarised as follows :

“ There is no correlation between the potency of a staphylococcus antitoxin expressed in international units and its bactericidal action ;

“ The biological tests employed to assay a serum in terms of the standard serum only take account of a few of the possible effects which the staphylococcus toxin may exert, and these are, moreover, the least important from the point of view of human pathology.”

It should be noted that, when this standard was established, the staphylococcus toxin was regarded as antigenically an indivisible unit. Since that time, the work of GLENNY and STEVENS, LLEWELLYN SMITH and PRICE, etc., had introduced the concept of multiple toxins.

As the present international standard serum, like that which is to replace it, consists of α antitoxin, the CHAIRMAN considered it advisable that this should henceforth be stated on the label of the ampoules.

Moreover, since there were several clearly defined staphylococcus toxins which are neutralised by specific antibodies, it might be considered whether toxins other than α toxin would not be used in due course for the production of sera and formol toxoids. Although no commercial product for the treatment of staphylococcus infections had so far been prepared with β toxin, the establishment of a standard preparation of β antitoxin might perhaps facilitate comparison of the results of the research conducted in the various countries.

“ A. In order to supply a second international standard for staphylococcus antitoxin, to take the place of the first

international standard, adopted in 1934, the stocks of which are now almost exhausted, the National Institute for Medical Research, Hampstead, has provided a large quantity of a dry, stable preparation of staphylococcus antitoxin. The sample ultimately adopted, with a view to its eventual adoption as a second international standard, was chosen from five staphylococcus antitoxins, large amounts of which were generously supplied by :

“ The Lister Institute, Elstree ;

“ The Wellcome Physiological Research Laboratories, Beckenham ;

“ The Pasteur Institute, Paris ;

“ The Connaught Laboratories, Toronto, and

“ The Lederle Laboratories, New Jersey.

“ The properties of these five antitoxins were investigated at Hampstead and Copenhagen, and, after consultation between the two institutes, it was recommended by the Chairman of the Permanent Commission on Biological Standardisation that the sample supplied by the Wellcome Physiological Research Laboratories, Beckenham, should be chosen for conversion into a dry, stable preparation. The sample was exactly assayed, in terms of the present international standard, and the weight of the new preparation, equivalent to one international unit of staphylococcus antitoxin, was determined at Hampstead, and the value so obtained was confirmed at Copenhagen.

“ The Commission accordingly recommends that the dry, stable preparation of staphylococcus antitoxin prepared at the National Institute for Medical Research, Hampstead, be adopted as the second international standard for that antitoxin, and that the international unit be redefined as the specific antitoxic activity contained in 0.2376 milligramme of the said dry, standard preparation.

“ B. The Commission further recommends that the second international standard now established be called the ‘International Standard Staphylococcus α Antitoxin’.

“ C. The Commission requests the Biological Standards Department of the Copenhagen Institute to be good enough to make a dry, stable preparation of staphylococcus β antitoxin, to be known as the ‘Provisional Standard Staphylococcus β Antitoxin’.

“ For the time being, this preparation would be used to facilitate the research work into staphylococcus immunity. Should β toxin be found to play an important part in pathology, this provisional standard might be adopted for international use after a unit of activity has been defined.”

8. TUBERCULIN

The international standard for tuberculin adopted by the Commission in 1931 consisted of Koch's old tuberculin. As the CHAIRMAN pointed out, the question now arises whether it would not be advisable for the Commission to adopt a second standard consisting of a purified tuberculin obtained on a synthetic medium, corresponding to the product known to American workers as P.P.D. (purified protein derivative). The advantages of tuberculin of this type are obvious ; as has been shown by K. A. JENSEN and his collaborators,¹ it enables approximately the same percentage of positive reactions to be obtained by the Mantoux test with two injections (1/50,000 milligramme and 1/500 milligramme) as with three injections of old tuberculin (1/100 milligramme, 1/10 milligramme and 1 milligramme) ; in a buffered medium, it yields solutions which remain stable for nearly a month and it is sufficiently active for the diagnostic test on cattle. Unfortunately, according to K. A. JENSEN, purified tuberculin and old tuberculin are difficult to compare, owing to the presence of glycerol in the latter. This argues in favour of the adoption, for purified tuberculin, of a special standard, which might be either a preparation of the P.P.D. type or purified tuberculin prepared at the Copenhagen Institute. Should the Commission decide to adopt such a standard, it would have to consider whether a unit of activity should be defined.

¹ K. A. JENSEN, G. BINDSLEY, S. MOELLER, A. HANSEN and P. LIND : “ Old Tuberculin and Purified Tuberculin : Standardisation Preparation of Stable Solutions ”, *Tubercle*, 1938, 19, 386 and 433.

Professor LECLAINCHE said that, from the veterinary standpoint, the question of tuberculin standardisation was of immediate interest; owing to the variety of techniques, and, still more, the variety of tuberculins used, considerable discrepancies in results had been observed among cattle. The abandonment of the subcutaneous route in favour of the intradermal route had not eliminated them; for it was estimated that, in judging negative reactions, the margin of error was between 30% and 40%, according to the quality of the tuberculin used.

In France, tuberculin was now prepared by a large number of industrial laboratories, and even by pharmacists and druggists; hence the great variations in the results obtained which were attributable to the impurities contained in these preparations. With a view to remedying these defects, a commission was to meet shortly at the Ministry of Agriculture, to draw up regulations for the preparation of tuberculin.

In the United States, the Bureau for Animal Industry was preparing a synthetic tuberculin on Dorset's medium and the percentage of error was much lower.

Although thousands of cattle had undergone the tuberculin test, the number of well-conducted experiments on which judgment might be based was very small except for the tests carried out at Berne; there, again, the results differed according to the tuberculin used. The standardisation of tuberculins therefore appeared to be highly desirable, but it might perhaps be best to standardise them first of all on a national basis, international standardisation coming later. The matter was urgent, because, in view of the discrepancies observed, Governments might decide to prohibit diagnosis campaigns on the grounds of cost and unreliability.

The Commission was looking for an ideal tuberculin; but what veterinary surgeons wanted was an immediate practical solution that would provide them with a product which would be as active and stable as possible, and would be identical in all countries. This would call for the use of a tuberculin obtained on a synthetic medium, and perhaps even purified as far as possible.

Professor IONESCU-MIHAIESTI pointed out that irregularities in tuberculin reactions in man had been observed in Roumania. The tuberculin supplied by the Bucharest Institute had formerly been prepared from Vallée's strain; it was now obtained from three

strains, and assayed against the international standard. Although the irregularities had thereby been reduced, they had not entirely disappeared. Investigations were being conducted into the utilisation of extracts rich in polyholosides obtained from tubercle bacilli of the human, bovine and avian types, and yielding strictly specific skin and intradermal reactions.

Dr. HARTLEY said that, since 1927, all tuberculins imported into, or prepared in, the United Kingdom had to comply with the international standard, the tolerated error being 30%. The titres found were fairly constant, but imported tuberculins tended to be too active, and then had to be diluted. He was in favour of the establishment of a standard tuberculin of the P.P.D. type, which might serve at first as a subsidiary standard, and eventually take the place of the present standard.

It was highly desirable that the potency ratio as between the new standard of the P.P.D. type and the old standard should be determined, but opinions differed as to the feasibility of such a comparison; whereas Dr. K. A. JENSEN did not think it possible, Dr. PARISH had shown that it could be made on the sensitised guinea-pig. Further investigations would therefore be necessary in order to elucidate the question.

Professor SORDELLI also believed it possible to assay P.P.D. in relation to old tuberculin, using the experimental method. He therefore supported Dr. HARTLEY's proposal to establish a standard for the P.P.D. type of preparation.

"The Commission considers it essential to establish a subsidiary international standard for tuberculin, corresponding as closely as possible to the preparation known to American workers as P.P.D. ; to that end, it requests the Copenhagen Biological Standards Department to prepare or procure a sufficient quantity of such tuberculin, the potency of which shall be defined in relation to that of the present international standard of old tuberculin."

9. AGGLUTINATION TESTS

In accordance with the resolution adopted by the Health Committee in February 1938, the Commission was called upon to pro-

nounce on the conclusions of the report of the experts who met in London in November 1937 to study the question of the standardisation of agglutination tests in general and of the Widal test in particular.¹

In this connection, Professor WEINBERG pointed out that a much clearer agglutination was obtained by the action of a specific bactericidal serum on a dilution of the corresponding culture than by the use of washed bacteria. He accordingly proposed that the Bucharest, Johannesburg, Paris and Warsaw Institutes should compare the results of the Widal test when carried out by the agglutination method recommended at the London meeting, and when carried out by precipito-agglutination.

Dr. GRASSER said he had sometimes obtained good results from the use of flocculation + agglutination. He was convinced that the reaction was much clearer and quicker when both the filtrate and the bacillus were used.

Mr. BRUCE WHITE thought that the standardisation of diagnostic agglutination tests should be approached with circumspection and due regard to the complexity of the phenomena on which they were based.

Whatever provisional steps might now be taken to secure greater uniformity in the results of the Widal test, the ultimate aim should be to establish as standards sera of the most univalent type available. It seemed probable that, by the use of purified flagellar antigen and of the " antigenes complets " of Boivin, H and O sera, more suited to serve as standards than those prepared against whole bacilli, might be obtained.

The use of suspensions of flagella in place of H cultures in the diagnostic test might be advantageous.

Professor HIRSZFELD agreed with Mr. BRUCE WHITE, and said that he would not introduce the technique recommended at the London meeting until a better knowledge had been obtained of the mechanism of agglutination. At Warsaw, where 60% of the Widal tests were carried out at the State Institute of Hygiene, he had observed that, as against seventy-two positive results with live bacilli, only sixty-six had been obtained when the same sera were used on killed cultures.

¹ Document C.H.1292.

Professor IONESCU-MIHAIESTI said that, while bearing in mind the London recommendations, he had undertaken research into the clinical importance of O and H antibodies.

In diagnostic tests for brucellosis, he had endeavoured to use Boivin's method in order to obtain a stable and complete antigen ; he had, however, found it impossible to prepare a flocculent antigen specific for the *melitensis*, *suis* or *abortus* type. While brucellosis in man was very rare in Roumania, it was widely prevalent among animals ; A. CIUCA, who had studied the types of brucella encountered, had examined 611 buffalo sera ; and although no case of abortion had ever been reported among those animals, 224 of the sera agglutinated *B. abortus*.

In the opinion of Professor SORDELLI, it would be premature to regard as final the conclusions on agglutination tests in general and on the Widal test in particular. As for the brucellæ, these afforded an example of a less complex type of agglutination than that of salmonellæ ; given a stable antigen, the tests were easy to carry out, and furnished comparable results. At the Buenos Aires Institute, a commercially sold antigen prepared by Huddleson's method was used ; it could, in any case, be easily prepared in the laboratory.

The CHAIRMAN referred to the reports prepared for the Commission by Dr. Laszlo DETRE, of the National Institute of Health, Washington, on the agglutination process,¹ and by Mlle. T. LEWIN, and Dr. St. PIWOWARCZYK, of the Bacteriological Laboratory of the Warsaw Faculty of Veterinary Medicine, on the diagnosis of brucellosis.²

“ The Commission takes note of the conclusions on agglutination tests of the report (document C.H.1292) of the experts who met in London in November 1937.

“ It considers it desirable that stable reagents (antisera and bacterial suspensions) should be rendered available for comparative use in the diagnostic agglutination reactions in the case of typhoid, paratyphoid A and B, and brucellosis.

¹ Document C.H./C.P.S.B.46.

² Document C.H./C.P.S.B.36.

“ These reagents should be of as high a degree of specificity and purity as possible, and further work should be undertaken in order to investigate :

“ (a) Whether it is preferable to use a standardised bacterial suspension or a dried preparation of bacteria for the diagnostic agglutination test, and,

“ (b) How, by the use of purified antigens O and H, the most highly specific agglutinating sera may be prepared.

“ In the meantime, it would be helpful if suspensions and agglutinating sera such as those now produced at the Standards Laboratory at Oxford were made available from an international centre for comparison with the reagents used in different countries and laboratories, and also to assist in co-ordinating further research on the subject. As many laboratories as possible should be encouraged to take part in the investigation of the standardisation of the agglutination tests.”

10. INTERNATIONAL CENTRE FOR THE IDENTIFICATION OF SALMONELLÆ

In pursuance of the recommendation adopted by the International Association of Microbiology, an International Centre for the Identification of Salmonella Strains has been set up, thanks to a grant from the Commonwealth Fund, at the State Serum Institute, Copenhagen, under the direction of Dr. F. KAUFFMANN. With a view to facilitating the serological identification of salmonellæ in all countries, this centre is willing to distribute the necessary immune sera and standard cultures free of charge, and to study any aberrant strains sent to it. It also proposes to stimulate the establishment, in every country, of national centres equipped for the identification of salmonella strains, which would thus be in a position to meet the requests for agglutinating sera made by scientific workers in the country concerned.

Dr. KAUFFMANN said that the production of the requisite fifty-one agglutinating sera had been begun at Copenhagen several months

before, and would probably be completed by the end of the present year. In addition to supplying these sera, the Copenhagen Centre had been called upon to furnish 225 standard strains since the beginning of 1938, and to identify twenty-nine cultures. It was now in touch with thirty institutes in Europe and overseas, which had agreed to act as national identification centres.

“ The Commission is happy to learn that an International Centre for the Identification and Classification of Salmonellæ has been set up at the State Serum Institute at Copenhagen with the support of the Commonwealth Fund. It greatly appreciates this new development, which it considers to be of undoubted value.”

11. DIPHTHERIA ANTITOXIN

(a) RESULTS OF THE ANNUAL COMPARISON OF NATIONAL STANDARDS AGAINST THE INTERNATIONAL STANDARD

The report constituting Annex 6 *a* sets forth the results of the periodical assays carried out by the State Serum Institute, Copenhagen, with a view to comparing the potency of the various national standards with that of the international standard preparation. These have in some cases revealed differences in potency—which do not, however, exceed 5%—according to whether they were performed by Ehrlich’s method or by the intracutaneous route on the rabbit. These slight discrepancies are of no practical importance ; they may possibly be due to differences in avidity.

As Dr. Louis MARTIN pointed out, Ehrlich’s method should, of course, still be regarded as the fundamental basis of these assays ; but as the intracutaneous method is more economical and easier to carry out, its use should be encouraged.

“ The Commission takes note of the report presented by the Copenhagen Institute on the periodical testing of the various national diphtheria antitoxin standards against the international standard.”

(b) DIPHTHERIA ANTITOXIN FOR THE FLOCCULATION TEST

The stock of diphtheria antitoxin No. 788 prepared by the Copenhagen Institute and adopted by the Commission in 1935 as the international standard antitoxin for assays based on flocculation has been used up more rapidly than was expected ; a new antitoxin, No. 1184, therefore had to be chosen to replenish it. The research carried out by the Copenhagen and Hampstead Institutes with a view to this selection are described in Annex 6 *b*. Before issue, antitoxin No. 1184 was submitted to Dr. G. RAMON, who tested it against his own standard and found that the concordance between the two preparations was satisfactory.

“ The Commission adopts diphtheria antitoxin No. 1184 prepared by the Copenhagen Institute as the new international standard antitoxin for the flocculation test.”

12. ANTI-DYSENTERY SERUM

Professor IONESCO-MIHAIESTI submitted to the Commission a preliminary note on the assay of anti-dysentery (Shiga) serum by the flocculation method. This note, the authors of which are Drs. Gh. ISTRATI and A. OLARU, is reproduced in Annex 7.

Annex 1a.

THE ASSAY OF TETANUS ANTITOXIN

Results of Investigations performed in Five Institutes¹

INTRODUCTION

At the Commission's session at Copenhagen in August 1934, the Statens Serum Institute was asked to draw up a scheme of comparative research work on the assay of tetanus antitoxin. Discrepancies in the results obtained at various institutes when assaying a given tetanus serum had frequently been observed, and it was desirable to carry out investigations in which the various factors causing the discrepancies would, as far as possible, be separated and controlled.

Dr. CLAUS JENSEN, in collaboration with Dr. L. WALBUM and Dr. G. C. REYMANN, suggested a plan of investigation, published in detail in a progress report.²

The main purpose of the investigations proposed therein was to determine the limits of variation in the results obtained in various institutes employing *the same method* to assay *the same sera* by means of *the same toxin*—as compared with the variations in titre observed when a number of different toxins and a variety of techniques are used.

The first step taken was to provide a suitable toxin produced by an absolutely pure strain of *B. tetani*.

Eleven strains were sent to Professor ZEISSLER (Altona), who kindly undertook to examine the strains by micromanipulation.

¹ Report submitted by the Department of Biological Standards of the State Serum Institute, Copenhagen.

² Cl. JENSEN: "Memorandum concerning the Titration of Tetanus Antitoxin": *Quart. Bull. Health Org.*, 1936, 5, 702.

Among those strains, which were found to be pure and highly toxigenic, one was selected for the production of a large supply of toxin. This strain—viz., No. 3 (National Coll. T.67. Tulloch Type 2)—had been used for the last ten years at the Statens Serum Institut for the routine production of the test toxin and to make the standard serum now distributed by the Institute.

After precipitation and desiccation, the toxin was distributed in ampoules, and labelled toxin C.35.

Five commercial anti-tetanus sera from different institutes were provided in order to get random samples of tetanus antitoxin. These sera were designated I, II, III, IV and V.

It was suggested to the institutes invited to participate in the investigations that they should determine the activity of these five sera against the international tetanus standard :

- (1) With toxin C.35, using the method proposed below ;
- (2) With their own routine toxin, using their own routine method ;
- (3) With toxin C.35, using their own routine method ;
- (4) With their own routine toxin, using the method proposed below. The guinea-pig and mouse were to be used simultaneously for the assay.

Proposed Method.

The technical details prescribed in the scheme had special reference to the preparation of the toxin-antitoxin mixtures ; it was provided that :

- (a) The reaction between toxin and antitoxin should take place at pH 7.38 and that the mixture should contain 0.1°/∞ chinosol ;
- (b) The mixtures should be allowed to stand for *twenty-four hours* at room temperature (18-20° C.) before injection ;
- (c) 0.5 c.c. of each mixture should be injected intravenously into the caudal veins of 6 mice weighing from 18 to 20 grammes.

It was added that the results after 5 × 24 hours were to be taken as definite.

For convenience, this method has been called the *Copenhagen method*, and will be so termed hereafter.

The Conduct of the Investigations.

During the summer of 1935, samples of toxin C.35, five commercial sera and the international standard of tetanus antitoxin were sent to the five institutes participating in the enquiry—*i.e.*, three European and two American institutes (in the progress report mentioned above, Dr. CLAUS JENSEN mentioned four European institutes ; however, as one of these did not take part in the final research work, an American institute took its place).

The participating laboratories are designated below by the letters D, H, P, S and W.

The reports from these institutes were addressed to the Department of Biological Standards, Copenhagen, in the course of 1936 and at the beginning of 1937.

The proposed scheme being very extensive, its execution in full would have occupied the research staff of the institutes for an unreasonable length of time. Although the experiments carried out do not entirely fulfil the original plan, the large number of assays are well worth publishing and will contribute to the solution of the question of the accuracy of tetanus titration.

The following table gives a synopsis of the methods used for the assay of the five sera in the different laboratories.

Laboratory	Assay by								
	Copenhagen method				Own method			Number of animals used	
	Toxin C.35		Own toxin		Toxin C.35	Own toxin			
	Mice	Guineapigs	Mice	Guineapigs	Guineapigs	Mice	Guineapigs	Mice	Guineapigs
D	+	—	+	+	+	—	+	531	231
H	+	—	—	—	—	+	—	519	—
P	+	—	—	—	—	+	—	694	—
S	+	+	—	+	+	—	+	288	112
W	+	+	—	—	—	—	—	822	258
						Total		2,854	611

Results of the Investigations.

The titres of the five sera, as indicated by the participants in the investigation, are given in Table 1. To answer the question which

the enquiry was designed to elucidate, a simple procedure would be to compare the differences between the various titres, and take these as a basis for an estimate of the accuracy of the assay.

Table 1.

TITRE IN INTERNATIONAL UNITS PER CUBIC CENTIMETRE OF THE FIVE SERA AS INDICATED BY THE INVESTIGATORS

		I.				
		<i>Copenhagen method</i>		<i>Mice (intravenous)</i>		
		Serum				
Laboratory	Toxin	I	II	III	IV	V
W	Toxin C.35	1,340	1,550	5,400	1,040	11,350
S		1,260	1,700	5,600	945-1,000	11,400
D		1,000	1,550	4,400	900	11,000
H		1,250	1,700	5,000	1,000	9,500
P		1,220	1,550	5,130	1,020	10,600
		<i>Guinea-pigs (subcutaneous)</i>				
W	Toxin C.35	1,400	1,900	6,200	1,150	12,500
S		1,260	1,615	5,300	945	11,400
		II.				
		<i>Own method</i>		<i>Guinea-pigs (subcutaneous)</i>		
D	Toxin C.35	1,200	1,620	6,400	850	12,000
S		1,140	1,880	5,600	700	11,400
		III.				
		<i>Copenhagen method</i>		<i>Mice (intravenous)</i>		
D	Own toxin	1,300	1,800	No test	920	12,600
S		1,260	1,700	5,600	945	11,400
		IV.				
		<i>Own method</i>		<i>Mice or guinea-pigs (subcutaneous)</i>		
P	Own toxin	1,260	1,350	4,630	1,160	9,520
H		1,300	1,700	5,500	970	11,500
D		1,250	1,900	8,000	1,000	14,000

An examination of the experimental data shows, however, that the various workers have assessed the strength of sera from different points of view—one, for instance, choosing the mortality on the

fifth day as end-point, while others have based their judgment on the result on the sixth or fourth day. In some assays, the test dose against the American standard has been used instead of the dose titrated against the international standard, etc.

For this reason, the titres shown in Table 1 cannot be regarded as strictly comparable, if they are to be taken as expressing variations due to purely technical and biological factors. Before the final treatment of the results, it appeared necessary to make certain that these values had been arrived at by a uniform mode of calculation.

There is, moreover, another question calling for attention—namely, the variation in resistance of the experimental animals in the different laboratories, as well as in the stock of the same institute.

I. NUMERICAL TREATMENT OF THE EXPERIMENTAL DATA

(a) EXPRESSION OF THE DOSE OF TOXIN AND DOSE OF SERUM IN TERMS OF THE RATIO OF THE ONE TO THE OTHER

The purpose of all assays is to state the amount of serum giving a defined end-point reaction with a given dose of toxin. The comparison of the results obtained with the same toxin would be quite simple if a constant unvarying test dose had been used throughout all the experiments, the result then being expressed as cubic centimetre of the serum tested. But as different workers have used slightly different test doses, and as in several experiments the dose of toxin has been varied against a constant dose of serum, the dosage is better expressed as *the ratio of the dose of toxin to the dose of serum*.

There are two conditions in this investigation which may justify this adaptation of the law of multiple proportions: (1) The test dose at the prescribed level of titration contains about 1,000 minimum lethal doses and (2) the differences in the dosage of toxin in no case amounted to more than 30%.

It will be admitted that if, for example, 1 mgrm. toxin + 0.20 A.U. causes an end-point reaction near zero, a mixture of

1.1 mgrm. toxin + 0.22 A.U. will give a similar reaction within the limits of variation.

In the following, the dosage will consequently be given as the ratio of the dose of toxin to the dose of serum. For several reasons, it has been found more convenient to express this ratio logarithmically as $\log. Tx/ser.$ or $\log. Tx/A.U.$

(b) DETERMINATION OF THE DOSE
GIVING THE END-POINT REACTION

The $\log. Tx/ser.$ dose ratio, giving the end-point reaction, must be calculated from each assay. The end-point chosen is 50% mortality 5 \times 24 hours after the injection. For practical purposes, we have called this dose ratio D_5 . We describe below a method of calculating D_5 in an objective manner.

Table 2 gives an example of the technique to be followed.

Table 2.

ASSAY OF TOXIN C.35 AGAINST THE INTERNATIONAL STANDARD
OF TETANUS ANTITOXIN

Laboratory P.

Six mice per dose.

Dose of toxin	Dose of serum	Log. Tx/ser.	Mice surviving on the						T_{50}
			First day	Second day	Third day	Fourth day	Fifth day	Sixth day	
Mgrm.	A.U.								
1.17	0.18	0.813	6	6	3	0	0	0	3.0
1.17	0.19	0.789	6	6	6	3	0	0	4.0
1.17	0.20	0.767	6	6	6	6	5	4	7.0
1.17	0.21	0.746	6	6	6	5	5	5	>9.0
1.17	0.22	0.726	6	6	6	6	6	6	>9.0

(The quantity T_{50} will be explained later.)

If the results—number of survivals—on the fifth day are considered separately, D_5 might be estimated as lying between 0.789 and 0.767, the former producing no survivals (0/6) and the latter 5 (5/6) out of 6 animals injected. The number of animals injected being fairly small for each dose, the experiments do not absolutely preclude

the possibility of D_5 being situated between 0.767 and 0.746. The value taken therefore appears rather arbitrary.

A better use of the observations can be made if the mortality rates on the days preceding and following the fifth are considered.

(c) EXPRESSION OF THE BIOLOGICAL EFFECT IN TERMS OF MORTALITY AND TIME OF DEATH

It is a well-known fact that the time of death depends on the amount of toxin injected. If the dose D_5 gives a 50% mortality on the fifth day after injection, mixtures containing more toxin will cause the death of 50% of the animals in a shorter time. A dose containing less toxin than D_5 will cause death to occur later, if at all.

In the assay of different sera, it has frequently been proposed to record the reaction by a figure indicating the time of death for the group of animals treated. Commonly, the "mean time of death" of the group is employed, calculated as the arithmetic mean of times of death of the several animals observed. The animals not dying by the last day of observation or the day after are excluded. This seems a little arbitrary.

We have tried to do more justice to the surviving animals by estimating *the time at which 50% of a group has died*, this quantity being called T_{50} .

D_5 is accordingly the dose ratio expressed in terms of $\log. Tx/Ser.$, having a $T_{50} = 5$.

For groups showing 100% mortality during the period of observation, the T_{50} and the mean time of death, calculated as above, will be identical. But in groups presenting survivors at the end of the period, the mean time of death will be a smaller quantity than the time in which 50% died. The following suggestion for calculating T_{50} , which has been used for the treatment of the present material, seems to give results somewhat nearer to the true value than mean death time.

The procedure used for the calculation of T_{50} of a group of animals may be illustrated graphically by plotting the observed survival rates against the corresponding days of observation. A straight line drawn to the best fit of these points and the intersection of

this line with the axis of 50% survival is taken as T_{50} . In practice, we have preferred to replace this graphical method by a mathematical formula representing much the same procedure :

$$T_{50} = T_{100} + \frac{N}{2} \cdot \frac{\Sigma(T - T_{100})}{\Sigma(N - S)}$$

N = number of animals injected ;

T_{100} = last day on which 100% survival is observed ;

$T - T_{100}$ = any day of observation reckoned from T_{100} ;

S = survivors on the T 'th day ;

$N - S$ = the total number of deaths up to the T 'th day.

The summations cover the period from the last day of 100% survival to the sixth day or the first day of 100% mortality.

Example :

Day	6 mice injected	Survivors
Second	6
Third	6
Fourth	4
Fifth	2
Sixth	1

$$T_{50} = 3 + \frac{6}{2} \cdot \frac{1 + 2 + 3}{2 + 4 + 5} = 4.7.$$

In the case of no death in the period of observation, the T_{50} is indicated as >9 .

The use of T_{50} to express the reaction has the advantage that data obtained from all days of observation are included in the estimation.

(d) USE OF REACTION CURVES TO DEFINE THE DOSE
GIVING THE END-POINT REACTION (D_5)

Returning to the figures given in Table 2, we shall now describe how the quantities T_{50} are used for the determination of the end-point.

The T_{50} are plotted against the corresponding log. Tx/ser. (For the axes of co-ordinates, the following proportions have been used : for $T_{50}/1 = 2$ c.m., for log. Tx/ser. $0.01 = 1$ c.m.)

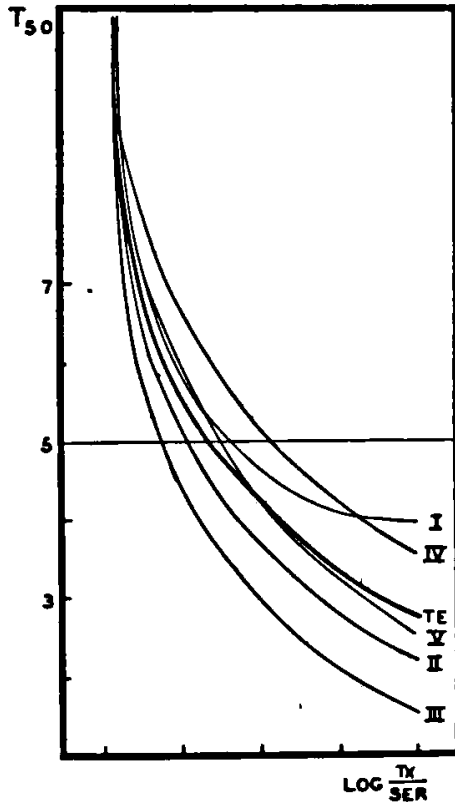
The last two T_{50} 's, >9 , are indicated as lines drawn from the 9 axis upwards. A curve is now drawn to the best fit of the points, the points >9 being regarded as asymptotes, and *the abscissa of the point of intersection of this reaction curve to the axis $T_{50} = 5$ is taken as the dose D_5* . In the example given in Table 2, D_5 was 0.777. From this value, the test dose $L+5$ can be calculated :

$$0.777 = \log. \frac{T_x}{A.U.} = \log. \frac{T_x}{0.2} = \log. T_x + 0.699$$

$$\log. T_x = 0.078.$$

Test dose $L+5 = \text{antilog. } 0.078 = 1.19 \text{ mgrm.}$

The reaction curves for each of the six sera examined are shown in the graph opposite. The data are derived from experiments carried out in one laboratory (W). The curves, drawn to the same proportions, have been so placed that the asymptotes of the curves are common. It is a remarkable fact that the slopes of the curves are distinctly different. This lack of parallelism of the reaction curves of sera has also been met with in experiments with other sorts of antitoxic sera, for which, as in the reaction curves for tetanus antitoxins, the mortality rate of one day—*e.g.*, fifth day—is plotted against the dose of serum. The phenomenon plays a rôle when reaction curves are used for the comparison of the potency of two sera, the result of the comparison depending upon the point of the curves chosen as endpoint.



(e) T_{50} IN THE ASSAY ON GUINEA-PIGS

In many of their records of the assays on guinea-pigs, the laboratories D and S have only given the observations up to the fourth day. For this reason, $T_{50} = 4$ has been found the most suitable. The corresponding dose is designated D_4 , and is calculated in a similar manner to D_5 by means of reaction curves.

II. VARIATION IN THE RESISTANCE OF THE ANIMALS

(a) VARIATION IN THE RESISTANCE OF MICE TO MIXTURES
OF THE SAME TOXIN AND SERUM

The variation of D_5 as determined with the same toxin and serum on different batches of mice can be estimated, not only from the protocols showing the estimation of the test dose of toxin C.35 against the standard serum, but also from the titrations of the five sera with this toxin.

The assays of the standard serum have, however, contributed most to the solution of the problem, as the test has been repeated up to six times in the individual laboratories. The assays of the commercial sera have generally been performed only once in each laboratory with the same toxin.

Table 3 gives a synopsis of D_5 for toxin C.35 and the international standard (TE), determined on different days in each laboratory, the mean from each laboratory and the standard deviation, the latter being partly indicated both in logarithmic terms and as a coefficient of variation ("per cent").

The mean values of all nineteen determinations and of their standard deviation are indicated at the foot of the table.

The variation in the resistance of the stock of mice in each institute is of approximately the same order of magnitude. It will be noticed that laboratory D has a somewhat higher standard deviation than the institutes H, P and W. A statistical test has shown that this difference is significant—*i.e.*, the stock of mice in laboratory D give a less uniform response than the stocks of laboratories H, P and W.

The remarkable result of this analysis is, however, that the deviations between the determinations of the test dose in various parts

of the world are not much greater than those occurring in the determinations of one and the same institute.

Table 3.
DEVIATIONS OF TEST DOSE FOR TOXIN C.35
IN TESTS WITH THE INTERNATIONAL TETANUS STANDARD

Laboratory	Copenhagen method			Mice (intravenous)	
	D ₅	Mean	Test dose L+ /5	Standard deviation	
				Loga- rithmic	Per cent
			Mgrm.		
W	0.760	0.771	1.18	0.013	3.0
	0.775				
	0.789				
	0.762				
D	0.833	0.796	1.25	0.028	6.7
	0.782				
	0.820				
	0.770				
S	0.774	0.774	1.11	—	—
	0.775				
P	0.767	0.767	1.18	0.005	1.2
	0.769				
	0.777				
H	0.770	0.767	1.17	0.008	1.9
	0.765				
	0.766				
	0.754				
	0.775				
All laboratories	0.770	0.775	1.19	0.021	5.0
	0.770				

The variation in the resistance of the mice, thus estimated from the variation in the determination of the test dose, has been confirmed by the comparison of the amount of each of the five sera giving $T_{50} = 5$ with the test dose as found in each laboratory.

The mean of D₅, as well as the standard deviation, is calculated for each serum. Finally, the standard deviation for all six sera is determined by dividing the sum of the squares of all deviations

from their respective means by the sum of degrees of freedom of each mean (Table 4).

Table 4.

DEVIATIONS OF D_5 FOUND IN DIFFERENT LABORATORIES WITH TOXIN C.35 AND SIX TETANUS ANTITOXINS

Serum	Copenhagen method		Mice (intravenous)	
	Mean of D_5	Degrees of freedom	Standard deviation	
			Logarithmic	Per cent
TE	0.775	18	0.021	5.0
I	3.854	3	0.0125	2.9
II	3.968	4	0.007	1.6
III	4.483	3	0.028	6.7
IV	3.773	4	0.0215	5.1
V	4.788	3	0.028	6.7
		35	0.0207	4.9

The combination of these results gives the following conclusion :

Using a defined method and the same toxin, different institutes can determine the test dose of the toxin, with a standard error of 4.9%, whichever of the six sera is chosen as standard serum.

This standard error indicates that 99 out of 100 determinations will be within the limits of 88.5% and 113%, if 100% is the true value : (commonly written : *Limits of error ($P = 0.99$) are 88.5 and 113*).

(b) VARIATION IN THE RESISTANCE OF GUINEA-PIGS TO MIXTURES OF THE SAME TOXIN AND SERA

The material for a similar estimation of the variation in the sensitiveness of *guinea-pigs* is more meagre, guinea-pigs being used for tests in three institutes only. Moreover, laboratories W and S were alone in using the Copenhagen method for the preparation of the toxin-antitoxin mixtures. The results from laboratories D and S are also comparable, however, as the same technique of preparation of the mixtures has been employed, differing from the Copenhagen method in this respect—that the time of contact was one hour at room temperature.

Tables 5a and 5b summarise the results of assays on guinea-pigs, the procedure having been the same as that mentioned in connection with Table 4.

Table 5a.

DEVIATION OF D_4 FOUND IN INSTITUTES W AND S WITH TOXIN C.35 AND SIX ANTITOXINS

Serum	Copenhagen method		Guinea-pigs (subcutaneous)	
	Mean of D_4	Degrees of freedom	Standard deviation	
			Logarithmic	Per cent
TE	0.814	7	0.026	6.2
I	3.905	2	0.008	1.9
II	4.025	1	0.017	4.0
III	4.539	1	0.024	5.7
IV	3.799	1	0.042	10.2
V	4.854	3	0.010	2.3
		15	<i>0.023</i>	<i>5.4</i>

Table 5b.

DEVIATION OF D_4 FOUND IN INSTITUTES D AND S WITH TOXIN C.35 AND FOUR ANTITOXINS

Serum	One hour combining time		Guinea-pigs (subcutaneous)	
	Mean of D_4	Degrees of freedom	Standard deviation	
			Logarithmic	Per cent
TE	0.693	4	0.012	2.8
I	3.762	1	0.003	0.6
III	4.442	1	0.025	5.9
IV	3.593	1	0.069	17.2
		7	<i>0.029</i>	<i>6.9</i>

The standard deviation of D_4 found in Table 5a—*i.e.*, 0.023 of D_4 or 5.4%—is of the same order of magnitude as that calculated from the titration in mice with the same method and reagents.

The interpretation of the second part of Table 5b is somewhat uncertain. The number of observations is too small to decide whether the difference in the technique of preparing the toxin-antitoxin mixtures has caused significant differences in the variation of D_4 . Nevertheless, the three tables show good concordance.

The conclusion of the analysis can be summarised as follows :

(1) Mice and guinea-pigs from different laboratories have shown the same degree of variation in their response to mixtures of the same toxin and sera. *The assay of tetanus sera should accordingly be expected to possess a like accuracy, whatever mice or guinea-pigs are used as experimental animals ;*

(2) Assays of different sera with the same toxin at various places can be assumed to agree to within similar limits of error as those calculated for the variation of the response in animals.

III. RELATIVE TITRES OF TETANUS SERA ASSAYED BY THE SAME METHOD AND WITH THE SAME TOXIN

(a) METHOD OF CALCULATING THE TITRE

In mixtures of toxin and serum giving the same reaction, the proportion of the dose of toxin to the dose of serum is given by the equation :

$$\frac{\text{Toxin}}{\text{Serum}} = A.$$

A is a constant factor, indicating the activity of the serum. The ratio of the activity of two sera is determined by the ratio of their A factors.

If the criterion chosen is $T_{50} = 5$ (50% mortality on the fifth day), it follows that :

$$D_5 = \log. \frac{\text{Toxin}}{\text{Serum}} = \log. A.$$

And the logarithm of the relative potency of the two sera is accordingly indicated by the difference of the D_5 's of the sera.

In the following, the titre in international units of the five commercial sera has been calculated uniformly by subtracting the D_5 of the standard serum from the D_5 of the serum tested. The antilogarithm of this difference will be the titre of serum in international units.

The whole procedure of calculating the titre of a serum from the experimental data is summarised in the following :

(1) The $\log. \text{Tx/ser.}$ or $\log. \text{Tx/A.U.}$ is calculated from the dose of toxin and serum or standard serum ;

- (2) The T_{50} for each group of animals is calculated ;
- (3) The T_{50} values are plotted against the log. Tx/ser. or log. Tx/A.U ;
- (4) The dose D_5 corresponding to $T_{50} = 5$ is determined by a curve drawn to the best fit of the plots ;
- (5) The difference between the D_5 of the standard serum and of the serum tested is calculated ;
- (6) The antilogarithm of this difference is the titre of the tested serum in international units.

(b) THE ERROR INVOLVED IN THE ASSAY OF THE FIVE TETANUS SERA WITH TOXIN C.35 USING THE COPENHAGEN METHOD

The Copenhagen method was used by all the laboratories participating in the enquiry. Two laboratories (W and S), besides assaying in mice, performed tests on guinea-pigs subcutaneously. Seven series of titres are thus available for the estimation of the error of this test.

The titres were calculated in the manner summarised above, and the results are given in Table 6, part A.

For laboratory D, only the titres of sera II and IV are recorded, the tests of the other three sera being too incomplete for the estimation of D_5 . For each serum, the mean of the titres is given at the foot of the column, and after each titre is placed the deviation from this mean, expressed as a percentage.

These means and deviations are calculated from the logarithmic values of the titres as obtained by the subtraction of the D_5 of the standard serum from the D_5 of the serum tested. The logarithmic deviations serve for the calculation of the standard deviation, which is given at the foot of the column for each serum, converted into terms of a percentage.

Finally, the squares of all logarithmic deviations are added together and divided by the degrees of freedom of all titrations (27). The square root of this quotient is the estimate of the standard deviation of the method. The logarithmic value of this quantity was found to be *0.0235*, of which the antilogarithm is *1.055*. The standard deviation may accordingly be indicated as 5.5%, as in the table. From this value, the limits of error ($P = 0.99$) are calculated as 87% and 115%.

These figures express *the accuracy of the assay of tetanus antitoxins with one toxin*, which was the principal aim of this investigation :

If one test toxin and a well-defined technique be used, 99 out of 100 assays of tetanus antitoxins will fall within the limits of 87% and 117%, if 100% is the true value.

Commonly, in the assay of commercial tetanus sera, the titre is wanted with an accuracy of 10%. It may therefore be of interest to indicate the accuracy of the test with one toxin as follows :

3 out of 100 titrations will give results differing more than $\pm 10\%$ from the true value.

It will be noticed that just 1 out of the 32 titrations recorded in Table 6, part A, differs by more than 10% (*viz.*, 12%). This seems to be the highest degree of accuracy obtainable by the assay of tetanus antitoxin.

It was concluded in Chapter II, in view of the variation in the sensitiveness of animals, that mice and guinea-pigs are likely to give the same accuracy in the assay of a tetanus antitoxin. This supposition is clearly confirmed by the results shown in Table 6, part A, the deviations of the titres obtained by the titration on guinea-pigs not being greater than those found in the mouse tests. But another fact which should be emphasised is that the assays on guinea-pigs do not deviate *systematically* from the means.

The investigation has thus given no reason for preferring either of the two species of animals from the point of view of the accuracy of the assay, and—with toxin C.35 at least—has shown no significant divergence between the titres obtained on guinea-pigs and those obtained on mice.

(c) ASSAYS WITH A COMBINING TIME OF ONE HOUR AND TOXIN C.35

Table 6, part B, shows the assays performed in laboratories D and S with toxin C.35 using a technique differing from the Copenhagen method by having a combining time of 1 hour at room temperature instead of 24 hours for the toxin-antitoxin mixtures.

The means of the values obtained in the two laboratories have been compared to the mean values of the five sera indicated in Table 6, part A. The deviations of the values of the five sera

obtained by differing methods are given at the foot of the table. For serums I, III and V, this difference is to be considered insignificant, while the deviation of serum II is somewhat greater, although not of definite significance. Only serum IV has a significant deviating value obtained with the method of a combining time of 1 hour. These deviations may be considered as the result of a difference in the avidity of the serum compared with the avidity of the standard serum.

Sera I, II, III, and V are supposed to have much the same degree of avidity as the standard, while serum IV is most probably much less avid than the standard serum.

IV. THE VARIATION IN TITRE OF TETANUS SERA TITRATED WITH VARIOUS METHODS AND TOXINS

The four laboratories D, H, P and S have assayed the five sera with the test toxin used for routine work in the respective laboratories and using the routine technique of the institute. All these institutes have accepted a combining time of 1 hour for the toxin-antitoxin mixtures as a routine. Other less important divergences from the Copenhagen method are subcutaneous injection of mice, as used in laboratories H and P, intramuscular injection of guinea-pigs used in laboratory S, and preparation of the toxin-antitoxin mixtures without considering the pH.

The results of the assays are given in Table 6, part D, in A.U. per c.c. Included are the results from Table 6, part B, indicating the mean values obtained with toxin C.35 and with the technique used at institutes D and S. Mean values are calculated according to the same procedure as was mentioned in connection with Table 6, part A, and the deviations from these are added after each titre.

The total deviations are used to estimate the limits of error of the tests performed with different toxins and methods using a 1-hour combining time. The calculation has been described in connection with Table 6, part A, and has resulted in a standard deviation of 14.3% and *limits of error* ($P = 0.99$) of 71% and 141%.

Laboratories D and S have performed assays with their routine toxins, but using the Copenhagen method. These results, together with the means of Table 6, part A, are summarised in part C.

Table 6.

**SYNOPSIS OF THE TITRES OF THE FIVE COMMERCIAL SERA TITRATED AGAINST THE INTERNATIONAL TETANUS STANDARD
Toxin C.35.**

A. 24 hours combining time.

Animal used	Laboratory	Dose of toxin neutralising 0.20 A.U. Mgram.	Serum I		Serum II		Serum III		Serum IV		Serum V		Standard error and limits of error (P = 0.99)
			A.U. per c.c.	Deviation %	A.U. per c.c.	Deviation %	A.U. per c.c.	Deviation %	A.U. per c.c.	Deviation %	A.U. per c.c.	Deviation %	
Guinea-pigs	W	1.30	1,228	+0.7	1,671	+5.0	5,521	+4.2	1,035	+3.8	10,790	+0.5	
Mice (intravenous)	W	1.18	1,253	+1.4	1,563	+1.9	5,636	+6.4	1,067	+6.9	10,820	+0.9	
Guinea-pigs	S	1.29	1,259	+1.9	1,596	+0.2	5,152	+2.8	910	+9.7	11,170	+4.2	
Mice (intravenous)	S	1.11	1,277	+3.3	1,722	+8.2	5,662	+7.4	991	+0.7	11,590	+8.2	
Mice (intravenous)	D	1.25	No value		1,483	+7.4	No value		942	+5.9	No value		
Mice (intravenous)	H	1.17	1,186	+4.2	1,585	+0.5	4,830	+9.7	1,030	+3.3	9,572	+12.0	
Mice (intravenous)	P	1.18	1,214	+1.9	1,545	+3.0	4,989	+6.2	1,016	+1.9	10,520	+1.9	
Mean titre			1,236		1,592		5,297		998		10,720		
Standard deviation ...				2.8		5.1		7.1		5.8		6.4	5.5% 87%-115%

B. 1 hour combining time.

Guinea-pigs	D	0.98	1,178		No value		5,433		898		No value		
Guinea-pigs	S	1.02	1,135		1,790		5,636		685		11,350		
Mean			1,156		1,790		5,534		785		11,350		
Deviation from mean of part A				+6.9		+12.5		+4.5		+27.1		+5.9	

Different Toxins.

C. 24 hours combining time.

Animal used	Toxin	Laboratory	Serum I		Serum II		Serum III		Serum IV		Serum V		Standard error and limits of error (P = 0.99)
			A.U. per c.c.	Deviation %	A.U. per c.c.	Deviation %	A.U. per c.c.	Deviation %	A.U. per c.c.	Deviation %	A.U. per c.c.	Deviation %	
Mice (intravenous)	K	D	1,419	+6.4	1,754	+2.3	5,623	+1.4	824	+13.8	10,470	+5.0	
Mice (intravenous)	7m5	S	1,349	+1.2	1,799	+5.0	5,861	+5.7	1,000	+6.7	11,810	+7.4	
Mice (intravenous) and guinea-pigs	C.35	Mean values from part A	1,236	+7.9	1,592	+7.7	5,297	+4.7	998	+6.4	10,720	+2.6	
	Mean		1,334		1,714		5,547		938		10,990		
	Standard deviation			7.2		6.7		5.4		11.7		6.7	7.7% 83%-121%

D. 1 hour combining time.

Mice (subcutaneous)	Tg.234	P	1,364	+10.2	1,402	+21.4	4,830	+20.5	1,219	+30.9	10,380	+10.4	
Mice (subcutaneous)	A.W.189	H	1,259	+1.6	1,687	+0.9	5,794	+0.5	986	+5.9	10,970	+4.5	
Guinea-pigs	K	D	1,265	+2.1	1,858	+9.2	7,586	+30.5	980	+5.2	13,190	+15.1	
Guinea-pigs	7m5	S	1,164	+6.4	1,824	+7.2	5,701	+2.1	760	+22.5	11,590	+1.2	
Guinea-pigs	C.35	Mean values from part B.	1,156	+7.2	1,790	+5.2	5,534	+5.2	785	+18.6	11,350	+0.9	
	Mean		1,239		1,702		5,821		931		11,460		
	Standard deviation			7.2		12.2		17.8		21.4		9.4	14.3% 71%-141%

The standard deviation of this set of assays performed with three toxins appears to be definitely lower than that given in Table 6, part D. In fact, the assays with toxins K, 7m5 and C.35 using the Copenhagen method have not given titres which differ significantly from the results obtained with one toxin.

It is impossible, however, to determine whether the fact that the same technique is used for the assay has brought about the concordance of results. It may be more reasonable to assume that the three toxins happen to possess the same properties. More toxins ought to have been examined for the solution of this problem.

The large deviations recorded in Table 6, part D, are most probably to be regarded as originating as much in the use of different test toxins as in that of a shorter combining time (1 hour).

It is generally admitted that differences in the avidity of various sera will give rise to larger deviations in the titre after a shorter combining time than after a longer combining time. Table 6, part D, provides, however, several instances of sera showing a high activity when tested with one toxin and a considerably lower value when tested with another. The extremes are represented by the values of serum IV, determined as 1,219 A.U. with toxin Tg 234 and 760 A.U. with toxin 7m5.

CONCLUSION

This investigation has given evidence of the fact that the accuracy of the assay of a given tetanus antitoxin is greatly decreased when different toxins are used for the titration. It is possible that uniformity in the technique of titration will result in a better concordance, but still unknown differences in the properties of toxins are likely to cause discrepancies.

The standardisation of the tetanus sera is not satisfactorily accomplished by the establishment of an international standard antitoxin. The preparation of a test toxin to be used in all laboratories would possibly solve the question, but in view of the immense amount required to meet the world demand, it will be necessary to make sure that a toxin of exactly the same qualities can be reproduced when the first lot is exhausted.

Annex 1b.

ASSAY OF THREE TETANUS ANTITOXINS

By

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TOXINS I, IV AND "MEZCLA "

Toxin I.—Obtained after three days of incubation, filtration, precipitation with $(\text{NH}_4)_2\text{SO}_4$, desiccation, etc.¹

Toxin IV.—Obtained in the same way as toxin I, but after thirty days of incubation.

"*Mezcla*" *toxin.*—Mixture prepared at the moment of use containing 0.0034 gm. of toxin IV + 0.35 c.c. of toxoid 5 in a volume of 10 c.c. The toxoid is prepared by the addition of 6‰ of formalin to toxin I, which is then dialysed and precipitated with acetic acid (pH 4). The precipitate is dissolved and adjusted to pH 7.2, preserved with 1/5,000 of merthiolate and passed through a Seitz filter. The volume is equal to one-tenth of the original toxoid.¹

Standard serum.—"Washington", from the National Institute of Health, having a strength of 5 "American" units per c.c.

¹ See A. SORDELLI, F. MODERN & J. FERRARI : *Revista del Instituto Bacteriologico*, 1936, 7, No. 4, page 622.

Diluent.—NaCl. 9 ‰.

Volume injected.—Guinea-pigs : 2 c.c. (intramuscular) ;
Mice : 1 c.c. (subcutaneous).

Combining time.—Guinea-pigs : one hour.
Mice : one hour.

Temperature of laboratory : 18°-22° C.

Dose of serum :

Guinea-pig : 0.1 American units = 0.2 international units.

Mouse : $\left\{ \begin{array}{l} 0.1 \text{ American units} = 0.2 \text{ international units.} \\ 0.01 \text{ American units} = 0.02 \text{ international units.} \end{array} \right.$

Weight of animals.—Guinea-pigs : 280-320 grammes.
Mice : 18-20 grammes.

Method.—Results were noted daily. Each dose was injected into six animals. The dose taken as an indicator was one killing three or more, but less than six, animals. Observation terminated after four days in the case of the guinea-pig and six days in the case of the mouse.

Sera to be tested.—The sera were sent to us by A. T. GLENNY. They were numbered 3010, 3234 and 3416, and in GLENNY'S opinion represented three different types of antitoxin. By means of these sera it was shown that the interrelation established between the standard serum, the test toxin and an unknown serum held good only for that toxin or toxins of identical *constitution* (the standard serum remaining, of course, the same throughout).

Test Dose of Toxins.

	Guinea-pig : 0.2 I.U. 1-hour incubation	Mouse : 0.2 I.U. 1-hour incubation	Mouse : 0.20 I.U. 1-hour incubation
Toxin I	0.22 mgrm. = 275 M.L.D.	0.30 mgrm. = 600 M.L.D.	0.027 mgrm. = 54 M.L.D.
Toxin IV	0.34 mgrm. = 113 M.L.D.	—	—
"Mezcla" toxin	0.29 c.c. = 33 M.L.D.	0.26 c.c. = 45 M.L.D.	0.032 c.c. = 5.4 M.L.D.

For neutralisation without previous contact, the dose of standard serum necessary to neutralise the test dose of the toxin was determined. The following values were obtained :

Toxin I	0.28 I.U.
Toxin IV	0.24 I.U.
" Mezcla " toxin	0.24 I.U.

By means of these values, the neutralising power of unknown sera without previous contact was likewise calculated.

First Test.

Guinea-pig.—Combining time : 1 hour.

Toxin I		Toxin IV		" Mezcla " toxin	
Serum (c.c.)	Result	Serum (c.c.)	Result	Serum (c.c.)	Result
<i>Serum 3010</i>					
1/2,000	6/6 ¹	1/2,500	6/6	1/3,330	6/6
1/1,660	2/6	1/2,000	2/6	1/2,860	2/6
1/1,400	2/6	1/1,660	0/6	1/2,500	0/6
<i>Serum 3234</i>					
1/10,000	6/6	1/9,090	6/6	1/7,140	6/6
1/9,090	2/6	1/8,330	1/6	1/6,250	6/6
1/8,330	0/6	1/7,140	0/6	1/5,000	0/6
<i>Serum 3416</i>					
1/10,000	6/6	1/10,000	6/6	1/9,000	6/6
1/9,000	5/6	1/9,000	6/6	1/7,500	4/6
1/8,180	4/6	1/8,180	5/6		
1/7,500	1/6	1/7,500	1/6	1/6,400	0/6

¹ 6/6 indicates that 6 animals out of 6 died.
 0/6 indicates that 0 animals out of 6 died.

Potency of Sera expressed in International Units.

Guinea-pig.—Combining time : 1 hour.

Serum	Toxin I 275 M.L.D.	Toxin IV 113 M.L.D.	" Mezcla " toxin 33 M.L.D. per test dose
No.			
3010	366	450	620
3234	1,908	1,740	1,124
3416	1,800	1,636	1,500

BIOLOGICAL STANDARDISATION

Second Test.

Guinea-pig.—Without previous contact.

Toxin I		Toxin IV		" Mezcla " toxin	
Serum (c.c.)	Result	Serum (c.c.)	Result	Serum (c.c.)	Result
<i>Serum 3010</i>					
1/2,000	6/6	1/2,500	6/6	1/3,330	6/6
1/1,660	5/6	1/2,000	4/6	1/2,860	6/6
1/1,400	2/6	1/1,660	1/6	1/2,500	4/6
<i>Serum 3234</i>					
1/8,330	6/6	1/8,330	6/6	1/6,250	6/6
1/7,140	5/6	1/7,140	5/6	1/5,550	6/6
1/6,250	1/6	1/6,250	0/6	1/5,000	1/6
<i>Serum 3416</i>					
1/6,400	6/6	1/6,400	6/6	1/7,500	6/6
1/5,620	3/6	1/5,620	3/6	1/6,400	6/6
1/5,000	2/6	1/5,000	0/6	1/5,620	3/6

Potency of Sera expressed in International Units.

Guinea-pig.—No contact.

Serum	Toxin I 275 M.L.D.	Toxin IV 113 M.L.D.	" Mezcla " toxin 33 M.L.D. per test dose
No.			
3010	464	480	600
3234	1,990	1,712	1,200
3416	1,570	1,350	1,350

Third Test.

Mouse (0.2 unit).—Combining time : 1 hour.

Toxin I		" Mezcla " toxin	
Serum (c.c.)	Result	Serum (c.c.)	Result
<i>Serum 3010</i>			
1/4,000	6/6	1/5,000	6/6
1/3,333	4/6		
1/2,850	0/6	1/4,000	0/6
<i>Serum 3234</i>			
1/8,330	6/6	1/1,500	6/6
1/7,140	0/6	1/4,160	0/6
<i>Serum 3416</i>			
1/9,000	6/6	1/9,000	6/6
1/7,500	0/6	1/7,500	2/6

Polency of Sera expressed in International Units.

Mouse (0.2 unit).—Combining time : 1 hour.

Serum	Toxin I 600	" Mezcla " toxin 45 M.L.D. per test dose
No.		
3010	666	900
3234	1,540	920
3416	1,620	1,620

Fourth Test.

Mouse (0.02 unit).—Combining time : 1 hour.

Toxin I		" Mezcla " toxin	
Serum (c.c.)	Result	Serum (c.c.)	Result
<i>Serum 3010</i>			
1/25,000	6/6	1/50,000	6/6
1/20,000	1/6	1/40,000	3/6
1/16,600	0/6	1/30,000	0/6
<i>Serum 3234</i>			
1/125,000	6/6	1/100,000	6/6
1/100,000	6/6	1/79,300	6/6
1/79,300	5/6	1/60,200	3/6
<i>Serum 3416</i>			
1/81,800	6/6	1/81,800	6/6
1/70,300	6/6	1/70,300	2/6
1/60,000	0/6	1/60,000	0/6

Polency of Sera expressed in International Units.

Mouse (0.02 unit).—Combining time : 1 hour.

Serum	Toxin I 54 M.L.D.	" Mezcla " toxin 5.4 M.L.D. per test dose
No.		
3010	450	800
3234	1,580	1,200
3416	1,300	1,500

BIOLOGICAL STANDARDISATION

Comparative Table of Antitoxin Values.

(In international units).

Method	Guinea-pig.— Combining time : 1 hour			Guinea-pig.— Without previous contact			Mouse (0.2 unit).— Combining time : 1 hour		Mouse (0.02 unit).— Combining time : 1 hour	
	I 275	IV 113	Mez- cla 33	I 275	IV 113	Mez- cla 33	I 600	Mez- cla 45	I	Mez- cla
Sera 3010	366	450	620	464	480	600	666	900	450	800
3234	1,908	1,740	1,124	1,990	1,712	1,200	1,540	920	1,580	1,200
3416	1,800	1,636	1,500	1,570	1,350	1,350	1,620	1,620	1,300	1,500

Annex 1c.

**THE STANDARDISATION OF TETANUS ANTITOXIN:
FACTORS INFLUENCING THE ASSAY**

By

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INTRODUCTION

During the period which has elapsed since the establishment of the various national standards and of the international standard for tetanus antitoxin, reports have been made from time to time that these standards are no longer equivalent. At one time, it was considered probable that one or more of the standards had declined in potency since its preparation, but a careful examination of the protocols on which the reports of non-equivalence were based suggested the possibility that the discrepancies might be accounted for in other ways.

In the course of the decade 1926-1936, the various national standards had been compared by several workers in different countries ; a variety of test toxins had been employed ; some workers had used guinea-pigs for their comparisons, others mice ; different antitoxin levels had been used for the comparisons ; the dose of toxin chosen had sometimes been sufficient to cause death on the fourth day (L_+) and sometimes scarcely enough to give traces of tetanus (L_0) ; some workers allowed their mixtures to combine for only thirty minutes at room temperature ; others left them as long as twenty-four hours before injection ; the majority of tests had been carried out using only one or two animals for each mixture ;

finally, some workers injected their animals intravenously, some intraperitoneally, some subcutaneously and some intramuscularly. To complicate matters, in 1935 a new serum had been substituted for the original preparation of the international standard.

As far back as 1927, it had been shown by HARTLEY (unpublished) that qualitative differences existed between the American and British standards. The differences were most apparent in tests on guinea-pigs, in which it appeared that the British standard had a much flatter neutralisation curve than the American standard. This could be shown with five different toxins. It was not so evident when mice were used as test animals. It was also shown by HARTLEY that tetanus toxin-antitoxin mixtures dissociated on dilution, the degree of dissociation varying with the sample of antitoxin. The subject has also been investigated in detail by GLENNY, BARR, ROSS and STEVENS (1932), and by the present writer, who found that compounds of the British standard antitoxin showed the dilution phenomenon, while those of the American and second international standards did not. The significance of these facts will be discussed later. In 1934, some experiments of mine indicated that the relative potency of sera is not independent of the test toxin used, and other experiments suggested that the species of animal used might influence the result.

In the summer of 1936, informal conversations were held at Copenhagen, where the whole matter was discussed. At this conference, the possibility was recognised that the reported differences of potency of the various standards might be due either to sampling errors—*i.e.*, to the fact that too few animals were used in the tests—or else to qualitative differences in the sera and toxins, resulting in differences in potency ratios when the test toxin, test animal or method was changed. A plan of future experiments was made to investigate the influence of such changes on the comparative potency of different samples of tetanus antitoxin.

PART I.—THE COPENHAGEN 1936 PLAN

The purpose of the proposed enquiry was to determine whether certain factors (the particular test toxin used, the time the toxin-antitoxin mixtures were allowed to combine before injection and

the route of injection selected) influence the estimates of relative potency of samples of tetanus antitoxin.

(1) It was decided that the work should be carried out at Hampstead.

(2) Antitoxin comparisons should be confined to the second international standard and the first British standard.

(3) Mice should be used as test animals.

(4) At least twenty mice should be injected with each mixture.

(5) Comparisons should be made both with intravenous and with subcutaneous injections.

(6) Both long and short combining times should be investigated.

(7) The test dose of toxin used should be such as to kill half the mice injected within six days when combined with 0.05 international unit of international standard antitoxin.

(8) Two toxins, C.35 and 458, suspected of being qualitatively different, should be used for the comparisons.

(9) Attempts should be made to estimate the precision of which tetanus antitoxin assay is capable.

THE EXECUTION OF THE PLAN

Materials.

Antitoxins.—Both standard antitoxins were used in glycerol-saline solution purporting to contain 10 international units per c.c.

Toxins.—C.35 was a dry toxin prepared at Copenhagen from strain T.67 (National Collection of Type Cultures, England), TULLOCH, type 2 ; 458 was a glycerinated toxin prepared at the Lister Institute, Elstree, England, in 1934, from strain 23 (Elstree), TULLOCH, type 6.

Method.

In each experiment, the neutralisation curves of the two antitoxins were compared, using a constant test dose of toxin and five doses of each antitoxin, each dose differing from the next by 10%. The reagents were diluted in boric-acid borate buffer of pH 8.0.

Mixtures, prepared so that the test dose of toxin and varying doses of antitoxin were contained in 0.5 c.c., were allowed to stand for a certain interval at room temperature, after which 0.5 c.c. of each mixture was injected into each of a group of twenty mice.

In each experiment, the two sera were compared under precisely the same conditions. These conditions were, however, varied from experiment to experiment. In all, eight comparisons of the two standards were made, each involving 200 mice. Thus :

No. of experiment	Toxin used	Contact time of mixtures before injection (hours)	Route of injection
1	C. 35	24	intravenous
2		24	subcutaneous
3		1	intravenous
4		1	subcutaneous
5	458	24	intravenous
6		24	subcutaneous
7		1	intravenous
8		1	subcutaneous

THE ESTIMATION OF THE RESULT

In statistical analyses of the response to a biological stimulus, it is usual to distinguish between the "quantitative" or "continuous" type and the "quantal" or "all or none" type. As an instance of the former, one may cite the production of antibody in response to the injection of antigen; the amount of antibody produced may be quantitatively measured. With many biological products, however, a quantitative measure of response is not easily obtainable. In these instances, it is usual to measure the proportion of animals which cross some fixed threshold that can be readily observed. This threshold may be death, anæsthesia, convulsion, or some other symptom, according to the drug administered.

The response to injections of tetanus toxin-antitoxin mixtures is intermediate in type between the continuous and quantal. Thus, while it is not at present possible to assign a quantitative value to the degree of response of any one animal to a dose of tetanus toxin, a carefully conducted titration of tetanus toxin by antitoxin results in a wealth of information, of which the percentage of animals

responding positively at a given threshold is only a single item. The record of a tetanus toxin-antitoxin titration shows the time of onset of tetanus in each animal, the rapidity of progression of symptoms, and the time of death ; one can study different thresholds by observing the percentage of animals just showing tetanus within a certain time, or the percentage dead within different periods after the injection ; one can also measure the mean survival time of the animals in any one group. One can thus study the regression on the dose of the mean survival time, or of the percentage dead or showing tetanus within different periods after injection. The problem is how to make the best use of all this information so as to obtain as precise an estimate as possible of the protective effect of the sample of antitoxin under test. A method for combining the different kinds of information provided by one test into a quantitatively accurate estimate of potency has not yet been evolved ; in this work, therefore, the estimates of potency were derived by confining ourselves to a statistical study of a quantal response—in this instance, the proportion of deaths occurring within six days. It is, however, recognised that this method does not make use of all the information available and is therefore inefficient. There is a good deal of truth in the contention made by some workers that results, calculated by statistical methods from dose-response curves, habitually underestimate the precision of which the assay is capable. For the laboratory worker judges the result of his experiment in an all-round way and makes mental allowance in his estimate for information of a type which cannot be considered by statistical methods. To take an instance, in two groups of mice, all the mice in both groups may survive the specified time-limit and would thus be recorded as giving no response if death were the measure of response adopted. The laboratory worker, on the other hand, may be able to distinguish the two groups quite clearly, in that one group may have remained perfectly healthy throughout the experiment, whereas the other group may have sickened and then recovered. If this or similar information could be taken into account, we should be justified in assigning a higher probability of significance to an event than that calculated by the statistical methods at present available.

THE STATISTICAL ANALYSIS OF THE EXPERIMENTAL RESULTS

I am indebted to Dr. J. O. IRWIN and Mr. E. A. J. SHRIMPTON, of the London School of Hygiene and Tropical Medicine, for the very able analysis of the results of the laboratory tests. Their report is embodied in the succeeding section.

The Rectilinearity of the Dose-response Relationship.

IRWIN and SHRIMPTON first tested whether the dose-response curves could be adequately represented by straight lines. By transforming the proportion of mice protected in each group into probits (BLISS, 1935) and plotting these against the logarithms of the corresponding doses, sixteen curves were obtained which in no instance differed significantly from straight lines when tested for goodness of fit by the χ^2 method. Moreover, by combining the evidence of the sixteen experiments, the following values were obtained:

$$\begin{aligned} \chi^2 &= 34.75 \\ n \text{ (degrees of freedom)} &= 47 \\ \sqrt{\chi^2} - \sqrt{2n-1} &= -1.31 \end{aligned}$$

The dose-mortality curve can be said to be adequately represented by a straight line if $\sqrt{\chi^2} - \sqrt{2n-1}$ is less than +1.65. Thus, in these experiments, the difference from a straight line is not significant.

The Relative Potencies of the Two Standards.

The equation of the straight line relating dose and response is given by $y = bx + c$, where y is the probit corresponding to the proportion of mice protected at log. dose x , and b is the slope of the line. For the assay of one sample in terms of another, a dose-response curve must be constructed for each. According to GADDUM (1933), "a comparison is only possible if the slopes of the two curves are equal, and all the data from both curves must be taken into account in calculating the value of b ". IRWIN and SHRIMPTON, making the assumption that there was no difference between the slopes of the international and British standards, calculated the relative potencies of the two standards under all eight sets of conditions. The values obtained are given in Table 1.

Table 1.
POTENCY OF BRITISH STANDARD IN TERMS
OF INTERNATIONAL STANDARD (COMMON SLOPE)

No. of experiment	Combining time, and route of injection	Toxin	Potency, British	Limits of error ¹ of R (P. 90)	Log. R S.E.
			Potency, international		
1	24 hours, i.v.	C.35	0.876	0.822—0.934	5.30
2	24 hours, s.c.		0.962	0.910—1.016	1.83
3	1 hour, i.v.		0.883	0.834—0.935	5.56
4	1 hour, s.c.		0.898	0.843—0.956	4.39
	Mean		0.905		
5	24 hours, i.v.	458	0.989	0.956—1.024	0.83
6	24 hours, s.c.		1.034	0.986—1.084	1.87
7	1 hour, i.v.		0.988	0.927—1.054	0.48
8	1 hour, s.c.		1.060	1.025—1.098	4.38
	Mean		1.018		

Before proceeding to discuss these values, it is necessary to consider whether we are justified in assuming that the dose-response curves of the two standards have the same slope.

The Slopes of the Dose-response Curves.

The values of *b* for the dose-response lines of the two standards were calculated by IRWIN and SHRIMPTON, and the results are given in Table 2.

Table 2.
SLOPES OF DOSE-RESPONSE CURVES

Combining time and route of injection	Toxin					
	C.35			458		
	International <i>b</i> ₁	British <i>b</i> ₂	$\frac{b_1-b_2}{S.E.}$	International	British <i>b</i> ₂	$\frac{b_1-b_2}{S.E.}$
24 hours, i.v.	49.6	19.9	3.40	69.1	57.2	0.55
24 hours, s.c.	48.6	19.9	3.32	38.6	28.3	1.34
1 hour, i.v.	38.4	27.0	1.42	55.8	26.3	2.04
1 hour, s.c.	32.2	18.3	2.40	54.3	32.8	2.20

¹ See Table 5, page 754.

It will be noted that, in every instance, the regression line of the international standard has a steeper slope than that of the British standard. The significance of the differences was tested by calculating the ratio of the difference to its standard error, and these values are also given in the table. In five instances, the individual differences are already statistically significant, and the uniformity of the result of the examination as a whole leaves no doubt as to its significance. This confirms the findings of HARTLEY, that the slopes of the dose-response curves of different samples of tetanus antitoxin may vary.

It was found that the fitting of a common slope to the dose-response curves of both standards, although only approximately correct, affected significantly the rectilinearity of only one of the eight curves (that using toxin C.35 with a twenty-four hour contact time and intravenous route). The other seven curves were neither of themselves significantly different from straight lines, nor, when their evidence was combined, was there any significant deviation. The divergence in the instance cited was, moreover, not sufficient to be of much practical importance, and the straight-line formulæ were therefore used in further calculations.

The Influence of Slope Differences on the Potency Ratio.

The demonstration that the dose-response curves of the two standards have significantly different slopes is exceedingly important, since, if the regression lines are not parallel, the estimate of potency ratio will not be independent of the degree of response selected as an end-point in the titration. This effect will be greater, the greater the difference in slope between the two preparations being compared. Actually, in comparisons of the British and international standards, the effect is not large. In Table 3, the ratio of the potency of the British to that of the international standard is given for three different end-points—viz., survival of 80%, 50% or 20% of the mice for six days.

It will be seen that when the protection-level selected as end-point is lowered, the serum with the flatter curve appears relatively stronger, and, when it is raised, relatively weaker. However, it will be seen from a comparison of Tables 1 and 3 that the change in potency ratio produced on changing the level from 50% to 80% or 20% survival was, in thirteen instances out of sixteen, within

the $P = 0.99$ limits of error of the experiment. Further, when the end-point chosen is 50% survival, the values obtained when the individual slopes are used differ but slightly from those computed from the common slope assumption.

Table 3.
EFFECT ON POTENCY RATIO OF SELECTING DIFFERENT END-POINTS
IN THE COMPARISON OF ANTITOXINS OF DIFFERENT SLOPE

Combining time and route of injection	Toxin	Potency of British in terms of international at given protection-levels		
		80%	50%	20%
24 hours, i.v.	C.35	0.816	0.865	0.917
24 hours, s.c.		0.909	0.963	1.020
1 hour, i.v.		0.861	0.880	0.899
1 hour, s.c.		0.855	0.895	0.937
24 hours, i.v.	458	0.983	0.989	0.995
24 hours, s.c.		1.017	1.036	1.055
1 hour, i.v.		0.954	0.993	1.031
1 hour, s.c.		1.037	1.061	1.086

On the other hand, the range of variability of end-points that are in common use is much greater than that shown in Table 3. The L_+ , as defined in the British Pharmacopœia, 1932 (deaths occurring on the average on the fourth day), would almost always result in a mortality of 100% within six days, whereas the L_0 end-point involves complete protection with not even any sign of tetanus. It is probable that a significant difference in the estimate of the relative potency of two sera of different slope might be found on changing from the L_0 to the L_+ end-points, as indeed is suggested by the results reported by MADSEN and WALBUM (1923).

Moreover, there is no reason to suppose that the British and international standards are extreme in regard to slope. It is fully possible that the examination of more sera would reveal wider divergences.

The Choice of a Suitable End-point.

The following arguments have been put forward in support of the selection of some particular end-point in tetanus toxin-antitoxin titrations.

GLENNY (personal communication) uses the L_+ (as defined in the British Pharmacopœia) because he considers that the change

in survival time for a given change in dose is at a maximum on the fourth day and that this end-point therefore results in the greatest precision of testing.

On theoretical grounds, one can argue that the best end-point is 50% survival, and that the period of observation should be long enough to ensure that no specific deaths occur beyond that time. In practice, this is not feasible, as very occasionally deaths occur even at periods as long as thirteen days after injection. Prolonging the test to this point involves an increased risk of deaths from non-specific causes, besides being inconvenient to the worker.

Alternatively, it can be argued that, in practice, antitoxin is required to protect all patients; not only 50%. There is evidence that samples of antitoxin with flat neutralisation curves (non-avid sera) are of less therapeutic value, unit for unit, than those with steep curves. In a comparison of a sample with a flatter curve than the standard, allowance would be made for this lack of quality if the full protection-level (L_0) were used. The objection to the L_0 end-point is that it is not easy to determine. But a compromise might be effected by taking what I shall call the Lt 50 end-point—viz., using a test dose of toxin which, when combined with the standard dose of antitoxin, produces in half the mice injected a definite degree of tetanus (which could be fixed by agreement) within six days. The choice of this end-point would weight the estimate of potency in favour of the more avid serum, and it should be relatively easy to determine.

The Influence of Toxin on the Slope of the Dose-response Curve.

It can be seen from Table 2 that, in six instances out of eight, the curve obtained by using toxin 458 has a steeper slope than the corresponding curve using toxin C.35. In three instances, the slopes with toxin 458 were significantly steeper than those with toxin C.35, and the combined evidence of all the eight experiments suggests that 458 has a real tendency to produce steeper slopes than C.35.

The Influence of the Particular Test Toxin on the Potency Estimate.

Returning to Table 1, in which the estimates of the potency of the British standard relative to that of the international standard are recorded for a variety of experimental conditions, it will be

seen that, in all the four experiments involving toxin C.35, the British standard appears to be weaker than the international standard. The significance of the difference is shown by the last column, where the ratios of the differences to their standard errors are recorded. In experiment 2, the observed difference is such as would occur by chance only about seven times in every hundred trials ; in experiments 1, 3 and 4, the probability is very much smaller, and there is no doubt that the difference in potency of the two standards is significant.

If this toxin only had been used for the comparison, the conclusion might have been drawn that the British standard had deteriorated in potency since its original standardisation. But examination of the results of experiments 5-8 shows that, when toxin 458 is used, the two assays in which the intravenous route was used make the British standard the lower, while the two in which the mixtures were injected subcutaneously return the British standard as the higher. In only one instance out of four was the difference in potency between the standards significant, and, in this case, the British standard showed the higher potency.¹ The influence of the toxin on the estimate of potency can be seen more precisely by considering the experiments in pairs, the experiments in one pair being carried out under the same conditions. When this was done, it was found that for each condition of experiment, the potency estimate of the British standard was significantly greater with toxin 458 than with toxin C.35.

The influence of the test toxin on tetanus antitoxin assay is considered further in Part II of this paper.

The Influence of the Route of Injection on Potency Ratio.

The influence of injection route on the estimate of potency can be seen by comparing experiments 1 and 2, 3 and 4, 5 and 6, 7 and 8 (Table 1). In each pair of experiments, the ratio of the potency

¹ In this connection, it should be noted that experiment 8 was repeated twice. The first test, performed at about the same time as experiments 1-7, gave a potency British/international of 1.0129, but provided inconclusive data with regard to slope. The second test, which is the one recorded in Table 2, was performed two years later. Toxin 458 is glycerinated and may have undergone some measure of qualitative change (e.g., further conversion to toxoid) during the intervening period, which might account for the higher potency ratio obtained at the later date.

of the British to that of the international standard was higher by the subcutaneous than by the intravenous route. When the results of all four pairs were combined, it was found that the difference was clearly significant.

This result is what might be expected. The British standard is known to dissociate from its combination with toxin more readily on dilution than the international standard. The technique of intravenous injection, which involves rapid dilution of the mixtures in the body fluids, would be expected to make the relative potency of the more dissociable serum lower than the technique of subcutaneous injection, where the absorption and dilution is slower.

For therapeutic purposes, a loose combination between toxin and antitoxin which readily dissociates is clearly undesirable. It is probably advisable, therefore, to select conditions of assay which distinguish in favour of firmly binding samples of antitoxin. The intravenous route has the merit of assigning a relatively lower potency to dissociating sera.

The Influence of Contact Time on Potency Ratio.

Both sera combine rather slowly with toxin, more antitoxin being necessary to neutralise the same amount of toxin after one hour than after twenty-four hours of contact. The difference is more apparent when the injections are given intravenously than when the subcutaneous route is used. The figures are shown in Table 4. That the difference is due to slow combination rather than to deterioration of the toxin on long standing was shown by setting up other series in which the toxin and antitoxin dilutions were

Table 4.

RATIO OF AMOUNT OF ANTITOXIN REQUIRED TO NEUTRALISE THE SAME AMOUNT OF TOXIN AFTER TWENTY-FOUR HOURS TO THAT REQUIRED AFTER ONE HOUR OF COMBINATION

Antitoxin and injection route	Toxin	Ratio
British standard, i.v.	C.35 (0.29 mgm.)	1.20
British standard, s.c.		1.13
International standard, i.v.		1.27
International standard, s.c.		1.07
British standard, i.v.	458 (0.023 c.c.)	1.17
British standard, s.c.		1.04
International standard, i.v.		1.15
International standard, s.c.		1.10

allowed to stand twenty-three hours before mixing and then injected after a contact time of one hour. The results were the same as those after a contact time of one hour with no previous standing period.

No significant difference in the speeds of combination of the two sera could be found, the potency ratio being sensibly the same whichever contact time was selected.

THE " AVIDITY " OF SERA

It has been shown that samples of antitoxin may differ in quality, the differences being manifested in the ease with which the toxin-antitoxin complex dissociates on dilution, in the steepness of slope of the neutralisation curve and possibly in other ways, such as the speed of combination with toxin. Sera that dissociate readily, are slow to combine and have flat neutralisation curves are frequently spoken of as " non-avid ". While, in many instances, such manifestations of " non-avidity " go hand in hand (GLENNY, BARR, ROSS and STEVENS, 1932), there seems no *a priori* reason for assuming that this will always happen. Indeed it is clear that sera which differ in " avidity " in one sense of the word may be indistinguishable in another. The British standard dissociates from combination more readily than the international standard, and its neutralisation curves are flatter ; no difference, however, could be found in the rate at which the two sera combine with toxin. It therefore seems desirable to avoid the use of the term " avidity ", which is used in different senses by different workers.

THE PRECISION OF ASSAY

In the Report No. 10 of Committees of the British Pharmacopœia Commission (report of the Sub-Committee on the Accuracy of Biological Assays, August 1936) the following statement is made on page 3 :

" The simplest and most satisfactory method of estimating the error of a test is to obtain independent estimates from different laboratories of the potency of a given sample or series of samples. The variance of the results gives a direct estimate of the variance of the test under practical conditions."

In the report, estimates of the limits of error of assay of several biologically active substances are made, sometimes from the internal evidence of the dose-response curves, sometimes from the variation in the results obtained independently by different workers. In one instance — that of staphylococcus antitoxin — estimates were made from the collected results of several workers by the hæmolytic and intracutaneous methods, and also from the internal evidence (obtained by a single worker) of the dose-mortality curves of mice injected intravenously and intraperitoneally. It was found that, when groups of six mice were used for the lethal methods, the limits of error were approximately the same as those estimated for the hæmolytic and intracutaneous methods. In these, no attempt had been made to standardise such details as end-point or contact time, and the workers had been urged to use their own test toxins and technique. Nevertheless, it is clear that a single assay by the hæmolytic method as ordinarily performed is as precise as an intravenous assay in which each mixture is given to six mice.

If the same procedure were adopted for tetanus antitoxin, would the same result be obtained? We have seen that estimates may vary according to the toxin used, the end-point selected and the route of injection. In Part II we shall see that the species of test animal employed may also influence the result. One would expect, therefore, that an estimate of the limits of error of the test based on the variability of results returned by many workers using different toxins, different animals and different methods would be much wider than that based on the internal evidence of single dose-response curves.

Limits of Error based on Tests carried out by Many Workers:

An estimate of the limits of error has been made from the results of twenty collected assays of each of five samples of tetanus antitoxin (HARTLEY, unpublished). In all, nine laboratories, ten toxins, four different injection routes, two different species of test animal and several distinct end-points were involved. It was found that the results obtained under these widely varying conditions were normally distributed, and hence it was possible to calculate the limits of error of assay of each sample. The five samples varied in the precision of which they were capable, because of the variation in slope of the neutralisation curves. For the antitoxin

of steepest slope, the limits of error ($P = 0.99$) were found to be 82-122%. For the antitoxin of flattest slope, the values were 67-150%.

This gives the "all over" error which might be expected in practice for a sample of tetanus antitoxin submitted for assay without any specification as to the method to be used. The error is much greater than that for staphylococcus, vibriion septique or oedematiens antitoxins, though not so great as that for antipneumococcus serum (type 1).

The consistency of assay of tetanus antitoxin when any single method is adhered to is, however, of a much higher order. An estimate of this was derived by IRWIN and SHRIMPTON from the comparisons of the British and international standards described above.

Limits of Error of Assay of Tetanus Antitoxin when Conditions of Experiment, Toxin and Animal are precisely defined.

Because the contact time had no significant influence on the potency ratio, the corresponding results for long and short contact times were combined. Thus, four estimates of potency under different conditions were obtained, and from these the variances of the logarithms (λ^2_{μ}) were calculated. From these values, the limits of error at various probability levels were derived (Table 5).

Table 5.
LIMITS OF ERROR OF TETANUS ANTITOXIN ASSAY

No. of animals in group	Toxin and injection route	Percentage limits of error ¹		
		P = 0.99 (a)	P = 0.95 (b)	P = 0.90 (c)
20	C.35, i.v.	94.4 — 106.0	95.7 — 104.5	96.5 — 103.8
	C.35, s.c.	94.0 — 106.4	95.3 — 104.9	96.1 — 104.0
	458, i.v.	95.1 — 105.1	96.3 — 103.9	96.9 — 103.2
	458, s.c.	95.6 — 104.6	96.6 — 103.5	97.2 — 102.9
6	C.35, i.v.	89.9 — 111.2	92.3 — 108.4	93.4 — 107.0
	C.35, s.c.	89.3 — 111.9	91.8 — 109.0	93.2 — 107.5
	458, i.v.	91.3 — 109.6	93.3 — 107.2	94.3 — 106.0
	458, s.c.	92.2 — 108.5	94.0 — 106.4	94.9 — 105.3

¹ It has been estimated that the results of the tests will be within the limits indicated in the columns :

- (a) For P = 0.99, 99 times out of every 100 times that the test is made ;
- (b) For P = 0.95, 95 times out of every 100 times that the test is made ;
- (c) For P = 0.90, 90 times out of every 100 times that the test is made.

It is seen that, when any single method is adhered to, a high degree of precision is attained. The accuracy is, for example, much higher than for antipneumococcus serum (type 1) when the same number of animals is used. Neither route of injection presents any advantage over the other from the point of view of precision of testing; nor is anything gained by leaving the mixtures in contact for twenty-four hours rather than for one hour. On the other hand, it is obviously an advantage to use a toxin of steep slope. With regard to the precision obtainable, there would seem to be no valid reason for selecting any particular method in preference to another.

To compare the precision with that of staphylococcus antitoxin assay, the limits of error were calculated for groups of six mice. These figures are also given in Table 5. Using the same number of animals and toxin 458, the assay is approximately as accurate as an intravenous assay of staphylococcus antitoxin.

In Table 5a, calculations are similarly made for two of the assays when the number of animals per serum dose varies from 1 to 20.

Table 5a.

LIMITS OF ERROR OF TETANUS ANTITOXIN ASSAY USING 5 DOSES FOR EACH SERUM AND DIFFERENT NUMBERS OF ANIMALS PER DOSE

1. *British/International Standards. Toxin 458, subcutaneous*

Number of animals per dose	Percentage limits of error		
	P. 0.90	P. 0.95	P. 0.99
1		85.59 - 116.93	81.84 - 122.19
2		89.60 - 111.61	86.80 - 115.20
3		91.42 - 109.38	89.09 - 112.25
4		92.52 - 108.08	90.48 - 110.52
5		93.28 - 107.20	91.48 - 109.30
6	94.93 - 105.34	92.97 - 106.42	92.16 - 108.51
10		95.20 - 105.03	93.87 - 106.42
20	97.17 - 102.92	96.59 - 103.53	95.62 - 104.58

2. *British/International Standards. Toxin C.35, subcutaneous*

Number of animals per dose	Percentage limits of error		
	P. 0.90	P. 0.95	P. 0.99
1		80.68 - 123.93	75.87 - 131.82
2		85.92 - 116.37	82.25 - 121.57
3		88.35 - 113.21	85.28 - 117.25
4		89.83 - 111.32	87.09 - 114.82
5		90.85 - 110.07	88.37 - 113.15
6	93.17 - 107.47	91.78 - 108.96	89.33 - 111.94
10		93.44 - 107.02	91.63 - 109.13
20	96.12 - 104.03	95.33 - 104.91	94.00 - 106.37

PART II.—FURTHER EXPERIMENTS ON THE FACTORS INFLUENCING TETANUS ANTITOXIN ASSAY

It has been shown in Part I of this paper that the comparative assay of tetanus antitoxin may be influenced by the particular toxin used, the end-point selected and the route of injection. It has moreover been reported by PETRIE (1938) that assays in guinea-pigs frequently give different results from those in mice.

A series of comparisons of samples of antitoxin (some of them national standards), performed in this laboratory under a variety of conditions, may serve to illustrate the degree of variation of comparative potency which may be encountered in practice. Several of the assays were made in guinea-pigs as well as in mice, and a variety of test toxins were used.

Before giving details of the results obtained, however, it becomes necessary to examine the slopes of the neutralisation curves of the various samples of toxin and antitoxin in both guinea-pigs and mice in order to obtain a measure of the precision of which the assays are capable and the differences in titre which may be considered significant with the numbers of animals employed. The calculations were made by the method of GADDUM (1933).

THE SLOPES OF THE DOSE-RESPONSE CURVES IN GUINEA-PIGS AND MICE

The slopes of the curves of neutralisation of three samples of toxin by three samples of antitoxin were examined, the titrations being carried out both in guinea-pigs and mice.

For all tests, the subcutaneous route was used, and the mixtures were left to combine for one hour at room temperature before injection. The test dose of toxin used was such as to cause the death of half the animals injected within six days when combined with 0.2 unit of the international standard antitoxin. With this dose of toxin, graded amounts of the antitoxin under test were mixed. In certain instances, tests in mice were performed with a dose of toxin such as to cause the above response when blended with only

a quarter of the same amount of antitoxin, namely 0.05 unit. The mice received the injected dose in a total volume of 0.5 c.c., the guinea-pigs in a total volume of 4 c.c. For guinea-pigs, dilution to the required volume was carried out immediately after mixture of toxin and antitoxin, so that the hour of contact occurred in the dilute state.

The slopes of the various dose-response curves are given in Table 6.

Several points are brought out by an examination of this table.

Table 6.
SLOPES OF NEUTRALISATION CURVES OF SAMPLES OF TETANUS TOXIN
AND ANTITOXIN, TESTED IN GUINEA-PIGS AND MICE

Antitoxin	Toxin	Guinea-pigs L + /5		Mice L + /5		Mice L + /20	
		Slope <i>b</i>	Total no. animals used <i>n</i>	<i>b</i>	<i>n</i>	<i>b</i>	<i>n</i>
4101	509	178	16	143	20	178	40
Int. st.	509	97	20	80.5	30	70.6	40
Brit. st.	509	49.4	20	67.2	30	35.2	50
4101	A.W.179	49.5	20	—	—	—	—
Int. st.	A.W.179	69	20	82.2	20	—	—
Int. st.	458	—	—	75.3	30	54.3	140
Brit. st.	458	—	—	—	—	32.8	140
Int. st.	A.W.189	—	—	—	—	47	108
Brit. st.	A.W.189	—	—	—	—	44	100
4101	C.35	100	20	73.3	12	—	—
Int. st.	C.35	87.5	20	58	18	32.2	100
Brit. st.	C.35	51	20	106.7	11	18.3	100

The Influence of the Test Animal on the Slope.

In seven experiments, it is possible to compare the slope obtained in guinea-pigs with the corresponding slope at the same antitoxin level in mice. In four instances, the guinea-pig slope was the higher, and, in three, the mouse slope was higher. In no instance was the difference significant in itself; neither did the combined evidence from the seven experiments point to any real tendency for the appearance of steeper slopes with either animal. If the seven experiments are divided into three groups according to the sample of antitoxin used in the mixture, it is seen that mixtures involving the serum 4101 have steeper neutralisation curves in guinea-pigs than in mice; that mixtures involving the British standard antitoxin have steeper curves in mice than in guinea-pigs; and that,

when the international standard is used, the slopes are sometimes steeper in mice and sometimes in guinea-pigs. The differences are not sufficient to be statistically significant with the numbers of animals used, so that it is doubtful how much importance should be attached to them, but they at least suggest the possibility that, for some samples of antitoxin, guinea-pigs are more suitable test animals than mice, and that, for others, the reverse is true. In this matter, the toxin appears to have very little influence.

In Table 6, the range of slope covered by all the tests in guinea-pigs is about the same as the range at the same antitoxin level in mice. It appears, therefore, that, in general, about the same numbers of mice or of guinea-pigs would be required to give the same precision of testing, but that, with certain particular antitoxins, one or other species of animal might give more precise results.

The Influence of Antitoxin on the Slope of the Dose-response Curve.

In Part I of this paper, it was shown that the international standard gave steeper neutralisation curves than the British standard when tested in mice. In Table 6, the question has been extended. It was found that, when mice were used, the combined evidence from all the possible comparisons showed that serum 4101 gave significantly steeper curves than the international standard, which, in its turn, gave significantly steeper curves than the British standard. There is no indication that the particular toxin used influences the magnitude of the differences in slope of the three sera, but the differences are accentuated when the tests are carried out at the lower level ($L_+/20$). In guinea-pigs, the differences are still apparent, though the tests have not been carried out on a sufficient number of animals for the level of significance to be as high. The serum 4101 appears to give steeper, but not significantly steeper, slopes than the international standard, and both these sera give steeper slopes than the British standard.

The Influence of Toxin on the Slope of the Dose-response Curve.

There are insufficient tests for this influence to have been determined very securely. It was found, however, that, in mouse tests, toxin 509 gives slopes which are as steep as, or steeper than, those produced by toxin 458, which, in its turn, usually produces steeper

curves than toxin C.35. In guinea-pigs, the influence of the serum on the slope is more pronounced than that of the toxin.

In one instance, combination between the British standard and toxin C.35 at the $L_{+}/5$ level in mice, the toxin and antitoxin appear to have a selectively high affinity for one another, beyond what one would expect. For C.35 is a toxin which, in general, gives flatter curves than toxin 509; but, in the above instance, the slope was steeper than that of the corresponding test when toxin 509 was used. Again, the British standard usually gives flatter curves than the international standard; but, in the test referred to, the slope of the British standard is higher than that of the corresponding test of the international standard. It will be remembered that a similar observation was made in Part I, where toxin C.35, usually of flatter slope than toxin 458, produced steeper slopes in two comparisons. It is difficult to know how much importance to attach to these observations, but, in my view, the possibility should be borne in mind that steepness of slope may not always be an additive function of the slopes of the toxin and antitoxin combining, but may depend in certain instances on the "goodness of fit" between toxin and antitoxin.

The Influence of the Dilution on the Slope.

This has only been examined in mice, but six pairs of experiments at different levels are available, and, in five instances out of six, the slope of the more concentrated mixture was the steeper. From the combined evidence, it was calculated that a similar result would occur by chance about four times in every hundred trials. It is thus probable that the difference is real. This is what one would expect, since the more concentrated mixtures contain a greater number of lethal doses.

COMPARATIVE ASSAYS OF SAMPLES OF TETANUS ANTITOXIN UNDER DIFFERENT CONDITIONS

Having obtained measures of the slopes of the curves of neutralisation of various samples of toxin by antitoxin, we can proceed to examine the comparative assays of samples of antitoxin with different toxins.

The Assay of Serum 4101 in Terms of the Second International Standard.

Serum 4101 is an antitoxin of steep neutralisation curve which it was hoped could be used as the new British standard to replace the current standard of rather flat slope. The serum was diluted so as to contain about sixty international units per c.c. and was assayed in terms of the international standard. In all, twenty-three assays were made in mice and nine in guinea-pigs, and nine different toxins were used. All injections were made by the subcutaneous route. The results are shown in Tables 7 and 8.

Table 7.
ASSAY OF SERUM 4101 IN TERMS OF INTERNATIONAL STANDARD USING DIFFERENT TOXINS : TESTS DONE IN MICE

Toxin	Level, international units	Contact time (hours)	Animals per dose	Interval between doses %	Titre, international units / c.c.	Remarks (level of significance, P = 0.95)
A.W.225 .	L + /20	1	3	20	90	Significantly >60
K		1	3	20	75	" "
A.W.179 .		1	3	20	70	" "
C.35		1	3	20	60	Not sign. different from 60
509		1	3	20	60	" "
A.W.189 .		1	3	20	60	" "
A.W.165 .		1	3	20	55	" "
T.g.235 . . .		1	3	20	55	" "
T.g.235 . . .		1	3	20	55	" "
458		1	3	20	55	" "
A.W.225 .		1	6	10	88	Significantly >60
509		1	20	5	63	" "
509		1	10	5	57	Mean = 59.0
509		1	10	5	57	Not significantly <60
509	1	10	5	59		
509	1	10	5	63		
509	L + /5	24	6	10	63	Mean 60.5
509		24	6	10	58	Not significantly >60
C.35		1	6	10	66	Mean 63
C.35		24	6	10	60	Not significantly >60
A.W.179 .		1	6	10	80	Mean 82
A.W.179 .		24	6	10	84	Significantly >60

It was found from Table 7 that the results in mice, while independent of the contact time used, were influenced by the toxin. Toxins could be divided into two groups—those giving values not significantly different from sixty and those giving values significantly higher.

In guinea-pigs, only three toxins were examined, none of which gave significantly different results with the numbers of animals used. The mean value for the guinea-pig results was, however, significantly different from many of the results obtained in mice.

Table 8.

ASSAY OF SERUM 4101 IN TERMS OF THE INTERNATIONAL STANDARD
TESTS DONE IN GUINEA-PIGS

Toxin	Level, international units	Contact time (hours)	Animals per dose	Interval between doses %	Titre, international units / c.c.	Remarks
509	L+ /5	1	2	10	>70	Mean = 73
509		1	2	10	75	
509		1	5	4	73	
509		24	2	10	72	Mean = 82.5
C.35		1	2	10	85	
C.35		1	2	10	85	
C.35		24	2	10	77	
A.W.179		1	2	10	80	
A.W.179		24	2	10	80	
Mean value...						77.5

The standard deviation of the titres obtained when different toxins were used (one result for each toxin) was calculated for mice and for guinea-pigs. The coefficient of variation was found to be 18.4% for mice and 7.6% for guinea-pigs. Thus, it again appears that toxin has less influence on guinea-pig results than on those obtained in mice. Moreover, the toxins used for the guinea-pig tests were selected as giving widely divergent results in mice. It is possible, however, that if more animals had been used for the guinea-pig tests, significant differences due to toxin might have been detected.

Both in guinea-pigs and in mice, the dose-response curve of the assay when toxin 509 was used was exceedingly steep, dose intervals of 2% giving appreciable changes in mortality rate.

With toxins 509 and C.35, the titre obtained in guinea-pigs was significantly higher than that obtained in mice. With toxin A.W.179, the value in mice was higher than with the other two toxins and equal to the value obtained in guinea-pigs. There is a slight though insignificant tendency for toxin C.35 to produce lower

values after twenty-four hours than after one hour, both in mice and guinea-pigs.

These findings will be further discussed later.

The Assay of Serum 4101 in Terms of the Current British Standard.

Only three toxins were examined, nine assays in mice and nine in guinea-pigs being made. All tests were carried out at the 0.2 unit-level and injections were made subcutaneously. The results are given in Table 9.

Table 9.
ASSAY OF SERUM 4101 IN TERMS OF BRITISH STANDARD

Animal	Toxin	Contact time (hours)	Animals per dose	Interval between doses %	Titre, international units / c.c.	Remarks
Mice ...	509	1	3	10	52	Mean = 56.5
	509	24	6	10	60	
	509	24	6	10	52	
	C.35	1	6	10	77	
	C.35	24	6	10	66	Mean = 63.7
	A.W.179 .	1	6	10	63	
	A.W.179 .	1	6	10	62	
	A.W.179 ¹ .	1	6	10	66	
A.W.179 .	24	6	10	70		
Guinea-pigs ...	509	1	2	10	79	Mean = 79.5
	509	1	2	10	80	
	509	24	2	10	77	
	C.35	1	2	10	100	Mean = 74.3
	C.35	24	2	10	90	
	A.W.179 ¹ .	1	3	15	ca75	
	A.W.179 ¹ .	1	3	15	73	
	A.W.179 .	1	2	10	75	
A.W.179 .	24	2	10	70		

In guinea-pigs, no significant change in value was obtained on altering the contact time, though, with all three toxins, the results were slightly lower with the longer time. In mice, C.35 gave a significantly lower result on prolonging the contact time ; with the other two toxins, there was no significant change.

The titres obtained are not independent of toxin either in mice or guinea-pigs, the differences being more marked after a short

¹ Tests carried out by Dr. A. J. H. DE MONTZ.

contact time than after a long one. If toxins are arranged according to the titre they assign to serum 4101, the order is not the same in guinea-pigs and mice.

The Assay of the British Standard in Terms of the International Standard.

This is an extension of the work reported in the first part of this paper. A total of forty-one assays were made involving eight toxins. Of these, thirty-one assays were in mice and ten in guinea-pigs. The results are given in Tables 10 and 11.

Table 10.

COMPARISON BETWEEN BRITISH AND INTERNATIONAL STANDARDS IN MICE

Toxin	Level, international units	Contact time (hours)	Route of injection	Animals per dose	Interval between doses %	Po- tency, British	Remarks
						Inter- national	
D.		1	s.c.	5	20	1.10	
A.W.189 .		1	s.c.	6	20	1.00	
A.W.189 .		1	s.c.	6	10	1.05	Mean = 1.07 Significantly >1.0
A.W.189 .		1	s.c.	6	10	1.15	
A.W.189 .		1	s.c.	20	10	1.08	
A.W.225 .		1	s.c.	6	20	0.83	Significantly <1.0
458		1	s.c.	3	20	1.00	
458		1	s.c.	3	20	1.00	
458	L+ /20	1	s.c.	6	10	1.08	Mean = 1.021 Not significantly >1.0
458		1	s.c.	20	10	1.06	
458		1	i.v.	20	10	0.99	
458		24	s.c.	20	10	1.03	
458		24	i.v.	20	10	0.99	
C.35		1	s.c.	20	10	0.90	Mean = 0.903 Significantly <1.0
C.35		1	i.v.	20	10	0.88	
C.35		24	s.c.	20	10	0.96	Significantly <1.0
C.35		24	i.v.	20	10	0.88	
C.35		1	s.c.	6	10	0.87	Mean = 0.904 Significantly <1.0
C.35	1	s.c.	6	10	0.94		
C.35	24	s.c.	6	10	0.89	Mean = 0.904 Significantly <1.0	
C.35 ¹	24	i.v.	6	10	1.00		
C.35 ¹	24	i.v.	6	10	0.93	Significantly <1.0	
C.35 ¹	24	i.v.	6	10	0.85		
K. ¹	L+ /5	24	i.v.	6	10	0.85	Mean = 1.11 Significantly >1.0
509		1	s.c.	6	12.5	1.00	
509		1	s.c.	6	12.5	1.15	
509		1	s.c.	6	10	1.15	
509		24	s.c.	6	10	1.07	
509		24	s.c.	6	10	1.07	
A.W.179 .		24	s.c.	6	10	1.20	Significantly >1.0
A.W.179 .		1	s.c.	6	10	1.20	

¹ Indicate tests carried out by Dr. J. IPSEN.

From the mouse tests, toxins can be placed in three groups according as the ratio of potencies of the two standards is returned as significantly greater than unity, equal to unity or significantly less than unity.

From the results with toxin C.35, it was concluded that the dilution of the test had no significant influence on the potency ratio. With none of the toxins was the result obtained after twenty-four hours of contact time significantly different from the result after one hour. The influence of injection route has been already discussed, and no further evidence on this point is available.

In both guinea-pigs and mice, the potency ratio is seen to be not independent of the toxin used. For this assay, toxins fall into the same order in both guinea-pig and mouse tests and with toxins C.35 and A.W.179, the guinea-pig and mouse results do not differ significantly. Toxin 509, however, gives significantly lower results in guinea-pigs than in mice. The order of toxins bears no relation to the order in other assays (4101 v. international standard, or 4101 v. British standard) in either mice or guinea-pigs.

Table 11.

COMPARISON OF BRITISH AND INTERNATIONAL STANDARDS IN GUINEA-PIGS

Toxin	Contact time (hours)	Animals per dose	Interval between doses %	Potency British International	Remarks
509	1	2	10	0.90	} Mean = 0.91 Significantly <1.0
509	1	2	10	0.90	
509	24	2	10	0.95	
509	24	2	10	0.90	
C.35	1	2	10	0.87	} Significantly <1.0
C.35	24	2	10	0.87	
A.W.179	1	2	10	1.22	} Mean = 1.185 Significantly >1.0
A.W.179	1	2	10	1.22	
A.W.179	24	2	10	1.10	
A.W.179	24	2	10	1.20	

COMPARISON OF THE AMERICAN AND BRITISH STANDARDS

Only twelve comparisons of these standards are available, involving five different toxins. Mice were used for all the tests. The results are summarised in Table 12, from which it will again be seen that the result depends on the toxin used.

Table 12.

COMPARISON OF BRITISH AND AMERICAN STANDARDS, USING MICE

Toxin	Level, international units	Contact time (hours)	Route of infection	Animals per dose	Interval between doses %	Potency, British U.S.A.	Remarks
D.	0.05	1	s.c.	3	20	1.20	Mean = 1.16 Significantly >1.0
D.	0.05	1	s.c.	3	20	1.10	
D.	0.05	1	s.c.	4	20	1.15	
D.	0.05	1	s.c.	3	20	1.20	
458	0.05	1	s.c.	3	20	0.91	Mean = 0.91 Significantly <1.0
458	0.05	1	s.c.	3	20	0.83	
458	0.05	1	s.c.	6	10	1.00	
458	0.05	1	s.c.	6	10	0.91	
K. ¹	0.2	24	i.v.	6	10	1.10	Significantly >1.0
K. ¹	0.2	24	i.v.	6	10	1.12	
C.35 ¹	0.2	24	i.v.	6	12.5	0.85	Significantly <1.0
A.W.179 ² .	0.2	1	i.m.	5	?10	1.36	Significantly >1.0

DISCUSSION

It has been seen that the particular test toxin used influences the comparative potency of samples of tetanus antitoxin. Have we any evidence as to how different toxins produce these different effects?

It has been shown that the slope of the dose-response curve is, with certain qualifications, an additive function of the toxin and antitoxin combining. Thus, in general, one can speak of toxins (or antitoxins) of steep or flat neutralisation slopes.

From the data on which Tables 1, 6, 9 and 10 were based, it was found that when toxins of steep slope are used, the potency ratios

$$\frac{4101}{\text{international standard}}, \frac{4101}{\text{British standard}}, \text{ and } \frac{\text{international standard}}{\text{British standard}}$$

are all lower than when toxins of flatter slope are employed. The numerator of each pair is a serum of steeper slope than the denominator, so that it appears that toxins of steeper slope make the antitoxin of steeper slope appear relatively weaker than does a toxin of flatter slope. The data are only complete for toxins 509 and C.35; and a summary is given in Table 13.

¹ Tests carried out by Dr. J. IPSEN.

² Test carried out by Mr. A. T. GLENNY.

Table 13.
CORRELATION BETWEEN POTENCY RATIO AND CAPACITY OF TOXIN
TO PRODUCE STEEP DOSE-RESPONSE CURVES

Test animal	Toxin	Antitoxins being compared					
		4101 / international		4101 / British		International / British	
		Com- bined slope	Po- tency ratio	Com- bined slope	Po- tency ratio	Com- bined slope	Po- tency ratio
Guinea-pigs	509	137	73	114	79.5	73	1.10
	C.35	94	85	75.5	95	70	1.15
Mice	509	112	59	105	52	53 ¹	0.90
	458	—	—	—	—	39.0 ¹	0.99
	C.35	66	63	90	77	21.7 ¹	1.11

We have seen that the higher the concentration (*i.e.*, the larger the number of lethal doses in the test dose), the steeper the dose-response curve. With toxins containing different proportions of toxoid, the dose of toxin combining with the same amount of anti-toxin will contain different numbers of lethal doses, so that the possibility arises that the differential action of different toxins may be attributable to a different content of toxoid.

This question was examined by determining the average lethal doses of four toxins, and comparing them with the combining power for antitoxin. The figures are given in Table 14.

Table 14.
SLOPE OF NEUTRALISATION OF TOXIN BY INTERNATIONAL STANDARD
AND NUMBER OF LETHAL DOSES IN THE TEST DOSE

Test animal	Toxin	L ₊ /5	L.D.50	L ₊ /5	Slope b
				L.D.50	
Mice	A.W.179	0.032 c.c.	0.000125 c.c.	256	82.2
	458	0.086 c.c.	0.00030 c.c.	290	75.3
	509	0.030 c.c.	0.00004 c.c.	750	80.5
	C.35	1.05 mgm.	0.0005 mgm.	2,100	58
Guinea-pigs	A.W.179	0.027 c.c.	0.0004 c.c.	70	69
	509	0.020 c.c.	0.000167 c.c.	120	97
	C.35	0.65 mgm.	0.0023 mgm.	260	87.5

The table does not indicate a correlation between ratio of toxicity to combining power of a series of toxins and the slopes of their

¹ Combined slope calculated from values at L₊/20 level.

neutralisation curves. This is rather surprising, since a positive correlation has been generally assumed. Moreover, when one and the same toxin is used, increasing the number of lethal doses in the test dose by using more concentrated mixtures does, in fact, steepen the curve. It must therefore be concluded that other factors in the test toxin besides its content of toxoid influence the slope of the neutralisation curve and mask the correlation. The nature of the quality in toxins that results in different potency estimates remains obscure.

These differences must be a function of qualitative differences in the sera as well as in the toxins used. They are in part due to the varying tendency of such sera to dissociate from combination on dilution. For it can be seen from Tables 9-11 that the ratio of potency of a dissociating serum such as the British standard to that of one which does not dissociate, such as 4101 or the international standard, tends to be greater when tested in mice than in guinea-pigs. This is what would be expected, for there is greater opportunity for dissociation when the larger animal is used. Guinea-pig tests thus differentiate in favour of firmly binding sera and against dissociating samples. Similarly, intravenous injection in comparison with the subcutaneous route distinguishes in favour of the more firmly binding serum. And again, tests at lower antitoxin levels weight against the more dissociable serum.

Differences in speed of combination of different samples of antitoxin with toxin probably also influence the assay. Thus, in the assay of serum 4101 in comparison with the British or international standards, there is a tendency with some toxins for lower results to be obtained after longer contact periods. This effect is not apparent in comparisons of the British and international standards. The amounts of serum 4101 neutralising the same amount of toxin after one hour and after twenty-four hours of contact were examined for toxins C.35 and 509 in both mice and guinea-pigs. In no instance did alteration in contact time alter this amount by as much as 5%. It was concluded, therefore, that 4101 combines with toxin more rapidly than either of the standard sera, which have been shown to be somewhat slow (and about equally slow) in combining. In this connection, one may recall the observations of RAMON, LEMÉTAYER and PIROSKY (1937), who found that antitoxin from a horse which had received a primary

stimulus many months before its hyperimmunisation combined more quickly with toxin than that from a horse of which the whole course of immunisation had been rapid.

The facts reported in this paper suggest that tetanus toxin and antitoxin are not unitary substances, but that differences exist, resulting in modification of the immunological behaviour without affecting the physiological action.

The possibility arises that strains of different type may vary in regard to the nature of the toxin they produce. In this connection, it will be remembered that TULLOCH (1919) reported that antitoxin from type 1 toxin was more efficacious against infections due to type 1 tetanus than against those due to other types. TULLOCH found that the toxin was not type-specific, but the relationships of toxin-antitoxin neutralisation were not investigated by such detailed quantitative procedures as are now available. It would seem desirable to investigate this matter further, and we are fortunate in having to hand a toxin from a pure type 2 strain (toxin C.35) together with an antitoxin prepared from it (the second international standard). These two reagents should be of considerable assistance in elucidating whether toxins are neutralised more fully by homologous than heterologous antitoxins.

On the other hand, the explanation may lie in quite another direction. MARRACK (1938) has suggested that the molecules of a single antigen or antibody may differ among themselves, and that qualitative differences in the behaviour of different samples of antisera may be explained in this way. If this is so, the fact that different methods of immunisation or serum concentration influence the quality of the antitoxin (GLENNY, BARR, ROSS and STEVENS), and that different conditions of culture or storage influence the quality of the toxin, might well be accounted for by supposing that such alterations in conditions influenced the proportions of the different kinds of molecules.

Until further research has elucidated the nature of the qualitative difference in samples of toxin and antitoxin, we have little guidance as to the best conditions under which assay is to be carried out. From the point of view of precision, it is immaterial whether mice or guinea-pigs are used; whether injections are made subcutaneously or by the intravenous route; or whether a contact time of one hour or twenty-four hours is allowed.

Decisions as to procedure must necessarily be tentative in our present state of ignorance, but, if it is agreed that assays that assign relatively greater value to antitoxins of good therapeutic quality are preferable to those that distinguish in favour of loose-binding or slow-binding samples, or those of flat neutralisation curves, then the following suggestions may provisionally be made :

- (1) The standard antitoxin should give as steep a dose-response curve as possible.
- (2) Groups of six guinea-pigs or six mice for each mixture should result in an adequate precision of testing.
- (3) A contact time of one hour is probably preferable to longer periods.
- (4) The intravenous route has some slight advantage over the subcutaneous.
- (5) Guinea-pigs will distinguish between dissociating and non-dissociating sera better than mice, and hence may be preferable.
- (6) The 0.05 unit-level is at least as good as the 0.2 unit-level.
- (7) There are certain advantages in selecting a test dose of toxin which, when mixed with the standard dose of antitoxin, will produce tetanus, but not death, within six days.

In conclusion, it may be stated that the variations in the conditions under which assays have been conducted are, in themselves, sufficient to account for the divergences reported among the national standards, without postulating that any of the standards has deteriorated since its establishment.

SUMMARY

1. The comparative assay of samples of tetanus antitoxin is influenced by the toxin used, the species of test animal, the route of injection and the end-point selected, and possibly also by the time of contact of the mixtures before injection.
2. The precision of assay is little affected by the conditions of experiment or by the species of test animal, but is influenced by the toxin used.

3. The degree of variation met with in practice is illustrated by records of assays.

4. It is recommended that assays should be performed under conditions which distinguish in favour of sera of good therapeutic quality rather than of samples of poorer quality.

5. The variation in conditions of assay that have been used is sufficient to account for the divergences reported in the national standards, without postulating deterioration of any of the standards.

My thanks are due to Dr. J. O. Irwin and Mr. E. A. J. Shrimpton for the statistical analysis of the results recorded in Part I ; to Dr. A. J. H. de Monte, Dr. J. Ipsen and Mr. A. T. Glenny for permission to include the results of assays performed by them ; to Mr. S. A. Price for assistance with some of the calculations in Part II, and to Dr. P. Hartley and Dr. J. W. Trevan for help and criticism throughout the work.

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Annex 1d.**COMPARATIVE ASSAYS OF INTERNATIONAL
AND AMERICAN STANDARD TETANUS ANTITOXINS
WITH WASHINGTON AND COPENHAGEN TEST TOXINS**

By

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The activity of commercial tetanus antitoxins produced the world over is at present expressed in terms of two units—the international and the American. The relation between these two units is given by the definition of the international unit adopted by the Commission at Geneva in 1926.

“ The unit is to be determined with the standard serum in such a way that its relation to the American unit is *exactly two international to one American unit.*”

The American unit is used in North and South America, whilst European preparations are indicated in international units. Some countries prefer to indicate both units on the label, as in Great Britain, where the Therapeutic Substances Regulations of July 25th, 1935 (Statutory Rules and Orders 1931, No. 633), lay down (page 32, item 7c) that :

“ The label on the container shall indicate—a statement that the numbers of units indicated are equivalent to one-half of those numbers of American units.”

The international and American standard preparations are both issued in glycerol solution, *the international containing 10 units per c.c.* and *the American containing 5 units per c.c.* According to the above definition, these two preparations should appear of exactly the same potency in comparative assay.

In recent years, in the Department of Biological Standards at Copenhagen, the routine solution of the international tetanus antitoxin has been compared every half-year with the contemporary American preparation using the test toxin C.35 and using a method described by Dr. CLAUS JENSEN.¹ Mice are injected intravenously with mixtures of toxin antitoxin allowed to combine for twenty-four hours at room temperature.

This method and toxin were used in the last comparative investigation performed at five institutes, a report of which is laid before the Commission. The results of the comparative assays of the international and American standards have been that the activity of the two standard solutions have been identical with an accuracy of 10%.

Guided by the findings of the above-mentioned investigation, which suggest that the results of the comparative assays are influenced by the toxins and the method used, we thought it desirable to make additional tests of the two standards, varying the method and the toxin. To limit the investigation, we selected only one toxin more for the test—namely, the American test toxin K at present used at the National Institute of Health, Washington, for routine assays, and kindly sent us by Dr. R. E. Dyer.

* * *

Scheme for the Investigation.

The American and international standards have been compared in the following way :

- (a) Using Copenhagen toxin C.35 and American toxin K ;
- (b) Using mice and guinea-pigs as experimental animals ;
- (c) Allowing the mixtures to combine for 1 hour and for 24 hours.

The injections were given intravenously in mice and subcutaneously in guinea-pigs. An isotonic phosphate buffer solution of pH 7.38 was used for the dilution of toxin and antitoxin.

¹ Cl. JENSEN : "Memorandum concerning the Titration of Tetanus Antitoxin". *Quart. Bull. Health Org.*, 1936, 6, 702.

Method of calculating the Results.

The criterion adopted was that the mixture of toxin and serum should give 50% mortality on the *fifth day* in the mouse test and 50% mortality on the *fourth day* in the guinea-pig test. A detailed description of a method of calculating these doses, taking into account the observations for all days, is given in the above-mentioned report.

*Experimental Results.**The Properties of the Toxins.*

Both toxins are strong preparations precipitated with aluminium sulphate in freshly prepared condition. The test dose for assaying on mice against 0.2 international unit contains a large number of M.L.D. : for toxin C.35, about 1,500 M.L.D., and for toxin K about 800.

The strain used for toxin C.35 is a pure strain micromanipulated by Professor ZEISSLER, Altona (Nat. Coll. T. 67, *Tulloch Type 2*). According to Dr. R. E. DYER, toxin K is produced by a strain called *Tulloch No. 3*.

Results of Comparative Assays.

The subjoined table gives the test dose against 0.2 international unit—or, more correctly, against 0.02 c.c. of the glycerol dilutions of the two standards. The ratio of the test dose against the international standard to the test dose against the American standard is given in the last column. This figure will indicate the relative activity of the two standards.

According to the definition of the Commission, this ratio should be exactly 1.

Conclusion.

Assayed with *test toxin C.35*, the *American standard preparation* appears to be about 6% *stronger* than the International, the ratio international to American being on the average 0.94.

Assayed with *test toxin K*, the *international standard preparation* appears 12% *stronger* than the American, the ratio international to American being found to be 1.12.

A reduction of the combining time from 24 hours to 1 hour resulted in a decrease of the test dose against both standards, but the relative activity of the two sera is uninfluenced by this change in the combining time. The test doses against the mice and the guinea-pigs are slightly different, but the ratio of the two standards is identical within the limits of error, whichever animal is used. The results obtained with one of the toxins show the same degree of variation as those of the investigations of the five institutes, in which the standard deviation as calculated from thirty-four assays was found to be 5.5%.

Our results gave us a standard deviation of 3.8% for assays performed with toxin K and of 3.5% for assays performed with toxin C.35.

The variations observed in the results obtained with one and the same toxin but with different animals and different combining times fall within the limits set by the standard deviation.

The differences due to the test toxin used are accordingly the only ones which are of any significance.

* * *

Discussion.

When the test was performed with the American toxin, the international unit worked out at 0.56 American A.U., and when the Copenhagen toxin was used, the international unit was found to be 0.47 American unit.

There is a significant difference between these two results, neither of which satisfies the conditions laid down by the Commission as to the ratio of the activity of the two standard sera.

In this connection, it will be of interest to quote a passage representing the German view of the international and the American tetanus standard (R. OTTO und H. HETSCH, "Die Prüfung und Wertbemessung der Sera und Impfstoffe", Arbeiten aus dem Staat-institut für experimentelle Therapie, No. 31, page 82, Jena, 1935).

" Careful conversion calculations of the titres of the standard sera at present in use in the various countries certainly shows that the units concerned are not quite equivalent to the

international unit as defined above. The English and Danish standard sera¹ are somewhat (about 20%) over strength, with the result that, when diluted in the manner prescribed, they yield a value slightly above a half of a former American unit. Accurate adjustment to the internationally agreed value will present no difficulties."

The assays referred to above show, however, that the "accurate adjustment" will be difficult. If various toxins are to be used for the comparison of the two standards, the international unit can never be "exactly" half an American unit. The range of variability when different toxins are used will be from 20% to 30%.

* * *

We wish to submit these experiments concerning the relation of the international tetanus antitoxin unit to the American unit for the consideration of the Commission, in order that steps may be taken, if possible, to secure a better agreement between the two standards.

¹ That is, international.

Determination of Test Dose against 0.2 International and 0.1 American Unit.

Animal	Toxin K				Toxin C.35			
	Date of experiment	International standard	American standard	Ratio : International -American	Date of experiment	International standard	American standard	Ratio : International -American
	<i>1 hour combining time.</i>							
Mice	11.VII.38	Mgrm. 0.83	Mgrm. 0.705	1.18	11.VII.38	Mgrm. 1.07	Mgrm. 1.14	0.94
	16.VII.38	0.76	0.67	1.14	16.VII.38	1.12	1.18	0.95
	5.VII.38	(0.77)	(0.69)	(1.12)	5.VII.38	(1.10)	(1.17)	(0.94)
Guinea-pigs	9.VII.38	0.70	0.65	1.07	16.VII.38	1.00	1.10	0.91
	24.VI.38	(0.74)	(0.64)	(1.16)				
	<i>24 hours combining time.</i>							
Mice	17-22.XII.36	0.92	0.81	1.13	7.V.37	1.15	1.19	0.96
					10.V.38	1.25	1.24	1.01
Guinea-pigs	26.VII.38	1.00	0.93	1.07	29.VII.38	1.43	1.56	0.91
	Geometric mean			1.12				0.94
	Standard deviation			3.8%				3.5%
	Mean error			1.4%				1.4%

Figures in the brackets are derived from experiments with one to two animals injected per dose.

Annex 1 e.**THE RESULTS OF TWENTY DIFFERENT ASSAYS
OF FIVE SAMPLES OF TETANUS ANTITOXIN**

At its session in August 1934, at Copenhagen, the Permanent Commission on Biological Standardisation discussed the question of the discrepancies in the results frequently obtained when the same sample of tetanus antitoxin is tested in different laboratories. As part of the international investigations instituted by the Commission with the object of obtaining further information on this subject, it was arranged that five institutes should undertake the assay of five samples of tetanus antitoxin according to a plan drawn up by the Commission. By the beginning of 1937, the five institutes had completed their tests and the results are collected and analysed in Annex 1a.

Examination of these results showed that, when samples of tetanus antitoxin are assayed in different laboratories, the variation in the results obtained are considerably larger than can reasonably be ascribed to the errors inherent to the methods of assay adopted (see Annex 1c). They are due to qualitative differences in tetanus toxins and antitoxins.

The fact that these variations do occur has an important bearing on the administrative control of tetanus antitoxin exercised in different countries. If such control is to be intelligent and one which can be justified, it is clearly necessary that an attempt should be made to arrive at the best estimate possible of the variations likely to be encountered under present-day conditions of testing. These conditions are, in fact, very variable indeed. Apart from such variations as those due to the personal factor, the animals used and the interpretation of the titrations, the actual methods of assay employed vary in many other details; mice and guinea-pigs are used as test animals, the number of animals used per serum

dose varies, different test toxins and different standards of reference are used, and the time of contact of mixtures and the route by which these mixtures are injected also vary in different laboratories. It is now possible to assign a relative importance to most of these factors on the *precision* with which a sample of tetanus antitoxin can be assayed ; but all these factors, and perhaps others, in greater or less degree enter into the determination of the potency of tetanus antitoxin carried out in different laboratories and, taken together, they account for the variable results obtained.

The questions raised by these considerations are, at the present time, of particular interest and importance to the British Pharmacopœia Commission, which is engaged in an enquiry into problems relating to the accuracy of biological assays. In a recent report,¹ the Commission has pointed out that the errors of biological assay—in contrast with most chemical assays—may be large, and it is accordingly necessary to measure them, state them with scientific precision and in a uniform notation. It is further stated that :

“ The simplest and most satisfactory method of estimating the error of a test is to obtain independent estimates from different laboratories of the potency of a given sample or series of samples. The variance of the results gives a direct estimate of the variance of the test under practical conditions. The disadvantage of this direct method of estimating the error is that the test must be repeated a large number of times, in order to make the estimate sufficiently accurate.”

By the beginning of 1937, the results of fourteen different assays of the five samples, carried out in accordance with the plan of the Permanent Standards Commission, had been received. It is possible that these data would have sufficed to permit of an estimate of the variations being determined, but, in view of the importance ascribed to the number of such repeated tests being as large as possible and, moreover, the fact that tetanus antitoxin assays are, in practice, carried out under such diverse conditions in different laboratories, it appeared that the value of the data would be greatly enhanced by extending the enquiry so as to obtain additional determinations of the potency of the five samples from other

¹ British Pharmacopœia Commission. “Report of the Sub-Committee on the Accuracy of Biological Assays” (No. 10), August 1936.

laboratories ; and, since the purpose of this part of the enquiry was to determine the errors likely to be encountered under the very diverse conditions under which tetanus antitoxin is assayed, it would be a further advantage if, in these later tests, the greatest possible variations in reagents and techniques were encouraged.

By courtesy of the Permanent Commission on Biological Standardisation, samples of the five antitoxins were placed at the disposal of the British Pharmacopœia Commission, which was able to arrange for further tests to be carried out. The data summarised below have been provided, in part, from the results of the enquiry first instituted by the Permanent Commission on Biological Standardisation, whereby fourteen of the assays were returned by five laboratories, and in part from an extension of this enquiry, carried out under the auspices of the British Pharmacopœia Commission, whereby four laboratories returned six assays.

The results of these twenty different assays of the five samples of tetanus antitoxin are summarised in Table 1. The figures in the lower part of the table represent the potency, expressed in international units per c.c., of the respective samples, and they are the actual values returned by the laboratory indicated in the column immediately above the figures as the result of the assay carried out under the conditions indicated in the remainder of the column in the upper part of the table. Inspection of the table shows that the twenty assays were carried out in nine laboratories, in which ten different test toxins, four different routes of injection, two species of animals, three different standards, varying contact times and varying numbers of animals per serum dose were employed. For convenience of subsequent reference, the assays numbered 1 to 5 are grouped together as a small series in which the same test toxin, method and standard were used ; the assays numbered 6 to 11 are grouped for convenience as the remainder of the assays in which mice were used as test animals, but in which other conditions of testing varied ; and the assays numbered 12 to 20 are those in which guinea-pigs were used as test animals, but in other respects the conditions under which the assays were carried out varied. In the last column, the geometric mean of all the assays of each antitoxin is given.

In Table 2, the limits of error ($P = 0.99$) of the tests of each sample of antitoxin are given. The percentage limits of error are

quoted to the nearest 0.5%, and, for their calculation, the logarithms of the titres have been used. In each case, the figures indicate that it is estimated that the result of the test will be within the limits stated 99 times out of every 100 times the test is made. It may be added that the calculation for the limits of error ($P = 0.99$) may be made when the error of the test, or its logarithm, is normally distributed ; the data in Table 1 were examined by two methods and the distribution found to be normal.

In Section A of Table 2, the limits of error of all the twenty different assays are given. In connection with the values quoted in this and the other six sections of the table, it is of interest to note that samples I, II and III are from bleedings from individual horses and are natural sera ; sample IV is a mixture of two sera consisting of four-fifths of one component and one-fifth of the other, and is also a natural serum ; and sample V is a concentrated, or refined, tetanus antitoxin prepared from samples of sera provided by a number of immunised horses. Apparently, when twenty different assays are conducted under the most diverse conditions of testing which could be achieved in the present enquiry, the extent of the variation in potency depends upon the quality, or properties, of the antitoxin ; in the series of twenty assays, the variation is smallest for sample I and greatest for sample III. These are samples of natural serum from individual horses, a form of tetanus antitoxin not commonly encountered among the antitoxins of commerce. Since most antitoxins are similar to sample V, the values found for this type of product are, perhaps, of special significance. It may be noted, in passing, that, of the seven estimates of the value for $P = 0.99$ for sample V, in five the value is practically identical with the mean of the five antitoxins, and in the remaining two the divergence is small.

It may be objected, however, that the values quoted in Section A are open to criticism on the grounds that they are unduly weighted by the inclusion of the assays numbered 1 to 5, which were carried out under conditions in which the personal factor, the quality of the animals used and the individual worker's interpretation of his titrations are the only variables entering into the assays, while in the remaining fifteen assays the conditions of testing are far more diverse. In other words, while it is the case that twenty different assays have been performed, the variability of the conditions of the

Table
The Results of Twenty Different Assays of

Number of assay :	Mice, same { toxin method standard					Mice, different			
	1	2	3	4	5	6	7	8	9
Particulars of method of assay :									
Laboratory	A	C	F	H	W	W	B	B	F
Test animal	mice	mice	mice	mice	mice	mice	mice	mice	mice
Number of animals per serum dose	6	6	6	6	6	6	1 (× 5)	1 (× 5)	6
Route of Injection	i.v.	i.v.	i.v.	i.v.	i.v.	i.v.	i.m.	i.m.	s.c.
Time of contact of mixture (hours)	24	24	24	24	24	24	?	?	1
Toxin used	C.35	C.35	C.35	C.35	C.35	K	179	165	234
Standard used	Intl.	Intl.	Intl.	Intl.	Intl.	Intl.	Brit.	Brit.	Intl.
Number of tetanus anti-toxin tested :									
I	1,260	1,240	1,220	1,200	1,000	1,300	1,240	1,270	1,260
II	1,700	1,550	1,550	1,700	1,550	1,800	1,480	1,310	1,350
III	5,600	5,400	5,130	5,300	4,400	—	4,450	5,400	4,650
IV	1,000	1,040	1,020	1,000	900	960	940	1,040	1,160
V	11,400	11,350	10,600	9,500	11,000	12,600	11,350	10,600	9,520

The figures in the lower part of the table indicate the potency of the sample, in international units per 1 (× 5) indicates that one animal per serum dose was used in the test, but the determination was

Tal
Summary, showing the Limits of Error ($P = 0$).

Group of assays :	A		B		C	
	Assays 1 to 20 (all assays)		Assays 1 to 5 (5 assays in 5 laboratories; same toxin standard and method)		Assays 6 to 20 (15 assays in 9 laboratories; 9 toxins, 3 standards, 7 methods)	
	Geo-metric mean	Limits of error ($P = 0.99$) %	Geo-metric mean	Limits of error ($P = 0.99$) %	Geo-metric mean	Limits of error ($P = 0.99$) %
Number of tetanus anti-toxin :						
I	1,229	82—122.5	1,180	78.5—127.5	1,245	83—120.1
II	1,640	73—137	1,607	88—114	1,654	69.5—143
III	5,495	67—150	5,140	78.5—127	5,631	64.5—155
IV	960	76—131	991	86.5—115.5	950	76—132
V	10,833	73—137	10,740	82.5—121	11,522	70—142
Mean for all five sera		73.5—136		82.5—122		71.5—146

1.

Five Samples of Tetanus Antitoxin.

toxins methods standards		Guinea-pigs. different									Geometric mean of all twenty assays
10	11	12	13	14	15	16	17	18	19	20	
H mice	E mice	A guinea-pig	A guinea-pig	C guinea-pig	E guinea-pig	L guinea-pig	P guinea-pig	W guinea-pig	W guinea-pig	W guinea-pig	
6 s.c.	2 i.p.	1-2 s.c.	1-3 i.m.	6 s.c.	2 s.c.	2 s.c.	2 (x6) s.c.	2 s.c.	2 s.c.	2 s.c.	
1 189 Intl.	0.75 509 Brit.	24 C.35 Intl.	1 7m5 U.S.A.	24 C.35 Intl.	0.75 509 Brit.	1 L Brit.	1 P Brit.	1 C.35 Intl.	1 K U.S.A.	1 C.35 Intl.	
1,300	1,140	1,260	1,200	1,400	1,430	1,150	1,250	1,200	1,250	1,080	1,229
1,700	1,330	1,615	1,880	1,900	1,930	1,800	1,850	1,620	1,900	1,600	1,640
5,500	4,290	5,300	5,900	6,200	6,470	5,500	6,200	6,400	8,000	—	5,495
970	900	945	800	1,150	1,040	850	900	850	1,000	840	960
11,000	8,780	11,400	12,000	12,500	13,250	11,000	12,650	12,000	14,000	11,400	10,833

c.c., returned by individual workers. repeated five times.

2.

of the Assays of Five Tetanus Antitoxins.

D		E		F		G	
Assays 1 to 5, and 12, 14, 18 and 20 (9 assays using toxin C.35)		Assays 6 to 11, and 13, 15, 16, 17 and 19 (11 assays using toxins other than C.35)		Assays 1 to 11 (11 assays in which mice were used)		Assays 12 to 20 (9 assays in which guinea-pigs were used)	
Geometric mean	Limits of error (P = 0.99) %	Geometric mean	Limits of error (P = 0.99) %	Geometric mean	Limits of error (P = 0.99) %	Geometric mean	Limits of error (P = 0.99) %
1,202	78—128	1,251	85—117.5	1,217	82.5—121.5	1,242	80—125.5
1,641	84.5—118.5	1,645	67.5—148.5	1,538	75.5—132.5	1,784	81.5—122.5
5,433	74—135	5,541	61.5—162.5	4,988	76.5—130.5	6,200	72.5—138
966	76.5—131	955	79.5—125.5	991	83—120.5	924	73.5—136
11,220	82—122	11,416	69.5—143.5	10,646	77—130.5	12,212	82—122
	78.5—127.5		70.5—141.5		78.5—127.5		77—130

tests were large in fifteen and small in five. Sections B and C of Table 2 show the limits of error when the assays are divided into these two categories and the data recalculated on this basis. Under Section B are given the limits of error for the small series of assays in which the conditions of testing are relatively constant, and, as would be expected, the variation in the results obtained are less than in the series of fifteen assays (Section C), in which the assays were conducted under much more variable conditions.

A further criticism which may be advanced is that, since the test toxin used is, perhaps, the most important factor influencing the variance of the repeated tests, twenty different toxins should have been used in performing the twenty assays. This was impracticable in the present enquiry, but the data available can be divided into two groups. Section D of Table 2 shows the limits of error for nine assays in which the same toxin (C35) was used; five of these assays are those numbered 1 to 5 referred to above and, in the remaining four assays (Nos. 12, 14, 18 and 20), guinea-pigs were used as test animals, and other small variations in the conditions of the assay are involved. The limits of error for this series of nine assays are somewhat larger than those shown in Section B but smaller than those given in Section E, which relates to eleven assays of the five antitoxins carried out under the most varied conditions of testing attained in this enquiry.

Sections F and G of Table 2 show the values (1) for the limits of error ($P = 0.99$) for eleven assays in which *mice* were used as test animals, seven different toxins and two standards being used, and other details of the assay being varied (Section F); and (2) for nine assays in which *guinea-pigs* were used as test animals, six different toxins and three standards being used and other details of the assay being varied (Section G). It is interesting to note that, examined from this point of view, the data provides support for conclusions reached in other investigations relating to tetanus antitoxin standardisation and reported in Annexes 1a and 1c. Thus the variations observed are about the same whether mice or guinea-pigs are used as test animals; for some antitoxins, the variations are less when mice are used as test animals; while with others, the variations are less when guinea-pigs are used; and with some antitoxins, the mean titre obtained from the assays in which guinea-pigs are used are higher than those obtained when mice are used as test animals.

Annex 1 f.**NOTE ON TETANUS ANTITOXIN**

By

Professor A. SORDELLI, Buenos Aires.

The quality of a tetanus antitoxin is revealed—although in a manner of which we are not yet fully cognisant—by the figure representing its antitoxic value. Since this figure may vary considerably (from 1 to 4, according to the standard antitoxin, the toxin and the method employed), the problem is to determine which of these figures should be taken to represent the true value of the antitoxin.

Its true value is, of course, its capacity to prevent or cure spontaneous tetanus, especially human tetanus.

As this point has not yet been determined by the method of clinical observation (and is not likely to be for a long time to come), a solution must be sought by the experimental method—in my opinion, the only one left.

I accordingly propose that the main outlines of an enquiry into this problem should be laid down, because, until it is solved, no final decision can be reached as to the method of assay to be recommended, nor, perhaps, as to the nature of the standard antitoxins to be selected.

PROGRAMME**A**

1. Choice of three antitoxins obtained by the same immunisation method and representing three types of dissociation—large, intermediate and small—in relation to dilution.

2. Choice of two antitoxins, one representing a type which combines rapidly and the other a type which combines slowly.

3. Choice of antitoxins obtained by a different immunisation process from that adopted under point 1, including the various types referred to in points 1 and 2.

B

1. Assay by a method very similar to ROSENAU's method (to be determined in advance, like the standard antitoxin and the test toxin to be employed).

2. The antitoxins should also be assayed by at least one other method, left to the choice of the participants, to reveal their quality. (Each participant should let the others know what technique he has adopted.)

3. Proposed methods of assay.

C

Determination of the preventive action of the different antitoxins on guinea-pigs inoculated with tetanus.

These experiments should be carried out either :

- (a) By a method to be agreed upon ; or
- (b) By this method and some other method to be selected by the experimenter.

D

Study of the results.

Annex 2**PROGRESS REPORT ON THE POSSIBILITY
OF STANDARDISING ANTI-SNAKE-VENOM SERA**

By

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INTRODUCTION

The Permanent Commission, at its session held at Geneva in September 1935, examined, among the resolutions referred to it by the Inter-Governmental Conference on Biological Standardisation, the recommendation that the possibility of standardising anti-snake-venom sera should be considered.

The question of anti-snake-venom serum appeared too far-reaching for the Commission to take up as a whole. It was felt, however, that work could be limited to the study of standardisation of a special anti-venom—namely, sera against the venom of the European viper. In pursuance of this suggestion of the Commission, the Department of Biological Standards, Copenhagen, established contact with institutes preparing European anti-viper sera with the view to ascertaining the principle upon which their sera are assayed and to studying the possibilities of an international standardisation of these preparations.

CHAPTER A**I. THE EUROPEAN VIPERS AND THE INTERRELATION
OF THE ANTIGENIC PROPERTIES OF THEIR VENOMS**

According to the elaborate monograph edited in 1937 by members of the experimental staff from the "Behringwerke" ("Die euro-

päisichen und mediterranen Ottern und ihre Gifte ") eighteen species and sub-species of the genus *Vipera* can be distinguished morphologically. The following five species are more predominant and their geographical occurrence is fairly well defined :

Vipera berus occurs in Northern Europe, Great Britain and most of France. The southern limit is Switzerland, Tyrol and the Carpathians. In the Balkans, it is rare.

Vipera aspis is common in South-Eastern France, the Alps as far as the Isonzo and throughout in Italy. It is not found in the Balkan peninsula.

Vipera ammodytes is to be found mainly in the Northern Balkans and up to the border of the *aspis* viper area in the west. In the south, it is replaced by the following :

Vipera berus bosniensis (mesocoronis), which appears in the Southern Balkans ;

Vipera ursini, which occurs most commonly in Hungary and Italy.

The venoms of these vipers are composed of several substances having different toxic and biological effects. Some of these appear to be common to the species, but the proportions in which they stand one to the other may vary. This has been concluded from the fact that it is possible to demonstrate a relationship of varying closeness in the antigenic properties of the venom of the European vipers. The closest relation has been found to exist between the venoms of *Vipera aspis* and *berus*, the next most nearly related venom being that of *Vipera ammodytes*. The *mesocoronis* and *Vipera ursini* have appeared antigenically more specific, as they are but slightly neutralised by anti-*ammodytes* and anti-*aspis* serum.

The venoms of the rest of the vipers are—according to the Behringwerke investigations—neutralised more or less by the available European commercial sera, 0.1 c.c. of such sera protects against 1 to 5 minimum lethal doses of various venoms.

The antigenic action of the venom is thus not entirely specific for the zoological species. Furthermore, it is a remarkable fact

that individuals of the same species—*e.g.*, *V. ammodytes* do not produce quite identical venoms. Indeed, it has been stated that different samples of venom from the same *individual* are not identical. This is evident from the experiments carried out in the Behringwerke ; and the assays in Copenhagen and Zagreb, referred to later on, confirm the finding that different samples of *V. ammodytes* venom may be composed of partial toxins in various amounts, and the relative activity of sera may depend markedly upon the sample of toxin used for the test.

II. EXISTING COMMERCIAL ANTI-VENOMS AGAINST EUROPEAN VIPERS AND THEIR PREPARATION

The following synopsis gives the names of the institutes which are the main producers of anti-viper venom for use in European countries, the name of the product and the antigen (venom) used for immunisation :

Institute	Place	Serum	Venom used for immunisation
Institut Pasteur	Paris	ER	Aspis
Behringwerke	Marburg	Polyvalentes Schlangen Serum	Ammodytes
Škola Narodnog Zdravlja (Hygienic Institute)	Zagreb	Serum Protive Otro- va Zmija	Ammodytes
Istituto sieroterapico	Milan	Siero antivipera	Ammodytes and aspis

Only two main species are used for the production of the sera against European vipers. The reason for this is apparently that these types of venom are easy to obtain in sufficient quantities. This therefore simplifies matters, as only these two types of sera need be taken into account. The indication of polyvalence of the sera does not refer to the use of more antigens for the production, but to the fact that the sera actually neutralise several species of European viper venoms.

III. METHODS EMPLOYED BY THE PRODUCERS FOR THE ASSAY OF EUROPEAN ANTI-VENOMS

Place	Species of test venom	Experimental animal	Route of injection	Indication of potency of serum
Marburg	Ammodytes	Mice	Intra-venously	Number of d.c.l. neutralised by 0.10 c.c. of serum.
Milan	Ammodytes	Guinea-pigs	Subcutaneously	Quantity of serum neutralising 1 mgrm. of venom (1 d.c.l.)
Paris	Aspis	Rabbits	Intra-venously	Quantity of serum neutralising 3.2 mgrm. of venom per kilogramme weight (10 d.c.l.)
Zagreb	Ammodytes	Mice	Intra-venously	Ratio of (dose of venom + 1 d.c.l.) to dose of serum.

The Marburg institute has chosen to keep the dose of serum constant (0.10 c.c.) and determine the amount of toxin, expressed in the *doses certe lethales*, which is neutralised. With such a method, the resistance of the experimental animals may influence the findings.

The Milan institute works with a fixed dose of venom expressed in milligrammes of the preparation and corresponding to about 1 *dosis certe lethalis* for guinea-pigs subcutaneously. This amount of venom is about 50 to 100 times the *dosis certe lethalis* for mice intravenously; the amount of serum generally found by the Milan institute to neutralise this test dose is small in comparison with that found in Marburg—namely, from 0.2 to 0.3 c.c.

The Pasteur Institute prefers to test the serum against several lethal doses (rabbits intravenously). The weight of the animal is allowed for in the dosage. Titres are expressed in cubic centimetres of the serum neutralising the test dose. The test requires fairly large amounts of serum and venom—about 3 to 4 mgrm. of venom and 5 to 10 c.c. of serum per animal injected.

The Zagreb institute uses a method described in detail by BANIĆ and LJUBETIĆ. These investigators have observed that the amount of serum required to neutralise 2 d.c.l. is much larger than twice the amount of serum neutralising 1 d.c.l. The authors explain this by assuming that a large part of 1 d.c.l.—say, four-fifths—is neutralised by the natural defences of the animal's organism. Only the

remaining fifth of the 1 d.c.l. requires neutralisation by the serum to protect the animal.

When 2 d.c.l. is given to the animal, much more serum is required—namely, the amount neutralising the supposed fifth of 1 d.c.l. + the amount of serum neutralising a full d.c.l.

The amount of serum required to neutralise higher multiples of d.c.l. appears to correspond to the sum of the amount protecting against 1 d.c.l. + the amount of serum neutralising $(D - 1)$ d.c.l.

Ammodytes venom Number of d.c.l. (x)	Amount of serum 145 just neutralising the test dose (Y)	Dose of venom—1 d.c.l. Dose of serum—the dose(S_1) ($1/a$)
1	0.0055 (S_1)	—
2	0.0264	47
5	0.08	50
10	0.18	50
20	0.42	45
30	0.60	48

The first and the second column of the above table is taken from the above-mentioned paper by BANIC and LJUBETIC. The figures in the last column are calculated to test the said hypothesis. This was expressed mathematically by the authors in the equation :

$$Y = (x - 1). a + S_1$$

Y is the amount of serum given in the second column of the table.

x is the corresponding dose of toxin expressed in number of d.c.l.

S_1 is the dose of serum protecting the mouse against 1 d.c.l.

a is a constant factor indicating the *amount of serum neutralising a given dose of toxin.*

We have calculated the reciprocal of a in the last column as

$$1/a = \frac{x - 1}{Y - S_1}$$

$1/a$ will indicate *the amount of toxin neutralised by 1 c.c. of the serum* which seems to be an adequate expression of the activity of a given serum, since all quantities depending on the variation in resistance of animals seem to be eliminated.

The values in the last column indicate that the coefficient is constant at the various levels of determination. This gives support to the theory of BANIC and LJUBETIC.

CHAPTER B

A MODIFICATION OF BANIĆ'S METHOD FOR ASSAYING
A SERUM IN TERMS OF A STANDARD PREPARATION

In selecting a method suitable for international use by comparing anti-snake venoms, we reviewed the above-mentioned routine methods of assay.

There is no doubt that all the methods yield satisfactory results in the internal routine assays of each institute, where ample supplies of the reagents can be prepared. But for purposes of international standardisation, the most economical method has to be used.

We have found the mouse to be the most suitable animal, since it requires but very little of the reagents. A standard preparation of anti-snake serum must be used in undiluted form, as the antibody content is much lower than that of the antitoxins against bacterial products. The Pasteur Institute's method requires more venom and serum than can be expected to be available for international use. The high test-dose of venom used in the Milan method also seems to be too uneconomical.

An important condition which an assay must satisfy to be suitable is that it should *determine the relation between the antitoxin and the venom, irrespectively of the level of test chosen*. In the method proposed by the Behringwerke using 0.1 c.c. of the serum against varying amounts of toxin, the weakest sera, of which 0.1 c.c. neutralises about 1 lethal dose will appear stronger than it really is when its titre is compared with that of sera neutralising several m.l.d. The evidence for this can be found in the statement of BANIĆ and LJUBETIĆ—that 1 d.c.l. only requires partial neutralisation to be ineffective. The most correct technique would therefore appear to be to perform the assays at different levels, as indicated by these authors, and to calculate the relation between the dose of serum and the dose of toxin which is perfectly immunised. It may be objected, however, that assay at different levels may require a considerable number of mice, and will thus make the method elaborate and expensive. In the Department of Biological Standards at Copenhagen, an attempt has been made slightly to modify the Zagreb method, so that the assay of one serum only requires about twenty mice.

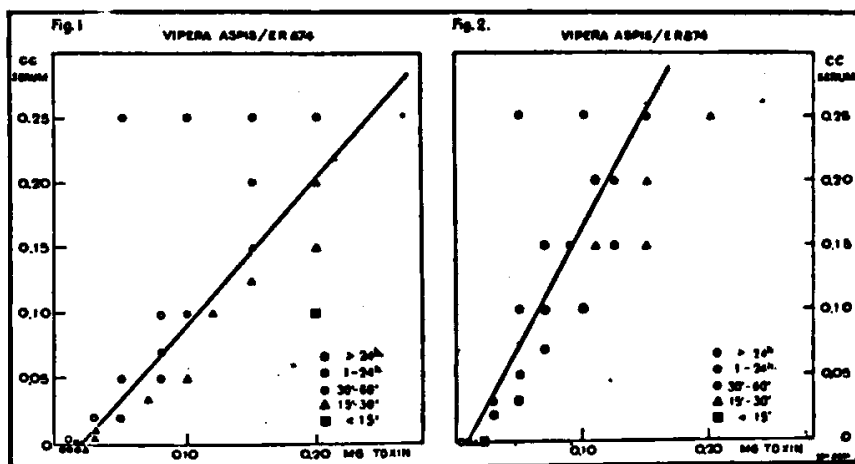
Principle of the Method.

The titre of a serum is calculated as the amount of the test venom neutralised by 1 c.c. of the serum.

The calculation is based upon a graphical record of the experiments.

Each mouse injected is marked in a co-ordinate system having the dose of venom as abscissa and the dose of serum as ordinate. When the death or survival is indicated at the plot corresponding to the mice, it is possible to draw a straight line which separates the dead from the surviving animals, the survivors being placed to the left and over the line, and the dead being placed to the right and under the line.

This straight line represents the neutralisation ratio of the venom and serum. The slope will serve as the titre of the serum, expressing the amount of venom neutralised by 1 c.c. of serum (see Figures 1 and 2).



Technical Details.

The doses were diluted in 0.5 c.c. of a 0.9% sodium chloride solution and injected intravenously into mice weighing about 18 grammes.

The mixture of serum and venom was injected immediately after mixing.

The moment of injection of each mouse was recorded and the animals were repeatedly observed during the first hour after injection. The moment when the heart-action ceased was recorded as time of death.

Experimental Procedure.

1. A diagram is provided (abscissa = mgrm. venom) (ordinate = c.c. of serum).

2. *Determination of the m.l.d.*—Mice are injected with 0.01 mgrm.—0.015 mgrm.—0.02 mgrm. The response (survival or death) is indicated at the abscissa.

3. Four mice are injected with mixtures of 0.25 c.c. of serum and, respectively, 0.05 mgrm., 0.10 mgrm., 0.15 mgrm. and 0.20 mgrm. of venom.

4. *Preliminary neutralisation line.*—A straight line is drawn on the diagram separating the dead from the surviving mice in the series of m.l.d. and the series injected with 0.25 c.c. of serum.

5. The rest of the mice (4-12) are injected with mixtures of 0.20, 0.15, 0.10 and 0.05 c.c. of serum and with doses of venom chosen from the diagram, following the principle that the mixture of serum and toxin should have co-ordinates lying in the neighbourhood and on both sides of the preliminary line.

6. The reactions of the mice are indicated on the diagram and the final neutralisation line can be drawn as indicated.

7. *Calculation of the activity of the serum.*—Two points on the neutralisation line are selected. The difference of the corresponding amounts of venom is divided by the difference of the corresponding amounts of serum.

Example (Figure 2). The line intersects 0.25 c.c. of serum at 0.145 mgrm. and 0.15 c.c. of serum at 0.093 mgrm.

$$\text{Titre} = \frac{0.145 - 0.093}{0.25 - 0.15} = \frac{0.052}{0.10} = 0.52$$

1 c.c. neutralises 0.52 mgrm. of venom.

Preliminary Results of Titrations performed in Copenhagen and Zagreb using the Modified Zagreb Method.

In collaboration with Dr. BANIĆ, of Zagreb, the Department of Biological Standards at Copenhagen has undertaken a series of

comparative assays of various European commercial anti-viper-venom sera.

The reagents were divided in equal parts between the two institutes, and the activity of the sera was to be measured against the sample of venom by the method proposed above.

The reagents used were :

A. *Venoms.*

1. *Vipera aspis* desiccated test venom supplied by Dr. CÉSARI, Pasteur Institute, Paris.

2. *Vipera ammodytes* (15) dissolved venom prepared at Zagreb, 1 c.c. containing 10 mgrm.

3. *Vipera ammodytes* (B38), a mixture of venoms from the Istituto Sieroterapico, Milan, and from the Zagreb Institute of Hygiene, dissolved in 50% glycerol saline (1 c.c. = 10 mgrm.)

4. *Vipera berus* (III 38), a mixture of venoms supplied by Dr. Václav STRIMPL, Kosice, and by Professor PETERSON, Tartu.

B. *Sera.*

1. Serum ER 874 (bled March 1st, 1938), Pasteur Institute, Paris. (*Aspis.*)

2. Serum No. 16, Zagreb. (*Ammodytes.*)

3. Siero antivipera, Milan. (*Ammodytes.*)

4. Serum No. 118, Marburg. (*Ammodytes.*)

Results of Titration intravenously in Mice.

The activity of the four sera against the four venom preparations as obtained in the two laboratories are summarised in Table 1. The calculation of the amount of toxin neutralised by 1 c.c. of the serum is made by drawing the neutralisation line as mentioned above.

In the experiments with the venom of *aspis*, it was evident that such a line could only be applied if it was placed between the animals dying in less than 35 minutes and the animals surviving or dead in more than 35 minutes. That is to say, that concording results are only to be expected if 35 minutes is the period of observation. This empirical fact is repeated in the experiments from both laboratories,

and is only found in titrations with *aspis* venom. In the case of *ammodytes* and *berus*, 24 hours is the period of observation which should be selected.

The position and slope of the neutralisation line cannot be determined absolutely in each experiment. The experimental data allow some variance as to the placing of the line. The extremities of this was determined in each experiment.

The results in Table 2 are therefore presented partly by these limits of determination (in brackets) and partly by the mean of the limit values, this last quantity being regarded as the titre.

The following conclusions may be drawn from Table 1 :

1. All the four commercial sera examined neutralise measurable amounts of *aspis*, *ammodytes* and *berus* venoms when assayed intravenously in mice.

2. The relative strength of the various sera as given by the intravenous test varies considerably *according to the venom used* for the test. Such a difference in relative titre also appears when two different venom preparations derived from the same species (*ammodytes*) are used as test venom.

3. There are indications that sera appear more potent when tested with venom of the same species as that used in their preparation. Serum ER is thus more potent against the homologous *aspis* venom than against the other venom species.

4. The agreement between the results obtained by the two institutes is fairly good, the limits of the determination taken in regard. The only serious deviation is found in the titration of serum Zagreb 16 against venom *aspis*.

Determination of Biological Effects of the Venoms.
(Results from Copenhagen.)

The minimum reacting dose of the four samples of venom was determined by the three following methods :

- (a) Intravenously in mice ;
- (b) Intracutaneously in rabbits ;
- (c) Intravenously in rabbits.

Table 1.

SYNOPSIS OF RESULTS OBTAINED IN ZAGREB AND COPENHAGEN WITH SAME PREPARATIONS OF VENOMS AND SERA

Figures indicate mgrm. of venom neutralised by 1 c.c. of serum.
(Figures in brackets indicate the estimated limits of determination.)

Venom	Serum							
	Milan		Zagreb 16		Behringwerke 118		ER 874	
	Zagreb	Copenhagen	Zagreb	Copenhagen	Zagreb	Copenhagen	Zagreb	Copenhagen
<i>V. aspis</i>	—	0.47 (0.44–0.50)	0.17 (0.15–0.19)	0.55 (0.50–0.60)	0.45 (0.35–0.60)	0.45 (0.33–0.60)	0.81 (0.75–0.87)	0.83 (0.80–0.87)
<i>V. ammodytes</i> 15 ..	0.20 (0.13–0.30)	0.69 (0.32–0.75)	0.50 (0.45–0.55)	0.45 (0.32–0.64)	0.58 (0.56–0.60)	0.42 (0.32–0.55)	0.31 (0.27–0.36)	0.23 (0.13–0.42)
<i>V. ammodytes</i> B38 ..	—	0.33 (0.27–0.42)	1.23 (1.00–1.50)	1.02 (0.83–1.25)	—	1.20 (1.15–1.32)	—	0.31 (0.27–0.38)
<i>V. Berus</i> III 38	0.30 (0.20–0.45)	0.36 (0.33–0.40)	—	0.48 (0.35–0.60)	—	0.38 (0.36–0.40)	0.51 (0.35–0.75)	0.63 (0.50–0.80)
	0.41 (0.38–0.45)							

BIOLOGICAL STANDARDISATION

Intravenously in mice.—All the four venoms killed the mice in almost equal doses ; no marked differences were observed in the resultant symptoms. The animals died apparently of dyspnoea and with slight paralysis of the muscles. The aspis venom appeared to have a somewhat more rapid action than the other venoms.

Intracutaneously in rabbits.—Three of the venoms—namely, those of aspis, berus and ammodytes B38—caused bluish diffusing hæmorrhage 5 to 15 minutes after the injection. No difference of reaction attributable to the species could be detected.

Intravenously in rabbits.—The aspis venom injected intravenously killed rabbits weighing about 3 kg. in the way described in detail by E. CÉSARI & P. BOUQUET. The animals died in a few minutes of severe convulsions and dyspnoea. The effect of the berus venom was very similar to this, while the ammodytes venoms appeared weaker in action. Ammodytes venom B38, killed in a dose of 2 mgrm. in some hours, but the dose had to be increased to 20 mgrm. for death to occur in a few minutes.

Table 2.

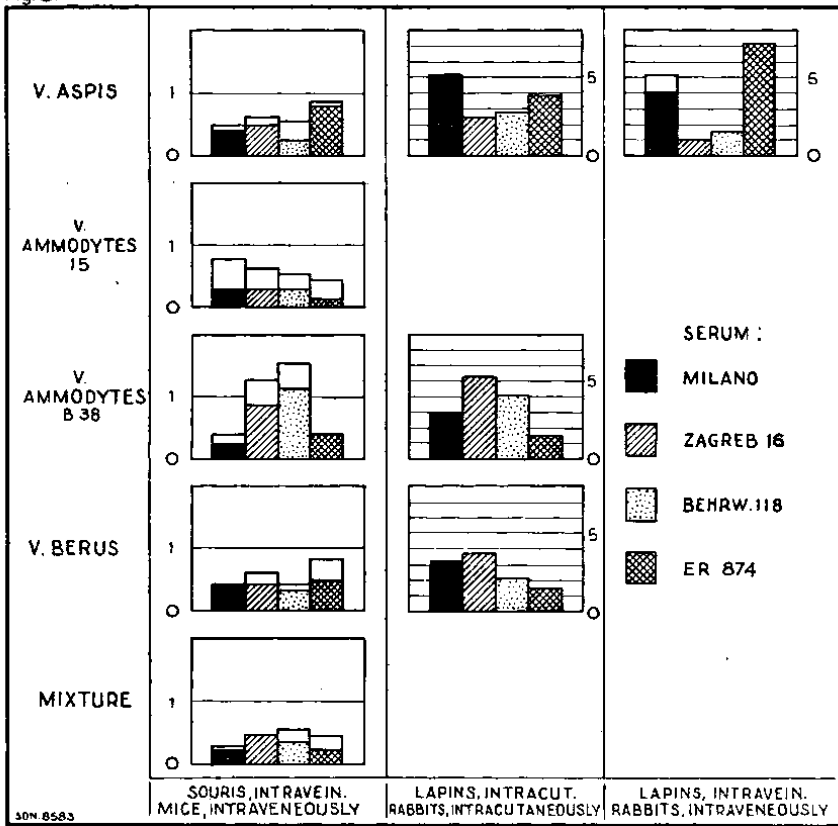
Venom	Dosis reagens minima		
	Mice (intravenously)	Rabbits (intracutaneously)	Rabbits (intravenously)
	Mgrm.	Mgrm.	Mgrm.
Aspis	0.005-0.01	0.005	1.00
Ammodytes 15.....	0.008-0.02	1.0 0	2.0-2.5
Ammodytes B38	0.010-0.02	0.010	2.0-20.0
Berus	0.005-0.009	0.020	1.00

The quantitative ratios in which the four venoms stand to each other are thus seen to vary according as they are determined by one or other of the biological reactions upon which these three tests are based. Special interest attaches to the two *V. ammodytes* venoms, of which B38 appeared a hundred times stronger than No. 15 by the intracutaneous test while No. 15 appeared the stronger by the intravenous test in rabbits. The three reactions would seem therefore to indicate that at least *three different partial venoms are contained in various amounts in the four preparations.*

Assay of the Activity of the Four Sera intracutaneously and intravenously in Rabbits.

Additional tests were performed to examine the neutralising value of the sera against the venoms intracutaneously in rabbits. The dose of serum preventing the hæmorrhagic effect was determined against various doses of the venoms, and the neutralisation coefficient could be calculated in a quite similar way as in the case of the mouse test. The results of the test are given in the second part of Figure 3.

Fig. 3.



A few experiments with the aspis venom intravenously in rabbits using the technic of the Pasteur Institute were performed. The activity of the sera were calculated as the amount of mgrm. neutralised by 1 c.c. in order to make the results comparable to those of the mouse tests. (Figure 3, third part.)

The conclusions of these experiments may be :

1. In the intracutaneous and intravenous tests in rabbits, the venoms are neutralised by much smaller amounts of serum than in the mouse intravenous test.
2. The relative strength of the sera vary according to the test animal and the route of injection.

Table 3.

MOUSE. TOXIN NEUTRALISED BY 1 C.C. SERUM

<i>Rabbits intracutaneously.</i>				
<i>V. aspis</i>	5.1	2.5	2.6	3.8
<i>V. ammodytes</i> B38	3.0	5.2	4.1	1.5
<i>V. berus</i> III.38	3.3	3.7	2.1	1.6
<i>Rabbit intravenously.</i>				
<i>V. aspis</i>	4.0-5.0	1.0	1.5	7.0

CHAPTER C

DISCUSSION OF THE PRINCIPLES APPROPRIATE TO THE STANDARDISATION OF THE ANTI-VENOM SERA

The principle hitherto adopted for standardisation of antitoxic sera has been to establish a stable preparation of a serum, representative to that type of serum, and to define a unit as the activity of a certain quantity of this preparation.

The standardisation of toxins is unnecessary so long as different toxin preparations of the same kind are known to give identical results, when used in comparative assays of various sera of the same type.

The standardisation of anti-snake-venom sera raises certain other questions, owing to the less well-marked specificity and to the complexity of the venoms. The varying composition of the antigens in the venoms results partly in cross-neutralisation effects as between venoms and antivenoms of different species and partly in differences in the antigenic properties of venoms from the same species.

The two sorts of commercial sera against European viper-venoms produced at present—namely, anti-ammodytes and anti-aspis—have proved effective both against the venom used for their production and against venoms from several other species of European vipers. The experiments reported above confirm, however, the findings of other published tests—that sera appear strongest when tested against the homologous venom.

This fact must be borne in mind in considering the establishment of a standard preparation for European vipers. Two possibilities might be considered : (1) a pooled standard preparation composed of all types of serum, or (2) more standards representing the different kinds of serum actually used for immunisation.

The first suggestion seems to be supported by the fact that most commercial sera actually are labelled as “ sera against European snakes ” without any indication of the antigen used for the production. One common unit for this sort of serum might appear sufficient. The well-marked geographical localisation of the species is, however, an argument in favour of labelling serum in terms of its effect against the bite of particular species. Moreover, the pooling of several kinds of serum or venom attenuates the specific effect which the various components might be capable of producing.

For these reasons, we are inclined to suggest the establishment of separate standards for sera against *Vipera aspis* and *Vipera ammodytes*.

The Nature of the Standard Preparations.

Working upon the established principle of standardisation, the first step in the case of snake venoms would be to select representative potent sera produced with aspis and ammodytes venoms. A certain quantity of these sera should be adopted as a unit, and the sera stored and distributed under conditions ensuring stability.

So far, however, as may be anticipated from publications on the subject, the determination of the activity in terms of this unit is likely to depend upon the venom used for the test. The ratio of activity of sera has been found to vary so considerably when they are assayed with different samples of venom from the same species that the question of establishing a *standard venom* to be used in connection with a standard serum becomes acute.

The conditions to be satisfied by a standard venom for a viper species are that it should consist of samples from as many individuals as possible and that it should be available in quantities as large as possible. Samples of the venom concerned should be collected from various places and homogeneously mixed, kept in dry condition and issued from a central laboratory either in dried condition or in a dilution of glycerol saline containing a fixed number of mgrm. per c.c. The mixture should be as representative as possible, so that a similar pool made some years later will be likely to display properties as close as possible to those of the initial preparation.

*Suggestion as to the Method to be used for the Assay
of Sera in Terms of the Standard Preparations.*

In defining standard preparations for the sera against bacterial toxins, the principle has been hitherto, not to standardise the method of assay because different biological tests have proved to give identical results. The choice of method has been left to the investigators, who have worked with that which was most convenient.

The research work which has been published so far suggests that the choice of animal and the method of calculating the result will influence the assessment of the relative activity of the sera. The difficulty in standardising anti-venom sera is increased by the fact that, not only a standard serum and a standard venom, but also a method has to be defined. We are inclined to suggest the mouse intravenous test both for aspis and for ammodytes sera. The assay of aspis sera performed at the Pasteur Institute by the intravenous test on rabbits admittedly yields fairly clear-cut results, but the large amounts of the reagents required for each test is a serious drawback, having regard to the limitation of the stock of standard preparations. The mouse test seems to us to have the following advantage :

- (a) Comparatively small quantities of the reagents are required ;
- (b) The mouse appears susceptible to more fractions of the venom than the rabbits ;
- (c) The mouse test can be applied for both ammodytes and aspis venom, which is not the case with the rabbit test.

Definition of the Unit.

The activity of anti-venom sera is well defined, when Banić's principle of indicating the amount of venom perfectly neutralised by the serum is employed. For practical purposes, it may be convenient to express the potency in units per c.c. Such a unitage could easily be referred to the standard venoms; if, for example, 1 c.c. of a serum neutralised 1 mgrm. of the standard venom, its potency could be labelled as 100 or 1,000 units per c.c. This could be settled by agreement between the institutes concerned, if the establishment of standard venoms for aspis and ammodytes is realised.

SUMMARY

1. To obtain an adequate expression of potency of anti-viper sera it is necessary to vary the dosage of serum as well as venom, and calculate the amount of venom perfectly neutralised by a certain amount of serum.
2. The relative potency of two or more sera is only constant when the same venom is used.
3. For the standardisation of European anti-viper venom sera, it is suggested that standard venom preparations of the species aspis and ammodytes are established and that the potency of the sera is expressed in reference to these preparations.

Reference.

- R. BIELING, A. DEMNITZ, O. SCHAUMANN, H. SCHLOSSBERGER, W. v. SCHUCKMANN & E. SCHWARZ: "Die europäischen und mediterranen Ottern und ihre Gifte". (Selbstverlag der Behringwerke, Marburg-Lahn, 1936).
- E. CÉSARI & Paul BOUQUET: "Recherches sur les antigènes des venins et les anticorps des sérums antivenimeux". (*Ann. de l'Inst. Pasteur*, 1935, 153, 307.)
- M. BANIĆ & A. LJUBETIĆ: "Die Titration eines Serums gegen Schlangenbisse an Mäusen". (*Z. für Hyg.*, 1938, 120, 390.)
- E. GRASSET: "On the Interrelation of the Antigenic Properties of Snake Venoms and its Bearing upon the Polyvalence and the Assay of Sera". (*Quart. Bull. Health Org.*, 1936, 5, 367.)

Annex 3 a.

STUDIES ON PERFRINGENS TOXIN

Communication from Dr. Ida A. BENGTSO
on Work done by Sarah E. STEWART and J. Marion CLAMPIT.

The character of the culture medium employed influences the nature of the toxic elements produced and consequently the nature of the antibodies evoked in the immune serums obtained by inoculating animals with the toxic products. Certain culture media favour the formation of hæmolysin and others do not. Antitoxins produced as the result of inoculating animals with toxins deficient in the hæmolytic factor, for example, fail to neutralise such toxins as contain the hæmolytic element. The question arises therefore—since the hæmolytic and certain other lethal components are not the same—whether instead of attempting to free the toxin of hæmolysin or other factors it would not rather be desirable to attempt to produce toxins containing all the toxic factors, and to use these for producing antitoxins. This would perhaps necessitate tests for lethal, hæmolytic and possibly others (myolytic).

The work of Miss STEWART and Mr. CLAMPIT is in line with the suggestion of Dr. WEINBERG—that a purer toxin is desirable. They have shown that a type A toxin produced from a medium made from dried chopped beef heart (10%) in a Bacto peptone beef infusion broth is not hæmolytic for sheep red cells, but that a toxin produced from peptone meat infusion broth is hæmolytic for these cells.

Further tests made to determine whether by varying the composition of the media toxins might be produced which did not contain the hæmolytic factor confirmed this hypothesis. Cultures on meat infusion broth containing 1% of each of four different peptones—Bacto, Parke-Davis, Proteose and Wittes—with and without cysteine, were incubated for twenty-four hours and tested

for the hæmolytic factor. In all except the media made with proteosepeptone, the hæmolytic factor was present in considerable amounts. It was present in small amounts in the proteose medium without cysteine, but with cysteine it was eliminated almost completely. Hæmolytic tests were made with sheep, rabbit, mouse and human red cells, and the behaviour of the filtrates was practically the same against all types of cells.

Experiments were undertaken to determine whether it would be possible to separate the hæmolytic factor from the other components of the toxin by means of graded collodion membranes. This was accomplished satisfactorily with type C filtrates and also with type A filtrates, though the results were less clear cut. The accompanying table shows the results with the type C filtrates.

Table 1.

Showing the Separation of a Non-Hæmolytic Toxin from a Hæmolytic Toxin.

Membrane used	Amount of filtrate	Toxicity for mice	Hæmolysin for sheep erythrocytes
	c.c.		
A 33a—about 1,000 mm. . . .	0.2	Died	++++
	0.1	..	++++
	0.05	..	++++
	0.25	..	++++
A 19a—about 60 mm.	0.2	..	+
	0.1	..	±
	0.05	..	—
A 24a—about 50 mm.	0.5	..	—
	0.2	..	—
	0.1	..	—
	0.05	Lived	—
CB 3.1 mm.	0.5	Died	—
	0.2	..	—
	0.1	..	—
	0.05	Lived	—

Some of the results with type A filtrates are shown in Table 2. A 1% proteose peptone medium which had previously been shown to give a poor hæmolysin was used. For the filtrations, several membranes varying in pore-size were used. The results obtained with membrane A 20 are shown in Table 2.

Table 2.

The Hæmolytic Action of Type A Toxins filtered through Collodion Membranes together with Toxicity Tests on Mice.

	Amount c.c.	Hæmoglobins for red cells				Toxicity for mice
		Hu- man	Mouse	Sheep	Rab- bit	
Toxin No. 1 (6 hr.- incub.)	0.5	±	±	±	±	1 c.c. died 0.5 c.c. died
	0.2	±	±	±	±	
	0.1	—	—	—	—	
	0.05	—	—	—	—	
	0.02	—	—	—	—	
Toxin No. 2 (8 hr.- incub.)	0.5	+++	±	±	+++	1 c.c. died 0.5 c.c. died
	0.2	+++	±	±	++	
	0.1	++	±	±	+	
	0.05	±	—	—	—	
	0.02	—	—	—	—	
Toxin No. 3 (12 hr.- incub.)	0.5	±	±	—	±	1 c.c. died 0.5 c.c. died
	0.2	—	—	—	—	
	0.1	—	—	—	—	
	0.05	—	—	—	—	
	0.02	—	—	—	—	
Toxin No. 4 (16 hr.- incub.)	0.5	—	—	—	—	1 c.c. lived 0.5 c.c. lived
	0.2	—	—	—	—	
	0.1	—	—	—	—	
	0.05	—	—	—	—	
	0.02	—	—	—	—	

The A 20 membrane removed practically all of the hæmolysins for all types of blood cells used, yet the filtrates were toxic, indicating the presence of the θ toxin. The results also show the maximum amount of toxin at a 12-hour incubation period for the particular culture medium used.

The antigenic relationship of some of the toxic components of the four types of B. perfringens.—Rabbits were immunised against types A and C toxins with a high hæmolytic activity and against those with no hæmolysins for sheep red blood corpuscles, the former prepared by growing the organism in peptone beef infusion broth

and the latter by growing in chopped beef heart medium. These antitoxins were tested for protective action in mice and for anti-hæmolytic activity as shown in Table 3.

Table 3.

Type A Antitoxins tested against Hæmolytic and Non-Hæmolytic A Toxins.

Sera (0.2 cc. of 1/10 dilution)	Type A hæmolytic toxin		Type A non-hæmolytic toxins	
	Hæmolysin for sheep r.b.c.	Protection for mice	Hæmolysin for sheep r.b.c.	Protection for mice
No. 67 antitoxin prepared against beef heart toxin (non-hæmolytic)	2 m.l.d.—	Lived	—	Lived
	4 m.l.d.++++	Died	—	..
	8 m.l.d.++++	..	—	..
	16 m.l.d.++++	..	—	..
No. 235 antitoxin prepared against a hæmolytic type A toxin ...	2 m.l.d.—	Lived	—	Lived
	4 m.l.d.—	..	—	..
	8 m.l.d.—	..	—	..
	16 m.l.d.—	..	—	..

In order to ascertain if the lack of protection afforded by some antitoxins for different toxins is due to a lack of antihæmolysin in the antitoxin, several commercial sera, as well as the American standard antitoxin, were tested against hæmolytic and non-hæmolytic type A toxin. Here, again, lack of protection was correlated with a lack of antihæmolysin in the antitoxin.

CONCLUSIONS

By varying the composition of the culture media, used toxins are produced which vary in the proportion of the various toxic factors. The presence or absence of the hæmolytic factor in particular is of importance.

Media prepared from dried chopped beef heart and from beef infusion broth with proteose peptone and cysteine favour the production of toxin without hæmolysin. Beef infusion broth made with certain other peptones favour the production of toxins containing hæmolysin.

The hæmolytic factor may be separated from the non-hæmolytic toxic factor by means of graded collodion membranes.

Antitoxins produced by the immunisation of animals with the non-hæmolytic toxin fail to protect against toxins containing hæmolysin.

Annex 3 b.

THE NECESSITY AND POSSIBILITY
OF ESTABLISHING A STANDARD FOR
SORDELLI ANTITOXIN

(Note submitted by the Department of Biological Standards
of the State Serum Institute, Copenhagen.)

The *Clostridium sordelli* was described in 1922 by Alfredo SORDELLI in *Rev. del Inst. Bact. Dept. Nac. d. Hyg.* (1923, 3, 1). This bacillus was isolated from a case of gangreneous appendicitis. The conditions of cultivation were very similar to the non-pathogenic *Cl. sporogenes*, but differed from this in producing a very strong toxin, lethal for rabbits, mice and guinea-pigs. The pathological-anatomical effects caused by this toxin were fairly similar to those produced by *Cl. œdematiens*. SORDELLI proposed the name *Cl. œdematis-sporogenes*. The toxin proved not to be neutralised by antitoxins of *Cl. perfringens*, *vibrion septique*, *Cl. œdematiens* or *histolyticus*, whereas an effective specific antitoxin could be produced by immunisation of rabbits and horses.

In 1928, HUMPHREY & MELENEY (*Proc., Soc. Exp. Biol. et Med.*, 1928, 25, 611) identified the bacillus isolated by SORDELLI with an anærobic bacillus (called *Cl. œdematoides*) isolated by HUMPHREY during an examination of samples of catgut that had been used at an obstetric clinic, in which several unexplained fatal cases had occurred. This identity of the two strains was confirmed by Ivan HALL, who had examined in 1927 the strain isolated by SORDELLI and confirmed the properties described by this author.

The name *Bac. sordelli* was proposed by HALL.

In 1931, HALL & GRAY (*Arch. Path.*, 1931, 12, 245) described "Septic Peritonitis in man due to *Bac. sordelli*".

WEINBERG (*Comp. rend. Biol.*, 1931, 107, 506) isolated from a case of acute appendicitis a bacillus which was shown by agglutina-

tion tests and neutralisation with specific anti-serum to be *Bac. sordelli*.

From this brief summary of the literature, *Cl. sordelli* is a specific, highly toxigenic anærobic bacillus isolated from human infection, but of rare occurrence.

In 1938, Sarah E. STEWART (*Journ. of Bact.*, 1938, 35, 13), of the National Institute of Health, Washington, reported on comparative studies of *Bac. sordelli* and the non-toxigenic proteolytic anærobie *Cl. bifermentans* (TISSIER & MARTELLI 1902, syn. *Bac. putrificus tenuis*, Zeissler). The two species were found to be identical in morphology, colony formation and biochemical reactions. Cross-agglutination and cross-precipitation reactions were also obtained, and sera produced with strains of *Cl. bifermentans* were found to give protection against 2-5 M.L.D. of sordelli toxin. The author therefore claims that the two species are identical and proposes the name "*bifermentans*" for both the toxigenic and the non-toxigenic variant, this name having priority.

The *Cl. bifermentans* seems to occur rather commonly in the intestine of man. It was isolated in 1927 by LØHR & RASSFELD from cases of gangreneous appendicitis and was not uncommonly found in wounds during the war. (Zeissler in Kolle Kraus & Uhlenhuth, *Handbuch der pathogenen Microorganismen*, 1928, IV, 1138).

PROPOSAL FOR STANDARDISING SORDELLI ANTITOXIN

In a letter of September 25th, 1936, Dr. G. W. McCoy, Washington, wrote to Dr. Th. MADSEN, Copenhagen, as follows :

" Concerning the matter of standardisation of sordelli anti-toxin ; we have made considerable progress on this problem. We have had a dried serum on hand for over a year ; this we expect to use as the American standard. We are determining the potency of this in terms of the unit proposed by Dr. SORDELLI.

" The question is in regard to an international standard ; since we have accomplished as much as we have, would it meet

with the approval of the others concerned if we should propose that the National Institute of Health prepare the international standard serum, and furnish the reagents, and suggest methods for the international testing ?

“ Several of the firms in this country are producing the antitoxin, and it seems desirable that we decide on a unit for measuring the potency of this antitoxin in the near future. This should complete the work on the standardisation of the gas-gangrene antitoxins. *Cl. sordelli* is of interest in that it produces a much stronger toxin than the other members of the gas-gangrene group, it being comparable with the organism of tetanus in this respect.”

Recognising the importance of the question raised by Dr. McCoy, Dr. Th. MADSEN accepted the offer of the National Institute of Health to prepare a provisional dried standard and a dry standard toxin. The technical details were discussed between the institute at Washington and the Department of Biological Standards, partly by correspondence and partly during a personal visit of Miss Ida BENGTON, Senior Bacteriologist, Washington, to Copenhagen.

From Professor Ivan C. HALL (Denver), the Statens Serum Institute was supplied with strains of *Bac. sordelli*, and Dr. WALBUM and Dr. REYMANN undertook the preparation of toxins from these strains for purposes of preliminary titrations of the sordelli antitoxin prepared by the Department of Biological Standards.

Miss BENGTON, during her visit in July 1937, supplied us with samples of the dry provisional standard sordelli antitoxin, a glycerol solution of this and a dry toxin prepared at Washington and gave the following information :

About 100 ampoules of a desiccated sordelli antitoxin are made available by the National Institute of Health for adoption as an international standard.

Each ampoule contains the residue of 10 c.c. of the original serum weighing 0.9669 gm.

The provisional unit proposed was determined in terms of the unit proposed by Dr. SORDELLI in the following way :

SORDELLI supplied the institute at Washington with his glycerol standard of sordelli antitoxin of which

1 c.c. contained 5 sordelli units (S.U.).

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SORDELLI supplied the institute at Washington with his glycerol standard of sordelli antitoxin of which

1 c.c. contained 5 sordelli units (S.U.).

1. 0.08 mg. of the standard toxin prepared at Washington was neutralised by 2 c.c. of a dilution 1 : 25 of SORDELLI's standard—i.e.,

$$\text{Test dose } L+ / 25 = 0.08 \text{ mgrm.}$$

2. One ampoule of the dry standard prepared at Washington (i.e., 10 c.c. of the original serum) was dissolved in 100 c.c. of 66% glycerol-saline. This primary solution was diluted to 1 : 34.96, in glycerol-saline, and the test dose proved to be neutralised by 0.2 c.c. of the secondary dilution again diluted to 1 : 20.

$1/25 \text{ S.U.} = 0.2 \times 1/20 \times 1/34.96 \times 10/100 \text{ c.c. of the original serum.}$

1 c.c. of original. serum = 1398.4 S.U.

0.09669 grm. of dry preparation = 1398.4 S.U.

1 S.U. = 0.06914 mgrm. of dry preparation.

The secondary glycerol dilution contains 4 S.U. per c.c.

TESTS PERFORMED AT COPENHAGEN

Samples of the dry preparation of the proposed standard serum and the dry test toxin from Washington were submitted to the Department of Biological Standards for examination.

In agreement with the experts in Washington, the following *technical details* have been used in the assay of toxin and anti-toxin :

1. Fresh solutions of the dry toxin *must be prepared just before every assay*, the toxin being rather unstable in solution.
2. The toxin-antitoxin mixtures are allowed to stand for 1 hour at room temperature before injection.
3. As experimental animals, *mice* weighing 18 to 20 gm. are used. The injections are given *intravenously*. (Intramuscular injection yields less regular results than intravenous. Intracutaneous assays on rabbits and guinea-pigs have given very uncertain results, the reactions—profuse œdema—being too indistinct.)

4. The mice should be observed for 3 to 4 days. The mice die more slowly than those injected with other gangrene toxins. The results on the third day after injection have been taken as definite.

* * *

Using the technique described above, we have performed the following tests :

- (a) Determination of m.l.d. of the American toxin.
- (b) Determination of the test dose at different levels of antitoxin.
- (c) Comparison of the glycerol solution made at Washington (1 c.c. = 4 S.U.) with a solution, made at this laboratory, of the dry serum preparation.

*Determination of the M.L.D. of American Test Toxin.
Three Mice per Dose. Mice intravenously.*

Dose	Survivals on the			
	First day	Second day	Third day	Fourth day
0.01 mgrm.	0			
0.005 mgrm.	3	0		
0.0025 mgrm.	3	1	0	
0.00125 mgrm.	3	3	3	3
0.00063 mgrm.	3	3	3	3

The m.l.d. is taken as 0.0025 mgrm.

Relation of Various Doses of the American Test Toxin to the Standard Serum.

Date	Dose of toxin	Neutralising dose of serum	Ratio $\frac{\text{toxin}}{\text{serum}}$	Number of m.l.d. per test dose
	Mgrm.	S.U.		
August 9th, 1937	0.05	0.02	2.5	20
August 5th, 1937	0.10	0.04	2.5	40
July 31st, 1937	0.25	0.10	2.5	100
August 2nd, 1937	0.25	0.11	2.25	100
August 14th, 1937	0.25	0.11	2.25	100
July 25th, 1937	0.25	0.11	2.25	100
August 9th, 1937	0.50	0.20	2.5	200
Results obtained at Washington	0.08	0.04	2.0	32

The law of multiple proportions appears to hold good, if a sufficient number of m.l.d. is contained in the test dose. The estimation of the end-point is, however, somewhat uncertain, when only a small test dose is used, as the following comparison will show :

*Assay with 20 M.L.D. (0.05 Mgrm.) and 200 M.L.D. (0.50 Mgrm.).
August 9th, 1937. Two Mice per Dose.*

Dose of toxin	Dose of serum	Survivals on the			
		First day	Second day	Third day	Fourth day
Mgrm.	S.U.				
0.05	0.024	2	2	2	2
0.05	0.022	1	1	1	1
0.05	0.020	2	2	1	0
0.05	0.018	2	2	1	0
0.05	0.016	2	1	0	
0.05	0.013	2	0		
0.5	0.32	2	2	2	2
0.5	0.29	2	2	2	2
0.5	0.27	2	2	2	2
0.5	0.24	2	2	2	2
0.5	0.22	2	2	2	2
0.5	0.20	2	2	1	1
0.5	0.18	2	0	0	0

We have preferred the test dose 0.25 mgrm. containing 100 m.l.d. and neutralised by 0.10 S.U.

Solution of the Dry Standard Serum Preparation and Comparison with the Solution made in Washington.

0.9657 mgrm. of dry serum was brought into a dilution flask, 0.06914 mgrm. being defined as 1 S.U. :

$$0.9657 \text{ mgrm.} = 13.9673 \text{ S.U.}$$

66% glycerol-saline is added to the volume of 698.36 c.c., so that :

$$1 \text{ c.c.} = 20 \text{ S.U.}$$

The solution made in Washington, mentioned above as the secondary dilution, contains in 1 c.c. 4 S.U.

COMPARATIVE ASSAY

Test Dose L+10—0.25 Mgrm. of American Test Toxin.

Date	Dose of serum dilution	Washington preparation diluted to 1 : 4 : Proportion of survivors on the third day	Copenhagen preparation diluted to 1 : 20 : Proportion of survivors on the third day
	c.c.		
August 14th, 1937	0.12	1/3	3/3
" " 	0.11	1/6	6/6
" " 	0.10	1/9	2/9
" " 	0.09	0/6	0/6
" " 	0.08	0/6	0/6
July 25th, 1938	0.12	4/6	5/6
" " 	0.11	0/3	2/6
" " 	0.10	0/6	0/6
" " 	0.09	0/6	0/6

By both assays, the Washington dilution appears to be a little weaker than that made in Copenhagen. It may be emphasised that the latter is of more recent preparation. There is, however, concordance within the limits of 10%.

CONCLUSIONS AND RECOMMENDATION

If the Commission decides to establish an international unit for the titration of sordelli antitoxin, the dry antitoxin prepared at the National Institute of Health, Washington, will be suitable for this purpose.

The unit of antitoxin may provisionally be accepted as 0.06914 mgrm. of this preparation. Before the final adoption, samples of different commercial sordelli sera should be assayed against the proposed standard by means of two or more toxins, and using the mice intravenous method proposed in this report.

Various institutes should be invited to take part in these comparative assays. The results of these tests will show whether the unit is of the same order of magnitude as the other gas-gangrene antitoxin units, and whether the assay depends on the toxin used.

From a later report by Sarah E. STEWART and Ida A. BENGTON from the National Institute of Health, Washington (Public Health Report, 1938), the definition of the unit in mgrm. of the dry preparation, kept in Washington, has been altered a little in consequence of further titrations of the preparation against the provisional standard from Buenos Aires. According to this, the provisional unit should be defined as *0.06668 mgrm. of the dry preparation as kept in Washington.*

Annex 3 c.

GAS-GANGRENE ANTITOXIN (VIBRION SEPTIQUE)

Proposal to change the Strength
of the Standard Solution

(Note submitted by the Department of Biological Standards
of the State Serum Institute, Copenhagen.)

At its session at Copenhagen in 1934, the Commission accepted as the international standard for gas-gangrene antitoxin (*vibrion septique*) a dry stable preparation made at the National Institute for Medical Research, London, from material supplied by Dr. WEINBERG, of the Pasteur Institute, Paris.

The dry standard serum was divided between the Hampstead and Copenhagen institutes, and the same preparation, dissolved in glycerol-saline, has been issued from Hampstead as the British national standard, and from the Biological Standards Department at Copenhagen as the international standard for this antitoxin.

At Copenhagen, the solution of the dry serum is so adjusted that : *1 c.c. contains 20 international units*. This strength was chosen to correspond with that adopted for the standard perfringens antitoxin and standard oedematiens antitoxin, which are both issued in a solution containing 20 A.U. per c.c.

From Hampstead, however, the British standard *vibrion septique* anti toxin is issued in a dilution having five times the strength of the international standard—*i.e.*, containing *100 international units per c.c.*



1. Attention has been drawn by several institutes receiving the international standard to the inconvenience of the relatively low

activity of the international preparation. Most assays of *vibrio septique* antitoxin are performed with a test dose of toxin corresponding to 1 A.U. Since each dose is usually given to six animals, a single assay may require 1 to 2 c.c. of the standard preparation, which is issued in phials containing only 7 to 8 c.c. The number of units thus furnished is hence too small.

2. Moreover, the relatively large quantity of glycerol per unit of antitoxin may have some influence on the assay—although no clear evidence has been adduced. The amount of glycerol given in a dose of the international standard corresponds to half the lethal dose of glycerol.

3. The use of the international standard may entail some risk of mistakes and waste of experimental animals for investigators accustomed to work with the British and American standard, both containing 100 A.U. per c.c. It would appear more reasonable that the British and international standard solutions, prepared as they are from identical material, should be issued in the same concentration.



The drawbacks mentioned above may be easily avoided by changing the concentration of the international standard preparation from 20 A.U. per c.c. to 50 A.U. per c.c. A strength of 100 A.U. per c.c. would involve too great a draw on the available supply of the dry preparation.

At present, 5 ampoules of the dry standard preparation are used yearly, and the stock consists of 65 ampoules. The change in the concentration of the glycerol solution to a content of 50 A.U. per c.c. would call for the use of 8 ampoules per year, and the stock would last for seven to eight years.

The most convenient solution of this problem could be arrived at if the National Institute for Medical Research would agree to modify the British standard preparation in such a way as to reduce the strength to 50 A.U. per c.c.

In our opinion, therefore, it would be an advantage if the Commission would authorise the Department of Biological Standards, Copenhagen, to prepare the solution of the international standard for gas-gangrene antitoxin (*vibrion septique*), so as to give it a strength of

50 international units per c.c.

Annex 3 d.

THE NECESSITY FOR CHANGING THE TECHNIQUE
OF THE PERFRINGENS ANTITOXIN ASSAY

By

M. WEINBERG and M. GUILLAUMIE.
of the Pasteur Institute, Paris.

One of us made some proposals in the Commission on Biological Standardisation concerning the assay of *perfringens* A antitoxin, based on the results of research that we have been carrying out for several years.¹

We thought it might be well to set out in this report the principal and most conclusive facts which, as we believe, fully justify our view.

In the last three years, we have often observed in our investigations into the assay of the type A *perfringens* toxins and the corresponding immune sera that the weight of the test dose of a sample of *perfringens* toxin may vary with the standard antitoxin used for the assay and that the antitoxic titre of a commercial *perfringens* serum depends, more or less, on the sample of toxin with which it is mixed. We deduced that, in order to compare the antitoxic potency of the sera prepared in different institutes, the testing laboratories must use the same sample of *perfringens* toxin the test dose of which would be determined with some particular standard antitoxin.

The experiments which enabled us to make these observations were carried out with fifteen samples of *perfringens* toxin prepared at different times.² The following are some of our results.

¹ M. WEINBERG and M. GUILLAUMIE : *C. R. de la Soc. de Biol.*, 1936, 123, 661 ; *Ibidem*, 1937, 126, 656 ; *C. R. de l'Acad. des Sciences*, 1937, 204, 1012 ; *C. R. de la Soc. de Biol.*, 1938, 129, 122.

² Each toxin is obtained by desiccating *in vacuo* the precipitate produced by the addition, saturated, of ammonium sulphate to VI. broths centrifuged twenty-four hours after seeding with the same strain of *B. perfringens* A.

In Table 1, we give the weight of the minimum lethal dose (m.l.d.) of five samples of *perfringens A* toxin, and the weight of the test dose of each of these samples determined with, respectively, the English and the French standard antitoxin.

Table 1.

Minimum Lethal Dose and Test Dose of Different Samples of Perfringens Toxin.

Sample of toxin	Minimum lethal dose (mgrm.)	Test dose	
		English standard antitoxin (mgrm.)	French standard antitoxin st. 1 (mgrm.)
E.8	0.14	4.2	2.8
E.10	0.06	1.1	0.9
E.11	0.07	3.4	1
E.9	0.14	2.65	3.2
E.14	0.08	1.8	2.3

Examination of these results shows that the weight of the test dose of each sample of toxin varies with the standard antitoxin used for the assay,¹ for the test dose of toxin E.11 is 3.4 mgrm. when determined with the English standard antitoxin and 1 mgrm. when the French antitoxin is used ; the test dose of toxin E.14 is 1.8 mgrm. with the English antitoxin and 2.3 mgrm. with the French antitoxin ; the unit of the English antitoxin capable of neutralising 4.2 mgrm. of toxin E.8 neutralises only 2.65 mgrm. of toxin E.9, the minimum lethal dose of which is, however, equal to that of toxin E.8 ; on the other hand, the unit of the French antitoxin, which neutralises only 2.8 mgrm. of toxin E.8, neutralises 3.2 mgrm. of toxin E.9.

Thus one unit of the French antitoxin neutralises a greater weight of toxins E.9 and E.14 than one unit of the English antitoxin, but a smaller weight of toxins E.8, E.10 and E.11. These results show differences of composition both as between the toxins studied and as between the two standard antitoxins used.

¹ Experiments on mice. The mixture of toxin and antitoxin is left for one hour at 37°, then injected into a caudal vein (0.5 c.c. per mouse). The toxin is dissolved and the antitoxin diluted with physiological saline solution.

The results grouped together in Table 2 show that *the antitoxin titre of a serum may vary with the sample of toxin used for the assay*; serum 417, for instance, is found to have 700 units when assayed against toxin E.1, 625 units when assayed against toxin E.4 and 875 to 900 units against toxin E.5 (for these assays, the test dose of each sample of toxin was taken the value determined with the French standard antitoxin). The case of antitoxin 376 is particularly striking. If toxin E.9 or E.11 is used for the assay, the titres found vary from 50 to 325 units. The antitoxin has from 50 to 75 units when the test dose of toxin E.11 determined with the English standard antitoxin is used and 325 units when the test dose of toxin E.9, obtained with the same standard antitoxin, is used. If the figures obtained by using the French standard antitoxin are taken as the test dose weights of these toxins, it will be seen that this antitoxin has 275 units when assayed against toxin E.9 and 225 against toxin E.11. It is therefore extremely difficult to give the real antitoxic value in this instance.

Table 2.

Variations in the Antitoxic Titres of Five Perfringens Antitoxins determined with Different Samples of Perfringens Toxin.

Sample of toxin	Test dose (mgrm.)	Antitoxic titre of sera Nos.				
		415	376	103	135	417
E.1	Fr. 1	425		275	575	700
E.4	Fr. 1.5	450		275	600	625
E.5	Fr. 2.9	450		400	800	875-900
E.9	Fr. 3.2		275			
E.11	Fr. 1		225			
E.9	E. 2.65		325			
E.11	E. 3.4		50-75			

Whereas it is sufficient to use the same volume of antitoxin 415 to neutralise one test dose of toxins E.4 or E.5 (1/450 c.c.), much more antitoxin 103 must be used to neutralise one test dose of toxin E.4 (1/275 c.c.) than to neutralise one test dose of toxin E.5 (1/400 c.c.). Antitoxin 415 tested with one test dose of these two toxins has 450 units; antitoxin 103 has 275 units when assayed

against toxin E.4 and 400 units against toxin E.5. Antitoxin 135 has 600 units when assayed against toxin E.4 and 800 against toxin E.5.

If we now compare the antitoxic values of the sera as against toxins E.1 and E.4, the great irregularity of the results will become evident. The titre found by using one test dose of toxin E.1 is *equal to* (antitoxin 103), *less than* (antitoxin 135), or *greater than* (antitoxin 417) that obtained with one test dose of toxin E.4.

To explain the difference in the results, we first supposed that the neutralisation of a toxin by the antibodies of certain sera is hampered by non-specific components of the serum or of the toxin. We then tried to find out whether a greater weight of toxin could be neutralised by leaving the antitoxin in contact with the toxin for several hours. This did not prove to be the case.¹

We then tried to purify the sera ; but neither separation of the globulin from the albumin, by adding to the diluted or undiluted antitoxin the required quantity of a saturated solution of ammonium sulphate, nor fractional precipitation by adding anhydrous sodium sulphate added to the previously warmed pure serum or to the serum diluted to five times its own volume, has, up to the present, enabled us to bring about any improvement in the assays.

These failures led us to the conclusion that the very small test dose of some toxins and the very low antitoxic titres of some *perfringens* sera in relation to certain toxins show that the standard antitoxin used to determine the test dose of the toxins, like the commercial serum used, does not contain certain of the antibodies capable of neutralising the corresponding antigens present in the toxins examined or, at all events, contains very little of them.

This observation led us to substitute for the standard antitoxin St₁ a *more complex standard* antitoxin. We then prepared standard St₃ by dissolving equal weights of three dried *perfringens* antitoxins, 415, 296 and 130.²

We determined the test dose of seven new samples of *perfringens* A. toxin with this antitoxin and, for the sake of comparison, with the English standard antitoxin as well. We also determined the test

¹ M. WEINBERG and M. GUILLAUMIE : *C. R. de la Soc. de Biol.*, 1937, 126, 656.

² Antitoxin 296 was added to antitoxin 415 because it neutralised greater quantities of toxin E.11 than antitoxin 415 alone.

dose of some of our former samples of *perfringens* toxin against antitoxin St₃. Here is the sum of our results up to the present.

Table 3.

Test Dose of Eleven Samples of Perfringens Toxin, Type A.

Sample of toxin	Minimum lethal dose (mgrm.)	Test dose determined with :		
		English standard antitoxin (mgrm.)	Standard antitoxin St ₃ (mgrm.)	Standard antitoxin St ₁ (mgrm.)
E.13	0.095	1.7	1.75	1.7
E.15	0.10	1.9	1.9	
E.20	0.12	2.8	2.8	
E.22	0.06	1.45	1.45	
E.14	0.08	1.8	2	
E.16	0.09	1.8	2.1	
E.21	0.10	3.7	3.9	
E.11	0.07	3.4	1.1	1
E.17	0.085	1.4	0.9	0.9
E.18	0.10	2.2	1.9	2.2
E.19	0.08	2.6	1.1	1.7

The figures in this table show that one unit of antitoxin St₃ neutralises the same weight of toxin as the English antitoxin in four cases, a slightly greater weight in three cases and a lower weight in four cases.

As will be seen :

(1) The test dose weight of toxins E.15, E.20 and E.22 is independent of the standard antitoxin used for the assay ; one antitoxic unit of the English antitoxin or the French antitoxin St₃ neutralises 1.9 mgrm. of toxin E.15, 2.8 mgrm. of toxin E.20 and 1.45 mgrm. of toxin E.22.

(2) Antitoxin St₃ neutralises greater quantities of toxins E.14, E.16 and E.21 than the English antitoxin ; one antitoxic unit of the former neutralises 2.1 mgrm. of toxin E.16, whereas the English antitoxin neutralises only 1.8 mgrm.

(3) The test dose of toxins E.11, E.17, E.18 and E.19 determined with the French antitoxin is smaller than the test dose determined with the English antitoxin. The difference between the values

determined with the two antitoxins is small in the case of toxin E.18 (1.9 mgrm. and 2.2 mgrm. are the figures found with the French and English antitoxins respectively); the difference is greater in the case of toxin E.17—viz., test dose 1.4 mgrm. in assays with English antitoxin and 0.9 mgrm. with antitoxin St₃. Finally, the differences may be very large—one unit of antitoxin St₃ neutralises only 1.1 mgrm. of toxins E.11 and E.19, whereas the English antitoxin neutralises 3.4 mgrm. of toxin E.11. and 2.6 mgrm. of toxin E.19—i.e., quantities two to three times as great as that which is neutralised by antitoxin St₃.

Thus, antitoxin St₃, which is as effective as the English standard antitoxin when assayed against four toxins (E.13, E.15, E.20, E.22) and is more effective than the English standard when assayed against three others (E.14, E.16, E.21), is not suitable for the neutralisation of toxins E.11, E.17, E.18 and E.19. We cannot therefore support JENSEN's opinion that each country should use a national standard to determine the test dose of toxins so as to reduce the consumption of the international standard.

Serum St₃, whose neutralising potency for toxins E.11 and E.19 is particularly low, is certainly deficient in some antibodies. We have therefore adopted as the test dose of our samples of *perfringens* toxin the weight determined with the English standard antitoxin. We have used this weight in ascertaining the antitoxic potency of three sera in relation to six toxins (Table 4). To carry out these assays, we chose samples of *perfringens* toxin of less widely differing test doses than the toxins E.1, E.4 and E.5 used for the assay of the antitoxins grouped in Table 2.

Table 4.

Antitoxic Titres of Three Perfringens Antitoxins determined with Different Samples of Perfringens Toxin.

	Toxins E.4 or E.5	Toxin E.13 T.d. : 1.7	Toxin E.14 T.d. : 1.8	Toxin E.15 T.d. : 1.9	Toxin E.18 T.d. : 2.2	Toxin E.20 T.d. : 2.8	Toxin E.22 T.d. : 1.45
Antitoxin 135 ..		575	550—575	550	200	300—400	300—400
Antitoxin 296 ..		400	450	300—350	300—350	250—300	400—450
Antitoxin 415 ..	450	400	450	800	400	800—850	450

These results show that the antitoxic values of the sera examined vary only to a slight extent with some samples of toxin and to a considerable extent with others. Thus, antitoxin 135 gives :

550 units when assayed against toxin E.15,
 550-575 units when assayed against toxin E.14,
 575 units when assayed against toxin E.13,
 200 units when assayed against toxin E.18,
 300-400 units when assayed against toxins E.20 and E.22.

Antitoxin 415 gives :

400 units when assayed against toxin E.13,
 450 units when assayed against toxins E.4, E.5, E.14 and E.22,
 800 units when assayed against toxins E.15 and E.20.

These divergent results are not surprising, since the wide variations in the composition of the *perfringens* toxins¹ entail wide variations in the qualitative composition of the corresponding immune sera, which makes the assay of these sera a very complicated matter. Only by an adequate number of observations can rash conclusions be avoided. Antitoxin 415, for instance, which neutralises toxins E.4, E.5, E.13, E.14, E.18 and E.22 to the same extent, is more effective in neutralising toxins E.15 and E.20 and, has very little effect on toxins E.11 and E.19.

CONCLUSIONS

The following conclusions may be drawn from the facts we have just summed up :

1. The weight of the *test dose* of the *perfringens* toxin may vary from one sample to another. This fact is sometimes observed even when the minimum lethal dose of the two samples of toxin is contained in the same weight. It is therefore obvious that *the chemical composition of the toxin may vary from one sample to another.*
2. The weight of the *test dose* of a single sample of *perfringens A* toxin may also vary according to the standard antitoxin used for

¹ PRIGGE has pointed out that the relative quantities of hæmotoxin and the zeta toxin agent in the filtrates of cultures of *B. perfringens*, type A, vary from one preparation to another within wide limits.

the assay. This fact can be explained only by *variations in the chemical composition of the standard antitoxins used.*

3. *The antitoxic titre of a perfringens A antitoxin may vary with the sample of toxin used for the assay.* The differences noted are sometimes considerable ; they may vary between 50 and 325 units (antitoxin 376).

4. The differences noted in the antitoxic titres of a single specific antitoxin determined with different samples of toxin cannot be explained either by the presence in the antitoxin of non-specific substances capable of neutralising part of the specific components of the samples of toxins used, or by variations in the speed with which the specific antibodies of the *perfringens A* antitoxin combine with the corresponding antigens of the toxins used.

Investigations carried out with purified *perfringens* antitoxin have not enabled us to improve the assays ; we take the view that the variations in the titres of the same antitoxin when tested against different samples of toxin must be due to the absence, or the presence in insufficient quantities, in the antitoxin examined, of certain antibodies capable of neutralising the corresponding antigens present in the toxins used.

5. We have attempted to make the determinations of the test dose of toxins more uniform by preparing a new and more complex standard antitoxin by mixing three *perfringens* antitoxins which have high titres and neutralise large quantities of certain samples of toxin used.

We established the test doses of eleven samples of toxin, for purposes of comparison, both with our new standard antitoxin and with the English standard antitoxin. This investigation showed us that one unit of our new standard antitoxin neutralises the same amount of toxin as the English antitoxin (four cases), or a slightly greater amount (three cases), or, in four cases, a smaller amount. In one case, the difference was quite large—3.4 mgrm. as against 1.1 mgrm. We came to the conclusion that the English standard antitoxin is richer in specific antibodies, and we adopted it to determine a toxin test dose to be used in the assay of *perfringens A* antitoxins.

6. However, the study of three *perfringens* antitoxins assayed with seven different samples of toxin, the test dose of which was established

with the English standard antitoxin, did not give us in every case the same antitoxic titres. One of the three antitoxins gave, according to the samples of toxin used, from 200 to 575 units, and another from 400 to 800 units.

Thus the strength of antitoxin 135 will be labelled as 200 or 575 units, according to whether the assay is carried out with toxin E.18 or toxin E.13.

7. Amongst the factors which play a very important part in the assay of *perfringens* antitoxin, there is the fact that the standard antitoxin and the toxin may show great differences in chemical composition from one sample to another.

It would therefore be logical to use the *same standard antitoxin* and the *same sample of toxin* for comparing the antitoxic value of the sera prepared in different institutes.

8. We believe, however, that the technique of assay, even when thus improved, will not give very precise information on the comparative value of the antitoxins until the different institutes use for the preparation of *perfringens A* antitoxins, the *standard toxin* made up of all the antigens secreted by *B. perfringens A*.¹

We should add that the only point of interest to the medical man is the therapeutic effect of a specific antitoxin.

In the future, therefore, efforts must be chiefly directed towards establishing the *curative titre* of the antitoxin. It is towards this object that we are at present working.

¹ This standard toxin may be represented either by the toxin of a single strain of *B. perfringens A* abundantly secreting all the antigens of this species, or by the mixture of the toxins produced by different strains.

Annex 4 a.**ASSAYS OF ANTI-ANTHRAX SERUM CARRIED
OUT AT THE CANTACUZINO INSTITUTE**

Preliminary Communication from Professor C. JONESCO-MIHAIESTI
(Bucarest)

As the outcome of certain suggestions made by the Intergovernmental Conference on Biological Standardisation held at Geneva in 1935, the Permanent Commission on Biological Standardisation decided at its session in October of that year to request Professor TOMCSIK and myself to undertake researches on the basis of a joint scheme, with a view to selecting a method for the standardisation of anti-anthrax serum.

We began preliminary investigations two years ago.

Professor TOMCSIK also undertook to follow up his researches into anthrax immunity ; starting from observations already made by him and his co-workers, his object was to establish a method of assay based on these observations. In this connection, Professor TOMCSIK outlined a plan of research which was communicated to me by the Secretariat of the Health Organisation.

* * *

All research workers who have studied the question of anthrax immunity agree that one of the chief difficulties which have hitherto prevented the adoption of a method of assay for anti-anthrax serum is our lack of knowledge regarding the mechanism of its action.

Moreover, knowledge is also lacking as to the mechanism of anthrax infection itself, particularly as regards the pathogenic properties of the bacillus.

Three antigen fractions of *B. anthracis*, of different chemical composition, have been extracted by different methods :

(1) A substance possessing the characteristics of the nucleoproteins, slightly active serologically, the action of which *in vivo* appears to be completely negligible ;

(2) A substance of a nitrogenous nature which was termed *substance P* by those who first isolated it, and which exists only in the capsular forms of the bacillus ;

(3) A substance of a polysaccharid nature, substance C, which is found both in the capsular and non-capsular forms of the anthrax bacillus, and after acid hydrolysis yields a large quantity of reducing sugar.

According to the most recent researches these last two antigen fractions, which are very active serologically, appear to play the principal part *in vivo*. Professor TOMCSIK found that sera with the highest titre of anti-capsular antibodies exerted the most marked protective action in the experimental infection of the mouse. The anti-polysaccharid antibody appears to be devoid of any protective action against anthrax infection in the animal.

It follows, therefore, that of the two antigen fractions C and P, *substance P*, or the capsular substance, represents the virulence antigen of the bacillus and is the real basis of its pathogenic activity ; the hydrocarbonic substance appears to play an accessory part in infection, and to be of importance solely from the point of view of the identification of the bacillus.

* * *

The programme of comparative researches drawn up by Professor TOMCSIK included, in the first place, the revision of these findings, and also proposed :

“ (1) The production of anti-capsular serum in the rabbit in a sufficient quantity for experimental purposes ;

“ (2) Experiments on horses ;

“ (3) The comparative study (on mice) of the protective action of the anti-capsular serum and the various anti-bacterial sera obtained in different countries (verification of our results) ;

“ (4) Repetition of the same experiments on other laboratory animals used for the standardisation of anti-anthrax

serum. Study of the protective action of sera on these animals after absorption by means of purified capsular substance.”

Our researches have covered part of this programme. Various difficulties arose which made it impossible for us to make them as extensive as we should have liked. Nevertheless, in spite of a regrettable shortage of animals even for orientation tests, we have so far employed a considerable number of experimental animals (more than 1,500 mice, 86 rabbits, 144 guinea-pigs).

We have sent Professor TOMCSIK anti-anthrax horse sera, our anthrax strains, and also extracts to be used for precipitation purposes.

We give below a brief summary of the results so far obtained from our assays.

From the outset of our researches, we have endeavoured for purposes of comparison to assay sera *in vitro* by the precipitation method, and *in vivo* by their protective powers on mice or guinea-pigs.

Precipitinogens : The following *precipitinogens* were used by us :

1. A trichloroacetic extract (obtained by the Boivin method) of anthrax bacilli of a highly virulent strain with practically no capsules (1), which usually killed mice when administered in the dose of 1/100,000-1/400,000 c.c. of a twenty-hour broth culture. The chemical analysis of this extract showed that it consists almost entirely of specific polysaccharid.

2. An extract prepared by the same method from a very attenuated strain of *B. anthracis* (which kills mice in 20% of cases in a dose of 1/500 c.c. of a 20-hour broth culture) and containing only a relatively small proportion of the specific polysaccharid ; it mainly consists of substance P (capsular).

3. Dr. IVANOVICS was good enough to place at our disposal a quantity of substance P prepared in his laboratory, which we used for comparison with the two extracts mentioned above.

Anti-anthrax serum : The sera employed were obtained from immunised horses, whose state of immunity had been maintained (in some cases for more than seven years) by a series of reinoculations every forty days on an average and terminating with a further bleeding.

The method employed for immunising the horses is outlined below:

The initial immunisation of the horses lasts for seven months on an average. The antigen inoculations consist in the administration of Pasteur's vaccine II to begin with, followed by the administration of virulent bacilli (every eight days). We use three routes for the injections : intradermal (at the beginning of the immunisation process), intradermal and subcutaneous from the fourteenth to the twenty-fourth inoculations ; after that the antigen is administered intravenously only. The maximum quantity of virulent culture administered (thirty-third inoculation) consists of the bacilli grown on two Roux dishes, the bacilli being suspended in 100/150 c.c. of physiological saline solution. The test bleeding is carried out ten days after the last antigen injection.

The following table shows the limit precipitin titres for a certain number of our sera. Each serum is given the name of the horse from which it was obtained. The second column shows the year in which immunisation was begun.

Table 1.

Sera	Year in which immunisation was begun	Extract C.F.35 (attenuated bacillus with a large number of capsules)	Extract C.5 (virulent bacillus with practically no capsules)
1. Rusca	1931	1/128,000	1/4,000
2. Sadova	1931	1/32,000	1/1,000
3. Ilarie	1931	1/16,000	1/1,000
4. Rio	1934	1/16,000	1/500
5. Crin	1935	1/8,000	1/500
6. Virlez	1936	1/2,000	1/500
7. Bujor	1936	1/2,000	1/100
8. Strigoi	1937	1/500	1/80
9. Despot	1937	1/160	1/20
10. Roma	1937	1/500	1/100
11. Sorento	1937	1/80	1/40
12. Tenerif	1937	1/500	1/160
13. Cerna	1937	1/80	1/20
14. Neapol	1937	1/20	1/20
15. Plevna	1937	1/100	1/20
16. Spaima	1937	1/500	1/80
17. Viscol	1937	1/80	1/40
18. Sinaia	1937	1/160	1/40
19. Berta	1937	1/2,000	1/160
20. Doina	1937	1/80	1/40

We are indebted to Dr. IVANOVICS for a small quantity of rabbit serum immunised against anthrax, and for a sample of purified substance P prepared by him, which enabled us to ascertain, as compared with our horse sera, the precipitin titre of his serum with our different extracts, and also the precipitin titre of our sera with the substance P prepared by him.

Table 2 shows the results of these titrations :

Table 2.

Sera	Year in which immunisation was begun	Dialysed extract C.F.35 (attenuated bacilli with large number of capsules)	Crude extract C.F.35 (attenuated bacilli with a large number of capsules)	Crude extract C.5 (virulent bacilli with practically no capsules)	IVANOVICS' extract (substance P)
1. Rusca	1931	1/256,000	1/128,000	1/16,000	1/128,000
2. Sadova	1931	1/128,000	1/256,000	1/64,000	1/256,000
3. Ilarie	1931	1/64,000	1/128,000	1/4,000	1/64,000
4. Rio	1934	1/64,000	1/32,000	1/4,000	1/128,000
5. Crin	1935	1/128,000	1/32,000	1/4,000	1/2,000
6. Virlez	1936	1/1,000	1/4,000	1/500	1/2,000
7. Bujor	1936	1/2,000	1/2,000	1/1,000	1/1,000
8. IVANOVICS ..	rabbit	1/256,000	1/256,000	1/256,000	1/256,000

In examining these two tables, the following points should be taken into consideration :

(1) The horses the immunisation of which was begun the longest time ago furnished sera with the highest precipitin titre (Rusca serum, seven years ; Sadova serum, seven years).

On the other hand, although their state of immunity was equivalent from a practical standpoint (measured by their resistance to inoculation of a same dose of antigen) horses, the immunisation of which was begun more recently, yielded sera the precipitin titre of which was very low or practically nil.

(2) As regards the various extracts employed : extract C.F.35 (attenuated bacilli with a large number of capsules), which contains comparatively little substance C and a great deal of substance P (capsular), is a better precipitinogen than extract C.5 (which is obtained from a highly virulent bacillus and consists almost entirely of substance C).

IVANOVICS' purified extract (substance P) comes between the two.

(3) On comparing the precipitin titre of the same serum with the three precipitinogens employed, we found that the antibody which precipitates the capsular substance appears to exist at a higher titre in most of our sera than the antibody of an antipolysaccharid nature (which acts on extract C.5) : see, for instance, Sadova serum, Rusca serum, etc.

Protective action : The protective action of these sera on animals infected experimentally was studied on mice and guinea-pigs.

As a test for virulence, we selected strain C.5, isolated from the spleen of a sheep. A large number of preliminary tests showed that the virulence of this bacillus—20-hour peptonised broth culture—injected subcutaneously was as follows :

1/200,000 c.c. kills mice weighing from 17 to 18 grammes in 3 to 7 days ;

1/400,000 c.c. kills 80% of mice weighing from 17 to 18 grammes in 3 to 8 days.

1/100,000 c.c. kills guinea-pigs weighing 300 grammes in 4 to 5 days.

On several occasions, we have observed considerable differences in the virulence of the same strain, according to whether it is cultivated on agar or in broth, an agar culture of the same age being in every case less virulent :

1/25,000 c.c. of an agar culture of a given strain is needed to kill a mouse weighing from 16 to 18 grammes, whereas 1/400,000 c.c. of broth culture of that same strain is sufficient to kill eight to ten mice of that weight.

As a rule, we employed for our tests *in vivo* from four to five minimum lethal mouse doses injected subcutaneously.

The serum to be assayed was administered in quantities varying from 0.1 c.c. to 1 c.c.

The serum was injected under the skin into the peritoneum or intravenously.

In some experiments, we injected the serum twenty-four or thirty-six hours before inoculation with the virulent culture, in other series at the same time as the culture (serum administered intravenously and culture administered subcutaneously).

Lastly, for a third type of experiment the serum was administered after the culture.

Some of the results of assay are given below :

		0.2 c.c. serum	0.4 c.c. serum	0.1 c.c. serum
Rusca serum	Precipitin titre between 1/28,000—1/256,000	8/10	8/10	3/10
Ilarie serum		8/10	4/10	5/10
Crin serum		10/10	9/10	7/10
Rio serum	Precipitin titre between 1/2,000—1/32,000	10/10	8/10	10/10
Bujor serum		9/10	8/10	9/10
Virlez serum		9/10	9/10	9/10
		0.1 c.c. serum	0.2 c.c. serum	0.4 c.c. serum
IVANOVICS serum (1/256,000)		9/10	4/10	3/10
Sadova serum (1/256,000)		9/10	9/10	7/10

(1) There is undoubtedly a parallelism between the precipitant action of a serum *in vitro* and its protective power *in vivo*. When the serum is injected into the peritoneum (twenty hours before the infecting injection) we find that the number of surviving mice increases with the dose of serum employed and its precipitin titre *in vitro*.

(2) The same parallelism is found when the serum is administered intravenously (simultaneous injection of the serum into the vein and of the bacilli under the skin).

	0.15 c.c. serum	0.3 c.c. serum
Rusca serum (1/128,000)	7/7	3/7
Bujor serum (1/2,000)	6/7	5/8
	0.2 c.c. serum	0.4 c.c. serum
Rusca serum (1/128,000)	6/7	3/7
Sinaiia serum (1/160)	6/7	7/7

(3) The same tests appear to show that too large doses of a serum rich in precipitant antibodies would have an unfavourable effect on the course of the infection.

	0.2 c.c. serum	0.4 c.c. serum	1 c.c. serum
IVANOVICS serum (1/256,000)	2/5	5/5	4/5
Sadova serum (1/256,000)	8/10	8/10	10/10
Crin serum (1/32,000)	10/10	9/10	7/10

The same quantities of a serum poor in precipitant antibodies appear to have a more marked protective action in certain cases.

(4) The IVANOVICS (rabbit) serum, which has a very high titre of capsular antibodies but is also very rich in polysaccharid antibodies, has the most marked protective power *in vivo*. (The horse serum at our disposal which was richest in polysaccharid antibodies had an antipolysaccharid titre of 1/64,000, whereas the IVANOVICS serum had a marked precipitant action with a titre four times as high.)

	0.1 c.c. serum	0.2 c.c. serum	0.4 c.c. serum
IVANOVICS serum (1/256,000)	9/10	4/10	3/10
Sadova serum (1/64,000)	9/10	9/10	7/10

CONCLUSIONS

1. These tests show that the protective value of an anti-anthrax serum depends on its precipitant antibodies.

2. A good anti-anthrax serum should contain at least two precipitins :

- (a) The anticapsular precipitin ;
- (b) The antipolysaccharid (or better the antisomatic) precipitin.

3. The capsular antigen (represented by the TOMSČIK and IVANOVICS substance P) undoubtedly plays a very important part in anthrax immunity.

We are, however, inclined to believe that, from an immunological standpoint, at least equal importance should be attached to the somatic antigen of *B. anthracis*, which, in our extracts, is represented by the polysaccharid fraction. It is the sera with the highest titre of antibodies acting on both antigen fractions which give the most active protection.



In order to confirm these findings, we propose to continue these researches by studying :

(1) Sera with a high titre of capsular antibodies (prepared, for instance, from attenuated bacilli which are very rich in capsular substance) ;

(2) Sera with a high titre of somatic antibodies (prepared from killed bacteria obtained from virulent strains without capsules).



Annex 4 b.

THE STANDARDISATION OF ANTI-ANTHRAX SERA

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In 1895, SCLAVO and, independently of him, MARCHOUX discovered that the serum of sheep inoculated first with attenuated, and then with fully virulent, anthrax bacilli effectively protected rabbits against anthrax infection administered in lethal quantities. The serotherapy and seroprophylaxis of anthrax are based upon this observation.

In the field of serotherapy, many attempts have been made to devise a reliable way of determining the activity of the various immune sera employed, but no method has yet been developed which could be used to arrive at an international standardisation. This lack of an adequate method is, in our opinion, due primarily to the fact that the activity of the immune sera produced up till now is too low to be accurately assessable in numerical terms by procedures involving the experimental errors which attach to the methods of assay so far available. Most of the latter do not, indeed, profess to determine the protective power of a serum in "units of activity", but claim only to show, on the strength of certain conventions and experiments, whether it is "ineffective", "adequate" or "highly efficient".

Even the most widely used test, that of SOBERNHEIM, yields no more than a general indication of this kind. It consists essentially of the intravenous injection into five rabbits of quantities of serum ranging from 2 to 5 c.c., followed by the subcutaneous injection of a one-thousandth loopful of a fully virulent culture. Given full virulence, such a dose is certainly lethal; it is, in fact, usually equivalent to several m.l.d. A sixth rabbit serves as a control, and is either left altogether untreated or intravenously injected with

normal serum. Referring to his method, SOBERNHEIM (1) says : " The experience of many years has shown that an anti-anthrax serum may be regarded as utilisable if not less than two of the previously treated animals survive and the remainder do not die until after the control animal. Completely regular series showing a direct correspondence between the dose of serum and the immunity of the animals are, however, of rare occurrence." He adds that if *more than two* animals survive, the serum should be regarded as highly efficient.

In practice, as SOBERNHEIM himself admits, the results obtained by this test give a very irregular picture of the protective power of the sera concerned. Experimental records show that the survival rate among treated animals does not exceed 30-50%. On the other hand, to diminish the dose of infection would be to accentuate individual differences and thereby to introduce a large factor of error in the interpretation of the results.

ASCOLI'S (2) test is performed on guinea-pigs. Here, however, the method in itself is inadequate, for only strains of attenuated virulence are used for infection, so that the protective power of the serum is not tested in relation to infection as under natural conditions. Moreover, though carried out under strict experimental conditions, this test yields results which are no more reliable and no more reducible to exact values than that of SOBERNHEIM.

MENDEZ' method (3) is similar to that of ASCOLI in that it also uses guinea-pigs. On the other hand, it involves an attempt to assess activity in numerical terms, one immunity unit being the amount of serum which retards the death of animals infected with 1,000 lethal doses of an attenuated anthrax strain until six to eight hours after the death of the controls.

RICKMANN and JOSEPH (4) modified ASCOLI'S method and, in addition, introduced the principle of assaying unknown sera in relation to a standard serum, the latter being any serum of which 1 c.c. protects a 250-gramme guinea-pig against 2 m.l.d.

Reference may also be made to LUSZTIG'S rat test (5). Nevertheless, even allowing for the results obtained by the author himself, this method does not appear to be satisfactory, and those workers who have tried it themselves (6) consider the SOBERNHEIM test to be more reliable.

As already stated, the failure to devise an accurate test for the assay of anthrax immune sera is perhaps to be ascribed not so much to the defects of the methods employed as to the low protective power exerted by the therapeutic sera so far produced.

That the general opinion of the efficacy of serotherapy in human anthrax should nevertheless be favourable is probably due to the fact that the protective and curative properties inherent in the sera take effect more successfully in the human organism, which is less sensitive to this form of infection than that of any of the experimental animals used. It should be said, however, that some clinicians take a less favourable view of the therapeutic properties of anti-anthrax sera, and it must be admitted that there is as yet no conclusive clinical evidence of their value. Especially have there been no comparative observations of the results of treatment with, respectively, the immune and the normal serum of the same animal species. Yet the non-specific action of serum is a factor which must be allowed for, particularly since the quantities administered in the serotherapy of anthrax are large (650-1,000 c.c.). Now it is a well-established fact that such treatment only benefits local anthrax processes, and, in conjunction with this, it is pertinent to reflect that there is a great deal of other evidence showing the favourable effects of non-specific protein treatment upon local infectious inflammations. At the same time, though the non-specific factor is thus undoubtedly to be reckoned with, it must be remembered that experiments on animals also yield evidence of a specific effect, even though not very powerfully exerted.

Experience has, in fact, shown that the sera of various animals (horses, asses, oxen, etc.) injected first with attenuated and later with virulent strains of anthrax exert a slight protective action against infection in experimental animals, when they are administered therapeutically. *Their protective activity—assuming that this can be quantitatively assessed—is not, however, associated with the presence, in co-variant proportions, of any antibody which would afford a possibility of measuring it, or of demonstrating its existence, in vitro.*

This is why, up till now, serological methods could not be used for the assay of these sera.

Recently, however, rabbit serum has been produced, which has as yet only been examined under experimental conditions, but which forms an exception in this respect, for it contains a demonstrable

antibody against the specific substance of the anthrax bacillus capsule.

The part played by the anti-capsular antibody in anthrax immunity—as studied by TOMCSIK and his fellow workers—is in some respects analogous to, though apparently less important than, that of a similar substance observed by American workers in the course of their studies on pneumococcus immunity. The anthrax anti-capsular antibody can be produced by the intravenous injection into rabbits of large quantities of heat-killed encapsulated anthrax bacilli (7, 8) and gives a specific reaction with the capsular substance (7). The latter, unlike that of the pneumococcus, is not a polysaccharid but a polypeptid (9). In addition to precipitating the purified capsular substance in highly dilute suspensions, these sera also agglutinate the encapsulated bacilli (10) and produce with the capsules the so-called “*Quellungsreaktion*” which has been observed, under like conditions, with the pneumococcus (11).

With these *in vitro* characteristics, this serum combines the highly important property of conferring on mice a marked degree of resistance to anthrax infection (12, 13, 14), and this passive immunisation of an animal which is notoriously sensitive to anthrax infection *may be attributed to the anti-capsular antibody*. The protective action of rabbit serum containing this substance is shown

Table 1.
The Protective Action of Different Commercial Anti-anthrax Horse Sera and of Rabbit Sera containing Anti-capsular Antibody.

Anti-anthrax serum	Number of mice infected	Number of mice surviving
Horse serum (Germany)	6	2
Horse serum (C.S R.)	6	0
Horse serum (Hungary)	4	0
Horse serum (U.S.A.)	4	0
Rabbit serum, No. P.III.	6	6
Rabbit serum, No. P.IV.	6	6
Rabbit serum, No. O.V.	6	6
No serum (control)	6	0

The rabbit sera were produced by TOMCSIK and IVANOVICS. The horse sera did not, but the rabbit sera *did*, contain anticapsular antibody. Serum treatment : 1 c.c., subcutaneously. The mice were infected, a few hours after serum treatment, with about 10-15 d.l.m. of an anthrax-strain (No. A₁₂) of moderate virulente.

in Table 1 (14) comparatively with the effect upon mice of *commercial therapeutic anti-anthrax (horse) sera containing no anti-capsular antibody*. As will be seen from the table, the sera used were produced by the institutes of a number of different countries.

The experiments recorded in this table were not carried out with fully virulent strains. It has been found, however, that rabbit serum containing the anti-capsular antibody confers a marked degree of protection against infection with a strain of full virulence. Thus, 1 c.c. of the serum of a rabbit immunised with heat-killed encapsulated bacilli usually protects mice adequately against 20 to 100 lethal doses, and it is even possible to obtain sera so highly active that 0.5 c.c. will protect mice against several thousand lethal doses. Table 2 sets forth the results of tests with sera of this kind.

Table 2.

The Protective Action of a Highly Potent Anthrax Serum containing Anti-capsular Antibody.

Infecting dose (in slant-agars)	Amount of serum in c.c.							
	0.5		0.1		0.05		No serum	
	Number of animals		Number of animals		Number of animals		Number of animals	
	Inoc.	Surviving	Inoc.	Surviving	Inoc.	Surviving	Inoc.	Surviving
1/10,000,000 ...			3	3	3	3	6	3
1/1,000,000	3	3	3	3	3	1	9	0
1/100,000	3	3	3	2	3	0	6	0
1/50,000	5	5						
1/10,000	3	3						
1/5,000	3	3						

Serum (No. XVI), subcutaneously. Sixteen hours after the serum treatment, the mice were infected subcutaneously with a fully virulent strain (A_{11}).

A regular parallelism is found to exist between the protective action of the anti-capsular antibody and the amount of serum employed or the dose of infection administered ; we are therefore justified in assuming that an exact method of assay can be found.

There is sufficient experimental evidence to show that the *protective efficacy* of the serum of rabbits immunised with heat-killed encapsulated bacilli is related to its *anti-capsular antibody content* (12, 13, 14). In this connection, it has been established : (1) That the serum of rabbits thus inoculated which prove refractory and

produce no anti-capsular antibody fails to exert any protective action ; (2) that the absorption of this antibody *in vitro* by means of specific capsule substance impairs the protective power of the serum ; and (3) that passively immunised mice may be deprived of their protection by the injection of minute quantities of purified capsule substance.

This discovery of the existence of an antibody against the capsule of the anthrax bacillus opens up new possibilities in regard to the production and assay of anti-anthrax serum. It is doubtful, however, whether experimental evidence confined to the satisfactory protection of mice enables us to look with confidence to the successful administration of anti-capsular antibody in human therapeutics. Another problem which remains to be solved is that of the production in sufficient quantities of serum containing this substance, since at present the only reliable method known to us is that of production by means of rabbits. This is a matter of some importance, for, even in rabbits, the process is attended by considerable difficulties.

Thus, in the course of their experiments, TOMCSIK and STANOVICS (8) immunised 164 rabbits with killed encapsulated anthrax bacilli. Of these, forty-two, or 25%, died in the course of immunisation, whilst, among the remaining 122, only seventy-seven produced serum containing anti-capsular antibody in any useful quantity. It is thought that conditions of anti-capsular antibody production are as unfavourable in other animals, notably in horses, which are otherwise most suitable on practical grounds. This is evidenced by the trials we have made with the immunisation of horses. Although carried out with great care and by means of anthrax strains with marked capsule production, they have given a result in some only of the animals. In no case, moreover, has any of the horse serum so far obtained contained anything more than a slight amount of anti-capsular antibody (16, 17). It should be added that a fairly large number of commercially marketed anti-anthrax immune sera have been tested and have been found to contain none of the antibody (14, 18).

In these circumstances, it appears doubtful whether the routine bulk production of anticapsular anti-body is a practical possibility. Even if it were, however, its value for use in human therapy is still open to question, since there is as yet nothing to show whether the protective effect observed in mice would also be obtained in man.

In animals other than mice it is not, for attempts to immunise them with anti-capsular antibody failed (14, 19). Rabbits and guinea-pigs treated with this substance (5 c.c. serum) died just like the control animals, save perhaps that they lived a little longer. Even prolonged injection of killed encapsulated anthrax bacilli failed to confer protection upon rabbits, whose serum proved effective, however, in the experimental passive immunisation of mice. Apparently, then, only the mouse is able to benefit by the protective action of the antibody, and we really do not know at present whether the human organism is similarly endowed or is as refractory as that of the other animals tested.

That the anti-capsular antibody plays but a secondary part in producing immunity to anthrax is further confirmed by our failure to detect its presence in the organism of actively immunised rabbits. The oedema fluid of toluene-treated rabbits was subcutaneously injected into other rabbits according to the method laid down by BAIL. As a result, the animals became immune to several lethal doses of infection, but it proved impossible to detect any anti-capsular antibody in their blood or organs (20). The serum of such rabbits conferred but little protection on mice, though the rabbits themselves displayed a high degree of immunity. In fact, they survived the administration of several thousand lethal doses. Some of the mice injected with 1 c.c. of the serum proved to be either altogether unprotected or able, at best, to resist a few lethal doses of infection (see Table 3).

Table 3.

Protective Action of a Rabbit Serum obtained from Rabbits immunised with Oedema Fluid (by Bail's Method).

Infecting dose (in slant-agars)	Serum treatment					
	Serum of immune rabbit		Serum of normal rabbit		No serum	
	Number inoc.	Number surv.	Number inoc.	Number surv.	Number inoc.	Number surv.
1/10,000,000	3	3	3	0	9	2
1/1,000,000	9	4	3	0	5	0
1/100,000	5	1			3	0
1/10,000	3	0				

The serum of immune rabbits did not contain anti-capsular antibody. The amount of serum injected was 1 c.c. The mice were infected subcutaneously with a fully virulent anthrax strain (A₁₁).

CONCLUSIONS

The evidence set forth above indicates that immunity to anthrax may be established by several different mechanisms. The immune sera severally produced by these mechanisms are known to be of different types.

One type of immune serum (hereafter referred to as type I) is obtained by injecting killed encapsulated bacilli into rabbits. These animals are not themselves immune, but their serum is highly effective against the experimental infection of mice. Its protective power is associated with the presence of a capsular antibody, and this circumstance opens up prospects of arriving at an accurate method of assay. *This type of serum, containing considerable amounts of anti-capsular antibody, is not to be found among the sera marketed for therapeutic purposes.* Experience shows that the production of immune serum containing anti-capsular antibody presents great difficulties, and the supplies at present obtainable are sufficient only for experimental purposes.

The immune sera belonging to the other type (type II) seem to be produced and to act in a wholly different manner. They are obtained from animals actively immunised by the injection of living bacilli or œdema fluid. The animals in question (rabbits, horses, etc.) themselves display a high degree of resistance to anthrax infection, but their serum confers but little protection, if any, upon mice, and is liable, moreover, to great individual variations in activity. It does, however, engender a certain, very small, measure of immunity in rabbits and guinea-pigs. *The anti-anthrax sera on sale for therapeutic purposes are of this type. There do not, at present, appear to be any prospects of arriving at a standardisation in exact numerical terms, and the older methods of assay, affording only a rough general indication, must continue to serve for the time being.*

Having regard to all the difficulties that have been discussed above, it is considered that the question of exact assay and standardisation cannot be profitably taken up until the rôle and properties of the various types of serum in human therapeutics has been elucidated. This question, in turn, cannot be broached until type I sera containing anti-capsular antibody are produced on a large scale.

The study of the therapeutic properties of these various sera will, however, be greatly facilitated if success can be achieved in producing type II sera in a form that will act more effectively upon experimental animals than the sera utilised in the past.

* * *

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Annex 5.**THE PREPARATION OF A SECOND INTERNATIONAL
STANDARD FOR STAPHYLOCOCCUS ANTITOXIN**

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In 1934, the Permanent Commission on Biological Standardisation accepted a dry, stable standard preparation of staphylococcus antitoxin, prepared at the National Institute for Medical Research, Hampstead, as the international standard for this antitoxin.

The stock of this standard, maintained at the State Serum Institute, Copenhagen, has, in the past four years, been depleted more quickly than had been anticipated, owing to an unexpected increase in the number of laboratories requiring the standard. At present, about fifty laboratories are supplied with the half-yearly routine issue from Copenhagen.

**THE SELECTION OF A SAMPLE OF ANTITOXIN SUITABLE
FOR USE AS A STANDARD**

In 1935, Dr. P. HARTLEY, by an arrangement made between Sir Henry DALE and Dr. Th. MADSEN, undertook the work of the replacement of the standard and the selection of a sample of staphylococcus antitoxin suitable for the purpose.

In 1935/36, observations were made indicating that different values were returned for the potency of the same sample of staphylococcus antitoxin according to the method employed for comparing the sample with the international standard. An explanation of the discrepant results has since been obtained by LLEWELLYN SMITH (1937)¹ But at the time when the selection of a sample of antitoxin for the preparation of the second standard was undertaken, the cause of the discrepant results was not known, and it was thought possible that they might be due to qualitative differences among samples of staphylococcus antitoxin, such as were known to occur among samples of tetanus and diphtheria antitoxins.

With this possibility in mind, it was decided to make as complete a study as possible of a series of samples of staphylococcus antitoxin prepared in different laboratories, by a variety of methods and by means of toxins prepared from different strains. From the results of this enquiry, it was anticipated that the Commission would be able to decide which of the samples examined would be most suitable for adoption as the new standard preparation, or whether a more truly representative standard would be provided by a "pool" or mixture of some or all of the samples.

Accordingly, in the spring of 1936, the Lister Institute, Elstree, the Wellcome Physiological Research Laboratories, Beckenham, the Connaught Laboratories, Toronto, the Pasteur Institute, Garches, and the Lederle Laboratories, Pearl River, New York, were asked whether they could supply quantities of up to 4 litres of unconcentrated staphylococcus antitoxin without preservative and of as high a potency as possible. In due course, samples were very kindly supplied by each of these Institutes, as indicated in Table 1. The quantity asked for was rather large, but it was necessary to prepare in advance for the possibility that any one of the five samples might be ultimately adopted as the new international standard.

THE ASSAY OF THE FIVE SERA

At Hampstead, the potencies of the five sera were determined by various methods, based upon the same biological reactions as

¹ M. LLEWELLYN SMITH : " The Influence of Glycerol on the Skin Necrosis produced by Staphylococcus Toxin ", *Brit. J. Exp. Path.*, 1937, 18, page 265.

were used in the establishment of the first international standard for staphylococcus antitoxin¹—namely :

- (a) By the hæmolytic method using rabbit erythrocytes ;
- (b) Intracutaneously, in guinea-pigs ;
- (c) Intravenously, in mice.

The assays by methods (a) and (b) were carried out at different levels of testing and by means of toxins prepared from a variety of different strains. Assays by method (a) were also performed using different times of contact of toxin and antitoxin before injection. In all, at least sixteen determinations were made of the antitoxic potency of each serum.

The results of these extensive tests led to the following conclusions :

- (1) *The antitoxic titres of the five sera are, within the limits of error of the tests, independent of the methods or toxins used.*
- (2) The assays made at different antitoxin levels and with different combining times resulted in the same estimates of potency, thus indicating that *none of the five sera differed markedly in quality from the present international standard.*

The mean potencies obtained are recorded in Table 1 in which are also recorded the estimated standard errors of the means. These estimates are larger than the true values, because equal "weight" was attached to all determinations. It appeared unnecessary to go to the trouble of calculating weighted figures as the precision of assay is obviously of a high order.

Additional comparisons of the five sera and the international standard were carried out at Copenhagen. The sera were assayed by the intracutaneous method in rabbits and by the hæmolytic method using rabbit red cells, the latter test being performed by a special technique permitting the comparison of the reaction curves of the five sera.

The results obtained at Copenhagen agreed perfectly with those obtained at Hampstead, and no significant difference in the qualities of the five sera was detected.

¹ P. HARTLEY and M. LLEWELLYN SMITH : " A Proposed International Standard for Staphylococcus Antitoxin ", *Quart. Bull. Health Org.*, League of Nations, special number, 1935, page 68.

Table 1.

SUMMARY OF INVESTIGATION OF FIVE SAMPLES OF STAPHYLOCOCCUS ANTITOXIN

No. of sample	Indicating titre of sample	Supplied by	Quantity available (c.c.)	Strain used in immunisation	Mean potency (international units per c.c.)	om.	Coefficient of variation %	No. of assays
1	Abyss	Lister Institute	3,700	Wood 46	409	2.97	0.73	18
2	L	Lederle Laboratories	3,500	Wood 161	200	3.7	1.85	16
3	6915	Wellcome Laboratories	5,000	Wood 46	412	4.67	1.13	16
4	645	Connaught Laboratories	3,200	Wood 46	209	2.82	1.35	16
5	S355	Pasteur Institute	1,000	72	289	5.8	2.00	16

The results of all the investigations were presented to Dr. MADSEN, Chairman of the Permanent Commission on Biological Standardisation. After consideration of all the data and having regard to the facts, first, that no significant difference in quality in the five samples had been demonstrated and, secondly, that the most potent serum (6915) was available in amount sufficient to satisfy the international and British requirements for about fifty years, Dr. MADSEN recommended that, rather than prepare a pool of two or more sera, *serum 6915, prepared by the Wellcome Laboratories, should be chosen to replace the first international standard for staphylococcus antitoxin.*

Table 2 (see opposite page) contains the results of the assays of the liquid serum 6915 performed at Hampstead and Copenhagen.

THE PRODUCTION OF A DRY, STABLE PREPARATION FROM
THE LIQUID STAPHYLOCOCCUS ANTITOXIN, 6915

The conversion of the chosen sample of staphylococcus antitoxin into a dry, stable preparation was carried out at Hampstead, the usual method¹ employed at this Institute being adopted. By

¹ P. HARTLEY: "A Simple Laboratory Method for the Desiccation of Serum and Other Protein Solution", *Quart. Bull. Health Org.*, League of Nations, special number, November 1936, page 735.

Table 2.

DETERMINATIONS OF THE ANTITOXIC POTENCY OF THE LIQUID SERUM 6915

Laboratory	Method of assay	Toxin and strain	Level of testing	Potency (international units per c.c.)	Dose interval between successive mixtures	
Hampstead	Hæmolysis of rabbit red cells	47.Wood 46	Lh	430	% 5	
		4A.Wood 46	Lh	410	5	
		4A.Wood 46	Lh	400	5	
		4A. Wood 46	Lh/2	460	10	
		4A.Wood 46	Lh/10	400	10	
		4A.Wood 46	Lh/20 ¹	410	20	
		4A.Wood 46	Lh/100	400	50	
		Bigger Aa	Lh	410	10	
		Néllis 37	Lh	410	10	
		Mx 31	Lh	410	10	
		Malmo 30/30	Lh	400	10	
		Dolman 24	Lh	400	10	
		46A. Barrs	Lh/2	420	10	
		Mouse intra-venous	47.Wood 46	L+	440	10
		Intracuta-neous (guinea-pig) . . .	47.Wood 46	Lr	380	10
46A. Barrs	Lr/10		410	10		
Copenhagen	Hæmolysis of rabbit red cells	Walker V/37	Lh/2	416	10	
		Walker V/37	Lh/2	447	10	
	Intracuta-neous (rabbit)	Walker V/37	Lr/15 ²	412	10	

¹ Lh/20 = the test dose of a hæmolysin just neutralised by 1/20 unit antitoxin.
² Lr/15 = the test dose of necrotising toxin just neutralised by 1/15 unit antitoxin.

means of a precision apparatus and with aseptic precautions, exactly 5 c.c. serum were distributed into each of about 800 ampoules. Samples taken at different stages during the distribution were all found to be sterile. The serum was then exposed to the dehydrating action of phosphorus pentoxide *in vacuo* until no further loss in weight occurred, as evidenced by the periodic weighings of ten selected ampoules. The ampoules were then filled with pure, dry nitrogen gas, sealed and placed in cold storage at -2° C. to -4° C.

THE ASSAY OF THE DRY PREPARATION IN TERMS
OF THE INTERNATIONAL STANDARD

A preliminary test on the redissolved product showed the ampoule to contain *2,068 international units*. Since the original material contained 412 international units per c.c. (Table 1), the content of antitoxin in each ampoule should be $412 \times 5 = 2,060$ *international units*. The conclusion was drawn, therefore, that no loss in potency had occurred during the drying process.

Table 3.

DETERMINATION OF THE POTENCY OF THE REDISSOLVED SERUM 6915

Laboratory performing test	Method of assay	No. of preparation of new standard	Titre (international units per c.c.)	Dose interval between successive tubes
				%
Hampstead	Hæmolysis of rabbit red cells	Sa ₂	20	5
			20	5
		Sa ₃	20	5
			20	5
		Sa ₄	20	5
			20 ⁹	5
		Sa ₅	20	5
			20	5
		Sa ₆	20	5
				20
Copenhagen	Intracutaneous (guinea-pig)	Sa ₃	20	10
	Intravenous (mouse)	Sa ₂	22.5	10
		Sa ₂	20	4
	Hæmolysis of rabbit red cells		22	4
		Sa ₃	20	4
	Intracutaneous (rabbit)		20	4
		Sa ₂	20	5
		Sa ₃	20	5

Mean of all values = 20.04.

In order to obtain solutions containing 20 units per c.c., the contents of other ampoules were dissolved so that the contents of one ampoule were contained in 103 c.c. Five such preparations

(Sa₂-Sa₆) were made ; Sa₂, Sa₄, Sa₅ and Sa₆ being prepared in 66% glycerol-saline, while Sa₃ was prepared in 0.01% merthiolate-saline. These solutions were all compared for potency with the corresponding solutions of the present international standard containing 20 units per c.c.

The tests, which are summarised in Table 3, show that there is no significant difference in potency between any of the solutions prepared from different ampoules of the new preparation, and, further, that there is no significant difference in potency between these solutions and the corresponding solutions of the first international standard.

It was therefore concluded that, when the contents of one ampoule of the new standard are dissolved in a volume of 103 c.c., the resulting solution contains

20 international units in each c.c.

DETERMINATION OF THE WEIGHT OF THE NEW STANDARD
PREPARATION THAT IS EXACTLY EQUIVALENT TO ONE
INTERNATIONAL UNIT OF STAPHYLOCOCCUS ANTITOXIN

The weight of total solids contained in each of ten ampoules was determined and found to be :

0.4878 gm. ; 0.4918 gm. ; 0.4888 gm. ; 0.4902 gm. ; 0.4902 gm. ;
0.4866 gm. ; 0.4899 gm. ; 0.4879 gm. ; 0.4905 gm. ; 0.4911 gm.
Mean = 0.48948 gm.
 $\sigma = 0.00164$ gm. Coefft. of variation = 0.335%.
 $\sigma_m = 0.00052$ gm.

Thus, since each ampoule contains 2,060 international units,

1 international unit of staphylococcus antitoxin is contained in
$$\frac{489.5}{2060} = 0.2376 \text{ milligrammes of the new standard preparation.}$$

SELECTION OF A SUITABLE DILUENT FOR ROUTINE
ISSUES OF THE STANDARD

Attention has already been drawn to a paper by LLEWELLYN SMITH, which shows that glycerol inhibits the necrosis produced by staphylococcus toxin in the skin of guinea-pigs.

In November 1937, I PSEN investigated the influence of glycerol in intracutaneous assays of staphylococcus, antitoxin in rabbits. He found that even at the full L+ level, the assays were not influenced by the amount of glycerol contributed by the standard antitoxin. A possible explanation is that the rabbit's skin is about twenty times more sensitive than that of the guinea-pig to staphylococcus toxin, so that a dose of toxin containing 50 necrotic doses for the guinea-pig will contain 1,000 necrotic doses for the rabbit. It was found that a maximal concentration of glycerol would inhibit, not a constant amount of toxin, but rather a constant number of necrotic doses (about three) for both animals. It is suggested that the effect of glycerol may be to inhibit absorption of toxin by the skin tissues. In practice, the difficulties due to the influence of glycerol in intracutaneous assays could be overcome by substituting rabbits for guinea-pigs as test animals. But this would doubtless cause inconvenience in some laboratories, and it seems preferable to issue the standard antitoxin as a solution containing no glycerol. Preparations in saline solution containing 0.01% merthiolate have been examined and appear to be altogether satisfactory.

Such preparations retain their potency unimpaired for periods up to one year at room temperature.

It is therefore proposed in future *to issue the international standard antitoxin as a solution containing 20 international units per c.c. in 0.01% merthiolate-saline.*

Annex 6 a.**STANDARD DIPHTHERIA ANTITOXIN****Report on Comparative Assays of National Standards
in the Years 1934-1938**

Submitted by the Department of Biological Standards
of the State Serum Institute, Copenhagen.

At the International Conference held in Paris in 1932, the Subcommittee on Biological Standardisation adopted the Ehrlich unit as an international unit for diphtheria antitoxin.

In order to make certain that the various sera adopted as national standards in different countries should always remain identical *inter se*, it appeared desirable that the Statens Serum Institut in Copenhagen, in its capacity as central laboratory, should proceed at least once a year to the comparative assay of such standard sera against the international standard in its safe-keeping.

Up to 1934, this was done by the staff of the Statens Serum Institut. The Ehrlich method of assay was used, and no discrepancies were found between the values claimed for the German, American, French and British standard preparations and the findings of the tests carried out at Copenhagen.

After the establishment in 1935 of the Department of Biological Standards in the Statens Serum Institut, the late Director, Dr. Claus JENSEN, carried out this comparative testing by the rabbit intracutaneous method devised by himself.

The intracutaneous assay of diphtheria antitoxin on rabbits and guinea-pigs is now used the world over, and seems to have replaced the Ehrlich method in many laboratories. It may be of interest to set forth the results of these comparative assays of national standards by the intracutaneous method.

Until 1937, the findings of these assays were sent each year to the central laboratories at Frankfort, Washington, Paris and London. Detailed descriptions of the reactions on rabbits were recorded. The activity of the sera was estimated in the usual way : comparison of the amounts of each serum giving the initial reaction.

The mixtures of toxin and antitoxin were so adjusted that each dose of antitoxin differed from the next by 5%. The value assigned to a serum could therefore be regarded as accurate to within 5%.

In some cases, the activity can be estimated more accurately by taking into consideration the intensity of the first reaction. An initial reaction greater than 8 mm. in diameter will justify the assumption that the end-point should be placed between the dose causing this reaction and the preceding dose, which produces none.

Table 1.

Assay on May 22nd, 1937 : Test Dose, 3 LR/30.

Standard	International	British	German	French	American
Dilution	1 : 10	1 : 10	1 : 10	1 : 6	1 : 6
c.c. of serum dil. :					
0.115.....	0	0	0	0	0
0.110.....	0	0	0	0	0
0.105.....	0-	0	0	12 <i>ri</i>	0
0.100.....	0	0	0	14 RI	10 <i>r</i>
0.095.....	10 <i>Ri</i>	10 <i>ri</i>	8 <i>ri</i>	16 <i>RIIn</i>	16 RI
0.090.....	14 RI	14 RI	12 RI	18 RIN	18 RI
0.085.....	16 <i>RIIn</i>	16 <i>RIIn</i>	16 <i>RIIn</i>	20 RIN	20 <i>RIIn</i>
0.080.....	20 <i>RIIn</i>	18 <i>RIIn</i>	18 <i>RIIn</i>	22 RIN	26 RIN
End-point	0.0975 c.c.	0.095 c.c.	0.095 c.c.	0.105 c.c.	0.100 c.c.
Activity	10.0 AU	10.2 AU	10.2 AU	5.56 AU	5.84 AU
Labelled as	10.0 AU	10 0 AU	10.0 AU	6.0 AU	6.0 AU

Abbreviations : *r* = slight redness R = pronounced redness
l = slight induration I = pronounced induration
n = slight necrosis N = pronounced necrosis.

For instance : 10 *Ri* = pronounced redness, slight induration of 10 mm. average diameter.

Table 2 summarises the results of comparative assays from 1935 to 1937. The titre of the German standard was found to be equal to that of the international standard. The British 1935 issue, which

had been prepared from a new batch of dry serum (D.45 and D.46), appeared to be 5% less active. In consequence of the test referred to, the dilution was changed, so that the British and international standards in the following issues were of identical activity.

Table 2.

Date	Level of test	International	British	German	French	American
April 2nd, 1935	LR/30	10.0	9.5	10.0	5.18	5.56
	„	10.0	9.5	10.0	5.18	5.45
	„	10.0	9.5	10.0	5.34	5.45
June 20th, 1936	„	10.0	10.0	10.0	5.71	5.71
	„	10.0	10.0	10.0	5.71	5.71
	„	10.0	10.0	10.0	5.42	5.71
May 22nd, 1937	„	10.0	10.2	10.2	5.56	5.84
	„	10.0	9.73	9.73	5.23	5.40
Value claimed	10.0 AU	10.0 AU	10.0 AU	6.0 AU	6.0 AU

The French and American standards appear to be definitely below the assigned value, the divergence ranging from 15% to 5% in the case of the French standard, and from 5% to 10% in the case of the American.

* * *

In 1938, these comparative tests were repeated in this department. The intracutaneous rabbit method was used, but the end-point was estimated by a method proposed by Dr. G. RASCH.

The method described above has the disadvantage that only the first reaction is taken into consideration. Unavoidable technical errors in this reaction thus strongly influence the estimate of the activity. Moreover, if the first positive reaction is 14 *ri*, for instance, the interpolation giving the end-point is rather a matter of subjective judgment.

RASCH therefore suggested that all the reactions of a series should be taken into consideration in estimating the end-point. The reactions are enumerated according to intensity and the numbers of the reactions are plotted against the logarithms of the doses. A reaction curve of best fit is drawn freehand and the point of intersection

between this curve and the abscissa axis is taken as the end-point. The procedure is exemplified in Table 3 :

Table 3.

Assay on April 26th, 1938 : Test Dose, 3 LR/30.

Standard	International	British	German	French	American
Dilution	1 : 10	1 : 10	1 : 10	1 : 500	1 : 6
c.c. of serum dil. :					
0.116	0	0	0	0	0
0.110	0	0	0	0	0
0.105	0	0	0	0	0
0.100	0	0	0	0	0
0.095	<i>r?</i>	<i>r?</i>	<i>r?</i>	8 <i>r</i>	14 <i>ri</i>
0.090	8 <i>r</i>	10 <i>ri</i>	8 <i>r</i>	10 <i>Ri</i>	16 <i>RI</i>
0.086	14 <i>RI</i>	12 <i>RI</i>	14 <i>RI</i>	12 <i>RI</i>	16 <i>RI</i>
0.082	18 <i>RI</i>	20 <i>RI</i>	16 <i>RI</i>	14 <i>RI</i>	20 <i>RI</i>
0.077	20 <i>RI</i>	22 <i>RI</i>	20 <i>RIIn</i>	18 <i>RI</i>	22 <i>RIIn</i>

Enumeration of the Reactions.

Reaction	Number	Reaction	Number
<i>r?</i>	1	14 <i>RI</i>	8
8 <i>r</i>	2	16 <i>RI</i>	9
10 <i>ri</i>	3	18 <i>RI</i>	10
10 <i>Ri</i>	4	20 <i>RIIn</i>	11
12 <i>ri</i>	5	20 <i>RIIn</i>	12
12 <i>Ri</i>	6	22 <i>RI</i>	13
14 <i>ri</i>	7	20 <i>RIIn</i>	14

Table 4.

Synopsis of Results of Experiments in April 1938.

Antitoxin units per c.c.

Rabbit No.	Level of test	International	British	German	French	American
6352	LR/300	10.0	9.85	9.71	460	5.69
6353	LR/300	10.0	10.6	9.25	490	5.27
6355	LR/300	10.0	10.35	9.48	483	5.94
6362	LR/30	10.0	9.98	10.0	481	5.69
Mean			10.17	9.61	479	5.52
Value claimed		10.0	10.0	10.0	500	6.0

British and German standards do not diverge to any extent from the international, while the American standard is lower, even allowing for the errors of the test. The values of the French standard are all somewhat lower than claimed, but not greatly so.

The French standard, in contrast to the other glycerinated solutions, is a dry serum 0.55 grm. of which, diluted in 9.5 c.c. distilled water, is claimed to contain 500 AU. This standard is kept in the Pasteur Institute, Garches.

During their establishment, the British and German standards were both controlled in this department by the rabbit method, but the French and American were controlled only by the Ehrlich method. The main differences between these methods are the time allowed for the toxin-antitoxin mixtures to combine before injection and the temperature at which this combination takes place. For the assay on guinea-pigs the mixtures are left at room temperature from a quarter to one hour, while the mixtures for the intracutaneous injection are placed at 37° for at least two hours.

It was possible that difference in avidity might have accounted for the lower values of the French and American standards. Accordingly, the rabbit test was performed with mixtures left at room temperature 20° for a quarter of an hour only.

The results were as under :

Table 5.
*Assays of National Standards by the Intracutaneous Method,
Quarter of an Hour Combining Time.*
July 1938.

Standard	Experiment I	Experiment II	Value claimed
	AU	AU	AU
International	10.0	10.0	10.0
British	10.6	10.0	10.0
German	10.3	9.45	10.0
American	5.95	5.84	6.0
French	No test	448	500

The British and the German standards thus conform to the international standard, while the American standard scarcely deviates from the value claimed. This test shows the French standard to be about 10% below strength.

Table 6 presents an Ehrlich test of the international, American and French standards by means of the same toxin as that used in the intracutaneous tests.

Table 6.

Toxin 43/28 : Test Dose, 0.18 c.c.

July 1938.

Standard	Dilution	1.00 c.c.	1.05 c.c.	1.10 c.c.	Titre
					AU
International	1 : 10	2, 2½, 3, 3	3, 3, 5, 6	No test	10.0
American	1 : 6	2, 2, 2, 2	3, 3, s, s	2½, 3, 3, 4	6.0
French	1 : 500	2½, 4, 4, 5	5, s, s, s	s, s, s, s	525

(The figures indicate day of death ; s = surviving at discharge.)

According to the Ehrlich test, the American standard conforms to the value claimed, but the French standard appears to be about 5% stronger than indicated. This finding agrees with a statement by Dr. G. RAMON, Garches, reporting to Dr. Th. MADSEN in a letter of November 1937 :

“ It is intentionally that our serum has a titre [for guinea-pigs] *appreciably higher* than that assigned to it.”

SUMMARY AND CONCLUSIONS

The British and German standard diphtheria antitoxins, when tested intracutaneously, have always been found to agree with the value indicated on the label. The American standard preparation appears, on the basis of the intracutaneous test, to be about 5% below strength, while this difference is not detectable by the Ehrlich test. The standard diphtheria antitoxin used at the Pasteur Institute at Garches appeared, when tested by the intracutaneous method, to be slightly below strength, but the Ehrlich test gave a definitely higher titre than that claimed.

It is possible that differences in avidity may account for these small discrepancies, which may indeed be considered of no practical interest. Attention will, however, be drawn in future to any differences in the results of tests carried out by the Ehrlich and the intracutaneous method.

Annex 6 b.

**STANDARD DIPHTHERIA ANTITOXIN
FOR FLOCCULATION TEST**

Note submitted by the Department of Biological Standards
of the State Serum Institute, Copenhagen.

At its meeting at Geneva in 1935, the Commission recommended that diphtheria antitoxin No. 788, prepared by the Statens Serum Institut, Copenhagen, be adopted for international use as standard serum for assays based on flocculation.¹

The Commission stated that, in adopting this standard, it had no other object in view than to eliminate if possible the discrepancies sometimes observable between the results of *in vitro* and *in vivo* assays.

* * *

Serum 788 has been kept in small ampoules containing 3 c.c. of the original serum in frozen conditions at — 16° C. Since 1935, a sample of it has been sent every half-year to thirty different laboratories.

In 1937, it became clear that the stock of serum 788 would be exhausted in the coming year. Accordingly, it had to be replaced by a new serum, and, to that end, a whole series of diphtheria antitoxins prepared at the Statens Serum Institut had to be tested.

A serum suitable as a standard for flocculation tests should comply with the following conditions :

- (1) A high potency ;
- (2) A ready, clear-cut flocculation ;

¹ Both the *in vitro* and the *in vivo* assay of this serum yielded a titre of 1,700 AU.

(3) A ratio of $\frac{\textit{in vivo}}{\textit{in vitro}}$ values as near to 1.00 as possible.

Although several sera were examined, we were able to find only one which we considered suitable—namely, *serum 1184*.

In vitro and *in vivo* assays gave the following results :

Serum 1184 : Assays in April 1937.

<i>In vivo</i> intracutaneous in rabbits	<i>In vitro</i> against serum 788	Kf.
1190	1175	22 min.
1250	1165	20 „
1230 Mean	1140 Mean	16 „
1230 1236 ± 26	1115 1150 ± 20	19 „
1260	1165	20 „
1260	1145	19 „
	1145	19 „

$$\text{Ratio } \frac{\textit{in vivo}}{\textit{in vitro}} = 1.07 \pm 0.035$$

This serum, in glycerol dilution, was controlled in this department and at the National Institute for Medical Research, Hampstead, with the following results :

Glycerinated Preparation of Serum 1184.

Assay at	<i>In vivo</i>	<i>In vitro</i>	Ratio $\frac{\textit{in vivo}}{\textit{in vitro}}$
Hampstead	512	500	1.02
Copenhagen	536,555,522	486,486	1.10

The proportion of the *in vivo* and *in vitro* values was thus shown to be unaffected by the glycerol.

Since, after June 1937, the stock of serum 788 had fallen to only nine ampoules, a glycerol dilution of serum 1184 was prepared to meet the demand for flocculating standard serum at the December issue :

200 c.c. of serum 1184 was transferred to a volumetric flask and the volume made up to 496 c.c. with undiluted glycerol.

This preparation was distributed in small flasks in the same way as the other standard preparations and labelled

DIF 3
 STANDARD DIPHThERIA ANTITOXIN
 FLOCCULATION TEST
 1 c.c. contains 500 international units.

Before the issue, a sample was sent to Dr. G. RAMON, at the Pasteur Institute at Garches, who kindly compared it with his standard preparation containing 500 AU per c.c.

Dr. Th. MADSEN received the following answer from Dr. RAMON :

[*Translation.*] " November 21st, 1937.

" The results which I have obtained with the two sera assayed against the same sample of anatoxin show a satisfactory concordance. I only noted a slight difference :

" (a) In the time of flocculation (yours was twice ours), which is of no importance ;

" (b) In the values of the same anatoxin supplied by the two sera, this value being slightly greater with your serum : by approximately 5% to 7%."

The ratio 1.05-1.07 has thus been confirmed by Dr. RAMON.

At the routine issues, the department now delivers serum 1184 together with the memorandum attached to this report.

That this standard will serve its purpose has been confirmed by Dr. M. BECKER, Sächsisches Serumwerk, Dresden, in the tests specified hereunder, in the course of which the preparation DIF3 was assayed comparatively with a laboratory standard No. 1209 against a toxin and ananatoxin.

Assay of Toxin 314.

Serum	Initial flocculation	Kf.	Result
DIF 3	0.29 c.c.	48 min.	29 : 1.08 = 26.85 Lf/c.c.
(1+4)	0.29 and 0.30 c.c.	45 min.	29.5 : 1.08 = 27.32 Lf/c.c.
1209	0.26 c.c.	75 min.	26.0 Lf/c.c.
(1+3)	0.37 and 0.28	70 min.	27.5 Lf/c.c.

Assay of Anatoxin 41.

Serum	Initial flocculation	Kf.	Result
DIF 3	0.54 c.c.	84 min.	54 : 108 = 50 Lf/c.c.
(1+4)	0.55 and 0.56 c.c.	60 min.	55.5 : 108 = 51.38 Lf/c.c.
1209	0.49, 0.50 and 0.51 c.c.	115 min.	50 Lf/c.c.
(1+3)	0.49, 0.50 and 0.51 c.c.	113 min.	50 Lf/c.c.

MEMORANDUM ON THE
STANDARD DIPHTHERIA ANTITOXIN FOR THE
FLOCCULATION TEST DIF 3

The preparation DIF 3 is a mixture of an antidiphtheritic serum and glycerol containing about 60% glycerol.

In vivo assays (subcutaneous injection into guinea-pigs and intracutaneous injection into rabbits) gave a titre of :

500 international units (AU).

Comparative *in vitro* assays (flocculation test) against Standard Serum DIF 1 (788) gave a value of 462 AU per c.c.

The ratio $\frac{\text{in vivo}}{\text{in vitro}}$ is accordingly 1.08.

The serum shows a clear-cut flocculation. When a test toxin containing about 20 flocculation units (Lf) is employed, the flocculation time (Kf) is approximately 20 min. at 45° C.

Example : *Assay of Test Toxin H.36.*

Test-tube No.	1	2	3	4	5	6	7
Standard serum DIF diluted to 1 in 5 (1 c.c. DIF + 4 c.c. 0.9% saline) 1 c.c. = 100 int. units (AU)	0.18 c.c.	0.19 c.c.	0.20 c.c.	0.21 c.c.	0.22 c.c.	0.23 c.c.	0.24 c.c.
Toxin H.36 undiluted.	1 c.c.	1 c.c.	1 c.c.	1 c.c.	1 c.c.	1 c.c.	1 c.c.
<i>Result :</i>							
0 min. after mixing..	—	—	—	—	—	—	—
10 min. after mixing..	—	—	—	—	—	—	—
15 min. after mixing..	—	—	—	—	—	—	—
19 min. after mixing..	—	—	—	—	(f)	(f)	—
21 min. after mixing..	—	—	(f)	f	f	f	f

(f) = Flocculation, visible only with magnifying glass.
f = Flocculation, visible to the naked eye.

Result : Initial flocculation in tube Nos. 5 and 6—*i.e.*, at 0.225 c.c.
= 22.5 AU.

1 c.c. of toxin therefore contains :

$$\frac{22.5}{1.08} = 20.8 \text{ flocculation units.}$$

Annex 7.

PRELIMINARY NOTE
ON THE ASSAY OF ANTI-DYSENTERY (SHIGA) SERA
BY THE FLOCCULATION TEST

By

Gh. ISTRATI and A. OLARU
(" Dr. I. Cantacuzène" Institute, Bucharest).

We set out to obtain a dysentery (Shiga) toxin which, placed in contact with homologous sera, would not give several zones of flocculation. We shall accordingly examine how such a flocculation test can be used for the titration of antidysentery (Shiga) sera.

METHOD

Preparation of the Toxin.—We used for our work the D 6 strain, which is of the " R " form.

We selected the " R " form of *B. Shiga* so as to eliminate traces of carbohydrate-fat or polysaccharid specific antigen in the autolysate, which traces might have distorted the test results. The D 6 strain of the " R " form does not contain any carbohydrate-fat antigen (A. BOUVIN).

The emulsion of D 6 " R " germs is prepared from cultures grown on agar at 37° for twenty-four hours.

The emulsion in physiological salt solution is prepared in such a way that 1 c.c. of microbe suspension contains 400 mgrm. of bacillary bodies. Chloroform (5%) is added to the emulsion, in order to kill the germs.

Proceeding in this way and seeding 100 6-litre flasks, of which the internal surface has been covered with nutrient agar, we obtain approximately 130 grm. of moist germs—*i.e.*, 315 c.c. of microbe emulsion at 400 mgrm. per c.c.

The suspension thus obtained is allowed to stand for twenty-four hours at laboratory temperature with an occasional shaking ; it is then placed in the thermostat at 37° for four to seven days, and then again left at laboratory temperature for two or three days.

The microbe emulsion with chloroform becomes sterile after two or three days at 37° (checked by repeated seedings).

Centrifuging yields an opalescent liquid which finally clarifies by simple filtering through a Chardin paper or a Chamberland L₂ filter.

It should be noticed that for the preparation of the toxin, which is to be used for the flocculation test, the D 6 strain of the " R " form was, of all the " R " strains of *B. shiga*, the one which yielded the best and the most constant result. This microbe strain has been preserved in the Institute's collection since 1924. It came from the Bacteriological Department of the Johns Hopkins Hospital at Baltimore, and is a fixed " R " strain with characteristic colonies and a positive reaction to Trypaflavine. One-three-hundredth of a 24-hour culture-tube kills a rabbit in three to four days. The broth filtrate, in doses of 1/200th to 1/400th of a c.c., and the dried substance in doses of 0.00001 grm., are toxic for mice weighing 15 to 20 grm.

The two toxins used in our experiments, when heated for thirty minutes at 100° C. become completely non-toxic, even 0.5 c.c. not being fatal to mice ; they are therefore thermolabile in BORVIN'S sense.

The anti-dysentery (Shiga) sera used by us were kindly supplied by the Behring Institute at Marburg, through the courtesy of the Director, Dr. DEMNITZ, to whom we wish to express our sincere thanks.

Flocculation Test.—Diminishing quantities of the sera to be examined are delivered into a series of agglutination tubes (the doses range from 1 c.c. to 0.01 c.c. according to the titre of the serum obtained on mice) ; and 1 c.c. of toxin is then added.

The tubes are placed in a water-bath at 50° and watched in order to determine the exact moment at which flocculation begins in the first tube.

We shall give here only a few tables to indicate the course of the test :

Table 1.

		c.c.											
Anti-dysentery serum.....		0.6	0.4	0.3	0.25	0.2	0.15	0.1	0.09	0.08	0.07	0.06	0.05
No. 1 = 800 AU/c.c.													
Toxin Chf XIII ..		1	1	1	1	1	1	1	1	1	1	1	1
Results obtained in water bath at 50° after :	1 h.	op.	op.	op.	op.	op.	op. op.	op. op.	op. op.	op. op.	op.	—	—
	1 h. 20 m..							+					
	1 h. 30 m..							++++					
	2 h.						+	(+++)	++	+			

op. = opalescence
 op. = marked opalescence
 The number of + signs indicates the degree of flocculation.

Table 2.

		c.c.												
Anti-dysentery serum		0.6	0.5	0.4	0.35	0.27	0.23	0.2	0.18	0.16	0.14	0.12	0.1	0.09
No. 10 = 440 AU/c.c.														
Toxin Chf XIII.....		1	1	1	1	1	1	1	1	1	1	1	1	1
Results obtained in steam bath at 50° after :	15 m. ..				op.	op.	op.	op.	op.	op.				
	30 m. ..								+					
	35 m. ..							+	++	+				
	40 m. ..						+	++	++	+				
	1 h. 15 m.					+	++	++	+++	++	+			
	1 h. 35 m.				±	++	S	S	S	S	S	+		

op. = opalescence.
 S = Sedimented floccules.

Table 3.

		c.c.									
Anti-dysentery serum		1.0	0.9	0.8	0.7	0.65	0.6	0.5	0.4	0.3	0.1
No.14 = 100 AU/c.c.											
Toxin Chf XIII		1	1	1	1	1	1	1	1	1	1
Results obtained in steam bath at 59° after :	20 m.	op.	op. op.	op. op.	op.	op.					
	1 h. 15 m..			+							
	1 h. 30 m..	++	++	(+++) ++	+						

op. = opalescence.
 op. = marked opalescence.
 op.
 The number of + signs indicates the degree of flocculation.

It should be noticed that the reading of the first tube showing positive flocculation can be easily made, even where the difference in doses of serum, from one tube to the next, is as little as 0.01 c.c.

Table 4.

		c.c.							
Anti-dysentery serum		0.2	0.15	0.13	0.11	0.1	0.09	0.08	0.07
No. 5 = 570 AU/c.c.									
Toxin Chf XI ...		1	1	1	1	1	1	1	1
Results obtained in steam bath at 59° after :	40 m.				±	+	±		
	50 m.			+	++	+++	++		
	1 h. 20 m..		++	+++	(++)	(+++)	(++)		

In the following table (Table 5), we have entered the results of the flocculation test carried out with fifteen anti-dysentery (Shiga) sera

(Behringwerke) assayed at the Behring Institute by the standard international mouse method and using 2 toxins, Chf XI and Chf XIII. It should be noted that the assay on mice was carried out using mixtures of toxin and anti-toxin with differences of 10 AU between one mixture and another.

Table 5.

COMPARATIVE TABLE OF ASSAY OF ANTI-DYSENTERY (SHIGA) SERA
(BEHRINGWERKE) BY THE STANDARD METHOD
AND BY THE FLOCCULATION METHOD, USING TOXIN CHF XI

No. of sera anti-dysentery sera (Behringwerke)	Titre of sera determined on mice	Quantity of serum flocculated with 1 c.c. of Chf XI toxin	Number of Lf per c.c. of Chf XI toxin	Titre of sera obtained referred to the average of Lf per c.c. of toxin	Difference in % between flocculation method and standard method	Titre of sera obtained by flocculation test, taking serum No. 1 as a standard	Difference in % between these two methods, with serum No. 1 as a standard in the flocculation test	Titre of sera obtained by flocculation test, using serum No. 15 as a standard	Difference in % between these two methods with serum No. 15 as a standard in flocculation test
1	2	3	4	5	6	7	8	9	10
	AU/c.c.	c.c.	Lf/c.c.	AU/c.c.	%	AU/c.c.	%	AU/c.c.	%
1....	800	0.07	56	860	+ 7.5	800	0	848	+ 6
2....	720	0.08	57	752	+ 4.4	700	- 2.7	742	+ 3
3....	840	0.075	63	800	- 5	746	-11.1	792	- 5.7
4....	580	0.105	60.9	574	- 1	552	- 4.8	566	- 2.4
5....	570	0.1	57	602	+ 5.6	560	- 1.7	594	+ 4.2
6....	630	0.1	63	602	- 4.4	560	-11.1	594	- 5.7
7....	420	0.145	58.8	415	- 1.1	386	0	409	- 2.6
8....	380	0.17	64.6	354	- 6.8	329	-13.4	349	- 8.1
9....	450	0.135	60.75	445	- 1.1	414	- 8	440	- 2.2
10....	440	0.13	57.2	463	+ 5.2	430	- 2.27	458	+ 3.6
11....	200	0.29	58	207	+ 3.5	193	- 3.5	204	+ 2
12....	190	0.33	62.7	180.2	- 5.1	169	-10.1	180	- 5.2
13....	230	0.26	59.8	231	+ 0.4	215	- 6.5	228	- 0.86
14....	100	0.66	66	91	- 9	84.8	-15.2	90	-10
15....	110	0.54	59.1	101	+ 0.9	103	- 6.3	110	0
		Aver. Lf/c.c.			Aver. error		Aver. error		Aver. error
		60.2 Lf/c.c.			+ 3.9% (-4.1)%		0% (-6.9)%		+ 3.7% (-4.7)%

Table 5 (continued).

COMPARATIVE TABLE OF ASSAY OF ANTI-DYSENTERY (SHIGA) SERA
(BEHRINGWERKE) BY THE STANDARD METHOD
AND BY THE FLOCCULATION METHOD, USING TOXIN CHF XIII

No. of sera anti-dysentery sera (Behringwerke)	Titre of sera determined on mice	Quantity of serum flocculated with 1 c.c. of Chf XIII toxin	Number of Lf per c.c. of Chf XIII toxin	Titre of sera obtained referred to the average of Lf per c.c. of toxin	Difference in % between flocculation method and standard method	Titre of sera obtained by flocculation test, taking serum No. 1 as a standard	Difference in % between these two methods, with serum No. 1 as a standard in the flocculation test	Titre of sera obtained by flocculation test, using serum No. 15 as a standard	Difference in % between these two methods with serum No. 15 as a standard in flocculation test
1	2	3	4	5	6	7	8	9	10
	AU/c.c.	c.c.	Lf/c.c.	AU,c.c.	%	AU/c.c.	%	AU/c.c.	%
1....	800	0.1	80	828	+ 3.5	800	0	858	+ 7.2
2....	720	0.14	100.8	591	-17.9	570	-20.8	612	-14.8
3....	840	0.1	84	828	- 1.4	800	- 4.7	858	+ 2.1
4....	580	0.16	92.8	517	-10.8	500	-13.7	536.2	- 7.8
5....	570	0.16	91.2	517	-10	500	-12.2	536.2	- 5.9
6....	630	0.15	94.5	552	-12.3	533	-15.3	572	- 9.2
7....	420	0.2	84	414	- 1.4	400	- 4.7	429	+ 2.1
8....	380	0.3	114	276	-27.3	270	-28.9	286	-24.7
9....	450	0.19	85.5	435	- 3.3	421	- 6.4	451.5	+ 0.33
10....	440	0.18	79.2	460	+ 4.5	444	- 1	476.6	+ 8.3
11....	200	0.45	90	184	- 8	175	-12.5	190.6	- 4.7
12....	190	0.5	95	165.6	-12.7	160	-15.6	171.6	- 9.3
13....	230	0.43	98.9	192.5	-16.3	186	-18	199.7	-12.7
14....	100	0.8	80	103.5	+ 3.5	100	0	107.2	+ 7.2
15....	110	0.78	85.8	106.1	- 3.5	102	- 7	110	0
		Aver. Lf/c.c.			Mean error		Mean error		Mean error
		82.8 Lf/c.c.			+3.8% (-10.4)%		0%— (-12.3)%		+6%— (-10.6)%

In Table 5 we have attempted, for each of the fifteen sera brought in contact with the two toxins (Chf XI and Chf XIII), to calculate the titre yielded by the flocculation test, both by taking the average Lf of 1 c.c. of toxin as a conventional basis and by selecting two of the fifteen sera as standards.

By taking the average flocculation index (*LI*) of the toxin in relation to each of the fifteen sera of known titre (*in vivo*), we calculated the titre which these sera should have, according to the flocculation test. These titres are shown in column 5 of Table 5.

In a second series of calculations, we took as a standard one of the fifteen sera of which the titre had been established by the *in vivo* method, and worked out the AU value of the other sera according to the results obtained by the flocculation method (see columns 7 and 9 of Table 5).

By comparing the calculated values with those resulting from titration *in vivo*, we find a very satisfactory concordance between the results yielded by the flocculation method and those obtained by titration *in vivo* according to the international method.

We then sought to determine whether the first flocculation tube represented a neutral mixture. For this purpose, we carried out a flocculation test (see Table 6) using serum No. 1 and toxin Chf XIII.

The mixtures indicated by roman figures I to VI were inoculated intravenously on mice in doses of 0.5 c.c. The results are shown in Table 7.

Table 6.

		c.c.									
Anti-dysentery serum	0.8	0.6	0.4	0.36	0.32	0.28	0.24	0.2	0.12	0.04	0.01
No. 1 = 800 AU/c.c.											
Toxin Chf XIII	4	4	4	4	4	4	4	4	4	4	4
No. of mixture inoculated on mice		I	II	III				IV		V	VI
Results obtained in stream bath at 59° after	10 m.	op.	op.	op.	op.	op.	op.	op.			
	35 m.			+							
	40 m.			++	+						
	45 m.		±	+++	++	+	±				

op. = opalescence.

Table 7.

Mouse		No. of mixture inoculated (see Table VI) 0.5 c.c. (intravenously)	Day of observation							
No.	Weight		1	2	3	4	5	6	7	8
666 ..	18 gr.	I	0	0	0	0	0	0	0	0
667 ..	"		0	0	0	0	0	0	0	0
668 ..	"	II	0	0	0	0	0	0	0	0
669 ..	"		0	0	0	0	0	0	0	0
670 ..	"	III	0	0	0	m.d.	m.d.			
671 ..	"		0	0	0	m.d.	p.tr.p.	pl.tr.		
672 ..	"		m.d.	m.d. +				p. +		
673 ..	"	IV	p.tr.							
674 ..	"		p. +							
675 ..	"	V	+							
676 ..	"		p.tr.							
677 ..	"	VI	p. +							
			p.tr.							
			p. +							

0 = mouse shows no abnormal symptoms.
 m.d. = walks with difficulty.
 p.tr.p. = paresis of hindquarters.
 pl.tr.p. = paralysis of hindquarters.
 + = mouse dead.

It follows from Table 7 that flocculation tube No. II represents the neutral mixture, since the mice remain alive, just as do those inoculated with mixture I, in which there is an excess of serum relatively to mixture II. Mixtures in which an excess of toxin is present (III to VI) give a mortality rate corresponding to the quantity of non-saturated toxin.

It follows from Table 8 that the titre of toxin Chf XIII lies between 500 and 1,000 l.d. per c.c.

In a paper to be published elsewhere, we shall give fuller details concerning these experiments.

CONCLUSIONS

In the light of the results of the titration of fifteen antidysentery (Shiga) sera by the flocculation method in contact with two D 6 " R "

Table 8.

Mouse		Toxin Chf XIII 0.5 c.c. (intravenously)	Day of observation							
No.	Weight		1	2	3	4	5	6	7	8
650 ..	18 gr.	0.5 c.c. 1/50	m.d.	p.tr.p.	+					
651 ..	"	= 1/100	m.d.	Op. +						
652 ..	"	0.5 c.c. 1/125	0	p.tr.p.	+					
653 ..	19 gr.	= 1/250	0	p.tr.p.	+					
654 ..	18 gr.	0.5 c.c. 1/250	0	m.d.	+					
655 ..	17 gr.	= 1/500	0	m.d.	+					
656 ..	18 gr.	0.5 c.c. 1/500	0	p.tr.p.	+					
657 ..	"	= 1/1,000	0	0	m.d.	m.d.	m.d.	m.d.	m.d.	m.d.
658 ..	19 gr.	0.5 c.c. 1/1,000	0	0	m.d.	p.tr.p.	pl.tr.p.	pl.tr.p.	p.tr.p.	p.tr.p.
659 ..	18 gr.	= 1/2,000	0	0	m.d.	m.d.	0	0	0	0
660 ..	"	0.5 c.c. 1/1,500	0	0	m.d.	m.d.	0	0	0	0
661 ..	"	= 1/3,000	0	0	p.tr.p.	p.tr.p.	p.tr.p.	pl.tr.p.	p.tr.p.	m.d.
662 ..	"	0.5 c.c. 1/2,000	0	0	0	0	0	0	0	0
663 ..	"	= 1/4,000	0	0	0	0	0	0	0	0

0 = mouse shows no abnormal symptoms.
 m.d. = walks with difficulty.
 p.tr.p. = paresis of hindquarters.
 pl.tr.p. = paralysis of hindquarters.
 + = mouse dead.
 Op. = paraplegia.

toxins, of which one is a mixture of four different toxins, we conclude that this method might be used with great precision for the assay of antidysentery (Shiga) sera, since the margin of error varies within very narrow limits around the titres obtained on mice by the standard method.

The margin of error resulting from the use of the flocculation method is insignificant, if compared with that entailed by the use of the standard method when a toxin-antitoxin mixture is used on a limited number of mice,¹ whose individual reactions to the dysentery toxin is, as is well known, highly variable.

The results so far secured justify the hope that the flocculation method may be used in current practice for the assay of anti-dysentery (Shiga) sera, taking a standard anti-dysentery serum as a basis of comparison.

¹ R. PRIGGE and O. HARTOCH: "Arbeiten a. d. Staatsinstitut f. exper. Therapie u. G. Speyer-Hause zu Frankfurt a. M.", 1930, 23, 1-26.

PROPOSALS

1. In order to collect fuller information on the advantages of the flocculation method, it would be necessary to examine by this method, and under the conditions outlined above, as many sera as possible, comparing the titres so obtained with those of the mouse assay. We propose to undertake this work shortly.
 2. In order to introduce the flocculation test into current practice, and in order to obtain comparable results from all laboratories, it would be necessary to prepare a standard serum assayed on mice in the best possible conditions, and to distribute it to the various laboratories.
 3. It should be mentioned that the flocculation method ought, for the present, to be used solely for the assay of strictly anti-toxic sera, collected from animals immunised by means of a toxin prepared from a Shiga " R " strain containing no carbohydrate-fat antigen, in order to eliminate the possibility of several zones of flocculation.
-

II A

**REPORT ON THE ADOPTION OF A NEW
INTERNATIONAL STANDARD OF VITAMIN B₁
AND ON THE DEFINITION OF THE EXISTING
UNIT IN TERMS OF THAT STANDARD**

The International Conference on Vitamin Standardisation, at its meeting in 1931, adopted as standard for vitamin B₁ (anti-neuritic, anti-beriberi) the adsorption product of vitamin B₁ prepared in the Medical Laboratory, Batavia (Java), by the method of SEIDELL, as described by JANSEN and DONATH. The international unit of vitamin B₁ was defined as the vitamin B₁ activity of 10 mgrm. of the standard adsorption product.

At the second Conference in 1934, the adoption of the above standard and unit was confirmed with the recommendation that "the potency of the standard adsorption product should be tested relatively to that of the crystalline vitamin B₁ preparations at present available, with the aim of ultimately adopting pure crystalline vitamin B₁ as international standard".

At that time, crystalline preparation of vitamin B₁ had already been isolated by the following investigators :

Professor B. C. P. JANSEN, Amsterdam ;

Professor R. A. PETERS, Oxford ;

Dr. A. SEIDELL, Washington ;

Professor U. SUSUKI, Tokio ;

Dr. R. R. WILLIAMS, New York ;

Professor A. WINDAUS, Göttingen,

and it was recommended that they should be asked to undertake the above comparison. As will be seen from the accompanying memorandum, this request received a generous response.

In the four years which have elapsed since the last meeting of the International Conference, the synthesis of pure crystalline vitamin

B₁ has been achieved by relatively inexpensive processes and this has greatly increased the amounts available of the pure material. This substance is now manufactured on a considerable scale by several firms in different countries and the desirability of adopting the pure substance as the international standard has become very great.

Through the good offices of Sir Henry DALE, a large supply of synthetic vitamin B₁ hydrochloride was contributed by the four manufacturing firms named in the accompanying memorandum. The samples were mixed and re-crystallised and the final material was examined for criteria of purity by Dr. A. R. TODD at the Lister Institute. A total of 55 g. recrystallised material is now available for issue as international standard, a supply sufficient for several years. Collective tests of this material have been organised by the Vitamin B₁ Sub-Committee of the Accessory Food Factors Committee (appointed jointly by the British Medical Research Council and the Lister Institute). For these tests, small samples were distributed to a large number of workers in Europe, the United States and Japan, who undertook to investigate the potency of this sample of synthetic vitamin B₁ hydrochloride in comparison with that of the existing international standard. As will be seen from the tables of results in the accompanying memorandum, the experts by whom the tests were made included a number of workers attached to university schools in different countries as well as the experts on the staffs of the four manufacturing firms by whom the material for the standard was presented.

The results of the biological tests, carried out by several different methods, show a satisfactory degree of concordance and are summarised in the accompanying memorandum. They have been submitted to the members of the International Conference on Vitamin Standardisation, who have unanimously agreed to the recommendation "that the specimen of pure synthetic vitamin B₁ hydrochloride which has been thus investigated should be adopted as the international standard of vitamin B₁ and that the unit should be defined as the potency of 3 microgrammes γ of the pure material".

This value for the unit represents the average value obtained for the amount of the synthetic material possessing vitamin B₁ potency equivalent to that of 10 mgrm. of the standard adsorption product

—*i.e.*, to the potency of the international vitamin B₁ unit as previously defined.

The introduction of the new international B₁ standard has become a matter of some urgency, as the supply of the existing standard, held for distribution by the Standards Department of the National Institute for Medical Research, Hampstead, is now exhausted and requests received for the standard cannot be met. For this reason, it is hoped that the consent of the Permanent Commission on Biological Standards may be obtained without delay to the issue of the new vitamin B₁ standard and to the re-definition of the vitamin B₁ unit, as described in this report.

London, July 1938.

(Signed) E. MELLANBY, *Chairman*,
(Signed) Harriette CHICK } *Technical Secretaries*,
(Signed) E. Margaret HUME }
*International Committee on Vitamin
Standardisation.*

Annex.**ON THE ADOPTION OF SYNTHETIC VITAMIN B₁
(ANEURIN) HYDROCHLORIDE AS INTERNATIONAL
VITAMIN B₁ STANDARD**

**Results of Investigations organised by the Vitamin B₁
Sub-Committee of the Accessory Food Factors Committee.¹**

The International Conference on Vitamin Standardisation, at its 1934 meeting, recommended that the potency of the existing vitamin B₁ standard, the standard adsorption product, " should be tested relatively to that of the crystalline vitamin B₁ preparations then available with the aim of ultimately adopting pure crystalline vitamin B₁ as international standard ". During the past two years, this possibility has been brought nearer by the discovery, almost simultaneously in three different countries of methods for production of the pure vitamin by synthetic processes.

Through the good offices of Sir Henry DALE, 70 g. of synthetic vitamin B₁ hydrochloride were generously provided by the following four firms : Messrs. Merck and Company, Rahway, N.J. ; Messrs. E. Merck, Darmstadt ; Messrs. F. Hoffman-La Roche, Basle ; and Messrs. I. G. Farbenindustrie, Elberfeld. The samples were mixed and the whole recrystallised by Dr. A. R. Todd at the Lister Institute. The final sample, 55 g., gave satisfactory criteria for purity as follows :

Vitamin B₁ (aneurin) hydrochloride : colourless monoclinic plates m.p.246-247° (decomp.). *Picrate* : yellow needles, m.p.208°

¹ This Committee is appointed jointly by the Lister Institute and the Medical Research Council ; Secretary : Dr. T. F. MACRAE, Lister Institute.

(decomp.). *Picolonate* : dimorphous, (a) yellow needles, m.p.165° (decomp.), (b) yellow prisms, m.p.226° (decomp.).

Specimens of this material and of the present acid clay standard were distributed from the National Institute for Medical Research to twenty-two laboratories for examination and biological and chemical determination of the potency of the crystalline vitamin in terms of the present standard. Seventeen reports have been received, comprising thirty-one separate comparative experiments.

The methods employed by the various participants and the results obtained are given in the following tables :

Method	Observer	Amount of synthetic vitamin B ₁ hydrochloride found equivalent to 10 mgrm. of the present international standard—i.e., to possess the potency of one international unit	Average for group
		Microgrammes	Microgrammes
1. Rat-growth	S. Ohdake, Tokio L. S. Fridericia, Copenhagen C. A. Elvehjem, Madison L. J. Harris, Cambridge T. F. Macrae, London H. v. Euler, Stockholm Messrs. I. G. Farbenindustrie, Elberfeld H. E. Munsell, Washington K. Coward, London R. R. Williams, New York W. L. Sampson, Rahway	2.0 2.5 3.0 3.0 3.0 3.1 3.45 3.7 3.85 4.0	3.2
2. Rat-curative	Messrs. E. Merck, Darmstadt E. M. Nelson, Washington R. R. Williams, New York W. L. Sampson, Rahway L. J. Harris, Cambridge N. B. Guerrant, Pennsylvania B. C. P. Jansen, Amsterdam P. di Mattei, Pavia	2.0 2.6 2.5 2.7 2.7 3.0 3.5	2.7

Method	Observer	Amount of synthetic vitamin B ₁ hydrochloride found equivalent to 10 mgrm. of the present international standard—i.e., to possess the potency of one international unit	Average for group
		Microgrammes	Microgrammes
3. Rat-bradycardia	R. R. Williams, New York	2.5	2.8
	W. L. Sampson, Rahway	2.5	
	L. J. Harris, Cambridge	2.67	
	Messrs. Hoffmann - La Roche, Basle	3.33 (subcut.)	
	Messrs. I. G. Farbenindustrie, Elberfeld	3.61 (orally)	
4. Pigeon-curative	Messrs. E. Merck, Darmstadt	1.9	2.8
	S. Ohdake, Tokio	2.4	
	K. Coward, London	3.3	
	P. di Mattel, Pavia	3.4-3.8	
5. Chick-prophylactic	C. A. Elvehjem, Madison	3.0	3.0
6. Catatorulin ¹	R. A. Peters, Oxford	2.2	2.2
7. Thiochrome fluorimetric	B. C. P. Jansen, Amsterdam	2.5	2.6
	Messrs. Hoffmann - La Roche, Basle	2.56	
	H. v. Euler, Stockholm	2.7	
8. Colorimetric (method of Kinnersley & Peter)	H. v. Euler, Stockholm	2.6	2.6

¹ After elution of the acid clay adsorbate with Ba(OH)₂.

The results obtained showed a satisfactory degree of concordance, when account is taken of the great diversity of the eight different methods employed. For the present purpose, it is obvious that less weight should be attached to results obtained by chemical methods than to those of biological tests. Of the latter, higher values for

the potency of the present standard in terms of the synthetic material were generally obtained with prophylactic, than with curative, methods. It is suggested that with sick animals there may be incomplete elution in the alimentary tract of the vitamin B₁ from the acid clay adsorbate, so that curative methods tend to give too low a measure of the vitamin B₁ potency of the present standard and relatively too high a value for the pure material. With growth tests, on the other hand, a higher value for the present standard in terms of the pure material is obtained because the animals, being healthy, are better able to elute the vitamin from the acid clay. The results obtained by the many investigators support this theory, for the rat-growth method gave the highest average value for the amount of the pure material possessing a potency equivalent to that of the present unit.

There is also the possibility that the presence in the acid clay adsorbate of other growth factors for rats, in addition to vitamin B₁, may account for the relatively high potency of the acid clay adsorbate shown in rat-growth experiments. While the basal diets used in these experiments seemed mostly to be well supplied with the other vitamins of the B group, it is still possible that a deficiency of some essential dietary factors other than vitamin B₁ may have influenced the results.

There are, therefore, two possible reasons for the differences found by the various methods :

- (a) Difference in availability to the animals of the vitamin B₁ adsorbed on the acid clay ;
- (b) Possible complications due to the presence in the acid clay existing international standard of factors other than vitamin B₁, which may be adsorbed from the rice polishings extract in the process of its preparation.

THE VALUE OF THE PROPOSED NEW VITAMIN B₁ UNIT

Amounts varying from 2 to 3.5 γ have been suggested by the various participants, as the quantity of the pure synthetic vitamin B₁ hydrochloride of which the potency is equivalent to that of 10 mgrm. of the present standard adsorption product—*i.e.*, the

potency of one international unit. A good average value would appear to be 3 γ .

It is proposed that pure synthetic vitamin B₁ be adopted as international vitamin B₁ standard and that the international unit be defined as the vitamin B₁ activity of 3 γ of the pure material.

In dealing with all international standards, it has been regarded as a fundamental principle that the unit should be defined as the specific activity of a definite weight of the standard substance without reference to any particular method, or methods, of biological comparison. This makes the unit independent of future improvements in testing methods. The adoption of the value as defined above, rather than the fractionally lower one indicated by some forms of test, would satisfy another fundamental principle by avoidance of any suggestion that, with a change of standard, the value of the unit had been reduced.

It has been urged by some participants that, with the isolation and synthesis of the pure vitamin B₁, the need for a unit has disappeared, and that dosage and activity should henceforward be indicated in actual weights of the pure vitamin. The Committee agrees that this may be desirable as an ultimate objective. It remembers, however, that the action originally taken, in adopting the old standard and defining an international unit, had as its object the removal of a prevalent confusion, due to the use of a multiplicity of units based on different animal reactions. It believes that abandonment of the use of an international unit at the present juncture, before those concerned with the dosage and measurement of vitamin B₁ have become familiar with the pure substance and the degree of its activity, would inevitably produce a relapse into the former confusion. It is hoped that a new definition of the value of the existing unit in terms of a pure standard will, in itself, familiarise investigators and practitioners with the activity of the pure substance, and make easier an ultimate transition to a notation more logically based on exact weights.

II B**MEMORANDUM¹ ON THE SECOND
INTERNATIONAL STANDARD VITAMIN B₁**

Prepared by the

Department of Biological Standards of the National Institute
for Medical Research, Hampstead, London, N.W.3.

INTRODUCTION

The report of the second International Conference on Vitamin Standardisation, held in London on June 12th to 14th, 1934, under the auspices of the Permanent Commission on Biological Standardisation of the Health Organisation of the League of Nations, contains the following recommendation concerning the international standard for vitamin B₁.

“The potency of the standard adsorption product² should be tested relatively to that of the crystalline vitamin B₁ preparations at present available, with the aim of ultimately adopting pure crystalline vitamin B₁ as international standard.”

The investigations, undertaken in respect of this recommendation, have been in progress during the past four years. On account of the difficulty of obtaining adequate amounts of the crystalline material, progress was at first slow; but, during the year 1936, the position was completely altered by the discovery, almost simultaneously in three different countries, of three methods for the production

¹ This explanatory memorandum is intended to be despatched with the standard preparation.

² The adoption of this product as the international standard for vitamin B₁ was confirmed at the Conference.

of pure vitamin B₁ by artificial synthesis. Co-operation was sought from the manufacturers concerned with the practical application of the different synthetic processes with the result that four firms generously furnished sufficient quantities of the synthetic vitamin, as prepared in their respective laboratories, to enable an international standard preparation to be made on a completely adequate scale.

In order to ensure that the preparation made from these four samples was completely homogeneous, it was decided to mix them in a common solution and crystallise the material from this in a state of perfect uniformity. For this purpose, the four samples were mixed, dissolved in an equal weight of hot distilled water and filtered from traces of insoluble material through a sintered glass filter. Ten volumes of hot absolute ethyl alcohol were added to the filtrate, which was then allowed to stand for eighteen hours at room temperature until crystallisation was complete. The crystals were then collected on a sintered glass filter, washed with one volume of cold absolute alcohol, and dried in a vacuum desiccator over phosphorus pentoxide. A total of approximately 55 grammes of the preparation was thus obtained.

In order to enable a decision to be made as to the suitability of the preparation for adoption as the international standard for vitamin B₁, and the international unit for vitamin B₁ to be redefined in terms of the new preparation, the Vitamin B₁ Sub-Committee of the British Accessory Food Factors Committee organised an extensive and international investigation. Small samples of the preparation of crystalline vitamin B₁ were distributed to a large number of workers in Europe, the United States and Japan for purposes of trial and for comparative assay in terms of the present international standard.

The results of the tests carried out by several different methods showed a satisfactory degree of concordance. They were submitted to the Members of the International Conference on Vitamin Standardisation who unanimously agreed to recommend that :

“ The specimen of pure synthetic vitamin B₁ hydrochloride which has been thus investigated should be adopted as the international standard of vitamin B₁, and that the unit should be defined as the potency of 3 microgrammes of the standard material. ”

This recommendation was adopted by the Permanent Commission on Biological Standardisation of the League of Nations Health Organisation.

The result of this decision is that the first international standard preparation, known as the standard adsorption product of vitamin B₁, is now replaced by the crystalline vitamin B₁ preparation described above.

The following particulars relating to the nature, properties and final dispensing of the new international standard for vitamin B₁, together with suggestions for its care, storage and use in assays, are submitted for the information of the directors of national control centres, to whom the standard is supplied for distribution to laboratories, institutes and research workers in their respective countries, and of the recipients of the standard through these or other channels.

DESCRIPTION OF THE STANDARD

The international standard preparation is a quantity of pure synthetic crystalline vitamin B₁ hydrochloride (aneurin chloride hydrochloride, or thiamin chloride hydrochloride) prepared in the manner described above, and stored at the National Institute for Medical Research, Hampstead, under conditions ensuring its permanence. The total quantity of the standard preparation is approximately 55 grammes.

The preparation contains approximately one molecule of water of crystallisation ; when protected from access of moisture it is stable.

Criteria of Purity.

Colourless monoclinic plates, m.p. 246-7° (decomp.).

Picrate : yellow needles, m.p. 208° (decomp.).

Picolonate : dimorphous (a) yellow needles, m.p. 165° (decomp.);
(b) yellow prisms, m.p. 226° (decomp.).

DEFINITION OF THE UNIT

The international unit has been defined as the antineuritic activity of 3 microgrammes of the international standard preparation.

FORM OF ISSUE OF THE STANDARD

The standard preparation has been distributed into small tubes of non-alkaline resistance glass, each containing approximately 20 milligrammes. After being kept for fourteen days over phosphorus pentoxide *in vacuo*, during which no loss of weight was recorded, the tubes were filled with pure, dry nitrogen gas and sealed by the flame. They are stored continuously at -2° C. in the dark.

PURPOSE OF THE STANDARD

The standard preparation is intended to be used in determining the sensitiveness to the curative action of vitamin B₁ of animals kept on a diet deficient in this vitamin. By the use of parallel series of animals, a determination can be made of the amount of a foodstuff or medicinal preparation under test which is equivalent in curative activity to a known weight of the standard. The anti-neuritic (vitamin B₁) activity of the substance under test can then be expressed as the number of international units of activity present in a given weight. The standard preparation may also be used as a basis of comparison, in the application and investigation of chemical methods of vitamin B₁ determination.

INDICATIONS FOR USE

For the convenience of those employing the standard, the following indications may be given :

(1) The daily dose of the preparation required to maintain satisfactory growth in a young rat of 50-100 grammes weight, kept on a diet which is free from vitamin B₁, but complete in all other respects including vitamin B₂ complex, is about 3 to 6 microgrammes ;

(2) Single doses of 10 microgrammes of the preparation, given to pigeons suffering from polyneuritis as the result of being maintained on a diet of polished rice, cure about 70% of the birds.

SUGGESTIONS REGARDING THE USE OF THE STANDARD PREPARATION

1. To open the tube, a deep file mark is made near, and around, the sealed end. The tube being held in an almost horizontal position, a hot point is applied to the file mark. A clean cut usually ensues, and the sealed end must be detached in such a way that glass splinters do not gain access to the material in the tube and cause errors in weighing.

2. After the tube has been opened, it is preserved in a small desiccator containing phosphorus pentoxide.

3. Precautions to be taken in the preparation of solutions : The pure vitamin B₁ hydrochloride, if completely desiccated by exposure to vacuum at a high temperature, is very hygroscopic. In the form adopted for the standard preparation, containing approximately one molecule of water of crystallisation, it is much less hygroscopic, but still gains weight if exposed to ordinary, moist air. It is preferable, therefore, to transfer the quantity required for a test to a small glass-stoppered weighing bottle, in which it can then be weighed on a microbalance, or an ordinary balance, according to the number of tests for which the sample is being taken. Even without such precautions, however, exposure to the air during weighing will not cause an increase in weight of more than about 0.6% if the operations are completed within five minutes.

Neutral and alkaline solutions of the standard are unstable, and aqueous acid solutions are readily infected by moulds, which inactivate the vitamin. It is recommended, therefore, that stock solutions (1 mgrm./c.c. is a convenient strength) should be prepared in 25% aqueous ethyl alcohol to which hydrochloric acid is added to make the solution approximately N/500 HCl. This solution is stable if kept at about 0°C. Solutions of suitable strength for animal dosage (20 to 100 microgrammes/c.c.) must be made at least twice weekly from the stock solution, by removing the alcohol *in vacuo* and making up to the required dilution with N/500 HCl. Such dilutions must be kept at a low temperature and examined daily for moulds. If more dilute solutions are required, these should be made up daily from the stock solution.

III

**REPORT OF THE THIRD INTERNATIONAL
CONFERENCE ON THE STANDARDISATION
OF HORMONES¹**

(Geneva, August 11th to 13th, 1938.)

I

The Chairman made an opening statement indicating, as the particular purpose of the Conference, an attempt to arrive at agreements for the adoption of a stable, material standard for each of the

¹ The following attended the meeting :

Sir Henry H. DALE, K.B.E., M.D., F.R.S., Director, National Institute for Medical Research, Hampstead, London, *Chairman*.

Members :

Professor S. ASCHHEIM, Laboratoire d'Embryologie comparée, Collège de France, Paris ;

Dr. D. K. M. CHALMERS, National Institute for Medical Research, Hampstead, London ;

Professor J. B. COLLIP, F.R.S., Department of Biochemistry and Pathological Chemistry, McGill University, Montreal.

Professor H. M. EVANS, Institute of Experimental Biology, University of California, Berkeley ;

Dr. C. HAMBURGER, State Serum Institute, Copenhagen ;

Professor E. LAQUEUR, Director, " Pharmacotherapeutisch Laboratorium der Universiteit ", Amsterdam ;

Dr. A. S. PARKES, National Institute for Medical Research, London ;

Dr. Oscar RIDDLE, Carnegie Station for Experimental Evolution, Cold Spring Harbor, Long Island, N.Y. ;

Dr. Philip E. SMITH, Professor of Anatomy, Columbia University, College of Physicians and Surgeons, New York ;

Dr. F. G. YOUNG, National Institute for Medical Research, Hampstead, London ;

Dr. R. GAUTIER, Member of the Health Section of the League of Nations Secretariat, Geneva, acted as *Secretary*.

(Footnote continued on page 888.)

recognised hormones of the anterior lobe of the pituitary gland, and analogous principles found in urine or serum, and for the definition of a unit of activity in terms of a weight of each such standard. He suggested that the discussion of actual methods for the biological measurement of these hormones and principles would be relevant only in relation to the application of such agreed standards and units in biological assays. He further suggested that the various items on the agenda might with advantage be taken in the order in which agreement was likely to be most readily attained, according to the indications of replies which had been received to a preliminary questionnaire, circulated among the members of the Conference and a number of other experts not present.

II. CONSIDERATION OF THE GONADOTROPHIC SUBSTANCE OF HUMAN URINE OF PREGNANCY

It was agreed :

(1) That this Conference agrees with the opinion expressed in the replies to the questionnaire circulated last year that it is both desirable and practicable to establish an international standard preparation for the gonadotrophic substance of urine of pregnancy.

(2) That the preparations of the gonadotrophic substance from human urine of pregnancy in the form of dry powders, which had been offered by manufacturers in different countries as contributions to the international standard, should, with the exception of one which several investigators had found to give atypical results, be mixed, after dilution of some preparations with an inert substance to approximately equal activity with the remainder ; and

Observers :

- Dr. R. W. BATES, Carnegie Institute, Cold Spring Harbor, Long Island, New York ;
Professor B. A. HOUSSAY, Instituto de Fisiologia, Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires ;
Dr. R. MORICARD, Chef de laboratoire à la Clinique gynécologique de la Faculté de Médecine, Paris ;
Dr. Kitty PONSE, Directeur-adjoint de la Station de Zoologie expérimentale de l'Institut de Zoologie et Anatomie comparée, Université de Genève, Geneva.

that this mixture, after further dilution with an equal quantity of inert material, should constitute the international standard.

(3) That, subject to confirmation, after practical tests by members of the Conference of the activity of the standard material so prepared, the specific gonadotrophic activity of 0.1 milligramme (= 100 gamma) should be accepted as the international unit for recording the activities of all preparations of human urine of pregnancy, but only of such.

(4) That when the definition of the unit in terms of this standard material has thus been confirmed and finally accepted, arrangements should be made for the compression of the standard material into tablets, each containing a suitable number, such as 100, of the agreed units, and for the packing of these tablets in suitable numbers, after complete desiccation, in sealed glass containers, under conditions excluding oxygen.

(5) That the standard shall thereafter be kept at a temperature below 0°C., and protected from light, at the National Institute for Medical Research, Hampstead, London, England, and distributed therefrom, on behalf of the League of Nations Health Organisation, to national centres for the control of such substances, and to other suitable research institutes.

(6) That the only tests for the comparative determination of gonadotrophic activity, in units as above defined, on which the Conference has evidence to justify recommendation, depend on :

(a) The observation of a direct or indirect gonadotrophic effect, shown by morphological changes in the gonads ; or

(b) The observation of secondary changes in the accessory reproductive organs, in animals not deprived of their gonads. When this type of test is used, the absence of substances directly causing such changes in the accessory reproductive organs should be assured, by control tests on animals deprived of their gonads.

(7) That each member of the Conference participating in the confirmatory tests on the standard material be requested to furnish, with his report, a detailed description of the method or methods of biological comparison used in his tests, with a view to the publication of an annex to the report of the Conference, dealing with methods of assay.

III. CONSIDERATION OF THE THYROTROPHIC SUBSTANCE OF THE ANTERIOR LOBE OF THE PITUITARY GLAND

It was agreed :

(1) That this Conference agrees with the opinion expressed in the replies to the questionnaire circulated last year that it is both desirable and practicable to establish an international standard preparation for the thyrotrophic substance of the anterior lobe of the pituitary gland.

The Conference then discussed the possibility of obtaining preparations of the thyrotrophic substance of the anterior lobe of the pituitary gland free from contamination by other anterior lobe principles, in particular the gonadotrophic substance, and from active constituents of the *pars intermedia* and the posterior lobe.

It was then further agreed :

(2) That the materials offered by several manufacturing and other organisations should be circulated among certain experts, including some members of the Conference, in order that they might be tested as to their suitability as constituents of a mixed preparation of the thyrotrophic substance in the form of a dry powder, to serve as the international standard preparation. The opinion was expressed that it would be desirable, if it were found practicable, to obtain all the contributions in the form of material prepared from the dissected anterior lobes of the pituitary glands of oxen only. In order to facilitate comparative testing of the different samples available, it was decided that one of these (referred to as " TH 5 " in document MM5) should be used as a provisional standard of reference for the others.

(3) That the specific thyrotrophic activity of 0.25 milligramme (= 250 gamma) of the preparation " TH 5 " would afford a suitable basis for the definition of an equivalent unit, for acceptance by international agreement, in terms of the standard preparation, as ultimately made ready for distribution.

(4) That the Chairman and Secretary should undertake to get some trial tablets made of the standard powder, when available, with the addition, if necessary, of a suitable basis to give the material the required consistency.

(5) That when these different trials were completed, and the definition of the unit in terms of this standard material had thus been confirmed and finally accepted, after examination in its completed form by the experts co-operating in the tests, arrangements should be made for the compression of the standard material into tablets, each containing a suitable number, such as 50, of the agreed units, and for the packing of these tablets in suitable numbers, after complete desiccation, in sealed glass containers, under conditions excluding oxygen.

(6) That the standard shall thereafter be kept at a temperature below 0°C., and protected from light, at the National Institute for Medical Research, Hampstead, London, England, and distributed therefrom on behalf of the League of Nations Health Organisation to national centres for the control of such substances, and to other suitable research institutes.

The Conference then discussed the nature of the available biological tests for thyrotrophic activity, particularly with regard to the necessity of excluding effects due to non-specific active constituents, either of the standard preparation or of other preparations assayed in comparison therewith.

It was then further agreed :

(7) That the only tests available for such comparative determination of thyrotrophic activity, which were free from this danger of interference by non-specific constituents, were tests based on the direct observation of changes induced in the thyroid gland itself, and that, in particular, indirect tests, based upon effects on metabolic rate, were not trustworthy when applied to such incompletely purified materials as are yet available.

(8) That each member of the Conference participating in the confirmatory tests on the standard material be requested to furnish, with his report, a detailed description of the method or methods of biological comparison used in his tests, with a view to the publication of an annex to the report of the Conference, dealing with methods of assay.

(9) That it is desirable that researches should be continued in appropriate centres, with the object of discovering methods for separating the thyrotrophic hormone more completely from other active principles of the pituitary gland, on a scale sufficient to enable the standard preparation, now adopted, eventually to be replaced by a new standard preparation, free from such other active principles.

IV. CONSIDERATION OF THE LACTOGENIC (CROP-GLAND-STIMULATING) SUBSTANCE OF THE ANTERIOR LOBE OF THE PITUITARY GLAND
(" PROLACTIN ", " GALACTIN ", " MAMMOTROPIN ")

It was agreed :

(1) That this Conference agrees with the opinion expressed in the majority of the replies to the questionnaire circulated last year that it is both desirable and practicable to establish an international standard preparation for the lactogenic (crop-gland-stimulating) substance of the anterior lobe of the pituitary gland.

(2) That the preparations of this principle offered by several manufacturing and other organisations should be circulated among certain experts, including some members of the Conference, in order that they might be tested as to their suitability as constituents of a mixed preparation of this principle in the form of a dry powder, to serve as the international standard preparation.

(3) That no contribution offered towards this standard preparation should be accepted, if it is found, on examination, to contain less than about 5 " Riddle-Bates units " of the specific activity in 1 milligramme.

(4) That the preparation made by careful mixture of the acceptable contributions shall constitute the international standard preparation without dilution.

(5) That this standard preparation shall be assayed by the co-operating experts in " Riddle-Bates units ", in comparison with the preparation named " L.P. 1 " in the table on page 4 of document MM5.

(6) That by comparison of the assays thus carried out, agreement shall be reached among the members of the Conference as to the activity of the standard preparation in " Riddle-Bates units " per milligramme, and that the international unit shall be thus defined in terms of the standard preparation.

The Conference then proceeded to discuss the possibility of obtaining a greater and more uniform activity among the different samples contributed for the preparation of the standard, by attempting to separate the active constituent in crystalline form, but concluded that, on the information before the Conference, such an attempt would be unlikely, under present conditions, to have an effect in the desired direction.

It was then further agreed :

(7) That the Standards Department of the National Institute for Medical Research be asked to consider the practicability of issuing this standard in two forms, one without dilution, the other suitably diluted with an inert substance and compressed into tablets of convenient dimensions, in order to effect economy in the use of the standard in tests requiring the use of small fractions of a unit.

(8) That, when the definition of the unit has thus been confirmed and finally accepted, the standard material shall be distributed into suitable glass containers, in the form of the untreated powder, and possibly also after dilution and compression into tablets as above suggested, and that the contents of such containers shall then be completely desiccated, and the containers sealed under conditions as nearly as possible approaching sterility and excluding oxygen.

(9) That the standard shall thereafter be kept at a temperature below 0°C., and protected from light, at the National Institute for Medical Research, Hampstead, London, England, and distributed therefrom, on behalf of the League of Nations Health Organisation, to national centres for the control of such substances, and to other suitable research institutes.

(10) That the Conference cannot, on the information before it, recognise any test as giving sufficiently quantitative results for the comparative assay of preparations in relation to this standard,

except those which depend on the measurement or observation of growth produced in the crop-gland of the pigeon or dove, whether as the result of systemic or of local administration.

(11) That each member of the Conference participating in the confirmatory tests on the standard material be requested to furnish, with his report, a detailed description of the method or methods of biological comparison used in his tests, with a view to the publication of an annex to the report of the Conference, dealing with methods of assay.

V. CONSIDERATION OF GONADOTROPHIC PREPARATIONS OF THE SERUM OF THE PREGNANT MARE

It was agreed :

(1) That it is desirable and practicable to establish an international standard preparation for the gonadotrophic substance of the serum of the pregnant mare.

(2) That preparations of this substance have been offered as contributions sufficient to enable a standard preparation eventually to be prepared by admixture.

(3) That samples of these different contributions should be distributed to experts, including members of the Conference, in order that they may report upon their suitability for inclusion in the standard preparation.

(4) That a mixture shall be made of those contributions regarded as suitable, and this mixture shall again be assayed by the experts, and that each member of the Conference participating in this assay shall be requested to indicate the quantity of the mixture which, in his opinion, has an activity suitable for adoption as 1 international unit, having regard to the dimensions of the units which have already attained general currency.

(5) That, after consideration of those reports, and agreement among the members of the Conference as to the quantity of the mixture to be accepted as representing 1 unit of activity, the mixture shall be so diluted with an inert material that 1 such unit

shall be contained in 0.1 milligramme (= 100 gamma) of the diluted powder. The preparation as thus diluted shall then be accepted as the international standard preparation for the assay of all preparations of the gonadotrophic substance of pregnant mare's serum, but only of such.

(6) That arrangements shall then be made for the compression of the standard material into tablets each containing a suitable number, such as 100, of the agreed units, and for the packing of these tablets in suitable numbers, after complete desiccation, in sealed glass containers, under conditions excluding oxygen.

(7) That the standard shall thereafter be kept at a temperature below 0° C., and protected from light, at the National Institute for Medical Research, Hampstead, London, England, and distributed therefrom, on behalf of the League of Nations Health Organisation, to national centres for the control of such substances, and to other suitable research institutes.

(8) That the only tests for the comparative determination of gonadotrophic activity, in units as above defined, on which the Conference have evidence to justify recommendation, depend on :

(a) The observation of a direct or indirect gonadotrophic effect, shown by morphological changes in the gonads ; or

(b) The observation of secondary changes in the accessory reproductive organs, in animals not deprived of their gonads. When this type of test is used, the absence of substances directly causing such changes in the accessory reproductive organs should be assured, by control tests on animals deprived of their gonads.

(9) That each member of the Conference participating in the confirmatory tests on the standard material be requested to furnish, with his report, a detailed description of the method or methods of biological comparison used in his tests, with a view to the publication of an annex to the report of the Conference, dealing with methods of assay.

VI. CONSIDERATION OF THE GONADOTROPHIC PRINCIPLE, OR PRINCIPLES, OF THE ANTERIOR LOBE OF THE PITUITARY GLAND

It was agreed :

That, on the information before it, the Conference is unable to recommend the establishment of a standard preparation for measurement of units of the gonadotrophic effects of preparations from the anterior lobe of the pituitary gland. It has before it the evidence that, in certain laboratories, preparations have been obtained in which different factors of the total gonadotrophic activity are more or less completely separated. In these circumstances, the Conference believes that future action, in the direction of establishing a standard or standards for the principle or principles in question, can best be accelerated by arranging for the exchange of specimens of the preparations claiming to present the separated activities, among the experts concerned and others interested, for co-operative trials and interchange of experience.

VII. CONSIDERATION OF THE CORTICOTROPHIC (ADRENOTROPHIC) SUBSTANCE OF THE ANTERIOR LOBE OF THE PITUITARY GLAND

It was agreed :

(1) That it is desirable to establish an international standard for this substance, but that, on the evidence as yet available, it does not seem to be practicable to collect sufficient suitably purified material to constitute a standard preparation, on the scale which would be necessary to make it effectively available for international distribution.

(2) That, in these circumstances, the policy most likely to accelerate action in the direction of establishing a standard would be the exchange of specimens among the experts concerned and others interested in co-operative trials.

VIII. CONSIDERATION OF THE GROWTH-PROMOTING HORMONE OF THE ANTERIOR LOBE OF THE PITUITARY GLAND

The Conference, after full discussion, accepted the following resolution by unanimous vote :

That the members of the Conference recognise that some of the objections which might be urged against the establishment of a standard for the growth hormone could be urged against some of the standards, for other forms of anterior pituitary activity, which they have already accepted ; that they are nevertheless of the opinion that the only action on which agreement can be reached, on this occasion, with regard to the growth-promoting hormone, is the arrangement of a co-operative investigation, with a view to the establishment of a standard for growth-promoting activity at the earliest date at which the basis for agreed action appears to be available.

IX. CONSIDERATION OF A STANDARD PREPARATION FOR THE WHOLE ANTERIOR LOBE OF THE PITUITARY GLAND

The Conference expressed the hope that the Standards Department of the National Institute for Medical Research, Hampstead, London, England, would be able to facilitate comparative research on the hormones of the anterior lobe of the pituitary gland for which international standard preparations had not yet been adopted, by preparing or acquiring a suitable quantity (not less than 2 kg. or more than 5 kg.) of anterior pituitary lobe substance of oxen, dried without fractionation, so that samples might be furnished to the participants, in different countries, in the co-operative investigations planned by the Conference.

The Chairman gave an undertaking that the National Institute for Medical Research would do what was possible in the direction desired.

X. CONSIDERATION OF THE PRINCIPLE, OR PRINCIPLES, OF THE " PARS INTERMEDIA " OF THE PITUITARY BODY

The question was raised as to the possibility of establishing a standard, or standards, for the principle, or principles, of the *pars intermedia* of the pituitary body, which in very small doses produce(s) expansion of the melanophores of the frog's skin, and in larger doses has important effects on metabolism in the mammal. After discussion, it was agreed :

That the available information was not sufficient to enable the Conference to consider the establishment of a standard for this type of activity on the present occasion. The hope was expressed that the further progress of investigations in this important field would make it possible for a future Conference to take action in this direction.

XI. CONSIDERATION OF OTHER HORMONES OF THE ANTERIOR LOBE OF THE PITUITARY GLAND, OR " ANTERIOR PITUITARY-LIKE " HORMONES

The Conference discussed the possibility of establishing standards for additional principles belonging to the group under consideration, such as the gonadotrophic substances contained in human urine after removal of the ovaries or at the time of the menopause.

It was agreed :

That no action in these directions was practicable at this juncture.

XII. CONSIDERATION OF NOMENCLATURE

It was agreed :

(1) That the fully descriptive term " anterior lobe of the pituitary gland " should be adopted for reference to the organ in question in the records of the Conference.

No general agreement was reached in discussion of the respective claims of the suffixes " trophic " and " tropic " in the construction of descriptive terms for reference to the active principles with which the Conference had dealt.

It was agreed :

(2) That the use of the forms with the suffix " trophic " or " trophique " in the official English and French versions of the discussions and decisions of the Conference would be acceptable to the members of the Conference. It was further agreed that the form " tropic " might, if necessary, be used with appropriate modifications in translations into other languages.

It was agreed :

(3) That the Conference recommend the adoption, for general scientific use, of the term " gonadotrop(h)in " for reference to principles with gonadotrophic action, with the addition, in each case, of a suitable adjective or descriptive phrase, to indicate the source of origin of the particular principle to which reference is made.

(4) That the Conference recommend the adoption, for general scientific use, of the terms " corticotrop(h)in " and " thyrotrop(h)in ", to denote the active principles of the anterior lobe of the pituitary gland acting on the adrenal cortex and on the thyroid gland respectively.

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GENERAL SURVEY OF MEDICO-SOCIAL POLICY
IN RURAL AREAS

FOREWORD

In 1939, the League of Nations is convening a European Conference on Rural Life.

The idea of such a conference was originally propounded by the 1931 European Conference on Rural Hygiene, which recorded the opinion that it would be desirable for its recommendations to be reviewed after a period of five years in the light of the studies undertaken in the meanwhile by the Health Organisation.

When this period had elapsed, the Health Committee proposed that a new conference should examine the questions of rural hygiene in their natural setting, considering that any real amelioration of the standard of health in the rural environment must depend, in the first place, upon the improvement of living conditions generally.

This view having found acceptance, the Assembly of the League of Nations decided to organise a European conference on rural life. This conference will consider, from the technical standpoint, the various problems involved in raising the social standards and level of well-being of the rural areas of Europe ; the Governments concerned will thus have an opportunity of discussing together the methods best

calculated to promote a higher standard of living and improved health protection. Accordingly, the agenda deals in turn with questions of vital statistics, agricultural economy, public health, nutrition, co-operation, education and rural planning.

* * *

One of the most important items of the agenda is that of medico-social policy ; and the Health Committee has given particular attention to the thorough technical preparation of the conference's discussions on this subject.

After an initial phase of documentary preparation, it organised, in October 1938, a consultation, attended by officers actively engaged in the organisation of the medico-social policy of their respective countries.¹

¹ This meeting was attended by :

- Dr. O. ALKS, Director of the Department of Public Health of Latvia, Riga ;
- Dr. W. Jerzy BABECKI, Deputy-Director of the Public Health Service of Poland, Warsaw ;
- Professor J. BALTEANU, Professor of Hygiene at the Jassy Faculty of Medicine, Member of the Health Committee ;
- Dr. C. VAN DEN BERG, Director-General of Public Health of the Netherlands, The Hague ;
- Professor D. COMBIESCO, Secretary-General, Roumanian Ministry of Public Health, Bucharest ;
- Dr. Ch. FAUCONNET, Director of the Swiss Federal Public Health Service, Berne ;
- Dr. N. M. GOODMAN, Medical Officer, Ministry of Health, London ;
- Dr. Béla JOHAN, Secretary of State, Royal Hungarian Ministry of the Interior, Budapest ;
- Dr. René SAND, Secretary-General, Section of Public Health, Belgian Ministry of Public Health, Brussels ;

The following also took part in this session, in the capacity of experts :

- Dr. B. BORČIČ, Director of the Institute and School of Hygiene, Zagreb ;
- Dr. M. KACPRZAK, Chief of Service, Polish Ministry of Social Welfare, Warsaw ;
- Dr. A. STAMPAR, former Director of the Yugoslav Public Health Service, Zagreb ;
- Dr. J. TOMCSIK, Director of the Hungarian State Institute of Hygiene and Professor at the University, Budapest ;
- Dr. N. M. ATWATER, Secretary of the American Public Health Association, New York ;
- Dr. G. ICHOK, Professor at the Institute of Statistics, University of Paris ;
- Dr. J. J. PATERSON, Medical Officer of Health, Maidenhead, Berkshire, United Kingdom.

This consultation enabled the participants to meet and discuss the best ways of co-ordinating the presentation of the various national reports which describe the action of the public authorities in the conduct of medico-social policy in rural areas.

They reviewed the main problems and the difficulties currently encountered as well as the means of coping with them which are afforded by the medico-social equipment available in their respective countries.

A drafting committee, consisting of Dr. B. BORČIČ (Yugoslavia), Dr. N. M. GOODMAN (United Kingdom), Dr. Béla JOHAN (Hungary), Dr. M. KACPRZAK (Poland) and Dr. René SAND (Belgium), met in December 1938 to examine the draft report kindly prepared by Dr. Kacprzak and Dr. René Sand. This comprehensive monograph, which is to serve as an introduction to the discussions of the 1939 conference, is reproduced below.

I. INTRODUCTION

The Importance of Health.

In the last analysis, man will always be the subject of all our endeavours ; whether our purpose be cultural or material, the action we undertake always has as its fundamental object the improvement of the condition of mankind and the protection, raising and enrichment of human existence.

We call civilisation the sum total of the means employed, by every people and every generation, to achieve that object more fully.

Such successive endeavours constitute the history of human progress.

In this gradual assertion of the ascendancy of life over death, *health stands in the forefront ; the oldest civilisations, like the religious movements of all times, show their concern for health. Good health is the prerequisite of well-being and ability to work, the safeguard of intellectual and moral balance, and the most valuable asset of the individual, the family and the community.*

Here, as in most other spheres, however, *scientific progress in the abstract greatly outdistances concrete achievement.* We have learnt how to lengthen the expectation of life, how to prevent or cure many diseases, how to abolish much suffering ; but we only apply that knowledge to a relatively limited extent. Doubtless, economic circumstances limit our possibilities of action ; but mere indifference, and, even more, the lack of organisation and of a broad general outlook, must also be held responsible.

Some countries have made persistent efforts to improve public health, and have been rewarded by a considerable decline in infant mortality and in the death rate from infectious diseases. Nevertheless, morbidity still remains unduly high, and a state of thorough good health is still far from being the general rule ; moreover, the victories won in the struggle against death are due more to improvements in the economic condition of the masses than to the direct

influence of health measures, which are seldom planned as part of a *rational programme*.

The Need for a Health Programme.

In view of the deficiencies still to be found in this field, and the immense advantage to be gained from concerted action in the interests of health, it is of the highest importance that each country should make a general survey of the state of public health and of its health equipment, and that it should, on that basis, construct a coherent plan for a medico-social policy, fixing, year by year, the stage to be reached and estimating and securing the financial resources required for the purpose. Such a task has lately been accomplished, and in a bold spirit of constructive realism, by a Commission appointed by the Federal Government of the United States.

The Need for a Rural Health Policy.

The steps taken in various countries to raise public health standards have invariably been more favourable to the urban population and to industrial workers. It was long believed that the farmer, living in close contact with nature, was in a privileged position from the standpoint of health. But as living and health conditions improved in the towns, urban mortality rates fell to such an extent that, in several countries, they are to-day actually lower than rural mortality rates. Villagers, living in small scattered groups, have been unable to improve their condition as effectively as town workers. The life of the peasant has altered comparatively little.

Yet the greater part of the human race lives on the land, the produce of which is essential to the existence of the whole of mankind. In addition, the birth rate has, for the most part, remained high in rural areas, thus enabling them to contribute a considerable proportion of the population of towns. It is therefore urgently necessary to set on foot, on behalf of the agricultural community, a health campaign appropriate to its requirements and economic conditions, and calculated to meet the particular difficulties to be overcome in rural areas.

The reason why a separate medico-social policy is needed for country districts is that, although scientific data remain constant from one region to another, their practical application varies according to local circumstances. Villages differ from towns by their remoteness, their small, scattered population, the type of activity carried on by their inhabitants, their mode of life, their habits of thought and their reactions. Not only the physical and economic possibilities, but also the social and psychological atmosphere of the countryside, call for different methods ; no effort must be neglected to make rural existence more attractive and more secure.

Such were the considerations which led the Council of the League of Nations, on the proposal of the Spanish Government, to instruct the Health Organisation to convene the European Conference on Rural Hygiene, which met at Geneva in June and July 1931. That Conference was followed by the Intergovernmental Conference of Far Eastern Countries on Rural Hygiene, held at Bandoeng (Java) in August 1937. These two Conferences, which had been carefully prepared by a series of surveys and other detailed preliminary work, laid down the principles, methods and means of action constituting a rural health policy, in a series of recommendations which were unanimously accepted by the delegates of twenty-three European nations at Geneva and thirteen Far Eastern countries at Bandoeng.

That programme has had an indisputable influence on the development of rural hygiene. Although actual methods have varied from country to country, the main lines laid down at Geneva have everywhere been followed. Before concluding its labours, the European Conference recommended that a new meeting should be held within the next five years for the purpose of surveying the progress achieved and adapting the 1931 recommendations to newer problems and to the latest advances in public health technique.

In the meantime, the problem broadened in scope. The Health Committee realised that considerations of health can seldom be divorced from economic, demographic and social factors. It accordingly proposed to the Assembly that the second Conference on Rural Hygiene should be transformed into a European Conference on Rural Life. This conference is to be held at Geneva in 1939 ; not only the Health Organisation and the Economic and Financial Organisation of the League, but also the International Labour Office, the International Institute of Intellectual Co-operation and the

International Institute of Agriculture are co-operating in the preliminary work under the guidance of a Preparatory Commission. A great deal of material has been collected as a result of investigations, meetings of experts, reports and statistics. But before giving a general review of this material, emphasis should be laid on the profound differences in the economic, health and cultural standards of rural populations from country to country.

Differences in Rural Environments in the Various Countries.

A number of different sets of conditions are found in this connection in different countries and regions. In some cases, the country is so highly industrialised that the agricultural community is in the minority, the greater part of the population living in towns. That is the position in the United Kingdom, Belgium and the Netherlands. The countryside is inhabited by industrial and clerical workers, who travel daily to office or factory, and by other categories of persons whose income is not derived from agriculture. Even here, however, some districts remain isolated and can to some extent be compared with typical agricultural countries.

In other cases, the peasant population represents half, or more than half, the total, but the most modern equipment is found in farms and rural dwellings. This is the situation exemplified by the Scandinavian countries and Switzerland.

Elsewhere, we may find that, despite the existence of large towns and a considerable degree of industrialisation in some parts of the country, from a third to half of the population is still employed in agriculture, conducted—notwithstanding various improvements—in the traditional manner. This is the case in Scotland, France and Germany.

Finally, there are countries in which the population is very predominantly agricultural, the villages retaining their traditional aspect, in spite of varying degrees of modification due to modern innovations.

It is clearly in this last category that the problems of rural life subsist in the fullest degree, and call for measures other than those which may apply elsewhere. Districts in which agriculture has been modernised constitute, in one sense, a foretaste of the

future, and in any case a useful field of suggestions for other more backward regions.

There can be no question as to the considerable gap subsisting, from country to country, as regards economic resources, cultural standards and the relative isolation of the peasant population, which conditions their mental attitude. To those differences must be added those found in legislation and administration.

Situations so varied require a wide measure of elasticity in the formulation of the principles of a rural medico-social policy. A given recommendation will seem too modest in some countries and too sweeping in others. Allowance must be made for national, regional and local circumstances. Our object here is, however, to draw inferences rather than to offer concrete solutions; we merely wish to map out a general line of advance, which each country will be free to follow in the light of its own requirements, possibilities of action and experience.

II. CURATIVE MEDICINE

Medical Care.

Medico-social policy in country districts should begin by the organisation of arrangements for *medical care*. This is the normal course of historical development for the protection of health, and it is but natural that the first step should be that of meeting the most immediate and keenly-felt need. The sick suffer, and to relieve them is a humanitarian duty; it is also the means of paving the way for preventive medicine, which, from the standpoint of public health, is more important than curative medicine, though as yet less appreciated by the public.

In some countries, provision for medical care in rural districts is relatively complete; elsewhere, it is still inadequate, or even almost entirely wanting in certain districts, owing to their isolation and lack of resources. To remedy this situation, the countries of central and eastern Europe, the Scandinavian countries and Scotland (mountainous and island regions) have adopted the system of approved provincial or local practitioners; these receive a specified allowance, plus fees from families which can afford to pay. In Great Britain,

France and Belgium, in particular, the public relief authorities pay doctors for attendance to the poor. Furthermore, through the extension of sickness insurance and the other forms of collective medical assistance, the sick are given access to the whole armoury of preventive and curative facilities, which it is to the interest of the responsible agencies to improve so as to save money. Attending the rural population thus becomes a reliable source of income for doctors, so that they will be more willing to settle in villages, and will be *distributed* more in accordance with the needs of the public. In some countries, young doctors have to work for a time as assistants to country practitioners, or to settle in rural districts at the outset of their career.

Specialists.

Though of outstanding importance, the work of the general practitioner is not sufficient in itself ; the patient must be able to obtain the necessary *drugs*, and it is no less essential for him in certain cases to consult *specialists*. Here again, the extension of sickness insurance may supply the solution by removing the chief obstacle, which is a financial one.

In England, a number of counties have been divided into districts, each provided with a medical centre where poor, insured and paying patients can consult specialists on certain days and at certain hours. This system apparently satisfies both the medical profession and the public.

Surgical operations, diagnostic examinations and special treatments must usually be carried out in hospital, and this applies also to analyses, unless they are performed at central or regional institutes.

Hospitals.

It is therefore essential for the *hospitals* to form a network extending over the whole country. With the modern development of communications, patients can now be sent, within a few hours, to large institutions where the necessary equipment and skill are available.

In thinly-populated districts in certain countries, chalet-hospitals with some ten or twenty beds have been established ; these are

linked up with larger institutions, which send one of their doctors when required, the resident staff consisting of a nurse-midwife only. Such chalet-hospitals receive midwifery and accident cases, and patients who cannot be treated at home, but whose condition is such that they need not, or cannot, be removed to the regional hospital immediately. The cottage hospitals in England are institutions of a more self-contained type, though they call in the services of local doctors. It is universally recognised that these cottage hospitals perform exceedingly valuable services.

The local hospital should never have less than fifty beds, and preferably at least a hundred, so that overhead expenses can be spread over a greater number of patients. It should contain a laboratory, a radiological department and an operating theatre. Its staff should include at least one resident surgeon and an adequate number of experienced nurses.

This hospital, serving the purpose of a sorting and diagnostic centre, should be in contact with an institution possessing more elaborate equipment and staff, and also with a tuberculosis sanatorium, a psychiatric hospital and a convalescent home. The curative institutions in a given district should form a co-ordinated whole, so that patients may be moved from one to another as required, the doctors working at different points in the hospital system as occasion demands. An adequate number of isolation beds should be reserved in these various hospitals for infectious cases, if there are no special institutions for them.

The peasant is frequently unable to pay his own hospital expenses, and the local resources of the public relief authorities are usually limited. The assistance of a local or national fund, or of the social insurance organisation, is indispensable, especially in cases of prolonged illness.

Dental Care.

Dental care is, needless to say, still more neglected in the country than in the towns; it is expensive, and there is a shortage of qualified staff. Once again, social insurance can provide a solution for the problem. Sweden has just set up a national dental service: dentists settled in all parts of the country receive a fixed salary for attending the poor, together with fees on a recognised scale from patients in more or less comfortable circumstances.

Confinements.

In the country, most confinements take place at home. For this reason, a midwifery service has been instituted in numerous countries ; the midwives also receive either a fixed salary or a separate payment for each confinement, apart from fees from families which can afford to pay.

Home Nursing.

Since attention has to be given at home to patients suffering from acute or chronic complaints, these midwives, in some countries, are nurses as well. This system has been adopted in England, where throughout the country the Queen Victoria Jubilee Institute maintains nurse-midwives, who are the country doctor's best assistants. The Institute draws its funds from donations and bequests, and from contributions from the local authorities and the public, either as annual subscriptions or as fees. In other countries, home nursing is undertaken by special nurses or health visitors.

To sum up, the immediate aim should be to ensure that every rural family receives a minimum of attention, especially in cases of confinement, infectious disease or accident, and in those requiring urgent medical aid. The final goal should be, however, to provide in all cases the services of doctor, midwife, nurse, specialists and dentist, in addition to laboratory analyses and hospital treatment, and, in any event, the necessary medicaments.

The public relief authorities, social insurance organisations, the Government, provincial and local authorities and private associations should all take their due share in this system. The essential is that the system should be complete and co-ordinated and that none should be excluded from its operation.

III. PREVENTIVE MEDICINE

The Two Aspects of Preventive Medicine.

While measures are introduced to provide the rural population with effective medical assistance, the task of *prevention* should be undertaken in both its aspects : the first, or impersonal, aspect being that which concerns environment (housing, water-supply, sewage-

disposal, foodstuffs)—which we shall discuss later—while the second, or personal, aspect concerns the preventive measures taken by the doctor and the health visitor in regard to families and individuals.

Medico-social organisation cannot be regarded as a plan to be immediately and universally applied ; the expense would in any case be an obstacle. All that can be done, therefore, is to prepare a stage-wise and co-ordinated programme, covering at one and the same time both central and local administrations, both environment of the family and the individual, both preventive and curative action.

Central Administration.

As regards the *central administration*, there is no doubt that the necessary co-operation between health,¹ public relief and social welfare institutions is impossible unless the central services in these three branches are either co-ordinated or are united in a single *Ministry of Public Health or of Social Affairs*, which keeps in close touch with the institutes of hygiene (if these are not directly under it) and co-operates as far as possible with the medical faculties. The Ministry should form advisory commissions or boards whose opinion it should obtain.

As the European Conference on Rural Hygiene recommended,² the central administration should work on “ the principle of the greatest efficiency combined with the greatest economy. This *principle of maximum efficiency* was the notion which governed the whole Conference. Its corollary is the *division and technical value of the work done*. Division by areas is intended to bring into direct touch with the scattered rural population a staff and institutions which are as many-sided as possible. A functional division is intended to place at the disposal of such a population over a wider area a specialised staff and specialised institutions. . . . Another corollary of the principle of maximum efficiency is the *principle of co-ordination and unity of action*. . . . Finally, all the recommendations of the Conference were inspired by the *principle of adaptation to local conditions*.”

¹ Including housing, nutrition, physical fitness, maternal and child welfare, school medical services, hospitals and the supervision of the medical profession.

² Geneva, 1931, Vol. I, page 11.

Both general and district or local health surveys are essential to the planning of an effective medico-social policy. *Monographs on both social and health conditions*, made more specific by means of health indices¹ or similar systems, should therefore be prepared for the country as a whole, for the various districts and for smaller areas. This is a modern application of the medical topography of Hippocrates. Mortality and morbidity statistics should also be made as complete and accurate as possible, since they will serve as a guide to the health administration and the medical profession in their work.

The central health administration cannot confine itself to stimulating and financially assisting local and private efforts ; the law must allow it to impose certain general measures (such as vaccination and the isolation of infectious cases) and to require the local authorities to take a certain minimum of sanitary measures. If need be, some authority to inflict penalties should be added to its powers of financial and technical assistance and technical supervision. The aim should be to achieve that nice balance between centralisation and decentralisation which will be best suited to the special conditions of the country. As the health services develop, gradual decentralisation seems desirable ; but the right of supervision by the central authorities should remain, together with their right to intervene in the event of technical errors or slackness on the part of local authorities or subsidised organisations.

The central health administration will call in the services of experts : engineers to inspect sanitation schemes, veterinary surgeons to inspect meat, chemists to inspect other foodstuffs, pædiatrists, tuberculosis specialists, psychiatrists, etc. (not to mention lawyers and statisticians) ; but it will consist chiefly of doctors having special knowledge of public health questions.

County Administration.

The powers of the county (departmental, provincial) health administration should extend to social preventive medicine (health

¹ This system of indices has been devised by M. Falk and M. Stouman, and was applied by the latter to the town of New Haven, to a Hungarian rural district and to the city of Brussels. It was adapted to rural districts by a Conference of Experts, which met at Geneva in June 1938.

visitors, maternal and child welfare, anti-tuberculosis work, etc.), public health (housing, water-supply, sewerage, etc.) and hospitals. The aim should be, not to carry out a uniform programme everywhere, but, on the contrary, to meet the most immediate needs, which vary from district to district, to arouse an interest in hygiene among the local public and their leaders, and to co-ordinate endeavours. Just as universal experience has shown the advantage of having polyvalent health visitors (but subject to the supervision of specialised superintendents), so it is now the rule to have polyvalent county health services.

The county health administration should be under the direction of a *full-time official who is a medical man specially trained for the work (diploma in public health)*. Here again, it is no longer in dispute that the simultaneous practice of medicine and performance of duties in the public health service inevitably tends to make a doctor neglect the latter in favour of urgent cases amongst his patients ; the independence that every official should enjoy is encroached upon, his mind is distracted from questions and considerations which should absorb his whole attention, and he becomes a rival to medical practitioners whose co-operation is essential to the discharge of his official duties.

Those public authorities who believe that they are saving money in this way lose more than they save in impaired efficiency and the multiplication of posts. The *part-time* system is not merely a regrettable second-best, but an actual error in organisation ; it would be better to reduce the number of posts than to turn them into subsidiary, not to say wasted, occupations.

The medical officer of health in charge of a county service should, where necessary, be provided with assistant public health officers, and should also be given the assistance of specialists, and, if necessary, of the district institute of hygiene, besides having at his disposal in any event inspecting or superintendent health visitors.

The county health administration constitutes *the link between the central and local administrations*. In some countries, it is entirely controlled by the central authorities ; in others, it is run by the county, subject to the supervision of the central authorities, the latter fixing conditions of employment, preparing a scale of salaries and pensions, confirming appointments, supervising the work done and providing financial assistance. The county health service

should in any event form part of the national organisation and should work on the same lines as the central health administration.

The essential function of the county health administration is to stimulate, co-ordinate and distribute work. The medical officer of health in charge of it should possess a thorough knowledge of the area, its resources, requirements and mentality ; he should pay personal visits to the mayors, the leading members of the medical and teaching professions, the social insurance organisations, the public assistance committees and private associations. In a number of countries, these various persons and agencies have been brought together in co-ordination committees, with excellent results.

Thus helped in his task, the county medical officer of health should endeavour to combine the institutions in his county into a well-balanced whole. The isolation in which each separate hospital, sanatorium and dispensary is only too often prone to work will give place to a system of interconnection. One hospital, well situated and equipped, will specialise in the treatment of acute affections, while another, less modern, will be devoted to chronic diseases and a third will become a convalescent home. Since 1929, the efforts of the authorities in Great Britain have been successfully directed to this end.

District Administration.

The county (province, department) is divided into administrative areas or districts, each of which—possibly several grouped together for the purpose—will have its full-time medical officer of health, who will be assisted by health visitors and a sanitary inspector, unless such auxiliary staff is provided at some other level in the hierarchy of services. But this division does not imply a dispersal of effort ; the county medical officer of health will be responsible for the public-health organisation of the whole county.

The district health service, which is the real executive body for purposes of public health policy, should, according to the opinion of authorities who have studied the question, have not more than from 20,000 to 50,000 people in its area, unless the medical officer of health has the help of one or more assistants. District health services will be created only as the necessary funds and staff become available. To divide up the country straight away into a number

of health districts, and to rely on doctors who have not had the necessary training and have to attend to their practice at the same time, without the requisite auxiliary staff and funds, would be to place the public health organisation on an entirely false basis from the outset.

The practice must be to proceed gradually, not to undertake too much at a time, and to make sure that whatever is done is done on a really sound basis.

The area comprised within a district will include both large towns, which generally have a health service of their own, and small towns and villages. At this *local and rural level*, the public health organisation may be developed either by the central health service or by local initiative. In either event, the work will be one of persuasion; but, in the first case, the health centre can be complete from the start, whereas, in the second, it will often be necessary to proceed by stages. In this second case, the villagers, or at all events the more enlightened among them, must be induced to support the local authorities in carrying out certain sanitary reforms—water-supply, manure-pits, cleaning of byres, tipping of household refuse. A health visitor, under the direction of a doctor, will begin by visiting infants, and this will gain her admittance to a certain number of households; later, she will extend her activities to pregnant women, school-children and consumptives, and will thus come into contact with most of the families. She will send children and adults requiring medical treatment to the local doctors. While giving no aid herself, she will apply to the public services, the public relief authorities and private organisations for help. She will endeavour to keep in touch with every child from birth to school-leaving age.

Soon the population will be ready to accept an infant welfare clinic; this will be followed by a pre-natal clinic, the medical inspection of school-children and children of pre-school age, and, perhaps, an anti-tuberculosis dispensary. In this way, a health centre will gradually be built up, with shower-baths, a first-aid post and, if there is no hospital near, a few beds for urgent cases or isolation. But here again, except in special circumstances, progress must be gradual after public opinion has been won over, and use must be made, to begin with, of municipal buildings, schools or other available premises. Little by little, a complete health centre will be

constituted, with provision for every form of preventive action and for urgent curative treatments, including, if necessary, the care of the indigent. In most countries where the population is mainly rural, the health centre will not work on purely preventive lines—the population would not understand if provision were made for the healthy and treatment were refused to the sick. But curative action will not be allowed to restrict the scope of preventive action.

If institutions such as infant welfare centres or a school medical inspection service already exist, these will be duly linked up by some suitable method of co-ordination : the best form of health centre is that of the polyvalent dispensary established in one building under a single management, but it may also take the form of separate, mutually supplementary, autonomous institutions.

Where there are a number of *health visitors*, each attached to a different type of dispensary, endeavours should be made, particularly in the country, to replace this specialisation by a system of allocation of each visitor to a defined area in which she should undertake polyvalent duties. Such polyvalent visitors are preferable to specialised workers ; first, because it is a mistake for several people to be looking after a family at the same time ; secondly, because a district visitor spends less time on the road than the specialised nurse with her larger area ; and, lastly, because an assistant who has sole charge of a limited area can get to know the families and win their confidence and can identify herself with the population in her district. The specialised superintendents attached to the departmental health service will give these polyvalent workers advice in difficult cases, supervise their activities and keep their training up to date.

The health visitor will take notes of individual cases, and keep a card index. But the medical officer will keep a check on the use she makes of her time and see that the greater part is devoted to what constitutes her real task.

The United States recommend one health visitor per 1,500 inhabitants. That is an ideal to be aimed at ; but, in present circumstances, the figure may be put at one assistant per 6,000 inhabitants in rural districts.

A threefold task devolves upon the health visitor in the dispensary and in the family : preventive action, education in hygiene and domestic economy, and social assistance. In principle, she should

not engage in regular sick nursing in the home, but should aim rather at enabling the families to undertake this themselves. If a qualified midwife is locally available, she can be trained for this purpose and attached to the health centre, to visit infants and pregnant women.

Voluntary help should not be rejected—on the contrary. But such helpers must be used according to their real ability, and not be entrusted with work which calls for professional technical training. Obedience, punctuality and discretion should be required of them. Such persons will often be the wives or daughters of local notabilities ; they should never be allowed to dominate in the control of the work. These voluntary helpers should be given definite duties which will make them feel that they are being of real use.

What is known in English-speaking countries as the *inspection of nuisances* is of fundamental importance ; this covers disinfection, inspection of housing, drinking-water, sewage and garbage disposal, foodstuffs, and, generally speaking, any source of insanitary conditions. Inspection is entrusted either to a medical officer, a health visitor or, preferably, a specially trained sanitary inspector, as in England.

Health Centres.

The *primary health centre* was described by the 1931 Conference as the terminal stage in the general public health armament of a country—that is to say, the smallest agency adapted to serve the public health needs of the smallest rural area. Health centres now exist in almost every country ; but in Latvia, Poland, Hungary, Yugoslavia and certain parts of France this institution has become an essential part of the public health machinery. The health co-operatives in Yugoslavia, the Red Cross, and other organisations in different countries, have helped to establish these centres.

The essential thing is the spirit in which they work. According to the experts who studied the health indices, they should fulfil the following conditions :

- (1) They should be engaged in at least two medico-social activities—*e.g.*, child welfare and anti-tuberculosis measures or school medical service ;
- (2) They should be placed in the charge of a medical man ;

- (3) They should employ the services of a health visitor ;
- (4) If local conditions permit, they should help to co-ordinate all the relevant activities in the territorial area for which they are responsible.

The premises and equipment of the centre may be very simple : a waiting-room, a consulting-room, shower-baths and living accommodation for the nurse or doctor, or they may be much more elaborate.

In the latter case, it becomes a *secondary health centre*—that is to say, according to the definition of the Conference, a more fully developed organisation responsible, in the first place, for co-ordinating the activities of all the public health work in its area, in particular that of preventive medicine agencies maintained by the public authorities, the sickness insurance institutions or private organisations.

In addition to the minimum requirements mentioned in paragraphs 1 to 3 for the primary health centre, the secondary health centre must be so equipped as to be able to supplement and second the work of the primary centre on the technical side. It must have direct or indirect access to facilities for the various kinds of laboratory examination—for instance, the services attached to an institute of hygiene or medical institute, together with the specialised diagnostic departments.

The division of work as between the primary and secondary centres will depend mainly on the means of communication available, and upon whether the population is concentrated or scattered.

The primary centre can extend its activities through local branch agencies, more especially infant welfare centres, or by means of mobile units.

The secondary centre should be in touch with a hospital, if it is not actually installed there. It will be placed in charge of the district health officer ; this will ensure the necessary connection between the hospital system, the network of health centres and the public health administration.

Special Activities.

Various special activities connected with medico-social policy are deserving of mention.

The creation in country districts of *experimental or demonstration centres* will make it possible, on the one hand, to develop technique to be employed and to assess the cost and results, and will also prove a stimulus to the authorities and the rural population. This method has been successfully employed in the United States, China, India and a number of European countries.

In Poland and Roumania, for instance, mobile units of doctors, students and auxiliary personnel spend a few days, possibly a few weeks, in a rural district, where they carry out a health survey, make the population health conscious, organise the supervision of infants and pregnant women, detect cases of tuberculosis, treat cases of trachoma, etc. As a result of their temporary stay in the area, the rural population have, in some cases, been impelled to erect shower-baths or a health centre themselves.

As another instance of such self-help, reference may be made to the achievements of the health co-operatives in Yugoslavia and Poland : out of their own resources, and with the help occasionally of subsidies and the advice of the public health services, villages have put up health centres themselves.

Yet another scheme is deserving of mention. In Belgium, the Société de médecine préventive, the Fédération médicale, the mutual benefit societies, the Government and 168 communes, representing a quarter of the population of the country, have distributed upwards of 300,000 *health record booklets (carnets de santé)*. These have just been made compulsory by Royal Decree, for the 1,200,000 school-children in the country. The booklet remains the property of the holder, and no one apart from the doctor attending the case and the doctors attached to the preventive services may ask to see it. Health booklets have been made compulsory also in Turkey and France for certain categories of persons. In Italy, the matter is under consideration, and many children already have a health record card (*fiche sanitaire*), a system which is now in force in several countries for infants, school-children and persons covered by social insurance. But the single health record booklet (*carnet de santé*) covering every period of life is even more useful to the attending physician, to the medical officer responsible for preventive medical examinations and, lastly, to the holder himself, who is thus encouraged to be permanently mindful of his health.

The health record booklet costs no more than the cost of printing. If the system employed in Belgium is adopted, it provides the material for compiling morbidity statistics. Doctors report the diagnosed disease or abnormal condition to the central service, without mentioning the person's name. Professional secrecy is thus safeguarded, as in the case of the notification of causes of death.

Acute Infectious Diseases.

In preventive action in rural districts, the first thing on which attention should be concentrated is infectious diseases connected with defective public health organisation and a low economic and social standard of living, such diseases being transmitted through the medium of insects (typhus in particular) or of human excreta (enteric fever and dysentery). They can be stamped out, but only by close collaboration between the medical profession and the representatives of the economic and social life of the community. The eradication of these diseases would have as a corollary an improvement of the economic standard of living and a general rise of the cultural level. The problem is closely connected with housing, clothing, physical cleanliness, drinking-water supplies, the disposal of sewage, household refuse and manure and, lastly, with measures to prevent the contamination of foodstuffs.

Vaccination is of very great importance in the case of smallpox and diphtheria, and also in that of typhus and typhoid, but, so far as the last two are concerned, this means of protection is not a substitute for measures of sanitation.

For infectious diseases spread by secretions from the mouth and nose, the measures in the country can be none other than those applied in the town. Two points should be specially emphasised: facilities for isolation and transport facilities. The cost of isolating infectious cases in hospital should not be charged to the family or there will be attempts at evasion. The problem of transport—highly important in the case of accidents as well—is one that calls urgently for the assistance of the public health authorities, since, in most countries, it cannot be solved satisfactorily by local means.

Maternity and Child Welfare.

Next comes the question of maternity and child welfare. Agricultural countries generally have a high infant mortality, and, as

long as this situation continues, there is no sphere in which preventive action in rural districts will score more outwardly manifest—nay, more facile—successes.

Again, the rural districts, where the birth rate is always higher than in the towns, constitute the nation's main resource in perpetuating its existence ; unfortunately, in some cases, the rural death rate has now come to stand at a higher level than that of the towns ; especially is this true of the infant mortality rate. Not that the latter is the only aspect of the problem ; all possible steps must be taken to protect and improve the health of rural inhabitants from birth onwards, and to inculcate sound hygienic habits, thereby raising the population to a higher biological level.

Such is the importance of this problem that the work of the health authorities should be largely judged on their child welfare work.

The first thing is to protect the mother. In country districts, the woman's position is more precarious than that of the man : as mother, nurse, housewife and worker, she is never free and can never rest. Even when the time of delivery is approaching, she does heavy work, a fact which is not without its influence on the child and which helps to produce the excessive death rate from tuberculosis among young women. Rural opinion should be educated and agricultural life so organised that, during the last few weeks of pregnancy, at all events, the expectant mother may be released from work liable to injure her own health and, indirectly, that of her offspring.

In agricultural districts, many women are assisted in childbed, not by a doctor or certificated midwife, but by " handy women ", neighbours or relatives with no knowledge other than their personal experience. The consequence is a high maternal and infantile mortality, and in many cases injury to the health of mother and child. If every woman in childbed is to have the assistance of a certificated midwife, the voluntary organisations or the central or local authorities must organise a service of midwives in receipt of adequate salaries, which might be further supplemented by fees from comparatively well-to-do families. In order to ensure that pregnant women shall employ the services of certificated midwives, a proposal has been put forward that any person called upon in an emergency to assist a woman in childbed shall immediately inform the nearest midwife, on pain of being prosecuted for the illegal practice of

medicine, even if there has been no payment for such services. Furthermore, to enable the mother to stay in bed for not less than seven to ten days, the private organisations or local authorities must be prepared, if there is no one to take over her domestic duties, to provide the assistance of a domestic help, as is the practice in the Netherlands, Great Britain and the Scandinavian countries. The institution of maternity homes, where pregnant women and women in childbed seeking privacy are received discreetly, renders invaluable service, as do the convalescent homes to which mothers can go to recuperate.

Medico-social protection during the first year of life should be so organised that every child may have the benefit of medical advice and the mother may receive instruction from the health visitor. In addition, arrangements should be made to assist indigent families by providing them with good milk or other food appropriate to the age and requirements of the child, and with layettes and other essentials. It is sometimes necessary to provide the mother with material support, to enable her to feed and look after her child.

Special consideration should be given to the pre-school age, as very little has been done, particularly in rural districts, to provide for the training and to protect the health of children from 2 to 7 years of age. The father is busy in the fields or on the farm and the mother is absorbed by domestic occupations, so that the child may be left to himself or given work to do which is beyond his strength (helping with agricultural work, looking after cattle, taking care of younger brothers and sisters, etc.) at an age when pastimes of an educative character should form his sole occupation ; lastly, his diet often leaves much to be desired, particularly from the point of view of quality.

The organisation of summer crèches, day nurseries, kindergartens and nursery schools would appear to be particularly necessary.

The health centre will comprise an ante-natal clinic, an infant welfare centre, a welfare centre for children of school age, and a school inspection service extending to day nurseries and kindergartens.

Only too often, this inspection simply means nothing more than the detection of the most obvious defects, which is not followed by any treatment unless the health visitor pursues the matter vigorously. Medical inspection should mean, for every child, a thorough

somatic, psychological, anatomical and functional survey, showing up the weak points and affording guidance for subsequent physical exercise, and even study and, later, the choice of a career.

These examinations will often point to the need for supplementary food, which should be supplied at school, and for medical and dental treatment. Such treatment may be provided in three ways : by sickness insurance covering the whole family, by school-children's insurance—as it exists in certain Swiss cantons—or by the school dispensary, which may, where appropriate, be incorporated in the medical service of the health centre.

The school age is the first period of life during which the individual comes under the control of a public institution. Advantage should be taken of this to detect defects of health, to correct them and to inculcate hygienic habits in the rising generation.

To what category of doctors shall the examination of children and pregnant women be entrusted, *where there is neither a welfare centre, a health centre nor a local medical officer ?*

There are five different possibilities :

(a) A medical practitioner living on the spot or in some neighbouring place may be appointed at a small allowance on a part-time basis to examine infants, school-children or pregnant women. But an official appointment such as this may tend to estrange the other practitioners.

(b) An obstetrician or pediatrician may be brought out from town on fixed days and at fixed hours. This system is costly when the distances are great. It, too, may create difficulties with the local practitioners.

(c) A mobile dispensary may be organised, installed in a motor-car, to take the medical specialist from village to village. This method is employed in the province of Liège in Belgium for radiological examination of school-children for tuberculosis. It is apt to be costly and, if used for pregnant women, infants and school-children in general, is open to the same objections as the system of bringing in town specialists.

(d) Infants, school-children and pregnant women may be conveyed by motor-bus to the nearest dispensary. The mere mention of this proposal is sufficient to demonstrate its impracticability in remote country districts.

(e) Lastly, recourse may be had to the body of local practitioners, each pregnant woman, infant and school-child being supervised by the family doctor, at the expense of the public health administration, public relief authorities or social insurance institutions, or of the persons themselves, when they can afford it. This solution offers several advantages in rural districts : it does not require special premises or equipment ; it stimulates medical practitioners to take an interest in preventive medicine ; it utilises the family doctor's knowledge of the past history, habits, living conditions and character of the person concerned and, lastly, it ensures the necessary treatment's being given if any abnormal condition is found to exist.

On the other hand, it means the dispersing of the preventive organisation, rendering collaboration between the school doctor and teacher more difficult and entrusting to a medical practitioner a task for which he is often not fitted. While the advising and preventive examination of pregnant women, infants and school-children are not in themselves particularly difficult, they call for an outlook quite different from that of curative medicine, as well as a special technique. The medical practitioner should in any case be required to possess the necessary material equipment, to have taken a post-graduate or practical course, and to enter all particulars of the case on the health card or record booklet. Difficult cases should be referred to a specialist.

Undoubtedly, wherever possible, the best plan is to establish a well-equipped ante-natal consultation clinic, infant welfare centre, and school medical inspection service in charge of a medical officer, who can thus obtain specialised experience, if he does not already possess it. But when the population is scattered and the necessary funds are not available, and this method is hence not feasible, recourse should be had to whichever of the five above-mentioned methods is most likely to produce the best results under the given conditions.

Tuberculosis.

Of the various social scourges which are prevalent in country districts, one calls for very special attention. The decline in the death rate from tuberculosis is less marked in the country than in

the towns, and in rural districts on the continent this disease takes a specially heavy toll among young women.

Tuberculosis being at once an infectious and a social disease, the problem of control must be attacked with due regard to both these aspects.

Tuberculosis is usually contracted at a very early age. In the rural environment, contact with the tuberculosis bacillus occurs more often than not in the family itself and the disease is perpetuated by contagion through several generations. The unhygienic habits of the rural population and their unsatisfactory housing conditions (cramped, ill-planned houses, overcrowded with adults and especially with children) are almost bound to result in repeated heavy infection by a member of the family who may or may not be known to be tuberculous. Improper diet—often inadequate in quantity and still more often in quality—hard work and long hours add to the effects of exposure and insanitary surroundings. Action is therefore required, on the one hand, to raise the level of rural housing and of peasant life in general by every possible means, and, on the other, by suitable instruction, to inculcate improved standards of individual hygiene. Another essential point is to provide facilities for the isolation of cases of open tuberculosis.

The detection of cases of tuberculosis requires the provision of mobile anti-tuberculosis dispensaries and sorting services at the primary health centres, and the co-operation of the medical profession. Confirmation of the diagnosis should be obtainable from anti-tuberculosis dispensaries, appropriately equipped with laboratories and X-rays, under the direction of a tuberculosis specialist, and forming part, for preference, of the secondary health centres.

The dispensary staff must not wait for the patient to present himself. It must seek him out in his own home, at school—among the teaching and domestic staff, as well as among the pupils—wherever there is reason to suspect that the disease is present. The connection between tuberculosis of cattle and human tuberculosis should be borne in mind. In every case, the source of the infection must be traced. The first thing to be considered will be protective measures for children, who must be safeguarded from infection and enabled to build up their power of resistance. The dispensaries should, in addition, concern themselves with the welfare of all the tuberculosis cases in their area. They should be given the

social assistance of the health visitor and medical care, including facilities for new methods of treatment, such as collapse-therapy.

As for isolation, this is often only feasible in the peasant's own home. The family cannot afford prolonged or repeated sanatorium treatment. All possible means must therefore be employed to facilitate the isolation of the patient and to teach those around him how to look after him without danger to themselves ; the means employed will vary according to the country and the given conditions. If it is impossible to separate the patient entirely from his family, by means of a partition for example, the Dutch method is recommended ; this consists of putting up a tent or erecting a light pivoting structure at the side of the house or in the garden.

Certain patients will, of course, require, for their own good and for the welfare of the community, to be isolated, at the expense of the authorities, in a sanatorium or hospital. Without this precaution, tuberculosis control is unthinkable. The sanatorium does not provide a complete remedy for a disease which is intimately bound up with the social conditions of the community, but is nevertheless a valuable means of lessening its ill effects. In addition to the large-sized institutions, recourse may be had, as in Norway and Hungary, to smaller institutions, which are comparatively cheap to erect and run.

It is not an easy matter in rural districts to train the patient for light work when he leaves the sanatorium. It has to be realised that, for many years, his output will be below normal and that it would be fatal for him to attempt to take up his old job. The problem is a difficult one, depending, as it does, on economic considerations, but some attempt should nevertheless be made to solve it.

Venereal Disease.

Save in exceptional circumstances, venereal disease is less frequent in rural than in urban districts. But treatment is hampered, among other reasons, by the patient's fear of his condition's becoming generally known.

The first step must be to undertake special educational action in rural districts ; the population should be made to understand that venereal diseases are to be regarded like any other infectious disease, that persevering treatment is required to cure them and the use

of secret remedies is bound to end in disappointment. The advertising of such products should be prohibited.

The doctor should systematically examine, for syphilis and gonorrhœa, pregnant women, sterile women or women in whom pregnancy has been interrupted and, generally speaking, any groups or individuals that appear to him suspect. He should arrange in every case for the dispensary or health service to conduct discreet enquiries as to the origin of the infection.

Treatment being costly, the health administration should supply the doctor with the necessary drugs without demanding to know the identity of the patient or, better still, treatment should be entirely free of charge, even outside the dispensaries.

Army doctors should inform the health service confidentially when infected members of the forces return to their village.

If there is a health centre, detection and treatment should be carried out there ; otherwise, the district medical officers and local practitioners should be responsible. Success can only be achieved if patients feel that they can count on absolute discretion being observed.

With the consent of venereal disease patients (on whom she should call if they break off their treatment), the health visitor should endeavour to prevail upon the persons living in their environment to come forward for examination.

Mental Derangement.

Cases of mental deficiency or disease, although fully as common in the countryside as in towns, receive even less attention there. Yet it cannot be denied that, out of any 100 children, several will be found to be mentally deficient or abnormal in character, while mental affections among adults are far from uncommon. The benefits to be derived from special education for backward subjects and the satisfactory results achieved by the early treatment of mental derangement are well known. Rural populations cannot be denied such advantages any longer.

Teachers and school doctors should devote the most careful attention to the detection of abnormality among pupils, while general practitioners should exercise the same watchfulness over adults and refer abnormal cases to specialists as soon as suspicious symptoms make their appearance.

The best solution would obviously be to attach a dispensary for mental disease to the Health Centre ; but it is generally difficult to secure the services of a competent psychiatrist.

Here again, the health visitor can render conspicuous service. In some agricultural countries, the village idiot or mentally defective is the butt of the community ; sometimes he becomes a habitual offender or a criminal. Assistance must be organised in such a manner as to provide treatment in special communities or in mental hospitals. The method tried out at Gheel in Belgium, and in similar settlements for mental deficients, shows that patients can be given a relatively free life at a reasonable cost, coupled with the requisite protection both for themselves and for society generally.

Other Diseases.

Some diseases, such as trachoma, rheumatic ailments, digestive troubles and certain skin diseases, appear to be produced or promoted by unsatisfactory social conditions. Investigations should be undertaken with a view to the organisation of systematic preventive treatment and cheap and efficient curative treatment.

The question of *alcohol* has not been touched upon here, despite its great importance, since no solution specially adapted to rural areas appears to present itself, apart from the limitation or supervision of home-distilling, and since the circumstances of the problem differ in each particular case. Anything capable of entertaining or interesting village populations will militate against alcoholism.

Finally, it should also be observed that, from a health standpoint, the presence in the countryside, for short or long periods, of town-dwellers on holiday, campers or groups of workers, frequently brings certain disadvantages in its train. Gypsies and tramps may also endanger the health of the village.

Co-ordination.

In a word, the principal aim of medico-social policy should be the co-ordination of activities and institutions. Such organisations, which are the product of the creative effort of their founders, bear in their aims and origins the stamp of an individuality which should

be respected ; but they may be prevailed upon to take their due place in a co-ordinated campaign, conducted in accordance with a well-thought-out plan which is adapted to local conditions and requirements.

To that co-ordination in the field (or, so to speak, in space) must be added co-ordination in time—*i.e.*, the organisation of the various medico-social activities in such a manner as to provide for the continuous and efficient protection of human beings at all ages, and against any danger that may threaten.

Herein lie both the main difficulty and the essential condition for success ; all institutions for treatment or prevention, and the whole hierarchy of health services, must be dovetailed and inter-linked so as to constitute a coherent whole working towards the same objective. To fit together these many component parts requires a considerable effort of organisation and co-ordination ; but it alone can lead to the desired result.

IV. THE FUNCTION OF SOCIAL INSURANCE INSTITUTIONS

Collective Organisation of Medical Care.

A system providing efficient medical care for rural populations calls for measures of collective organisation making available all the facilities of modern medical science for the maintenance of health and the detection and treatment of disease in its earliest stages.

Compared with other methods of collective organisation (such, for instance, as the system under which individuals pay subscriptions for medical attendance, and that of individual medical assistance entrusted to practitioners appointed by public or autonomous authorities, whether or not accompanied by financial participation by the patients), social sickness insurance has the two-fold advantage of associating those concerned more closely with the preservation of their own health, both in a financial sense and generally, by making them conscious of its importance, whilst at the same time making them appreciate more fully the importance of a rational health and welfare organisation. A sickness insurance scheme—whether compulsory, or voluntary but recognised and subsidised by public

authority—which is planned to cover all agricultural labourers and their families, and, as far as possible, the independent farmer, will help powerfully to provide efficient individual medical care.

Medical Care as the Chief Function of the Sickness Insurance Medical Services.

The difficulties of organisation, which formerly arose owing to the wide dispersion of agricultural populations, now no longer impede the extension of sickness insurance to rural areas. It is desirable that agricultural workers should have the benefit of all the medical care afforded by sickness insurance schemes, in so far as this is not already provided by some public medical service open to the whole rural community. The same facilities should also be extended to the members of the insured person's, family, and, in the first place, to the wife or husband and to their children until they reach adult life.

The medical services attached to the insurance system should offer patients, and make available to their doctors, every facility for effecting an early and complete diagnosis in the light of the social and occupational circumstances of each individual.

Insured persons and members of their families should be entitled, free of charge : to the services of a duly qualified general practitioner ; to drugs and other therapeutic requisites of adequate quality in sufficient quantities ; to any necessary surgical procedures and the services of specialists ; to attendance in childbirth ; to preventive and remedial dental treatment ; and to treatment and maintenance as in-patients in a suitable institution, where the type of ailment, or the family or living conditions of the patient, make this necessary.

While taking every care, in view of the limited resources at its disposal, to practise reasonable economy, and while avoiding in all cases useless or superfluous prescription or treatment, the sickness insurance medical service should collaborate in establishing an efficient organisation for medical care in rural areas. It should provide facilities for the better geographical distribution of doctors ; for the transport of insured persons or, where required, of the practitioners and auxiliary staff ; for diagnosis and the treatment provided under the insurance scheme ; and for up-to-date hospital treatment through the participation of the insurance funds in

defraying the expenses incurred and through suitable contributions towards the development and improvement of hospital equipment and health equipment generally.

Participation of Insurance Funds in Social Disease Control.

In the interests of the group of persons in its care, the insurance system should help in the campaign against social diseases ; for these, while specially prevalent in rural areas, cannot be controlled or prevented by medical treatment alone, but call for systematic preventive measures coupled with cheap but efficient medical treatment and social action.

Action by the insurance funds in the campaign against social disease is the more necessary the less developed are the other agencies engaged in this work. It should be such as to secure for the beneficiaries of the insurance system an improvement and extension of preventive and curative treatment, unless such treatment is already available to all concerned through the operation of a public medical service.

Success will depend, in the first place, upon systematic efforts to detect cases of disease and upon early diagnosis. The task devolving upon insurance funds is to help in the work of detection and to facilitate the precautionary examination of persons exposed to or suspected of infection, and the periodical examination of any sections of the community which are specially exposed to risk. The insured person's right to consult a doctor at any moment will conduce to early diagnosis.

Insurance funds should also co-operate in organising therapeutic measures, consisting of treatment and general or special medical care supplemented by economic and social assistance and after-care and supervision. Benefits in cash are also a considerable factor in the struggle against social diseases, when they enable the standard of nutrition and housing to be maintained or improved. Other benefits, particularly those provided by the social assistance service, may prove essential to successful treatment—*e.g.*, supervision of the due observance of the attending physician's instructions, education of the patient and those living in association with him, and such forms of occupational assistance as special facilities in cases of change of occupation and re-adaptation to social life and work.

Co-operation between insurance funds and other agencies or institutions engaged in combating social disease, as also with the medical profession, must necessarily proceed on the basis of a pre-arranged joint programme designed to co-ordinate the work of all participants, fill any gaps and eliminate duplication. Such a scheme can be based either on a system of sharing out the work among the various agencies, or on team work by all concerned ; in the latter case, its execution can be entrusted either to a body created *ad hoc*, or to some existing agency which is particularly qualified to carry out one particular part of it.

Participation of Insurance Funds in the General Preventive Action.

Insurance funds can make a substantial, though indirect, contribution to the development of preventive and curative institutions by providing facilities enabling such establishments to be patronised by insured persons. They may even participate directly in the improvement and extension of these institutions, provided they are assured that their standard of efficiency is adequate and that they really will be thrown open to the members of the funds.

Insurance funds should assist in spreading hygienic habits among insured persons and their families (personal hygiene, diet, etc.).

Finally, insurance institutions can contribute to the local improvement of public health by encouraging the construction of healthy dwellings through the grant of mortgage loans and building advances. Further, by investing capital in undertakings of social and economic value, they can strengthen rural economy and promote rural sanitation (extension of means of communication, water-supplies, etc.).

V. NUTRITION

The aim of modern public health work is not merely to prevent disease but also to improve the standard of physical and mental fitness and the well-being of the population. Among the many factors upon which an influence must be exerted to that end, diet stands in the forefront.

Public health departments have accordingly called in specialists, set up national committees to work in conjunction with the various

League organs, and drawn up programmes designed to implement national nutrition policies. Apart from its health aspect, the problem involves economic, agricultural, social and educational considerations. Health services must therefore collaborate with every organisation whose activities are concerned with these various matters.

Their first action should be to carry out surveys. It has already been shown by their means that even where the diet of peasant families is quantitatively adequate (*i.e.*, calories), it generally shows great qualitative deficiencies (protein, vitamins and mineral salts). Rural populations do not by any means consume as much of their own produce—milk, butter, eggs, meat, vegetables and fruit—as could be desirable. Pregnant women, nursing mothers and children frequently suffer from a definite deficiency of these essential nutrients.

Not only the selection of foods, but also the method of preparing them, are based on traditions at variance with the teachings of modern science. Each country should make a study of current methods of preparation in order to determine what loss in nutritive and protective foods is involved.

The fiscal and Customs systems, transport policy, and the organisation of production and distribution, also influence the diet of the population to an extent which must be borne in mind. In this branch of work, too, popular education must be resorted to. In the United States, visiting "nutritionists" or "dietitians" study the food habits of families and promote improvements by suitable propaganda. They work in close contact with the medical profession. In Czecho-Slovakia, Hungary and Yugoslavia, mobile units are now engaged in a similar task in villages, where they organise practical demonstrations for housewives. The staff of these units is specially trained. In other countries, female assistants visit country housewives for purposes of instruction. Efforts are being made to develop the domestic economy teaching in primary and secondary schools and to make it more practical.

Every endeavour should be made to provide pregnant women, nursing mothers and children of all ages with clean milk and fresh vegetables and fruit. School canteens are no less necessary in the countryside than in towns. The Health Centres will have to study this question in addition to carrying out investigations and education.

The problem of clean milk is both one of the most important and one of the most difficult to solve. While of the highest value as a food, milk may prove dangerous if it is not collected, carried and preserved with all necessary precautions. Where it is not possible to pasteurise milk efficiently, boiling is the only method which can render it completely safe.

The provision of rural slaughterhouses is much to be desired. Meanwhile, and for as long as cattle are slaughtered in the village, efficient inspection must continue.

Although information is already available concerning the nutrition of rural populations in a few European countries,¹ it will be necessary to amplify and supplement these data.

Fresh investigations were contemplated at the meetings of Directors of Schools and Institutes of Hygiene and of representatives of National Nutrition Committees.

In order to provide a uniform foundation for these investigations, the Health Organisation has prepared a detailed guide ("Guiding Principles for Studies on the Nutrition of Populations"²) for the use of health authorities. It is to be hoped that the fullest possible use will be made in rural areas of the methods there described, as they enable a comparison to be made between the actual diet of the populations concerned and the standards laid down by the Technical Commission on Nutrition of the Health Organisation;³ it will thus become possible to lay down the foundations of a rational nutrition policy for those populations.

¹ The results of the studies already undertaken have been published in the report of the Mixed Committee on Nutrition (see pages 181 *et seq.* and 273 *et seq.* of document A.13.1937.II.A.) and in the *Bulletin of the Health Organisation* (Vol. V, No. 3, pages 554 *et seq.*). Further information will be found in the documents prepared after the second meeting of Representatives of National Nutrition Committees, and in a special report prepared for the Conference on Rural Life.

² Document C.H./Com.Exp.Alim./50(2).

³ See, in this connection :

(a) Report on the Physiological Bases of Nutrition : *Bulletin of the Health Organisation*, Vol. V, Extract No. 6, September 1936 (document C.H.1197(2) ;

(b) Report of the Technical Nutrition Commission on the Work of its Third Session : *Bulletin of the Health Organisation*, Vol. VII, Extract No. 8, June 1938 ;

(c) Report of the Special Committee of the Technical Nutrition Commission on its Meeting of August 22nd-24th, 1938 (document C.H. 1355, September 1938).

VI. PHYSICAL TRAINING

Every medico-social policy should include a scheme of up-to-date physical exercises, accompanied by the appropriate medical supervision.

The object is twofold : on the one hand, the effects of occupational work and of a defective mode of living must be corrected ; on the other hand, some relaxation must be provided, a fresh interest created and the monotony of daily existence broken.

Although landworkers perform strenuous physical labour, especially at harvest-time, at other times they stand just as much in need of suitable exercise as town-dwellers.

Physical training should begin in school, and be continued through the agency of clubs and similar institutions for young people and adults.

Sports-grounds should be provided, either at the school or separate from it ; swimming exercises should be given ; and various national games, together with cycling, football and other forms of sport which are already popular in the countryside, should be facilitated. There exist certain gymnastic methods which are specially adapted to rural conditions ; they have given very satisfactory results, not only in their countries of origin, but elsewhere.

Physical training requires the assistance of a competent instructor, who may be the school-teacher himself, and the co-operation of a doctor—either a specialist in athletics, or a general practitioner who has studied the subject. Medical supervision of physical training and sports is one of the tasks for which the Health Centres should be equipped. Each individual should be examined first when he begins physical exercises or goes into training for some particular sport ; this examination should be subsequently renewed, with the object of detecting any ill effects caused by over-violent exercise or prolonged physical strain.

VII. RURAL PLANNING

The dwelling of the landworker is still, in many cases, damp, dark, inconvenient and overcrowded. This is one of the main

causes of the spread of contagious infections and social diseases, and also of the rural exodus. Such dwellings should, on the contrary, be light, comfortable, attractive and adapted to the life and work of the countryman. It should have a pure water supply and suitable arrangements for the disposal of sewage and garbage.

The improvement of agricultural conditions of life, particularly as regards rural planning, is of paramount importance to all European countries, even the most highly industrialised and advanced. That improvement should aim at providing a healthy life for the rural population, this being the essential basis of any rational public health and social welfare organisation.

Rural planning frequently forms part of a national plan entrusted to special organisations.

However that may be, one of the most important objects of medico-social policy is to set up standards for what may be termed "healthy rural dwellings and a healthy countryside". These standards should be adequate to meet the physiological requirements of those concerned in respect of space within and around the dwelling, ventilation, protection from heat, cold and damp; insolation, light, pure water,¹ and sewage and garbage disposal. Standards of this type are already in existence in some countries, while the Housing Commission of the Health Organisation has devoted much time to defining those standards in terms of climate, customs and local conditions.

The health authorities should ensure the strict enforcement of those standards in the preparation and execution of any planning scheme; that scheme should deal not only with the hygiene of dwellings and outhouses, water-supplies and sewage disposal, but should also include plans for the proper siting of new dwellings and of communal buildings, for the construction and maintenance of public highways, and for hygiene of school buildings, market premises and cemeteries. Efforts should also be made to render villages more attractive, while preserving their rustic and traditional character.

Close co-operation will be necessary between the organs participating in rural planning and the various technical groups such as

¹ In some countries especially ice-borne bacterial infections raise problems for which a solution must be found.

doctors, hygienists, agronomists, architects and various types of engineer.

For this purpose, it is essential that the public health system should have at its disposal, even in its rural outposts, a qualified staff including sanitary engineers, sanitary inspectors and housing inspectors.

An extensive propaganda campaign, in which the Health Centre and the visiting assistants can play a leading part, should be launched so as to reach every institution or body concerned, as well as the rural population itself. The various aspects of this question, which is of paramount importance, and the numerous technical problems it raises, are dealt with in a special report.

VIII. EDUCATION OF RURAL POPULATIONS IN HEALTH MATTERS

Everything that has been said above shows the fundamental importance of securing *the understanding support and help of the rural populations themselves*. Success depends on the introduction of modern ideas of health protection into every part of the landworker's existence. The circumstances of his daily life and toil, including his dwelling, equipment and the distribution of labour, should be so organised as to make the application of rules of health simple—nay, automatic ; he must be taught to lead a healthy life without thinking about it. And so agricultural communities should be taken one by one, interested, instructed and convinced. Persuasion is a slower process than compulsion ; but it alone can give lasting and positive results. *Education should pave the way for legislation and for the organisation of health in the countryside.*

The education given should be based upon general and local information. On the one hand, public opinion should be enlightened as to the needs of the agricultural population ; on the other, when action in a particular village is being initiated, general concepts should be conveyed by individualised illustrations, villagers being shown, for example, that the death of a child or of the father or mother in some particular family could have been prevented ; or again, that if, because of defective equipment or the absence of

proper precautions, milk is of doubtful purity and therefore fetches a low price, greater care would enable the producer to secure a bigger profit. In other words, each peasant must be made to realise that hygiene pays.

Once that has been achieved, we shall secure, though not without much effort and delay, the requisite degree of understanding and co-operation. We shall even obtain support for the work, either in the form of willingness to pay additional taxes, or in the form of subscriptions, gifts of fuel or food (for instance, when a crèche is being started) and personal help in the shape of labour when a dispensary is being built, a sports-ground opened, etc.

In the sphere of health, as in any other, it must be borne in upon the population that it is its duty to be active, and not merely to wait passively until public authorities improve its lot. The greater the degree of decentralisation and liberalism in the country's system of government, the more necessary this personal participation becomes. Agricultural organisations demand tariff protection, cheap credit and better means of communication from the Government ; but the peasant population must also practise self-help, understand its own particular problems, co-operate actively in their solution, thus becoming the author of its own progress.

Popular education in health can be conducted in a number of different ways : newspaper articles, posters, pamphlets, lectures, films, etc. Among the most powerful means are broadcast talks, travelling exhibitions, mobile units and theoretical and practical instruction in health subjects in schools and barracks. By way of supplement to civic, hygienic and domestic training, which should form part of all primary education, the Junior Red Cross organisations are already actively engaged in teaching school-boys and school-girls the rudiments of health and sound daily habits.

Both the central and the local health authorities should steadily pursue their efforts in this direction and supplement them by organising health campaigns and special health, child welfare, or cleanliness weeks or days, and the like.

In the villages, even more than in the towns, the cleanliness of the household and the health of the members of the family is in the hands of the housewife. It is therefore essential that she should be won over to this cause and that the necessary knowledge should be imparted to her. At the same time, the instruction of the father

of the family must not be neglected, since he can do much to help his wife in this connection. Even more important, however, is the younger generation ; education in domestic economy and hygiene, beginning at school, must be continued by the health visitors and by every available propaganda method.

IX. TRAINING OF DOCTORS AND AUXILIARY PERSONNEL IN PREVENTIVE AND SOCIAL ACTION

One lesson which emerges from the experience of every country is the *need for training the medical profession for the accomplishment of its preventive and social duties*. Doctors who have been practising for twenty years or more have in most cases only received training in the purely technical aspects of hygiene. Although, in recent years, the scope of public health instruction has in many cases been broadened, it still remains true to say that faculties and academies of medicine, the medical Press, medical associations and the profession itself still concentrate on laboratory research, refinements of diagnosis and the search for new methods of treatment. The preventive and social functions of the practitioner are no longer ignored, but little more is done than to make passing reference to them. They still do not permeate teaching in lecture-rooms and hospitals, nor do they figure prominently in university examinations, Press articles, theses, papers read to learned societies or debates in professional medical circles. At the same time, it is being gradually realised that doctors have to concern themselves not only with the fate of sick persons but also in that of the community as a whole.

Medical students must therefore be given a better understanding of their future preventive and social duties, while practitioners should be brought to realise that they represent the main line of defence of the health of the community.

The reform of medical teaching is a question ever under discussion but never settled. The syllabuses have now reached saturation point, and what is required is therefore not to add further courses of lectures but rather to imbue medical teaching with a new spirit.

In the initial stage of training, teaching in physiology should consist in the study of the normal human being as observed by the students on themselves, on school-children, infants in crèches,

etc., with all the relevant observations regarding constitution, character, predispositions, symptoms of nutritional, respiratory and circulatory deficiencies, etc.

In his lectures on pathology and therapeutics, and in the clinical courses of medicine, surgery, obstetrics, pediatrics and other special subjects, the professor will have opportunities of dealing with methods of prevention, social factors and remedies, and the social significance of diseases. This part of the training will be greatly facilitated if a social department is attached to the hospital.

Finally, lectures on hygiene should be given from a social standpoint and be accompanied by visits, demonstrations, practical exercises and courses affording grounding in preventive and social medicine, in occupational medicine and in public relief and social insurance medicine. It is recommended that an independent chair of social medicine should be founded to stimulate this development and to assist in the creation, within the faculty, of an active research and training centre.

Medical training and medical progress itself both tend towards specialisation. But it must not be forgotten that, in the countryside, even more than in towns, the chief part is still played by the general practitioner ; medical faculties must therefore concentrate their efforts on him. Special attention should be given to the adequate preparation of students in the fields of obstetrics, pediatrics, maternal and infant hygiene, current medicine and minor surgery ; students should attend out-patients' departments as well as hospital wards.

What we have said above, however, concerns future doctors only. So far as the existing practitioners are concerned, the chief means of action are Press articles and books, papers read to learned societies, congresses and refresher courses, demonstrations and practical courses. In some countries, refresher courses are now compulsory, either for the profession as a whole (in which case they consist chiefly of clinical courses), or for doctors engaged on public health work or attached to public health institutions ; in other countries, the Government or the social insurance funds compensate doctors who attend such courses. Medical associations could contribute actively by participating in this form of training and by encouraging it.

In any event, the training of doctors and students is—like the education of the public—an essential prerequisite of the development

of a medico-social policy. It is no less necessary to impart some knowledge of practical hygiene to the teaching profession, while engineers, agronomists and architects should also be given such instruction. Houses, offices and factories are still being built which violate the most fundamental canons of public health, while land improvement, levelling and irrigation schemes are still carried out in such a way that, owing to the lack of proper precautions, they promote the spread of malaria.

Finally, a system *for training public health officers and assistants should be organised.*

This question can be dealt with in a few words : the meetings of directors of schools and institutes of hygiene have already laid down the conditions under which such training must be given, and we are justified in saying that the problem has already been solved in many European countries. It must not be forgotten that, since these experts have an educational rôle to play, some notion of educational principles is just as necessary to them as their social and hygienic training.

The institutes and schools of hygiene, whose relations with health authorities on the one hand and universities on the other are dealt with in the recommendations put forward by the various meetings of directors already held, have a part to play which is steadily growing in importance and which will continue to do so.

In most European countries, they already advise the local authorities, carry out surveys and investigations, give demonstrations, undertake analyses, manufacture and distribute sera and vaccines and take charge of the treatment of rabies, carry out theoretical and practical research, and train—sometimes also find positions for—health personnel, including public health officers, health visitors and inspectors. With the latter, they keep in close contact by organising refresher and practical courses. In a word, they are at once technical bodies, research centres and training institutions, exercising an influence which extends throughout the sphere of public health policy and organisation. They contribute to the spread of the principles of prevention and social medicine among the medical profession, in administrative and governmental circles and even among the general public.

Being particularly well qualified to investigate those aspects of rural hygiene which are still obscure or controversial, they are often

called upon to take an active part in the organisation of public health in rural areas.

The permanent links created by the Health Organisation of the League of Nations between directors of schools and institutes of hygiene have powerfully aided progress in this direction ; a satisfactory medico-social policy applying to the countryside is closely bound up in with vigorous growth of their activities.

INTERNATIONAL LISTS OF CAUSES OF DEATH

adopted by the

FIFTH INTERNATIONAL CONFERENCE

FOR REVISION, PARIS, OCTOBER 3RD-7TH, 1938

HISTORICAL NOTE

In 1893, the International Institute of Statistics adopted at Chicago the Nomenclatures of Causes of Death prepared at its request by Dr. Jacques BERTILLON.

In 1898, the American Public Health Association proposed that these nomenclatures should be revised every ten years, and the following year this proposal was adopted by the International Institute of Statistics.

In conformity with this principle, the French Government convened successive Conferences for Revision at Paris in 1900, 1909, 1920, 1929 and, finally, 1938. The first three Conferences were prepared by Dr. BERTILLON himself, the founder of international medical nomenclature, but his death in 1922 made it necessary to work out a fresh procedure for the preparation of future revisions.

RÔLE OF THE HEALTH ORGANISATION OF THE LEAGUE OF NATIONS

From its earliest days, the Health Committee realised the importance of the question and took an active interest in it. In May 1922, the States Members of the League of Nations were invited, on the initiative of the Health Committee, to adopt the International Nomenclature which had just been published¹ after its third revision.

During the years that followed, groups of experts of the Health Organisation devoted themselves to the study of connected subjects :

¹ With the technical assistance of M. K. STOUMAN, of the Epidemiological Intelligence Service of the League of Nations.

the definition of a still-birth, the choice of the cause to which a death should be assigned in the statistics in the case of more than one cause being indicated on the death certificate, the age-groups in which statistics should be published, choice of a standard population for the standardisation of rates, etc.

From 1926 to 1929, the Committee of Statistical Experts of the Health Organisation carried out studies in preparation of the Fourth Revision of the International Nomenclatures, both as regards diseases and causes of death.

RÔLE OF THE JOINT COMMITTEE

In 1929, a Joint Committee was set up composed of statistical experts of the Health Organisation and of the International Institute of Statistics. As the latter had, since 1927, been making independent studies on the same questions, the Joint Committee not only avoided regrettable overlapping but was largely responsible for the success of the Fourth Conference on Revision which met in Paris in October 1929.

This Conference expressed the wish that future Decennial Conferences should also be prepared by the Joint Committee.

It was therefore this Joint Committee, reconstituted,¹ which studied the mass of documents furnished in response to the request of the

¹ The composition of the Joint Committee was as follows :

<i>International Institute of Statistics.</i>	<i>Health Organisation of the League of Nations.</i>
Dr. L. DE BERARDINIS, Head of the Demographic Statistics Division of the Central Institute of Statistics of Italy.	Mlle. J. BACKER, Chief of the Division of Demographic Statistics of the Norwegian Central Statistical Bureau.
Dr. A. BOHAČ, Vice-President of the Statistical Office of Czecho-Slovakia.	Professor HAVEN EMERSON, Chairman of the Nomenclature Committee of the American Public Health Association.
Dr. C. BRÜSCHWEILER, Director of the Swiss Federal Bureau of Statistics, assisted by Dr. ZURUKZOGLU.	Dr. M. KACPRZAK, Head of the Service of Sanitary Statistics of Poland.
Dr. F. W. BURGDÖRFER, Director of the Reich Statistical Office.	Dr. S. MANUILA,* Director of the Central Institute of Statistics of Roumania.
M. M. HUBER, Honorary Director of the French General Statistical Office.	Sir Sylvanus P. VIVIAN, Registrar-General of England and Wales, assisted by Dr. Percy Srocks.
Dr. N. M. JOSEPHUS JITTA, President of the Health Council of the Netherlands.	M. N. . . .,* of the Medical Statistics Services of the Union of Soviet Socialist Republics.

* Was unable to take part in the meeting.

French Government by the authorities of twenty-four countries, and the synthesis¹ of these documents which had been drawn up by the Committee's secretariat.

During its session from May 2nd to 5th, 1938, the Joint Committee, under the chairmanship of M. Michel HUBER, drew up draft revised Nomenclatures² which served as a basis for the work of the Fifth Conference on Revision.

FIFTH INTERNATIONAL CONFERENCE FOR THE REVISION OF THE NOMENCLATURES

The Conference, convened by the French Government, met at the Ministry for Foreign Affairs in Paris from October 3rd to 7th, 1938; twenty-two countries and five international organisations nominated delegates.

Opened by M. Marc RUCART, Minister for Public Health, the Conference elected as :

President : Professor TIFFENEAU, Dean of the Paris Faculty of Medicine ;

Vice-Presidents : Sir Humphry ROLLESTON (England and Wales), Dr. DE BERARDINIS (Italy), Dr. BURGDÖRFER (Germany), Dr. DUNN (United States of America) and Dr. IVERSEN (Denmark) ;

Secretary-General : M. Michel HUBER (Chairman of the Joint Committee, Vice-President of the International Institute of Statistics) ;

Deputy Secretaries-General : Dr. BIRAUD, of the Secretariat of the League of Nations, and M. BUNLE, of the French General Statistical Office.

As the outcome of the Conference, a Convention was signed recommending that the Governments adopt³ the Revised International Nomenclatures of Causes of Death as from January 1st, 1940. These

¹ Documents C.H.-I.I.S./Nomencl./23 and 23a.

² Document C.H.-I.I.S./Nomencl./25.

³ According to a study by the Epidemiological Intelligence Service, published in the *Epidemiological Report* of the League of Nations, Vol. 15, No. 4-6, pages 49-70, 1936, the population of the countries using the International Nomenclatures represents 95.2% of the total population (631 millions) for which trustworthy statistics of causes of death are available, the proportion covered by the Detailed International Lists being about 72%, by the Abridged Lists 21.7% and by the Intermediate List 1.6%.

Nomenclatures are three in number : detailed (200 items), intermediate (87 items) and abridged (44 items).

A Nomenclature of Causes of Still-birth (15 items) was also drawn up.

As regards Nomenclatures of Causes of Morbidity, the Conference considered that, although they should, generally speaking, correspond with the Lists of Causes of Death, Lists of Diseases should be drawn up separately with the help of suitable experts. In this way, they might be made to meet the needs of the widely differing organisations which use them, such as social insurance institutions, hospitals, military medical services, health administrations, etc.

The Conference therefore made a special recommendation (No. 2) to the effect that the Joint Committee should study this question.

It also recommended (No. 1) that the Joint Committee should be entrusted with the preparation of the Sixth Revision of the Lists of Causes of Death, for which a Conference will be convened by the French Government in 1948.

During the next few years, studies will also be carried out on the question of the classification of joint causes of death by a special Subcommittee, for which the Vital Statistics Services of the United States Government will act as secretariat (Recommendation No. 3).

The three Lists of Causes of Death adopted do not differ greatly from their predecessors.

Apart from bringing the lists up to date in accordance with the progress of science, particularly in the chapter on contagious diseases, and making certain practical improvements suggested by experience in the chapters relating to maternity and to accidents, the Conference endeavoured to make no changes in the contents, number and even the numbering itself of the various items, so that statistics based on the successive Lists should be as comparable as possible, and employees of the registration and statistical services of the different countries should have their habits of work changed as little as possible.

Many possible improvements in matters of form and order were abandoned in order to achieve this practical object.

A fact worthy of notice is that all the recommendations of the Conference were adopted unanimously, and that without the necessity of a single vote.

This result was obtained thanks to the spirit of conciliation and method shown by those participating in the Conference, and also to

the considerable work done in preparation for the Conference, amongst others by the national Nomenclature Committees set up for this special purpose in England and the United States.

* * *

CONVENTION

[*Translation.*]

The delegates undertake to recommend to their respective Governments the adoption of the Lists of Causes of Death and to take into consideration the recommendations annexed to the present Convention so as to ensure the uniformity and comparability of statistics of causes of death as from January 1st, 1940.

They recognise the desirability of a revision of these Lists every ten years, the next revision to take place during 1948. Unless any other arrangement is made, the French Government is invited to arrange for that purpose and on that date the meeting of a further International Commission.¹

Countries which have not taken part in the Commission¹ or which have not signed the present Convention may accede to it at their request.

IN FAITH WHEREOF the respective delegates have signed the present Convention.

DONE at Paris, October 7th, 1938.

[Here follow signatures.]

RECOMMENDATIONS

A. RECOMMENDATIONS RELATING TO THE REVISION OF THE INTERNATIONAL LISTS OF CAUSES OF DEATH AND DISEASES

1. Powers of the Joint Committee.

The Conference recommends that the Joint Committee appointed by the International Institute of Statistics and the Health Organi-

¹ This term is used traditionally in the text of decennial Conventions to designate the Revision Conferences; the latter term has been preferred elsewhere, as it corresponds more closely with actual facts and prevents possible confusion with the Joint Committee or special commissions.

sation of the League of Nations should remain in existence to prepare for the International Conference to be convened in 1948 by the French Government for the purpose of the sixth decennial revision of the International Lists of Causes of Death.

2. International Lists of Diseases.

In view of the importance of the compilation of international lists of diseases corresponding to the international lists of causes of death,

The Conference recommends that the Joint Committee appointed by the International Institute of Statistics and the Health Organisation of the League of Nations undertake, as in 1929, the preparation of international lists of diseases, in conjunction with experts and representatives of the organisations specially concerned.

Pending the compilation of international lists of diseases, the Conference recommends that the various national lists in use should, as far as possible, be brought into line with the detailed International List of Causes of Death (the numbers of the chapters, headings and sub-headings in the said List being given in brackets).

3. Death Certificate and Selection of Cause of Death where more than One Cause is given (Joint Causes).

The Conference,

Whereas, in 1929, the United States Government was good enough to undertake the study of the means of unifying the methods of selection of the main cause of death to be tabulated in those cases where two or more causes are mentioned on the death certificate,

And whereas the numerous surveys completed or in course of preparation in several countries reveal the importance of this problem, which has not yet been solved,

And whereas, according to these surveys, the international comparability of death rates from the various diseases requires, not only the solution of the problem of the selection of the main tabulated cause of death, but also the solution of a number of other questions,

(1) Warmly thanks the United States Government for the work it has accomplished or promoted in this connection ;

(2) Requests the United States Government to continue its investigations during the next ten years, in co-operation with other countries and organisations, on a slightly wider basis, and

(3) Suggests that, for these future investigations, the United States Government should set up a Sub-Committee comprising representatives of countries and organisations participating in the investigations undertaken in this connection.

B. RECOMMENDATIONS RELATING TO THE USE OF THE INTERNATIONAL LISTS AND COGNATE QUESTIONS

4. Comparability of Statistics from the Point of View of Time.

With a view to avoiding a break in the continuity of the series of death rates by causes as a result of the Decennial Revision of the Lists of Causes of Death,

The Conference recommends that deaths in 1940 should be classified in all countries by age and by cause :

- (1) According to the rules in force from 1930 to 1939 ;
- (2) According to the new rules adopted for 1940-1949.

5. Instruction of Medical Practitioners and Students in the Making-out of Death Certificates.

The Conference considers it of the utmost importance that serious efforts should be made in every country to give medical practitioners and students special instruction in the principles on which death certificates should be made out.

6. Age Groups.

The Conference recommends that statistics of causes of death should in every case be compiled separately by sexes and for the following age groups :

Under one month, one month to under 1 year, 1 year to under 5 years and so on, by five-year groups, up to 80 years, 80 years and over.

In countries where it is not possible to adopt such a detailed tabulation, the adoption of ten-year groups is recommended :

Under 1 year, 1 year to under 5 years, 5 years to under 15 years and so on, by ten-year groups up to 75 years, 75 years and over.

The Conference recommends that, in the special tables relating to infantile mortality, the first year of life should be sub-divided as follows :

Twenty-four hour periods during the first week ; second week ; third week ; from three weeks to one month ; second month ; third month ; by months from four to six months ; seventh to ninth month ; tenth to twelfth month.

7. Deaths by Occupation.

The Conference recommends that mortality statistics should be compiled by occupation and age groups for the principal causes.

8. Certificates relating to Still-births.

The Conference recommends that countries utilising certificates of still-births insert the following questions in the certificates :

Did death occur before birth ?
Did death occur during birth ?

9. Ratification of the Protocol.

The Conference recommends to those Governments which are parties to the Arrangement¹ signed in London on June 19th, 1934, the ratification, as soon as possible, and in any case before

¹ The Governments adhering to this Arrangement undertook to adopt as a minimum a list chosen by them as basic list from among the International Nomenclatures drawn up by the Decennial Conferences for Revision.

Although the Intermediate List was chosen in 1934 as the basic list, it should be remarked that most of the countries adhering to the Arrangement have not limited themselves to this minimum and have in fact used the Detailed List.

January 1st, 1939, of the Protocol¹ signed in Paris on October 6th, 1938.

The Conference points out that ratification by four-fifths of the participants is necessary to enable the new Intermediate List of 1938 to be utilised as the basic list in the place of the Intermediate List of 1929 by countries which are parties to the 1934 Arrangement.

¹ This Protocol, signed on October 6th by the representatives of the Governments adhering to the London Arrangement of June 19th, 1934, designates the Revised Intermediate List as the basic list.

1. DETAILED LIST OF CAUSES OF DEATH¹ (200 items)

N.B.—Each numbered item corresponds to a compulsory division. The sub-divisions shown by the letters a, b, c, etc., are optional.

For the convenience of international comparisons, it is recommended that the tables should show the total number of deaths for each of the chapters I to XVIII. In addition, when a cause of death is spread over several compulsory divisions, it is essential to reserve a line in the tables for the total deaths from that cause—e.g., tuberculosis (all forms), Nos. 13 to 22 ; pneumonia, Nos. 107 to 109 ; homicides, Nos. 165 to 168, etc.

When a cause gives rise to no deaths or very few deaths, the corresponding line may be deleted; this will be shown by the following note at the head of the tables : “ The following headings have been omitted, no death having been recorded during the year : No. . . . , No. . . . The following headings have also been omitted, very few deaths having been recorded : No. . . . , No. . . . (state total number of deaths for each item).”

I. INFECTIVE AND PARASITIC DISEASES (1 to 44)

Diseases due to Bacteria.

1. Typhoid fever.
2. Paratyphoid fevers.

(If possible, specify the type, A, B, C, etc.)

¹ The extended list of terms to be included under or excluded from the various items, together with an index of these terms and the proceedings of the Fifth Conference on Revision, will be given in the official volume relating to the Revised International Nomenclatures which is to be published (in French only) in 1939 under the auspices of the French Government.

The Lists published here are translated from the French version adopted by the Conference, but thanks are due to the General Register Office, London, and the Bureau of the Census (Service of Vital Statistics), Washington, for their efforts at unifying the various English versions hitherto in use. The present translation of the official French version corresponds very closely to the American and British Lists, the main differences occurring in the optional sub-divisions of some items.

3. Plague.
 - a. Bubonic, septicæmic and secondary pulmonary plague (infection by fleas or other biting insects).
 - b. Primary pneumonic plague (infection through respiratory tract).
 - c. Unspecified plague.
4. Cholera.
5. Undulant fever (Brucellosis).
 - a. Infection by *Brucella melitensis* (*Melitococcus*).
 - b. Infection by *Brucella abortus* Bang.
 - c. Unspecified.
6. Cerebral-spinal meningococcal meningitis.
7. Malignant pustule and anthrax (*Bacillus anthracis*).
 - a. Malignant pustule.
 - b. Septicæmic and visceral anthrax.
 - c. Unspecified anthrax.
8. Scarlet fever.
9. Whooping-cough.
10. Diphtheria.
11. Erysipelas.¹
12. Tetanus.²
13. Tuberculosis of the respiratory system (including mediastinal glands).
 - a. With mention of occupational disease of lung.
 - b. Without mention of occupational disease of lung.
 - c. Tuberculosis of unspecified site.
14. Tuberculosis of the meninges and central nervous system.
 - a. Meninges.
 - b. Other sites.

¹ Erysipelas with no known cause or following a slight lesion or wound to be classed here. Deaths from erysipelas after a serious accident or operation to be classed under violent death or the disease which necessitated the surgical operation.

² Tetanus with no known cause or following a slight lesion or wound to be classed here. Deaths from tetanus after a serious accident or operation to be classed under violent death or the disease which necessitated the surgical operation.

15. Tuberculosis of the intestines and peritoneum (including mesenteric and retroperitoneal glands).
 - a. Intestines.
 - b. Other sites.
16. Tuberculosis of the vertebral column.
17. Tuberculosis of the bones and joints (excluding vertebral column).
 - a. Bones (except vertebral column).
 - b. Joints.
18. Tuberculosis of the skin and subcutaneous cellular tissue.
19. Tuberculosis of the lymphatic system (excluding mediastinal (13), mesenteric and retroperitoneal (15) glands).
20. Tuberculosis of the genito-urinary system.
21. Tuberculosis of other organs.
 - a. Addison's disease specified as tuberculous.
 - b. Others.
22. Disseminated tuberculosis.¹
 - a. Acute generalised miliary tuberculosis.
 - b. Chronic generalised tuberculosis.
 - c. Unspecified.
23. Leprosy.
24. Purulent infection and septicæmia (not associated with pregnancy, childbirth or the puerperium).²
 - a. Septicæmia.
 - b. Pyæmia.
 - c. Gas gangrene.
 - d. Generalised infection by *Bacillus coli*.³
25. Gonococcal infections (all sites).

¹ Tuberculosis of two or more organs is to be included here, unless one of the organs affected is the lung, in which case the death is assigned to No. 13 (Tuberculosis of the respiratory system).

² Deaths from septicæmia with no known cause or following a slight lesion or wound to be classed here. Deaths from septicæmia after a serious accident or operation to be classed under violent death or the disease which necessitated the surgical operation. Septic sore throat to be classed under No. 115b.

³ Localised infection with *B. coli* to be classed according to the organ affected.

26. Other bacterial diseases (dysentery excepted).
- a. Glanders.
 - b. Tularæmia.
 - c. Others.

Dysentery.

27. Dysentery.
- a. Bacillary dysentery.
 - b. Amœbic dysentery.
 - c. Other protozoal dysentery.
 - d. Other or unspecified forms of dysentery.

Diseases due to Protozoa.

28. Malaria.
- a. Benign tertian.
 - b. Quartan.
 - c. Tropical (malignant) tertian (including blackwater fever).
 - d. Other or unspecified malaria.
29. Other diseases due to parasitic protozoa (except spirochætes).

Diseases due to Spirochætes.

30. Syphilis.
- a. Locomotor ataxia (tabes dorsalis).
 - b. General paralysis of the insane.
 - c. Aneurysm of the aorta.
 - d. Other forms of syphilis.
 - da. Congenital syphilis.
 - db. Syphilis of nervous system (except tabes and general paralysis of the insane).
 - dc. Syphilis of the circulatory system (except aneurysm of the aorta).
 - dd. Other or unspecified forms of syphilis.

31. Relapsing fever.
 - a. Epidemic louse-borne (*Sp. obermeieri*).
 - b. Transmitted by other vectors (*Sp. duttoni*).
 - c. Unspecified.
32. Other diseases due to spirochætes.
 - a. Spirochætosis ictero-hæmorrhagica (Weil's disease).
 - b. Others.

Diseases due or attributed to Filterable Viruses.

33. Influenza.
 - a. With respiratory complications specified.
 - b. Without respiratory complications specified.
34. Smallpox.
 - a. Variola major.
 - b. Variola minor (alastrim).
 - c. Unspecified.
35. Measles.
36. Acute poliomyelitis and polioencephalitis.
37. Acute infectious encephalitis (lethargic or epidemic).
 - a. Acute lethargic (or epidemic) encephalitis.
 - b. Sequelæ of encephalitis lethargica (Parkinsonism, post-encephalitic Parkinsonian syndrome).
 - c. Unspecified encephalitis lethargica.
38. Other diseases due or attributed to viruses.
 - a. Yellow fever.
 - b. Rabies.
 - c. Herpes zoster (Zona).
 - d. German measles.
 - e. Varicella (Chicken pox).
 - f. Others.

Diseases due or attributed to Rickettsia.¹

39. Typhus and typhus-like diseases (Rickettsioses).
 - a. Louse-borne exanthematic typhus.
 - b. Typhus-like diseases transmitted by other vectors.
 - c. Other and unspecified typhus-like diseases.

¹ Trachoma is classified under No. 88 (Diseases of the organs of vision), without regard to its etiological agent.

Diseases due to Helminths.

- 40. Ankylostomiasis.
- 41. Hydatid disease.
 - a. Hydatid disease of liver.
 - b. Hydatid disease of other and unspecified organs.
- 42. Other diseases due to helminths.¹

Diseases due to Fungi.

- 43. Mycoses.

Other Infective or Parasitic Diseases.

- 44. Other infective or parasitic diseases.²
 - a. Venereal diseases (other than syphilis and gonorrhœa).
 - b. Pernicious lymphogranulomatosis (Hodgkin's disease).
 - c. Mumps.
 - d. Other infective or parasitic diseases.

II. CANCER AND OTHER TUMOURS (45 to 57)

- 45. Cancer and other malignant tumours of the buccal cavity and pharynx.
 - a. Lips.
 - b. Tongue.
 - c. Other and unspecified sites.

¹ The numbers of deaths due to the various species of helminths should be stated in a footnote to the tables.

² The numbers of deaths from the various causes should be stated in a footnote to the tables.

46. Cancer and other malignant tumours of the digestive organs and peritoneum.
 - a. Œsophagus.
 - b. Stomach and duodenum.
 - c. Intestines other than duodenum or rectum.
 - d. Rectum.
 - e. Liver and biliary passages.
 - f. Pancreas.
 - g. Peritoneum.
 - h. Other or unspecified digestive organs.
47. Cancer and other malignant tumours of the respiratory system.
 - a. Larynx and trachea.
 - b. Bronchi, lungs and pleura.
 - c. Unspecified respiratory organs.
48. Cancer and other malignant tumours of the uterus.
 - a. Cervix uteri.
 - b. Other or unspecified sites.
49. Cancer and other malignant tumours of other female genital organs.
50. Cancer and other malignant tumours of the breast.
51. Cancer and other malignant tumours of the male genital organs.
 - a. Scrotum.
 - b. Prostate.
 - c. Other or unspecified male genital organs.
52. Cancer and other malignant tumours of the male and female urinary organs.
53. Cancer and other malignant tumours of the skin (scrotum excepted—51a).
54. Cancer and other malignant tumours of the brain and other parts of the nervous system.
 - a. Glioma (not specified as benign).
 - b. Sarcoma.
 - c. Other and unspecified malignant tumours.
55. Cancer and other malignant tumours of other or unspecified organs.
 - a. Adrenal glands.

- b.* Bones.
 - c.* Thyroid gland.
 - d.* Other and unspecified organs.
56. Non-malignant tumours (including dermoid cysts).
- a.* Ovaries.
 - b.* Uterus.
 - c.* Other female genital organs.
 - d.* Brain and other parts of the nervous system.
 - e.* Other and unspecified organs.
57. Tumours of undetermined nature.
- a.* Ovaries.
 - b.* Uterus.
 - c.* Other female genital organs.
 - d.* Brain and other parts of the nervous system.
 - e.* Other and unspecified organs.

III. RHEUMATISM, DISEASES OF NUTRITION
AND OF THE ENDOCRINE GLANDS, OTHER GENERAL DISEASES
AND VITAMIN-DEFICIENCY DISEASES (58 to 71)

58. Rheumatic fever.
- a.* Acute rheumatic pericarditis.
 - b.* Acute rheumatic endocarditis.
 - c.* Acute rheumatic myocarditis.
 - d.* Other forms, including acute articular rheumatism and rheumatic pleurisy.
59. Chronic rheumatism and other rheumatic diseases.
- a.* Rheumatoid arthritis.
 - aa.* Chronic rheumatic polyarthrititis.
 - ab.* Arthritis deformans.
 - ac.* Others.
 - b.* Other forms of chronic articular rheumatism.
 - c.* Other forms of chronic rheumatism.
60. Gout.
61. Diabetes mellitus.
62. Diseases of the pituitary gland.

63. Diseases of the thyroid and parathyroid glands.
 - a. Simple goitre.
 - b. Exophthalmic goitre.
 - c. Myxœdema and cretinism.
 - d. Other diseases of the thyroid gland.
 - e. Diseases of the parathyroid glands.
64. Diseases of the thymus, including hypertrophy (status lymphaticus).
65. Diseases of the adrenal glands (not described as tuberculous).
 - a. Addison's disease, not specified as tuberculous.
 - b. Others.
66. Other general diseases.
 - a. Osteomalacia.
 - b. Other general diseases.

Vitamin-deficiency Diseases (67 to 71).

67. Scurvy.
 - a. Infantile scurvy (Barlow's disease).
 - b. Other forms.
68. Beri-beri.
69. Pellagra.
70. Rickets.
71. Other vitamin-deficiency diseases.

IV. DISEASES OF THE BLOOD AND BLOOD-FORMING ORGANS
(72 to 76)

72. Hæmorrhagic conditions.
 - a. Primary purpura.
 - b. Hæmophilia.
 - c. Other and unspecified hæmorrhagic conditions.
73. Anæmias (excluding splenic anæmia—75a).
 - a. Pernicious anæmia.
 - b. Other hyperchromic anæmias.
 - c. Hypochromic anæmias.
 - d. Other and unspecified anæmias.

- 74. Leukæmias and aleukæmias.
 - a.* Leukæmia.
 - b.* Aleukæmia.
- 75. Diseases of the spleen.
 - a.* Splenic anæmia.
 - b.* Banti's disease.
 - c.* Other diseases of the spleen.
- 76. Other diseases of the blood and blood-forming organs.
 - a.* Agranulocytosis.
 - b.* Erythrocytosis.
 - c.* Hæmoglobinæmia.
 - d.* Other diseases.

V. CHRONIC¹ POISONING AND INTOXICATION (77 to 79)

- 77. Chronic or acute alcoholism (ethylism).
 - a.* Acute alcoholism.
 - b.* Chronic alcoholism.
 - c.* Unspecified alcoholism.
- 78. Lead poisoning.
 - a.* Specified as occupational.
 - b.* Not specified as occupational.
- 79. Chronic poisoning by other mineral and organic substances.
 - a.* Occupational poisoning.
 - b.* Poisoning by narcotic² and soporific drugs.
 - ba.* Narcotics.
 - bb.* Soporifics.
 - c.* Other non-occupational poisoning.
 - d.* Unspecified poisoning.

¹ This chapter only includes chronic forms of poisoning. As an exception, acute alcoholism is also included, but all other acute poisonings are classed under accidents, suicides or homicides, as the case may be.

² Narcotics are here defined as substances which may cause addiction and which are listed in or covered by the International Conventions on Opium and Narcotic Drugs (Hague Convention of January 23rd, 1912; Geneva Conventions of February 19th, 1925, and July 13th, 1931; see League of Nations documents O.C.1(1); C.88.M.44.1925.XI and C.455.M.193.1931.XI).

Acute accidental poisoning by an overdose of a narcotic or soporific is to be classed under No. 179.

VI. DISEASES OF THE NERVOUS SYSTEM AND SENSE ORGANS
(80 to 89)

80. Encephalitis (non-epidemic).
 a. Intra-cranial abscess.
 b. Other forms.
81. Meningitis (non-meningococcal).
 a. Simple meningitis.
 b. Acute cerebro-spinal meningitis (not due to meningococcus).
82. Diseases of the medulla and spinal cord, other than locomotor ataxia (30*a*) and disseminated sclerosis (87*d*).
83. Intra-cranial lesions of vascular origin.¹
 a. Cerebral hæmorrhage (not due to injury at birth—160*a*).
 b. Cerebral embolism and thrombosis.
 c. Softening of the brain.
 d. Hemiplegia and other paralysees of unstated origin.
 e. Other intra-cranial effusions.
84. Mental disorders and deficiency (excluding general paralysis of the insane—30*b*).
 a. Mental deficiency.
 b. Schizophrenia (dementia præcox).
 c. Manic-depressive psychosis.
 d. Other mental disorders.
85. Epilepsy.²
86. Convulsions in children under 5 years of age.³
87. Other diseases of the nervous system.
 a. Chorea.
 b. Neuritis (non-rheumatic).

¹ Deaths from accidents following an attack of apoplexy are classified under No. 83.

² Deaths from accidents following epileptic fits are classified under No. 85.

³ For persons aged 5 years or over, an enquiry should be made as to the true cause of death. If no further particulars are obtainable, classify under No. 87*e*.

- c. Paralysis agitans (Parkinson's disease).¹
 - d. Disseminated sclerosis.
 - e. Others.
88. Diseases of the organs of vision (including trachoma).
89. Diseases of the ear and of the mastoid process.
- a. Otitis and other diseases of the ear, without mention of mastoid (antrum) disease.
 - b. Diseases of the mastoid process.

VII. DISEASES OF THE CIRCULATORY SYSTEM (90 to 103)

90. Pericarditis (including chronic rheumatic pericarditis).
- a. Chronic pericarditis specified as rheumatic.
 - b. Others.
91. Acute endocarditis² (excluding rheumatic endocarditis—58*b*).
- a. Acute bacterial endocarditis.
 - b. Sub-acute bacterial endocarditis.
 - c. Other forms of acute or sub-acute endocarditis (excluding arteriosclerotic endocarditis).
92. Chronic affections of the valves and endocardium.
- a. Aortic valvular disease unassociated with mitral disease.
 - b. Other specified valvular disease (including sequelæ of rheumatic fever).
 - c. Unspecified valvular lesions or endocarditis.²
93. Diseases of the myocardium, including aneurism of the heart.
- a. Acute myocarditis.
 - b. Chronic myocarditis specified as rheumatic.

¹ Excluding Parkinsonism and post-encephalitic Parkinsonian syndrome (37*b*).

² When the death of a person under 45 years of age is attributed to endocarditis with no other indication, enquiry should be made as to the nature of the disease.

- c. Myocardial degeneration, infarction and sclerosis, and other chronic myocarditis, not specified as rheumatic.
 - d. Myocarditis not specified as acute or chronic.
94. Diseases of the coronary arteries and angina pectoris.
- a. Diseases of the coronary arteries.
 - b. Angina pectoris without mention of coronary disease.
95. Other diseases of the heart.
- a. Functional heart disease without mention of organic lesion.
 - b. Heart diseases specified as rheumatic but otherwise undefined.
 - c. Other and unspecified diseases of the heart.
96. Aneurism, except of heart (93) and aorta (30).
97. Arteriosclerosis, excluding diseases of the coronary arteries (94), renal sclerosis (131*b*) and cerebral hæmorrhage (83).
98. Gangrene.
99. Other diseases of the arteries.
100. Diseases of the veins¹ (varices, hæmorrhoids, phlebitis, etc.)
- a. Varices.¹
 - b. Other diseases of the veins.
101. Diseases of the lymphatic system (lymphangitis, etc.).
102. High blood pressure (idiopathic).
103. Other diseases of the circulatory system (including hypotension).

VIII. DISEASES OF THE RESPIRATORY SYSTEM (NOT SPECIFIED AS TUBERCULOUS) (104 to 114)

104. Diseases of the nasal fossæ and annexa.
- a. Diseases of the nasal fossæ.
 - b. Others, including sinusitis (state site).

¹ See footnotes to No. 195*b*.

- 105. Diseases of the larynx.
- 106. Bronchitis.
 - a.* Acute.
 - b.* Chronic.
 - c.* Not distinguished as acute or chronic.
- 107. Broncho-pneumonia, including capillary bronchitis.
- 108. Lobar (pneumococcal) pneumonia.
- 109. Pneumonia (unspecified), including acute congestion of the lung.
- 110. Pleurisy (not specified as tuberculous).
 - a.* Empyema.
 - b.* Other or unspecified forms of pleurisy.
- 111. Congestion (chronic or unspecified), œdema, embolism, hæmorrhagic infarction and thrombosis of the lungs.
 - a.* Hæmorrhagic infarction of the lung (including pulmonary embolism).
 - b.* Acute œdema of the lung.
 - c.* Chronic or unspecified congestion of the lung.
- 112. Asthma.
- 113. Pulmonary emphysema.
- 114. Other diseases of the respiratory system (except tuberculosis—13).
 - a.* Silicosis.
 - b.* Other occupational respiratory diseases.
 - c.* Gangrene of the lung.
 - d.* Abscess of the lung.
 - e.* Other diseases of the respiratory system not specified as occupational.

IX. DISEASES OF THE DIGESTIVE SYSTEM (115 to 129)

- 115. Diseases of the buccal cavity and annexa, and of the pharynx and tonsils (including adenoid vegetations).
 - a.* Diseases of the teeth and gums.
 - b.* Septic sore throat.

- c. Other diseases of the pharynx and tonsils.
 - d. Diseases of other and unspecified sites.
- 116. Diseases of the œsophagus.
- 117. Ulcer of the stomach or duodenum.
 - a. Stomach.
 - b. Duodenum.
- 118. Other diseases of the stomach (except cancer and other malignant tumours).
- 119. Diarrhœa and enteritis (under 2 years of age).
- 120. Diarrhœa, enteritis and ulceration of the intestines (2 years of age and over).
 - a. Diarrhœa and enteritis.
 - b. Ulceration of the intestines (except duodenum).
- 121. Appendicitis.
- 122. Hernia, intestinal obstruction.
 - a. Hernia.
 - b. Intestinal obstruction.
- 123. Other diseases of the intestines (including intestinal infection by *B. coli*).
 - a. Diverticulitis.
 - b. Other diseases of the intestines.
- 124. Cirrhosis of the liver.
 - a. With mention of alcoholism.
 - b. Without mention of alcoholism.
- 125. Other diseases of the liver.
 - a. Acute yellow atrophy (not associated with pregnancy (144c) or the puerperium (148c)).
 - b. Other diseases of the liver.
- 126. Biliary calculi.
- 127. Other diseases of the gall-bladder and bile-ducts.
 - a. Cholecystitis without record of biliary calculi.
 - b. Others.
- 128. Diseases of the pancreas (other than diabetes—61).
- 129. Peritonitis without stated cause.

**X. DISEASES OF THE URINARY AND GENITAL SYSTEMS
(NOT VENEREAL, OR CONNECTED WITH PREGNANCY OR THE
PUERPERIUM) (130 to 139)**

- 130. Acute nephritis.
- 131. Chronic nephritis.
 - a.* Secondary to acute nephritis.
 - b.* Arteriosclerotic kidney.
 - c.* Chronic nephritis not otherwise specified
- 132. Nephritis not stated to be acute or chronic.
- 133. Other diseases of the kidneys and ureters (not connected with pregnancy).
 - a.* Pyelitis, pyelonephritis and pyelocystitis.
 - b.* Others.
- 134. Calculi of the urinary passages.
 - a.* Calculi of the kidneys and ureters.
 - b.* Calculi of the bladder.
 - c.* Calculi of unstated site.
- 135. Diseases of the bladder (except tumours).
 - a.* Cystitis.
 - b.* Other diseases of the bladder.
- 136. Diseases of the urethra, urinary abscess, etc.
 - a.* Stricture of the urethra.
 - b.* Others.
- 137. Diseases of the prostate.
 - a.* Hypertrophy of the prostate.
 - b.* Others.
- 138. Diseases of other male genital organs (not specified as venereal).
- 139. Diseases of the female genital organs (not specified as venereal, or connected with pregnancy or the puerperal state).
 - a.* Diseases of the ovaries, Fallopian tubes and parametria.

- b.* Diseases of the uterus.
- c.* Diseases of the breast.
- d.* Other diseases of the female genital organs.

**XI. DISEASES OF PREGNANCY,
CHILDBIRTH AND THE PUERPERAL STATE¹ (140 to 150)**

140. Post-abortive² infection.
- a.* Spontaneous, therapeutic or of unspecified origin.
 - aa.* With mention of pyelitis.
 - ab.* Without mention of pyelitis.
 - b.* Abortion induced for reasons other than therapeutic.
 - ba.* By the woman herself.
 - bb.* By other persons.
 - bc.* By persons unknown or unstated.
141. Abortion³ without mention of septic conditions.
- a.* Spontaneous, therapeutic or of unspecified origin.
 - aa.* With record of hæmorrhage, trauma or shock.
 - ab.* Without record of hæmorrhage, trauma or shock.
 - b.* Abortion induced for reasons other than therapeutic.
 - ba.* By the woman herself.
 - bb.* By other persons.
 - bc.* By persons unknown or unstated.
142. Ectopic gestation.
- a.* With mention of infection.
 - b.* With mention of hæmorrhage but not of infection.
 - c.* Other cases.

¹ The puerperal period is here defined as the period of six weeks immediately following upon the expulsion of the product of conception ; puerperal diseases are those originating in the female genital system during this period.

Delayed deaths from diseases which originated in the female genital system during pregnancy, childbirth or the puerperium as thus defined should be included in this section regardless of the interval between delivery and death.

² The word "abortion" here means the expulsion of a non-viable product of conception—*i.e.*, occurring before seven months (twenty-eight weeks) gestation.

143. Hæmorrhage of pregnancy.¹
- a.* Hæmorrhage from placenta prævia.
 - b.* Hæmorrhage from premature separation of placenta and other accidental hæmorrhage during pregnancy (except with abortion—141).
 - c.* Other and unspecified hæmorrhages of pregnancy.
144. Toxæmias of pregnancy.¹
- a.* Eclampsia of pregnancy.
 - b.* Albuminuria and nephritis of pregnancy.
 - c.* Acute yellow atrophy of liver associated with pregnancy.
 - d.* Other toxæmias of pregnancy.
145. Other diseases and accidents of pregnancy.¹
146. Hæmorrhage of childbirth and the puerperium.
- a.* Hæmorrhage from placenta prævia during childbirth.
 - b.* Hæmorrhage from premature separation of placenta during childbirth.
 - c.* Other hæmorrhages during childbirth.
 - d.* Other hæmorrhages after childbirth.
147. Infection during childbirth and the puerperium.
- a.* General or local puerperal infections (including puerperal tetanus) with mention of pyelitis.
 - b.* General or local puerperal infections (including puerperal tetanus) without mention of pyelitis.
 - c.* Puerperal thrombophlebitis.
 - d.* Puerperal embolism and sudden death.
148. Puerperal toxæmias.
- a.* Puerperal eclampsia.
 - b.* Puerperal albuminuria and nephritis.
 - c.* Acute yellow atrophy of liver (post-partum).
 - d.* Other puerperal toxæmias.
149. Other accidents of childbirth.
- a.* Laceration, rupture during parturition or other trauma of pelvic organs (without mention of hæmorrhage).
 - b.* Other accidents of childbirth.

¹ This heading is only to include deaths of women whilst still in the pregnant state (before the expulsion of the product of conception).

150. Other or unspecified diseases of childbirth and the puerperium.
- a.* Mastitis during the puerperium and lactation.
 - b.* Puerperal psychoses.
 - c.* Other and unspecified diseases.

XII. DISEASES OF THE SKIN AND CELLULAR TISSUE
(151 to 153)

151. Carbuncle, boils.
152. Cellulitis, acute abscess.
153. Other diseases of the skin and annexa, and of the cellular tissue.

XIII. DISEASES OF THE BONES AND ORGANS OF MOVEMENT
(154 to 156)

154. Osteomyelitis and periostitis.
- a.* Acute.
 - b.* Chronic.
 - c.* Unspecified.
155. Other diseases of the bones, except tuberculosis (16, 17).
156. Diseases of the joints and other organs of movement.
- a.* Diseases of the joints (except tuberculosis—17*b*, and rheumatism—58, 59).
 - b.* Diseases of other organs of movement.

XIV. CONGENITAL MALFORMATIONS (157)

157. Congenital malformations.¹
- a.* Congenital hydrocephalus.
 - b.* Spina bifida and meningocele.
 - c.* Congenital malformation of heart.
 - d.* Monstrosities.

¹ This item and those of the following chapter only apply to children born alive.

- e.* Congenital pyloric stenosis.
- f.* Cleft palate, harelip.
- g.* Imperforate anus.
- h.* Cystic disease of kidney.
- i.* Other stated congenital malformations.
 - ia.* Central nervous system.
 - ib.* Circulatory system.
 - ic.* Digestive system.
 - id.* Genito-urinary system.
 - ie.* Other sites.
- j.* Unspecified congenital malformations.

XV. DISEASES PECULIAR TO THE FIRST YEAR OF LIFE
(158 to 161)

(See other causes of infantile mortality—*e.g.*, Nos. 119, 157, etc.)

- 158. Congenital debility.¹
- 159. Premature birth (still-births² excluded).
- 160. Injury at birth (still-births² excluded).
 - a.* Intra-cranial or spinal hæmorrhage due to injury at birth.
 - aa.* With mention of operation.
 - ab.* Without mention of operation.
 - b.* Other intra-cranial or spinal injuries at birth.
 - ba.* With mention of operation.
 - bb.* Without mention of operation.
 - c.* Other birth injuries.
 - ca.* With mention of operation.
 - cb.* Without mention of operation.
- 161. Other diseases peculiar to the first year of life.
 - a.* Asphyxia during or after birth, atelectasis.
 - b.* Intoxication due to maternal toxæmia.

¹ This title only includes deaths of children born after full-time gestation. When, in addition to congenital debility, a more definite cause of death is mentioned, the death should be classified under this cause.

² Each country should state in a footnote the definition of a "still-birth" applied in its statistics. (See note to Nomenclature of Causes of Still-birth) page 986.

- c. Infections of the new-born, including non-syphilitic pemphigus.
- d. Melæna neonatorum.
- e. Other specified diseases (including gangrene or hæmorrhage of umbilicus, icterus neonatorum, acute catarrhal hepatitis).

XVI. SENILITY, OLD AGE¹ (162)

162. Senility, old age.

- a. Old age.
- b. Senility with mention of senile dementia.
- c. Senility without mention of senile dementia.

XVII. VIOLENT OR ACCIDENTAL DEATHS (163 to 198)

Suicide.

163. Suicide by poisoning.

- a. Suicide by solid or liquid toxic or corrosive substances.
 - aa. By corrosive substances.
 - ab. By analgesic and narcotic drugs.²
 - ac. By soporific drugs (not liquid anæsthetics).
 - ad. By other or unspecified solid or liquid poisons.
- b. Suicide by poisonous gas.
 - ba. By coal-gas, including other gases in domestic use.
 - bb. By motor exhaust gases.
 - bc. By other poisonous gases.

164. Other forms of suicide.

- a. Suicide by hanging or strangulation.
- b. Suicide by drowning.

¹ Enquiry to be made in all cases where the death certificate of a person aged under 65 years gives only "senility". If additional information is not available, classify under No. 200 (Cause unstated or ill-defined).

² See definition under No. 79, page 962.

- c. Suicide by fire-arms and explosives.
- d. Suicide by cutting or piercing instruments.
- e. Suicide by jumping from high places.
- f. Suicide by crushing.
 - fa. Suicide on railways.
 - fb. Other suicide by crushing.
- g. Suicide by other or unspecified means.

Homicide.

- 165. Infanticide (infants under 1 year).
- 166. Homicide by fire-arms (ages 1 year and over).
- 167. Homicide by cutting or piercing instruments (ages 1 year and over).
- 168. Homicide by other or unspecified means (ages 1 year and over).

Accidental Deaths¹

(or deaths not known to be due to suicide or homicide).

(As far as possible, deaths due to occupational accidents should be stated apart under each heading.²)

- 169. Accidents³ on railways (and on tramways circulating on special tracks not on roads or streets), including pedestrians killed by trains and victims of collisions between trains and road vehicles (motor vehicles excepted—170a).

¹ Deaths caused by erysipelas (11), tetanus (12) and septicæmia (24) following an accident are included under these diseases if the lesion or wound was slight, but under accidents if the wound was apparently serious enough to cause death. Deaths from accidents following an attack of apoplexy or an epileptic fit are included under No. 83 or No. 85 respectively.

² The following subdivisions, for example, might be used :

- (a) Occupational accidents.
- (b) Accidents at home : excluding occupational accidents occurring during paid work carried out at home (classified under (a)), but including accidents to housewives during their housework.
- (c) Accidents due to sport.
- (d) Other accidents.

³ Deaths occurring in the circumstances specified under the Nos. 169 to 176 should always be classified under these titles, whatever the cause of death, and not under the following titles. Deaths due to operations of war, however, are always to be included under Nos. 196 and 197, whatever may be the place, cause or circumstance of death, and not under the Nos. 169 to 195.

170. Automobile accidents¹ (all accidents in which motor-driven road vehicles are involved alone or in collision with trains, tramcars, other road vehicles or all other users of the road).
- a. Collisions with trains.
 - b. Collisions with trams.
 - c. Other automobile accidents.
171. Other road transport accidents,¹ excluding automobile accidents (170).
- a. Tramway accidents (on roads).
 - b. Other road transport accidents.
172. Water transport accidents,¹ including all accidents on or from vessels or boats of any description (except seaplanes), whether at sea, on inland waterways, in harbours or along the coast.
173. Air transport accidents,¹ including all accidents due to aviation.
174. Accidents¹ in mines and quarries.
175. Agricultural² and forestry accidents.¹
- a. Accidents from farm machinery and vehicles (excluding road accidents).
 - b. Injuries by animals in farming, etc.
 - ba. By venomous animals.
 - bb. By other animals.
 - c. Other agricultural and forestry accidents.
176. Accidents¹ caused by machinery, excluding accidents due to transport (169 to 173), agricultural or forestry machinery (175), or in mines or quarries (174).
177. Food poisoning.
178. Accidental absorption of poisonous gases.³
179. Other acute accidental poisoning (not by gas).³

¹ Deaths occurring in the circumstances specified under the Nos. 169 to 176 should always be classified under these titles, whatever the cause of death, and not under the following titles. Deaths due to operations of war, however, are always to be included under Nos. 196 and 197, whatever may be the place, cause or circumstance of death, and not under the Nos. 169 to 195.

² Including occupational accidents to gardeners, or in market gardening or nurseries, but excluding accidents in the course of private gardening.

³ Except accidents from transport, accidents in mines and quarries, agricultural and forestry accidents, or accidents due to machinery, classed under Nos. 169-176, and deaths from operations of war, classed under Nos. 196 and 197.

180. Conflagration.¹
181. Accidental burns (conflagration excepted).¹
182. Accidental mechanical suffocation.¹
183. Accidental drowning.¹
184. Accidental injury by fire-arms.¹
185. Accidental injury by cutting or piercing instruments.¹
186. Accidental injury by fall, crushing, landslide, etc.¹
187. Cataclysm (all deaths, whatever their cause).
188. Injury by animals.¹
189. Hunger or thirst.¹
190. Excessive cold.¹
191. Excessive heat.¹
192. Lightning.
193. Other accidents due to electric currents.¹
194. Attack by venomous animals.²
195. Other accidents.³
 - a. Vaccinia and other sequelæ of vaccination against smallpox.
 - b. Other accidents due to medical or surgical intervention.
 - ba. Anæsthetic accidents.⁴
 - bb. Other accidents.⁵
 - c. Lack of care of the new-born.
 - d. Other and unspecified accidents.

¹ Except accidents from transport, accidents in mines and quarries, agricultural and forestry accidents, or accidents due to machinery, classed under Nos. 169-176, and deaths from operations of war, classed under Nos. 196 and 197.

² Except in the course of agriculture and forestry (175ba).

³ The creation of the new subdivisions under this title does not modify the general rule according to which deaths should be classified under the disease which necessitated an operation.

⁴ This sub-title does not include deaths from anæsthesia known to have been administered in the course of medical or surgical treatment of pre-existent disease or injury, which are classed to those causes. It includes only anæsthetic accidents in experiments, in normal childbirth, in operations for sterilisation or for æsthetic purposes, or in operations whose purpose was unstated and could not be ascertained.

⁵ This sub-title includes the sequelæ of preventive inoculation (except vaccination against smallpox) or of operations for sterilisation, ritual circumcision, æsthetic operations, etc., without curative purposes. It does not include deaths from surgical or medical treatment known to have been given for the alleviation of pre-existent disease or injury, which are classed to those causes.

196. Deaths of persons in military service during operations of war.
 - a. From poison gas.
 - b. From wounds.
 - c. From other or unspecified causes.
197. Deaths of civilians due to operations of war.
 - a. From poison gas.
 - b. From wounds.
 - c. From other or unspecified causes.
198. Legal executions.

XVIII. ILL-DEFINED CAUSES OF DEATH¹ (199 and 200)

199. Sudden death.¹
200. Causes of death unstated or ill-defined.¹
 - a. Ill-defined causes.
 - b. Found dead, cause unknown.
 - c. Other deaths from unknown or unspecified causes.

¹ Enquiry to be made in all cases where the death certificate only indicates "death from natural causes".

2. INTERMEDIATE LIST OF CAUSES OF DEATH

(The numbers in brackets refer to the detailed nomenclature, giving complete details as to the contents of each item.)

I. INFECTIVE AND PARASITIC DISEASES

1. Typhoid and paratyphoid fevers (1 and 2).
2. Plague (3).
3. Scarlet fever (8).
4. Whooping-cough (9).
5. Diphtheria (10).
6. Tuberculosis of the respiratory system (13).
7. All other forms of tuberculosis (14 to 22).
8. Purulent infection and septicæmia (non-puerperal)¹ (24).
9. Dysentery (27).
10. Malaria (28).
11. Syphilis (30).
12. Influenza (33).
13. Smallpox (34).
14. Measles (35).
15. Typhus fever² (39).
16. Diseases due to helminths (40, 41, 42).
17. Other infective or parasitic diseases (4 to 7, 11, 12, 23, 25, 26, 29, 31, 32, 36, 37, 38, 43 and 44).

II. CANCER AND OTHER TUMOURS

18. Cancer and other malignant tumours of the buccal cavity and pharynx (45).
19. Cancer and other malignant tumours of the digestive organs and peritoneum (46).

¹ Not associated with pregnancy, childbirth or the puerperium.

² Including typhus-like diseases due to *Rickettsia*.

20. Cancer and other malignant tumours of the respiratory system (47).
21. Cancer and other malignant tumours of the uterus (48).
22. Cancer and other malignant tumours of the breast (50).
23. Cancer and other malignant tumours of other or unspecified organs (49, 51 to 55).
24. Non-malignant tumours or tumours of undetermined nature (56 and 57).

III. RHEUMATISM, DISEASES OF NUTRITION
AND OF THE ENDOCRINE GLANDS, OTHER GENERAL DISEASES
AND VITAMIN-DEFICIENCY DISEASES

25. Rheumatic fever (58).
26. Chronic rheumatism and gout (59, 60).
27. Diabetes mellitus (61).
28. Diseases of the thyroid and parathyroid glands (63).
29. Other general diseases (62, 64 to 66).
30. Vitamin-deficiency diseases (67 to 71).

IV. DISEASES OF THE BLOOD AND BLOOD-FORMING ORGANS

31. Pernicious and other anæmias (73).
32. Leukæmias, aleukæmias and other diseases of the blood and blood-forming organs (72, 74 to 76).

V. CHRONIC POISONING AND INTOXICATION

33. Chronic or acute alcoholism (77).
34. Other chronic poisonings (78 and 79).

VI. DISEASES OF THE NERVOUS SYSTEM AND SENSE ORGANS

35. Non-meningococcal meningitis (81).
36. Diseases of the medulla and spinal cord, other than locomotor ataxia (82).

37. Intra-cranial lesions of vascular origin (83).
38. Mental disorders and deficiency (84).
39. Epilepsy (85).
40. Other diseases of the nervous system (80, 86, 87).
41. Diseases of the eye, ear and their annexa (88, 89).

VII. DISEASES OF THE CIRCULATORY SYSTEM

42. Pericarditis (including chronic rheumatic pericarditis) (90).
43. Chronic affections of the valves and endocardium (92).
44. Diseases of the myocardium, including aneurism of the heart (93).
45. Diseases of the coronary arteries and angina pectoris (94).
46. Other diseases of the heart (91 and 95).
47. Arteriosclerosis and gangrene (97, 98).
48. Other diseases of the circulatory system (96, 99 to 103).

VIII. DISEASES OF THE RESPIRATORY SYSTEM

49. Bronchitis (106).
50. Pneumonia and broncho-pneumonia (107 to 109).
51. Pleurisy (non-tuberculous) (110).
52. Other diseases of the respiratory system, except tuberculosis (104, 105, 111 to 114).

IX. DISEASES OF THE DIGESTIVE SYSTEM

53. Ulcer of the stomach or duodenum (117).
54. Diarrhoea and enteritis (under 2 years of age) (119).
55. Diarrhoea, enteritis and ulceration of the intestines (2 years of age and over) (120).
56. Appendicitis (121).
57. Hernia, intestinal obstruction (122).
58. Cirrhosis of the liver (124).
59. Other diseases of the liver and biliary passages, including biliary calculi (125 to 127).

60. Other diseases of the digestive system (115, 116, 118, 123, 128 and 129).

**X. DISEASES OF THE URINARY AND GENITAL SYSTEMS
(NOT VENEREAL, OR CONNECTED WITH PREGNANCY
OR THE PUERPERIUM)**

61. Nephritis (130 to 132).
62. Other diseases of the kidneys and ureters (133).
63. Calculi of the urinary passages (134).
64. Diseases of the bladder, except tumours (135).
65. Diseases of the urethra, urinary abscess, etc. (136).
66. Diseases of the prostate (137).
67. Other diseases of the genital organs, not specified as venereal, or connected with pregnancy or the puerperal state (138 and 139).

**XI. DISEASES OF PREGNANCY,
CHILDBIRTH AND THE PUERPERAL STATE**

68. Diseases and accidents of pregnancy (142, 143, 144, 145).
69. Abortion without mention of septic conditions (141).
70. Post-abortive infection (140).
71. Infection during childbirth and the puerperium (147).
72. Other accidents and diseases of childbirth and the puerperium (146, 148, 149, 150).

XII. DISEASES OF THE SKIN AND CELLULAR TISSUE

73. Diseases of the skin and cellular tissue (151 to 153).

XIII. DISEASES OF THE BONES AND ORGANS OF MOVEMENT

74. Diseases of the bones and organs of movement, except tuberculosis and rheumatism (154 to 156).

XIV. CONGENITAL MALFORMATIONS

75. Congenital malformations (still-births excepted) (157).

XV. DISEASES PECULIAR TO THE FIRST YEAR OF LIFE

76. Congenital debility (158).
77. Premature birth (still-births excluded) (159).
78. Injury at birth (still-births excluded) (160).
79. Other diseases peculiar to the first year of life (161).

XVI. SENILITY, OLD AGE

80. Senility, old age (162).

XVII. VIOLENT OR ACCIDENTAL DEATHS

81. Suicide (163, 164).
82. Homicide (165 to 168).
83. Automobile accidents (all motor-driven road vehicles) (170).
84. Other violent or accidental deaths (automobile accidents excepted) (169, 171 to 195).
85. Deaths of persons in military service during—and of civilians due to—operations of war (196, 197).
86. Legal executions (198).

XVIII. ILL-DEFINED CAUSES OF DEATH

87. Causes of death unstated or ill-defined (199, 200).
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3. ABRIDGED LIST OF CAUSES OF DEATH

(The numbers in brackets refer to the detailed nomenclature, giving complete details as to the contents of each item.)

I

1. Typhoid and paratyphoid fevers (1 and 2).
2. Plague (3).
3. Scarlet fever (8).
4. Whooping-cough (9).
5. Diphtheria (10).
6. Tuberculosis of the respiratory system (13).
7. All other forms of tuberculosis (14 to 22).
8. Malaria (28).
9. Syphilis (30).
10. Influenza (33).
11. Smallpox (34).
12. Measles (35).
13. Typhus fever¹ (39).
14. Other infective or parasitic diseases (4 to 7, 11, 12, 23 to 27, 29, 31, 32, 36 to 38, 40 to 44).

II

15. Cancer and other malignant tumours (45 to 55).
16. Non-malignant tumours or tumours of undetermined nature (56 and 57).

III, IV and V

17. Chronic rheumatism and gout (59 and 60).
18. Diabetes mellitus (61).

¹ Including typhus-like diseases due to *Rickettsia*.

19. Chronic or acute alcoholism (77).
20. Vitamin-deficiency diseases, other general diseases, diseases of the blood and chronic poisonings (58, 62 to 76, 78, 79).

VI

21. Non-meningococcal (simple) meningitis and diseases of the medulla and spinal cord (81, 82).
22. Intra-cranial lesions of vascular origin (83).
23. Other diseases of the nervous system and sense organs (80, 84 to 89).

VII

24. Diseases of the heart (90 to 95).
25. Other diseases of the circulatory system (96 to 103).

VIII

26. Bronchitis (106).
27. Pneumonia and broncho-pneumonia (107 to 109).
28. Other diseases of the respiratory system (104, 105, 110 to 114).

IX

29. Diarrhoea and enteritis (119 and 120).
30. Appendicitis (121).
31. Diseases of the liver and biliary passages (124 to 127).
32. Other diseases of the digestive system (115 to 118, 122, 123, 128 and 129).

X

33. Nephritis (130 to 132).
34. Other diseases of the urinary and genital systems (133 to 139).

XI

35. Puerperal¹ infection (140 and 147).
36. Other diseases of pregnancy, childbirth and the puerperium (141 to 146, 148 to 150).

XII and XIII

37. Diseases of the skin, cellular tissue, bones and organs of movement (151 to 156).

XIV and XV

38. Congenital debility and malformations, premature birth, and diseases peculiar to the first year of life (157 to 161).

XVI

39. Senility, old age (162).

XVII

40. Suicide (163, 164).
41. Homicide (165 to 168).
42. Automobile accidents (all motor-driven road vehicles) (170).
43. Other violent or accidental deaths (suicide, homicide, and automobile accidents excepted) (169, 171 to 198).

XVIII

44. Causes of death unstated or ill-defined (199 and 200).

¹ The term "puerperal" is to be understood here in its widest sense and not in the restricted sense indicated in Chapter XI of the Detailed List of Causes of Death.

4. LIST OF CAUSES OF STILL-BIRTH¹

I. STILL-BIRTH CAUSED BY DISEASE IN OR ACCIDENT TO THE MOTHER

1. Chronic disease in the mother.
 - a. Syphilis.
 - b. Other² (tuberculosis, chronic malaria, chronic nephritis, chronic heart disease, diabetes mellitus, chronic alcoholism, chronic occupational poisoning, etc.).
2. Acute disease in or accident to the mother.
 - a. Toxæmia during pregnancy (albuminuria, eclampsia).
 - b. Other² (retroplacental hæmorrhage, detachment of normally inserted placenta, etc.).
3. Over-exertion.
 - a. As a result of overwork.
 - b. Other.
4. External violence : abdominal trauma, trauma to other parts of the body.³
5. Others.

¹ Each country should state in a footnote the definition of a "still-birth" applied in its statistics. A definition of "still-birth" for the purposes of the international comparability of statistics was drawn up in March 1924, by a Special Committee of the League of Nations Health Organisation, composed of Dr. DUDFIELD, Dr. HEDREN, Dr. Eardley HOLLAND, M. HUBER and Dr. NEY :

" . . . A dead-birth (still-birth) is the birth of a (viable) fœtus, after at least twenty-eight weeks pregnancy, in which pulmonary respiration does not occur : such a fœtus may die either : (a) before, (b) during or (c) after birth, but before it has breathed."

The adoption of this definition was recommended in 1929 by the Committee of Statistical Experts of the League of Nations, and in September 1936 by the International Institute of Statistics after further study by Dr. DE BERARDINIS.

² Each of these causes might constitute an optional sub-division.

II. ANOMALIES OF THE FÆTUS, PLACENTA OR CORD

6. Congenital malformations incompatible with life.
7. Vicious insertion of placenta.
8. Other anomalies of the placenta and cord.

III. DEATH OF THE FÆTUS BY INJURY OR OTHER CAUSES

9. Abnormal presentation of the fœtus.
10. Malformations of pelvis (contracted pelvis).
11. Prolapse of the cord.
12. Prolonged labour or uterine inertia.
13. Obstetrical operations (without indication as to the object of the operation).
 - a. Operations causing mutilation.
 - b. Other obstetrical operations.
14. Other causes¹ (malformations of the genital organs, pelvic tumours, ruptured uterus, etc.).

IV. STILL-BIRTH DUE TO OTHER CAUSES

15. Other or unspecified causes.

¹ Each of these causes might constitute an optional sub-division.

~~15. Other or unspecified causes.~~

CURATIVE MEDICINE IN RURAL AREAS¹

By

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GENERAL CONSIDERATIONS

Economic loss from sickness is a primary factor in the determination of the prosperity level of a nation ; in fact, it may be said that a nation's standard of civilisation depends in part upon the quality of medical care provided for the population. This being so, there can be no doubt that it has not yet been sufficiently developed either in quantity or in quality, even in the most prosperous and advanced countries in America. This deficiency, which is in many cases the result of an ill-balanced distribution of available resources, is reflected in an enormous amount of suffering and an unnecessarily heavy death rate and consequent economic loss which must and can be prevented. Rural populations suffer more than town-dwellers, partly no doubt because of their attitude of mind, which is compounded of apathy and indifference, deep-rooted tradition and primitive customs, and partly because of their conditions and way of life, but also in large measure because of the negligence of the public authorities. The latter are, however, beginning to recognise the necessity of providing the help required, and are now devoting much care to their needs for the sake of the whole country whose future will be imperilled if the rural population continues to live under conditions which are incompatible with a healthy and normal existence. One of the most pressing problems is that of providing them with adequate medical care. But this is one of many problems, all closely interlinked and connected with public health, economics, sociology, agriculture and education, which must

¹ It is intended to submit this report to the Intergovernmental Conference of American countries on Rural Hygiene, which will meet in Mexico in 1939.

all be solved before success can be achieved in bringing to these rural peoples the well-being and progress which are their due.

BASIS OF A PROGRAMME

In planning to provide proper medical care for rural populations, the initial difficulty encountered is the impossibility of devising a standard programme, uniform in every detail, for all countries, or even for the different parts of a single country. To be successful, a programme must be based on previous knowledge of a series of factors which may vary considerably—viz., density of population, habits and customs, educational and cultural standards, economic structure and resources, degree of development of existing health services, funds and qualified staff available for the new undertakings, and especially accurate nosographic data, which must be compiled as a preliminary to any sound organisation. In view of the usual insufficiency of such information as regards rural areas in most American countries, immediate and more strenuous efforts are needed to set up or improve bio-statistical services.

Despite these difficulties in drawing up a standard programme, there are a number of general principles which should always be observed in the organisation of a system of medical care, whether newly instituted, or old-established and in need of modernisation. In fact, whatever the system adopted, close contact will have to be established with the people to make them understand the value and importance of the proposed services, to overcome pre-conceived ideas and deep-rooted habits, and to gain the confidence and co-operation of those on whom the success of the programme prepared will finally depend. In this work of persuasion and instruction, a variety of means will have to be employed, such as the wireless, the cinema and the visiting nurse ; three others whose co-operation is indispensable are the parish priest, the schoolmaster and the housewife, on whom rests the chief burden of responsibility for home life. " No law, no effort, can help those who will not help themselves." This assistance which the rural inhabitants, and particularly those whose standard of life and education is lowest, are asked to furnish will be all the more valuable and the efforts made to improve their health will be all the more lasting, if, at the

same time, some help and concessions are offered in the spheres which most nearly concern them—viz., those of economy and agriculture.

Such co-operation always entails some financial contribution on the part of the beneficiaries towards the cost of assistance services. Whatever form it may assume, whether taxation, insurance or some other form of local subscription, it must always be paid and will increase with the expansion of the services ; this will be obvious enough once it is appreciated that the benefits accruing from them are bound to be reflected in a rise in the standard of living.

Local contributions do not, however, imply decentralised services, the advantages and disadvantages of which will doubtless be debated just as vigorously at the Mexico Conference as when the matter was raised at the Java Conference in 1937. Though decentralisation may permit of a better adaptation of the service to local requirements, and may make it easier to find persons with a first-hand knowledge of the customs and habits of the people to carry out the programme, thereby yielding certain definite advantages at less expense, on the other hand it has the drawback of greater looseness in the matter of general basic standards and principles, and of being less independent of harmful political influences, which are generally more active, more violent, and more uncompromising in municipalities ; it also has the disadvantage, in most cases, that the staff engaged is neither the most suitable nor the most capable, since it cannot be transferred or replaced with the same facility ; the results achieved are hence usually less satisfactory, and certainly less uniform. That is why, with a decentralised system, some central machinery of supervision is necessary to maintain the standard of efficiency and the uniformity called for by the general programme. Moreover, such supervision would still be required if, under some opposition regime, it were decided to introduce a gradual decentralisation. The functions of this co-ordinating body would be to remedy the defects and imperfections of local organisations and to link them up with like agencies in adjacent rural areas and neighbouring towns, and with similar services in the same region, thus avoiding duplication of effort, waste of energy and superfluous exertion ; by ensuring the proper allocation of duties, it should link the activities of the assistance services with others essential to their efficient operation.

State intervention is consequently required, either with or without the support of the Federal Government, for the successful carrying-out of the prescribed programme, if only to stimulate, to assist technically and financially, and to co-ordinate and harmonise the efforts of official organisations, the medical profession, agricultural and commercial undertakings, so-called "party" organisations, co-operative societies, private assistance associations (which, in exchange for the grants they receive, must submit to technical and administrative supervision), and either voluntary or compulsory sickness insurance funds. In providing medical care in rural districts, help may indeed be obtained from all these sources, and a preference for one or more of them must depend on circumstances.

Whereas, at the Geneva Conference, the Europeans agreed that, "when health insurance applies to the entire body of agricultural workers, it enables effective medical care to be provided in rural districts under the best condition", the North Americans, though taking different views as regards the suitability for towns and industrial areas of the two types of insurance—compulsory or voluntary—were at one in urging that rural or poverty-stricken areas "should subsidise physicians or employ salaried physicians to furnish general medical services to residents of the area"; and recommended that the other assistance services should be financed on the same basis, and that, where necessary, two or more counties should join forces for this purpose. This is the system of district organisation now being introduced into the public health services in Brazil, under the control of State Departments, which will receive from the municipalities obligatory financial contributions to a Health Fund, an institution that might with advantage be established everywhere. In any case, the tendency is towards a system of organised medicine planned on the lines adopted for public health services as a whole.

PUBLIC HEALTH AND MEDICAL CARE

One of the crucial—and possibly one of the most highly controversial points in the matter of organisation, concerns the respective merits of the unitary and dual principles—namely, whether public

health services and assistance or curative medicine services should or should not be operated by one and the same staff.

Though there are links and points of contact between the two fields—and hygienists themselves would be the first to recognise the invaluable assistance which they may obtain from medical practitioners in their work, which is sometimes conducted in the field of curative medicine—it is a truism that these two extensive branches differ in many respects, and can be more successfully developed if kept separate, and provided with a competent staff and adequate financial resources. In any case, co-operation between the two will always be necessary in order to direct them to a common end : such co-operation will be better ensured by unitary control, which will permit the gradual carrying-out of a balanced programme, and will likewise prevent over-development of one activity at the expense of the other—for it usually happens that curative medicine takes precedence over public health.

This marked disequilibrium is due to the mentality of a backward and uneducated people, and to their rulers, who do not always appreciate the value of public health work ; also, and more especially, to the small number of public health specialists and to the lack of a technical controlling and supervising body able to judge of the real requirements in these two fields of action. For though financial stringency is often put forward as an explanation of the neglected development of public health services, in many cases this has not prevented the organisation of elaborate arrangements for medical care.

A recent enquiry in the United States of America revealed that, for every 30 dollars per head spent on the prevention or cure of sickness, less than 1 dollar was allocated to public health services—65 to 80 cents in big cities, and 35 cents in country districts—whereas \$1.90 and \$2.50 per head respectively should rightly have been earmarked for health services pure and simple. Yet even though curative medicine proper absorbed such an enormous proportion of this expenditure, it was unable to turn it to the best account, or to achieve all the objects desired : that was because there was unnecessary expenditure in various directions and, what is more important, because the appropriations for rural and semi-rural areas proved insufficient for the provision of adequate medical services.

Other and even more striking examples of the same disequilibrium can be found in this continent : it is nearly always a sign of failure to appreciate the ultimate purpose of health services, the results of which are often less spectacular than those of curative medicine and are neither impressive nor indisputable until the facts have been carefully compiled and presented in statistical form.

To make the governing authorities and the people "public health conscious" is undoubtedly an essential condition for success. It is really more important than the economic factor. If the directing authorities lack the public health mentality, the funds at their disposal, however ample, will all be spent on curative medicine. Consequently, the building-up of a public health mentality is a preliminary requirement to be borne in mind when planning public health services. If the value of public health is properly appreciated, then if there is a competent staff available, the work will not suffer very much when lack of funds compels its amalgamation with curative medicine as a single administrative entity with a staff combining the two functions. The danger of such a combination is much less than would arise if, owing to a shortage of funds and personnel, public health work had to be entrusted to doctors who, having been trained more especially in curative medicine, would naturally prefer to devote their energies to this than to public health work. These considerations may be urged to justify the attitude of MOUNTIN, who takes the view that, in the United States, where public health work is organised on practical lines, there is no serious objection to the amalgamation in rural areas of the preventive and curative services. C. E. WALTER goes so far as to say that "the most important activity of the health department of the future will be in the medical care field"—in industrial medical services, for example, which have been developed to such a high pitch in that country. There is also a tendency in some States to set up public welfare departments to co-ordinate all activities for the protection of health, including medical care. Josephine ROCHE even affirms that "the health service of the future will probably be expanded to cover other fields than the control and prevention of the communicable diseases. With the co-operation of the medical profession, the control and prevention and cure of all the ills of the flesh must be the ultimate goal of the health department." In Ceylon, candidates for appointment as provincial medical officers

must possess, in addition to considerable medical experience, a diploma in public health and practical experience of public health work.

There are, however, intermediate methods of organisation between the unitary and the dual systems. One of these, that of unified administration, recently established in Brazil, is strongly to be recommended, because it ensures the co-ordination and equilibrium required for the full and harmonious development of both activities. This system may eventually develop into the dual system either wholly or in part : only in the end the unitary system may be re-established if either funds or competent personnel for the operation of the dual system cannot be found. That will often be the case with rural services.

This question deserves to be further elucidated. It is nowadays generally acknowledged that one of the best forms of public health organisation outside the big towns is that which consists in dividing up a region into sectors or districts, the areas, population, general conditions and available resources of which allow of their efficient administration. The size of such districts will thus vary and may be enlarged or reduced ; the number of townships or equivalent administrative units they comprise will likewise vary. In this way, adequate public health machinery is installed in each sector, each of the various activities being entrusted to technicians, instead of everything being left in the hands of a single public health official, as happens with the system of county health units. After choosing the strategical or busiest point for the centre of each district and installing a health unit in each one (health centre), the authorities must see that the organisation is kept as mobile as possible, so that staff can be moved all over the district as the service requires. In this way, not only the control of acute communicable diseases, but also sanitation, control of foodstuffs and other health activities, such as those connected with dispensary services (pre-natal and child hygiene, tuberculosis and venereal diseases), can cover the entire district. So far, the dual system may apply, as there may be a regional hospital in the same district centre, with a separate organisation, but closely linked with the health unit, thus approximating to Davis and Ross's scheme for a county hospital health centre. If, however, owing to lack of funds or of competent personnel, it is impossible to provide a complete staff for this health unit to deal

with public health work throughout the district, there is no reason why, at other township centres in the district, which will probably have out-patient clinics attached to the regional hospital, part of such work (at any rate the collection of statistics, epidemiological investigations, immunisation and other urgent measures) should not be carried out by the local medical assistance officer working in a two-fold capacity, partly under the supervision of the chief public health officer of the district.

But this stage cannot be reached if it is impossible, for reasons of economy, to have in the district a hospital, or at any rate an out-patient clinic, with its own doctor; and there will then be no alternative but to make the staff of the health unit responsible for medical care: it will have to practise curative medicine, but—a fundamental point—without serious interference with its specific tasks and only during fixed hours, which must not be exceeded except in very urgent cases. The principle of the interlocking of these two activities is a fundamental one, which must always be respected, and under the dual system it will be observed: it invites close collaboration between public health and medical staffs, working harmoniously together. They must convince the people that, while one service relieves them when they are attacked by disease, the other prevents the occurrence or spread of disease. That is the principle of co-ordination, a corollary to the principle of maximum efficiency, on which so much stress was laid at the European Conference on Rural Hygiene, the first of the series promoted by the Health Organisation of the League of Nations.

Another preliminary question to be decided is, which of the two services, public health or medical care, should come first in the initial programme. If health work is taken first, it will increase the efficiency of the out-patient clinics and medical assistance hospitals, thereby also prolonging the benefits of curative work; this is undoubtedly the cheapest method of improving the health of the rural population, but it is none the less certain that to their uneducated minds the benefit of being cured of illnesses will be much more obvious and striking. Large-scale preventive treatment of the population for the control of ankylostomiasis was the forerunner of permanent municipal health units in the United States and other countries in which the Rockefeller Foundation is operating. And those who have started with propaganda for public health services

in a rural area can testify to the painful position in which they were placed, on being consulted by the inhabitants, by not being able to treat their complaints. If when an infant hygiene dispensary is opened there is no corresponding children's out-patient clinic in the neighbourhood, it will be hard to persuade a mother that it is doing more good by looking after healthy infants, when it does nothing for her sick child.

HOSPITALS

Hospitals are undoubtedly the terminal agency of curative medicine services. Without hospital facilities in well-equipped buildings, there can be no proper medical assistance in rural districts.

Indeed, it would be impossible, generally speaking, to treat all patients at home, or just in out-patient clinics, even in those equipped with beds. It is not enough to diagnose a complaint, determine the method of treatment and provide proper medicines ; it is often necessary for the patient to be kept in an institution where special therapeutic and dietetic treatment can be properly given, and this is practically impossible in ill-equipped rural homes. Besides, medical care is not restricted to clinical cases, many of which it may be possible to treat at out-patient clinics, but must be prepared to deal with surgical cases, which can often be attended to only in hospitals. With reference to children's diseases in particular, Dr. Charles HENDEL SMITH, Director of the Children's Service at Bellevue Hospital, New York, recently enumerated four cases in which he considered that hospitalisation was advisable : (a) necessity for a surgical operation ; (b) necessity for special treatment, such as blood transfusion ; (c) necessity for special apparatus for difficult diagnoses ; (d) unsatisfactory home conditions—this will usually be the case in rural areas.

Hospitals are also needed for preventive medical work, although, in the light of modern knowledge, these no longer have the same importance as preventive institutions as was formerly thought. Though isolation may mean the neutralisation of a known source of infection, the cases which are known and can be isolated do not really represent more than a fraction of all the sources of infection. " As a matter of fact, the practical value of isolation varies with

each disease, depending upon the degree of its communicability, the time when it is communicable, the promptness by which it may be recognised, the modes by which it is transferred, the existence of latent infections, missed cases, carriers, susceptibility of the community, economic importance and other factors." Though its results may often prove disappointing, that is no reason for abandoning hospitalisation, which still remains one of the most useful methods of controlling communicable diseases.

The value of isolation is largely dependent on the intelligence and care with which it is practised, and it is not always hospitals that show the best results. YOUNG compared the results of hospitalisation in diphtheria—a disease requiring the most rigorous segregation—not only with isolation at home (distinguishing between cases attended by trained and cases attended by untrained nurses), but also with non-segregation. The percentages of secondary cases were, in these four sets of circumstances, 0.15, 0, 1.8 and 4.88 respectively. It will thus be seen that hospitalisation is not indispensable as a prophylactic measure.

Looking at the problem from a wider angle, it may be recalled that English experience has shown that hospitalisation of cases of communicable disease has little or no effect in preventing the spread of an epidemic. SMILLIE, emphasising the inefficacy of such measures, states plainly that, in the United States, " the result has been, and probably will continue to be, a curtailment by health departments of expenditure for extensive communicable disease hospitalisation ".

From the narrow standpoint of medical care, the advantages of hospitalisation in the case of certain contagious diseases are by no means striking. To take again the case of diphtheria, BARDACHZIE and SIKKIES pointed out in *Med. Klin.* 1934, that in a large percentage of cases hospitalisation was actually a drawback, because it favoured secondary infection. As regards measles, the experience of the William Parker Hospital led EMERSON, HAVEN and HOPPING to consider the removal of children under two, especially those with symptoms of broncho-pneumonia, as contra-indicated: even when home conditions were unfavourable, it was preferable, they said, to leave the patients there if proper nursing could be provided. In *The Lancet* of July 20th, 1933, FORBES goes even farther, and declares categorically that " it is usually best, however bad the

home conditions, and however poor the nursing, to leave even the severe measles cases at home, warm in bed with the window open". BARDACHZIE and SIKEIES also agree that, for this disease, home treatment is enough. HERMAN, too, is against hospitalisation, because of the danger of pneumococcus and streptococcus pneumonia. For scarlet fever, Marguerite WALES recently published in the *American Journal of Public Health* a comparison of results obtained in New York and Chicago, relating these to the percentage of hospitalisation, which is high in the latter and low in the former city. For the period 1928-1932, the respective fatality rates were 0.7% and 2%, while the general death rates were 1.18 and 4.46 per 100,000.

The modern tendency is thus towards a modification of the methods of control of some infectious diseases, especially of those peculiar to infancy: "More money for immunisation and less for contagious diseases hospitals should be the slogan of all progressive health departments."

But the problem cannot be approached from this angle alone, and as a means of providing medical care, hospitals remain an absolute necessity.

In the opinion of the authorities, the establishment of hospitals in rural districts attracts doctors away from the large towns and thus enables those districts to obtain the necessary medical staff. "The lack of hospitals has undoubtedly been a prominent factor in the abandonment of smaller rural communities by physicians." The same editorial in the *Journal of the American Medical Association* adds that "an increase in the number of modern hospitals, therefore, even though small, will help to bring a wider distribution of physicians".

But unless they are built on the basis of a general plan, with due regard to the requirements of the territory, or at least of the districts in which it has been decided to begin or extend public health work, the result may be productive of little good, and the money and efforts employed may be wasted, especially if no provision is made for a corresponding development of the sanitation, personal hygiene and preventive medicine services.

In deciding on a programme, though it cannot be expected to be identical for all American countries, or even for every part of the same country, the choice will generally lie between the system of

large medical centres with branch hospital and subsidiary medical stations—the system proposed for the United States by the committee which prepared the well-known work *Medical Care for American People*—and the more modest system of regional or district hospitals controlling a subsidiary network of dispensaries. Under the former system, the branch hospitals may even, as an emergency measure, be left in the hands of competent auxiliary personnel : certain countries considered it advisable to adopt this system for a time owing to the shortage of doctors and precarious economic conditions.

It came in for special mention by the Committee which drew up the preliminary report of the Intergovernmental Conference of Far Eastern Countries ; the Committee pointed out that, properly organised, this system is able to render efficient service to the population of a wide area. It has, however, certain considerable drawbacks—in particular the possible promoting of low standards of professional competence.

In establishing a network of hospitals, certain fundamental points must always be borne in mind : one of the most important is that sites must be chosen in relation to local, and particularly to economic conditions, to nosological data and communication facilities. In fact, successful hospital organisation in rural districts depends largely on transport and permanent communication (telegraph and telephone) facilities, and, of course, on a good road system. At the fourth International Hospitals Congress, DISTEL of Hamburg defined as ideal a radius of operation of from 30 to 35 kilometres, so that patients could be brought to the hospital in half an hour.

No hard and fast rule is followed in regard to the ratio of population to the number of beds required in a general hospital. Before deciding this point, the characteristics and rate of increase of the population, as well as their occupations and living conditions, etc. must be taken into account. This ratio accordingly varies from two to seven beds per thousand,¹ the smaller figure being that required in rural districts. The European Conference on Rural Hygiene (Geneva, 1931) considered that a rational organisation

¹ In Brazil, ten States have less than one bed per thousand inhabitants, eight less than two, and only three more than two (São Paulo, Rio Grande do Sul and Mato Grosso). The ratio in the Federal District is seven per thousand.

called for about two beds per thousand of the population. Though this may be taken as an acceptable standard, it will hardly be feasible in some American countries, where the population is scattered and transport facilities are few, to keep to the minimum figure of fifty beds recommended by the same Conference. The latter had in view the high maintenance costs of small hospitals : " Hospitals with thirty beds and under are the most uneconomical units to operate " (STONE, *Hospital Organisation and Management*). To come down to a minimum of thirty beds, which should be the initial provisional minimum for hospitals planned for a greater capacity, though naturally not at first built up to the maximum, means that each hospital will serve an area of at least 15,000 inhabitants, and should preferably be situated in a centre with a population of not less than 5,000.

But, in practice, these figures have to be modified, since the ratio 2 : 1,000 merely covers medical and surgical (including maternity) cases, and does not include beds required in general hospitals for acute infectious diseases, for tuberculosis, and for the accommodation, even though but temporary, of psychopathic cases.

The advisability of isolating cases of acute contagious disease and tuberculosis in general hospitals is being increasingly recognised. Even in large centres of population, where special establishments exist for such cases, the practice of accommodating them in infirmaries and special wards of general hospitals has its advocates and supporters. It is, moreover, beneficial to patients by reason of the greater facilities for diagnosis and treatment provided by general hospitals, which are usually more complete and up to date and possess specialised equipment. At the same time, it helps the personnel by training them in the practical treatment of infectious diseases and in hospital technique (an essential factor in a successful service) ; it reduces the cost of medical services ; and it enables the practice of institutional isolation to be extended, if necessary, because a patient is always less reluctant to enter a general than an isolation hospital. At the 1927 annual meeting in Cincinnati of the American Public Health Association, a special committee emphasised the advantages of this new tendency from the point of view of the public health services. Two years later, the American Hospital Association adopted a similar resolution in favour of the isolation of contagious cases in general hospitals, particularly in

centres of under 100,000 inhabitants, since these centres require less than 150 beds for this purpose, and it is uneconomical to maintain isolation hospitals with fewer (RICHARDSON). JAMES WALLACE recently stated that when the incidence of contagious disease is mild, or when it fluctuates, patients should be sent to general hospitals.

The advisability of admitting tuberculous cases to general hospitals (where there is no obstacle to a successful treatment) was emphasised by the principal United States organisation, the National Tuberculosis Association, as far back as 1924 ; attention was further drawn to it in 1933 by the Henry Phipps Institute " as a measure of sound economy in the expenditure of public funds, a protection to the home and a means of training physicians and nurses in the diagnosis and management of the disease ". The same year, the percentage of tuberculous cases among all patients in nineteen Philadelphia hospitals was only 0.8, but these cases actually represented almost 20% of the number of tuberculous kept in institutions (Dorothy WIESNER).

Again, temporary hospitalisation of psychopathic cases in general hospitals will make up for the lack of special accommodation which frequently exists, and will prevent a greater evil—the utterly inhuman practice of confining these unfortunates in prison. The establishment of psychiatric hospitals for acute cases, of settlements where occupational therapy is compulsory, and of services providing medical care outside the home, together with the development of a mental prophylaxis and social assistance service, must obviously be one of the primary aims of any good health organisation.

A third principle to be observed in establishing a hospital system in rural districts is that while hospitals may be built on simple lines they must always be well planned, provided with qualified personnel, both technical and administrative, and be properly equipped and rationally organised. STONE's dictum should be borne in mind—viz., that, in practice, small hospitals should comprise the same features as the larger ones, but reduced to their simplest terms. Certain features, such as the width of corridors, can hardly be reduced proportionately if they are to serve their true purpose : others, such as privies, baths and lavatories ; pharmacies and laboratories ; gynaecological and operating rooms, staff and service lifts, etc., could be grouped into units (STEVENS, *The American Hospital*). Other

points which should not be forgotten are the advantages of concentration, provision for future extensions and the various recommendations now being made for the comfort of patients, such as limiting the size of wards, the proper equipment of general wards and private rooms (which is not such an expensive item as might be supposed—SEtz), rest rooms and restaurants, proper lighting and ventilation, the prevention of noise and smells, suitable sanitary installations, proper central food distribution services, conveniently placed kitchens and laundries which can be cheaply fitted out with modern equipment.

Though identical in their main lines and differing but slightly in detail, these problems of organisation and administration (medical, nursing, social, dietetic, etc.) are often more complex in small than in large hospitals, because they need more elastic treatment. Limited financial resources and a smaller amount of work make it necessary for members of the staff to discharge a variety of duties (CHAPMAN, *Hospital Organisation and Operation*). The superintendent may require a wider knowledge of hospital administration problems than would be needed in large hospitals ; the pharmacist may also be in charge of the small laboratory ; the radiologist and the social worker may likewise perform other functions. The organisation of the clinical personnel, and particularly the getting together of a good specialist staff, presents similar difficulties. These will, no doubt, disappear once the idea of keeping this staff exclusively for the rural hospital has been abandoned and arrangements are made for the attendance on fixed days of specialists from some important near-by medical centre. It will, however, be still more difficult to obtain a good nursing staff, since it is understood that they are not to be saddled with other work and that the standard ratio of nurses to patients must be observed (STONE).

W. B. SELTZER recently dealt with the problem of supplies for small hospitals. He showed that the system which it was advisable to adopt did not differ fundamentally from that recommended for large hospitals : it was merely a question of quantities and greater distance from supply centres.

OUT-PATIENT CLINICS

Whatever be the planned capacity of regional hospitals, a string of outlying out-patient clinics or medical stations should be established, including, of course, the out-patient departments attached to the hospitals themselves. The site of such clinics must be determined by local conditions, as in the case of hospitals. The ratio of one doctor per 2,000 inhabitants, which was decided on as the minimum for Europe, and which should be adhered to wherever possible, should be taken as a criterion in selecting the most appropriate sites for these clinics. Their special purpose will be to provide free treatment for out-patients and to send serious cases to the hospital. That does not mean that these small organisations are to be deprived of all autonomy and responsibility, for they have to keep in close contact with the population. Such contact will naturally be better maintained by a home visiting service, if possible and practicable, and especially through the work of visiting nurses and social workers. If all these component parts are fitted smoothly together, the result will be an efficient, complete and properly supervised medical care service.

The ideal out-patient clinic should have at least one doctor, assisted by a staff of nurses and midwives and a dentist. But though such an arrangement is feasible in the United States, and might be adapted to other American countries, it will be beyond the reach of a great many. The doctor, at any rate, should not be dispensed with, but should no doctor be available, a capable nurse may be put in charge of the clinic as an emergency measure, under the direct supervision of the regional hospital doctors. Similarly, these outlying clinics should be enabled, wherever possible, to call on the services of specialists ; either patients should be sent to their consulting-rooms in the large towns or they themselves should pay a visit on fixed days to the small centres in which the clinics are established.

It may be desirable to instal a few beds in these clinics—from four to six to begin with—for hospitalisation where a patient lives a long way away or the nature of his complaint renders his removal to a more distant hospital neither necessary nor desirable. These

beds can also be used for first aid and for maternity cases which, while not requiring removal to a maternity hospital, cannot be attended at their own homes by a domiciliary obstetric service. They will also solve difficulties of hospitalisation in remote rural districts pending the adopting of the recommendation for a minimum limit to the number of beds in regional hospitals. This fact was acknowledged by the European Conference when examining the situation in certain countries such as Yugoslavia, where the system referred to was successfully adopted.

To supplement these out-patient clinics, and as a substitute for them in certain regions—like the Amazonas—with extensive waterways, a scattered population and a complete lack of means of easy communication, an itinerant medical service is required. There is no doubt that this new type of unit can be of great value if the programme of work is properly adapted to local conditions : this was the conclusion arrived at by the Preparatory Committee of the Intergovernmental Conference of Far Eastern Countries in respect of certain Asiatic regions. American experience points to the same conclusion for both medical care and public health services. A properly equipped professional staff of such mobile units could travel by motor-boat, automobile, rail or air (as already in Uruguay), not to mention the simpler modes of transport which have been, and may continue to be, employed : they would follow a fixed itinerary and could thus pay periodical visits to a great many small communities.

LABORATORY SERVICES

These itinerant units, like the fixed out-patient clinics, should be provided with laboratory services for simple examinations and analyses not requiring any special technique or complex apparatus, such as sputum, fæces, urine and blood tests. Any case needing greater professional skill or more elaborate technique should naturally be left to the regional hospitals, or even to the main centres to which they should be attached. If the staff does not include a laboratory technician, as it may well not, these tests should be carried out by the doctor or nurse or some competent local pharmacist. In any case, physicians and local services should

possess the necessary outfits for the collection and transport of specimens for outside examination, and facilities for their quick and safe carriage to these centres must obviously be at hand. "In addition to the establishment of a service of this kind, doctors must also be given the necessary information as to service technique to enable them to obtain satisfactory specimens, the circumstances in which they should employ the laboratory services, the data obtainable and what conclusions can be drawn from them. These are important points, which will enable proper use to be made of the laboratories and assist the normal development of co-operation between them and rural medical services." (PARISOT.)

There will also be plenty of opportunity to establish first-aid stations in rural population groups which have no out-patient clinic. Equipped with the necessary first-aid material and put in charge of adequately, if not elaborately, trained personnel, these stations will add another link to the chain of rural medical service.

SUPPLY OF DRUGS

A further link in the chain is the provision of adequate facilities and resources for the rapid making-up of medical prescriptions. The supply of cheap and effective remedies to patients is as important as having them medically examined. It is therefore desirable that, wherever there is, at any rate, an out-patient clinic, there should be at least one pharmacy in the vicinity in the charge of a qualified pharmacist. Where this is not a feasible, recourse must be had to unqualified dispensing chemists¹ of proven competence. This measure has been officially approved in Brazil for districts with no legally established pharmacy within a radius of twelve kilometres, if no qualified pharmacist cares to set up there. The approval of such dispensing chemists is announced on public bills together with the application for a licence to practice. Only one pharmacy of this kind may be established in each place, and it must of course be kept under strict supervision.

Supervision must also be extended to the strict licensing of medicines, with the special object of preventing the advertising of

¹ *Farmacêutico prático.*

quack remedies which is carried to extremes in rural districts. The chief aim of the service should be to provide the population with effective remedies at reasonable prices : it is surprising how much money is squandered in the United States on so-called "secret formula medicines purchased by the patient for a self-diagnosed disease or condition. The annual sales of such 'patent medicines' amount to 360 million dollars, most of which is money wasted. This is 10% of the total spent for all medical services and commodities." The report from which the above quotation is taken also states that less than a third of the total sum spent on medicines was laid out on doctors' prescriptions. It is therefore clearly necessary to reduce the prices at which medicines are supplied ; these prices will of course be higher if advertising costs and middlemen's profits have to be included. The establishment of Government-maintained organisations, undertaking not only supervision but also the preparation of many of the medicines required, as is the practice in large hospitals, is therefore a measure worthy of serious consideration. Another desirable measure would be, after deciding on a standard quality for the minimum number of medicines essential for rural medical assistance, to furnish them in certain cases to the out-patient clinics and to allow doctors, where necessary, to make up their own prescriptions, like the French *médecins pro-pharmaciens* in communes where there is no pharmacy. Supervision would be exercised over the distribution of these official standard medicines. There is plenty of evidence of the abuses which arise, if such precautions are not taken, when drug-supply stations, in the charge of ignorant people unconnected with the medical service, are set up in primitive rural districts. The supply of medicines will constitute another important function of out-patient clinics and will be one of the primary duties of their personnel. Even in these circumstances, considerable wastage can occur if the supervision is not strict enough and supplies are distributed in large quantities to patients for subsequent use.

THE MEDICAL PRACTITIONER

The pivot of the entire rural medical assistance organisation, the mainspring of its action and the real co-ordinator of its whole work,

will obviously be the medical officer. A multiplicity of problems has to be studied in connection with the selection of future medical officers, such as the ground-work and completion of their medical education which must be kept constantly up to date, methods of attracting them to, and settling them in, rural districts and inducing them to renounce the professional advantages offered by large towns, means of providing compensatory remuneration and guarantees for the security of their position. These problems raise anew the whole subject of organised medicine. In view of its undoubted success in raising the general standard of efficiency in other professions and occupations, the system of preliminary vocational aptitude tests is nowadays being applied to medicine ; Moss is one of those who advocate the selection of candidates by the most modern methods, including natural vocational guidance tests. If this method can be most suitably applied where there is a surplus of candidates in the medical schools and is one of the means employed to solve this problem, it can also be turned to account in a system of organised medicine to select the most competent practitioners for rural districts where, in addition to technical training, certain physical and psychological qualities appropriate to the surrounding conditions and the characteristics of the population among which they would have to work are required.

This is not the place for a discussion of the advantages and possibility of instituting in American countries a course of training for rural doctors of a lower standard than that prescribed for those who intend to practice in large centres. The Java Intergovernmental Conference of Far Eastern Countries, which had the question on its agenda, recorded in plain terms its view that the development of medical education should be accelerated as much as possible till it attained the modern Western standard.

In a recent and admirable report which threw considerable new light on the matter, BURNET dwelt at length on the modern tendency in medical education. " Simplification is the order of the day ; over-extensiveness is giving place to thoroughness, the quantity of the subjects taught to the quality of the knowledge acquired." What is wanted is what he rightly calls " the basic doctor", equipped with accurate and precise fundamental knowledge as a basis for specialisation after his ordinary studies are completed. Such fundamental knowledge must comprise what are commonly called

specialised clinical subjects, such as dermatology, pediatrics and psychiatrics, of which no doctor can now afford to be ignorant, especially those who intend to practise in rural districts, where problems in these subjects are continually arising. This type of medical education, which—especially the clinical part—must be essentially practical, can best be completed by a year of work in a hospital : “ Medicine must be learnt, it cannot be taught ”, said FLEXNER, one of the pioneers of modern medical training. Another important point to remember is that the spirit of preventive medicine should permeate the whole programme of medical studies and be emphasised by clinical professors themselves (GORTER). On this point, all modern opinion agrees with George NEWMAN, who distinguishes, apart from preventive medicine for groups, preventive medicine for individuals, which is a function of the clinical doctor. Doctors serve society and society now demands not only that it be cured of infectious, parasitic, constitutional and hereditary diseases, but that they be prevented or at least diagnosed and treated at an early stage.

With this permeation of medical studies by the spirit of preventive medicine—which will, moreover, continue to be taught by a special professor, either as a separate subject or jointly with hygiene, possibly in two stages, as in Canada—clinical medicine and public health work will be drawn closer together, as they need to be, for the benefit of doctor and public health officer alike. Thus, the still frequently subsisting antagonism between these two branches will disappear. The more advanced countries are endeavouring to eliminate it by ensuring their co-operation and mutual assistance in work in which they do not clash but are mutually complementary. “ Since neither fully succeeds alone, each must continue to supplement the other. Each in its own field has made enormous advances, each from its own angle. Co-operation is increasing as each—medicine and public health—understands the other’s problem better ” (H. W. HILL). The tale of American achievement would not be complete without a reference to what is both preached and practised in the United States. The Committee which compiled *Medical Care for the American People* emphasised in its conclusions that this principle involves a new orientation of the medical curriculum : “ Preventive service to patients and instruction and guidance in the basic principles of personal hygiene should form an increasing

part of the work of the individual physician, whether in his office, in the patient's home or in the hospital". On the other hand, outstanding public health specialists like VAUGHAN, of Detroit, are inclined to maintain that certain functions of the public health services should be transferred to the private physicians, and this theory has been put into practice, notably in the campaign against diphtheria and smallpox and by the institution of periodical health examinations. A proper co-ordination of services is thus shown to constitute "probably the ideal method for securing a co-operative effort leading to the control of a specific infectious disease" (FISHBEIN). "As regards rural districts, experiments made in the State of Michigan and elsewhere have met with equal success" (DARLING).

If a fundamental purpose of medical education is to train the doctor for practice in rural districts, in which he may, no doubt, get valuable help from the specialists attached to the departmental hospital or the nearest large centre, it is none the less necessary that he should be able to refresh his knowledge and keep it up to date. Every kind of facility should be afforded him for this purpose, from wireless lectures to "refresher courses" (*Fortbildung*) and special schools—post-graduate schools—which should be set up in large centres, and which, indeed, in some countries, are compulsory. To enable doctors to follow these courses, a system of periodical holidays is sometimes instituted like those arranged in Italy for the *medici condotti*, whose positions are kept open and temporarily filled by newly qualified doctors employed, as in Germany, as *locum-tenens*; study-grants are also given. All these advantages are more easily procurable under an organised medical system.

Under this system, too, it will be easier to induce doctors to settle in rural districts, a difficult but highly desirable proceeding. There is, in every country, clear evidence of an unequal distribution of doctors, who generally concentrate in the large centres, whereas an even ratio of one per 2,000 inhabitants is required. In France, ROUSSY showed that there were still population groups with no doctor. In Hungary, BURNET pointed out that 2,542 out of 3,409 communes had none, and, in the United States, where approximately 50% of the population live in places with under 5,000 inhabitants, less than 20% of the new graduates settle in these areas. Yaking only a few States of Brazil, it has been ascertained that in the

Amazonas (extreme north), out of twenty-seven municipal districts in the interior, twenty-five (92.5%) have no doctors in their respective chief towns. In Pernambuco (north-east), there is none in seventeen (20%) of the eighty-three municipal districts, but, in Minas Geraes (centre), only five (2.5%) of the 216 municipal districts are without doctors. In the south, of the 258 municipal districts in São Paulo, forty-one (15%) have not a single doctor, but in Rio Grande do Sul (extreme south), where the situation is much better, only one of the eighty-six districts is without a doctor. In these last four States, which are among the largest in Brazil, there is one doctor for every 5,400, 4,600, 5,750 and 3,400 inhabitants respectively.

Considerable facilities should be afforded to doctors wishing to practise in rural districts. Preference in public appointments, total or partial exemption from the payment of school fees to those who undertake to set up outside the towns, as well as local housing, installation and transport facilities should all be guaranteed by the administrations. This is a natural step in the organisation by the public authorities of a rural medical service, which, of all the constituent parts of the system of organised medicine, seems most fully to meet the real needs of many American countries. The doctor thereby becomes a Government servant and receives an adequate salary for attending the poor—underpayment means bad work and poor results—and his emoluments may be increased by private practice, by increments for length of service and by promotion in due course to the rank of official medical officer, a position already recognised in Brazil. The medical officer should be safeguarded from the effects of political changes, which can best be ensured by State participation in the organisation of the medical service, though local co-operation, and particularly local facilities, will still be indispensable to his establishment.

Organised medicine assumes a variety of forms : State medical services, voluntary or compulsory health insurance and medical services organised by agricultural or commercial enterprises, provident and mutual benefit or co-operative societies. Sometimes workers themselves are responsible for the institution of these services, for which there is no standard type for all countries. But whether imposed by circumstances or whether, as many think, it is the easiest and best way to a complete medical service covering

all the various branches, the fact is that organised medicine is gradually spreading and is undoubtedly the system best adapted to poor countries and to most rural districts.

AUXILIARY PERSONNEL

The problems arising in connection with the auxiliary personnel are the same as those raised by the provision of doctors. The efficiency of the service largely depends on the care with which these assistants are selected and on their proper distribution. It is they who are brought into the closest contact with the rural inhabitants, and this fact explains why the success of both public health and curative medical work is largely dependent on their training. First nurses, then attendants who assist both nurses and doctors in hospitals and out-patient clinics, and lastly midwives, are, in the matter of organised medical care, the three most important categories of medical assistants. Actually there are others, such as laboratory technicians or assistants, dentist and even medical students. It is a good plan to attach students coming from rural districts to the organised curative medicine services for a few months during the vacation. This will give them an opportunity to work together and try their skill amid professional surroundings in the type of community from which they come and in which they may later follow their professional careers as doctors. A scheme of this kind will facilitate their future settlement in rural districts.

In organising medical services, more attention should be paid to nurses than to any other group of assistants.

A good and well-trained nursing staff is an indispensable requirement of both public health and curative medicine to-day. Many important health problems, particularly those involving a change in personal habits, can only be satisfactorily solved with the help of nurses. Education in health matters is what is chiefly required, and for work of this kind the persuasive and insistent action of a capable woman is the best instrument to employ. Consequently, of the \$2, or its equivalent in other currencies, which represents the annual *per caput* expenditure advocated nowadays for public health services, half should be allocated to the nursing staff.

The part nurses play in assisting the medical practitioner is no less prominent ; on that point, the authorities are unanimous. To cite only one of the greatest, the famous surgeon BILLROTH has affirmed that a surgeon's reputation depends half on his own technical skill and half on the scrupulous attention to detail of the nurse in the operating-room. Without her willing and skilful assistance, he says, the surgeon's professional career would be represented, not by a series of brilliant successes, but by a huge cemetery.

And now, what of the nurse's work in rural districts ? The prevailing shortage of doctors may necessitate the most competent nurses' taking over for a while a large part of the work, and possibly even the management, of out-patient clinics. It must be fully understood that this can be no more than an emergency measure, for it is a dangerous practice to entrust medical work to auxiliary personnel and it inevitably leads, among other things, to a deterioration of the service. On this account, it is strictly prohibited in European and American countries possessing well-organised medical services.

Even with this qualification, it is no exaggeration to say that, at the present day, the technical training of a good nursing staff must, in view of the responsibilities of the work, be a primary consideration in the organisation of public health and medical assistance services. This training should be in accordance with modern principles : " increasing emphasis is being placed in the curriculum on the social and health aspects of nursing as an inherent part of the preparation of all nurses, whether they enter the field of private duty, institutional nursing or public health " (Report of the Sub-Committee on the Educational Qualifications of Public Health Nurses of the Committee on Professional Education of the A.P.H.A., *Year-Book 1936/37*). In addition, candidates for the nursing profession should be carefully selected, and required to undergo vocational aptitude tests.

If the number of nurses is fixed at at least one for every so many of the rural population as have one doctor allotted to them, such a standard will prove impossible of immediate attainment, and this for two reasons. The first is that, in many American countries, the training of nurses has not expanded at the same rate as the training of doctors. The second is that, like doctors, nurses who

train and qualify at the best training schools are attracted to the large centres. Brazilian experience on this point is striking. It is very rarely that a girl from the country returns there after attending such a school and gaining her diploma.

For this reason, and also because they will always be required in medical assistance services, a body of attendants, or nurses' assistants, should be recruited and trained : in some countries, they will constitute the bulk of the hospital and dispensary personnel for some time to come.

A similar system—namely, that of public health visitors—has been instituted in Brazil to stimulate the work of the public health services. The introduction of this emergency measure was made possible by selecting a small group of teachers and other persons of the same cultural level. This corps of public health visitors was able to enter on its duties almost immediately, under the direction of one or more trained nurses from training schools of high standing, who had been seconded by the National Health Department from their selected staffs to various State organisations. These assistants follow a rapid and simplified course of instruction, in which the medical officers co-operate ; and though the quality of their work is hardly comparable with that of public health nurses, it is nevertheless not to be despised, since, wherever these assistants have been introduced, they have given a notable stimulus to public health work. In the *Tropical Diseases Bulletin* for November 1937, COCHRANE, dealing with anti-tuberculosis work in the tropics, emphasised the fact that a high standard of training for visiting assistants was unnecessary at the outset of the campaign.

To provide for the simultaneous training of nurses and attendants, schools should be set up to give courses for both, and also for midwives (as in the Italian colonies) and health visitors, and—on the pattern of the Belo Horizonte School in Brazil—emergency courses similar to those of the Red Cross. Girls from the better classes are thus attracted to these schools, and those who take the Red Cross course will constitute a valuable nucleus for a future nursing staff. The course for attendants should be thrown open to large numbers, and especially to persons coming from rural districts ; they should be given a starting salary, and those who are most efficient a guarantee of immediate advancement. All these courses should be practical, and based on the principles of preventive

medicine : that for assistants should be simple and short, lasting only one year, as in the Belgian Congo schools.

An important question is the training of midwives in rural districts. They should be paid by the public authorities, as in many European countries (*e.g.*, Spain and Italy) ; their number should be proportionate to the population and the birth rate ; and they should be introduced gradually into rural areas to take the place of the unqualified "handy women", picturesquely termed in Brazil *matronas*, *aparadeiras* or *curiosas*. Some midwives may also be nurses, as in England, but subject in every case to the restrictions necessary to prevent this practice from becoming general ; or they may perform certain nursing duties (pre-natal or child hygiene), an accepted practice in Europe, the Far East and the French Colonies. In any case, for some time to come there will still be untrained women doing this work in rural areas. But instead of harassing them—a mistaken policy—it is better to try, as in Brazil, to educate them a little and instruct them in the elements of hygiene ; then register those who are approved, and prescribe rules and directions for their professional employment, which is possible in cases recognised as normal. The Java Conference, in its final conclusions, recommended this method as advisable for a transition period. Before long, these unqualified women will be replaced by certificated midwives, and then will be the time to attempt the gradual introduction of a domiciliary obstetric service, linked with the out-patient clinics and regional hospitals. Only cases requiring medical attention would then need to be removed from their homes. The rational establishment of such a service to meet local conditions will of course facilitate the limitation of the number of beds in the hospital maternity wards.

In the ideal programme, every curative medicine organisation should also have a social service attached to it as soon as possible, for the importance and value of such a service to modern organisations is increasingly recognised. It is not enough for a patient to receive attention from doctors and nurses, who know nothing of the conditions in which he lives or of his economic, material and moral situation, and are consequently unable to relieve that state of mental depression or moral suffering which so often obstructs a cure and undoes much of the doctor's work. The importance ascribed by modern psychologists to the effect of moral factors on

health is now acknowledged ; and it is precisely, in CABOT's phrase, the application of moral means to the cure of the sick which forms the basis of social assistance work. The methods it employs are in the last analysis designed effectively to prepare, reinforce and extend the work of the doctor and nurse. Without it, the assistance given by hospital services is one-sided and may prove quite unavailing. The social service links together in the same chain doctor, patient, family and hospital organisation. Because it enables an insight to be gained into the patient's living conditions, social and economic obstacles to be overcome, and even his whole environment to be changed and his fears and anxieties removed ; because, too, it facilitates the introduction of occupational therapy in hospitals, a valuable psychological factor in effecting a cure, the social service assists medical treatment by putting it on a surer and more solid foundation and by hastening and often completing the patient's recovery. On leaving hospital, he will be kept under constant observation by the social service, which will also greatly assist the doctor by seeing that his instructions are carried out, that the patient is living under proper conditions and that he is given suitable work. In short, by thus readjusting him to society, the social service will prevent the possible recurrence of the causes of his illness and make him a more valuable member of the community. Moreover, by thus hastening the success of medical treatment and obviating the need for patients to remain in hospital for long periods, the social service enables better use to be made of the beds available and the whole organisation to be operated more efficiently. Another advantage is that it provides a reliable means of ascertaining whether patients are in a position to pay for hospital treatment. Now there can be no doubt that the various problems which have been briefly enumerated here will be found in most rural districts, and because " the medical-social problems are the same in the small and in the large hospitals, varying only in volume and detail " (MACEachern), the ideal to aim at is the institution of the same social service in rural areas, which may, if necessary, be placed under the direction of a certificated and specially trained nurse, as is done in France, Germany, and even in the United States (MacMullen).

THE PRESENT USE OF NATURALISTIC MEASURES IN THE CONTROL OF MALARIA¹

By

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CONTENTS

	Page
I. Nature and Scope of Naturalistic Methods	1017
II. The Theory of Naturalistic Control.	1021
III. Classification of Mosquito Control Measures.	1025
IV. Naturalistic Methods in Practice :	
A. Larva Control Measures	1026
(a) Chemical Measures :	
1. The Pollution of Water	1026
2. Changing the Salt Content of Water.	1029
(b) Physical Measures :	
1. Natural Fills (Warping, Silting)	1030
2. Sluicing.	1032
3. Flooding	1033
4. Fluctuating Water-level	1034
5. Intermittent Drying	1035
6. Agitation of the Water Surface	1035
7. Stagnating and Setting Water in Motion	1036
8. Muddying	1037
9. Shading or Exposing to Sunlight.	1037
10. Drying Land by planting Trees.	1040
(c) Biological Measures :	
1. Fish and Other Natural Enemies.	1040
2. Changing the Fauna and Flora.	1043
3. Off-season Attack	1045
B. Control of the Adult Mosquito.	1045
V. General Remarks and Conclusions.	1052

¹ This enquiry was proposed by the Reporting Committee of the Malaria Commission of the League of Nations at its meeting (October 27th-30th, 1937) and authorised by the Health Committee.

I. NATURE AND SCOPE OF NATURALISTIC METHODS

The spread of malaria is principally governed in nature by two well-known characteristics of anopheles mosquitoes. In the first place, every species, in spite of tendencies to spread into unusual breeding-places, is restricted in its multiplication and distribution by an adaptation to certain types of surface water in which alone it can breed in effective numbers ; and, secondly, of the 180 odd species which may be considered potential vectors (since all that have been tested easily become laboratory hosts of the malaria parasite), the great majority are rendered comparatively harmless in nature because their biting habits do not bring them into frequent and especially repeated contact with man.

A good example of the operation of these two factors in combination to reduce transmission is found in the plain of Naples, which is naturally free from malaria, although it is adjacent to highly malarious districts to the north and to the south. Near Pompeii is a large marshy area in the delta of the River Sarno, known as the Orti di Schito, which has been converted into a patchwork of small market-gardens intersected by numerous canals. It is evident that none of the dangerous vectors of southern Europe (*atroparvus*, *elutus*, *labranchiæ*, *superpictus*) is sufficiently well adapted to these fresh and flowing waters to be able to maintain itself, while the anophelines which do breed there in conspicuous numbers (*typicus*, *bifurcatus*), do not often resort to man for their blood meals, and hence do not spread malaria. No antimalaria measures need be taken by the community, and we may refer to this as "natural" control of malaria transmission, under conditions which at first sight might seem ideal for the spread of the disease—so much so that the situation presented a difficult problem for the early Italian malariologists to explain.

In contrast to this, we have an artificially created malaria-free zone around Viareggio, the most popular of Italian beach resorts. Between Viareggio and the hills lies an extensive marsh and shallow lagoon at sea-level, the cause of much malaria in the eighteenth century. It had been observed by the end of the Middle Ages that malaria was exceptionally severe around such coastal lagoons, which

received streams from the hills, and it was held that the mixing of salt and fresh water might favour the development of the " miasma " due to emanations from organic material decomposing in stagnant water.¹

MISSIROLI (1934) has described the automatic gates invented by ZENDRINI and installed by the Republic of Lucca in 1740 in the canal at Viareggio. The gates are composed of two leaves swinging on hinges and coming together at an obtuse angle in the centre, and are functioning efficiently. They open in winter or whenever the water in the canal is higher than the sea, but close in the dry summer season when the level of the water in the marshes is low and the sea would otherwise flow in. In this way, ZENDRINI, without knowing it, completely changed the character of the larval habitat around Viareggio.

It is reasonable to suppose that brackish-water breeders such as *elutus* or *labranchiæ* were the chief vectors of malaria at that time, as they still are in the coastal zones farther south, and that the empirical measures taken were successful in eliminating them, gradually perhaps, but at small cost. Only fresh-water anophelines are found in this area to-day, " one more indication ", adds MISSIROLI, " that not the introduction of stabled animals, but the modification of the larval habitat determines the prevalence of one anopheline species over another ". However, the dominant species at present are all cattle-biters by preference, and the introduction of crop-rotation during the past century, with the consequent large production of legumes and other forage crops, has undoubtedly stimulated animal husbandry and has progressively increased the deviation of anophelines from man to his domestic animals. Thus, by deliberate intervention, man has succeeded in reproducing about Viareggio the " natural " barriers to malaria transmission found in the Orti di Schito.

We know of no better way to describe such imitations of natural processes than " naturalistic control ", a term introduced by

¹ In 1863, GIORGIONI (quoted by MISSIROLI) wrote : " Among other causes which if they cannot alone produce malaria, at least increase its malignity, is the mixing of salt and fresh waters, as BANE, LANCISI, ZENDRINI and other physicists and doctors assert. Even if the reason for such a phenomenon is unknown, it is not possible to doubt the fact when we have seen pestiferous marshes become almost innocuous as soon as the entrance of salt water into them has been stopped."

WILLIAMSON (1935). The word "biological" as applied to mosquito control is not so descriptive, nor so general, and might better be reserved for interventions designed to upset a natural balance of flora and fauna in a community or *biocenosis* (through the introduction, for example, of a natural enemy), as contrasted with purely physical or chemical changes in the conditions favouring mosquito production or activity.

The word "mesological" introduced by BERTILLON in 1883 (but never acquiring currency) "conveniently expresses the investigation of the mutual relationships existing between living beings and their surroundings" (*Oxford Dictionary*), but is unfamiliar and does not differ essentially from the usual sense in which we use the word "ecological". The latter term, however, includes the mutual relationships of organisms to each other in a collectivity and is on the whole not as pertinent as "naturalistic".

The field of application of naturalistic methods to malaria control is not limited, of course, to the mosquito. The final aim of all anti-malaria work is the interruption of malaria transmission, and we are as much interested in the natural conditions affecting the life of the parasite as in those which concern the vector. At one time, it was suggested that a chemical constituent of clover-honey known as coumarin might be toxic to the malaria parasite in the bodies of infected mosquitoes sucking this honey, and if this were true, the wide cultivation of clover would be a naturalistic method of malaria control directed against the parasite.

Ageing, temperature and various physical conditions affect the parasite in the mosquito, just as immunity and other inhibitory influences are brought to bear upon it in the human body, but no practical way has yet been found of turning these things to account in the fight against malaria. The present report will be limited, therefore, to the entomological factor, and in this field, *naturalistic methods may be defined as the deliberate extension or intensification of natural processes which tend to limit the production of mosquitoes or their contact with man.*

It has been objected that this grouping cuts across other classifications, that it serves no particularly useful purpose in doing so, and merely results in stringing together a highly diversified set of miscellaneous procedures on the bond of a somewhat artificial relationship. This Committee believes, on the contrary, that we

have never had a satisfactory classification in which all forms of mosquito control could find a logical place ; that such a classification would be extremely useful as an approach to knowledge and a basis for orderly thinking ; and that the conception of naturalistic control makes possible a comprehensive rearrangement of our ideas on this subject which seems to serve this purpose very well. Thus direct toxic and mechanical measures of destruction or defence taken against mosquitoes are properly distinguished from measures designed to bring about a change in natural conditions of a permanent or semi-permanent kind so as to create a new and relatively stable situation unfavourable to the life and activity of the malaria-carrying mosquito.

This classification serves also to focus attention on a field which has been virtually ignored by engineers and health officers, and unexplored by all but a handful of biologists.¹ This field is a most important one, since it concerns mainly those scattered rural populations of the world whose principal enemy is malaria, and on whose behalf little or nothing has yet been accomplished. The problem is to find something practicable and effective for numberless agricultural communities whose chronic state is one of poverty, ignorance and disease. For this reason, WILLIAMSON emphasises the point that in this type of work more than in any other it has been possible to utilise village labour and cheap or free material locally available—" free gifts of the countryside "—so as to reduce the cost mainly to that of administration. In the opinion of the recent Inter-Governmental Conference of Far-Eastern Countries on Rural Hygiene (L.o.N., 1937 *b*), " great hope is offered for the control of rural malaria in selected areas by these naturalistic methods which are relatively inexpensive and can suitably be carried out by the peasants themselves ".

¹ Interest is, however, increasing. The United States Public Health Reports for March 11th, 1938, in describing the dedication of the Henry R. Carter Memorial Laboratory at Savannah, Georgia, stated : " Many observations have been made which indicate the possibility of controlling malaria or preventing the production of the mosquito vector of the disease by means of some method other than mechanical. The Public Health Service therefore decided to make an intensive search for a natural or biological method of controlling production of the malaria-carrying mosquito." The staff of the laboratory includes two medical malariologists, two entomologists, a limnologist and a physicist. WILLIAMSON (1936) has rendered a service by publishing a list of references (with a running commentary) of all the important publications up to 1935 in the field of rural malaria control by naturalistic methods.

We do not overlook the fact that some of these methods may also be expensive and highly technical, and far beyond the capacity of peasants to carry out unaided; but many are economical, simple and effective, so that the term "naturalistic control" has come to have a connotation of cheapness. The results may often fall far short of perfection, but the question is only, are they worth the trouble and expense involved? It is not expected that they will replace oiling, paris-greening or drainage, screening or insecticides where these would be more effective and where the expense can be borne by Government, industry or organised agriculture. Frequent opportunity arises, however, to combine naturalistic with other methods, and there is every reason to do so, wherever it seems feasible in a given area.

II. THE THEORY OF NATURALISTIC CONTROL

Any naturalistic attack on the mosquito in its breeding-places is based on a principle of species sanitation, which is that it is not necessary to render water unfit for mosquito breeding in general, but only for the particular species proved dangerous in the actual area to be controlled. The plan goes somewhat farther than this in suggesting that, if it is impossible to do anything better, the water need not be rendered absolutely unfit for breeding purposes even for that species, but only ill-adapted to the requirements of the anopheline concerned. In short, as Sir Malcolm WATSON says, a malariologist need not necessarily suffer from hydrophobia. The conception is that at least certain species of *Anopheles* are rather more rigidly confined than we have supposed to definite types of surface water, and if these are rendered unsuitable for breeding purposes the species is not able to resort to other waters except in a sporadic way—sufficient, perhaps, to preserve the species locally from extinction. Thus when WALCH (1930) eliminated *sundaicus* from certain Javan fish-ponds, this dangerous variety was unable to maintain its previous density by breeding in other types of water accessible to it, but became greatly reduced, so that malaria transmission fell off considerably.

It is quite true that some species have a much wider range of adaptability than others, and a good example is the European *atroparvus*, which is often found breeding in what might be termed "sub-marginal" waters unsought, for one reason or another, by the other anophelines of the area. It is thus found in a great variety of situations—in fresh water and in saline, in running water and still, in rice-fields, coastal marshes, canals and drains, from Scandinavia to the heel of Italy and from Portugal to the Black Sea. The penalty which it seems to pay for its wide tolerance of chemical and physical factors in water is the disadvantage it suffers in competition with strictly fresh-water forms in their natural habitat. Thus, in the Netherlands, it seems clear that, as irrigation sweetens the land reclaimed from the sea, *atroparvus* is gradually replaced by the fresh-water breeder *messeæ*; yet *atroparvus*, at the height of its season, will spread into waters of low salinity previously occupied by *messeæ*.

On the north German coast, where marshes and canals are much less salty than in the Netherlands, *atroparvus* is found breeding in great numbers in water with relatively little salt (less than one part per thousand), and in the laboratory it shows normal growth and survival at all stages from egg to adult in fresh water, like *messeæ*. The lack of salt is therefore not an inhibiting factor, and where *atroparvus* is virtually the only species, as in Portugal and western Spain, it breeds in all types of fresh water which would be hospitable to *A. maculipennis* in general, from upland marshes and slowly moving streams and canals, to rice-fields on the estuaries and deltas of the coastal plain. The general picture is one which suggests the existence of competition between nearly related forms.

In the case, then, of such widely adapted insects as *atroparvus*, the question would arise as to the possibility of altering conditions so as to favour a less dangerous but competing anopheline species. Land reclamation in the Netherlands has had this effect, and something like this seems to be taking place at the present time in the Ebro delta in Spain. The reclaimed portions, planted mainly with rice, produce characteristically the harmless *maculipennis* variety *subalpinus*, while *atroparvus* still predominates elsewhere. Farther south, near Valencia, where malaria was epidemic a century ago, there is at present an extensive and healthy rice-growing area producing only *subalpinus*. Nevertheless, the rice-fields of Portugal

produce only *atroparvus*, and an attempt to introduce *subalpinus* a few years ago from Valencia was apparently unsuccessful.¹

When an anopheline seems to breed in different types of water in different parts of its range, it is always to be suspected that we are dealing, not with a homogeneous species, but with a number of varieties which, however much they may resemble one another physically, may in fact be separate species, often mutually sterile and with quite different adaptations and behaviour. Thus the American species, *A. crucians*, suspected of differences in breeding habits in the northern and southern parts of its range, turns out to be two different mosquitoes, and the same discovery has been made about *A. gambiæ* in Africa and *A. stephensi* in India. Effective naturalistic control presupposes, therefore, a much more intimate knowledge of the specific status and bionomics of the insect enemy than do the more mechanical methods of drainage or recurrent poisoning of surface waters.

The competition which takes place between related forms of insect life in a breeding-place is only one aspect of the natural balance which comes to be established in every stable community or *biocenosium* of plant and animal life. This balance is never static, but is in constant flux as changing conditions favour or restrain one component or another. The addition of an exotic form, especially one of an active and predatory type, which succeeds in maintaining itself as a new and permanent member of the community, will cause a general readjustment, leading eventually to a new balance after a sufficient lapse of time. It is in such a way that we should regard the introduction of *Gambusia* to a region, and the permanent effect of this disturbing element on the *biocenosium* and eventually on the anopheline density will be apparent only after several years, and not, as is generally expected, after several days.

Naturalistic methods aimed at the adult mosquito are as yet based almost entirely on the observation that each species appears to have a range of preferred hosts, not necessarily the same from

¹ Recent invasion of new areas by dangerous anophelines is also known. For example, *A. sudaicus* was found in 1930 to be invading deltaic Bengal and subsequently coastal Orissa in British India, and, about the same time, the island of Celebes in the Netherlands East Indies. *A. gambiæ*, introduced from Africa about 1930, has since occupied a considerable area in north-east Brazil.

place to place, in the presence of which it ignores other accessible sources of blood. If this range includes man, the mosquito is usually a vector ; if it does not, there may be no malaria at all in spite of a high anopheline density. As with breeding, there is always a tendency to sporadic biting outside the normal range, which is dangerous only in exceptional circumstances.

However, the terms "zoophilic" and "anthropophilic" are undoubtedly misleading if they are used qualitatively to describe a mosquito, or to distinguish one species from another, because the same anopheline may well be both. Man is usually only one of a number of hosts which a given anopheline will readily attack, and the anopheline may prove to be an important vector even when man does not head the list in order of preference.

For example, the precipitin test applied to the stomach contents of *labranchiæ*, the principal malaria vector of the Pontine Marshes, showed only about one individual in nine with human blood, as contrasted with *elutus*, which, in the Balkans, contains human blood half the time. In a non-malarious place, the proportion is very much less. In Viareggio, the summer resort mentioned above, only 0.25% of the anophelines taking shelter in buildings had recently bitten man. It is clear that domestic animals attract some species of *Anopheles* more than others.

At one end of the scale, we have a species like *gambiæ*, which bites human beings almost exclusively, even though, as in Kenya, cows and human beings may occupy the same hut at night ; while at the other end are anophelines like *subalpinus* in the Mediterranean basin, and a number of tropical forms, which seem to have no contact with man at all. In between the two extremes are species like *superpictus* of the Near East, and the *maculipennis* varieties of the Volga basin, which are without doubt deviated by animals from man, so that the more live-stock man possesses, the less he is likely to be bitten. The relative attractiveness of stables and dwellings is thus seen to be a matter of specific host preferences, and its effectiveness in reducing malaria transmission depends on how much the anopheline in question is drawn instinctively to man (anthropophilic index), as well as on how many domestic animals there are.

To sum up the case for naturalistic measures, we may say that anopheline species are different bionomically as well as structurally,

and even closely allied forms are never alike in their inherited instincts or in their behaviour, which is conditioned in part by their surroundings. A careful study of their habits of breeding, feeding, resting, mating, wintering, and so forth, may reveal a point of attack through methods analogous to those which in nature so often restrict the multiplication and activities of insect species. It is insisted that such a study must be carried out locally and may have little validity in another region even where the vector is reported to be the same species of Anopheles. On the basis of studies which have been made, more or less thoroughly, in various parts of the world, a number of naturalistic methods for reducing malaria transmission by controlling the breeding and activities of Anopheles have been reported, and in the following table an attempt is made to list them all, whether they seem promising or not. The classification is based on that suggested by RUSSELL and HACKETT in a communication to the third International Congress of Malaria at Amsterdam (1938).

III. CLASSIFICATION OF MOSQUITO CONTROL MEASURES

Natural.—Restriction of anopheline breeding or contact with man by natural environmental conditions.

Artificial.—Restriction of anopheline breeding or contact with man through conscious human intervention :

	Against aquatic stages	Against adults
I. <i>Mechanical</i> :	<i>e.g.</i> , ditching.	<i>e.g.</i> , screening.
II. <i>Toxic</i> :	<i>e.g.</i> , Paris-greening.	<i>e.g.</i> , insecticide sprays.
III. <i>Naturalistic</i> :		
(a) <i>Chemical</i> :	1. Pollution of water.	1. Creating repellent barriers of odorous plants.
	2. Changing salt content of water.	2. Administering drugs like sulphur which cause odorous perspiration.
(b) <i>Physical</i> :	1. Natural fills, warping, silting.	1. Destruction of shelters, clearing.
	2. Sluicing.	2. Creation of plant barriers to flight.
	3. Flooding.	3. Rendering bedrooms or dwellings unattractive as resting-places.

MALARIA

Against aquatic stages	Against adults
4. Fluctuating water-level.	
5. Intermittent drying.	
6. Agitating.	
7. Stagnating (ponding) or setting water in motion.	
8. Muddying.	
9. Shading or clearing.	
10. Drying by planting.	
(c) Biological :	
1. Natural enemies (pre- dators).	1. Introduction of natural enemies.
2. Changing flora and fauna.	2. Deviation by animals.
3. Off-season attack.	3. Winter killing.

IV. NATURALISTIC METHODS IN PRACTICE

A. LARVA CONTROL MEASURES

In the following pages, the various methods of naturalistic control will be critically discussed, in the order in which they are listed in the above outline. All the more useful ones have been applied by members of the Committee themselves as practical antimalarial procedures in various parts of the world, or have, at least, been observed in operation over a certain period of time. The fact that a few rather fantastic ideas are found to be grouped under the standard of naturalistic control should not detract from the solid merit and practicability of measures which have stood the test of time and expert appraisal.

(a) *Chemical Measures.*1. *The Pollution of Water.*

It has long been appreciated that sullage and sewage-polluted waters do not breed vector anophelines, with the exception of *A. sudaicus*, which, in this respect, shares the adaptations of *A. subpictus*. It has been reported that *sudaicus* bred in sewage-polluted waters in Singapore does not carry malaria, but the evidence

for this is purely epidemiological and far from conclusive. We shall consider here only the effect of pollution and microbic action on breeding, and not the supposed influence of such processes on the susceptibility of the adult mosquito to malaria infection, about which we still know very little indeed.

Pollution of water may be secured either by turning in industrial and organic wastes, or by starting microbic processes in the breeding-place itself. The soapy effluent from washing wells and sullage water from house drains is highly toxic to some *Anopheles* larvæ. There is evidence pointing to the efficacy of polluting head water with piggeries in *A. maculatus* territory, and, in rural Singapore, there is a district several square miles in extent where this method alone is sufficient to prevent malaria. FRY used pollution against an inland vector in India by placing horse manure in channels. This, however, caused a fly nuisance, and there are many obvious objections to the use of organic animal wastes as a larvicide.

Pollution by vegetable matter in the form of industrial wastes has often been tried with success. *Bagasse* from sugar-cane mills in the Philippines in one reported case seemed to be keeping a stream free from *flavivirotris*; the refuse from the Government Sisal Experiment Station in Ceylon is alleged to have a similar action, while the numerous large pits used for macerating *canepa* hemp in Italy do not breed anophelines.

Pollution by green vegetable matter decaying in water is a frequent occurrence in nature. WILLIAMSON (1928, 1936 *b*) has reported that, in Malaya, vectors do not breed in shallow, standing waters where the "available soil nitrogen ratio" reaches 0.3%. Nevertheless, a few anopheline species have an extraordinary adaptation to such conditions. As regards vectors, *A. umbrosus* breeds in peat water under tropical forest, and larvæ of *A. multicolor* are found in Egyptian drains in the middle of decaying vegetation, and in village cesspools.

The deliberate use of vegetable pollution as an antimalaria method is due to WILLIAMSON. Stagnant pools, such as engineering borrow-pits, into which green cut vegetation has been thrown, breed culicines only, vector anophelines being inhibited. The lethal effect of a fortnight-old brew of cut green grass is remarkable. There is no need for the filling to cover the water surface and act in any way as a mechanical deterrent to oviposition. An open surface layer

remains quite free of anopheline vectors. WILLIAMSON has, in the past, advocated the extension of this method in the form of *herbage-packing* to shallow, small volume, running channels, but now favours sluicing or palm leaf-cover in such circumstances. He believes a closely trampled cover will prevent egg-laying. Actually, as one of us has shown (SENIOR WHITE, 1936), the effect of such "herbage-packing" in streams is not mechanical, but biological. About a fortnight after packing is carried out, the water of the channel smells like a septic-tank effluent; it is crystal clear, but forms a bacterial scum if allowed to stand. A black sludge is deposited at the bottom. The water is deprived of oxygen entirely, and bottom algal growth on sand changes from a Chlorophyceous alga to masses of white fungus. The mosquito fauna changes from vector anophelines to various culicines.

When packing running water, it is essential that there should be a complete and thick cover of packing above the water. This interferes with its flow and raises the general level, imposing a limit to the size of channel that can be packed, dependent on the volume of flow and on the height of the banks. The method has definite limitations. It cannot be installed until the rains are over, as freshets wash it out. In running water, apparently not every plant is suitable. The best so far found in India are *Cleistanthus* species and *Holorrhena antidysenterica*. The first of these are fish poisons; the latter contains several alkaloids.

It is very important that green cut vegetation be used, for dry straw will only result in a hay infusion, favourable to larval growth. Also rotting will fail once cold weather has brought the sap "down". Only *Diospyros*, apparently, rots in cold weather, but this plant has an economic value that renders its general use difficult. Presuming that repairs to packing are carried out as required, one "charge" lasts for three to four months—i.e., to the end of the transmission season in the monsoon tropics—but chemical treatment before the close of the rains is necessary for several months (June-October). In Malaya, under different climatic conditions, herbage-packing is effective for at least six months. In moving water, re-oxygenation, permitting of vector breeding, is rapid. Only lengths of a few yards, where cattle or carts trample the packing under water, can be considered safe. An attempt to pack and leave open alternate lengths of fifty yards or more failed to be effective. This method

is particularly successful in pits holding seepage water and in sluggishly flowing streams.

Further research with botanical and chemical aid is required to provide a larger range of suitable plants for every region, and for an understanding of the processes underlying this method, which is undoubtedly a most promising one.

2. *Changing the Salt Content of Water.*

We have mentioned the effect of the Zendrini gates at Viareggio, which turned a brackish-water lagoon into a fresh-water marsh and have kept the surrounding territory free from malaria for two-hundred years. Precisely the opposite procedure has been effective in Durazzo, the principal port of Albania. Here it was decided to turn the adjacent marsh into a sea-water lagoon to stop the breeding of *A. elutus* by excess of salt. This was accomplished by reversing the usual automatic tide-gate so as to admit the sea at high water instead of excluding it. Within two years, breeding over an area of fifteen square kilometres was reduced to zero, while the profits to the Government of an existing fish concession, which has been greatly benefited, more than equalled the cost of the operations.

In the Netherlands, malaria has always been endemic in the province of North Holland, due to the presence of a brackish-water breeder. The creation of new "polders" by diking and pumping is not expected permanently to increase the malaria, since past experience has shown that abundant irrigation will, in the course of a few years, wash all the salt out of the soil and cause the retreat of the vector before the invasion of a harmless fresh-water-breeding anopheline. Since the authorities count on this process to solve the malaria problem, it may be considered an example of naturalistic control.

Non-interference with natural conditions which prevent anopheline breeding should also be stressed. Mangrove swamps in Malaya and elsewhere are malaria-free so long as they remain in their natural condition, in which there is free tidal access. The effect of salt is so closely linked with movement of tides and penetration of larva-eating fish that this is one of the best examples of combined action working to reinforce a particular naturalistic method. There is, moreover, a close association between naturalistic and hydrotechnical

measures in any project in which the access or exclusion of tidal waters is concerned.

The danger of interference with the water of a breeding-place without expert knowledge is clearly shown by the following instance (WASHBURN, 1933). Falmouth, a hitherto malaria-free town on the north coast of Jamaica, is surrounded on three sides by saline swamps, partly under mangrove. A road traverses the swamps, bridging a channel which connects them. This channel was closed for an unknown reason, cutting off the western part of the swamp from the sea. Two dry seasons followed, during which the western swamp became partially dry, and some of the mangrove were felled for firewood. The third year was one of exceptional rainfall. The western marsh became rain-water filled, and a river overflowed, flooding the eastern swamp. The anopheline population rose twenty times in the catching stations, mainly *A. albimanus*, the vector in Jamaica. In a population of 8,000, there were 4,400 cases of malaria and 138 deaths; the spleen rate rose from 5% to 90%. Following the usual temporary measures, the channel under the bridge was re-opened, while a new canal first drained off the fresh and later admitted the sea water all over the swamps. *A. albimanus* was gradually replaced by *A. grabhami*, and the original healthy conditions were re-established.

(b) *Physical Measures.*

1. *Natural Fills (Warping, Silting).*

A marsh can sometimes be successfully filled up by turning a silt-bearing stream into it. To be successful, the matter undoubtedly calls for engineering skill, as results depend on an appreciation of the volume of silt in suspension, the reduction in velocity necessary to cause this to be precipitated, and the disposal of the resulting clear water, which may, until the fill is completed, itself require treatment as a breeding-place. Without a full appreciation of the situation, such action may, temporarily at any rate, exacerbate it. Filling by silting is no more for a health officer to undertake without the advice of the engineer than for the latter to undertake without the advice of the malariologist, able to appreciate possible repercussions on the local anopheline fauna. For example, cracks developed in newly dried hydraulic fills on reclaimed tidal land at

Singapore airport, offering potential breeding-places to *A. ludlowi* (*sundaicus*). HUNTER employed natural silting with finely divided soil particles in dealing with this, and the danger was completely averted by dumping loads of suitable earth along the edges of these fillings.

Many of the great pieces of land reclamation in Italy have been accomplished by this method over centuries of time. Apart from the Po delta, the principal examples are the marshes of Ravenna and the so-called Maremma of Tuscany. In both these cases, rivers from the Apennines, which is a disintegrating mountain chain, have been diverted whilst in flood into large diked areas and allowed to drop their silt through stagnation. Such waters often contain as much as 16% by volume of suspended material. The result is that, in the course of a single winter, 30 centimetres or more of soil can be deposited over many thousand acres.

In this way, at Ravenna and Grosseto, in the course of the past century, practically the entire area below sea-level has been filled sufficiently to permit of natural drainage, thus eliminating the former pumping and bringing the final extinction of malaria into view. This has the advantage of being a permanent solution of the malaria problem, but it can only be carried out on this scale by a country prepared to plan over a period of centuries. On a much smaller scale, the method is frequently used in other parts of the world. Old quarries and brick-pits can often be silted up very cheaply by the diversion of small streams. KNIFE, in Bulgaria, filled a considerable marsh by diverting a watercourse over a sandy and easily eroded cliff at one side of the area. STRICKLAND & MURPHY (1932) also used the method in Assam, diverting a silt-bearing stream through a marsh, whereby the marsh was converted into sandy flats.

In training streams with earth beds in flat land, much use can be made of groins of jungle stakes interwoven with withies placed at varying obtuse angles in the current of the stream. By this means, loops in the course can be silted up during freshets, thus maintaining the stream in a straight, through channel that may, depending on the gradient, give a flow too swift for breeding. Good examples of this type of work are the experiments of WORTH (1937) in Ceylon in the control of anopheline breeding in river-beds. The results of these experiments have shown that pools and shallows which

formed the main breeding-places of anopheline mosquitoes during the epidemic of 1934 can be enormously reduced and often entirely eradicated by the adoption of suitable engineering devices. The work is expensive and requires unusual engineering skill, but it offers a very promising field for future development.

Silt can also be deposited by this arrangement over marginal seepage areas, the fill being later provided with subsoil drains and bound by turf or dibbled grass against scour by subsequent freshets. Such methods demand a resident inspector skilled in watching the daily changes in the regimen of the stream, to avoid under-cutting banks, etc. The inspector must command enough labour to make frequent changes in the positions of the groins. The skill of the Bengali villagers who evolved the method thus adapted for the control of their estuarine channels, is not possessed by the villagers of other areas in India where it has been used against stream-breeding anophelines.

2. *Sluicing.*

The main principles in the construction of an efficient antilarval flush is that a sufficiently large volume of water should be discharged suddenly, at a minimum of once a week, oftener in some cases, with the object of causing a wave to pass down the channel or stream. This wave, as it flows onwards, causes the stranding of mosquito larvæ, pupæ and eggs. Larvæ which are not stranded are drowned by the turbulence of the flowing water. There is no doubt, too, that, in sluiced channels, particularly those in fairly flat country, the soil disturbance and the liberation of silt and organic debris has a deterring effect upon further larval breeding (WILLIAMSON & SCHARFF, 1936 ; RUSSELL, 1932).

There are certain precautions which are necessary to ensure efficient sluicing. Care should be taken that the head waters above the sluice are free from breeding. It should be noted that the mere emptying of a channel, or of the reservoir, will not injure larvæ, and these may be washed down undamaged. This may be overcome by adopting subsidiary methods of larva control, such as shading, use of larvicidal poisons or stone-packing. Further, it must be observed that soft, friable banks require special protection against erosion, but that this protection is only needed for a few yards below the outfall of sluices. Elsewhere, the erosive action of the flushes

is negligible compared with that caused by normal flow augmented by storm water.

It may, in some cases, be necessary to abolish side pools and seepages not reached by the flush. If a channel is too wide, it is sometimes advisable to obstruct it with rocks in order to promote stranding or turbulence.

The advantage of sluicing is that it makes oiling unnecessary or, if oiling has been carried on in the upper reaches, it helps in distributing the oil below by casting it against the banks where it is most needed. Further, unlike oiling, sluicing is not destructive to vegetation and, given suitable climatic conditions and sufficient depth of not too rocky soil, it permits the growth of shade plants along banks.

Various types of sluice have been designed, such as the hand sluices made of clay subsoil pipes and wooden gates, to the more permanent screw-down gates and automatic sluices, which, once constructed, give little trouble and discharge large volumes of water at frequent intervals. According to RAJA RAM (1935), the method of flushing a stream by opening a sluice-gate in a dam at intervals was originally recommended by GRAHAM in 1913, and has been practised in the Gumti River, Lucknow, continuously since 1916. The gate of the weir is dropped at 5 a.m. every Sunday and raised again at noon the same day. The effect is to lower the river level by about 3 feet at the weir, and larvæ are flushed out from various storm-water drains opening into the river above the dam, in which the water is headed up during the week.

Sluicing is evidently an important measure which finds increasing application from year to year. It is restricted at present to fairly small streams and channels where there is plenty of water available. Its effectiveness seems to depend on a number of things: turbulence, splashing, stranding, the stirring up of silt and the possibility of developing shade which oiling would prevent. Most of the criticisms have been directed at the erosion which it causes, but a considerable experience with the method in Penang shows that this is not serious and can be prevented.

3. *Flooding.*

BENTLEY (1925) considered that the annual flooding of the Bengal delta was a major instance of natural control. Not only were the

silty flood waters inimical to breeding of the local vectors, but also the general rise of level reduced the "amount of breeding edge" and, by raising the water-level above that of the aquatic vegetation, exposed larvæ to attack by fish and other predators. BENTLEY attributed the increasing malariousness of the western half of the delta to prevention of flooding by road and railway embankments, and the embanking of tidal rivers to prevent salt water from spilling on to reclaimed land. The question is, however, a very controversial one (see STRICKLAND, 1938), and while the Bengal Government takes an interest in preventing further obstruction to flooding, any project for removing embankments which already exist would meet with great resistance and would probably be financially impracticable.

We are not aware of any other delta where a comparable state of affairs exists. Nor are we aware of either natural or naturalistic control of malaria by flooding outside deltaic areas.

4. *Fluctuating Water-level.*

The raising and lowering of impounded water levels at frequent intervals to control anopheline breeding has found successful application for years in North America, where the principal vector is a pond breeder. This tends to strand larvæ and protective floatage on the shore, to kill rooted aquatic vegetation in the shallows, and to deprive larvæ of natural protection from enemies. The malaria officers of the Tennessee Valley Authority have induced engineers to build their dams so that each carries a "malaria surcharge". This permits seasonal and periodic fluctuations in water level of the reservoirs and thus helps to maintain clear shore lines which sharply limit mosquito breeding. The malariologists in charge of this scheme are convinced that the method is a useful one (BISHOP, 1936).

The general idea underlying the artificial fluctuation of water level has had applications elsewhere. A large marsh in the Tiber delta has been surrounded with an embankment and periodically filled from the river by pumping, in order to irrigate 1,000 acres of land. The rapid changes in water level seem to have made it impossible for either rooted or floating aquatic vegetation to maintain itself, so that the water surface is now an open body of water free from anopheline larvæ at all times, requiring no larvicidal

treatment. The artificial lake in Singapore Botanical Gardens is an excellent example of the permanent value of a naturalistic method in the midst of an artificially controlled area. A fluctuating level may often prove the ideal way of solving a particular malaria problem.

In Malaya, SCHARFF opened up a saline pool, breeding *sundaicus* at the edges, to tidal influence. The resulting rise and fall of the pond was sufficient (without any apparent change in the fauna or flora) to give complete freedom from larvæ in an observation period which now extends over three years.

5. *Intermittent Drying.*

The proper handling of irrigation water either by intermittent drying or the use of alternative channels is a common procedure in many countries and should be enforced wherever irrigation causes a malaria hazard or a mosquito nuisance. Rice-fields present a special problem, which will probably find a solution only along naturalistic lines (HILL, 1937). It is the subject of field experiment in Bulgaria, Portugal, Egypt and Madras. In some cases, it appears to increase the rice yield, as in Bulgaria, and, in others, to decrease it slightly, as reported personally to one of us from Egypt. SMALT (1937), in the Netherlands East Indies, records a 30% reduction in *aconitus* density by intermittent draining, without "much" affecting the yield of rice. Other workers in the same area claim to have secured an improved rice yield after anti-*aconitus* measures. In French Indo-China (L.O.N. 1937 a), the Public Health Service has experimented in Annam with drying off the rice-fields after three days of irrigation, and leaving them dry for the next three. This cleared them of all larvæ. "From the agricultural point of view, the paddy harvest differed neither in quantity nor in quality from that simultaneously grown on neighbouring rice-fields which were always under water." Periodical drying is not, of course, applicable where the flooding of rice is entirely dependent on an intermittent seasonal rainfall, as in parts of India.

6. *Agitation of the Water Surface.*

This method makes use of the knowledge that mosquitoes require still water in which to lay their eggs. It is also founded upon the observation that mosquito larvæ cannot survive in water which is

in constant agitation. Various devices exist for putting this knowledge into practice, but one of the most simple methods is that which was carried out with great success in Penang (SCHARFF, 1935). It was found that, where irrigation wells, constructed with simple precaution against seepage formation and freed from vegetation, are kept filled by means of constantly splashing water, no larvæ of the malaria-carrying *Anopheles* can breed. In this way, some 185 irrigation pools have been constructed or modified to suit the needs of the farmers on Penang Hill.

The pools are fed by water from jungle-protected hill streams, carried on split-bamboo conduits. The surplus water overflows into neighbouring pools situated at lower levels. The end of the bamboo pipe is arranged to be at least four feet above the pool: the consequent splashing and rippling of the surface is effective in preventing mosquito breeding. The labourers soon learned the value of this method and were readily persuaded to carry on the work, thus saving themselves from the crippling effect of malaria and allowing agriculture to flourish without danger to other residents near by.

The agitation of water surfaces by wind and rain are undoubtedly the cause of much larval mortality. The only attempt we know of to produce such an effect in large bodies of water was the practice of the Tennessee Coal, Iron and Railway Company of sending launches periodically around lakes in the Birmingham (Alabama) district with the intention of creating waves to destroy larvæ and strand floatage (KIBBY, 1923, 1925).

7. *Stagnating and Setting Water in Motion.*

These two methods are opposite expressions of a single operation, which may be employed according to whether the species it is desired to combat normally requires moving or standing water. Ponding was used with success against *A. maculatus* in a hill stream in Malaya, by WILLIAMSON (from 1931 to 1934). The stream was turned into a series of pools by earth and timber dams, surface covering and larvivorous (*Utricularia*) pond plants introduced, and edible and larvivorous fish cultivated, whereupon *maculatus* breeding ceased. The reverse process, of setting water in motion, has for long been completely successful in the United States of America against *quadrifasciatus*, being the

underlying principle of all the ditching done there, though the method was widely practised and its effectiveness realised before the biological nature of its action was appreciated.

8. *Muddying.*

The presence of silt in suspension is fatal to the larvæ of most anophelines, though there are exceptions. RAMSAY (1931) has shown that it is this factor which keeps *A. minimus* out of many situations in Assam until after the rains, causing great fluctuations in the amount of breeding and in the importance of breeding-places affecting any particular settlement. The silt-laden water from Malayan alluvial tin-mine areas effectually prevents breeding.

GRIFFIN, Chief Engineer of the Public Health Department, Bengal, has made a naturalistic use of this phenomenon in his "flood-flush" method, whereby the silty estuarine waters of that delta are, with the use of suitable sluices, allowed to flow into tributary drainage channels and borrow-pits that are normally dangerous, thus eliminating *sundaicus* and the local carriers of the *annularis* group. The method is very effective, but requires skilled engineering to lay out, while the cost of the sluices, their hand operation and the digging and maintenance of the distributory channels, though much less than continual expenditure on chemical larvicides, does not bring the method into the "cheap and simple" category. Muddy water cannot, however, be depended upon to prevent the breeding of all species. In Egypt, for example, *pharoensis* larvæ are not uncommonly found in rice-fields and ditches, flooded with the turbid water of the Nile. On the contrary, in Malaya, the turbidity caused by ploughing in rice-fields is reported to be fatal to first and second instar larvæ. This method is frequently applied, though unconsciously, by keen cultivators in the fallow season. If sufficiently encouraged and rationalised, it may be found to be a reliable method of malaria control.

9. *Shading or Exposing to Sunlight.*

It was discovered long ago by WATSON that the principal inland vectors of Malaya are sensitive to the presence or absence of sunlight on surface waters. The natural habitat of *umbrosus* is peaty marshes in virgin jungle, while that of *maculatus* is seepage areas in sunlight, or stretches of hill streams open to the sky. STRICKLAND

showed that hill streams shaded by jungle breed only the *aikeni* group, all non-vectors. When streams are cleared by villagers or for plantation agriculture, *maculatus* in Malaya (and *minimus* in Assam) at once begin to breed, and *aikeni* virtually disappears. In the lowlands, WATSON dealt with *umbrosus* where possible by clearing and ditching jungle, but the Government implemented STRICKLAND's discovery by prohibiting the felling of jungle over streams.

There remained the problem of streams previously cleared. These have been dealt with in Malaya by mechanical and toxic methods. In Assam, RAMSAY (1936) has introduced the procedure of creating low, dense shade over streams to replace felled jungle. The plants used are mainly local (duranta, lantana, hibiscus and "tarapat"). A similar *maculatus* problem (OVERBEEK & STOKER, 1938) in the tea-plantations of western Java has been dealt with by planting *Tithonia diversifolia*, a Mexican marigold, a bush which grows quickly and gives an intense shade. This method is extensible to all sun-loving vectors in the moist tropics, but is not feasible in the monsoon tropics, where all vegetation is burned up and dried down at the time breeding starts with the break of the rains. Non-deciduous plants able to give a thick cover do not flourish under such conditions. Seepage trickles on stream banks can in this case be covered after channelling with stones forming a mound about six inches high.

Shading is a measure extensively practised in Malaya in dealing with "seepage" wells which are a prolific source of *A. maculatus*. Villagers can be readily persuaded to surround such wells with huts of thatch, because of the privacy and additional protection which this method provides. The exclusion of sunlight from these wells is entirely efficacious so far as the breeding of *A. maculatus* is concerned. Occasionally a non-vector species such as *A. leucosphyrus* invades such wells, and this alteration of the fauna is welcome as an indication of the success of the method. Small drains are also covered with coconut fronds, or with a thatch of *lallang* (a common coarse Malayan grass) placed upon bundles of twigs (fascine drainage) laid in mosquito-breeding ditches. The effect is one of shading, and while this method requires some maintenance, it is much cheaper than oiling. Soon a quick growth of weeds and shrubs works its way through the bundles and provides

additional living shade. From Mauritius, Indo-China and other parts of the world, come reports of the successful use of shade, and it is evident that widespread investigation and experimentation with this method is being carried on for the control of many different carriers.

An entirely different use of shade has been made in Cuba (CARR, 1938). Two rivers near Havana were cleared of water hyacinth to prevent breeding of *A. albimanus*, but it was not possible mechanically to keep these rivers free from algæ such as *Spirogyra*, which now grew very rapidly. This growth was prevented by shading the rivers with a double row of *Ficus benjamina* spaced two metres apart. Young trees of considerable size were secured by "layering" the branches of large trees.

The attempt to reproduce jungle cover has, however, received a good deal of criticism, especially when it is suggested as a substitute for more perfect but more expensive methods. Animal damage is one of the difficulties, for pigs may root in the centre of a planted area, elephants browse in it, and human beings make paths through it without the opened areas being evident to superficial inspection. Planted shade vegetation must be able to withstand storms, must be adapted to the terrain, must not be suitable to animals as food, and must be cultivated, often fenced and always watched. BARROWMAN (1936) sums up the situation by saying: "In practice, the method bristles with difficulties: to keep shade is very effective, but to improvise shade in open land is rarely satisfactory, at least on estates."

We believe that BARROWMAN is right in emphasising the fundamental importance of the original preservation of shade and the aiding of natural jungle as a control method. It is much easier and more effective than to produce shade *de novo*. BARROWMAN also calls attention to the fact that shade and sunlight as control measures must be thought of from the larva's point of view. "A shady swamp may be miles in extent and feet in depth, stretching over the countryside, or it may be inches in extent, a fraction of an inch in depth, nestling in the side of a drain. . . . It is not enough, therefore, for the control of *A. umbrosus*, merely to fell the jungle. The entire surface must be clean weeded so as to expose every tiny pool of water, or the water must all be defined in channels and these channels then kept open to sunlight by clean weeding." And on

the other hand, to keep out *A. maculatus*, the shade must be continuous and dark. The growing of secondary jungle is rarely easy, but RAMSAY has had success in Assam, and the Netherlands workers in Java. In its varied applications, the manipulation of sunlight and shade presents itself as one of the more important measures of naturalistic control.

10. *Drying Land by planting Trees.*

We have been able to trace only one definite suggestion regarding this in recent times. DE BOER (1936), in Uganda, reports an attempt to plant trees which will grow in water-logged land. It is claimed for this method that it reduces the water held up, permitting of easy drainage ; that it changes the character of the undergrowth from papyrus to Umbellifers and ferns, which produce a heavy shade ; and that the planted trees (Eucalyptus, Cassia and Casuarina) have an economic value as timber. Reports from Palestine and other areas, however, seem to show that the antimalarial results can usually be secured more rapidly and economically by simple drainage.

(c) *Biological Measures.*

1. *Fish and Other Natural Enemies.*

Gambusia has now been introduced, we believe, into every major region of the world. It is a hardier fish than "millions" (*Lebistes reticulatus*) of Barbadoes, or any of the other top-feeding minnows. It is also the most adaptable, tolerant to wide ranges of temperature, salinity and pollution, easily acclimatised to the tropics or to regions of the temperate zones with hot summers and rigorous winters, and transportable over long distances without undue mortality. It is viviparous, and the rate of multiplication is such that, in the latitude of Italy, females emerging from hibernation in May can each have three broods by September, and can give rise to three successive generations during the summer. No epizootic disease is reported to which it is susceptible. It lives on surface food and is especially attracted by moving prey such as mosquito larvæ, which seek protection in thick surface vegetation.

The effectiveness of *Gambusia*, however, should not be judged, as it usually is, by its ability immediately to clear a breeding-place of

larvæ. It should rather be regarded as an upsetting factor in a balanced ecology, where it exerts constant pressure on the mosquito component. In one well-studied region at least—the northern Dalmatian coast including the peninsula of Istria—*Gambusia* alone has, in ten years, reduced anopheline density below the threshold of malaria transmission. In many other areas, it has not been completely successful, but is considered responsible for a significant diminution in the anopheline population, and only in a few places has it been reported as total failures, not worth the trouble and expense of maintenance.

Most of the objections raised on economic grounds to its importation have been entirely academic. It is feared that its omnivorous voracity will destroy the ova or fry of food- or game-fish in still waters. In central Italy, carp and tench are stocked for food purposes in canals in the rice areas, and since malaria is of no public health importance in this region, the cultivators properly opposed the introduction of *Gambusia* on the ground that there was no reason to run the risks inherent in any method of biological control. The introduction of a new member into a naturally balanced community causes a general disturbance which affects all the organic constituents of the community or biocenosis. This is the element of danger in methods of biological control of insects and parasites in general.

The introduction of *Gambusia* into California was combated by the California Fish and Game Commission owing to the fact that some species of fish introduced into the waters of the State have proved harmful to other fish life and a menace to the valuable fish interests and to the waterfowl. It was thought that the *Gambusia* might eat the eggs of game-fish and even their young in the earliest stages. HILDEBRAND, whose opinion was sought, stated that, after a study of *Gambusia* over many years, he has at no time found this fish to be a serious enemy of any of the food- and game-fish, nor has anyone ever to his knowledge raised such a complaint. The Commission ultimately decided not to oppose the introduction of *Gambusia*, and, as a matter of fact, *Gambusia* had already been brought clandestinely into California, and is now found widely distributed throughout the State. Mr. J. O. SNYDER, in charge of the Bureau of Fish Culture, California Fish and Game Commission, has written to one of us (April 1933): "I should hesitate

greatly to oppose the introduction of *Gambusia* for mosquito control in any region."

However, Professor Massimo SELLA, who, with GRASSI, was instrumental in introducing *Gambusia* first into Spain in 1922 and subsequently into Italy, has informed the Committee of at least two complaints on the part of Italian fish breeders which seem well founded. Both have to do with fish culture in coastal lagoons, and it is alleged that *Gambusia* devours the small "cefalo" (mugil) fry as they enter the lagoon from the sea, and can populate fishponds with a salt concentration equal at least to that of sea water. On the other hand, predatory fish (*Labrax lupus*) and eels, which are the more important products of such lagoon-culture in Italy, eat the *Gambusia*, and the general balance between damage and utility may turn out to be on the credit side.

As for inland waters, no protest seems to have been raised against *Gambusia* as a source of trouble. Experimental combinations of carp and *Gambusia* have been tried by FERMI with reported success in Sardinian lakes. The carp feed on the surface algæ and keep them down, while the *Gambusia* destroys the mosquito larvæ, left unprotected. The experiment was ended by the local peasants' fishing out all the carp. We are informed that a similar experiment is now in progress in a region of numerous fishponds in south-western Hungary, but the results have not yet been published.

Many claims have been made as to the value of indigenous fish, and there is little doubt that, without their presence, mosquito density would be much greater than it is; but they have long been members of a balanced community, and it is in the nature of things impossible to keep their numbers for any length of time above normal. To render native fish more effective against mosquitoes than they habitually are requires mechanical interference to remove shelter from their prey, or legal protection from human depredation. It is possible that providing hatcheries might somewhat increase their effectiveness, as has been suggested for *Panchax* in India, but we do not know that this has been tried.

Other natural enemies can be dismissed with a few words. They consist of protozoal parasites, planarian and myrmethid worms, arthropod predators of several orders, fungi and plants like *Utricularia*. Native species of all these groups do an enormous amount of execution among larvæ, the net result of

which is to keep the mosquito population down to its present level. More than this cannot be expected from indigenous forms, although detailed studies of their life histories, now more or less unknown, might indicate ways of utilising them, and apparently no attempt has been made to introduce exotic forms as in the case of fish.

2. *Changing the Fauna and Flora.*

The best-known example of the application of this measure is the so-called "hygienic exploitation" of fishponds in the Netherlands East Indies (OVERBEEK & STOKER, 1938). The cultivation of the marine fish called *Chanos chanos* in Java is of considerable dietary value and economic importance. This fish is cultivated in artificially constructed salt-water ponds, in which *A. ludlowi (sundaicus)* breed in association with floating algæ consisting of *Enteromorpha*, *Chætomorpha*, *Spirogyra*, etc., the fish breeders being firmly convinced that these algæ are necessary for the cultivation of the fish. The ordinary method of control, such as draining or filling, besides being expensive, would have meant abolition of a valuable industry. WALCH (1930), in conjunction with the Fisheries Department, got over the difficulty in the following manner. The bottom of the ponds are laid dry for a couple of days at least once a month, followed by filling up the pond with fresh sea water. During the draining period, the fish remain in side ditches of the ponds dug for the purpose. The object of this procedure is to kill the top algæ by drying and to promote the development of the blue algæ (*Cyanophyceæ*) or "cream of mud", which grow on the bottom while the pond is drying. These algæ remain much longer at the bottom of the ponds and do not rise to the surface until they have grown into a thick layer. It is upon these *Cyanophyceæ* that the fish live. The algæ rise to the surface in broad sheets and compact masses and no mosquito larvæ can penetrate these, so that, by the introduction of larvivorous fish such as *Haplochilus panchax* (Kepala Timah) into the ponds, any larvæ that might be present are eaten.

The result of these measures which have been carried out around Batavia has been the practical abolition of malaria in the area so treated. It should be noted that the work was very expensive. The ponds had to be acquired, and major channelling done to get sea water into the ponds; extensive changes were made in the ponds themselves. The cost was borne and the project was successful

in Batavia, where an important seaport was to be protected. But the expense has probably delayed the extension of the work since WALCH's death.

By another method, resembling that of FERMI (1933) in Sardinia and of the Hungarian experiment described above, WALCH dealt with fresh-water carp-ponds in the Netherlands Indies. The ponds are full of submerged water plants and vegetation and breed anophelines such as *A. aconitus*, *A. hyrcanus* and *A. barbirostris* until WALCH's method of biological control is introduced. This consists of introducing, in addition to the carp, a species of fish *Puntius javanicus*, which feeds exclusively on plants, as well as the larvivorous *Panchax*; and, as a preliminary, the edges of the pond are clean weeded. By these simple means alone, the breeding of larvæ is completely abolished.

Certain plants are inimical to the presence of larvæ, probably by their mechanical interference with oviposition and restriction of free surface for larval life. Such are the various species of *Lemna*, especially *minor*, and the ferns *Salvinia cucullata* and *Azolla*. A complete cover of *Lemna minor* connotes an absence of larvæ, but the growth varies in extent and density very rapidly. We are not aware of any botanical researches on conditions favourable or the reverse to the growth of these plants, and such are a great desideratum. In India, a pool with any considerable growth of *Wolffia arrhiza* is usually almost or completely free from all anopheline larvæ. The hypothesis regarding the value of *Chara* as a plant inimical to the presence of larvæ has been exploded, mainly through the work of MATHESON & HINMAN (1928).

In regard to any proposals to reduce the food content of breeding-waters, it should be borne in mind that larvæ are apparently almost omnivorous. Further, they are capable of utilising solutes and colloids in suspension. They must, if purely plankton feeders (but many species also browse along rootlets, etc.), be able to extract sufficient nutriment from the maximal daily filtration capacity of about 1 c.c. to achieve their development. Little work, however, has yet been done on their basic metabolism, and virtually nothing quantitative on the micro-plankton of typical breeding-places, in comparing conditions where larvæ are numerous or sparse. Such detailed studies are a prerequisite to progress in control along these lines.

In areas of India where *culicifacies* is not a vector, control of the *fluviatilis* group in sandy streams and rivers can be obtained by training the post-rains flow so that it traverses sand and does not come into contact with earth margins. This involves considerable labour and supervisory skill. A fallen branch or washed-down debris stranded at the edge will permit of *fluviatilis* breeding. We have been informed by LEESON that he thinks he has noticed similar breeding-edge differences between *funestus* and *gambiæ* in Africa, but made no particular observations. The method, very effective against *fluviatilis* in India, is useless where *maculatus* and *culicifacies* (and *gambiæ* in Africa) are vectors, as these breed readily against sand. The underlying principle of this discovery is not known. Possibly the micro-algal flora of sand and earth differ as a source of food.

Changing the flora, however, is not always a safe method of attack, and may result in altering conditions for the worse. It has been found, in India, that the mechanical cleaning of village tanks against the vectors of the *annularis* group, combined with the special removal of *Pistia stratiotes* against *A. ramsayi*, may result in letting in *A. varuna* breeding against tree roots at the cleaned edge. The displaced carriers are poor vectors, carrying by weight of numbers. The vectorial status of *varuna* on the plains is unknown, but a few may be as dangerous as large numbers of the displaced vectors.

3. Off-season Attack.

RICE (1935) in Assam has suggested a concentrated attack on *A. minimus* larvæ in the cold season when breeding is already much reduced by climate, and the same would apply to larvæ during a long dry season. This would probably fail to produce results proportionate to the expense involved, for the reasons adduced under "winter killing". Both of these methods, while intensifications of a natural process, become, in operation, mechanical or toxic.

B. CONTROL OF THE ADULT MOSQUITO

All but one of the eight naturalistic methods suggested for dealing with the adult mosquito can be dismissed very briefly. The erection of *barriers of repellent plants* is, as far as we can find out, nothing

more than a mediæval myth. The *odour of perspiration* may be the reason why certain rare individuals are not bitten by mosquitoes, but no food or drug has been found which produces this effect. As for *destruction of shelters*, we know of no instance where a small radius of clearing about houses or inhabited centres has done any good, but many instances where it has done great harm. Nevertheless, the cutting of underbrush and trees around dwellings is an obligatory antimalaria measure in many tropical settlements. Just the opposite has also been suggested in the shape of a *tree barrage to obstruct flight*. No serious attempt seems to have been made to evaluate the results in either case.

A few years ago, a great deal was heard about *rendering bedrooms unattractive to anophelines* as resting places. It was observed in Europe that *A. maculipennis* tended to congregate in the day-time in places which were dark, humid, warm and free from draughts, and it was assumed that, if a certain combination of physical circumstances caused anophelines to remain in houses, the reverse might also be true—namely, that the absence of these conditions would tend to keep them out. Except, however, in the case of *atoparvus*, which over-winters in human habitations, the evidence is that there is a wide dispersal of anophelines at night even among forms which tend to rest in houses by day.

An intense malaria is often caused by anophelines like *flaviviridis*, *maculatus* or *pharoensis* which rarely rest in houses, but seek unknown day-time resting places out of doors. To these, the attractiveness of the bedroom lies in the occupant; not in the physical conditions. The studies of BARBER & RICE (1935) on *elutus* in Macedonia made this very clear. Infected *elutus* were found in stables nearly as often as in houses. The infection of infants occurred everywhere in the village, although *elutus* density was much greater in certain shelters than in others.

In particular, the authors held under observation for several years two different types of house intermingled in the same village—old houses, commonly with thatched roofs, dark, moist and in bad repair, and new houses, better lighted, better ventilated and more tightly built. With regard to density, infection and human blood in the stomach, the *elutus* taken in old and in new houses showed no important differences constant over two years. The proportion of infants infected was not significantly higher in old

houses than in new. "The results on the whole do not offer much encouragement to the hope that improvement in housing other than by screening would be an effective anti-malaria measure in this region. . . . In summary, we are inclined to believe that, in this region, there are only two kinds of house important in malaria, the unscreened and those provided with screens and with people disposed to use them properly." CHRISTOPHERS & MISSIROLI reviewed the whole subject in a report on housing and malaria presented to the Malaria Commission in 1933. The conception (states the report) that a dark, damp and dirty house suffers from malaria in proportion to its attractiveness to anophelines is against the general trend of opinion. The places where anophelines congregate in the day-time give no indication of where they are likely to be found at night. "There seems no doubt", concludes the report, "that screening is the only really effective means of controlling malaria through housing."

The *introduction of natural enemies* has not proved to be effective in the case of mosquitoes on the wing. The outstanding experiment was that of Dr. C. A. R. CAMPBELL (1925) of San Antonio, Texas, who conceived the idea that bats could be housed and made to multiply like bees and when sufficiently numerous would destroy all mosquitoes within a wide radius of the roosts which he had invented. It is now well known that the bats would not live in the roosts, and that even where there are great numbers of bats, a mosquito population may still maintain itself in sufficient density to produce an intense malaria.

There are other natural enemies of adult mosquitoes, such as swallows, ants, spiders and other insects. The mosquito is a frail animal, always in danger, short-lived and surrounded by natural foes and hazards. This has been discounted by nature, which provides a high rate of multiplication. The question is whether we can permanently increase the number of the enemies to the point where the anophelines are faced with local extinction. There is no evidence that anyone has been able to do this, or even to produce a measurable effect on anopheline density over a period of years in this way.

The *winter killing* of adults is practised in many places, and may be considered an intensification of a natural process. It is the common experience of all who have undertaken malaria control

in temperate climates that a cold winter or spring makes little or no difference to the anopheline density in summer. The insects recover their numbers in an amazingly short time from scattered survivors, after the most devastating experiences. In Durazzo, Albania, the salinification of the only breeding-place which could be found for miles around brought the numbers of anophelines down to such a point after three consecutive years of effective control that none was to be found in eight scattered catching stations visited weekly during the entire summer of 1936 (HACKETT, 1937). Three years before, these same stations had yielded 29,000 *elutus* on one visit.

Nevertheless, the silting up of the effluent canal produced an area of relatively fresh water in 1937, which amounted to several thousand square metres and which, in July, was producing as many anophelines per square metre as ever before, to our knowledge. It seems clear that no amount of winter killing, however meticulously carried out, could hope to destroy as high a percentage of hibernating anophelines as three years of salinification of the entire lake, and in view of the rapid return to normal July densities upon the temporary failure of this measure, it appears impossible to justify the expense of the incomplete results obtained by any sort of winter campaign we can hope to wage, with our present methods.

In contrast to the ineffectiveness of the above methods which lack the support of measured results, the attraction exerted upon anophelines by domestic animals is undoubtedly a major factor in determining the amount of transmission by certain vector species. In many parts of Europe, and often in the tropics above a certain altitude, as well as in scattered areas of low elevation throughout the world, we observe the phenomenon of "anophelism without malaria" which depends on the fact that none of the species present include man in their range of preferred hosts. Turning to malarious areas, we often find the same situation with regard to the majority of the anopheline fauna, masked by the presence of one or more vectors.

Thus in the portion of the Po delta which has been reclaimed for some years, we find that malaria has completely disappeared in spite of the continued presence of a dense anopheline fauna, consisting of the species *atroparvus*, *messeæ*, *subalpinus*, *typicus* and *claviger*, while, in the unreclaimed area which is still malarious, the harmlessness of the above species in the same density was for

a long time unappreciated, owing to the addition of the vector *elutus* to the faunal list.

Up to about 1930, our knowledge of the contact of the various species with man was based on the place of capture and the percentage of females found infected in nature. The precipitin test, as modified by RICE & BARBER (1935), to permit the rapid and inexpensive examination of large numbers of insects, is a procedure which can be used to determine much more accurately the relative importance of the common hosts of the anopheline species.

Our attempt to summarise present knowledge of this subject has shown how inadequate this is even with regard to the most dangerous vectors. Furthermore, the figures which we have do not often justify generalisations, because they are based on the study of selected groups of insects found resting in particular situations such as houses and stables, which always give highly different anthropophilic indices, none of which may be applicable to the anopheline population at large. Recent developments in technique have led to the cultivation of captive colonies of many anophelines, including all the palearctic vectors, and use of such material would permit a more accurate determination of instinctive host preferences.

Of the 180 species in the *genus Anopheles*, only some twenty-four have so far been shown to include man in their normal range of preferred hosts, and no more than fifteen of these have been incriminated as vectors over more or less widespread areas. The breadth of contact with man of the individual species in this group varies from over 80% in the case of such species as *gambiæ* and *minimus*, to 5% or less in the case of species like *philippinensis*, which are vectors only by force of the enormous numbers in which they are produced.

With such species as the latter, though man is included in their range, he is not the most preferred host, and it is conceivable that if the other hosts sufficiently outnumber man, then the vectorial capacity of such species would disappear, for it should be borne in mind that since a mosquito must bite two different men to transmit malaria, animal deviation acts to square, not double the chances against transference of infection. *A. maculatus* seems to be one case of this phenomenon. The carrier *par excellence* of the hills of the Malayan sub-region, it is almost without significance in the malarious areas of Assam and South India.

It has been suggested that this may be due to lack of fodder, and hence of cattle, and the fact that the populations of the latter area do not use milk as a significant item in their diet. Observations and experiments on these lines have been carried out by TOUMANOFF (1936) in French Indo-China. He showed that the two major carriers, *minimus* and *jeyporiensis* var. *candidiensis*, behave differently under the influence of stabular attraction. More than 50% of the *minimus* cannot be diverted by such means, whereas *jeyporiensis* is more susceptible to the influence of stabled animals, and is in nature the less dangerous of the two.

The same author worked through a long list of minor vectors, showing that they were almost completely deviated, naturally or experimentally, by animals, and could be very dangerous in their absence. The situation was not the same in every locality studied, and he says: "the data given . . . emphasise very well that the behaviour of any species can differ according to the country it inhabits".

The varying position of man on the scale of preferred hosts has from time to time been the reason for attempts to deviate certain vector species away from man, and thus interrupt malaria transmission due to them. The earliest of such attempts, made before the introduction of the precipitin test, was that of SCHÜFFNER. Having observed that, in Central Sumatra, stabled buffaloes were many times more attractive to *A. sinensis* than man, when faced with a *sinensis*-borne epidemic on the east coast of that island, where the buffaloes were not housed at night, he had a number of protective stables built, but without effect, the anophelines continuing to bite the labourers in their barracks to the same extent as before. WALCH (1932) later showed, with the precipitin test, that the east coast form of *sinensis* is but slightly attracted to animals. The presence of animals reduced their anthropophilic index from 90% to 83% only, whereas with the facultative human feeder *maculatus*, the index was reduced from 97% to 11%.

The only other attempt known to us at naturalistic control by this method was the work of FALLERONI against *labbranchiæ* at Ardea, Province of Rome (ESCALAR, 1933). He constructed a ring of pigsties around a small village situated on a hill. The result was a great diminution in malaria; but, unfortunately, the health authorities thought it necessary to catch and destroy all the

mosquitoes in the sties and in the houses daily throughout the season. This vitiated the experiment as a test of zooprophylaxis, although it may give some support to trapping as an antimalaria measure.

It is still a question what the effect of an animal barrier really is in the case of vector species like *labranchiæ* with a strong attraction to human blood. BARBER & RICE found that *elutus* in northern Greece were no more attracted to the local domestic animals than to man, and many infected *elutus* were found to have animal blood in their stomachs, showing that they turned easily from one kind of host to another. The animals acted merely to increase the blood supply and not to deviate the anophelines. P. F. RUSSELL (1934), in the Philippines, found that unstabled carabao, tethered at night at each of the four sides of a typical *nipa* house, not only failed to keep out *minimus* var. *flavirostris*, but actually increased the numbers of unblooded females in the house.

Flavirostris, like *elutus*, seems to bite man and cattle indifferently, and in such circumstances, animal barriers are not an effective protection. There is, however, a great deal of malaria transmitted by anophelines with a low anthropophilic index, and this is evidently the proper field for zooprophylaxis. The downward trend of malaria in northern Europe, and particularly in northern Italy, during the past century discredits the idea occasionally brought forward that a general increase in stabled domestic animals may increase both the production of such anophelines, and the numbers entering houses to bite man.

It is not surprising that we find so few practical applications of this principle, since the sudden deliberate increase of domestic animals in a rural population is not economically practicable as a purely antimalaria measure. Deviation is not to be obtained so much by improvising an animal barrier, as by stimulating a balanced agriculture with emphasis on animal husbandry, a process requiring time. The necessity of rotating rice with green fodder crops has increased the number of animals and brought about deviation unintentionally in the Po valley ; the same evolution is proceeding, under Government stimulation, with a definite antimalaria aim, on the Pontine Marshes. In the Volga basin, in view of the exclusive occurrence of anophelines with a low anthropophilic index, we may expect an analogous transformation to take place in the future, as intensive agriculture is extended.

V. GENERAL REMARKS AND CONCLUSIONS

It seems clear to the Committee that insufficient advantage is being taken, by those responsible for mosquito control, of our rapidly increasing knowledge of mosquito bionomics and of the subtle differences between harmful and harmless anophelines in instincts and adaptations. We do not suggest that this knowledge is as yet nearly adequate to the purpose ; it is, in fact, extremely fragmentary. Intensive cultivation of this field of research and scientifically planned applications of the results open up new prospects for malaria control, especially in rural areas now almost neglected.

Malaria is the farmer's worst enemy, but rural agricultural populations have little money to spend on its control. It has been demonstrated in this and other fields of public health that, by encouragement and education, even the poorest and most ignorant peasant can often be stimulated to work to protect himself and his family, as well as his crops, from parasites and disease. In such circumstances, any attempt to control malaria must be based on principles of simplicity and economy, and naturalistic measures offer almost the only hope of practical accomplishment. While not exclusively cheap and non-technical in application, they propose, where feasible, to utilise relatively costless local materials and such methods as the country people themselves might be expected to undertake of their own accord or else can be relied upon to maintain once they are set on foot. Such measures often improve the land or render some economical service to the population which, in the end, creates wealth, and it is in this direction that experimentation should be stimulated and progress achieved.

Engineers and health officers have not in general paid much attention to the practical implications of the findings of the biologist. There are several reasons for this attitude. Very often the biologist himself fails to present his results in a form intelligible or convincing to those with different training and viewpoint. He may be indifferent to the practical side of his research, and fail to do his part in establishing a satisfactory relationship between laboratory and field. The engineer, by virtue of his training, dislikes half-measures, and

is apt to regard imperfect results as partial failures rather than as partial successes. The health officer, responsible to a lay administrator, is naturally unwilling to experiment with the health of the population committed to his charge.

There is no need, however, to relax an established control of malaria transmission in order to experiment with naturalistic methods. These have special potentialities in those rural areas where no anti-malaria measures have until now seemed feasible. There is also frequent opportunity of combining naturalistic with other methods of control. There is no need whatever, except in the research field, for keeping a control method "pure". As for the reluctance and criticism arising from a fear of incomplete success or delay in securing results, we would like again to stress the point that, in dealing with rural malaria, speed and perfection are costly out of all proportion to their worth. We believe in taking a long-time view of the malaria problem and in having the patience to prefer steady progress, slow and imperfect though it may be, to an indefinite postponement of any work whatever.

Furthermore, it is evident, in all forms of naturalistic control, that we should bring as many different measures as possible to bear on every breeding problem, and should plan each measure so as to provide a generous margin of security over and above the minimum experimental requirements found necessary to establish control—principles referred to by WILLIAMSON as "combined operation" and "excess dosage".

The Committee submits the following conclusions :

1. *Naturalistic Measures.*—Malaria control methods constituting deliberate extensions or intensifications of those natural processes which tend to limit the production of mosquitoes or their contact with man may logically be grouped together in a class known as naturalistic measures.

2. *Adaptability to Rural Conditions.*—These naturalistic measures are of particular importance because they have special adaptability to rural areas where, up to the present time, little or nothing has been accomplished as regards malaria control. The Committee desires to stress the fact that rural malaria, especially in the tropics, is one of the principal unsolved problems in the field of public health

and that, in naturalistic methods of control, there appears to be a potential solution.

3. *Present Knowledge of Anopheline Biology Inadequate.*—Knowledge of mosquito ecology is increasing rapidly, but it is much less than is required to exploit the potentialities of naturalistic control. The Committee urges the importance of further study of mosquito biology. It suggests the need for special investigative units for observations of mosquito ecology in field and laboratory on a basis which definitely orients the studies towards control of mosquito-borne disease. In such units, there should be close co-operation between medical malariologist, biologist, chemist, engineer and agronomist.

4. *Experimentation by Health Officers.*—In addition to the need for special studies, it is concluded that many health officers could institute limited practical tests of naturalistic methods in their own areas. The comparative cheapness of many naturalistic methods should be a constant stimulus to the health officer to experiment with them, in the hope of saving funds from a limited budget and thus being in a position to extend activities to numerous rural populations whose financial resources hold out no other hope of relief from malaria.

5. *Integration of Malaria Control with Agriculture and Pisciculture.*—Since rural malaria is so closely bound up with agriculture and pisciculture, there is need to integrate these subjects with malaria control, and, in this respect, naturalistic methods have special potentialities.

6. *Relationship to Established Measures.*—The Committee opposes the substituting of antimalarial measures already well established and effective by naturalistic measures without the most careful and extended field studies and experimentation. The special applicability of naturalistic measures is to rural problems which have found no other practicable solution.

7. *Promising Measures of Larval Control.*—Some of the naturalistic methods proposed for larval control have had undoubted success in certain areas and have possibilities of more general application. These are herbage-packing, sluicing, shading and the use of exotic fish like *Gambusia*.

8. *The Attack on the Adult Mosquito.*—Among the naturalistic measures suggested against adult mosquitoes, the only one which seems to hold out any prospect of success at present, or to be worth expenditure of public funds, is that of deviating certain anopheline species from man to animals which are their preferred hosts. This is not, however, so much a measure which can be improvised to protect rural habitations, as it is an agricultural policy which administrations could encourage in areas where biological study of the vectors gives hope of eventual success.

9. *The Combined Attack offered by Most Naturalistic Methods.*—In general, the naturalistic methods suggested for larval control offer the advantage of a combined attack on more than one vulnerable point in the biology of the larva. For example, herbage-packing not only pollutes water, but also shades it, and may provide mechanical obstruction to egg laying. Salinification may destroy larval food as well as larvæ. Shading may limit oviposition or larval growth, or it may inhibit sheltering algæ.

10. *Necessity for Scientific Team-work.*—It is possible, as Sir Malcolm WATSON has recently said in connection with naturalistic control, that a “new era has opened for tropical regions”. That we are still so far from the goal of malaria control is due in part at least to the inadequacy of present and past studies on larval ecology. These have been left largely to medical malariologists and have not commanded the attention of biological, chemical and physical scientists. Only through balanced team-work can we hope (in the phrase of the diploma of British Civil Engineers) “to bend to the service of man the great forces of nature” in combating malaria.

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Figure 1.—Old type of fish-pond near Batavia, showing abundant growth of surface algæ, *Enteromorpha* sp., among which *A. ludlowi* larvæ thrive.



Figure 2.—New type of fish-pond near Batavia, after sanitating a clear surface, which gives no protection to *A. ludlowi*. Photo showing

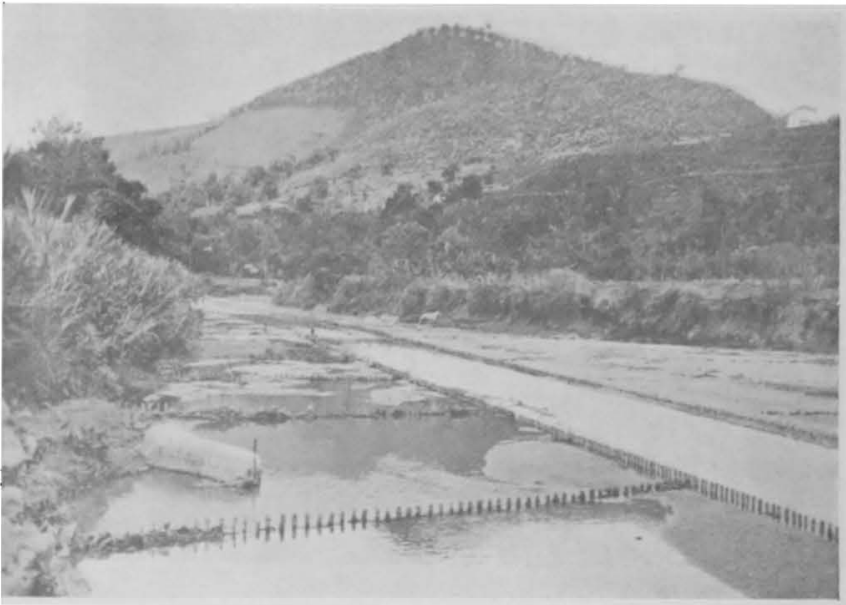


Figure 3.—River-training for mosquito control in Ceylon.



Figure 4.—Shade control in Assam. Looking down into a ravine densely shaded by planted *Tarapat* and infiltrated jungle.



Figure 5.—Drain in a Malay village covered by villagers with coconut fronds preventing anopheline breeding.



Figure 6.—Anti-larva sluicing in Malaya. One type of dam with hand-operated release.



Figure 7.—Anti larva sluicing in Malaya. Advancing wave or spate of water down a stream-bed



Figure 8.—Williamson's automatic tipping sluic-gate or "jigger", with counterbalancing weight, seen from up-stream, awaiting discharge when water level rises. (Courtesy of K. B. Williamson.)



Figure 9.—A similar jigger set in concrete about to discharge the reservoir into a flat grassy channel. (Courtesy of K. B. Williamson.)



Figure 10.—The jigger shown in Figure 9 automatically discharging a reservoir estimated to contain about 15,000 gallons of water. (Courtesy of K. B. Williamson.)

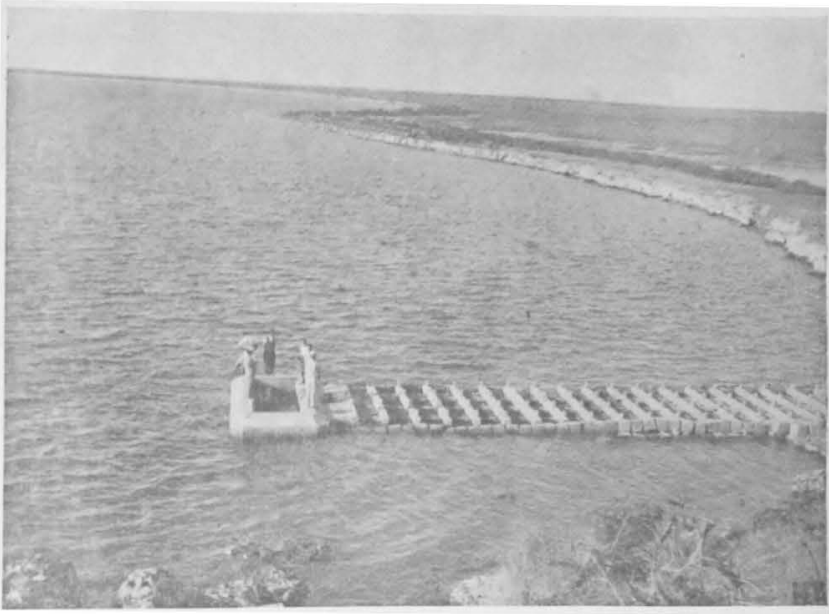


Figure 11.—Salinification of the Durazzo (Albania) marsh : Concrete basin with salt-water intake valves, connecting the Adriatic by triple line of meter tiles, with the fresh-water marsh seen in the background.

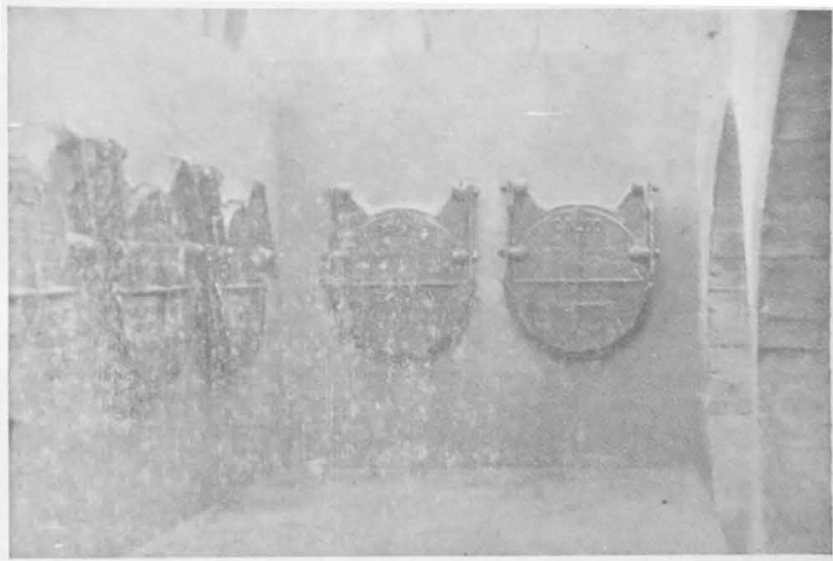


Figure 12.—Salinification of the Durazzo marsh : Inside of the intake basin, showing the inlet valves on the left and the mouths of two of the three tile lines on the right.

L A G U E O F N A T I O N S

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TABLE OF CONTENTS OF VOLUME VIII (1939).

	Page
Report on the Work of the Health Organisation between May 1938 and April 1939 and on its 1939 Programme	1
Health Indices :	
Their Place in Public Health Reports	60
Skeleton Standard Report on the State of Health of the Population and Factors influencing it	63
Rural Housing and Planning, by M. M. VIGNEROT	87
Leptospiroses, by Dr. B. WALCH-SORGDRAGER	143
Technical Study of the Comparative Effects of Morphine and of Certain Habit-forming Drugs : Eucodal, Dicodide, Dilaudide, Acedicone	387
Doping : A Study of the Means employed to raise the Level of Performance in Sport, by Dr. Ove BØJE	439
Rural Dietaries in Europe, by Dr. E. J. McDougall	470
Report on Bread in Several European Countries, by Dr. E. J. McDougall	498
Tuberculosis in Rural Areas, by Dr. G. ICHOK	551
The Organisation of Public Health in the Rural Areas of Belgium, by Dr. René SAND	617
<i>Annex</i> : Public Health Organisation of the Province of Luxembourg, by Dr. M. GRAFFAR	640
<i>Appendix</i> : Application of the Health Indices selected for Rural Districts to the Province of Luxembourg, by M. Willy SELLESLAOS	649
The Recent Trend of Medico-Social Policy in Europe, by Dr. R. H. HAZEMANN	662
Report of the Housing Commission on its Meetings held from June 26th to July 1st, 1939	732

	Page
Enquiry on the Assay of Gas-gangrene Antitoxin (Perfringens) :	
I. Comparative Titrations of Gas-gangrene Antitoxins (Perfringens), by J. IPSEN, M. LEWELLYN SMITH and A. SORDELLI	797
II. Comparison of Test Toxins from Various Institutes, by J. IPSEN	825
III. The Antigenic Constitution of Perfringens Toxins produced with Various Strains and Media, by J. IPSEN and R. DAVOLI	833
IV. The Preparation of Test Toxins suitable for the Assay of Gas-gangrene Antitoxins (Perfringens), by J. IPSEN	849
A Proposed International Standard for Gas-gangrene Antitoxin (Sordelli), by L. BENGSTON and J. IPSEN	856
Analysis of the Assays of Various Samples of the Gonadotrophic Substance of Urine of Pregnancy, by C. W. EMMENS	862
Memorandum on the International Standard for the Gonadotrophic Substance of Urine of Pregnancy	884
Analysis of the Assays of Various Samples of the Gonadotrophic Substance of Pregnant Mares' Serum, by C. W. EMMENS	887
Memorandum on the International Standard for the Gonadotrophic Substance of Pregnant Mares' Serum	898
Analysis of the Assays of Various Samples of the Lactogenic Substance of the Anterior Pituitary Gland, by C. W. EMMENS	901
Memorandum on the International Standard for the Lactogenic Substance of the Anterior Pituitary Gland	909

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**REPORT ON THE WORK
OF THE HEALTH ORGANISATION BETWEEN
JUNE 1938 AND APRIL 1939
AND ON ITS 1939 PROGRAMME**

CONTENTS

	Page
INTRODUCTION	2
I. PREVENTION AND TREATMENT :	
A. Malaria	3
B. Cancer	10
C. Leprosy	11
D. Bilharziasis	13
E. Rabies	16
II. MEDICO-SOCIAL ACTION :	
A. Rural Hygiene	17
B. Nutrition	27
C. Housing	32
D. Physical Education	36
III. EPIDEMIOLOGY AND HEALTH STATISTICS :	
A. Epidemiological Intelligence Service	38
B. Decennial Revision of International Lists of Causes of Death	40
C. Health Indices	41
IV. BIOLOGICAL STANDARDISATION	43
V. CAMPAIGN AGAINST NARCOTIC DRUGS	52
VI. UNIFICATION OF PHARMACOPOEIA	53
VII. ANTI-EPIDEMIC ACTION IN CHINA	55

INTRODUCTION

The Health Committee's three-year plan of work extends up to the end of 1939; its results, therefore, can only be ascertained next year.

The present report, however, endeavours to show that the programme is being steadily and systematically carried into effect in accordance with the general ideas on which it is based.

At first sight, the work done may seem to be rather varied, but its deeper unity of purpose can nevertheless be easily discerned. It consists in providing public health administrations with data, and with information on means for solving their technical problems, and even giving them the direct assistance which they may require in the fulfilment of their daily tasks.

The data furnished consist, in the first place, in the publications of the Service of Epidemiological Intelligence and Public Health Statistics, and also in the results of the investigations designed to throw light on the conditions surrounding certain public health problems. An instance in point is the report on bilharziasis now under preparation, the monographs which will be laid before the European Conference on Rural Life, and, lastly, the collective study tours and the international course in malariology.

In the second place, this international information has reference to the means of action which are available to public health administrations, for the purpose both of combating disease by organised action and of raising the level of health. Examples are afforded by the general reports of the Malaria Commission and of the Housing Committee. Similarly, conferences and meetings of experts are held in order to collate and compare the experience gained in various ways on the national plane and to arrive in this way at general conclusions, with the help of special technical enquiries where necessary.

The Health Committee is also endeavouring to introduce some measure of international uniformity into the standards, units of measurement, formulæ, terminology and even methods of investigation used in the various countries. Examples of this kind of

work are biological standardisation, unification of pharmacopœiæ, studies of public health indices and malaria terminology and the handbook on nutrition surveys.

Finally, the help given by the Health Committee to public health administrations may be of a direct character, as in the case of the assistance given to China in its anti-epidemic campaign.

All this activity can be summed up in the expression "international collaboration". Such collaboration is only of value if it rests upon a sound technical basis, that is to say, upon the best scientific knowledge available in the various countries. This is why it is incumbent upon the Health Committee to extend its thanks to the members of its various technical committees.

I. PREVENTION AND TREATMENT

A. MALARIA

At the third international Congress, held at Amsterdam in September 1938, Professor SERGENT, President of the Malaria Commission, described the work of the Commission and drew a striking picture of the work achieved since the previous Congress¹ with the object of providing health authorities with improved means of action in their campaign against malaria. He showed that the work could be classified under four main headings : drug prophylaxis, anti-malarial action, epidemiology and technical research—a classification which could undoubtedly be adopted with advantage in future.

1. *Drug Prophylaxis.*

Speaking at the last annual meeting of the General Advisory Health Council, Professor SERGENT had himself outlined the contents of the fourth general report of the Malaria Commission, which, like the third report, deals with the question of malaria treatment. The latest report marks a definite stage in the work of the Commission, representing as it does the result of a series of general and

¹ The second international Malaria Congress was held at Algiers in 1930.

experimental studies on anti-malarial drugs, more particularly synthetic products.

It must not be thought, however, that those studies, which occupy a position of paramount importance in the Commission's programme, are looked upon as being complete. At no stage have they lost sight of the original purpose in view—namely, to bring about a reduction in the cost of treatment and an extension of the use of anti-malarial products, in order that increasingly large numbers of patients may benefit by the treatment. As is shown below, the members of the Commission are pursuing their own research work and will continue to communicate the results to the Secretariat. But, in the view of the Health Committee, the progress already made in this work and the conclusions which may be deduced from it as regards treatment and prevention justify the calling of an inter-Governmental conference on anti-malarial drugs, to study production, prices and methods of distributing such medicaments.

As far back as 1933, the Health Organisation had suggested such a conference, investigations at that date having shown that the consumption of quinine was well below the minimum necessary for the treatment of the known cases of malaria. It was, however, decided to adjourn the date in view of the trials then planned with totaquina and synthetic drugs. The results of those trials were embodied in the third and fourth general reports, in which the Malaria Commission expresses its opinion as to the resources now available to the health administrations in endemic areas for the treatment and drug prophylaxis of malaria. This therefore seems a suitable moment for reverting to the project of an inter-Governmental conference.

The Council of the League has consulted the Governments concerned on the desirability of summoning a conference, and favourable replies have been received from the following countries : Union of South Africa, United States of America, Australia, Belgium, United Kingdom, Bulgaria, Egypt, France, Greece, Hungary, India, Iraq, Mexico, Peru, Poland, Roumania, Turkey and Yugoslavia.

A questionnaire has just been despatched to the various health authorities with a view to supplementing and bringing up to date the relevant documentation in the possession of the Secretariat (document C.H. /Malaria 272). This questionnaire covers the present

state of production in relation to world requirements, cost price, price to buyers and retail prices and methods of distribution. The Secretariat has also approached the cinchona-producing countries with plantations in full activity and countries which have made experiments in cultivation. Finally, it is endeavouring to collect information on the consumption of quinine for use in diseases other than malaria.



In the sphere of research relating to treatment and prophylaxis, the following contributions have been received by the Secretariat :

(a) Lieut.-Colonel SINTON has shown that the stimulating action of quinine and atebirin on the appearance of gametocytes, observed by several workers during treatment of natural infections, is not found in the case of intentionally induced infections with *P. falciparum*. These results once more confirm the value of the experimental evidence contributed by malaria therapy to the study of natural infections (document C.H./Malaria 267).

(b) SINTON, HUTTON and SHUTE have selected proseptasine from among the sulphonamides and investigated its properties in the causal prophylaxis of infections induced with *P. vivax* and *P. falciparum*. They show what are the determining factors as evidenced by rapidity of absorption, concentration in the blood and period of elimination. Their investigations are still at the experimental stage (document C.H./Malaria 271).

(c) The Socola Malaria Therapy Station, in Roumania, has attempted to determine, by experimental means, the comparative value of the various methods of administering atebirin in causal prophylaxis. Some patients undergoing therapeutic treatment were given intravenous inoculations of a known number of *P. vivax* or *P. falciparum* sporozoites, once or twice a week. The administration of atebirin was stopped either simultaneously with that of the sporozoite inoculations or three weeks after the last infection.

After observations lasting from twelve to thirty-four weeks, CIUCA, BALLIF, CHELARESCU and LAVRINENKO arrived at the following results :

Small daily doses (0.06 gr.) of atebirin did not prevent the appearance of attacks during prophylactic treatment.

The bi-weekly dose of 0.20 gr., continued for three weeks, was definitely more effective, but still failed to inhibit the clinical attack, the incubation period lasting from fifty-two to eighty-seven days. With the same dosage continued for six weeks, however (without re-infecting the patients in the last three weeks), the results were much more satisfactory.

The conclusion appears justified that a bi-weekly dose of 0.20 gr. of atabrin continued throughout the malaria season gives results which are all the more satisfactory if the drug is administered for a further three weeks after the risk of re-infection has disappeared (document C.H. (Malaria 265).

2. *Anti-Malaria Action and Anti-Anopheline Measures.*

In turning to the question of "naturalistic" methods, which are so closely linked up with the special characteristics of the vector species and with local conditions, the Malaria Commission was chiefly concerned with the problem of rural malaria in poorer countries.

A critical survey of what had so far been done in this connection was first of all required. This need was met by the publication of a memorandum by Dr. L. W. HACKETT, Dr. P. F. RUSSELL, Dr. J. W. SCHARFF and Dr. R. SENIOR WHITE.¹

Naturalistic methods are there defined as "the deliberate extension or intensification of natural processes which tend to limit the production of mosquitoes or their contact with man". In their able report, these authors draw attention to the need for fuller investigations into the biology and ecology of anopheles. They lay stress on the desirability of establishing experimental centres and of studying the cost of measures before proceeding to apply them. All such measures should be fitted into an agricultural and fish-breeding plan, especially in regions in which it has not proved possible to employ other anti-anopheline methods.

A note by Lieut.-Colonel COVELL (document C.H. (Malaria 256) describes a number of naturalistic methods employed in India: larvicidal fish, sluicing and flushing of water courses, silting, etc.

The study of these methods is to be continued.

¹ *Bull. Health Org.*, 1938, 7, 1016.

3. *Epidemiology.*

An exceptionally severe epidemic in Ceylon in 1935 had formed the subject of two papers, one by Professor SCHILLING and one by Dr. SENIOR WHITE, revealing certain gaps in the existing knowledge of malaria epidemiology in the island. The Malaria Commission pointed out the desirability of investigations to determine the causes of recurring epidemics of this type in certain countries.

(a) Lieut.-Colonel COVELL has forwarded the results of studies carried out after the Punjab epidemic of 1908 by CHRISTOPHERS—and subsequently taken up and carried still farther by GILL—with the object of arriving at a forecast of epidemics and even predicting their geographical extension and relative gravity. According to GILL (document C.H./Malaria 257), the determining factor is a loss of equilibrium between infection and immunity. The data on which forecasts are based comprise four factors: the humidity and rainfall factor, the spleen-rate factor, the economic factor, and lastly, the “epidemic potential” factor represented by the coefficient of variability of the mortality rate over a long period.

A scheme of action has been instituted in India with the object of lessening the effects of future epidemics (document C.H./Malaria 257).

(b) A report by Lieut.-Colonel NICOL (document C.H./Malaria 258) outlines the measures taken against malaria epidemics in the Punjab, where the disease accounts for some 130,000 deaths annually. The report embodies the instructions sent to medical officers and gives a table showing the various vector species and the methods of destruction.

(c) A note by PARROT and CATANEI (document C.H./Malaria 270) on factors connected with the outbreak of epidemics in Algeria stresses the important part played by premunition.

(d) Professor SCHWETZ laid before the Malaria Commission a proposal that a systematic study of *endemic malaria in Central Africa* should be undertaken, with particular reference to the distribution of the different species of plasmodium among the native inhabitants and the connection between quartan fever and local

species of anopheles. The Secretariat has approached authorities in Equatorial, West and East Africa with a view to collecting epidemiological information on the species of plasmodium, their seasonal frequency and their distribution according to age-groups. The information thus obtained is to be completed by an examination of the geographical distribution of varieties of anopheles.

4. *Technical Research.*

It will be remembered that the Malaria Commission drew up a programme of research which malariologists were asked to carry out. An account is given here of contributions received in connection with the bionomics of anopheles and malaria immunity.

(a) *Bionomics of Anophelines.*

This study, which is connected with the differentiation between species of anopheles, has been facilitated by the instructions drawn up on the basis of a preliminary report which was the work of L. W. HACKETT and A. MISSIROLI.¹ It has led to further research, dealing more particularly with the *longevity of anopheles*.

SINTON and SHUTE have shown that anopheline longevity is not affected by malarial infection except when the latter is extremely severe or circumstances are otherwise unfavourable.

The collaboration established, under the auspices of the Health Organisation, between the Horton Laboratory and the Roumanian experimental stations led to the publication of a valuable report by SHUTE and UNGUREANU on the infection-potential of *A. atroparvus*, *A. typticus* and *A. messeæ*, in relation to the varying longevity of these anophelines in Northern Moldavia. The study reveals significant differences in the capacity of the three varieties as vectors.

Further progress has been made in determining the geographical distribution of *A. maculipennis* varieties. The Pasteur Institute at Algiers has forwarded the results of investigations carried out on the subject in Algeria under the direction of Et. SERGENT. The Institute has also drawn attention to certain anatomical peculiarities of the eggs of *A. maculipennis* (document C.H. /Malaria 269).

¹ *Quart. Bull. Health Org.*, 1934, 3, 654.

(b) *Immunity.*

The research work of CIUCA, BADENSKI, IONESCU and TERITEANU provides experimental proof of the mechanism of immunity in man. If a large quantity of *P. Knowlesi* virulent blood is injected into the blood stream of immune paralytics, their own blood has, within six hours, lost all power to infect *M. rhesus*. It can therefore be concluded that protective principles which destroy the parasites in less than six hours exist in the blood of immune human beings (document C.H. /Malaria 262).

5. *Malaria Terminology.*

A sub-committee consisting of Sir Rickard CHRISTOPHERS (Chairman), Dr. L. W. HACKETT, Professor W. SCHUFFNER and Professor SERGENT has undertaken the difficult task of standardising the terminology used by malaria workers. It is preparing a commentary, with descriptions, explanations and equivalents of the terms, and an alphabetical glossary giving the definitions required.

This undertaking, which is due to the initiative of Dr. EJERCITO, will satisfy a manifest need, as the same word is not at present invariably given the same meaning by the different schools of malarialogists, while some terms thought to be synonymous do not, in fact, always convey the same idea.

The glossary will be published in English and French, and possibly in other languages later.

6. *Fifth International Course in Malariology.*

The first part of the course was held at the King Edward VII College of Medicine, Singapore, from April 25th to May 20th, 1938.

The course was attended by eighteen medical graduates sent by the Far Eastern health administrations. One came from Australia, two from the Philippine Islands, five from India, one from the Netherlands Indies, one from Indo-China, six from Malaya and two from Siam.

Lectures were given by the teaching staff of the College of Medicine and officials of the Straits Settlements Government Health

Service. Professor H. GAILLARD, Director of the School of Medicine and Pharmacy, Hanoi, lectured in protozoology, pathology and immunity.

In addition, special lectures were given by Dr. R. B. JACKSON, Malariologist, Hong-Kong, by Dr. J. G. OVERBEEK, Head of the Malaria Control Service, Java, and by Mr. J. J. A. FLOOR, technical adviser to the Asiatic Petroleum Company.

After the termination of the first part of the course, sixteen candidates spent ten days in the State of Selangor, Federated Malay States, in practical work in the field, and subsequently paid a visit to Penang to study methods of sluicing for the control of hill malaria.

B. CANCER

For the past ten years or so, the work of the Health Organisation on cancer has been confined to one limited and specific object — the study of the effects of radiological treatment on the neoplasm of the *cervix uteri*—statistical studies previous to 1929 having revealed a striking increase in the mortality from uterine cancer.

This enquiry is necessarily a long-drawn-out undertaking. The original intention was to publish information about the methods employed in the principal clinics which had favourable results to record, with a view to dispelling possible misunderstandings as to the value of radiological treatment. But the Committee of Experts which met in 1928 soon came to the conclusion that it would be useless to attempt to utilise the data published by the clinics without first standardising their methods of observation, their clinical records and the methods employed in the statistical assessment of recurrences and survivals. The essential purpose of the enquiry now proceeding is accordingly to obtain a uniform statistical presentation of the results of treatment. The enquiry was started in 1929, the first steps taken being to lay down precise and uniform rules for the definition of the various stages of uterine cancer and for the recording of the results of treatment.

It was understood that a period of five years should be allowed to elapse before these results were published, and that is why the first report did not appear till July 1937. It described the clinical condition in 1936 of patients treated in 1930.

The second annual report (document C.H.1338) was published in 1938. It describes the results observed in 1937 in cases treated in 1931 and preceding years in nine different clinics, as compared with six in the first report.¹

The Committee directing the enquiry is doing its best to ensure uniform statistical presentation.² In its second report it drew attention to the need for securing even greater comparability in the statements supplied by the clinics. It also slightly modified the definitions of the various stages of the neoplasm and gave them greater precision.

The third annual report will appear this year ; its preparation is already well advanced. It will be based on results supplied by about twenty clinics. In this connection, the Committee has decided not to include clinics whose data do not comprise at least 100 cases—on the understanding, of course, that their results may be dealt with later when they arrive at that figure.

C. LEPROSY

In 1931, the Brazilian Government placed at the disposal of the League of Nations an International Centre for Research on Leprosy, established at Rio de Janeiro. The object of the centre was to undertake any work which might contribute towards the prevention of leprosy by means of epidemiological, clinical and biological research, with special reference to treatment. The Centre was therefore instructed to promote international co-operation by

¹ The following are the nine clinics :

- The Centre des Tumeurs de l'Université de Bruxelles ;
- The Liverpool Radium Institute ;
- The Marie Curie Hospital, London ;
- The Radium Centre for Carcinoma of the Uterus, London ;
- The Institut du Radium de l'Université de Paris ;
- Radium-hemmet, Stockholm ;
- The Hospital for the Treatment of Cancer, New York ;
- The Woman's Hospital in the State of New York ;
- The Institut du Cancer, Paris.

² This Committee has the following composition :

- Professor J. HEYMAN, Radium Institute, Stockholm, *President* ;
- Dr. A. LACASSAGNE, Radium Institute of the University, Paris ;
- Lieut.-Colonel A. B. SMALLMAN, Ministry of Health, London.

organising a specialised course of instruction open to doctors and hygienists of countries desiring to take advantage of these facilities.

The Research Centre was inaugurated on June 12th, 1934. Its efforts have been concentrated on epidemiology, chemistry and pharmaceuticals, treatment and diagnosis, bacteriology and immunology.

In pursuance of agreements concluded with a number of Brazilian States, the Centre has carried out studies on the incidence of leprosy, with the particular object of determining the relationship between endemicity and the geographical and climatic conditions, housing and standard of living of lepers. The data collected in this manner are now being collated and will be published in a general report. More elaborate epidemiological studies are still being carried out in northern districts of the State of Rio de Janeiro, which possesses a network of institutions for combating the disease and for isolating cases showing open lesions.

In 1935, the League of Nations sent a specialist in chemotherapy, Dr. H. I. COLE—former chemist to the Culion Leper Colony in the Philippines—to the Centre. Under his direction, the Chemistry and Pharmaceutics Section undertook the manufacture of specific remedies for the purposes of the Centre's therapeutic research and for supplying the various institutions and countries collaborating with the Centre. During 1938, 864 litres of remedial preparations for use in the treatment of leprosy were supplied in this way; they included iodised ethyl esters, creosoted ethyl esters, and purified *Hydnocarpus Wightiana* oil.

The same Section has also proceeded with investigations primarily designed to increase the therapeutic action of chaulmoogra remedies and to utilise Brazilian chaulmoogras. Dr. COLE and his colleagues have succeeded in isolating in a pure state two new homologues recognised as active principles of chaulmoogra acid—namely, the alepic and aleprylic acids. A third, aleprestic acid, has now been purified up to 75%.

In addition to the above three homologues, Dr. COLE has also succeeded in extracting chaulmoogric, hydnocarpic, gorlic, oleic and palmatic acids from the *Hydnocarpus Wightiana* oil.

Research into diagnosis and treatment has been carried out at the Curupaity Leper Colony and in the dispensaries of the Ministry

of Public Health. The use of lepromine and lepronine, the dosage of chaulmoogra derivatives, and the influence of diet—particularly of large doses of pure vitamin A—on the course of the leprous infection have been investigated. Professor OZORIO DE ALMEIDA has continued to work on a method of treatment using oxygen under pressure on patients previously sensitised with small doses of methylene blue. The results were laid before the Cairo Congress, after which Dr. WADE, President of the American Leprosy Foundation, proceeded to Rio de Janeiro to investigate the method ; this will probably be tried out at the Carville Leper Colony in the United States.

The Centre has also done some work on leprosy in rats, the Witebsky test, lepromines and the lepromatous antigen.

The Centre's laboratories have been thrown open to young workers. An annual course of leprology has been organised in conjunction with the Faculty of Medicine, the Oswaldo Cruz Institute and the Public Health Department ; it was attended by twenty-one doctors in 1938. Finally, a Review of Leprology, including contributions from foreign collaborators, is now published under the auspices of the Centre.

* * *

The agreement concluded between the Brazilian Government and the League of Nations was for a period of five years and terminates on June 12th, 1939.

A general report on all the work carried out by the Centre is to be published before the end of 1939.

D. BILHARZIASIS

In June 1939, Dr. HILMY Bey, Under-Secretary of State at the Egyptian Ministry of Public Health, asked the Health Committee to undertake work on bilharziasis similar to that of the Malaria Commission. He argued that it was manifestly essential, in view of the dangerous spread of the disease, to organise international collaboration in order to ensure effective preventive action by the administrations concerned.

Bilharziasis in its three recognised clinical forms is found, generally speaking, in all tropical and sub-tropical countries ; its geographical distribution is, of course, conditioned by that of those species of bilharzia which are parasites of man, and by the distribution of the local species of vector mollusc.

In response to Dr. HILMY Bey's proposal, the Health Committee convened a meeting of experts¹ in December 1938, under the chairmanship of Professor LEIPER, of the London School of Hygiene and Tropical Medicine. Their report (document C.H.1395) notes that, while the knowledge so far available affords an adequate basis for the control of the disease, special emphasis should be placed on the importance of local factors—namely, the species of vector mollusc and its ecology, the conditions of life and the habits and customs of the population, and, lastly, methods of agriculture and irrigation. Bilharziasis constitutes a public health problem alike for the country in which it is prevalent and for the adjacent regions. Migration, colonisation and troop movements are factors which cannot be ignored if the introduction and spread of the disease is to be prevented.

Attention has been directed to the danger that bilharziasis may be introduced into Tunis, Southern Morocco and even Algeria. In Tanganyika and Rhodesia, it appears to be connected with the importation of labour into thinly populated territories.

Large-scale investigations have been carried out, more particularly in Egypt and the Sudan, notwithstanding the scepticism arising from difficulties in the matter of treatment and prophylaxis. Although these investigations date back only as far as 1930, upwards of 560 notes and memoranda are already available.

* * *

The experts agreed as to the expediency of collecting fuller information about the various local factors, by means of a critical

¹ The names of these experts were as follows :

Dr. R. T. LEIPER, Professor of Helminthology and Director of the Department of Parasitology at the London School of Hygiene and Tropical Medicine (*President*) ;

Dr. O. F. H. ATKEY, late Director of the Sudan Medical Service ;

Dr. E. BURNET, Director of the Pasteur Institute, Tunis ;

Professor Edmond SERGENT, Director of the Pasteur Institute, Algiers.

survey, to be undertaken by specialists, of the literature published up to date, including the reports of public health services, but omitting purely clinical and pathological data. Supplemented by a bibliography, such a survey of the existing knowledge and means of action available at the present time would be invaluable to health officers working in the field. It might be accompanied by an illustrated nomenclature of the species of mollusc which are concerned in the propagation of bilharzia diseases, and by regional bibliographies of the fresh-water molluscs.

While recognising that there are few tropical diseases in which the ætiology is so clear, treatment so satisfactory, or preventive measures so obvious, the experts are of opinion that bilharziasis cannot be considered as though it constituted an isolated problem in the health of a community. All those factors which come within the scope of rural hygiene have a close bearing upon it : the soil, agriculture, irrigation, housing, water-supply, nutrition and sewage disposal. The study of bilharziasis is therefore bound to contribute to the elucidation and solution of the wider problem of rural hygiene.

Finally, it would be desirable to encourage further investigation and research, especially into the following problems :

I. *Epidemiology* :

1. Regional surveys of the incidence of different species of *Schistosoma* in man and domestic animals.
2. Clarification of the zoological and biological relationships of *S. hæmatobium*, *S. mattheei*, *S. intercalatum* and *S. bovis*.
3. Regional surveys of molluscan fauna, observation of seasonal variations, breeding-seasons, natural enemies.
4. Observations on seasonal variations in the incidence of *Schistosoma* infections of known molluscan vectors.
5. Experimental determination of the susceptibility of molluscan species not yet incriminated as natural vectors.
6. Observations on the distribution of vectors outside known regions of *Schistosoma* infection.

II. *Prophylaxis* :

1. Assessment of relative value of present methods for destruction of molluscan vectors ; new methods.
2. Assessment of relative value of present methods of treatment ; new methods of treatment, especially simplification of mass treatment of carriers and young children for prophylaxis (*per os*).

III. Education and Propaganda :

Possibility of utilising local customs and conditions for purposes of education and propaganda.

E. RABIES

On the occasion of the fifteenth anniversary of the introduction into Roumania of anti-rabic vaccination, and as a tribute to the memory of Professor Victor BABES, an international Conference was held at Bucharest in May 1938 ; it was attended by representatives of the Roumanian Health Ministry and anti-rabic institutes, the Pasteur Institute of Paris, the Veterinary School of Alfort, and the anti-rabic institutes of Cracow, Istanbul, Kassa (Kosice), Warsaw, Vienna and Zagreb. The Health Committee was represented on this occasion by Professor CIUCA.

The Conference recommended that closer co-operation should be established, under the auspices of the Health Committee, between the anti-rabic institutes of Central and Eastern Europe. It was contemplated that this co-operation should not be limited to the mutual communication of technical data or statistics, but that facilities should be provided, in particular, for members of the scientific staff of a given institute to spend some time in others in order to study the results obtained with the vaccination methods there applied.

The Health Committee favourably received this suggestion, and arrangements have already been made for one of the members of the Jassy Anti-Rabic Institute to visit the Novi Sad Institute in order to familiarise himself with Hempt's method.

The Bucharest meeting also intimated to the Health Committee that the need was felt for a further international rabies conference to be attended by representatives of anti-rabic institutes throughout the world. Before, however, considering the possibility of convening such a conference, the Health Committee felt that it should have before it supplementary information as to the main questions which arise at the present time in the field of rabies prevention. Professor G. PROCA, former Director of the Babes Institute at Bucharest, has kindly undertaken to prepare a comprehensive report on the various aspects of this question.

Although, under the terms of the decision taken by the Health Committee, the analytical reviews of the results of anti-rabic vaccination are henceforward to be prepared only every two years, it appeared preferable to keep to the one-year interval in the sending of questionnaires to institutes. It may be anticipated that the ninth review—which will appear in 1939 and will deal with the results for the years 1936 and 1937—will raise the aggregate figure of persons treated available for statistical analysis above one million.

II. MEDICO-SOCIAL ACTION

A. RURAL HYGIENE

The report submitted to the General Advisory Health Council at its annual assembly last year gave a prominent place to the Health Organisation's work on problems of health in rural areas. An account was given of the Bandoeng Conference of Far Eastern countries (August 1937). Moreover, two similar events were in preparation at the time, one concerned with the American continent, and the other of a more general character—namely, the European Conference on Rural Life.

In 1939, these conferences still stand in the forefront owing to their important bearing on the work of the Health Organisation. While stimulating the interest of the national administrations, and of the public generally, in the protection of the rural populations, they also provide an opportunity of determining how best to give practical effect to the conclusions arrived at in the technical work on disease prevention and medical and social protection which has been carried out under the auspices of the Health Organisation. Rural hygiene is conceived of as the sum total of all the activities which public authorities are called upon to undertake in order to improve the health of economically backward populations. Those activities are complex and diversified; they are closely bound up with local circumstances and contingencies; hence the need is not so much for new, untried solutions as for a joint examination of conditions and of methods of action in order to turn scientific knowledge and technical experience to practical account.

The *Bandoeng Conference* (August 3rd-13th, 1937) submitted a series of conclusions that were reviewed in last year's report. The Conference had asked that the Health Organisation, and, in particular, the Singapore Bureau, should collaborate in the action it had suggested, with a view to establishing international co-operation and providing for the comparison of methods and results. This is a lengthy task, which must perforce occupy a number of years. A brief outline of the progress made in the past twelve months is given below.

At the 1936 Assembly, thirteen delegations of Latin America and the delegations of Spain and the Netherlands requested that *a similar conference should be summoned for the benefit of the American continent*. Subsequently, the Mexican Government asked that the Conference should be held at Mexico City; the date was then fixed for November 1938, and the agenda was published in last year's report.

At the end of the summer of 1938, however, the Mexican Government pointed out that the complexity and importance of the questions to be considered hardly permitted of adequate preparation within the period stipulated. It also urged that some Governments would not be in a position to bring their delegations together in time, as the Pan-American Health Conference was to be held just before and the eighth International Conference of American States very shortly after. It was accordingly decided to adjourn the date of the proposed conference; no final decision has yet been taken with regard to another date.

The Health Organisation and the International Labour Office have already completed the preparation of part of the technical documentation in Spanish, relating more particularly to malaria, the co-operative movement, nutrition and dietary surveys. A report on curative medicine in rural areas, by Dr. DE BARROS BARRETO, has been published in the *Bulletin*,¹ and steps have been taken, in agreement with the Pan-American Sanitary Bureau, to complete the work required in preparation for the Conference.

The *European Conference on Rural Life* is to open on October 16th, 1939. It is dealt with in some detail on page 23, in view of the prominent place it occupies in the Health Organisation's programme of

¹ *Bull. Health Org.*, 1938, 7, 989.

work for 1938 and 1939. It may be claimed that most of the technical organs of the League of Nations are this year assigning a large part of their working resources to the task of ensuring the success of this Conference, which appears to have aroused keen interest among the European public administrations.

*Inter-Governmental Conference of Far Eastern Countries
on Rural Hygiene.*

During the eighteen months which have elapsed since the Conference ended, most of the Far Eastern countries have taken steps, in liaison with the Singapore Bureau, to give effect to its recommendations, an account of which was given last year.

Health Surveys.

Health surveys have already been set on foot in one district of the Punjab, and in the State of Negri-Sembilan in Malaya. They are experimental in character, and are subsequently to be extended to other areas, provinces or States. In the Netherlands Indies, two areas have been selected for detailed surveys on the lines of the scheme annexed to the Conference's report. In the Philippine Islands, the possibility of health surveys to be carried out by ten epidemiologists in particular districts is under consideration. In Hong-Kong, a general economic survey is to be carried out, and the conclusions of the Conference will be given full consideration.

The Singapore Bureau has distributed to all health administrations the publications of the Health Organisation likely to be of use to those responsible for carrying out such surveys.

Anti-Tuberculosis Work.

The Government of the *Netherlands Indies*, with the assistance of private organisations grouped into a Central Association for Tuberculosis Control, has set up a number of consultation bureaux with X-ray equipment for screening. It is also proposed to establish five sanatoria. There is, however, difficulty in obtaining a sufficient number of medical officers with special knowledge of tuberculosis.

A Committee is also investigating the incidence of tuberculosis on the basis of the " Rules " published as an annex to the report

of the Bandoeng Conference (pages 102-109) for mass research on tuberculin sensitiveness. In the course of the investigation, the Mantoux test has already been applied to 30,000 persons of both sexes in the Poerwokerto Health Unit area. The concentration of tuberculin administered was, in the first place, 1 in 10,000 and subsequently 1 in 100 for those who had not reacted. The results have not yet been analysed.

In *Indo-China*, the authorities are organising case-finding and treatment services, one of the chief features of the organisation being travelling dispensaries with X-ray services.

In the *Philippine Islands*, much of the same programme has been adopted, comprising diagnostic work, sanatorial treatment and preventive work. In addition, an extensive programme of epidemiological, bacteriological and clinical research has been drawn up. The Tuberculosis Division of the Health Service is to be provided with nine mobile X-ray units, which will also be able to give pneumothorax treatment and provide for the general treatment of patients. At Manila, there is a modern institute at which tuberculosis staff undergoes specialised training.

At *Hong-Kong*, the Director of Medical Services proposes to carry out a survey of the incidence of tuberculosis infection, the plans for which have been drawn up in conjunction with the Director of the Singapore Bureau.

In *Malaya*, a similar survey was carried out in 1938 in the schools at Kuala Lumpur, where the modified Mantoux test was applied to 1,500 pupils. The Director of Medical Services proposes to extend the survey to the various rural areas of Malaya.

The Indian Research Fund Association has had plans drawn up for a survey to ascertain the incidence of tuberculosis infection, the morbidity rate, the mortality rate and the forms taken by the disease in certain representative areas of *India*. Several of the Indian States have also begun to organise anti-tuberculosis work. The same is true of *Burma*, where plans for an anti-tuberculosis campaign are under discussion.

Nutrition.

After consideration of the recommendations of the Bandoeng Conference, the Government of the *Netherlands Indies* has drawn up a three-year programme of work, providing for practical inves-

tigations to bring out the most serious deficiencies in the nutrition of the inhabitants. A medical officer of the Public Health Service has been appointed to direct and co-ordinate the investigations, which will be carried out under the direct supervision of native assistant advisers familiar with local conditions. The Nutrition Institute will in the meantime proceed with the following technical investigations : physical condition and state of nutrition, incidence of deficiency diseases, analysis of foodstuffs, etc. This programme of work will be carried out in liaison with the Technical Commission of the Health Organisation.¹

In the *Philippine Islands*, a law is to be introduced setting up an Institute of Nutrition in accordance with the recommendations of the Bandoeng Conference. The Institute's duties will be to conduct original research, to determine the food value of local foodstuffs, to determine the food requirements of the people, and to formulate sound dietary standards. The foundation of the Institute will not, however, put an end to the educational work carried on by the Department of Public Health.

The Government of *Indo-China* has set up a Commission comprising representatives of the Departments of Public Health, Agriculture, Economic Affairs and Public Works, which has considered the general recommendations of the Bandoeng Conference with a view to deciding how far Indo-China could conform to them.

The Commission is making an effort to improve rice crops and to promote the cultivation of foods to make up the deficiency of proteins and fats. The necessary investigations are being carried out by the Agricultural Research Institute and the Pasteur Institute.

In *Siam*, the possibility of creating a Division of Nutrition in the Department of Public Health is under consideration. A medical officer was sent to Japan for six months to study nutrition questions. The Director of the Singapore Bureau has also been asked for information regarding possible programmes of study for a medical officer of the Department in either Europe or eastern countries.

A survey lasting three months has been carried out in various parts of the country to obtain data regarding the physical condition of the people, and its relationship to nutrition.

¹ For further details on the Institute's work, see document C.H./Com.Exp. Allm.55.

attention upon the part which the public authorities play or should play in any endeavour to bring about an improvement in living conditions among the inhabitants of rural districts. The term "public authorities" is here to be taken in its widest sense, to include, throughout the scale, all authorities and all organisations working for the improvement of rural life, either in general or in some particular sphere. The Conference has therefore an essentially social significance; its work is to be based upon direct and objective observation of the life of the peasantry, in order that its conclusions may not remain abstract, but may possess concrete and immediate value.

The agenda drawn up by the Preparatory Committee covers demographic questions, economic questions, agricultural credit and insurance, medico-social policy, nutrition, rural planning, the co-operative movement and general and technical education.

The documentation is being prepared on parallel lines: national and technical.

Most of the European countries have, at the time of writing, practically completed the preparation of a national monograph describing the particular features of rural life within their own frontiers; these monographs as a whole will provide a vivid picture of the different forms of economic, social and intellectual life found in the various parts of Europe.

The technical documentation must, on the other hand, disregard to some extent the conditions peculiar to each country and devote itself to general problems, defining their scope, their main component factors and the solutions which have been adopted, with an indication of what results may be expected from them.



The Health Committee, for its part, has endeavoured to make adequate technical preparation in regard to the following questions referred to it for that purpose:

- (1) The state of health in rural areas;
- (2) Medico-social policy;
- (3) Nutrition;
- (4) Rural planning.

1. *The State of Health in Rural Areas.*

Dr. ICHOK, Professor at the Paris Statistical Institute, has consented to prepare two monographs, for which purpose he has had access to the archives of the Service of Epidemiological Intelligence and Public Health Statistics. The first of these monographs is designed as a general medico-statistical survey, covering vital statistics, general mortality, infant mortality and the incidence of the principal diseases in rural areas in Europe. The second will deal specifically with the problem of tuberculosis.

A further monograph on typhoid fever is in course of preparation.

2. *Medico-Social Policy.*

This question will be of paramount importance for the 1939 Conference. The Health Committee has accordingly prepared a documentary study of the methods in use in various European countries for raising health standards in rural areas, with particular reference to the extent to which the recommendations of the European Conference on Rural Hygiene of 1931 have been applied. Secondly, in October last, the Health Committee organised a consultation, attended mainly by officers responsible for the direction of medico-social policy in certain typical European countries.¹ This meeting gave them an opportunity of discussing the work still to be completed in preparation for the Conference. A Drafting Committee was set up to present a general technical report for the

¹ The following attended the meeting :

Dr. René SAND, Secretary-General of the Health Division, Ministry of the Interior and Public Health, Brussels (*President*) ;

Dr. O. ALKS, Director, Department of Public Health, Riga ;

Dr. W. J. BABECKI, Vice-Director, Public Health Service, Warsaw ;

Dr. J. BALTEANU, Professor of Hygiene, University of Jassy (Roumania) ;

Dr. C. VAN DEN BERG, General Director of Public Health, The Hague ;

Dr. B. BORČIĆ, Director of the School of Hygiene, Zagreb (Yugoslavia) ;

Professor D. COMBIESCO, Secretary-General, Ministry of Public Health, Bucharest ;

Dr. Ch. FAUCONNET, Director, Federal Public Health Service, Berne ;

Dr. N. M. GOODMAN, Medical Officer, Ministry of Health, London ;

Dr. B. JOHAN, Secretary of State, Ministry of the Interior, Budapest ;

Dr. M. KACPRZAK, Chief of Division, Ministry of Labour and Social Welfare, Warsaw ;

Dr. A. STAMPAR, late Director of the Yugoslav Health Service, Zagreb ;

Dr. J. TOMSČIK, Director, State Institute of Hygiene, Budapest.

Conference, on the basis of a draft prepared by Dr. René SAND and Dr. KACPRZAK.¹

The report in question, entitled "General Survey of Medico-Social Policy in Rural Areas",² after a general introduction, deals with the part played by *curative medicine* in rural areas and the methods best adapted to provide the rural population with such medical attention as is required. *Preventive medicine* is discussed in great detail, fundamental principles capable of rapid application at a reasonable cost being concisely outlined. The rôle of social insurance is treated in a special chapter, and a series of notes is added on nutrition, physical training, rural planning and the education of rural populations in health matters. In a chapter on "The Training of Doctors and their Assistants in Preventive and Social Action", the need for training an adequate body of competent personnel, to establish the practice of public health as an integral part of rural life, is emphasised.

A further note of a documentary character is being prepared. It traces the action taken in the various European countries in application of the recommendations of the 1931 Conference on Rural Hygiene.

3. Nutrition.

In this sphere, the Health Organisation will lay before the Conference the fruits of the activities of its Technical Commission.³ The studies carried out under the auspices of the League of Nations have shown that there is a lack of exact information on the conditions governing the diet of populations, particularly those in rural areas. Doubtless it is already clear that the state of nutrition is often defective; yet precise data as to the extent and real gravity of undernutrition are lacking in the great majority of countries, and there is accordingly little information available regarding the nature of the dietary deficiencies.

It is therefore to be expected that the main concern of the Conference will be to investigate the state of physical fitness and the

¹ The following attended the meeting :

Dr. René SAND (*President*) ; Dr. N. M. GOODMAN, Dr. B. JOHAN
and Dr. M. KACPRZAK, see footnote on page 25.

² *Bull. Health Org.*, 1939, 8, 901.

³ See the chapter dealing specifically with nutrition, on page 27.

state of nutrition of rural communities, in order to determine what steps should be taken to remedy any defects of diet noted.

In addition to a general survey of nutrition in European rural areas, the Technical Commission will lay before the Conference Professor Bigwood's work, "Guiding Principles for Studies on the Nutrition of Populations".¹

Should national organisations undertake investigations into the general state of health and nutrition, the Technical Commission would be most willing to place the experience of its members at their disposal by appointing one of its members to give advisory opinions regarding the organisation of the investigations and to facilitate the study and comparison of results.

4. *Rural Planning.*

The programme of the Housing Commission included, as its third stage, a study of the rural dwelling and its outhouses and a survey of planning in rural areas. Work on these questions was begun in the latter half of 1938 in order that technical documentary material might be available by the time the Conference meets.²

The method followed was the same as that applied in the sphere of medico-social policy. A tour of investigation was first carried out. This was followed by the consultation of a group of technicians appointed by the various national housing committees (December 1938).³ All the work which led up to the preparation of a general report is discussed in the section on "Housing", to which the reader is referred.

B. NUTRITION

As from 1938, the work of the Technical Commission was to be directed along two main lines : in the first place, in pursuance of a recommendation adopted by the General Advisory Health Council in 1937, it was to undertake the study of nutrition in Asia and tropical countries generally ; in the second place, the Commission was to deal with qualitative and quantitative surveys designed to bring any nutritional deficiencies to light.

¹ See further comments on this work in the section on "Nutrition".

² See the section on "Housing" on page 32.

³ See footnote on page 35.

In both cases, the work called for was the logical outcome of the Commission's previous activities. In 1937, the Commission had laid down the general principles for the composition of a sound diet calculated to ensure optimum growth and body maintenance. At its 1938 meeting, the Commission added a series of conclusions relating chiefly to requirements in vitamins, inorganic constituents, fats and proteins, to the problem of milk and to the nutritive food requirements of infants. That work as a whole represented, so to speak, the charter of the Commission, and was necessarily of a general character. It had been clear from the outset that particular attention would have to be paid to the conditions obtaining in the Far East and in tropical and sub-tropical countries.

It was also only proper to consider the question of the extent to which diet in common use in any part of the world falls below the standards recommended by the Commission. Since much material is available on the most suitable methods of investigation, the Commission's natural function is to examine those methods and to deduce definite conclusions regarding the technique to be applied for the twofold purpose of assessing the actual consumption of foods and the state of nutrition.

1. *Nutrition in the Far East, Tropical Countries and Colonial Territories.*

A Special Committee of the Technical Commission met in August 1938. Dr. W. R. AYKROYD, Director of the Nutrition Research Laboratories, Coonoor, India, was present.¹

¹ The Committee's report is published in the *Bulletin of the Health Organisation*, 1938, 7, 666.

The following attended the meeting :

- Sir Edward MELLANBY, Secretary-General of the Medical Research Council, London (*President*) ;
- Dr. W. R. AYKROYD, Director of the Nutrition Research Laboratories, Coonoor, India ;
- Dr. Ed. J. BIGWOOD, Professor of Physiology at the University of Brussels ;
- Dr. Lela E. BOOHER, Chief of the Foods and Nutrition Division, Bureau of Home Economics, U.S. Department of Agriculture, Washington ;
- Dr. Harriett CHICK, Head of the Division of Nutrition, Lister Institute, London ;
- Dr. L. S. FRIDERICIA, Professor of Hygiene at the University of Copenhagen ;

The Committee found that the standards laid down in its previous reports in regard to the physiological bases of nutrition were universally applicable and that they could be expressed in terms of the dietary habits of the various peoples. They represent an ultimate goal to be aimed at in all countries. At the present time, however, in certain parts of the world, they are obviously out of immediate reach. In these circumstances, it becomes necessary to endeavour to raise the existing level of diets to a degree not beyond the bounds of practical possibility, but, at the same time, less remote from the optimum standard.

With particular regard to the Far East and to tropical countries, the Committee considered that fuller information was required on dietary habits, the incidence of diseases connected with dietary deficiencies, and the nutritional value of local foods. It reached certain conclusions regarding national programmes of action with a view to improving the nutritional state, and urged, *inter alia*, that certain adjustments should be made in the sphere of agriculture to increase the production of protective foods.

The function which the Health Organisation and the Technical Commission may discharge in this respect is to co-ordinate and assist by every means at their disposal the carrying-out of surveys by the various competent institutions. Negotiations are now in progress to enable the Coonoor Laboratory to act as a liaison centre between such institutions and the Technical Commission.

2. *Survey of the Diet and the State of Nutrition of Population Groups.*

This question was first considered by the Technical Commission in November 1937. At the beginning of 1938, Professor E. J. BIGWOOD, of the University of Brussels, was invited to prepare a handbook laying down the principles to be followed in carrying out dietary surveys. His draft guide was examined in detail by the Special Committee which met in August 1938. It was published

Dr. A. MAYER, Professor at the Collège de France, Paris ;
Sir John BOYD ORR, F.R.S., Director of the Rowett Institute of Animal
Nutrition, Aberdeen.

Dr. W. Ph. KENNEDY, Professor of Physiology, Royal College of Medi-
cine, Baghdad, attended the meeting as observer.

in its final form in March 1939 under the title " Guiding Principles for Studies on the Nutrition of Populations " and was communicated to National Nutrition Committees.

Proceeding from the principle that a complete study should comprise both an enquiry into the food consumed and an investigation of the effect of dietary habits on the state of nutrition, Professor BIGWOOD has divided his handbook into two parts.

(a) *Dietary Surveys.*—Four types of dietary survey can be distinguished, and the author begins by examining them in the first four chapters of his report. In the first category, the investigations cover the food supplies of the whole country, calculated with the help of statistics of production, imports and exports, but not necessarily indicating the quantities of foods actually consumed. This is an example of the purely documentary type of survey as contrasted with the other three types, which are directly concerned with various social groups, with families or with individuals. Although the methods applied in types 2, 3 and 4 vary, they have, nevertheless, certain features in common. They are examined in Chapter V, in which the author distinguishes between the weighing method, that of household record books and that of questionnaires. The first provides a complete record of the quantities of foods consumed and the amounts available at the beginning and at the end of the period covered by the enquiry. A fairly accurate computation of the total consumption of the group, but not of the individuals composing it, can therefore be obtained. The household record-book gives results which are less accurate ; it is, however, an easier form of investigation and one less likely to cause an unconscious change in dietary habits while the enquiry is in progress. The questionnaire method, lastly, can be applied in two ways : either the individuals concerned fill in the forms—which must then be of a simple character—or this is done by the investigators, in which case the replies will be fuller and more precise. The ensuing chapters discuss the scope and duration of the surveys, the personnel required and the classification of foods. Chapter X is devoted to an analysis of the data and factors to be taken into consideration in establishing the physiological value of the diet. The author discusses the highly important question of food-composition tables, the computation of the energy-value of

the diet and its composition in respect of protective principles. Here the reader will find the essential facts concerning the energy-yielding elements, the biological value of proteins, the inorganic elements and vitamins.

A further chapter is devoted to the study of the scales of family consumption coefficients which have to be used in comparing the results of enquiries concerned with groups of different age and sex composition.

The last two chapters of Part I deal with diets from the economic standpoint and the statistical significance to be assigned to the results of the surveys. Since the investigator must necessarily confine his attention to a certain portion of the community, he must be able to determine how far observed mean values are likely to coincide with the true mean values for the whole.

(b) *Enquiries into the State of Nutrition of Populations.*—Part II of the handbook, which is based on the conclusions of a group of experts who met in December 1936,¹ recommends three types of enquiry, each corresponding to different requirements. The first is adapted to large-scale demographic investigations or to a rapid preliminary classification of very large numbers of individuals. A record is made of the age, sex, physical appearance, height and weight of each individual. In addition, every child is subjected to a simple clinical examination. All children whose diet appears to be deficient should undergo medical examination and be the subject of a medico-social enquiry with particular reference to diet.

The second type of enquiry corresponds to investigations of a more detailed and more elaborate scientific character covering a limited number of individuals. The method is the same as that recommended for the first type, but it is supplemented by research into the diet of the child, an exhaustive medical examination, an enquiry into the economic and social position of the family, and by as many as possible of the following tests: additional somatometric data, photographs and tests specially designed to reveal any latent pre-deficiency condition.

The third type of enquiry is of a bio-typological character. In addition to the tests required under the first type of enquiry, it

¹ See *Bull. Health Org.*, 1937, 6, 129.

involves a detailed scrutiny of morphological characteristics and biological functions. It must include, as far as possible, somatometric and physiological measurements, psychological tests, a full medical and psychiatric examination, research into dietary habits, and a review of the child's school record.

The author assigns an important place to physiological methods capable of yielding early specific evidence of unapparent conditions of pre-deficiency which clinical examinations fail to disclose ; he deals in particular detail with methods for detecting latent hypovitaminoses and iron deficiency.

The handbook is completed by examples of surveys of various types in a number of different countries ; it also comprises a terminological index, bibliographical references and some twenty specimens of record cards and biometric tables.

3. *The Feeding of Refugees.*

During its August session, the attention of the Special Committee was drawn to the fact that, even in Europe, disturbing conditions existed in which the problem was no longer to lay down the bases for a satisfactory diet, but rather to prevent the population from dying of starvation. This was, more particularly, the position in Spain, and, to cope with it, the Society of Friends sought guidance in the preparation of an emergency diet for the refugees.

The Committee suggested a diet of this character. It is composed of whole wheat, brewer's dried yeast, cod liver oil and various salts, and is so designed as to include vitamins and essential inorganic constituents. At the same time, the Committee pointed out that such a diet was at most adequate to sustain life and to prevent the appearance, during a limited period, of the more serious effects of malnutrition. It could only be looked upon as an emergency diet, to be supplemented at the earliest possible moment by fresh foods.

C. HOUSING

In August 1937, the Housing Commission published a report on the hygiene of environmental conditions and noise-abatement.¹ At the beginning of 1938, it turned to the second part of its pro-

¹ "The Hygiene of Housing", *Bull. Health Org.*, 1937, 6, 505.

gramme of work, which covers the manifold problems involved in the hygiene of buildings and dwellings and in national urban and rural planning.

1. *Insolation and Illumination.*

The Commission called a second meeting of experts in June 1938 for the purpose of reviewing the work done since August 1937 on insolation and natural and artificial illumination in relation to housing and town planning.¹

The definition of human needs in the matter of natural and artificial lighting is a task calling for the collaboration of the biologist, the clinical physician, the ophthalmologist and the hygienist. But in order to ensure environmental conditions in keeping with the requirements laid down, the architect, the engineer and the town-planning expert must also be called in. Lastly, the assistance of the physicist, the climatologist and the meteorologist must be sought to determine the various radiation factors in man's environment. Enough has been said to show how complex is the problem of insolation and illumination.

¹ The following attended the meeting :

- Dr. W. MÖRIKOFER, Director, Physico-meteorological Observatorium, Davos, Switzerland (*President*) ;
 Mr. Harry BUCKLEY, Honorary Secretary, National Illumination Committee of Great Britain, National Physical Laboratory, Teddington, England ;
 Professor Alfred GIGON, Director, " Polyclinique médicale de l'Université ", Basle ;
 Dr. James E. IVES, Member of the American Committee on Hygiene of Housing, Washington, D.C. ;
 M. H. VAN DER KAA, Chief Inspector of Public Health, The Hague ;
 Dr. Vojtech KRCH, Professor at the Polytechnicum, Prague ;
 Mr. Richard James LYTHGOE, Reader in Physiology of Sense Organs, University of London ;
 Dr. A. MISSEARD, Professor at the " École nationale supérieure des Beaux-Arts and at the École supérieure des Travaux publics ", Paris ;
 Mr. Cecil J. MORREAU, Member of the Illumination Research Committee of the Department of Scientific and Industrial Research, Guildford, Member of the Science Standing Committee of the Royal Institute of British Architects, England ;
 Dr. Brunon NOWAKOWSKI, Professor of Hygiene, University of Wilno ;
 M. Th. NOWAKOWSKI, Architect, Director, Building Committee of the Town of Warsaw ;
 Professor J. PARISOT, Director, Health Institute, Nancy, President of the Health Committee and of the Housing Committee of the Health Organisation ;
 M. Gunnar W. PLEIJEL, Architect, Stockholm.

The experts' report¹ covers the many aspects of the problem and brings together all the available knowledge on the question. It begins with a consideration of the climatology of natural radiation and sets out the methods employed to provide the amount of such radiation which is needed by the individual. It sums up the results of research into the thermal, visual, physiological, psychological and bactericidal effects of radiation from the sun and the sky and defines human needs in this respect in the light of present knowledge.

The second part of the report deals with the methods at the disposal of engineers, architects and town-planning experts for adapting their plans and projects to conditions of insolation and illumination in keeping with the requirements of modern hygiene. It deals with the orientation of buildings, fenestration, the space between buildings, building materials and the necessity for open spaces in the shape of gardens, recreation grounds, playing-fields, swimming-pools, etc.

The last part of the report is devoted to physiological and psychological questions connected with natural and artificial lighting. Due prominence is given to the visual functions—also a complex question, since visual efficiency is determined by a variety of factors. The investigations hitherto carried out show that the problem of optimum lighting is essentially economic and technical in character.

In this connection, it is to be observed that, as further progress is made, the public becomes more exacting; the standards in force for the lighting of dwellings have accordingly risen steadily in the various countries. New technical methods in architecture and town planning are being applied to a growing extent. They bring an ever-increasing proportion of sun and light to citizens who, up to now, have been more or less deprived of them. It is, however, still necessary to continue these efforts if a complete solution is to be found for what is one of the most important social problems of the present time.

2. Rural Housing and Planning.

Since the special problems involved in rural housing and planning appear on the agenda of the European Conference on Rural Life,

¹ *Bull. Health Org.*, 1938, 7, 581.

the Housing Commission has been called upon to make a technical contribution to the preparatory work of the Conference.

The European Conference on Rural Hygiene held in 1931 had already drawn attention to the importance of "sanitation", this term being taken in its wide sense as implying the creation of an area both healthy and productive, through measures for the disposal of sewage and refuse, supplies of drinking water, a healthy and comfortable type of dwelling, a scientific use of the soil, land improvements and bonification.

A meeting of experts was held in December 1938, attended by representatives of the various national housing committees.¹ The discussions centres on a report prepared by M. M. VIGNEROT, Chief Engineer of the Service du Génie rural, of the French Ministry of Agriculture, after a study tour covering Belgium, Czecho-Slovakia, Latvia, the Netherlands, Poland, Sweden and Yugoslavia.

The experts reaffirmed the view that rural planning implies the institution of a healthy mode of life in a productive environment, and that it is a necessary basis for all measures for the sanitary and social protection of the community. Without doubt it represents one of the most important factors in the social rehabilitation of agricultural populations. It contributes to the improvement of their living conditions, which are universally recognised as too markedly inferior to those of urban communities.

M. VIGNEROT's report, entitled "Rural Housing and Planning", examines in turn the conditions for the rational planning of the

¹ The following attended the meeting :

- Professor J. PARISOT, Director, Health Institute, Nancy, President of the Health Committee and of the Housing Committee of the Health Organisation (*President*) ;
- Dr. N. M. GOODMAN, Medical Officer, Ministry of Health, London ;
- Mr. H. VAN DER KAA, Chief Inspector of Health, Member of the National Housing Committee, The Hague ;
- Mr. W. F. J. M. KRUL, Director, State Bureau for the Supply of Drinking Water in the Netherlands, The Hague ;
- M. V. MADERA, Municipal Engineer, Prague ;
- M. Anders O. MOLIN, Civil Engineer, Stockholm ;
- M. Z. RUDOLF, Engineer, Chief of the Sanitary Engineering Division, Ministry of the Interior, Warsaw ;
- M. F. SENTENAC, General Inspector for Roads and Bridges, Chief of the Services of Water-supply and Sanitation, Paris ;
- M. M. VIGNEROT, Rural Engineer, Paris ;
- Dr. H. A. WHITTAKER, Director, Division of Sanitation, State Department of Health, Minneapolis, U.S.A. ;
- Dr. Nils H. WRANNE, Chief Medical Inspector, Linköping, (Sweden).

rural dwelling and its outbuildings with due regard to the health, comfort and work of the agriculturist and of the housewife. It next deals with the organisation of the communal life of the village : public works, buildings and the equipment required to provide for the common needs of a more or less closely settled community. The author then turns to questions of planning which are of concern alike to villages and to isolated farms : supply of drinking-water, electricity and gas and disposal of sewage and refuse.

The last section of the report is concerned with forms of propaganda designed to reach the individual in his native environment, to make him realise what is required to raise rural standards of living, and to awaken in him a desire for suitable measures to improve his conditions of existence.

3. *Planning.*

In the preparatory studies for the 1939 Conference, the Housing Commission has dealt with problems of planning simply from the standpoint of rural areas. Its current programme of work includes the study of the health questions connected with urban planning, zoning, the provision of open spaces, the planning of water resources, the disposal of sewage and refuse, measures to combat air-pollution, communications and transport, etc. The Commission will probably meet again towards the end of June 1939 and will then survey the results of the work done under its auspices during the past three years.

D. PHYSICAL EDUCATION

By the beginning of 1938, the Health Committee had practically completed the preliminary studies it had decided to carry through before going into the substance of the fundamental problems connected with physical development and fitness. This preliminary stage culminated in the publication of a general report entitled "Physique and Health" by Dr. C. WROCZYNSKI, Chief Medical Adviser to the Polish Ministry of National Education.¹

¹ *Bull. Health Org.*, 1937, 6, 551.

In July 1938, the Health Committee called together a Committee of Rapporteurs¹ to examine the following items :

(a) Discussion of the results of research work so far carried out on the physiological effects of physical exercise ; definition of the conclusions to be derived therefrom, with a view to formulating the physiological bases of rational physical education ;

(b) Preparation of a programme of studies to supplement the results of research work so far carried out ;

(c) Preparation of a list of somatometric and functional texts to be recommended for the purpose of measuring physical fitness and form in individuals.

In their report,² the Committee of Rapporteurs drew attention to the meagre nature of the scientific information so far available concerning the physiological consequences of physical exercise. The Rapporteurs nevertheless laid down a series of rules which should be followed by those who take physical exercise. They urge the desirability of its being undertaken under medical supervision, and emphasise the fact that the aim should not be to develop champions but to benefit the whole community. They stress the inadvisability of allowing strenuous competitions between widely differing categories of individuals, especially children and adults, and make suggestions concerning the proper distribution of physical exercise during the day, during the week and in relation to meals.

In view of the present dearth of scientific evidence on the subject of physical education, the Rapporteurs drew up a programme of

¹ The following attended the meeting :

Dr. H. LAUGIER, Professor of Physiology at the Sorbonne, " Directeur de la Recherche scientifique au Ministère de l'Éducation nationale ", Paris (*President*) ;

Colonel A. BAUER, President of the Swiss National Association for Physical Education, Berne ;

Dr. J. DILL, Professor of Industrial Physiology, Fatigue Laboratory, Harvard University, Boston ;

Professor E. HANSEN, Director of the Institute for the Theoretical Study of Gymnastics, Copenhagen ;

Dr. B. A. McSWINEY, Professor of Physiology, Sherrington School of Physiology, St. Thomas's Hospital, London ;

Dr. C. WROCZYNSKI, School Medical Inspector at the Ministry of Education, Warsaw.

² *Bull. Health Org.*, 1938, 7, 609.

laboratory research, the results of which may prove suitable as a basis for a rational scheme of physical education. The programme includes physiological, anthropometric and psychological research. It is designed to reveal the effects of physical exercise on the functions of the body and the specific effects of different types of exercise at different ages. It also includes a study of the characteristics of athletic types in different countries and aims at defining the relationship between intellectual and physical development.

The Committee, in addition, drew up a provisional medical examination form. Urging the desirability of standardising such examinations for all countries, it expressed the hope that it might be possible, on the basis of observations from health administrations, official organisations and experts, to prepare a standard record card suitable for general adoption.

The report has accordingly been forwarded to official administrations and institutions for their comments.

III. EPIDEMIOLOGY AND HEALTH STATISTICS

A. EPIDEMIOLOGICAL INTELLIGENCE SERVICE

There are really outstanding events to record in the working of the Service, which proceeded normally.

The *Weekly Epidemiological Record*, of which the number of copies has had to be increased, was modified in certain details, chiefly by the deletion of various incidental data. This has made it possible to give greater prominence to new information concerning pestilential diseases communicated by the Singapore Bureau. It has also been possible to do more justice to the numerous short articles prepared by the Service on various contagious diseases, such as poliomyelitis in autumn and influenza in winter.

The *Annual Epidemiological Report* appeared at the end of 1938. The figures published in it relate to the demography aspects and the frequency of contagious diseases in 397 large towns (with a total population of 155 million) and in upwards of 150 countries and territories having a total population of 1,961,000,000 (93% of the population of the world). These data have been checked as far as

possible by the national health administrations or statistical services before publication.

The disturbances in China have inevitably made it very difficult to continue the relations of the Eastern Bureau with Chinese ports. Nevertheless, the Bureau was able to maintain regular contact with most of these. The Anti-Epidemic Commission sent to China also communicated regular information regarding health conditions, especially in connection with the frequency of cholera, smallpox and typhus among the refugees.

After Japan's decision, in the autumn of 1938, to cease all co-operation with the technical organs of the League of Nations, the Eastern Bureau was informed that the Japanese authorities would henceforth confine themselves to supplying the information stipulated in the International Sanitary Convention of 1926. They therefore report only the first cases of plague or cholera, epidemics of typhus and smallpox and the measures taken in regard to quarantine.

The Government of India has recently decided that the epidemiological intelligence now being communicated weekly by cable to the Bureau should no longer relate only to *some* of the important ports but should now include *all* Indian ports which have international traffic.

As stated in last year's report, an investigation was undertaken in 1938 to enquire into the practicability of broadcasting the Singapore Bureau's *Bulletin* on short waves from the Radio-Nations Station at Geneva. Since Saigon and Antananarivo have ceased to broadcast this message on long waves, listeners in various parts of Australia, New Zealand and South Africa have experienced considerable difficulty in picking it up.

This investigation gave a satisfactory result, and the new broadcasts in AA code were started on February 17th, 1939.

Arrangements have also been made with the British naval station in Singapore, which began to broadcast the message in the AA code on June 9th, 1938. However, these new broadcasts are still in the experimental stage, and are liable to such modifications in regard to time and wavelength as the authorities concerned may desire.

B. DECENNIAL REVISION OF INTERNATIONAL LISTS OF CAUSES OF DEATH

In 1938, the French Government summoned the International Conference for Revision, which sat from October 3rd to 7th.¹ As in 1929, the technical preparations for the Conference were entrusted to a Joint Committee set up by the International Institute of Statistics and the Health Organisation.² The secretariat of the Committee, and of the Conference itself, was provided jointly by the Institute and the Epidemiological Intelligence Service, the latter being responsible more especially for the technical side.

The Conference made no far-reaching changes in the three nomenclatures, which contain 200, 87 and 44 titles respectively ; it adopted a list of causes of still birth.

¹ The Bureau of the Conference was composed as follows :

Professor M. TIFFENEAU, Dean, Faculty of Medicine, Paris, *President* ;
Dr. L. DE BERARDINIS (Italy), Dr. F. W. BURGDÖRFER (Germany),
Dr. DUNN (U.S.A.), Dr. IVERSEN (Denmark) and Sir Humphrey ROLLESTON (England), *Vice-Presidents* ; M. Michel HUBER, President of the Joint-Committee, *Secretary-General* of the Conference ; Dr. Y. BIRAUD, of the League of Nations Secretariat and M. BUNLE, of the " Statistique générale de la France ", *Vice-Secretaries General*.

² The composition of the Joint Committee was as follows ;

International Institute of Statistics :

Dr. L. DE BERARDINIS, Head of the Demographic Statistics Division of the Central Institute of Statistics of Italy ;
Dr. A. BOHAC, Vice-President of the Statistical Office of Czechoslovakia ;
Dr. C. BRÜSCHWEILER, Director of the Swiss Federal Bureau of Statistics ;
Dr. F. W. BURGDÖRFER, Director of the Reich Statistical Office ;
M. M. HUBER, Honorary Director of the French General Statistical Office ;
Dr. N. M. JOSEPHUS JITTA, President of the General Council of Public Health of the Netherlands.

Health Organisation of the League of Nations :

Mlle. J. BACKER, Chief of the Division of Demographic Statistics of the Norwegian Central Statistical Bureau ;
Professor Haven EMERSON, Chairman of the Nomenclature Committee of the American Public Health Association ;
Dr. M. KACPRZAK, Chief of Division, Ministry of Labour and Social Welfare, Warsaw ;
Dr. S. MANUILA, Director of the Central Institute of Statistics of Roumania ;
Sir Sylvanus P. VIVIAN, Registrar-General of England and Wales.

These new lists are to be applied as from January 1st, 1940. They are published, with the recommendations of the Conference, in the *Bulletin of the Health Organisation*.¹ The *Manuel international des Nomenclatures*, which contains the Minutes of the Conference and the list of the terms for inclusion in or deletion from each of the titles, has been published under the auspices of the French Government, with the financial assistance of the International Institute of Statistics and the technical assistance of the Epidemiological Intelligence Service. For the first time, the English and American editions of the nomenclatures tally with it in all respects.

The Conference recommends that the Joint Committee should remain in existence, to prepare for the decennial revision in 1948 and, in the meantime, to continue the preparation of the international lists of diseases. This task will entail much technical labour, but it will facilitate both the national and international comparison of statistics compiled by health administrations, social insurance organisations, hospitals, military health services, etc. In the closing months of 1938, the Commission internationale de standardisation et d'étude du matériel sanitaire² requested the Health Organisation to undertake an investigation, for the benefit of military health services, into the question of the uniform, simple and practical nomenclature of diseases.

C. HEALTH INDICES

The investigations on health indices undertaken by the Health Organisation are intended to provide an assessment of the state of health of a community in all its various aspects and to make information available as to the effect upon it of geographical, social and economic conditions and of public health measures. The first stage of these investigations resulted in the publication of a general survey, comprising a draft scheme of *Health Indices* prepared by M. STOUMAN and M. FALK.³

This was accompanied by an account of an experimental application of such a scheme to the City of New Haven in the United

¹ *Bull. Health Org.*, 1938, 7, 945.

² Of the International Red Cross Committee.

³ *Bull. Health Org.*, 1936, 5, 901.

States. Similar experimental studies were carried out later in Brussels¹ and in the rural district of Mezökövesd² in Hungary.

These showed that the scheme of indices of M. STOUMAN and M. FALK required certain modifications in order to make it adaptable to local conditions.

Entering upon the second stage of its work in this field, the Health Committee accordingly convened a meeting of statisticians and rural hygiene specialists (April 1938);³ to prepare a kind of catalogue of indices which may be regarded as being the most typical and easiest to apply in the health surveys to be carried out in rural areas (document C.H./1331(1)).

In the course of the third stage of its work, the Health Committee set up a Committee on Health Indices, which met in October 1938,⁴ and prepared the first draft outline of a standard report, such as might be used to show the health conditions obtaining in a whole country or in a given area.⁵ The model is intended to apply equally to rural, urban or industrial areas, or to a whole country. It comprises three principal parts : indices of vitality and health (demography, mortality and morbidity), environmental indices (external environment and social environment), indices of public health activity (personnel and equipment of health services and other medico-social services).

The Committee hopes that this report may be of value for elaborate health surveys carried out for the purpose of assessing the

¹ *Bull. Health Org.*, 1938, 7, 122.

² *Ibid.*, 1937, 6, 766.

³ The following attended the meeting :

Dr. J. BALTEANU, Professor of Hygiene, Faculty of Medicine, University of Jassy (Roumania) ;

Dr. B. BORČIĆ, Director, School of Hygiene, Zagreb (Yugoslavia) ;

Dr. M. KACPRZAK, Chief of Service, Ministry of Labour and Social Welfare, Warsaw ;

Dr. KLIMA, Chief of the Statistical Division, State Institute of Hygiene, Prague ;

Dr. J. TOMSČIK, Director, State Institute of Hygiene, Budapest.

⁴ The following attended the meeting :

Dr. R. M. ATWATER, Executive Secretary, American Public Health Association, New York (*President*) ;

Dr. M. KACPRZAK, Chief of Service, Ministry of Labour and Social Welfare, Warsaw ;

Dr. J. PATERSON, Medical Officer of Health, Maidenhead, Berks (England) ;

Dr. J. TOMSČIK, Director, State Institute of Hygiene, Budapest.

⁵ *Bull. Health Org.*, 1939, 8, 60.

health conditions obtaining in a given population, its living conditions and the work of the health services. The use of the model report and of the numerical indices provided would enable a comparison to be made between the situation existing in two areas or countries or in the same area at different dates.

IV. BIOLOGICAL STANDARDISATION

1. *Sera.*

The tasks of the serologist members of the Permanent Commission on Biological Standardisation when they met in October 1938¹ were : to decide the adoption of standards for sera not yet included among the twelve already standardised, to provide for the replenishment of the stocks of certain standard preparations of which the demand had exceeded expectations and to reconsider certain of the previously adopted standards whose use had raised new theoretical and practical problems. To guide them in their discussions they had at their disposal no fewer than twenty-one original memoranda,

¹ The following were present :

- Dr. Th. MADSEN, Director of the State Serum Institute, Copenhagen (*President*) ;
- Dr. Percival HARTLEY, Director of the Department of Biological Standards, National Institute for Medical Research, Hampstead, London ;
- Professor L. HIRSZFELD, Director of the Department of Bacteriology and Experimental Medicine of the State Institute of Hygiene, Warsaw ;
- Professor C. IONESCO-MIHAIESTI, Director of the Sera and Vaccine Institute " Dr. T. Cantacuzino ", Bucharest ;
- Professor Louis MARTIN, Director of the Pasteur Institute, Paris ;
- Professor A. SORDELLI, Director of the Bacteriological Institute of the National Department of Health, Buenos Aires.

The following also attended the meeting as experts :

- Dr. E. GRASSET, South African Institute for Medical Research, Johannesburg ;
- Dr. Johs. IJSEN, State Serum Institute, Copenhagen ;
- Dr. F. KAUFFMANN, State Serum Institute, Copenhagen ;
- Professor E. LECLAINCHE, Director of the " Office international des Epizooties ", Paris (attended the meeting on October 21st) ;
- Dr. Margaret LLEWELLYN SMITH, National Institute for Medical Research, Hampstead, London ;
- Professor M. WEINBERG, Pasteur Institute, Paris ;
- Mr. P. BRUCE WHITE, National Institute for Medical Research, Hampstead, London.

the result of the experiments conducted during the last two years. These papers and the report of the Commission have been published in a number of the *Bulletin* devoted specially to biological standardisation.¹

Although the assays effected in relation to the international standard for *tetanus antitoxin* were satisfactory for purposes of practical routine work, it was none the less true that the concordance of results was not as good as may be expected from a biological assay in spite of the many variable factors involved. In order to determine how far the factors likely to produce variations could be eliminated, the Commission drew up in 1934 an extensive research programme, the execution of which was entrusted to the laboratories of Buenos Aires, Bucharest, Copenhagen, Hampstead and Washington. From the numerous assays performed under this scheme, it appears that the variations observed are not due to any lack of accuracy of the test itself, but to the circumstance that the toxins display qualitative differences. The toxin is thus the main factor, among the various influences likely to affect the precision of assay.

This raises a question of principle—namely, can the factor of variation inherent in the toxin be eliminated by recourse to a test toxin which would be distributed at the same time as the standard serum? If this were so, the Commission would be called upon to select a toxin and to have it prepared in sufficiently large quantities to enable the official institutes and factories to use it for the test of their tetanus antitoxin production.

But as Professor SORDELLI pointed out, this is not all. On the evidence of the assays conducted at various levels—that is to say, in which different doses of toxin have been taken as indicators of neutralisation by serum—it may be asked how far the antitoxin unitage which is given on tetanus antitoxin ampoules really indicates the prophylactic or therapeutic activity which the serum is capable of exerting. This is a theoretical question of great importance, but one, however, which is not of practical moment, since the sera supplied at the present time are made up of mixtures in which the qualities peculiar to the various antitoxins—their “avidity” in particular—offset each other.

¹ *Bull. Health Org.*, 1938, 7, 683.

In both these matters, the Commission held that further research was necessary ; this will be undertaken on the lines of a pre-arranged plan in the Institutes of Buenos Aires, Copenhagen and Hampstead. The first problem will be to see whether the variations in titre observed when using toxins prepared from the same strain and by the same methods are smaller than those observed when the tests are performed with toxins prepared by different methods. Secondly, fuller information is needed about the nature and properties of the reagents, their method of preparation and their interaction, so as to obtain for samples of tetanus antitoxins potency values more accurately representative of their clinical activity.

It would be a mistake to infer from the above that the administrative control of tetanus antitoxin is valueless. The tests made in Great Britain and at Copenhagen with ten different toxins have shown that, in 99% of assays, the range of variation lay between 73.5% and 136%. Since the variations in titre to be expected under such divergent experimental conditions—which, as a matter of fact, reflect those of routine work—are now known, control is facilitated, for any antitoxin with a titre between the given limits can be regarded as acceptable.

Professor WEINBERG's observations on the assay of *gas gangrene (perfringens) antitoxin* led to similar conclusions—namely, that, in order to obtain comparable data in all laboratories, the same standard serum and the same sample of toxin should be used. The latter should contain all the antigens of the perfringens bacillus—or, at least, most of its harmful components—since only a serum prepared from such a toxin could be taken as a suitable standard. As, however, no such serum has yet been prepared, the comparative assays should for the time being be carried out in relation to the international standard antitoxin and with a single test toxin.

In view of Professor WEINBERG's interesting observations, the Commission instructed the Copenhagen Institute to prepare a large quantity of perfringens toxin. This toxin will be distributed to interested laboratories, for the purpose of carrying out further investigations into problems relating to the determination of the potency of perfringens antitoxins.

The standardisation of the *anti-snake venom sera* is still in its initial phase, the Commission having decided for the moment to limit consideration to the venoms of European vipers. As a result

of investigations carried out jointly by the Copenhagen and Zagreb Institutes, a method of assay has been worked out ; it was also shown that anti-viper serum should be standardised in relation to the venom of *V. aspis*, which is found in the south of France and north of Italy, and *V. ammodytes*, which occurs in the Balkans, and that a standard serum would have to be established and a standard venom used for each of these species. If all experimenters used the same venom for assay purposes, it would be possible to express the potency of a serum in terms of the number of milligrammes of venom neutralised. In this way, the use of the vaguer criterion of lethal doses neutralised as a means of expressing the strength could be avoided. The tests are being continued, the chief difficulty being the constitution of stocks of standardised venom of the right quality.

Two international standards of *anti-pneumococcus serum*—namely, those corresponding to types I and III—were adopted in 1934. Since then, the serum therapy of pneumonia has made great strides ; thirty-two types of pneumococcus have been identified and this has made it possible to provide for the swift determination of the type of causative agent concerned and for treatment by means of the homologous serum with the striking clinical results which are now common knowledge. The question arose, therefore, whether standards should be established for other types, especially those most frequently encountered. Since this question is, at present, at a stage in which fresh developments are constantly taking place, the Commission took the view that no further anti-pneumococcus serum standards need be set up for the time being.

The study of *anti-anthrax serum* standardisation has been further prosecuted by the Bucharest and Szeged Institutes. Research has been specially directed to the elucidation of the part played in the immunisation process by the capsular antigen of the anthrax bacillus. This research is, however, still in its initial phase ; it will be continued on more extensive co-operative lines, the Paris Pasteur Institute and the Buenos Aires Bacteriological Institute having promised their support.

So far as *tuberculin* is concerned, the Commission thought it essential to establish side by side with the standard for Koch's old tuberculin set up in 1931, a subsidiary standard consisting of purified tuberculin produced in a synthetic medium and corresponding to the preparation known in the United States as " purified

protein derivative" (P.P.D.). The advantages of this type of tuberculin are obvious ; it gives solutions which remain stable for nearly a month, it is sufficiently active to be used in diagnostic tests on cattle and yields about the same percentages of positive reactions with a two-injection Mantoux test as the old tuberculin with three injections. The preparation of this new standard has been entrusted to the Copenhagen Institute.

The Commission decided to replace the international *staphylococcus antitoxin* standard, the stock of which was nearing exhaustion, by a new preparation, and to label this "international staphylococcus α antitoxin standard". It has recently been shown that the staphylococcus produces various kinds of toxin (α , β , γ) and that there are corresponding antitoxins endowed with distinct properties. Now the international standard antitoxin was obtained with a type— α toxin. The Copenhagen Institute has, however, been requested to prepare an antitoxin of type β , in order to provide for the contingency of its being used in the treatment of staphylococcus infections.

The Commission had before it a proposal for the establishment of a *Sordelli antitoxin*. The question of the Sordelli bacillus is one which is primarily of interest to the American continent, where cases of infection by this organism have been reported much more frequently than in Europe. In these circumstances, the antitoxin chosen as the international standard was that of the Washington Institute, the unit of activity to be defined only when a series of comparative assays have been carried out.

Dr. A. FELIX kindly allowed the Commission to see, before publication, his report on the standardisation of *anti-typhoid serum*.¹ The Commission was of opinion that this memorandum should be taken as the basis of a comparative investigation and that the anti-typhoid serum prepared by the Lister Institute of London should not be used for this work, in which the Bucharest, Buenos Aires, Copenhagen, Joannesburg, London, New York, Paris, Santiago de Chile and Warsaw Institutes have agreed to participate.

As in previous years, the Copenhagen Institute has compared the potency of certain national *diphtheria antitoxin* standards with that of the international preparation. The degree of concordance

¹ See *Journal of Hygiene*, 1938, **38**, 750.

observed was highly satisfactory. The assays have, however, in some cases, revealed differences in potency not exceeding 5%—and therefore of no practical importance—according to whether they were performed by Ehrlich's method or by the intracutaneous route on the rabbit. Ehrlich's method should of course still be regarded as the fundamental basis of these assays.

The Commission had also to pronounce upon the conclusions of the report of the experts who met in London in November 1937 to study the standardisation of the *agglutination tests*, more particularly the Widal test. A noteworthy conclusion is that recommending the creation of an International Centre from which it would be possible to obtain standard sera, standard suspensions and standard cultures, and so make the results of the Widal test more uniform and more inter-comparable.

The experts further considered that certain rules should be observed—namely, that separate suspensions should be used for the estimation of H and O agglutinins, that the suspensions should be killed and preserved and that their agglutinability be standardised.

Several members of the Commission objected to the technique recommended ; it was pointed out that much clearer agglutination was obtained by the action of a specific bactericidal serum on a dilution of the corresponding culture than by using washed bacteria. The Commission accordingly thought that investigations should be made with a view to ascertaining whether it is preferable to use a standardised bacterial suspension or a dried preparation of bacteria, and how, by the use of purified O and H antigens, the most highly specific agglutinating sera may be prepared. In the meantime, it would be helpful, however, if an international centre could supply suspensions and agglutinating sera, to facilitate further comparative research in this field.

Lastly, the Commission was glad to learn that, with the help of the Commonwealth Fund, an International Centre for the Identification and Classification of *Salmonellæ* had been set up at the Copenhagen Institute.

2. *Vitamin B₁*.

Last year's report hinted that the international standard, constituted by an adsorption product of vitamin B₁ prepared by the

Seidell method, would shortly be replaced by the pure crystalline vitamin B₁. This replacement is now an accomplished fact. Through the generosity of American, German and Swiss factories, the Hampstead Institute was able to collect 70 grammes of synthetic (aneurin) vitamin B₁ hydrochloride. Samples of the substance were then handed over to twenty-two laboratories, which determined its potency in terms of the existing standard. Thirty-one tests made by eight different methods revealed a very satisfactory degree of concordance, so that the average value of 3γ of pure vitamin may be taken as the potency equivalent of an international unit.

The results of these tests have been referred to the experts who participated in earlier international conferences for the standardisation of vitamins. They unanimously recommended that the tested sample of synthetic vitamin B₁ hydrochloride should be adopted as the international standard, and that the unit—the value of which remains unaltered notwithstanding the change made in the standard preparation—should be defined as the potency of 3 microgrammes of this substance. This recommendation was subsequently approved by the members of the Permanent Commission on Biological Standardisation, and the international standard preparation now issued by the Hampstead Institute is therefore the pure vitamin B₁.

3. *Third Conference on the Standardisation of Hormones.*

Whereas the first two Conferences were concerned with the establishment of standards for sex hormones, the third Conference¹

¹ The following attended the meeting :

Sir Henry H. DALE, K.B.E., M.D., F.R.S., Director, National Institute for Medical Research, Hampstead, London (*President*) ;

Professor S. ASCHHEIM, Laboratoire d'Embryologie comparée, Collège de France, Paris ;

Dr. D. K. M. CHALMERS, National Institute for Medical Research, London ;

Professor J. B. COLLIP, F.R.S., Department of Biochemistry and Pathological Chemistry, McGill University, Montreal ;

Professor H. M. EVANS, Institute of Experimental Biology, University of California, Berkeley (U.S.A.) ;

Dr. C. HAMBURGER, State Serum Institute, Copenhagen ;

Professor E. LAQUEUR, Director, Pharmaco-Therapeutisch Laboratorium des Universiteit, Amsterdam ;

Dr. A. S. PARKES, National Institute for Medical Research, London ;

dealt with the standardisation of the hormones of the anterior lobe of the pituitary gland and analogous principles found in urine or serum. Though some of those hormones have only recently been isolated and their clinical use is, hence, still limited, experience shows that it is always better, in biological standardisation, to forestall developments, and not wait until different units based on the appearance of a given reaction in a particular animal have found their way into laboratory practice. Before, however, any of these hormones could be standardised, a certain supply had to be collected to serve as the stock of international standard. This has only been possible thanks to the generous help of several manufacturers, to whom the Commission herewith desires to express its gratitude.

In the case of the gonadotrophic substance of human urine of pregnancy, the various samples received were assayed and then mixed, after some of them had been diluted to adjust them to the mean potency value. This mixture, after further dilution with an equal quantity of inert material, constitutes the international standard. The unit is defined as the specific gonadotrophic activity of 0.1 milligramme of this preparation. The Hampstead Institute will shortly begin to issue this standard.

The standard preparation for the thyrotrophic substance of the anterior lobe of the pituitary gland was obtained in the same way, except that a particular sample was selected as a provisional standard of reference for the assays ; control test will have to be made before this sample—0.25 milligramme of which will correspond to one unit of activity—can be issued as an international standard.

Dr. O. RIDDLE, Carnegie Station for Experimental Evolution, Cold Spring Harbor, Long Island, N.Y. ;

Dr. Ph. E. SMITH, Professor of Anatomy, Columbia University, College of Physicians and Surgeons, New York ;

Dr. F. C. YOUNG, National Institute for Medical Research, London.

The following also attended the meeting as observers :

Dr. R. W. BATES, Carnegie Station for Experimental Evolution, Cold Spring Harbor, Long Island, N.Y. ;

Professor B. A. HOUSSAY, Institute of Physiology, University of Buenos Aires ;

Dr. R. MORICARD, Chief of the Laboratory, Gynæcological Clinic of the University, Paris ;

Dr. Kitty PONSE, Acting Director, Station for Experimental Zoology, Zoological Institute of the University, Geneva.

The Conference had to be content with indicating the procedure to be followed in standardising the lactogenic hormones of the anterior lobe of the pituitary gland and the gonadotrophic substance prepared from the serum of the pregnant mare, as the assays undertaken for the selection of samples suitable for inclusion in the standard preparations of these two principles had not yet been completed. Once the standards have been established, as they will be in the near future, it will be possible to define the unit of activity on the lines laid down by the Conference.

In the case of each of the hormones just referred to, the Conference thought it necessary to specify what biological tests would enable a comparative assay to be made without risk of interference by non-specific constituents.

On the subject of the other hormones in the *pars intermedia* or in the anterior lobe of the pituitary gland (gonadotrophic principle, corticotrophic substance, growth-promoting hormone), the Conference considered that, in the present state of knowledge, these hormones could not be standardised. In order, however, to facilitate the comparative research work to be done on these hormones, it asked the Hampstead Institute to prepare a stock of ox anterior pituitary lobe substance, dried without fractionation, so that samples could be supplied to laboratory workers and be used by them as a basis of comparison.

Finally, in regard to nomenclature, the Conference recommended the adoption of the terms "corticotrophin" and "thyrotrophin" to denote the active principles of the anterior lobe of the pituitary gland acting on the adrenal cortex and on the thyroid gland. The term "gonadotrophin" should be used in referring to principles with gonadotrophic action, with the addition of a suitable adjective to indicate the origin of the active principle.

From what has been said, it will be seen that the work of biological standardisation is progressing and expanding; it is of some interest to observe that the research it has entailed has raised afresh problems of outstanding theoretical importance that had been exercising the minds of many serologists. At the same time, the essential objective to be aimed at remains a practical one and may be briefly stated as follows: to make the results of the prophylactic and therapeutic use of biological agents comparable from country to country; to place in the hands of the physician a reliable weapon with a

known range of action ; to provide public health authorities with clear evidence for the rejection of any preparations which are below the requisite standard and, finally, to simplify the work of the producers, who, henceforth, need only assay their export products in terms of international units.

V. CAMPAIGN AGAINST NARCOTIC DRUGS

The Health Committee shares with the Permanent Committee of the Office international d'hygiène publique the duty of giving technical opinions to the organs responsible for international supervision over the traffic in, and manufacture of, narcotic drugs.

In accordance with the procedure laid down in the 1925 and 1931 Conventions, two questions are at present being studied : that of desomorphine and that of preparations made from extract and tincture of Indian hemp. On both questions, the Permanent Committee of the Office international d'hygiène publique has now given an opinion and submitted a report (November 10th, 1938) which the Health Committee is to examine at its thirtieth session, in May 1939.

The attention of the Advisory Committee on Traffic in Opium and Other Dangerous Drugs was drawn by the Governments of Canada and the United States to the fact that numerous cases of codeine addiction have come to light in those two countries. The Advisory Committee accordingly asked the Health Committee for a technical opinion as to the possible significance of codeine as a habit-forming drug. As a first step, the Health Committee gave instructions for a critical survey to be made of the information published on the question up to date;¹ this report is to be examined by the Health Committee at its next session.

The Health Committee was also requested by the Advisory Committee to study the pharmacological properties of eucodal, dicodide, dilaudide and acedicone. This study, the main purpose of which is to collate the information contained in existing technical publications, will form the subject of a report which will soon be ready.

¹ See P. WOLFF : " The Significance of Codeine as a Habit-forming Drug " ; *Bull. Health Org.*, 1938, 7, 546.

In pursuance of a resolution adopted by the International Conference on the Suppression of Opium-smoking (Bangkok, 1931), the Health Committee had undertaken an investigation into the various methods employed in the treatment of drug addicts in the chief European and North American countries, and brought together a valuable collection of clinical data.

In July 1938, the Advisory Committee requested it to resume its examination of the question, taking into account methods of treatment introduced since the original investigation. A general report based on the original findings and on the new data now available will accordingly be published.

VI. UNIFICATION OF PHARMACOPŒIÆ

The potential value of the creation of a limited international pharmacopœia has long been urged. Pharmacists often meet with difficulties in making up prescriptions for customers from foreign countries. The same problem arises when a ship has to replenish its medical stores in foreign ports.

Moreover, the varying standards as to strength, and particularly as to purity, of the drugs at present found in the various national codices are a source of difficulty both to the practitioner and to the manufacturer, part of whose supplies are intended for the international market. He is sometimes obliged to manufacture a special preparation of the same drug for each country to which he is exporting.

The question of the possible unification of pharmacopœiæ was dealt with by an international conference which met at Brussels in 1925. The outcome was a Convention creating an International Secretariat under the auspices of the Belgian Government. That Government, as depository of the Convention, requested the Council of the League of Nations to consider how permanent contact might be instituted between the Health Organisation and the International Secretariat.

In agreement with the Belgian Government and in liaison with the International Pharmaceutical Federation, a Technical Commission of Pharmacopœial Experts was set up in November

1937.¹ Its instructions were to prepare a programme of studies and to select drugs suitable for examination.

The Commission met in May 1938.² Its members undertook to prepare draft monographs on each of the drugs previously selected by the Commission. The standard form of monograph to be adopted was worked out, and it was also decided to prepare a general description of reagents and analytical procedures, and statements of certain general principles for the unification of pharmacopœiæ. The preparation of a report on maximum doses and on the possibility of defining average doses was entrusted to two members of the Commission.

Some seventy monographs have already been completed in draft form, as has the report on maximum and minimum doses. The Commission is to meet again on May 10th next to examine this material and put it into final shape. When this has been done, the monographs will be forwarded to the International Secretariat at Brussels for distribution to the countries signatories to the 1925 Convention. The Commission hopes that the final outcome of its endeavours will be the adoption of these monographs by the appropriate national bodies and, in due course, their incorporation into a limited international pharmacopœia.

In carrying out its task, the Commission has had the assistance of a Sub-Committee consisting of specialists on galenical pharmacy.³

¹ This Commission has the following composition :

Dr. C. H. HAMPSHIRE, Secretary, British Pharmacopœia Commission
(*President*) ;

Professor H. BAGGESGAARD-RASMUSSEN, " Pharmaceutiske Laereanstalt ", Copenhagen ;

Dr. E. FULLERTON-COOK, Chairman of the Committee of Revision of the Pharmacopœia of the United States of America, Philadelphia ;

Professor E. EDER, Professor at the Pharmaceutical Institute of the Polytechnicum, Zurich ;

Professor L. VAN ITALLIE, Director of the Institute of Pharmacology, Leyden ;

Professor M. TIFFENEAU, Dean, Faculty of Medicine, Paris ;

Professor Edgar ZUNZ, Laboratory of Pharmacodynamics and Therapeutics, University of Brussels.

(Dr. E. FULLERTON-COOK was not present at the meeting in May 1938.)

² Its report was forwarded to the International Pharmaceutical Federation.

³ The *Reference Sub-Committee on Galenical Pharmacy* has the following composition :

Dr. C. H. HAMPSHIRE, Secretary, British Pharmacopœia Commission
(*President*) ;

Mr. H. BERRY, Dean of the College of the Pharmaceutical Society,
University of London ;

VII. ANTI-EPIDEMIC ACTION IN CHINA

Last year's report included a statement of the circumstances in which the League of Nations had been led to modify to some extent its arrangements for technical collaboration with the Chinese Government in the organisation of a scheme for preventive anti-epidemic action in Chinese territory. A number of doctors, epidemiologists, bacteriologists and sanitary engineers had been sent to China towards the end of 1937 with the equipment, supplies and resources required to enable them to advise and assist the Chinese technical services.

It was clear that any form of anti-epidemic action must be closely dependent upon the military situation. As far back as the summer of 1937, the Chinese Government, then still at Nanking, had laid down the bases of organised action for the prevention of epidemics. At that time, these threatened to spread in two regions: northern China, and the country around Shanghai, from which refugees were already fleeing in such numbers that the first need was for anti-epidemic units capable of functioning up and down the main lines of communication. Technical experts were detached from the Central Field Health Station at Nanking and placed along the Shanghai-Nanking railway and in the northern area, to form units commanding the important junctions of the lines of communication.

The technical staff of the League of Nations, upon arrival in China, was incorporated, with its sanitary equipment, in the system which had thus been created in broad outline (January 1938). Three units were thus set up: the first, under Dr. H. MOOSER (Switzerland), began to operate in north-west China, with its headquarters at Sian-Fu; the second, under Dr. R. C. ROBERTSON (United Kingdom), established itself at Chang-Sha in central China; the third unit, under the direction of Médecin-Général A. LASNET

Professor J. BÜCHI, Institute of Pharmacy, Polytechnicum, Zurich;
Professor A. GORIS, Director of the Central Pharmacy of Hospitals
and Civil Asylums, Paris;

Dr. J. A. C. VAN PINXTEREN, Hillegersberg, Netherlands;
Dr. S. A. SCHOU, "Pharmaceutiske Laereanstalt", Copenhagen;
Professor N. WATTIEZ, School of Pharmacy, University of Brussels.

(France), was allotted the southern regions and made Nanning its headquarters.

Some idea of the size of these units may be gained from the fact that they comprised about 150 persons each and that they were provided with the technical equipment required for diagnosis, isolation of contagious cases, vaccination, delousing, etc. To give an example, the second unit had set up a central laboratory equipped for every form of bacteriological, serological and parasitological examination. The third unit was able itself to produce the anti-cholera and anti-typhus vaccines required by all three units. All three worked in close collaboration with the Central Government of China, which, it is important to note, remained responsible for anti-epidemic action. The Government itself had under its orders some forty groups organised by the Chinese Red Cross, each consisting of two doctors, five health inspectors and various assistants and nurses, amounting altogether to about twenty persons. These units were well staffed and well officered ; they were able to collaborate closely with the League units and rendered valuable service, particularly in connection with the isolation, treatment and vaccination of cholera cases.

The three League units were soon compelled to split up, in order to despatch mobile teams along the lines of communication, most of which run from east to west. The laboratories had also to be subdivided, owing to the difficulty of maintaining access to supplies. Thus the second unit set up a branch laboratory at Chang-Teh for the bacteriological diagnosis of cholera ; it also established three mobile laboratories, seventeen anti-epidemic teams, and several emergency hospitals for the isolation of infectious cases.

A broad survey of the epidemic situation in China in 1938 shows that cholera, malaria and smallpox represented by far the greatest dangers.

The first signs of cholera appeared in May 1938 ; the map published in the *Weekly Epidemiological Record* of October 13th reveals the disease in practically every district, though the incidence was highest in the central and southern areas and the occupied parts in the east.

The fight against cholera proved extremely arduous. It necessitated a very large personnel, in the first place to detect, isolate and treat cases, and in the second place to carry out vaccination.

The main efforts of the units were concentrated on the refugee camps and on the population of the towns in which those camps had been established. In Chang-Sha, for example, 81,973 inoculations were carried out in July alone.

In that same month, the Chinese Government requested the Health Organisation, by cable, to supply it with six million doses of anti-cholera vaccine. Thanks to the generous help extended by bacteriological institutes and health administrations in thirteen different countries,¹ it proved possible, in less than four weeks, to despatch over eight million doses free of charge.

Many other forms of action against cholera were also employed: sanitation, disinfection of drinking-water, control of markets, supervision of roads and rivers, hospital and other treatment, propaganda, etc. One particular task was to provide quarantine arrangements for the refugees on their arrival at stations and ports. By means of these measures, the units were able to keep the situation under control throughout.

The problem of malaria was hardly less acute, especially in central China, where refugees were bringing infection into the midst of the civilian populations. In the southern area, many outbreaks occurred suddenly in the spring, and to a more serious extent in the autumn, in all the districts impregnated with malaria. Investigations had to be made to obtain an exact idea of the terms of the problem. Obviously, in the conditions then obtaining in China, there was only one method of combating the disease—namely, to carry out temporary prophylaxis by means of preventive quinine treatment.

Smallpox occurred chiefly during the cold season; by means of systematic vaccination, the units succeeded in preventing serious epidemics.

Although unit No. 1 had to deal with some cases of plague at Yu-Lin, it is true to say that the disease remained purely local in character and was not such as to cause serious apprehension. There were also some sporadic outbreaks of typhus fever, of dysentery,

¹ The United States of America, Argentine, Australia, Burma, Ceylon, Denmark, Egypt, Indo-China, Malaya, Netherlands, Roumania, Turkey and Yugoslavia.

The American Red Cross alone supplied three million doses, while the Cantazène Institute and the Turkish Ministry of Health supplied one million each.

and, to a lesser extent, of typhoid, trachoma, diphtheria and cerebro-spinal meningitis ; but at no time was there a real epidemic focus.

The essential task of the units despatched by the League of Nations was, in effect, to assist the central and provincial authorities in their efforts. The units provided, as it were, the nucleus around which a systematic anti-epidemic organisation has developed ; at the same time, they have contributed additional material resources. Whilst co-operating closely in the maintenance and improvement of a public health service which had been somewhat disorganised by circumstances, their rôle as technical helpers involved close collaboration in the general direction of anti-epidemic measures—namely, the organisation of early detection and of an information service through which epidemic outbreaks might quickly become known ; medical assistance to refugees ; the isolation and treatment of infectious cases, the provision of delousing stations, shower-baths and sterilising posts ; general immunisation, sanitation and the organisation of sanitary measures. The units also gave their help to local hospitals and health services ; they outlined schemes for public health services, including the provision of latrines, the suitable treatment of drinking-water and of household refuse, the protection of wells, etc. They further themselves supplied a large proportion of the vaccines, drugs, disinfectants and chemical products required.

All this work was achieved in circumstances of particular difficulty. The influx of refugees—for the most part entirely destitute—caused migrations of populations, the magnitude of which it is difficult to realise. A veritable tidal wave swept across central and southern China, creating the gravest problems in connection with the supply of essential foodstuffs. If it is added that the units themselves were compelled to evacuate certain districts and to move eastwards, the full difficulty of their task will be better appreciated. At no stage, however, did they lose control of the situation.

* * *

In September 1938, it was decided to continue, for another year, the assistance furnished to the Chinese Government.

The fundamental bases of that assistance must clearly remain unchanged—that is to say, the technicians and equipment sent to

the spot will still be at the disposal of the Chinese Government, the latter retaining full responsibility ; it is too early to say what changes will require to be made in the organisation which operated last year. It is likely, however, that the system of three units working in different parts of China will be replaced by some more elastic machinery better adapted to a changed situation. The details are at present under consideration. In March 1939, the Secretary-General sent one of the medical experts of the Health Section to the spot to study the situation with the Chinese authorities and the Anti-epidemic Commission ; this expert is due back some time in May.

HEALTH INDICES

THEIR PLACE IN PUBLIC HEALTH REPORTS

The search for numerical indices capable of describing the state of health and vitality of the population, as well as factors, both of environment and of sanitation, which might influence it, has given rise since 1936 to a number of studies carried out under the auspices of the Health Organisation.

The scheme of "Health Indices" drawn up by STOUMAN & FALK,¹ inspired, on the one hand, by the health surveys used for teaching purposes by certain institutes and schools of hygiene, and, on the other, by the appraisal forms for health work² in use in the United States of America, combined the advantages of presenting the elements of a survey in an objective numerical form and, at the same time, covering a wider field than the appraisal forms, since these health indices apply, not only to sanitary activities, but also to the geographic, social and economic factors influencing public health.

The "indices" proposed by STOUMAN & FALK were, in the first place, given a trial by STOUMAN himself. The first experimental application was made in an American town of average size, New Haven (Connecticut),³ which was particularly suitable, in view of the fact that a health survey had been carried out there a few years previously by Professor WINSLOW.⁴

The next experiments carried out by STOUMAN were for a rural district (Mezőkövesd) of Hungary,⁵ and then Brussels.⁶

In the meantime, KACPRZAK and TOMCSIK were applying the indices experimentally in rural districts of Poland and Hungary.⁷ These trials showed that it was necessary to simplify the "indices"

and to adapt them to local conditions, and, more particularly, to rural conditions, if they were to be applied to rural areas.

In November 1937, the Directors of European Institutes and Schools of Hygiene, at a meeting in Geneva, suggested the use of the health indices for general or specialised health surveys and recommended that the geographical framework for such enquiries should correspond to a "natural region".⁸

In April 1938, a group of experts* selected a series of indices suitable for rural areas.⁹ These indices were recently used by SELLESLAGS for the Belgian province of Luxemburg, in comparison with the whole of Belgium.¹⁰

Finally, in October 1938, a special Committee on Health Indices,** working on the basis of the experience accumulated during the preceding trials, drew up, not merely a revised list of indices, but the framework of a standard report on public health with selected numerical indices incorporated in its various chapters.

The framework of the report and the indices it includes are so drawn up as to apply equally to rural or urban areas, or to a whole country.

It is interesting to note that the system of health indices has followed a trend similar to that of the American appraisal forms, which were

* The group included :

Professor L. BALTEANU, Hygienic Institute, Iasi, Roumania.
 Dr. B. BORČIČ, Director of the Hygienic Institute, Zagreb, Yugoslavia.
 Dr. M. KACPRZAK, State Hygienic Institute, Warsaw, Poland.
 Dr. J. KLIMA, State Hygienic Institute, Prague, Czecho-Slovakia.
 Professor J. TOMCSIK, Director of the State Hygienic Institute, Budapest, Hungary.
 Secretary : Dr. R. H. HAZEMANN, of the Health Section.

** Composed as follows :

Chairman :

Dr. R. ATWATER, Executive Secretary, American Public Health Association, New York.

Members present :

Dr. M. KACPRZAK, Chief of Service at the State Hygienic Institute, Warsaw ;
 Dr. J. PATERSON, Medical Officer of Health, Maidenhead, Berks, England ;
 Professor J. TOMCSIK, Director of the State Hygienic Institute, Budapest.

Members absent :

Professor J. PARISOT, President of the Health Committee, Director of the Regional Hygienic Institute, Nancy ;
 Dr. A. HÖJER, Director of the Health Administration of Sweden, Stockholm.

Secretary :

Dr. Y. BIRAUD, Member of the Health Section.

first established for towns, then for rural areas, and finally became general.¹¹

In drawing up the following skeleton standard report, the Health Organisation had the assistance of two hygienists with personal experience in the application of health indices in Central Europe, a British official experienced in drawing up health reports, and the Secretary of the Committee on Administrative Practice of the American Public Health Association, which had established the latest edition of the "Appraisal Form for Local Health Work".¹²

The framework of a standard report is given on the following pages, with an introductory note to facilitate the use of the report.



References

- ¹ K. STOUMAN and I. S. FALK : Health Indices : A Study of Objective Indices of Health in Relation to Environment and Sanitation. *Bulletin of the Health Organisation*, Vol. V, No. 4, December 1936.
- ² H. S. CUMMINS : The Survey Method of stimulating Public Health Administration in the United States of America. *Document C.H. 805*, May 1929.
- ³ K. STOUMAN : Health Indices for the City of New Haven, Connecticut, U.S.A. *Bull. Health Org.*, Vol. V, No. 4, pp. 997-1081, December 1936.
- ⁴ C. E. A. WINSLOW : *Health Survey of New Haven*. Quinluplack Press Inc., New Haven, Conn., 1928.
- ⁵ K. STOUMAN : Health Indices in an Experimental Study of a Rural District of Hungary. *Bull. Health Org.*, Vol. VI, Extract No. 14, 1937.
- ⁶ K. STOUMAN : Health Indices established in an Experimental Study of the City of Brussels. *Bull. Health Org.*, Vol. VII, Extract No. 3, 1938.
- ⁷ J. TOMCSIK : *Report on the Activities of the State Hygienic Institute of Hungary during the Year 1937*. (In Hungarian, with English and German summaries). Budapest, 1938.
- ⁸ Report on the Meeting of Directors of Institutes and Schools of Hygiene, Geneva, November 22nd to 27th, 1937. *Bull. Health Org.*, Vol. VII, pp. 167-190; Extract No. 4, 1938.
- ⁹ *Commentaires concernant les indices sanitaires des districts ruraux. Document C.H. 1331/1*, June 14th, 1938.
- ¹⁰ W. SELLESLAGH : Application des indices sanitaires des districts ruraux à la Province de Luxembourg (Belgique). *Document C.H. 1416*, April 1939.
- ¹¹ *Appraisal Form for Local Health Work*, prepared by the Committee on Administrative Practice, American Public Health Association, New York City, 1938.
- ¹² Note on the Work done as regards Health Indices. *Document C.H. 1346*, June 1938.

SKELETON STANDARD REPORT ON THE STATE OF HEALTH OF THE POPULATION AND FACTORS INFLUENCING IT*

INTRODUCTORY NOTE

The following list gives the headings and sub-headings of the various chapters which should be contained in a complete health report covering either an entire country or a region or a local area.

Under each heading, a short general statement of the prevailing conditions should be given, supplemented by figures as far as possible. In order to render the reports comparable from one area to another, and, still more important, from one period to another in the same area, a series of numerical indices is suggested under each heading. Although these indices have been selected with care, it is to be expected that only part of them will be obtainable for any given area in the form suggested. It is clear that when statistical data are not available in the form suggested, such figures as are available should be used instead, or, failing these, a short statement might be given summarising the situation. It is possible, too, that certain figures may be available only for the whole of a country and be given only in a "national" report, while other data may only be obtainable for, or characteristic of, a local area and their use restricted to a "local" report. Hence a national report, although drafted on the same lines as local reports, would not be merely the sum of the local reports.

In certain cases, it may happen that an aggregate figure is made up of component parts based on widely different conditions. It would then be best to give figures for representative areas rather than meaningless averages. Thus, in a semi-industrialised country, it would be preferable to give, besides a general statement, instances taken from both industrial and agricultural areas.

* The following is a slightly amended version of document C.H. 1382.

The plan of the report covers a number of points (meteorology ; distribution of population, industry and agriculture ; etc.) which do not change materially from year to year or are available only for census years. Where the plan is used for successive annual reports, it may be sufficient to give references to data already published in a previous report.

General Particulars to be given.—The area covered should be stated clearly, together with the basic year of the enquiry. In general, all the figures given should refer to the year of the enquiry, unless otherwise specified in the text. The census year would appear to be preferable in some cases, as the information then obtained is more reliable ; if this year is used, this should be stated in each case. An endeavour should be made to use the age-groups indicated ; if other groups are used, these should be stated.

Important Items.—In the following list, the items given in italics are considered of particular importance, and a special effort should therefore be made to include them in every report.

Abbreviations.—The letters “ N ” and “ L ” indicate respectively that the sub-heading or item which they precede should be used only for National or Local reports.

Statistics of deaths by causes are accompanied in the report by the number or numbers in the detailed International Lists of Causes of Death adopted in 1929 and 1938. Where no indication as to year is given, the numbers are the same in both editions.

General Plan :

- I. *Indices of Vitality and Health.*
- II. *Indices of Environment.*
- III. *Indices of Public Health Activity.*

* * *

I. INDICES OF VITALITY AND HEALTH

A. DEMOGRAPHY

1. Population.

Last census (date.....) number

Last estimate (date.....) number

Percentage distribution at the last population census into :

i. <i>Urban</i> ¹	o'
ii. <i>Rural</i> ¹	o'
		o
		100

2. Density of Population.

General statement on the dispersion or agglomeration of the population.²

Population per square kilometre

i. In urban communes

ii. In rural communes

3. Composition of Population.³

Sex and age distribution of population at last census :

If possible in groups covering five years (0-1, 1-4, 5-9, 10-14 years, etc.).

Otherwise according to the available age groups.

4. Birth-rate.⁴ ** ***

Live-births per 1,000 population

Illegitimate live-births per 100 live-births

¹ Indicate administrative method of differentiating "urban" and "rural" areas.

² If the report refers to a suburban area, the fact must be clearly stated.

³ In some countries or regions, it will be desirable to add a special item (3a) under "Composition of the Population" to give the main racial or national elements as percentages of the population; in immigration countries, the proportion of natives and of foreign-born, etc.

⁴ Give the official definition of still-births; also the rules for the declaration of births and still-births:

Time limit for registration of births;

Are infants born alive but dying before registration recorded as live births?

** Indicate how far registration is complete.

*** Where the figures relate to a local area, state whether corrected for residence.

5. **Fertility.**⁴

Number of live-births for the last census year per
1,000 women at ages 15-49⁵

B. MORTALITY

6. **Maternal Mortality.**

*Deaths from diseases or accidents due to pregnancy,
child-birth and puerperal condition, including
those due to abortion (Nos. 140-150), per 1,000
live-births*

7. **Still-births.**^{4 **}

Number of still-births per 1,000 live-births

8. **Infant Mortality.**^{4 ***}

Infant mortality under one year per 1,000 live-births

Infant deaths per 1,000 live-births :

From (a) *Diarrhoea or enteritis, 0-2 years (No. 119)*

(b) *Pulmonary affections, 0-1 year
(Nos. 106-114)*

9. **Neonatal Mortality.**⁴

Mortality under one month per 1,000 live-births

10. **Mortality due to Communicable Diseases.**

Deaths per 100,000 population, due to

(a) *Typhoid affections (Nos. 1 and 2)*

(b) **Tuberculosis :**

i. *Respiratory tuberculosis (1929 : No. 23 ;
1938 : 13)*

ii. *Other forms (1929 : Nos. 21-32 ; 1938 :
Nos. 14-22)*

(c) *Diphtheria (No. 10)*

(d) *Other important communicable diseases (spe-
cify)*

⁴, ^{**}, ^{***} See preceding page.

⁵ If calculated on a different age-group, indicate the age-group.

11. Other Specified Causes of Mortality.

(a) Deaths per 100,000 of persons 50 years and over.¹¹

- i. Cancer and other tumours (1929 : Nos. 45-55 ; 1938 : Nos. 45-57).....
- ii. Diseases of the heart and circulation (Nos. 90-103)
- iii. Cerebral haemorrhage (1929 : No. 82) or Intracranial lesions of vascular origin (1938 : No. 83)

(b) Deaths per 100,000 population (all ages) :

- i. Influenza (1929 : 11 ; 1938 : 33).....
- ii. Other respiratory diseases : Bronchitis and pneumonia (Nos. 106-109)
- iii. Suicide (1929 : Nos. 163-171 ; 1938 : Nos. 163-164)
- iv. Accidents (1929 : Nos. 176-195 ; 1938 : Nos. 169-195)

12. Certification of Causes of Death.

(a) Percentage of deaths from unknown or ill-defined causes (Nos. 199-200)

(b) Percentage of deaths from other insufficiently-defined causes : Convulsions under 5 years (No. 86), Congenital debility (No. 158) and Senility (No. 162)

(c) Percentage of deaths whose cause is certified or decided by :¹²

- i. The attending physician
- ii. A medical official who examines the body and questions the family^{12*} ...
- iii. A non-medical official

13. General Mortality.^{4**}*Number of deaths per 1,000 population*^{4**}^{4**} See page 65.¹¹ Or of 40 years and over, in which case specify.¹² Indicate which method is normally preferred by law.^{12*} Including coroners' inquests where medical advice is available.

C. MORBIDITY

14. Apparent Morbidity and Case-fatality from Communicable Diseases.

	Per 100,000 population		Apparent case-fatality rate ($\frac{d \times 100}{c}$)
	Cases (c)	Deaths (d)	
<i>Typhoid fever</i> ¹⁴
<i>Diphtheria</i>
<i>Scarlet fever</i>
.....
<i>Malaria</i>
<i>Trachoma</i>
.....

15. Tuberculosis.

General statement as to whether tuberculosis is considered to be increasing, stationary or declining in cities and rural areas respectively.

- (a) Number of cases of open tuberculosis (Tb. bacillus test positive) newly registered or reported during the year :
- i. Per 100,000 population
 - ii. Per 100 deaths caused by tuberculosis (all forms)
- (b) Tuberculin skin-testing¹⁵ : percentage of positive reactions according to age (in years) among certain groups of the population (school-children, recruits, etc.)

¹⁴ State if paratyphoid fevers are included.

¹⁵ Specify technique and nature of each group tested.

16. Venereal Diseases.

General statement on the prevalence of venereal diseases and means adopted to ascertain prevalence (such as notification, enquiry, etc.). If figures are available, state their value and significance.

(a) Syphilis :

- i. Number of cases reported, registered or otherwise discovered¹⁶ during the year, per 100,000 population
- ii. Percentage of positive sero-reactions among certain groups of the population (pregnant women, etc.)^{16*}

(b) Gonorrhoea :

Number of cases, reported, registered or otherwise discovered¹⁶ during the year, per 100,000 population

17. General State of Health of the Population.

General statement on the health conditions of the population and of special groups, such as school-children, recruits, etc.

(a) Results of school medical inspection :

- i. State of nutrition of school-children.¹⁷
- ii. Chief physical defects detected.

N. (b) Health conditions of recruits : percentage and main causes of rejections.

¹⁶ Cross out what does not apply.

^{16*} Specify group and method of its selection, so as to make it clear whether it is a fair sample, representative of the general population, or, on the other hand, made up of individuals particularly exposed to, or suspected of, syphilis.

¹⁷ According to an international group of experts (*Cf. Bulletin of the Health Organisation, 1937, 6, pages 129-204*), the state of nutrition of the young can be assessed by the regular collection of the following information :

- (a) Age,
- (b) Sex,
- (c) Physical appearance (slim, average or thickset type),
- (d) Weight,
- (e) Height (if necessary, also height when seated).

A simple clinical examination covering the colour, firmness and elasticity of the skin, a rough estimate of the amount of subcutaneous fat and muscular development, and condition of the teeth, is sufficient to distinguish between apparently normal children and those whose nutrition seems defective and who therefore require special medical examination.

18. Infirmities.

Prevalence of infirmities as revealed by censures, special surveys and records of official or private welfare organisations. If available, give numbers of inmates of special institutions :

- (a) Insane and feeble-minded
- (b) Blind
- (c) Deaf-mutes
- (d) Cripples
- (e) Other infirmities

II. INDICES OF ENVIRONMENT**EXTERNAL ENVIRONMENT****A. METEOROLOGY****19. Meteorological Information.**

General statement on prevailing climate.

- N.** For national reports, precise meteorological data may be given for several representative stations—*e.g.*, in the capital and in regions with different climates.
- L.** For local reports, state whether the meteorological station is in the area covered or at what distance and in which direction.
 - (a) Temperature : mean monthly (month by month) :
 - i. Highest (Centigrade)
 - ii. Lowest (Centigrade)
 - (b) Rainfall :
 - i. Annual (in mm.)
 - ii. Number of days with rainfall
- L.** (c) Average hours of sunshine per day

B. HOUSING

20. Type of Dwelling.

Short general statement on types of houses prevailing in urban and rural areas (tenement houses, one-family houses, etc.).

21. Overcrowding.

(a) Percentage (at last census) of the population which is lodged as follows²¹ :

1 person per room ^{21*}
2 persons " "
3 " " "
4 " " "
5 " " "
6 persons or more per room
					-----	%
					100		

(b) In the absence of such information, percentage of the population living in dwellings with more than two persons per room.^{21**}

²¹ The Committee of Statistical Experts of the League of Nations has proposed the following standard table for the publication of housing statistics, from which the indices given under item 21, (a) and (b), may readily be computed (document C.226.M.128.1938.II.A, page 14) :

Number of Family Households of Different Sizes occupying Different Numbers of Rooms.

Number of persons per family household	Number of family households occupying rooms						Total number of family households
	1	2	3	4	5, etc.	10 and more	
One							
Two							
Three.....							
etc.....							
Ten and more							
Total number of family households							

^{21*} Give official definition of "rooms"; are the kitchen, bathroom, etc., considered as rooms ?

^{21**} The ratio of 2 persons per room is mentioned because it is officially adopted in several countries as the basis of computation of overcrowding, and not because the Committee on Health Indices considers it a satisfactory standard of hygienic housing.

(c) In the absence of indices (a) and (b) :

Percentage of dwellings containing (at the last census) :

1 room ^{21*}%
2 rooms%
3 „%
4 „%
5 „%
6 „%
(or more)	_____
	100%

22. **Newly Built²² or Improved ^{22*} Dwellings.**

General statement on house-building and improvements.

Indicate the part played by State, local or semi-private agencies in collective building schemes, if any, and the class of population for which such schemes are intended. (Industrial or agricultural workers, officials, lower middle class, large families, etc.)

Number of houses or dwellings (as a percentage of all houses and dwellings in existence) :

- (a) Built²² during the last years %
 (b) Improved^{22*} during the last years %

C. SANITATION

23. **Disposal of Excreta.**

(A) *General statement on methods in use for the disposal of human excreta.*

Percentage of total population or (if this figure is not available) percentage of dwellings²³ :

(a) With closets :

- i. Connected with sewerage system..... %
 ii. Other approved systems (describe approved type) %
 iii. Other types not approved %

(b) Without closets %

^{21*} See preceding page.

²² State whether this refers to houses completed or building permits issued.

^{22*} *i.e.*, having been made "sanitary" in accordance with the standards of the local authority.

²³ Specify which percentage is given.

(B) General statement on the methods of disposal of animal excreta :

Percentage of manure-heaps (containing solid and liquid stable manure) with watertight bottom %

24. Water Supply.

General description of water-supply systems in urban and rural areas.

(A) TYPE OF SUPPLY.

	Number of sources	Percentage of population served
(a) Public :		
i. Piped water-supply
ii. Common wells, springs and cisterns
(b) Private sources

(B) INSPECTION OF WATER.

	Number of inspections of water-supply	Number of analyses of water	Percentage of satisfactory samples ²⁴
(a) Public supply :			
i. Piped water-supply
ii. Common wells, springs and cisterns
(b) Private sources

(C) IMPROVEMENTS.^{24*}

	Percentage of sources condemned ^{24*}	Percentage of sources improved ^{24*}
(a) Public supply :		
i. Piped water-supply
ii. Common wells, springs and cisterns
(b) Private sources

²⁴ Indicate standard of purity.

^{24*} During the year, or else state period.

D. CONSUMPTION

25. Food-consumption.

N. (a) *Per capita* annual consumption of the various staple foods, such as :

	Kgr.
Cereals
Potatoes
Sugar
Vegetables (state chief kinds)
Fruit (state chief kinds)
Meat and fish
Fats (state kinds)
Dairy produce ²⁵

(b) *Illustrations of the number and composition of the various meals of the day* in different groups of the population (factory workers, peasants, etc.).

N. For national reports, state districts taken as samples.

(c) Specify the foods consumed according to season, giving general indications—*e.g.*, how many meat meals are eaten per week ; whether little meat is eaten, much cereal food, few potatoes, vegetables and dairy produce. Such general indication may be given for the items listed under (a) above.

26. Alcohol Consumption.

Short statement of types and quantities of alcohol consumed, and class of consumer.

N.	Consumption <i>per capita</i> per annum	
	Litres	Alcohol content in litres ²⁶
(a) Beer and cider
(b) Wines
(c) Strong spirits
Total

²⁵ State whether milk is generally consumed raw, pasteurised, boiled or treated in any way, or if any special precautions are taken with regard to milk intended for the use of children.

²⁶ If there are difficulties in computing these figures, the average alcoholic content of the beverages may be given as a percentage.

SOCIAL ENVIRONMENT

A. OCCUPATIONAL ENVIRONMENT

27. Occupations.

Gainfully-occupied population engaged in :

	Number	Percentage
(a) Agriculture, forestry and fishing
(b) Mines and quarries
(c) Industry
(d) Commerce
(e) Transport
(f) Public administration and national defence
(g) Liberal professions
(h) Domestic and personal services
(i) Others
Total	100

28. Distribution of Gainfully-occupied Population.

Percentage of total gainfully-occupied population :

(a) Employers and independent workers%
(b) Salaried employees%
(c) Wage earners%
(d) Unpaid family workers%
Total	100

29. Agricultural Utilisation of the Soil.

Percentage of total area under consideration :

(a) Cultivated%
(b) Pasture%
(c) Forest%
(d) Other%
Total	100

30. Size of Holdings.

	Holdings		Agricultural population	
	Number	Percentage of total holdings	Number	Percentage
0-1 hectare
1-4.9 hectares
5-9.9 "
10-19.9 "
20-49.9 "
50-99.9 "
100 and over
Total	100	100

31. Crops.

Principal crops.³¹

	Area cultivated Hectares	Percentage
(a) Wheat
(b) Rice
(c) Rye
(d) Maize
(e) Other cereals (specify)
(f) Potatoes
(g) Hay and fodder
(h) Sugar beet
(i) Other crops for industrial purposes (specify)
(j) Fruit
(k) Grapes
(l) Vegetables
(m) Other crops
		100

32. Live-stock.

Number of animals per head of agricultural population (*cf.* item 27a): ³² ^{32*}

(a) Cattle
(b) Horses
(c) Pigs
(d) Sheep
(e) Goats

³¹ Give particulars for important crops only.

³² State whether for the year under review or for the last agricultural census.

^{32*} Give particulars for other animal species of local importance (buffaloes, camels, etc.).

33. **Industry.**

Descriptive statement of main industries (*e.g.*, metal, textiles).

(a) Number of industrial establishments according to number of employees :

	Number of establishments
i. With less than 5 employees
ii. 5-24 employees
iii. 25-99 employees
iv. 100-499 employees
v. 500 or more employees

Total number of industrial establishments

(b) Home industry : general statement on prevalence, type of work, general conditions, etc.

B. COMMUNICATIONS AND ELECTRIFICATION

34. **Means of Communication.**

General statement.

(a) Roads : Number of kilometres permanently fit for vehicular traffic :

i. Per 100 sq. km.
ii. Per 1,000 population

(b) Licensed motor vehicles : Number per 1,000 population

L. (c) Public passenger transport : Percentage of the population whose communes or other local units^{**} are crossed and served by a regular railway or omnibus service

(d) Telephones : Number of telephones per 1,000 population

^{**} Indicate average area of unit.

35. **Electrification.**

Percentage of dwellings provided with electricity..

If exact figures are not obtainable, describe availability of electricity.

C. EDUCATION

*General statement.*36. **Cultural Level.**

(a) School attendance : Percentage of children of school age regularly attending school³⁶

(b) Post-school education : Type and attendance of educational institutions for young people beyond compulsory school age (secondary schools, professional schools, schools of domestic science, etc.)

(c) Illiteracy : Percentage of illiteracy among persons aged 10 years and over^{36*}

If this information is not available, state the percentage of illiterates either among recruits or at time of marriage (specify).

³⁶ State the age-limits of compulsory school attendance.

^{36*} State the limits of the age-group covered.

III. INDICES OF PUBLIC HEALTH ACTIVITY

A. PERSONNEL AND EQUIPMENT

7. Medical and Auxiliary Professions.

(A) Number (per 100,000 population) of :

- i. *Doctors*
- ii. Registered dentists³⁷
- iii. Licensed midwives
- iv. Qualified nurses in practice :
 - (a) Total
 - (b) In institutions

(B) *Staff of health services and other public^{37*} medico-social services.*

	Medical Off- cers	Bedside (clinical) Nurses	Public Health Nurses ^{37**}	Sanitary Inspec- tors	Others ^{37***}
<i>Full-time staff :</i>					
(a) Engaged exclusively in :					
i. Preventive medicine.
ii. Curative medicine..
(b) Engaged in both cura- tive and preven- tive medicine
<i>Part-time staff :</i>					
(a) Engaged exclusively in :					
i. Preventive medicine.
ii. Curative medicine
(b) Engaged in both cura- tive and preven- tive medicine

³⁷ Without a degree entitling them to general medical practice.

^{37*} Indicate in a descriptive statement, or by a footnote, what services are performed by voluntary or semi-public bodies, such as voluntary (private) associations or societies receiving grants or subsidies from public funds for work done for the benefit of the community.

^{37**} Social workers should be listed separately if not identified with public health nurses.

Public health nurses are persons attached to a medico-social service who have received an adequate training and visit homes for the purpose of tracing cases of infectious disease, advising, educating and materially and morally assisting families.

They are sometimes described as "visitors", "visiting nurses", "health nurses", "health assistants" or "welfare workers". In practice, all of them work for the rehabilitation of the individual in the family life, and of the family in the community, by improving both health and economic and social conditions.

When a single nurse visits a family (which is deemed preferable to having a number of specialised nurses calling in succession, except on certain occasions when the technical assistance of a specialised nurse is necessary), the public health nurse is known as a "family" or "general" (polyvalent) nurse, as distinct from a specialised (monovalent) nurse.

^{37***} Specify classes and qualifications—e.g., dentists, sanitary engineers, veterinarians, laboratory workers, etc.

38. Clinics and Health Centres.

(A) Number of health centres³⁸(B) *Distribution of specialised clinics* :^{38*}

	Number of clinics			
	Independ- dent (a)	In health centres (b)	Total (a + b)	
			Number	Per 100,000 population
i. Pre-natal
ii. Infant
iii. Pre-school
iv. School
v. Tuberculosis
vi. Venereal disease
vii. Mental
viii. Others (specify)
Total

39. Hospital Institutions.

(a) *Public and private hospitals* (not including³⁹ convalescent homes, mental hospitals, sanatoria, asylums for old people, etc.).

	Number of insti- tutions	Number of beds ^{39*}	Number of of beds per 1,000 population
i. For communicable diseases
ii. For maternity cases
iii. For children
iv. Others (including general hos- pitals) ^{39**}
Total

³⁸ A description of a health centre as it is here understood is given in the Appendix.^{38*} The word "clinic" here means a consultation centre and not merely a session of such a consultation centre.³⁹ If, for local administrative reasons, hospitals cannot be readily differentiated in the statistics from other institutions, indicate which types of institution are included here.^{39*} Give in this column the number of all beds reserved for the type of case indicated, whether in special hospitals or special wards in general hospitals.^{39**} The "other" beds (iv) include the beds in general hospitals which are not reserved for communicable diseases, maternity cases or children.

(b) Tuberculosis Institutions :	Number of beds ***	Number of beds per 100,000 population
i. Tb. wards in general hospitals
ii. Sanatoria
 (c) Other Institutions :		
i. Services for chronic diseases
ii. Mental disease institutions
iii. Others (convalescent, old age, etc).

B. MEDICO-SOCIAL ACTIVITY

40. Health Instruction.

General statement covering activities for popular health education, such as issue of pamphlets, lectures, wireless talks, newspaper publicity, cinema films, exhibits, etc.

41. Maternal and Infant Health Services.

General statement.

(a) Number of pregnant women :	Per 100 live-births
i. Attending pre-natal clinics
ii. Visited at home by nurses
 (b) Number of births :	
i. In institutions
ii. At home, attended by doctors
Midwives
Others
 (c) Number of infants (under one year) :	
i. Attending infant clinics
ii. Visited at home by nurses

42. Health Services for Children.

General statement.

(a) *Pre-school age.*—Percentages of children of pre-school age :

i. Attending children's clinics	%
ii. Visited at home by nurses	%

*** See preceding page.

(b) School age.

(A) Percentage of school-children :

- | | |
|--|---------|
| i. Medically examined during the year.. | % |
| ii. Visited at home by nurses | % |
| iii. Receiving adequate treatment after
medical inspection | % |
| iv. Receiving adequate dental care from
public dentistry services | % |
| v. Diagnosed as mentally deficient, men-
tally backward, etc. | % |

(B) If supplementary feeding is supplied to schoolchildren, indicate the nature and extent.

43. **Industrial Hygiene.***General statement.*

- (a) Factory inspection. Give particulars of special measures in unhealthy or dangerous trades.
- (b) Medical examination of workers.

44. **Control of Special Diseases.**(A) *Tuberculosis.*

General statement on the control of tuberculosis in urban and rural areas.

- (a) Cases of open tuberculosis (Tb. bacillus test positive) expressed as a percentage of total cases on registers in dispensaries or institutions, or otherwise known %
- (b) Number of dispensary consultations per registered person per year
- (c) Number of home visits by public health or specialised nurses, per registered person per year

(B) *Venereal Diseases.*

General statement on the control of venereal diseases and prostitution.

- (a) Number of cases of syphilis at contagious stage at time of first consultation, per 100 cases registered %
- (b) Number of attendances (consultations and treatments at clinics for venereal diseases, per year per case of syphilis registered)

45. **Active Immunisation.**

(a) *Smallpox.*

- i. Number of vaccinations of infants under one year of age %
- ii. *Ditto*, as a percentage of live-births %
- iii. Number of vaccinations at all ages %

(b) *Diphtheria.*

Number of persons immunised (all ages)⁴⁵... ..

(c) *Typhoid fever.*

Number of inoculations (specify according to groups concerned—*e.g.* age-group, contacts, etc.).

(d) Other diseases^{45*} (specify).

46. **Laboratory Work.**

	Number of samples examined			
	Total number examined	Total found positive	Per known case of infection	
			Number examined	Found positive
(a) <i>Typhoid affections</i>
(b) <i>Diphtheria</i>
(c) <i>Tuberculosis</i>
			Per 100,000 population	
(d) <i>Syphilis</i>

⁴⁵ Also state numbers and percentage in different age-groups.

^{45*} In countries where BCG vaccination against tuberculosis is practised, the figures should be given as follows :

Tuberculosis (BCG).

- i. Number of vaccinations of infants under one year of age %
- ii. *Ditto*, as a percentage of live-births %
- iii. Number of vaccination at all ages

State if vaccination is as a rule limited to infants in contact with tuberculosis patients or applied more generally.

47. **Food Inspection and Control.**

General statement.

C. SOCIAL WELFARE

General statement on organisation of social welfare services, with statistical figures where available.

48. **Health Insurance.**

General statement.

(a) Number of persons and percentage of total population covered by health insurance schemes (state whether compulsory or voluntary) :

	number	
i. Insured members%
ii. Dependents%

(b) Number of days of sickness during the year, per 1,000 insured members

49. **Public Medical Assistance.**

General statement (giving percentages if possible).

50. **Social Protection and Relief of Mothers and Children.**

General statement.

51. **Relief of the Aged.**

General statement.

Number and/or percentage receiving old-age insurance benefits, pensions or relief, during the year.

52. **Unemployment and Relief of Unemployed.**

	Maximum**		Minimum**	
	Date	Number	Date	Number
(a) Number of unemployed known
(b) Number receiving :				
i. Unemployment insurance benefit
ii. Relief or assistance

** Owing to the considerable seasonal fluctuations in unemployment in certain countries, it is useful to give figures for the periods of maximum and minimum unemployment.

Appendix

THE HEALTH CENTRE

- A. *The Primary Health Centre* is the agency adapted to serve the public health needs of the smallest administrative unit. It should :
1. Carry on at least two medico-social activities ;
 2. Be placed under the direction of a doctor ;
 3. Be provided with at least one general (polyvalent) public health nurse, who will visit homes in connection with the various activities of the centre ;
 4. Assist, if local conditions permit, in co-ordinating all the medical and social activities of its district.
- B. *The Secondary Health Centre* is a more fully developed organisation. Its personnel is larger and the scope of its work wider than that of the primary centre. It should :
1. Carry out the work of a primary centre (in its immediate neighbourhood) and therefore conform to rules 1-3 under A above ;
 2. Co-ordinate the activities of the local primary health centres in its area ;
 3. Collaborate with other medical and public health organisations in its area (including social insurance and voluntary bodies) ;
 4. Be so equipped technically as to be able to assist the primary centre wherever necessary ;
 5. Carry out the following general duties :
 - (a) Tuberculosis control ;
 - (b) Venereal-disease control ;
 - (c) Maternal welfare work ;
 - (d) Infant welfare work (including the child of pre-school age) with special emphasis on the welfare of the child of school age (school polyclinics) ;

HEALTH INDICES

- (e) Health education—first, for the general population ; second, by means of special courses and field work for doctors, nurses, midwives, and sanitary engineers and inspectors ;
 - (f) Sanitation ;
 - (g) Laboratory analyses of a simple and routine character ;
6. Deal with the prevention of those diseases constituting a serious local problem ; and
 7. See that there is satisfactory provision of first aid in urgent cases and prompt transport of sick and accident cases ; undertake this service if no other organisation can do so.
-

RURAL HOUSING AND PLANNING

CONTENTS

	Page
INTRODUCTION	89
I. THE RURAL HOUSE AND ITS OUTBUILDINGS	91
A. <i>General Measures taken to improve Rural Housing :</i>	
General Considerations	92
Official and Private Bodies engaged in the Improvement of Rural Housing	93
Methods used	94
Technical Studies and Research for the Improvement of Building	96
Sanitary Laws and Regulations on Housing	97
B. <i>General Arrangements for Houses and their Outbuildings :</i>	
Merging or Division of Living-quarters and Farming- premises	98
Special Arrangements for Housing (Number of Rooms, Size of Houses and Rooms).	98
Building Materials and Methods	100
Internal Planning of Houses	101
C. <i>Drinking-water in Houses and Outbuildings</i>	102
D. <i>Disposal and Treatment of Human and Animal Dejecta in Houses and Outbuildings</i>	104
E. <i>Quantitative Extent of Improvements to Rural Houses and their Outbuildings</i>	106
F. <i>Training of Sanitary Engineers</i>	107
II. COMMUNITY PLANNING	107
A. <i>Installations and Establishments for Community Life</i>	107
B. <i>Development Plan</i>	108
III. AREA PLANNING	109
The Supply of Drinking-water	110
Disposal of Waste Water and Other Waste Substances	113
Electricity	116
Gas	117
IV. PROPAGANDA FOR THE IMPROVEMENT OF HEALTH AND SOCIAL STANDARDS AMONG RURAL POPULATIONS	117
ANNEXED NOTES ¹	119
LIST OF PREPARATORY DOCUMENTS	142

¹ The figures in parentheses in this report refer to the annexed notes, a list of which is given on the page mentioned above.

FOREWORD

This report has been drawn up by M. M. VIGNEROT, Chief Engineer of the Rural Engineering Department of the French Ministry of Agriculture, after a tour of investigation under the auspices of the Health Organisation in Belgium, Czecho-Slovakia, Latvia, the Netherlands, Poland, Sweden and Yugoslavia. The tour lasted from July 25th to September 20th, 1938.

At the meeting of experts representing the National Housing Committees, held at Geneva from December 6th to 9th, 1938, the report was used as a basis for discussion and was later approved by the group of experts¹ in its present form.

¹ The following were present at the meetings of December 6th, 7th, 8th and 9th, 1938 :

- Professor J. PARISOT (*President*), President of the Health Committee, Chairman of the Housing Commission of the Health Organisation, Professor of Hygiene and Social Medicine at the University of Nancy ;
- Dr. Neville M. GOODMAN, Medical Officer, Ministry of Health, Member of the Health Committee, London ;
- M. H. VAN DER KAA, Chief Health Inspector, Member of the Housing Commission of the Health Organisation, The Hague ;
- M. W. F. J. M. KRUL, Director of the State Drinking-water Supply Office of the Netherlands, The Hague ;
- M. V. MADERA, City Engineer, Prague ;
- M. Anders O. MOLIN, Civil Engineer, Stockholm ;
- M. Z. RUDOLF, Dipl.Eng.M.S., Chief of the Sanitary Engineering Division, Ministry of the Interior of Poland, Warsaw ;
- M. F. SENTENAC, Inspecteur général des ponts et chaussées, Head of the Water and Sanitation Department of the City of Paris (Préfecture de la Seine) ;
- M. Maurice VIGNEROT (*Rapporteur*), Chief Rural Engineer, Ministry of Agriculture, Member of the Conseil supérieur d'Hygiène publique of France, Paris ;
- Mr. H. A. WHITTAKER, Director, Division of Sanitation, State Department of Health, University of Minnesota, Minneapolis (U.S.A.) ;
- Dr. Nils H. WRANNE, Chief Medical Inspector, Linköping (Sweden).

The following were also present :

- M. F. VON BÜLOW, Head of the Agricultural Department of the International Labour Office ;
- Dr. M. KACPRZAK, Head of the Health Statistics Department at the Social Welfare Ministry, Warsaw ;
- Dr. René SAND, Secretary-General, Ministry of the Interior and Public Health of Belgium, Brussels.

INTRODUCTION

In the programme of the European Conference on Rural Life to be held at Geneva in 1939, prominence has been given to a study of improvements in the planning of rural houses (house and out-buildings), the planning of dwellings grouped together into villages, and the planning of the areas in which such houses or villages are built.

This study is the logical outcome of the European Conference on Rural Hygiene held at Geneva in 1931, at which it was shown that the organisation of medical assistance and health services in the countryside, however important and necessary it might be, should be carried out in healthy surroundings if it is to produce its full effect. The word "sanitation" was to be taken in a very general sense to mean the creation of an *environment which will be both healthy and productive*, by the proper disposal of water and waste matter, by providing a pure drinking-water supply and hygienic and comfortable dwellings, as well as by making rational use of agricultural land with the aid of land improvements and "bonifications".

Agreed recommendations on these points were drawn up by the delegates and experts of the twenty-three nations represented.

It was of interest to see whether these recommendations had borne fruit, and whether fresh aspects of the problem had been revealed in the course of their application; it seemed advisable to make a pause on the road to improvement in rural standards of living, to survey and discuss the results obtained and the tendencies prevailing.

It should first be pointed out that, in 1935, the Health Organisation of the League of Nations, recognising that the rational planning of houses and villages and area-planning in the countryside were questions of prime importance, set up a Housing Commission to study the special features of the general problem. The Commission instigated the setting-up in various countries, some of them outside the League, of National Committees in which these questions were studied from the special point of view of each country.

At the same time, the Health Organisation opened an enquiry into rural housing and sent a standard questionnaire to several countries. Some countries undertook this enquiry and sent their results to the League.

Then a European Exhibition of Rural Housing, held at the request and under the ægis of the League Health Organisation, took place in 1937 in Paris, at the Porte Maillot Centre of the Universal Exhibition of Art and Technique. In a building specially put up for the purpose by the French Government, thirteen nations, in accordance with a programme they had adopted in common, exhibited valuable documentary material on the various points in the planning of rural life which had been the subject of the work of the Conference of 1931.

Lastly, the League of Nations, whose attention was thus drawn to the problem of rural life in Europe with its manifold aspects — demographic, economic, social, financial — a problem vitally affecting the peace and prosperity of all nations, decided to call together the European Conference on Rural Life in 1939 at Geneva.

As its contribution to the work of the 1939 Conference, the Housing Commission has been called upon to draw up the present report on the rural house and its outbuildings, supplementing its own material with a monograph dealing with a number of countries in Northern and Eastern Europe ; the substance of the monograph was mainly obtained by a direct enquiry, and was discussed in December 1938 by a group of experts representing the various national housing committees.

The meeting has been able once more to show that rural planning helps to create a healthy standard of living in a productive environment, and that it is the whole foundation of health and social welfare ; for it may be said to be the first stage in the effective prevention of disease, since it seeks to remove causes which, within its sphere of influence, may affect health. Rural planning also provides a basis for the social improvement of the working classes in the countryside, by raising the standard of living, which is everywhere acknowledged to be too far beneath that of dwellers in towns and industrial centres. Bearing this in mind, the present report will examine consecutively the conditions for the rational planning of the rural house and its outbuildings, taking into consideration the health, comfort and occupations of the farmer, and especially

of the farmer's wife. This study of rural planning in the home and the farm will be followed by the planning of communal life in the village—*i.e.*, the public works, buildings and plant required for the communal services of a more or less concentrated population. The planning of rural areas will then be dealt with as it affects country villages and isolated farms, the distribution of drinking-water, electricity, gas and sewerage.

The last part deals with propaganda and how it may be developed ; its object is to reach the individual in his own surroundings, to teach him what is needed to raise the standard of living in the countryside, to convince him and arouse in him the desire to bring about the proposed improvements, to make him demand, or at least accept, measures calculated to attain that object and to show him what means he has at his command of rendering his work easier and making his efforts and sacrifices bear fruit.

It should be pointed out at once that effective results seem most likely to be attained through the activities of cultural and occupational societies and associations working directly in their own rural environment.

At the end of the main chapters and important subsections of the present report, there will be a brief note describing what the experts have specially singled out in the achievements and tendencies of the various countries.

I. THE RURAL HOUSE AND ITS OUTBUILDINGS

The rural house is defined as a house in the country, as opposed to a house in a town or industrial centre. Rural houses fall, however into the following classes :

- (1) The country residence with no occupational character ;
- (2) The house used for agricultural work, lived in by the working farmer, the agricultural labourer or the rural craftsman, who usually practises his craft and works a small agricultural holding at the same time.

The present report is concerned with the second of these classes.

A. GENERAL MEASURES TAKEN TO IMPROVE RURAL HOUSING

General Considerations.

In many European countries, steps have been taken, mainly during the past twenty years, to provide the rural population—farmers, foresters, farm labourers, craftsmen—with housing accommodation, not only satisfactory from the standpoint of personal and family health, but also offering such amenities and comfort as would keep the farming population on the land by opening up prospects of a healthy, rational existence, comparable from the social standpoint with life in urban or industrial centres.

The movement towards the cities and industrial centres has become much more marked in the younger generation, who are no longer willing to live in conditions their parents accepted.

It is therefore necessary to provide for the rural dwelling arrangements analogous to, but not the same as, those which are successfully followed in the cities.

It has been recognised in all countries that the farmer's house cannot be considered apart from its outbuildings (accommodation for live-stock, crops and implements), and all the measures taken make more or less adequate provision for both these kinds of housing, with which are naturally linked the problems of drinking-water supply and the disposal of sewage in such a way as to render it innocuous and serviceable for farming purposes.

Country districts suffer from the existence of slums; Swedish and Belgian statistics, for instance, show that at least a third, and sometimes half, of the slums are situated in the countryside. The statistics show the great seriousness of the resulting diseases, especially tuberculosis.

A study made by M. R. Marique, Director-General of the Société nationale de la petite propriété terrienne, Brussels, brings out the characteristic differences between rural and urban slums.

In the country, the slum building is an isolated feature, merging into the landscape and hard to detect. When paying their routine welfare visits, visiting nurses, who enjoy the confidence of the rural population, play a great part in detecting such conditions.

The country slum is often owned by the occupier, and its harmful character is sometimes due more to the insanitary interior lay-out than to the bad condition of the building itself. Technical advice and loans on cheap terms can do a great deal for the sanitary improvement of such buildings.

If no improvement is possible, another house must be built. Consideration should then be given to the creation of small holdings with cottages and outbuildings.

Families living in country slums are poorer than those in town slums, and families in the country are often very large, so that very cheap loans on very cheap terms are necessary.

In the country, as in the town, sanitary building regulations are required, and must be enforced by a local or, if necessary, higher authority.

For this purpose, it seems eminently desirable that the sanitary condition of dwellings should be watched in every commune by a special official. Several communes may join together to pay the official, who would then have more independence. It is the duty of the regional authorities or councils to influence the communal authorities to provide healthy houses in place of insanitary ones and to enforce the sanitary regulations in connection with rural buildings of all kinds.

In the Netherlands, the registration of houses and their occupiers is compulsory. As a result, the housing inspector can at any time discover any overcrowding in his district.

When the family leaves a slum building for a healthy home, it needs proper attention and guidance. Visiting nurses can do very valuable work in this connection, and, in some countries, school-teachers have achieved useful and quick results (Czecho-Slovakia).

This question, which is specially connected with propaganda, will be discussed in Part IV of the present report.

Official and Private Bodies engaged in the Improvement of Rural Housing.

In consequence of their economic, social and political circumstances, different countries necessarily follow different internal policies to achieve this purpose. In all cases, however, there is intervention by the State (central authorities), provinces (regional

authorities), communes (local authorities) (1)¹ and societies or associations interested in health, education or agriculture, and more or less closely connected with the central authorities of the country.

There are signs of, or a definite trend towards, co-ordinated or controlled collaboration between these various elements. (2)

Special stress should be laid on such collaboration between Government Departments and private cultural or occupational bodies ; for the latter find it easier to penetrate the rural environment from which they come and whose confidence they possess.

Methods used.

These methods, variously applied, are more or less developed according to their nature. They consist as a rule of advice (plans, estimates, specifications, instructions for the execution of work) (3) non-recoverable grants either in money or material, long-term, sometimes even very long-term, loans at low rates of interest or even free of interest, with a bonus in the form of the remission of a certain proportion of the debt when the work is properly executed. (4)

In connection with advice given in the form of standard plans or models, some countries point out that if these are given to peasants and handed over by them to craftsmen or small building contractors, it is difficult to carry them out. Accordingly, when such plans are prepared, they are intended now not to be given direct to the parties themselves, but to be passed to the technical services which have to advise those parties on the spot in the light of each peasant's special circumstances, or to supply them with plans adapted to those circumstances. In different countries, these technical experts may be central or provincial government officials or private architects and engineers, whose schemes will, before being put into effect, be referred to the departments which have to decide about the loans or grants.

Such technical advice is indispensable, for the peasant's chief need everywhere is to be given a frank explanation of the best methods to follow in his building schemes, the kind of materials and how to use them, and the choice and use of artificial materials.

Financial help must also be given by the public authorities, because all building costs much more in a rural than in an urban

¹ For this note, as well as for the following, see page 119, "Annexed Notes".

community, agriculture also always gives a small return, and, if he lives on his produce, a peasant sometimes has very little ready cash ; he can, on the other hand, supply labour and transport for building operations.

Such financial help is equally necessary for the improvement of farm labourers' dwellings, for they, unlike factory-workers or clerks, cannot in any country afford to buy their own houses. It is, moreover, extremely difficult and sometimes impossible, without financial assistance, for agricultural employers to afford the necessary cost of improving their labourers' houses.

Providing an agricultural labourer with a suitable house means that he must pay a rent of about a quarter of his wages. It is very difficult to make people agree to pay more than a sixth, and sometimes even a tenth, of their wages for rent, as they are accustomed to do for very defective houses. In addition, the agricultural labourer, on account of his wages, cannot pay the normal rent for a good house except by stinting his food and that of his family. Thus, in some countries (Netherlands, Great Britain), special assistance is provided for the agricultural labourer who lives in the suitable house that has been found for him ; in this way, he has to pay a rent equal only to an eighth or a sixth of his wages, instead of a quarter or a third. Large families may also have a fourth room (Netherlands) without a great increase in rent ; this is in order to avoid overcrowding, which is still excessive in almost every country.

The problem of housing the agricultural worker is somewhat complex ; its solution lies, not only in getting rid of overcrowding, but also in fitting up the house so as to make it healthy and comfortable (water, heating, lighting, etc.). These observations are to be taken into account when planning houses for agricultural workers, and also for the small farmer working with his family, who, too, has to meet the cost of building or improving his house. This consideration is in many cases an inducement merely to improve, whenever this is hygienically possible, the occupied premises of existing houses by rational arrangement.

In the case of settlement on land obtained by dividing up the large estates (agrarian reform allotments) (Latvia, Poland, Czechoslovakia, Yugoslavia), or settlement on land reclaimed for agricultural working (Netherlands), or the transfer of farms to the open

fields (Sweden), where complete villages have to be built, it is obvious that preliminary plans must be drawn up for buildings and villages and areas by co-ordinating the activities of the health services and the agricultural services.

But the same necessity arises when it is proposed, generally for reasons of economy, merely to improve existing buildings (Belgium, United Kingdom, France, Netherlands). Regional standard plans for houses are then drawn up and adapted to each special case.

During the past twenty years in most countries, and nearly fifty years in some, legislation has been introduced to promote the building of cheap houses or the purchase of small holdings with a cottage attached. As in the case of housing regulations (see below, Sanitary Laws and Regulations on Housing), the chief object of such legislation is to supply urban dwellings, cheap, healthy and as comfortable as possible, for the working class and persons of modest income who live chiefly on their earnings.

Such houses are built by private companies, or provincial or communal administrations, and are either rented to the occupiers or sold to them, the price being paid off in comparatively small annual instalments. They are built either in urban or industrial centres, or in their suburbs, so as to relieve the congestion in the centre.

Agricultural labourers are included in this class of poorer persons living chiefly on their earnings ; but their wages are usually paid partly in cash and partly in kind ; so that it is difficult, if not impossible, for them to make cash payments, as has been said above.

In spite of the steps taken, too often extemporaneously, to adapt these laws to agricultural labourers, cheap housing legislation has been comparatively ineffectual in rural areas.

In certain countries, the standard of living of the small farmer is considered to be often inferior to that of the agricultural labourer. Measures for improving the housing conditions of this population group are therefore required.

Technical Studies and Research for the Improvement of Building.

Systematic studies are being conducted in the various countries to find types of building suitable both from the health and from the practical farming standpoint and reasonable in cost. New materials

and the way to use them, and standardised materials and parts ready to be assembled on the spot, are also studied. Research work of this kind is going on continually and, as a result, standard appliances, for ventilation and economical heating, for instance, are being introduced. Economical heating has been specially studied in such countries as Poland. It is a useful way of preventing the overcrowding caused by the tenants' occupying the same room day and night during the winter.

Sanitary Laws and Regulations on Housing.

All countries now have their housing laws and by-laws. (5) These lay down the health conditions which must be observed in houses, and aim at the abolition of slums. Some of these laws and regulations contain only a few clauses applicable to the rural house or its outbuildings and to the sanitary arrangements (water—manure); others, however, have a large number of clauses, frequently detailed. In this connection, there is an interesting point to be made—viz., that whereas sanitary regulations on housing generally have for many years been conceived primarily from the standpoint of urban or industrial centres, the more recent housing regulations are taking into consideration the characteristic features of the countryside. Ignorance of those features, or the insufficient attention given to them, deprived such regulations, when applied to the country, of most, if not all, of their real value.

Another obstacle in securing practical results was the fact that the enforcement of housing regulations was entrusted to the subordinate local authorities, whose representatives, being elected by the population, were not prepared to use their statutory powers to compel their fellow-citizens to comply with measures which they themselves felt were too hard to carry out. In most countries, this obstacle has, to a great extent, been surmounted by vesting the responsibility for enforcing these measures in a higher authority (district or even provincial) with greater independence and experience, whose difficult task is lightened by the technical and financial assistance given to the rural population (see above).

B. GENERAL RULES FOR HOUSES AND THEIR OUTBUILDINGS

Merging or Division of Living-quarters and Farming-premises.

The arrangements vary from country to country, and from district to district in any one country.

Sometimes, the dwelling-house is separated by a dividing wall from the quarters used for housing live-stock and storing crops and implements, with which it forms a single building under one roof. In this case, however, the plan always provides for an internal party-wall between the family dwelling and the stables. There is usually a communication between the two, but, as far as possible, it does not lead directly into the living-quarters. Generally, if there is no passage, the dairy or a room for preparing food is placed in the middle.

Sometimes, the dwelling-house is completely separated from the outbuildings—an arrangement which seems to be preferred in all countries. The outbuildings themselves are often separated one from the other and arranged in a yard, sometimes in no special order, sometimes forming the actual sides of the yard, which is thus enclosed on three, or even on all four, sides by buildings.

The yard may be larger, or smaller, and have more or less adequate arrangements for leading off rain-water. Sometimes it forms a garden, with lawns, trees and flower-beds. (6)

Special attention should be paid to the planning of the farmyard and its surroundings.

Special Arrangements for Housing.

Number of Rooms.

In addition to the kitchen-cum-living-room, which very often contains a bed, rural dwellings have a number of bedrooms varying from one to three or sometimes four. There is a marked tendency to increase the number of rooms so as to have at least three (parents, girls, boys), or, at the very least, two, the kitchen-cum-living-room being used in the latter case as the parents' bedroom. Reference

is made—the phenomenon is found in all countries—to the “ best room ”, or reception or show room, which is often kept unused, to the detriment of the home. Sometimes, in a small dwelling of one room plus kitchen, the occupants all sleep in the kitchen, and keep the other room for visitors or for displaying the family treasures, which are often very remarkable as specimens of family or regional art. This is an additional reason for increasing the number of rooms, in order to avoid the too frequent overcrowding of rural houses.

The way in which the rooms are divided between the ground floor and the first floor (when there is a habitable first floor) depends on the country or district.

In modern buildings, when water is laid on in the house (cistern under the roof), wash-hand basins, bathrooms and water-closets are installed. These are still very recent innovations, but everything possible is being done to make them practical and inexpensive. (7)

Size of Houses and Rooms.

Dimensions are shown by indicating either the cubic content of the dwelling, or the area it covers, together with the height of the rooms from floor to ceiling. Sometimes those dimensions are laid down in the health regulations applying to buildings, sometimes in separate instructions and sometimes, again, they are merely shown on the plans handed to those concerned.

The minimum floor-space of a living-room should, it appears, not be less than 9 square metres. It is generally greater in all countries, and current averages run to 15 or 16 square metres. We sometimes find, however, rooms of 5 square metres, which it is very difficult to use for living purposes ; but, in those cases, there are several similar rooms, and the whole may be considered as one large room divided by partitions. They are always provided with windows.

Combined kitchens and living-rooms are, as a rule, fairly, and sometimes very, spacious ; they vary in floor-space from 15 to 20 square metres, and are often provided with annexes such as sculleries and larders, which increase the available space.

There is some variety from country to country in the statutory or customary height of rooms ; for living-rooms, the minimum

suggested is 2.20 metres on the upper floors or in attics, while, in practice, the following heights are current :

Ground floor : 2.40 to 3 metres, generally 2.70 to 2.80 metres ;
Upper floor : 2.20 to 2.80 metres, generally 2.30 to 2.70 metres.

An appropriate total area for the dwelling-house proper of agricultural workers and small farmers, including the kitchen, would be from 35 to 50 square metres for each family.

The minimum dimensions of rooms, and especially the area, must be stipulated with a view, not only to ensuring sufficient air-space, but also to allowing for the necessary furniture, especially the bed, in relation to openings such as doors and windows. (8)

Building Materials and Methods.

The materials generally used for rural buildings are either those locally available (stone, wood, unbaked or baked bricks, hand-made tiles, straw or reeds for thatching) or materials supplied by relatively distant factories and works (cement for concrete and external surfacing, asbestos-cement compound, artificial stone made of cement, wooden frameworks, standardised doors and windows, asphalt, various materials for heat insulation, etc.). Every one of these materials is found in use in all countries.

The increase in transport facilities and mass-production in industry make it possible to obtain factory-worked materials at reasonable prices on the spot, and also the skilled workers who can use them. Nevertheless, each building undertaking must be on a sufficient scale to cover costs, unless the factories and skilled workers are very near to the smaller type of undertaking. Concrete is coming more and more into use ; it can be prepared and used for rural buildings by local workers, and even by the farmers themselves, provided—as is often the case—they can obtain advice on the spot.

In some countries, wood remains the material most generally used, and, suitably employed, gives complete satisfaction ; but, in other countries, efforts are being made to discourage its use and to substitute non-combustible materials.

Floors of beaten earth, both in the house and in the outbuildings, are still common in certain countries ; but in new buildings, floors built of hard, washable substances are the rule.

Building methods vary considerably. In some cases, the work is carried out to a plan by firms of contractors, whereas, in other cases, local workers undertake sections of the work for a fixed sum. Sometimes, again, the work is done by the farmer himself, especially the transport of materials, foundation-work, and the supply of local products, while professional workers carry out the actual work of building at certain periods of the year (Yugoslavia).

In some countries (*e.g.*, Poland) the materials are prepared in advance in standardised form, and the contractor merely assembles them (*e.g.*, in the installation of agricultural settlements).

In every case, new buildings have a stone foundation, raising the ground floor from 0.30 to 0.50 metres, and sometimes more, above ground-level. Wherever land configuration allows, a cellar is provided ; this should preferably be built under the kitchen.

Internal Planning of Houses.

The general tendency is towards larger windows ; where the climate makes it necessary, double windows are gradually replacing single ones. Fanlights are often placed at the top of the windows to allow air to enter without opening the windows themselves.

Health regulations relating to building include provisions ensuring that the windows are large enough to allow sufficient light to enter. The area of the opening stipulated varies from one-fifth to one-eighth of the area of the room, according to the country concerned.

Investigations have been carried out, and are still in progress, with regard to heating. This is a paramount question if overcrowding, resulting from the whole family's remaining in one room during the winter, is to be avoided. Some types of stove can be fitted in the wall between two rooms, thus heating both at once. The use of cooking-ranges which heat a hot-water tank feeding both the kitchen and the washing-places is now general. Central heating is available in some new types of house.

A heating system in which hot air circulates inside the walls is in use in Poland.

Electric cookers are also in use in certain districts. In others, oil is used for cooking, and coal for heating.

As a rule, steam and smoke are carried away through the kitchen chimney by their natural upward movement. The bread-oven is sometimes next to the cooking-range, sometimes in a room by itself, and sometimes in a special small building, completely detached from the house.

C. DRINKING-WATER IN HOUSES AND OUTBUILDINGS

The question of collective supplies of drinking-water will be examined in the second part of this general survey ; here we are concerned only with individual supply and the distribution of drinking-water in the house and its outbuildings.

According to the district, water may be found either in the phreatic (immediately subjacent) layer (wells of a depth of 8, 12, 15 and sometimes 20 metres) or at a greater depth, in which case borings have to be made to liberate captive underground waters, which are then forced under their own pressure to a point near the ground-level, although seldom emerging above it ; the latter type of water is often more or less ferruginous. In some regions, use is made of rain-water collected in cisterns, but the general tendency is to substitute collective supplies for this form of supply (Netherlands) ; where it is not possible to provide adequate collective supplies at once and throughout the district, plans and suggestions for the efficient construction of rain-water cisterns are handed to the builders, and health officials supervise the work (Yugoslavia, Carniola).

Springs and fountains are also used as sources of water-supply. Here, again, advice is given, and the work is sometimes carried out under the supervision of official sanitary experts (Yugoslavia).

Generally speaking, however, the most frequent practice is to use the phreatic layer, which only necessitates relatively shallow wells. Water from such wells is brought to the surface either by means of a suction-pump, which is the most general device adopted, or by a system of chains and buckets. Everywhere it is sought to substitute pumping systems for old-fashioned buckets and winches and for direct leverage by means of a pole with a counterweight.

Pumping allows the opening of the well to be covered up—a course recommended everywhere. In well-building, use is made,

apart from ordinary masonry of stone or brick which is cemented and made watertight, of vertical concrete pipes. In some countries, it has been noticed that such pipes tend to leak at the joints, and they are therefore surrounded with an external layer of concrete, or, in some cases, replaced by a single homogeneous concrete structure.

The provision of a flat, watertight, concrete or paved surface round the opening of the well is being urged, and is becoming more and more general ; its object is to prevent infiltration from the surface in much-trodden ground.

Wells are generally placed at some distance from human or animal living-quarters. In some countries, the distance is laid down by regulation (*e.g.*, not less than 10 metres) ; but such a stipulation is only possible in the case of fairly homogeneous ground, uniform in character as regards water infiltration and circulation.

Some of the above requirements are rendered compulsory by sanitary regulations, but this compulsion is only effective in so far as control is efficient.

Some countries (United Kingdom, Czecho-Slovakia) are very strict, and any well found to be contaminated must be put into a satisfactory state of sanitation by its owner, otherwise it is closed by order of the authorities, and the house, not being provided with drinking-water, is condemned ; if they deem necessary, the authorities may also have the well rendered safe from contamination at the owner's cost.

The purification of water by chlorination must be regarded as merely provisional until the contaminated well can be rendered sanitary.

It has been suggested that whenever the public water-supply in country districts cannot economically be extended to some isolated farms, the latter should be given subsidies similar to those allotted to the public water-supply authorities for the provision of drinking-water (especially by wells).

Many farms have two supplies of drinking-water, one for the house and the other for the outbuildings. Pumping can be carried out by hand, but motors are installed where possible—electric motors as soon as electricity becomes available on the farm.

D. DISPOSAL AND TREATMENT OF HUMAN AND ANIMAL DEJECTA IN DWELLINGS AND OUTBUILDINGS

There are three aspects to this question : privies, manure and household refuse.

All countries are seeking to provide privies or closets where none exist and to improve those already available. Improvement relates both to the actual structure of the privy and to the disposal of dejecta.

Plans and advice are given to farmers to further this object. Investigations of great interest are being steadily pursued by Government and provincial authorities and by institutions and associations, especially Institutes and Schools of Hygiene, and experiments are carried out with various types of privy. Rules are then drawn up and placed at the public's disposal.

Although satisfactory results have been obtained in many cases, the work of improvement must continue.

It has been found that, wherever water under pressure is available, closets are being fitted with flushing devices. In such cases, a double sealed tank with a ventilating shaft is built, from which the liquefied dejecta flow either into the liquid-manure pit, or into a watercourse, or—better—into percolating drains traversing arable soil.

The pollution of small watercourses or lakes by the unpurified influx of waste water from isolated farms may give rise to serious disadvantages and dangers. For that reason, methods of pre-treatment or purification mentioned in the previous paragraph are highly recommendable.

In districts where peat is plentiful, it is mixed with the dejecta, the disposal of which is thus rendered easier. Dry earth is also used satisfactorily.

Privies raised above the ground, with a movable receptacle underneath which can be withdrawn through an opening, are frequently found.

Another arrangement sometimes found in the case of rows of labourers' cottages is a series of privies (one for each family) under a common roof, with an open trench into which the dejecta drop.

The excrement is then mixed more or less thoroughly with peat—large quantities of paper being present—and from time to time removed with a spade to the manure-heap.

Where there is a tank (which should be sealed) emptied by a direct method, generally with a bucket, it is found that one privy often contains several seats each with its own tank ; only one seat should be in use at a time, the next coming into use when the tank of the first is full. The usual number of seats is three ; but as, in practice, all the seats are used indifferently, this system ceases to have any value.

The usual form of the seat is a wooden coffer with a movable pierced lid. Although the privies are generally kept very clean, this system is unsatisfactory if the users are careless.

The so-called " Turkish " form is much less common, although it has many advantages.

Privies (except water-closets) are usually placed outside the dwelling, either in a lean-to-shed, or entirely separate, and sometimes next to the manure-platform. In this last case, the dejecta either drop on one part of the platform or fall into a pit connected with the liquid-manure tank.

Attention is nevertheless drawn to the disadvantages, from the health point of view, of mixing human dejecta with the liquid or solid animal manure. The disease-bearing germs may be conveyed with the manure to the fields or gardens, thus contaminating the vegetables that are to be eaten raw or even the water supply.

As regards animal excrement, systematic efforts are everywhere being made to secure that manure shall be deposited on non-porous flat surfaces, generally of concrete, or in shallow non-porous trenches near at least one side of which carts can be brought ; at the same time, or as a second stage in the installation, a liquid-manure tank is provided for the collection of the liquids from the platforms or trenches and from the runnels which are now more and more frequently built into the floors of stables, byres and sties ; these are connected with the tank by watertight underground channels.

On small farms, the manure is often stored under a roof.

Liquid-manure tanks are now generally provided with pumps used both to spray manure-heaps (in order to stimulate fermentation) and to fill barrels for spreading over arable fields and meadows. If there is no pump, this work is done with a bucket.

Most sanitary regulations include stipulations relating to privies and manure-heaps, with special reference to the possibility of contamination of the water supply.

Household refuse is generally added to the manure.

Where there is a group of cottages whose tenants do not possess large enough gardens or fields, or have no live-stock and hence no manure to dispose of, household refuse is placed in closed containers, which are then carried away to be added to the farm's manure supply.

E. QUANTITATIVE EXTENT OF IMPROVEMENTS TO RURAL HOUSES AND THEIR OUTBUILDINGS

Statistics relating to the number of improvement operations carried out are drawn up in a number of different ways, and are difficult to interpret. They need enquiries which are not easy to conduct, both on account of the care with which the questions must be framed, and on account of the character of the data required for answering them adequately. Staff trained to carry out such enquiries is not readily available. In some countries, therefore, it is considered sufficient to undertake sample investigations in a number of typical parishes in a given area, confining visits to the most typical dwellings and selecting them in such a manner as to permit of generalisation, which can always be checked subsequently.

In pursuance of the work of the European Health Conference held at Geneva in 1931, the Health Organisation of the League of Nations has drawn up a detailed questionnaire which has been despatched to a number of countries, with a view to an enquiry into rural housing in Europe. Some countries have now completed this enquiry ; but the results have so far been communicated to the Health Organisation in a few cases only, and no general conclusions have yet been drawn.

Moreover, the available statistics generally refer to " cheap dwellings ", and those of a definitely rural character are not always clearly distinguishable from the others.

Nevertheless, the documentation so far brought together makes it clear that considerable efforts have been made to secure an improvement in the character of rural houses and their outbuildings. (9)

F. TRAINING OF SANITARY ENGINEERS

It would be extremely desirable to provide special training for sanitary engineers. Some countries have dealt with this matter to a greater or less extent. The universities of the United States have means of training doctors and engineers for public health duties in sanitary engineering, together with health assistants. The engineers who take this course are civil engineers or engineering chemists. Both engineers and doctors do some of the work and follow some of the courses together.

II. COMMUNITY PLANNING

The object of planning rural communities is to provide their inhabitants with such common services as they cannot, or cannot adequately, provide for themselves (*e.g.*, on farms).

These rural communities may consist of a very small group of farms situated very close to each other and constituting a hamlet, or a relatively large group of farms forming a village, in which may be found small dealers' or craftsmen's shops and public buildings and installations. The latter type is dealt with in this part of the report. The common services of the hamlets will, of necessity, be less extensive; such services will be more widespread and of greater importance as the size of the village more nearly approaches that of a small town.

A. INSTALLATIONS AND ESTABLISHMENTS FOR COMMUNITY LIFE

Administrative Buildings.—These are generally the council office, schools and fire-stations.

Places of Worship.—Churches and religious institutions.

Health Buildings and Premises.—Health centres, social hygiene dispensaries, health co-operatives, baths, showers, etc.

Communal Centres.—Where all kinds of sporting, cultural and artistic societies and associations hold their meetings ; where the inhabitants meet together for professional, cultural or artistic purposes in a hall suitable for celebrations, dramatic performances, cinema shows or wireless auditions. The communal centre may house the communal library, with its reading-room and home lending department. The school and adult education libraries may be housed in the school premises. The communal centre may also contain the communal museum, containing collections and documents on the history and economic and social development of the village.

Sports Grounds, Promenades, Public Gardens—for the leisure and recreation of the inhabitants.

Public and Communal Services.—Fair-grounds, covered markets, public weigh-bridges to control the weight of animals and agricultural produce, slaughter-houses, wash-houses, co-operative buildings for the production, conversion and sale of agricultural produce. This category of public services includes road upkeep (streets, highways, pavements, rainwater gutters), water-supply mains, hydrants, sewers, installations for the purification of sewage, electric mains and transformers, gas mains, etc.

B. DEVELOPMENT PLAN

For this purpose, it is desirable that a *plan for the layout, amenities and future expansion* of the community should be drawn up. On this plan should appear the various works, buildings and plant referred to above—both those already in existence and those which it is proposed to establish in due course, having regard to the financial resources of the local authority that is responsible for drawing up the plan.

For urban and industrial communities, such plans are compulsory, but for rural communities they are as a rule optional, and are not very often made, except plans for the alignment of houses along existing or future roads.

These layout plans are of prime importance, however ; if necessary, they may be sketchy and rather in the nature of programmes than

finished plans. They may be drawn up parallel with the carrying-out of the general development programme or plan, and of course co-ordinated with it.

The value of these plans justifies the financial aid that the authorities may grant the communes for the purpose. As the general plan is being carried out, the successive stages must be marked on it.

For public constructional works, grants varying in size are made by the Government, provincial authorities, agriculturists, unions and societies and associations for the improvement of public health. The situation in this respect varies very widely in different countries ; but, while much still remains to be done, it is everywhere realised that such improvements are necessary in order to raise the intellectual standard of country people, as well as to protect their health.

For instance, in the elementary schools, there are communal clubs and baths open to the public on certain days ; and, in some countries (such as Czecho-Slovakia and Yugoslavia), the highly developed co-operative societies have communal clubs and baths on their premises. (10)

Public water-supplies, evacuation of waste water and waste substances, and electrification are sometimes local (communal) and sometimes regional (inter-communal), and will be examined in the following chapter.

III. AREA PLANNING

In this part of our report, we shall examine the position and tendencies in the different countries—always of course from the rural standpoint—as regards public supplies of drinking-water, the disposal and treatment of waste water and other waste substances, and the supply of gas and electricity.

The fact that the inhabitants are concentrated in definite localities makes such undertakings cheaper, considered on the basis of cost per head, and guarantees the minimum consumption which will render the undertaking economically self-supporting ; further, this concentration signifies that the undertaking is essential in proportion to the density of the population.

It follows that, in certain countries or districts where the density of the rural population is low and the inhabitants are often widely scattered—even central village communities being sometimes extremely small—this type of undertaking is less imperative than in towns, and often too costly. In more densely populated areas, it is deemed essential to the economic and social existence and the health of the community. In the latter case, the public authorities must contribute both on the technical plane (where appropriate) and, in most cases, financially, while also supervising the working of the undertakings and plant.

THE SUPPLY OF DRINKING-WATER

The principles outlined above are specially important in connection with public supplies of drinking-water in rural areas. (11)

In thickly populated countries or districts, systems for the public supply and distribution of drinking-water are well developed or in course of rapid development. As the amount of water required is generally considerable, extensive or deep reservoirs have to be built in places suitable by their natural configuration.

In rural areas with widely scattered farms or very small centres of population, on the other hand, the amount of water required is relatively limited ; hence adjacent local supplies generally prove sufficient.

Every intermediate degree between those two extremes is to be found.

The question that arises is whether water-supply systems are to be undertaken on a district basis or on a purely local basis—*i.e.*, to cover one village or a small group of villages. The advantages of a large-scale system are obvious from the standpoint of the efficiency and effective supervision of the undertakings and installations ; this type of system has been largely employed in Belgium and the Netherlands, where the density of the population is high and rural communities are close to one another. But it appears to be much less advantageous in countries with a scattered population and small, widely separated communities—except where there are no local supplies of drinking-water, as in the Carso province of Yugoslavia.

In France, where districts vary greatly as regards density of rural population and distance between villages, both regional and local systems are applied, according to the particular circumstances.

Particular attention has been paid to the possible advantages of constituting regional groups of villages for the purpose of organising drinking-water supplies. The system applied in the Netherlands has been specially studied from this standpoint. The first fact to be noted is that it is not invariably necessary to create a single supply system for the whole district concerned ; the essential requirement is to have some regional organ capable of centralising the planning, construction, maintenance, operation and normal working of all the public water-supply plants in the district. The central organ for the district carries out its plans by successive co-ordinated stages corresponding to the regional supplies available ; as it covers a fairly extensive area, an average price can be imposed ; in this way the better-placed communities share indirectly in the necessarily higher cost of supplying smaller, scattered communities, and even, to some extent, isolated farms. As regards these last, a possible solution is to bring the water-mains as near as is economically possible to the isolated buildings, a hydrant being placed at the nearest point. The farm is then no longer compelled to draw supplies from a well, but uses the public supply, which is under constant vigilance. In some cases, it may even prove advantageous to the farm to instal, at its own cost, a connecting pipe between the mains and the farm buildings themselves.

The means for carrying out this regional type of water-supply organisation vary from country to country. In the Netherlands, there is a Central Institute, with its own technical, economic, geological, chemical and bacteriological departments, which collaborates, more or less fully according to needs, with the twenty-five existing regional systems, to which another is now being added. Those systems are operated by companies set up by the provincial and local authorities concerned under a concession valid for the whole territory in question. The Central Institute also exerts a further co-ordinating influence by assisting in the preparation of a national plan for the public supply of drinking-water. The mayor of each village acts as agent of the provincial company. As the province does not grant water concessions to villages in its territory,

the latter are compelled, in order to obtain public supplies, to become participants in the provincial company.

Existing private undertakings are allowed to continue, but their concessions are gradually being repurchased by the central regional organisations.

Belgium possesses a national undertaking for drinking-water supplies. Villages are under no compulsion to join this undertaking in order to obtain supplies ; they are, however, encouraged to do so by means of substantial grants offered by the Government and the provincial authorities.

In Poland and France, villages are empowered to form voluntary associations for the express purpose of organising public water-supplies. Poland endeavours to solve this problem through the Federation of Cities, which has formed a special commission for the study of various systems in use in various countries. So far, the national scheme of Belgium seems to correspond best to the needs and conditions of Poland, but until now, no definite system has been adopted. Two large-scale regional water-supplies (one Governmental and the other communal) are, however, already in existence in Upper-Silesia.

In Yugoslavia, there are no regional groups, properly so called, supplying water under concession ; but provincial bodies exist which draw up regional schemes (particularly in the Karst topographical regions) operated by means of contributions proportionate to the social status of the consumers. In this way, the better-placed inhabitants contribute towards the cost of supplying those less favoured.

Systematic investigations of the regional and national sources of supply of drinking-water have been undertaken, in varying degrees, in all the countries concerned. The great importance of such investigations is obvious, especially in connection with the constitution of regional associations of villages.

Supervision of public supplies of drinking-water as regards both the construction of reservoirs or intakes and the working of the installations, is found in all countries ; it is often in the hands of Institutes of Hygiene, which are particularly well equipped for the purpose.

Only passing reference can be made to the problem of protecting central water-supply installations against aerial attack in war-time ;

the appropriate measures fall within the sphere of "passive defence" and require special study, to which attention is drawn.

DISPOSAL OF WASTE WATER AND OTHER WASTE SUBSTANCES

Generally speaking, we find that, even in urban or industrial centres, modern systems for the disposal and purifying of waste water and other waste substances are much less common than systems for supplying drinking-water. (12) They are even less frequently found in the countryside, though this is partly due to the fact that the population is scattered, and that it is generally possible to collect and dispose of human or animal dejecta on the farm itself.

Nevertheless, it is observed that, when a rural community, even a small one, acquires a piped water-supply, it becomes much more essential to provide for the disposal of waste water, as the quantity becomes considerably greater than it was.

For that reason, it is recommended that to every scheme for the supply and distribution of drinking-water there be added some indication, more or less detailed, of what is intended in the immediate or near future as regards the disposal of the increased quantities of waste water.

The problem of purifying waste water before allowing it to flow into a stream or into the soil is of importance, and has given rise to interesting investigations and experiments in various countries, which have been concerned at the same time with the hygienic aspect, the question of the cost of the installation, and that of running expenses. In the case of rural communities, the expenditure must be as limited as possible; yet public health must be safeguarded. It is also essential to instal purifying systems which are of simple working and practically automatic, since, in the case of small rural communities, skilled personnel is difficult to provide and the wages bill might otherwise prove prohibitive.

Particular attention is drawn to the method of disposing of waste water by causing it to flow into streams or lakes. A comment has already been made on the subject with reference to isolated farms. In many countries, there is no alternative, at least in the larger towns, to streams and lakes as sources of public water-supply.

The need for protecting such streams and lakes renders the adoption of large-scale plans even more urgent as regards the purification of waste water than as regards supplies of drinking-water.

The self-cleansing action of streams and lakes, involving, up to certain limits, the direct destruction of organic substances and pathogenic germs, is well known. But the limitations of this process have not yet been exactly ascertained. Research on the point is most desirable, since it will enable artificial purification, before waste water flows into stream or lake, to be limited to what is strictly necessary, and the costs to be consequently cut down to the minimum—a vital point for rural communities. In some countries (*e.g.*, the Netherlands and Poland), regular analyses of the water of streams are conducted.

In connection with the purification of waste-water conduits, it is reported that the public health authorities in France, and particularly the Conseil supérieur d'hygiène publique, require purification by stages (more or less complete decantation, partial filtering, complete filtering) before waste water is allowed to flow into a stream or lake or into the sea. Regular supervision and tests provide practical indications of the stage of purification required. To ensure that, where complete filtering is deemed necessary, no material obstacles will arise, local authorities are under an obligation, before undertaking any sanitation works, to purchase a piece of land, of sufficient size and suitably placed, on which plant for the complete purification of waste water can, if the need is confirmed, be erected.

The carrying-through of regional plans for the disposal and treatment of waste water is a more difficult undertaking than that of regional plans for water-supplies. It would appear practicable, in most cases, only to the extent of setting up an official regional body to supervise and control the construction and efficient working of the various purifying plants, plans for which have in the first place been submitted to and approved by the competent authority.

It must be added, however, that in the case of large centres including several distinct urban units, the best results are secured when the several units combine to operate a common system of sanitation (*e.g.*, in France, the Paris and Lyons urban areas).

On farms, the disposal and treatment of *waste substances* (household refuse) are provided for by methods already indicated in this

survey. Only where such substances, after conversion into fertilisers by the "compost" method, cannot be employed (*e.g.*, owing to the absence of a vegetable garden), does the need arise for collection by the community or local authority.

The refuse is then placed in closed metal containers, from which it is transferred to closed metal tanks carried on lorries or trucks, and conveyed to the treatment plant (see document C.H./Com. Hab.77).

The method of treatment will depend upon the size of the rural community or group of neighbouring communities co-operating for the disposal of household refuse: either incineration, or fermentation in special cells, as practised in urban or industrial centres.

In small rural centres, where such methods would prove uneconomic, the system known as "controlled tipping", to which attention is drawn, may be resorted to. The precautions required are set out in document C.H./Com.Hab.74. It will be sufficient to recall here that this system, if it is to be effective, requires much care, and therefore a considerable degree of supervision. Refuse treated by this method should also preferably contain only a moderate proportion of empty tins and paper. Rats can be kept out of these tips, but an infestation by crickets has been reported in some cases.

The problem of *fly-control* is closely linked with that of the disposal and treatment of waste substances (household refuse, manure, cesspools).

Neither the investigations carried out in the various countries, nor the reports submitted, give evidence of resort to systems or devices for destroying flies in country districts. Some information will, however, be found in document C.H./Com.Hab.77, Geneva, November 26th, 1938 (Netherlands).

The investigations and experiments undertaken on the initiative of the Health Organisation with a view to the solution of the fly problem do not appear up to the present to have been put to practical use.

A survey of the published documentation¹ reveals the need for further work in the form of investigations and experiments *in each*

¹ J. PARISOT and L. FERNIER: "The Best Methods of treating Manure Heaps to prevent the Hatching of Flies", *Quart. Bull. Health Org.*, 1934, 3, 1-31.
Edm. and Et. SERGENT: "Fly-free Manure Heaps", *Quart. Bull. Health Org.*, 1934, 3, 299-303.

M. THOMSEN: "Fly Control in Denmark", *Ibid.*, 1934, 3, 304-324.

"The Fly Problem in Rural Hygiene", *Ibid.*, 1936 5, : L. Report of the Meeting of Entomologists held in London on December 16th and 17th, 1935,

country. For the problem is of a local character and a given method, successfully used in one country, will not necessarily succeed in another, at least unless it is modified in ways which have still to be determined.

Nevertheless, it appears certain that fly-control becomes easier if manure is placed on platforms insulated from the surrounding ground. This requirement harmonises with the need for avoiding pollution of the soil or of watercourses, and with the desire to preserve the full fertilising properties of manure.

ELECTRICITY

The stage of rural electrification reached in different countries varies greatly. (13) It is well advanced in Belgium, France, the Netherlands and Sweden, subject to the reservation that, even where the centre of the group (*e.g.*, the central village) has been electrified, outlying areas (hamlets and isolated farms) are not always linked to the system; the obstacles to complete electrification, in such cases, diminish as the density of the population increases and the distance separating outlying areas from the centre of the group, or the main power-line, dwindles.

In other countries, electrification has proceeded more slowly on account of the distance between farms and the scattered character and small numbers of the population of rural communities. The construction of central power-stations, recently completed or now in progress, to supply towns and industrial centres, will allow country areas to be supplied in the future in varying proportions.

Electrification of country areas is encouraged by the Government, provincial and local authorities, and, in some countries (especially Sweden and Czecho-Slovakia), co-operative societies of consumers of electric power.

page 211; II. E. ROUBAUD: "The Biothermic Method of Fly Destruction and the Ease with which it can be adapted to Rural Conditions", page 214; III. F. LORINCZ and G. MAKARA: "Investigations into the Fly Density in Hungary in the Years 1934 and 1935", page 219; IV. F. LORINCZ, G. SZAPPANOS and G. MAKARA: "On Flies visiting Human Faeces in Hungary", page 228.

B. A. R. GATER: "The Fly Problem in the East: A Research Programme", document C.H./Hyg.Rur.E.H.15(1).

GAS

Coal gas, used almost wholly as a source of heat, is only found in the countryside in the immediate neighbourhood of towns and industrial centres. Gas mains, being very expensive to construct, cannot be extended into districts where the probable number of consumers is very limited, as is the case at any appreciable distance from such centres.

In some countries, the practice of using types of gas which are richer in calories than coal gas (*e.g.*, butane and propane gas), transported in a compressed or liquid state in containers, has become fairly general among individual consumers. Nevertheless, the collective use of these transportable types of compressed gas for purposes of public supply is at present very limited.

In some countries (Netherlands, Czecho-Slovakia, Yugoslavia), use is sometimes made of natural (methane) gas resulting from deep boring of wells.

IV. PROPAGANDA FOR THE IMPROVEMENT OF HEALTH AND SOCIAL STANDARDS AMONG RURAL POPULATIONS

Attention has already been drawn—on the occasion of the European Conference on Rural Hygiene held at Geneva in 1931—to the need for propaganda designed to raise housing and community-planning standards in rural areas. This propaganda has taken many and varied forms in the several countries ; its object is to reach agriculturists on the spot, and to make them understand or appreciate more fully the advantages offered by these fundamental improvements in the conditions of rural existence.

Many countries devote constant attention to such propaganda, to the improvement of the machinery of propaganda, and to the co-ordination of the efforts of occupational and cultural associations and bodies with the activities of the public authorities.

The part played by visiting nurses and by teachers has already been stressed (see Part I, A : " General Considerations "). Mention should also be made of village branches of cultural associations

(*e.g.*, the sokols in Czecho-Slovakia) and of professional agricultural organisations in a number of countries. An important part is played by the more or less intensive training, of a general or specifically sanitary character, given to young recruits during their military service.

Attention has already been drawn in the present report to the advice and technical information made available to inhabitants of the countryside, and especially to the functions of experts brought in to assist in carrying out rural public works.

It has been found that even the carrying-out of a survey—*i.e.*, the mere collection of information on public health or sanitary matters—is of value in stimulating progress.

Fixed or travelling exhibitions, lectures, cinema films, broadcasts and meetings held in village halls are all propaganda methods in current use. In a remarkable guide to the documentation relating to propaganda in Czecho-Slovakia, mention is made of the useful activities of associations created by the former inhabitants of a country district now living in the same town, through which they can keep in touch with their villages, take an interest in their prosperity, and help in improving the living conditions of the present inhabitants.

Too much importance cannot be attached to the need for co-ordinating all propaganda efforts and to the supply of exact scientific information to all those who, at any stage, contribute to the fulfilment of this difficult and important task.

ANNEXED NOTES

- (1) Official Organisations for the Improvement of Rural Housing.
- (2) Private Organisations for the Improvement of Rural Housing.
- (3) Methods (Advice).
- (4) Methods (Subsidies and Loans).
- (5) Health Laws and Regulations to do with Housing.
- (6) Houses and Farm Premises combined or separate.
- (7) Special Arrangements affecting Houses (Number of Rooms).
- (8) Special Arrangements affecting Size of Houses and Rooms.
- (9) Estimate of Results achieved in the Improvement of the Rural House and its Outbuildings.
- (10) Community Planning.
- (11) Supply of Drinking-water.
- (12) Disposal of Waste Water and Other Waste Substances.
- (13) Electricity.

* * *

(1) Without going into details of the administrative organisations which deal with the improvement of rural houses and their outbuildings, mention may nevertheless be made of the departments of the central administrations which do so.

Belgium.—Ministry of Agriculture (Rural Building and Engineering Department).

France.—Ministry of Agriculture (Rural Engineering Department, Farm Labour Department).

Latvia.—Ministry of Agriculture (Rural Building Bureau).

Netherlands.—Ministry of Labour (Health Administration and Housing Inspection Department).

Poland.—Ministry of Agriculture (Rural Building Department).

Sweden.—Ministry of the Interior and Labour (General Labour Administration, Rural Housing Department), and Ministry of Agriculture (Royal Administration of Agriculture and its provincial rural economy societies).

Czecho-Slovakia.—Ministry of Public Health and Physical Education (Social Hygiene Section of the Institute of Public Health), and Ministry of Agriculture (through the agricultural councils of the provinces, and especially the Agricultural Building Institute of the Agricultural Union of the Czecho-Slovak Republic).

Yugoslavia.—Ministry of Social Policy and Public Health (Sanitation Section of the Central Institute of Hygiene at Belgrade, School of Public Health at Zagreb, provincial institutes of public health, and health co-operative societies).

These State authorities supervise the efforts of the provincial administrations to improve rural houses and their outbuildings. The provincial administrations have a staff of health experts either under their direct control or placed at their disposal by the Government—in Belgium, Government agronomists ; in France, rural engineers and inspectors of farm labour ; in Latvia, technical experts and district inspectors ; in Sweden, provincial technical experts ; and in Yugoslavia, the sanitary experts of the institutes of public health.

(2) These societies and associations and their fundamental activities are as follows :

Belgium.—Société nationale de la petite propriété terrienne, founded in 1935. Its object is to extend the benefits of the laws on cheap housing to small holders. It buys large estates and cuts them up into small farms by building on them and purchasing implements and live-stock. It grants loans at reduced rates for the transfer of these small farms, when ready for cultivation. It helps only poor people, others being assisted by the credit companies approved by the State Savings Bank. The Société nationale has set up approved regional societies (1936), of which there are fifty-seven ; they are co-operative, and are administered by a governing body which includes the representatives of the public authorities and the major national organisations.

It receives its funds from the State in the form of loans, at an interest and amortisation rate of 2.3%, repayable in sixty-six yearly instalments. The Society itself grants loans, at a rate of interest of 2.5%, up to an age-limit of fifty-five years (ten-yearly loans).

Through its approved regional co-operative societies, it makes sure that the dwellings and outbuildings of its borrowers are kept in good condition.

La Commission nationale pour l'embellissement de la vie rurale (National Committee for the Improvement of Rural Amenities) :

By holding congresses and exhibitions since 1913, this Committee has done much to improve rural housing ; it has set up technical bureaux, in co-operation with the Government, for the restoration of the areas laid waste by the war ; special days are set aside for the study of questions concerning the lay-out of rural areas. Its general work, which is very varied and extensive, helps to raise the standard of living in the countryside.

The Boerenband, or Ligue des Paysans (Peasants' League) : This is an influential Christian, social and economic association, which, through its local parish sections (guilds), helps all the branches of agricultural work ; it also deals with farmers' demands and the vocational training of its members and with improvements in methods of cultivation.

The Boerenband has a technical bureau at its headquarters in Louvain, with a special section for rural construction which draws up complete plans for farms, rural dwellings, agricultural buildings and co-operative or club premises. The cost of drawing up these plans is refunded at a fixed rate.

The other peasants' leagues do not appear to play any part in improving rural housing.

France.—There are no private institutions (farmers' unions or syndicates) which systematically assist in the building or improvement of rural dwellings and their outbuildings. Such bodies, especially the chambers of agriculture, work side by side with the public authorities in the National Committee for the Improvement of Rural Housing and in similar committees in the departments.

The permanent assembly of presidents of chambers of agriculture makes written studies of rural dwellings as part of its official work.

Latvia.—The Latvian Chamber of Agriculture supplies standard plans for rural houses to farmers on request.

Netherlands.—The societies for developing the polders, once the polder has been created and made fit for cultivation (drainage, water-supply, roads and canals), divide it up into plots, on which complete farms are built, and are then leased out. Labourers' cottages are also built and leased. The finished polder includes communal centres, with public buildings and shops. Farmhouses are scattered singly over the plain, surrounded by the land which

they have under cultivation. Rural buildings in the polders are planned with great care, and excellent specimens have been erected.

Poland.—The chambers of agriculture, of which there are thirteen, have each a section for small holders, in addition to their various sections for economics, statistics, production, teaching, accounting and finance. The small holders are supplied with rural building plans, and have the assistance of a building inspector.

The chambers of agriculture are responsible for distributing State subsidies and loans, except loans granted by the Agrarian Bank. At Warsaw, there is a Union of Chambers of Agriculture and Agricultural Organisations, which is in direct touch with the Ministry of Agriculture.

The Polish Health Society has published a technical work on housing in villages and small towns (general and detailed plans, preliminary building measurements).

Various works of this kind have been published.

Sweden.—The General Society for Swedish Agriculture includes departments which supply plans for the construction of rural houses and farm buildings.

Czecho-Slovakia.—On the lines of the agricultural councils and the Central Federation of Agricultural Co-operative Societies which had consultation bureaux for rural building, the Agricultural Building Institute was founded in 1928 ; it forms part of the Agricultural Union of the Czecho-Slovak Republic.

It draws up plans of farms, tests materials, gives advice, organises conferences and takes part in exhibitions. It does not give standard plans, but supplies designs for buildings suited to the situation of each member ; it works by correspondence, and also through the provincial institutions of the Agricultural Union. The consultants pay 1% of the amount of the estimates to cover the cost of making the designs. In the exhibition grounds at Prague, the Agricultural Union has built a model farm of the average type, fitted out for agricultural work ; in it are to be found specialists to give any information required.

The Czecho-Slovak Society for the Improvement of Rural Amenities does similar work to that of the Belgian society of the same name. It has had a small-scale model constructed of the

model village of Sany, in Bohemia, and has published a documentary plan entitled " The Villages of Moravia ".

The work of the Society for Rural Hygiene is confined to information and propaganda.

Yugoslavia.—In Yugoslavia, there are no societies or associations for rural building. Mention should nevertheless be made of the work of the Health Co-operative Societies, which assist all individual efforts to improve the health and standard of living of country dwellers.

(3) Advice is given in the following forms :

Belgium.—Plans, explanatory notes, directions for cowsheds and their annexes (sheds for calves, rooms for preparing food, premises for sick cattle, dairies, liquid-manure tanks, manure-pits) and directions for pigsties, hen-runs, fodder-silos and buildings required on small farms.

France.—Assistance is given by the technical service (rural engineering) of each committee for rural building in the departments for the designing of buildings (with visits to the site if necessary), examination of the plans and estimates, supervision of the work, if requested, and of the contractors' accounts. General directions are given to the departmental committees by the technical service (rural engineering) of the National Committee for encouraging the Improvement of Rural Housing. The scales for repayment of costs by the consulting farmers are approved by the National Committee.

Latvia.—Plans, estimates, conditions of contract and practical instructions are drawn up or examined by the Rural Building Bureau ; model plans for labourers' cottages are sent to employers.

Netherlands.—See Societies and Associations.

Poland.—Standard plans for labourers' cottages, farms of less than 12 hectares and of more than 12 hectares, and artisans' dwellings.

Sweden.—Plans of houses for agricultural and forest workers, small holders and artisans.

Czecho-Slovakia.—Standard plans for rural houses and out-buildings.

Yugoslavia.—Schemes for rural buildings are drawn up in specific cases, in place of the standard plans originally sent out.

(4) The organisations granting subsidies and loans for the building or improvement of rural houses and their outbuildings are as follows :

Belgium.—Ministry of Agriculture (subsidies for building cow-houses and their annexes, established on a sliding scale on the proposal of a jury under the chairmanship of the Government agronomist).

France.—The Caisse nationale du Crédit agricole, which is attached to the Ministry of Agriculture.

Latvia.—The Agrarian Bank for loans ; the Ministry of Agriculture for grants in kind.

Netherlands.—The Ministry of Agriculture for loans to private building societies and communes building houses, for awards to private enterprise, and for loans for the acquisition of small agricultural holdings including a house.

Poland.—The Ministry of Agriculture for loans.

Sweden.—The Ministry of Agriculture for loans from the Small-holdings Establishment Fund.

Czecho-Slovakia.—The National Land Office, which is directly under the Council of Ministers, grants loans to settlers who received small holdings after the agrarian reform.

Yugoslavia.—The Ministry of Social Policy and Public Health for loans from the Health Fund of the State Mortgage Bank.

The loans are granted under the following general conditions :

Belgium.—See Societies and Associations.

France.—Loans by the Caisse nationale du Crédit agricole at 3%, to be paid back in thirty equal annual instalments, up to a maximum of 100,000 francs per farm.

Latvia.—Loans by the Agrarian Bank at 2% interest, to be paid back in twenty-eight equal yearly instalments for the labourers' cottages and in forty-one yearly instalments for farmhouses and outbuildings.

Netherlands.—See Societies and Associations.

Loans to agricultural labourers for the acquisition of a small holding with a house—one-tenth of the capital to be paid by the borrower, and the remainder to be paid back in thirty equal yearly instalments (rate of interest unknown).

Poland.—Loans at 3%, to be paid back in forty-five equal yearly instalments.

Sweden.—Loans from the Small-holdings Establishment Fund (rate of interest and time-limit for repayment unknown).

Czecho-Slovakia.—See Societies and Associations.

Yugoslavia.—Loans to communes of less than 2,000 inhabitants and to authorities other than communes for the building of model houses, granted by the State Mortgage Bank (Health Fund), free of interest, repayable over ten years.

(5) The main sanitary laws and regulations containing provisions on housing are as follows :

Belgium.—There are no building regulations for rural communes.

France.—Law of February 15th, 1902, for the Protection of Public Health—Sanitary Regulations for the Departments in application of the said law, drawn up on the basis of the standard departmental sanitary regulations issued by the Ministry of Public Health.

Latvia.—Law on Housing (few provisions relating specifically to rural districts).

Netherlands.—Law of 1902 on Housing.

Poland.—No information available.

Sweden.—Law of 1919 on Town-planning and the Construction of Buildings, and general regulations for the application of the same. Contains little regarding rural districts.

Czecho-Slovakia.—No information available.

Yugoslavia.—Law of November 7th, 1931, containing building regulations.

(6) *Belgium.*—The plans supplied to peasants include the house, a cowshed and a storeroom for crops in a single building, adjoining which are a stable for one horse and an oven and privy. In the yard, provision is made for a chicken-run, a tool-shed, a silo for fodder and a manure-pit with liquid-manure tank, both in concrete (type of farm suitable for stock-raising in Flanders).

France.—The lay-out of farm buildings varies greatly according to the district, from a type in which all the buildings are more or less widely separated from one another in the yard, to one in which the house and other premises are united in the same building, with an intermediate type in which the buildings are arranged on three or even four sides of a closed yard.

Latvia.—The buildings are generally spaced round a yard (dwelling-house, cowshed and storeroom). Fodder is usually stacked in ricks in the yard. Agricultural labourers are generally lodged in part of the house, but there is a tendency to lodge them in separate houses built for two, and sometimes for three and four, families.

Netherlands.—Isolated houses are most in demand amongst rural labourers. The house and its outbuildings as a whole (workshop, barn, cowshed, pigsty, shed, fuel and implements storeroom, etc.) are usually united under the same roof, though the annexes are sometimes grouped together in a building adjoining the house. In the new villages and farms on the polders, two agricultural labourers' families are generally lodged in the same building.

In the case of farms, according to the district, the houses and annexes are either under the same roof, in which case the building containing the annexes shares a party-wall with the house or is connected with it by a small building containing a room for the preparation of food, or the annexes are grouped together in a building completely separate from the house, or again, the buildings stand separately round the sides of a closed yard. Fodder is very often stacked in ricks in the yard.

Poland.—The plans supplied to peasants or agricultural labourers comprise separate buildings for the house and annexes. In the small farms of agrarian reform settlers, the house, the cowshed-stable and the barn form separate buildings round a yard.

The German type, in which the cowshed-stable was built on to the house, is tending to disappear.

Sweden.—The plans supplied comprise a house completely separated from its annexes. The latter building contains sheds for live-stock, crops and implements, and also manure, which is stored under a roof built on to the cowshed.

In larger farms, the barn generally forms a separate building and the buildings as a whole are arranged round a yard with garden.

Agricultural labourers' houses are generally of the double type (two families).

Czecho-Slovakia.—In the new villages and settlements, the sheds for live-stock are built on to the house, while the barn with store-room for implements is in a separate building, though sometimes it also is built on to the house.

Yugoslavia.—The annexes are either built on to the house or separate, according to the district. In the plans for the new villages (settlements), the annexes are completely separate from the house.

(7) *Belgium.*—The plans supplied comprise :

In the basement : Cellar and dairy.

On the ground floor : Two rooms (kitchen-living-room and a bedroom) and an entrance hall from which staircases lead to the upper floor and cellar.

On the upper floor : Two attic bedrooms and a third bedroom, with bathroom. A corridor separates the bedrooms and leads directly to the bathroom.

The bedrooms are of good size.

The plans of the Société nationale de la petite propriété terrienne also comprise a scullery-washroom on the ground floor.

France.—Householders are recommended to improve rural houses having only a ground floor surmounted by a loft, by building an

upper floor in place of the loft and fitting bedrooms there. If the height of the loft allows, attic bedrooms can sometimes be fitted up in it.

Householders are also recommended to instal a separate scullery communicating with the kitchen and to have a minimum of three bedrooms (parents, girls, boys), the common kitchen-living-room being able to take a bed at need. A covered porch or a hall, or both, is highly recommended.

Latvia.—The houses in the most modern farms have :

On the ground floor : Porch, hall, kitchen with bread-oven and separate scullery, two bedrooms with stove, and staircase leading to the upper floor ;

On the upper floor : Two bedrooms.

Another type intended for the agrarian reform settlements has a kitchen with bathroom.

Some agricultural labourers' houses have only the ground floor surmounted by a loft, and comprising two bedrooms and a kitchen.

Netherlands.—The latest types of house on the polder most recently built over, comprise :

On the ground floor : Hall, kitchen-living-room with separate scullery ; two bedrooms, staircase to upper floor.

On the upper floor : Two bedrooms and a small loft.

The labourers' lodgings (generally two in each labourers' house) comprise :

On the ground floor : Hall, kitchen-living-room with separate scullery, the living-room being available for sleeping if necessary.

On the first floor : Two or three bedrooms.

In communes with less than 10,000 inhabitants, the proportion of houses with three or more habitable rooms was 36% in 1899, 45% in 1909, and 71% in 1930.

Poland.—The old-style rural houses usually consist of the ground floor surmounted by a loft. The smallest new type comprises the ground floor with hall, kitchen and larder, and one bedroom. Another type is being built with two bedrooms on the ground floor and one or two bedrooms on the upper floor.

In houses in the agrarian reform settlements, it is proposed to add a bathroom to the present type.

Sweden.—The standard plans of houses for agricultural and forest workers and small holders comprise :

Basement : Concrete cellar (washroom, dairy, provision store-room).

Ground floor : Porch, hall, kitchen, living-room (with alcove for small children), one or two bedrooms, staircase to upper floor.

Upper floor : One attic bedroom and a loft in which another bedroom could be fitted up if necessary.

The collective agreements between employers and agricultural labourers stipulate that the lodgings of the latter shall include two rooms and a kitchen, a clothes-closet and a store-room.

It has been observed that rural workers retain the habit of sleeping many people in the same room in order to keep a separate parlour.

An investigation in 1936 showed that rural lodgings comprising a kitchen and one bedroom represent a third of the whole, while those containing a kitchen and two bedrooms amount to hardly three-fifths. The kitchens are generally used for sleeping, and one of the rooms, if there are several, or, if not, the only room, is kept as a parlour ("best room").

Czecho-Slovakia.—A common type of house has ground floor and loft, with kitchen, living-room (benches along the walls), three bedrooms containing several beds, and a wash-room with bath. The staircase to the loft is in the hall.

The ground floor is sometimes built over a cellar, and there is a veranda porch in front of the house. In many cases, there are only two bedrooms.

Agricultural labourers' houses containing several lodgings usually comprise a kitchen with larder and one bedroom ; on the upper floor there is a loft without bedroom.

Yugoslavia.—Rural houses properly so called usually comprise a hall, a kitchen-living-room with larder, and two, or sometimes three bedrooms ; on the upper floor is a loft. The inhabitants frequently gather in one room during the winter.

Around Zagreb, the ground floor is occupied by the wine-cellar and the provision storeroom ; on the upper floor, which is reached by a staircase leading to a balcony surrounding the house, there is

a hall, two bedrooms and a kitchen, from which a staircase leads to the loft.

A recent standard type, built according to the plans of a provincial institute of hygiene, comprises ground floor with hall, kitchen, four bedrooms, lavatory and larder. The cellar is used for wine-making, and is reached directly from outside.

When there is an upper floor, it contains a bedroom and a loft.

(8) *Belgium*.—The general type of building for a small holding with outbuildings under the same roof as the living-quarters measures $11 \times 15 = 165$ square metres. Such a building is only provided when the small holder has from 3 to 10 hectares (according to the fertility of the soil) of ground.

France.—The minimum dimensions are laid down in the Departmental Sanitary Regulations issued in pursuance of the Law of February 15th, 1902, on the Protection of Public Health, and in the administrative regulations accompanying the Law of August 31st, 1929, on the Improving of the Housing of Agricultural Labourers. The minimum floor-surface of a living-room is 9 square metres, and the minimum height from floor to ceiling 2.70 metres. On the top floor (attic loft) the 9 square metres floor-surface is measured at 1.30 metre from the ground and the cubic content of the room must not be less than 22 cubic metres.

Latvia.—The minimum height is 2.3 metres ; it is, however, recommended to allow from 2.6 metres to 2.8 metres, though 2.3 metres is admissible for the top story.

In the labourers' cottages, the floor-space, kitchen included, must be from 40 to 50 square metres for one family, from 50 to 80 square metres for two families and more than 80 square metres for three families.

In recently erected buildings, heights of 2.70 metres on the ground floor and 2.30 metres on the first floor are met with.

Netherlands.—The minimum dimensions are laid down by the Housing Law (*Woningwet*) of June 2nd, 1901.

Rooms seem to range from 2.70 metres to 2.80 metres in height ; the living-rooms are fairly big, but the bedrooms seem small (in some cases, 5 to 8 square metres).

Poland.—The regulations for cheap housing may be applied to rural housing. The standard plans supplied to peasants usually allow for rooms 2.80 metres high on the ground floor, and 2.40 metres high on the first floor. The rooms are large.

Sweden.—As already stated, collective agreements between agricultural employers and labourers fix the minimum area of a family dwelling at 35 square metres, excluding the hall and store-room.

Investigations made in Sweden show that half the living-rooms in dwellings with two rooms and kitchen have not as much as 15.2 square metres floor space, and the kitchens 15.5 square metres ; that the average area of dwellings of one room and kitchen is 36.2 square metres, and of dwellings with two rooms and kitchen 50 square metres ; that only 10.8% of dwellings with two rooms and kitchen are more than 2.70 metres high ; that a good 20% are less than 2.10 metres high ; that more than 25% of the people occupying small dwellings have less than 10 cubic metres of air-space per person ; and that almost half the members of families with three children or more under 15 years of age do not even enjoy this minimum of air-space in their bedrooms (overcrowding).

The standard plans provide for rooms 2.40 metres high on the ground floor and 2.20 metres high on the upper floor. The kitchen-living-rooms are rather large, as they have separate sculleries and pantries ; bedrooms are about 12 square metres, but have cupboards extra ; some have an area of from 20 to 25 square metres, but these are often partitioned.

Czecho-Slovakia.—The model farm at the Prague Fair, which is constructed according to the standard rules recommended by the Agricultural Building Institute, has a kitchen of 18.80 square metres and bedrooms of from 15 to 20 square metres ; the heights are 3 metres on the ground floor and 2.70 metres on the upper floor.

Yugoslavia.—The Law of November 7th, 1931, regulating building, lays down the following minimum dimensions : 3 metres for ground-floor rooms, 2.80 metres on the upper floors, 2.50 metres in attics and 2.25 metres in lofts. A margin, however, is allowed in the case of dwellings which do not cover more than 100 square metres and have not more than one floor or three rooms ; the minimum

height of the rooms is reduced to 2.50 metres, and of attics to 2 metres.

In practice, the standard plan height of 2.70 metres on the ground floor is used for these smaller dwellings ; the kitchens have a floor-space of 15 or 16 square metres, and the bedrooms from 12 to 16 square metres. In larger dwellings with a height of 3 metres, bedrooms cover from 20 to 25 square metres and kitchens 25 square metres.

(9) *Belgium.*—According to the information obtained, the operations of the Société nationale de la petite propriété terrienne up to the end of 1937 comprise 1,055 transactions, falling under the following heads : gardens or additional gardens—65 ; small farms with living-quarters and farm-buildings—planned 563, bought 70 ; slums demolished and rural dwellings constructed—70 ; buildings erected for small farm-holdings—84 ; land bought to be added to small farm-holdings—102 ; small farm-holdings purchased—108 ; live-stock and implements purchased—4. The 1,055 borrowers concerned in these transactions comprised : 72 farm labourers, 81 artisans, 275 small holders and 627 other persons of the poorer class,

It should be borne in mind that the Société nationale was founded on February 27th, 1935, and is thus still in its infancy.

France.—The decennial agricultural statistics for 1929 show that, between 1919 and 1929, 255,377 farm-buildings were built, comprising : 21,056 complete farms, 48,632 farm houses, 10,921 farm labourers' dwellings, 60,006 stables and byres, 38,278 barns and 76,484 sheds for produce. These works were carried out by the farmers with or without loans from the Crédit agricole.

Latvia.—The Agrarian Reform Act of September 24th, 1920, enabled 200,000 farm labourers to become landowners ; living-quarters and farm-buildings were erected on the small farms produced by breaking up the large estates affected by the Agrarian Reform Act.

Netherlands.—Many houses were built between 1916 and 1923 (period of housing shortage) with Government assistance, more particularly as a result of the special facilities granted to builders in 1920. More than 80,000 dwellings were thus erected, but it is

impossible to say how many of these are in the country. Statistics for the years 1921-1937 show that, during that period, 787,996 dwellings were built, of which 188,245 (about 25%) were in communes with fewer than 10,000 inhabitants (about 40% of the population of the country). Under the 1918 Agricultural Labourers Act, 5,242 loans were made, between 1919 and 1937 inclusive, to agricultural labourers for the purchase of land and the building of a house. Most of these houses are new erections.

Poland.—In connection with the agrarian reform which came into force in 1919, agricultural settlements were created with dwelling-houses and farm-buildings. Between 1935 and 1937 inclusive, the State supplied 242,000 cubic metres of building-timber. In 1937, 1,660 farms (4,400 buildings) were created, and, in 1938, 1,896 new farms were in process of creation.

Sweden.—Between 1905 and 1935, 80,000 one-family houses, with or without farm attached, were built with Government help. It is estimated that housing conditions have thus been made satisfactory for 400,000 persons (one-tenth of the rural population).

Improvement work on the dwellings built was begun in 1933 ; by December 31st, 1936, 31 million kronor had been allotted as direct grants for housing improvements, and 7.5 million kronor as loans for new construction. 32,000 dwellings were thus improved, and, at the same time, work was given to a large number of unemployed. The share of rural dwellings in this relief work has not been ascertained.

Czecho-Slovakia.—According to statistics, by December 31st, 1930, there had been built (1919-1930), under the laws for encouraging housing construction, 3,862 family dwellings for working farmers, being 10.25% of the total number of buildings, and 1,236 dwellings for agricultural labourers, being 3.43% of the total number of buildings.

Agrarian reform legislation has enabled 72,000 settlers (out of 305,000) who did not own houses to build them with State help.

Yugoslavia.—It is impossible to ascertain from statistics what proportion of the 85 million dinars in cash and 3.5 million dinars in kind expended by the State between 1931 and 1936 inclusive

on rural improvements generally is accounted for by dwelling-houses and farm-buildings.

(10) *Belgium*.—No special information, except about the public drinking-water supply, sewerage, and electricity supply.

France.—Community planning is in the hands of the communes ; under the Law of March 14th, 1919, as amended by the Law of July 19th, 1924, it is compulsory for every commune, other than rural communes, to draw up a plan for its layout, amenities and future expansion.

Public buildings and facilities (wash-houses, shower-baths, communal clubs, covered markets, fair-grounds, public weigh-bridges for live-stock and agricultural produce, slaughter-houses, etc.) are established and maintained by the communes, with assistance from the Government or the Departments. Health institutions (dispensaries of various kinds, maternity and infant consultation clinics, etc.) are run sometimes by the communal authorities, sometimes by the Departmental Health Service, and sometimes by private societies or associations for the advancement of public health.

The Government broadcasting stations issue special agricultural broadcasts at regular intervals.

Latvia.—The new villages built after the agrarian reform consist of a number of widely scattered farms, with only a small central nucleus, including the mayoral offices or community house, the church and the school. There are no public baths in Latvia, except in the towns ; every farm has a steam-chamber, but the modern tendency is to replace this by a bathroom.

Netherlands.—Where new villages have been built on the polders, they have been admirably planned by the administrative authorities. For instance, on the most recently reclaimed polder (Wieringermeerpolder) there are broad highways with footpaths and turf strips, stone gutters, piped drinking-water and sewerage, and all the usual public buildings.

Poland.—A community plan has been drawn up for every district centre, and includes water-supply, sewerage, town-planning, street alignment and public buildings. The progress of its execution is shown day by day on a map.

Loans are made by the Ministry of Public Assistance for the construction of communal shower-baths and steam-baths. Shower-baths are installed in the schools for the use of the children, and the public are admitted to them on certain days.

On the agrarian reform allotments, sites are set aside for the church, the school, the community house and the communal club, which, together with a few shops belonging to small traders or consumers' co-operative societies, form the communal centre.

Elementary schools are in course of construction, and the old buildings are used as community houses ; the communal clubs have a large hall for meetings and for listening to broadcasts, a library and several small meeting-rooms. In some cases, all these institutions—school, communal club and community house—are combined in one building.

Sweden.—At the Ministry of Communications there is a Town and Village Building and Planning Department, which superintends the drawing-up of plans.

Village planning schemes are approved by the provincial governing authorities after examination by and on the advice of its official architect, and, if necessary, its official road engineer, both of whom are Government servants. In regard to village planning, the general law contains very few clauses dealing specially with villages, except in connection with street alignment ; but its provisions may be amplified by provincial and communal by-laws.

The Swedish Public Baths Association makes grants and supplies plans for the construction of public baths.

Czecho-Slovakia.—Public baths are fairly common in the towns, but not yet in the country, except in a few small villages ; they involve a great deal of expense for the communes.

There is a Rural Broadcasting Society, which since 1926 has given two broadcasts every day, at noon and at 6 p.m. Each district has a special meteorological service, whose weather reports are broadcast by the society's centre. Funds are drawn from the Radio-Journal Association, which is Government-controlled ; the Broadcasting Society has a special reporter at each of the six Government broadcasting stations.

The co-operative supply societies, which are highly developed and well organised, generally build their own premises in the

villages, and include a communal centre (entertainment and meeting hall for the cultural societies in the village).

There are a large number of private associations and societies for the advancement of intellectual and moral life in the countryside, the improvement of rural life, and the proper use of the people's leisure, especially that of the young. The ideal would be to build in every village a community house in which the villagers would meet to listen to lectures on agriculture, social institutions, health questions and social progress generally.

The library is often housed in the elementary school.

The agricultural co-operative societies have put up numerous buildings for their own purposes and also for the use of their members (meeting-rooms, public baths).

Reconstructed villages, and those built in consequence of the agrarian reform, are laid out on modern principles.

Yugoslavia.—The Building Law of November 7th, 1931, deals with community planning.

Under the Law of January 10th, 1930, on assistance for village improvement, loans, free of interest, may be made for that purpose to communes with a population of not less than 2,000. Help is also given by the institutes of hygiene and health co-operative societies, whose premises contain meeting-rooms, entertainment halls, reading-rooms and libraries.

(11) *Belgium.*—At January 1st, 1938, 33% of the 2,671 communes in Belgium possessed their own public supply of drinking-water, this figure corresponding to 60.5% of the total population of the country. Under the Act of August 26th, 1913, a national undertaking for water-supply was created ; its working is governed by an agreement between the Government and the nine provinces of Belgium, dated May 15th, 1914. This national undertaking carries out research, draws up plans, supervises construction operations, and manages the supply system. Its object is to control all sources of water-supply throughout the country. The minimum consumption taken as basis of calculation is 30 cubic metres per head of population per annum (roughly 80 litres per head per diem) for a fixed charge fluctuating between 30 and 80 francs ; the charge for additional supplies is 2.50 francs per cubic metre. These prices include the hiring of meters.

France.—Since 1903, the Government, through the Ministry of Agriculture, has subsidised installations for the supply and distribution of water to rural communes or groups of communes. As from 1938, communes may also issue loans at 3%, repayable in thirty annual instalments.

At March 1st, 1937, somewhat over a third of all French communes possessed a public supply of drinking-water. Since 1930, the rate of increase has been approximately 500 communes a year.

The average daily quantity available per head is generally limited to 125 litres.

The progress of rural electrification facilitates the extension of water-supplies, as it enables automatic electric pumping-stations to be installed.

Latvia.—As villages consist of widely-separated farms, and as the central nucleus of the rural community is extremely small, regional systems of water-supply do not exist ; separate systems, supplying single farms, are the rule. In the Agrarian Reform settlements, artesian wells are found, which supply neighbouring farms with the help of pumping-systems.

Netherlands.—The organisation of public supplies of drinking-water in the Netherlands is highly developed ; it is systematically conducted by a Government Bureau for Drinking-water Supplies.

There are seventy towns with over 5,000 inhabitants, and 994 communes with under 5,000 inhabitants, classified as rural communities, in the Kingdom.

In 1931, all the towns and 514 rural communes possessed water-supply systems ; in other words, 48% of all communes and 63% of the total population were supplied.

At January 1st, 1936, 720 communes, or 82% of the total, possessed a public supply of drinking-water.

At present (1938), this number is 900 (84.5%).

In 1931, there were twelve regional water-supply services ; at present, there should be fourteen.

Poland.—Acting through the Federation of Towns, the Ministry of the Interior advances loans to the communes for the supply of drinking-water to the public. The Federation possesses a bureau of specialists. Schemes to be undertaken are transmitted to the

Ministry by the county authorities. Loans are granted at the rate of 2% and are repayable in fifteen or twenty years ; reductions of the amount to be repaid are often granted.

The public supply of drinking-water is chiefly undertaken by the towns ; it is proposed subsequently to extend the supply to villages remote from urban or industrial centres. The amount supplied per head of population per day varies from 30 to 120 litres, the general tendency being to fix it at 80 litres. The selling-price of water varies from 0.18 to 0.50 zloty.

Sweden.—The Government does not at present make grants for the supply of drinking-water, financial support for such schemes coming only from the provincial authorities. Farms are, in general, scattered over the country, and the rural communities are usually very small.

Czecho-Slovakia.—Systems for the supply of drinking-water are numerous in the north-western part of the country (an industrial region rich in subterranean water), and relatively scarce in southern Bohemia and Moravia (granite regions). Statistics established in 1928 give the following proportion of the Czecho-Slovak population as being supplied with drinking-water : 44.3% in Bohemia, 35.5% in Moravia and Silesia, 38.5% in Slovakia and 1.6% in Sub-Carpathian Russia (a thinly populated district). The proportion of communes having a regular water-supply was 46% of the communes with between 2,000 and 5,000 inhabitants, and 16% of those with less than 2,000 inhabitants. The number of communes or parishes supplied with drinking-water is at present 11.34% of the total number, with a population of 39% of the total population of the country (51% in Bohemia). The length of piping is estimated at 13,660 kilometres (about the same as that of the railways).

Yugoslavia.—The public supply of drinking-water comes within the sphere of the Ministry of Social Services and Public Health. From 1927 to 1937, 7,807 schemes of this nature were carried out at a cost of over 203 million dinars, two-thirds of which were at the expense of the State, one-sixth at that of the provincial administration (banovine), and one-sixth (installation and transport charges) at that of the beneficiaries. Regional supply schemes on a large scale are at present being carried out in Croatia and Slovenia.

In the Carso District, communal reservoirs are being constructed, which are fed exclusively by rain-water collected from roofs. Twenty litres of water are allotted daily to each inhabitant, though thirty litres are given if possible. Elsewhere, at least 100 litres are supplied per inhabitant.

(12) *Belgium*.—On January 1st, 1938, the number of communes throughout the Kingdom possessing main sewerage was 506 (19%), the population served by the above amounting to 5,255,781 (63% of the total Belgian population). The statistics include both complete systems with purification plant and mere covered gutters receiving only rain-water, but not sullage water or excrement.

In general, the sewers are situated in the larger towns and built-up areas.

* *France*.—Drainage in rural communities is less advanced than the supply of drinking-water. A private investigation conducted in 1932/33 showed that 80% of towns with over 5,000 inhabitants possess sewerage systems, though these were of unequal value and often out of date, so that the proportion of towns with over 5,000 inhabitants which were served by a satisfactory sanitary system did not exceed 25%.

In areas with less than 5,000 inhabitants (rural communes), the proportion of satisfactory sanitary systems was then estimated as being between 1% and 12%, according to the district.

Latvia.—Farms are widely scattered about the country, and rural communities are reduced to a bare minimum of public or collective buildings and a few retail shops; the disposal or treatment of waste water and refuse has hitherto been performed by individuals.

Netherlands.—Since 1920, a Government Institute for the purification of residuary water has been in existence, and has devoted itself chiefly to the purification of water in towns and rural communes by methods suited to the local situation. In the Netherlands, the population is very dense, and sewers are usually to be found in rural communes, though they flow directly into the streams. The Government Institute is endeavouring to remedy this defect.

Poland.—The Federation of Towns mentioned in connection with the water-supply performs similar work to encourage the installation

of sewers. Farms are scattered about the country, so that the same remarks apply as in the case of Latvia (see above).

Sweden.—Same remarks as for Latvia.

Czecho-Slovakia.—Drainage systems exist in most of the large towns. They are comparatively rare in the smaller towns, and still more so in the countryside.

Yugoslavia.—The same remarks apply as in the case of Czecho-Slovakia.

(13) *Belgium.*—The electrification of the countryside has reached a very advanced stage in Belgium. Of 2,671 communes, only about twenty have still to be electrified. This applies, however, more particularly to the electrification of the central built-up areas of communes, as many outlying farms are not yet electrified. The Governments grant a 25% subsidy for the electrification of isolated areas when undertaken by the communes if this work is not self-supporting and if the consumers guarantee a certain minimum consumption. The cost of the work that still has to be done in order to complete the electrification of the Belgian countryside is estimated at sixty million francs.

France.—On January 1st, 1937, 96% of the 38,013 French communes were electrified. The population of these communes amounts to 39.5 millions (89% of the total population of France). The 1,500 communes that still have to be electrified have a population of 755,000. Isolated portions, not yet electrified, of communes that are electrified, have a population of about 4 millions. Thus, some 11% of the population of France is not yet supplied with electricity.

The Government has greatly encouraged the electrification of the countryside through the technical collaboration of its engineers (Rural Engineering Service) and by means of subsidies and long-term loans bearing low interest. The Departments and companies holding concessions have given financial assistance to the communes, which are generally grouped in inter-communal rural electrification syndicates. There are also many co-operative societies for the distribution of electric power.

Latvia.—The fact that the farms are scattered throughout the communes makes the electrification of the countryside more difficult.

Some electrified farms show the way in which the farmer can derive the greatest advantage from the use of electrical power. The passage of lines conveying current and the proximity of electrified built-up areas constitute the basis on which the electrification of the countryside is at present proceeding. A large central station for the production of electricity, situated 45 kilometres upstream from Riga, will increase the electrified area of the countryside.

Netherlands.—The electrification of the countryside has reached a very advanced stage. The Netherlands is very densely populated, and the large towns, which generally produce and distribute current as a municipal service, are able to supply neighbouring communes. There are also provincial central power-stations. There is no Government service responsible for electrification.

Poland.—There are, in Poland, large central stations for the production of electric power. Electrification started in the urban and industrial centres, but, for the past two years, it has been extending to the countryside in certain regions.

The work of electrification is receiving the special attention of the Government, which, in the Law of March 21st, 1922, made legislative provision therefor.

Sweden.—There is a Swedish Union for the Electrification of Rural Districts. Provincial societies belonging to this union exercise a co-ordinating influence over co-operative societies for the distribution of electric power. In 1922, there were 1,200 co-operative societies of this kind. They generally purchase from the producer, and distribute the current to their members.

Notwithstanding the fact that the farms are widely scattered in some districts, 50% of rural houses are now electrified.

Czecho-Slovakia.—Under the Law of July 22nd, 1929, the Government grants subsidies for the work of electrification when systematically carried out in the country by combined undertakings (provinces, villages). Electricity consumers' co-operative societies are responsible for the distribution of the current produced by public corporations or by the State. These co-operative societies are constituted by villages and are federated. They receive subsidies from the Ministry of Agriculture through the unions of co-operative societies and the councils of agriculture.

Yugoslavia.—The countryside has been electrified in the neighbourhood of factories, towns and lines conveying current. Wherever it is possible, electrification is always welcomed.

LIST OF PREPARATORY DOCUMENTS

	Document No.
“The European Conference on Rural Life and the Problem of Housing”	C.H./Com.Hab.51
“First Draft of Guiding Principles for the Study of Rural Housing (formulated in 1935)”	C.H./Hyg.Rur./E.H.1
“Draft Report on Rural Housing and Planning”, by M. M. Vignerot, Paris	C.H.1388.
“Notes sur la Maison rurale et ses dépendances, en Belgique, Lettonie, Pays-Bas, Pologne, Suède, Tchécoslovaquie et Yougoslavie”, by M. M. Vignerot (French only)	C.H.1386 and 1386 (a) to (f)
“Report on Water Supply and Sewage Disposal for the Isolated Dwelling”, by H. A. Whittaker, Minneapolis, U.S.A. (English only)	C.H./Com.Hab.70
“Density of the Population and Open Spaces,” by H. van der Kaa, The Hague (English only) . . .	C.H./Com.Hab.69
“L'alimentation en eau potable aux Pays-Bas” by W. F. J. M. Krul, The Hague (French only) . . .	C.H./Com.Hab.71
“Sewage Treatment in the Netherlands”, by H. J. N. H. Kessener, The Hague (English only) . . .	C.H./Com.Hab.72
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“L'Habitation rurale aux Pays-Bas”, by H. van der Kaa, The Hague (French only)	C.H./Com.Hab.78 (out of print)
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“Report on the Principles of State Control of Water Supply and Sewage Disposal in Poland”, by Z. Rudolf, Warsaw (English only)	C.H./Com.Hab.82
“Water Supply and Drainage Conditions in the Country : Some Technical Problems concerning Sweden”, by Anders Molin, Stockholm (English only)	C.H./Com.Hab.83

LEPTOSPIROSES

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TABLE OF CONTENTS

	Page
Introduction	144
I. LEPTOSPIROSES IN MAN	146
1. Epidemiology	146
2. Clinical Features of Leptospirosis icterohæmorrhagica	159
Incubation	160
Clinical Symptoms	160
Complications	174
Diagnosis	175
Prognosis	177
Treatment	177
Chemotherapy	178
Serum Treatment	179
3. Clinical Forms of Leptospirosis in Man	190
A. Meningitis Leptospirosa	190
B. Mud Fever due to <i>L. grippolyphosa</i>	201
C. Leptospiroses in Japan	208
D. Leptospiroses in the Netherlands Indies	215
E. Leptospiroses in the Federated Malay States	230
F. Leptospiroses in the Andaman Islands	232
G. Leptospiroses in Australia	236
4. Summary of the Differences between the Various Forms of Leptospirosis in Man	239
II. LEPTOSPIROSES OF RATS AND OTHER RODENTS :	
A. Leptospiral Infection in Rats	254
B. Leptospiral Infection in Mice and Field-mice	302
III. LEPTOSPIROSIS IN DOGS	309
IV. PREVENTION OF LEPTOSPIROSES	338
V. REFERENCES	346

INTRODUCTION

In the past, under a variety of names ("typhus icterode", "bilious typhus", yellow fever, acute yellow atrophy of the liver, etc.) and usually in connection with epidemics, diseases have frequently been described which resemble what would now be called Weil's disease or leptospirosis icterohæmorrhagica. The history of leptospirosis icterohæmorrhagica cannot, however, be examined here. For a review of former epidemics and cases the reader is referred to the treatise by MARTIN & PETTIT and Section VII of the "Handbuch der Pathogenen Mikroorganismen" in which Weil's disease is discussed by UHLENHUTH & FROMME. Only a few indications need be given here.

Whilst it is often impossible to say whether such diseases were genuine cases of leptospirosis icterohæmorrhagica, and whilst other diseases may have been present among the epidemics formerly described, it is worthy of note that, in addition to such obvious symptoms as jaundice and hæmorrhage, congestion of the conjunctiva, dry tongue, etc., others, less obvious, such as the "crise urinaire" (LARREY, 1800¹), were observed. Thus FLONQUIN, who regarded the "typhus icterode" which occurred in Smyrna in 1885 as a separate disease, drew attention to the fall of temperature during a period of from 10 to 12 hours, which normally occurred in the middle of the febrile phase. Even very atypical forms, such as a nictic and abortive cases, were already known (DIAMANTOPOULO, 1884). Besides studying the pathology of the disease, DIAMANTOPOULO considered its epidemiology. His attention was drawn by his colleague CONSTANT to the fact that some of the cases had occurred in the neighbourhood of an open sewer, and he decided to make a closer examination of this possible cause of the disease. In this way, he opened up a line of investigation which the Japanese research workers followed out on their own account, thirty years later, with successful results. Frequent cases of the disease and epidemics were subsequently reported. The four cases described by WEIL led, in some countries, at least, to a closer examination

¹ So far as the disease occurring among Napoleon's troops may be assumed to have been leptospirosis icterohæmorrhagica.

of the disease, its symptoms and the circumstances in which it occurred, and thus, no doubt, to the rediscovery of what had already been known at an earlier stage. The disease appeared to be endemic in many places and sometimes gave rise to epidemics, particularly among soldiers and persons working in mines and sewers, on canals and in damp agricultural districts. The study of the disease, was only placed on a sound basis when the specific cause was discovered by INADA & IDO, who transmitted the disease experimentally to guinea-pigs in 1913, and, in 1914, discovered the spirochæte which they called *Spirochæta icterohæmorrhagiæ* and demonstrated to be the actual cause of the disease.¹ In 1915, without being acquainted with the work of these investigators, HUEBENER & REITER, in the German army, and, almost simultaneously, UHLENHUTH & FROMME, transmitted the disease to guinea-pigs with the blood of a patient. In the blood, HUEBENER & REITER found, *inter alia*, long-drawn-out motile organisms, but did not recognise them as spirochætes, while UHLENHUTH & FROMME found spirochætes with flat coils and fairly active movements in the guinea-pig's liver and blood. Subsequently, HUEBENER & REITER called this organism *Spirochæta nodosa*, as it showed a row of iridescent points under the dark-ground illumination, while UHLENHUTH & FROMME gave it the name of *Spirochæta icterogenes*.

After Weil's disease had thus been found to occur at the front and the etiological agent had been described, new cases were constantly announced ; for example, in the British Army in Flanders (STOKES & RYLE, and STOKES, RYLE & TYTLER), in France (MARTIN & PETTIT, CLÉMENT & FIESSINGER, COSTA & TROISIER, GARNIER & REILLY, etc.), on the Belgian front (RENAUX), in Italy on the Isonzo and in the Trentino (MONTI), and among Canadians in Salonica (McKENZIE, communication to Noguchi). In the following years it became possible to identify the disease in many countries by means of bacteriological and serological investigation, even when it did not occur in epidemic form, and in cases where it assumed forms hitherto unrecognised—*e.g.*, when it was so mild that it could

¹ The spirochæte had been observed on a former occasion by STIMSON (1907) in kidney sections obtained from a victim of the disease. He called it *Spirochæta interrogans* owing to its peculiar shape. We do not know whether an account of this was published at the time. The fact was later reported by PACKCHANIAN.

not be diagnosed without a serological examination or when it took on the appearance of meningitis (COSTA & TROISIER, BLOCH & HÉBERT). The disease has now been bacteriologically demonstrated in the following places and countries :¹

<i>Africa</i>	<i>America</i>	<i>Asia</i>	<i>Australia</i>	<i>Europe</i>
Belgian Congo (Stanleyville)	Argentina Brazil	Andaman Is. Banka	Queensland (Brisbane)	Austria (Vienna)
Egypt (Cairo)	Canada Chile	Billiton Borneo		Belgium Czecho-Slovakia
Morocco	Colombia Ecuador Guadeloupe Mexico Peru Surinam United States Venezuela	Br. India (Calcutta) Celebes Cochin-China Federated Malay States Japan Java Philippines Sumatra Tonkin		Denmark England France Germany Greece (Salonica) Italy Netherlands Norway Poland Portugal Scotland Sweden

Weil's disease is, however, not the only form of human leptospirosis. In Europe, but more especially in other continents—first in Japan and later in the Netherlands Indies, Federated Malay States, Russia, Andaman Islands, Netherlands, Australia, etc.—diseases have been described which are more or less related to it, though occasioned by other leptospiræ.

I

LEPTOSPIROSES IN MAN

1. EPIDEMIOLOGY OF
LEPTOSPIROSIS ICTEROHÆMORRHAGICA

WITH PARTICULAR REFERENCE TO THE NETHERLANDS

The following gives a survey of the history of Spirochætosis icterohæmorrhagica in the Netherlands.

In 1924, a year after sewer-rats had been shown to be heavily infected, the first case of leptospirosis icterohæmorrhagica was bacteriologically demonstrated in the Institute of Tropical Hygiene

¹ We cannot guarantee that this list is complete.

in Amsterdam. It may be assumed that the disease occurred in the Netherlands before that time—probably sporadically (*e.g.*, SLINGENBERG's cases, 1903). It is improbable that there were epidemics as these would have been recorded. After 1924, the number of cases in the Netherlands increased considerably for several years, and, in 1932, a definite epidemic occurred.

NUMBER OF CASES IN THE NETHERLANDS

Table 1a gives the number of cases examined in the laboratory of the Institute of Tropical Hygiene. Next to this are given the cases reported to the Public Health Service. The disease began to be reported in 1929 and, in 1932, notification became compulsory.

Table 1a.—NUMBER OF CASES IN THE NETHERLANDS

	Number of cases bacteriologically demonstrated at the Institute of Tropical Hygiene	Deaths	Number of cases reported to the Public Health Service	Deaths
1924 /25'	28	7		
1926				
1927	7	2		
1928	8	0		
1929	13	2	13	2
1930	20	4	26	4
1931	18	2	30	3
1932	84	5	207	16
1933	55	4	156	11
1934	45	8	118	17
1935	26	1	93	3
1936	30	4	69	7
1937	40	5	96	13
	374	44	808	76

The sudden increase in the number of cases in 1932 is due, not to compulsory notification alone, but also to the fact that an epidemic of the disease occurred at the time. In that year, the number of cases was also greater than it ever had been in France, though the increase was more gradual than in the Netherlands. The disease usually occurs sporadically. Local foci of varying importance have occasionally been discovered sometimes when the disease was already known to be prevalent, and sometimes when a single case led investigators to make enquiries in the patient's environment. The majority of cases occur in a few large towns. This fact will be dealt with further on.

INCIDENCE OF THE DISEASE IN THE VARIOUS PROVINCES

Table 1b gives the incidence of the disease in the various provinces. The most remarkable feature is the difference in the case frequency rate. The severely infected provinces are in a low-lying part of the country with abundant water, and this doubtless promotes dissemination. It cannot, however, be the only cause. Though Friesland has at least as much water and is for the most part as low as the provinces of North and South Holland, few cases occur there.

Table 1b.—NUMBER OF CASES FROM 1924 TO 1937, INCLUSIVE :
DISTRIBUTION BY PROVINCES

		Per 100,000 inhabitants
Friesland	14	2.4
Groningen	11	2.4
Drenthe	7	2.5
Overijssel	27	4.0
Gelderland	33	3.7
Utrecht	73	13.0
North Holland	149	7.6
South Holland	489	21.6
Zeeland	8	2.4
North Brabant	19	1.4
Limburg	22	3.4
Netherlands	852	8.9

Other local causes must therefore exist. This is also clearly brought out by a comparison of the figures for some of the larger towns, which show equally marked differences (Table 1c). It will be seen that there is no sort of parallelism between size of population and number of cases.

Table 1c.—NUMBER OF CASES OF LEPTOSPIROSIS ICTEROHÆMORRHAGICA
IN SOME OF THE LARGE CITIES OF THE NETHERLANDS

	Amsterdam (780,000 inhabitants)	Rotterdam (596,000 inhabitants)	The Hague (483,000 inhabitants)	Utrecht (161,000 inhabitants)	Dordrecht (60,000 inhabitants)
1924-1932	12	71	2		
1933	7	54	3	5	41
1934	8	41	0	3	5
1935	5	23	2	0	5
1936	6	23	0	1	2
1937	16	19	1	3	1
				7	0
	54	231	8	19	54

Rotterdam and Amsterdam, for example, are both low-lying towns in districts with abundant water. Though the population

of Amsterdam exceeds that of Rotterdam by one-third, the number of cases is much smaller. Rotterdam has always had the greatest number of cases, amounting to about one-third of the total number in the Netherlands.¹

In some instances, the local causes of a high incidence can be clearly indicated.

For example, Dordrecht, a town lying amid large rivers, had three swimming-pools, all of which were supplied with water from the same river. In one of the pools the water flowed through freely, in another it was changed several times a day, and in the third pool, which was situated in the centre of the town, it remained stagnant, and was befouled by numerous rats. In the first pool, one case of Weil's disease occurred for a total of 23,968 bathes, in the second, three cases occurred—*i.e.*, one case of Weil's disease for 32,428 bathes—whereas in the third, 34 cases occurred—*i.e.*, one for 4,229 bathes. With the closing-down of the last-named establishment, the number of cases in Dordrecht at once reverted to "normal" proportions. In other places, special causes are not so easy to determine. There is no doubt, however, that in Rotterdam, for example, which is a thickly-populated commercial town with numerous waterways, the number of rats is particularly large, and that, after a vigorous anti-rat campaign, the number of cases decreased.

CLASSIFICATION OF CASES ACCORDING TO CAUSE

Table 2 indicates, *inter alia*, the causes to which the cases known in the Netherlands must be attributed. If the 12 cases due to a *L. canicola* infection are subtracted, there remain 337 cases of leptospirosis icterohæmorrhagica occurring from known causes—*viz.*, 60 (= 18%) due to accidents (*i.e.*, a fall in the water), no less than 197 due to swimming (= 60%), making together 78%, and 68 cases of occupational origin (= 22%). Of these 68 cases, no less than 16

¹ The fact that, during the last year, the number of cases reported in Amsterdam has suddenly increased should not, in our opinion, be ascribed to an actual increase in the prevalence of the disease, but to the special interest of medical men, which has resulted in the identification of a number of very atypical cases. Thus, where endemic or epidemic conditions are such that the number of cases is small, the evidence contributed by a single physician may suffice to alter the significance of the whole epidemiological data.

Table 2.—DISTRIBUTION OF CASES ACCORDING TO CAUSE, AND BY SEX AND AGE

Total number of cases	Manner of infection																		Deaths			Age groups									
	Number			Accidents			Swimming			Occupational			Unknown			<i>L. canicola</i> infections						1-10	10-40		40-60		>60		Un-known		
	M	F	C	M	F	C	M	F	C	M	F	C	M	F	C	M	F	C	M	F	C	M	F	C	M	F	M	F	M	F	M
374	323	40	11	43	9	8	172	23	2	65	3	0	35	1	1	7	4	1	42	2	0	11	187	23	42	7	15	1	79	9	

M = Male. F = Female. C = Children.

were fishermen, and half of the 52 others were engaged in work which had to be performed on or in the water (divers, seamen, reed-cutters, etc.), while the other half were occupied in places overrun with rats (slaughter-houses, sewers, butter factories, barns and stables).

Thus, in the great majority of cases (91%) the infection was due to some form of *contact with water*, and in 9% to an occupation bringing the persons concerned into frequent contact with *rats*. Even where the disease is caused by contact with water, the real cause of the infection remains the rat, which carries the leptospiræ and passes them into the water through the urine.

The following details show how easy it is to contract the disease from an *accidental fall in the water*.

Out of 972 persons who fell in the water in Amsterdam between 1928 and 1932, 13 contracted the disease—i.e., 1 in 75 of these involuntary bathers. The spot at which such accidents occur is of great importance, and the Amsterdam canals have a particularly bad reputation. The swallowing and sucking into the lungs of much water—together with additional causes such as unconsciousness, drunkenness, etc.—tend to promote infection, as SCHÜFFNER observed.

That the risk of contracting the infection through *swimming* is, on the other hand, comparatively small will be obvious from the following :

In Rotterdam, for example, there were only 71 cases in 1932, though 1,630,000 bathes in public baths were recorded. If all 71 cases were due to bathing, the proportion, in Rotterdam, where the degree of infection is high, would only be 1 in 23,000 ; some of the 71 cases, however, were due to other causes ; besides, the total number of bathes must have been much larger, as those in natural surroundings are not included. The number per case of infection must, therefore, be considerably higher than 23,000 to 1. In other towns, the number of bathes per case is even larger.

This does not alter the fact that 60% of the cases in the Netherlands are due to bathing.

Alike by case observation and by experiment, numbers of investigators have studied how the infection enters the human body. Entry into the body appears to take place through the normal or abraded skin, through the ingestion of micro-organisms with food,

etc. (INADA, UHLENHUTH & FROMME, VAN THIEL). VAN THIEL concluded from his experiments with guinea-pigs that infection occurred through the abraded skin with comparative ease and that it was far more difficult to contract the disease through food. It was found, however, that the infection was readily carried along the nasal mucous membrane by inspiration, and further that it entered with comparative ease through the mucous membrane of the eye, at any rate more easily than through the mouth. APPELMAN had already demonstrated by means of bathing experiments with guinea-pigs that infection through the skin was by no means frequent though possible (one of the ten guinea-pigs was infected in this way). VAN THIEL also argued that the conjunctiva seldom came into contact with infected water, so that the greatest risk of infection was through the nose.

The great predominance of cases connected with water over those connected with rats has been noticed in every country (LAVERGNE, MASSON & STUMPF). It is also observable where a leptospira other than *Leptospira icterohæmorrhagiæ* was the cause of the disease.

In Japan, frequent cases occurred in damp coal-mines, in low-lying country (particularly in rice-growing districts) and in marshy soil, whereas dry coal-mines were not affected. GOEZ mentions cases in West Africa in low-lying districts with a heavy rainfall near swamps and rivers. Cases were found to occur on new undertakings situated in damp districts, where drainage systems were built, and among patrols in damp forests (Netherlands Indies), persons working in the mud (Andaman Islands), and sugar-cane cutters in Queensland, where the land had become boggy through previous rains and the pools of water and the sugar-cane itself could be contaminated by rats. Epidemics and sporadic cases have also been reported after swimming and bathing,—for example, in the Arno, Elbe, Seine, Tiber, Vesle, Vistula, Amazon, the Rio de la Plata, Thames, Meuse and Amstel. Outbreaks have also occurred after the opening of swimming-baths (Stanleyville and Borneo).

The disease can similarly be contracted as a result of *drinking* from springs which must have been contaminated by rats—*e.g.*, in Lisbon (JORGE); in Syra, a number of cases occurred among customers of a restaurant where the drinking-water had been contaminated by numerous rats; another case was reported after Plata river water had been drunk (BARROS).

In many places, however, the direct agency of the rat was more evident—*e.g.*, the cases among sewer-men in Brisbane, reported by JOHNSON, BROWN & DERRICK in 1937. UHLENHUTH mentions cases among cooks at the front during the great war; BUCHANAN, cases in mines and butchers' shops (1924); TROISIER & BOQUIEN mention the case of a dish-washer in a restaurant, who cut his finger on a fish-bone (1930). DAVIDSON, CAMPBELL, RAE & SMITH, cases among fish-workers in Aberdeen (1934); Hamilton FAIRLEY, cases among London sewer-men (1934); SEYFFARDT, cases among Leipzig sewer-men (1936); and, in the Netherlands, in slaughter-houses, barns, stables, etc.

The rats (and field-mice) which are found to be carriers of leptospiræ and the strains which they transmit are discussed further on, together with other details, in the chapter on rats (part II).

It must be remembered that other animals, as well as rats and field-mice, may transmit leptospiræ. A case observed by SANDER of a butcher who contracted Weil's disease eight days after having killed a jaundiced pig appeared to indicate that pigs could be carriers. KLARENBECK did, in fact, succeed in isolating *L. icterohæmorrhagiæ* from a young pig. Pathogenic leptospiræ were also found in wild foxes and in those bred in fox farms (DUNKIN & LAIDLAW, SMITH, MACRAE), and also in cats (ESSEVELD & COLLIER). SANDIMAN found that horses gave a strong serological reaction. Foals also proved to be easily infected (NIESCHULTZ & WAWAROENTOE). As a carrier, the dog is probably more important than any of the above. It is certain that human beings can contract a *L. canicola* infection from the dog, and there is no reason why this should not occur as easily with *L. icterohæmorrhagiæ* (see below the chapter on leptospirosis among dogs in part III).

Special causes for outbreaks of leptospirosis icterohæmorrhagica are sometimes reported in certain districts. IDO, HOKI, ITO and WANI drew attention to the influence of the acidity of the soil. In mines, where the soil and the water gave an acid reaction, the disease did not occur, whereas it was endemic when the reaction was alkaline or neutral. SARDJITO & ZUELZER ascribe the greater prevalence of leptospirosis in Sumatra than in Java to the reaction of the surface water, which is more acid in Java than in Sumatra.

Only one case due to direct (sexual) contact is known (DOELEMEN). Infections have also occurred in the laboratory in various places

(INADA, UHLENHUTH & FROMME, GOEBEL, MARTIN & PETTIT, BEGER, WADSWORTH and his colleagues, TARASSOV, POSTMUS, UHLENHUTH & ZIMMERMANN). In such cases, the infection is usually contracted through a wound in the fingers caused by an injection needle or infected piece of glass, sometimes through infectious material splashing into the eye or merely through handling the experimental animals. Thus, in the Netherlands, an assistant contracted the disease in a fatal form in a laboratory where no experiments with leptospiræ were being made. He had merely handled rats a great deal, which afterwards turned out to have been infected with leptospiræ.

BEGER reports a laboratory infection caused by a leptospira strain, which was not *L. icterohæmorrhagiæ* but *L. hebdomadis* (this had also caused a laboratory infection in Japan). In Amsterdam, besides one infection with a classical strain, one Rachmat strain infection and later one *L. grippotyphosa* infection occurred. TARASSOV had already recorded a laboratory infection with *L. grippotyphosa*. In various laboratories in the Netherlands, where rats are used a great deal, the practice has recently grown up of vaccinating the staff against leptospirosis.

DISTRIBUTION OF CASES ACCORDING TO SEX AND AGE

Table 2 also gives the cases recorded in the Institute for Tropical Hygiene, Amsterdam, classified according to sex and age, together with particulars of the number of deaths. The striking feature is the large number of men—323—as compared with only 40 women. This has also been noted in other countries (Japan, etc.). Where such differences occur, they can frequently be attributed to social causes. In the Netherlands, too, some such causes can be indicated.

Cases of occupational origin, for example, relate mainly to men; the number of men falling in the water is also larger than that of women. Where the disease is non-occupational, the difference in the incidence of infection between men and women sometimes disappears. KOTORII, for example, found that, out of 418 patients suffering from "Hasamiyami" (not caused by *L. icterohæmorrhagiæ*, however, but by *L. autumnalis*) 291, or 61%, were men. This group did not include any miners, but consisted of peasants,

merchants, teachers and school-children, among whom a fair proportion of women and girls might be expected; and indeed they accounted for 39% of the cases. SMITH & DAVIDSON found there were also many women patients among workers in the fish industry. In 1936, they tested the serum of 210 fish-workers, 50 men and 160 women. Of the 50 men, 12, and of the 160 women, 39 gave a positive reaction, the proportion being therefore about the same in both sexes.

So far as swimming is concerned, it is not so easy to explain why the female section of the population in the Netherlands is less liable to catch the disease. ROMYN has shown, however, that certain ways of swimming, particularly the crawl stroke and the side stroke are much more liable to produce infection, since the body is liable to go under water for fairly long stretches. There is hence more opportunity of contracting the infection through the nose or the conjunctiva. As women dive less than men, do not use the crawl stroke to the same extent and are slower swimmers, they are less likely to contract the disease. ROMYN's 45 patients in Dordrecht consisted of 13 female and 32 male patients, though the number of bathes taken by men and women in the town was approximately the same.

The number of children, in our records, is exceptionally small, one-third that of women, though children swim a good deal. Small epidemics have occurred among children in England (HINDLE & BROWN) but they consisted of only a few cases. MARIE & GABRIEL also observed several cases among children.

The classification according to age-groups (Table 2) shows that the largest number of cases occurs among persons in the prime of life: 221 cases of not more than 40 years of age and 64 cases over 40. This is only natural if we consider the ætiological influence of swimming and of certain occupations on infection.

The great influence of age on the fatality of the disease is also evident from the following figures:

	Died	Fatality rate
Out of 11 persons aged from 1 to 10	0	0 %
Out of 210 persons aged from 10 to 40	15	7.1 %
Out of 49 persons aged from 40 to 60	12	24 %
Out of 15 persons aged 60 and over	9	60 %
Out of 85 persons of unknown age	8	
370	44	11.9 %

THÖRNER reported in 1917 that old age (and addiction to drink) had an adverse effect on the prognosis. JORGE found that the highest percentage of fatal cases occurred among men over 60 years of age. The same would appear to apply to other forms of leptospirosis. KOTORII reported in 1935 that, out of 418 patients suffering from "Hasamyami", 8 died, nearly all men over 50 years of age.

SEASONAL INCIDENCE OF LEPTOSPIROSES

Table 3 (a) gives the incidence of the disease during the various months of the year. Most cases occur between June and November inclusive, the largest number being in July, August and September; this is, of course, due to swimming. Similar evidence is afforded by Table 3 (b), in which the figures, sub-classified by causes, are also set out by months. In this table, the number of cases due to swimming is particularly noteworthy. Infection is, however, possible throughout the year, even in the middle of winter. Lastly, the table gives the number of patients infected by *L. canicola*. The small number of these cases makes it difficult to draw any conclusions as regards incidence during the various months.

It has been stated that, in general, the rat and the field-mouse, and, to a certain extent, other carriers of leptospiræ, are responsible for the cases of leptospirosis occurring among human beings. The leptospiræ pass out in the rats' urine, come into contact with water, mud, food, etc., and thence find their way into the human body. The length of their survival outside the body of their hosts depends further on special circumstances—pH, etc. VAN THIEL's experiments have shown that they can sometimes live for a long time—*e.g.*, 22 days—in surface water. In this connection, see the chapter on rats below.

OCCURRENCE OF PATHOGENIC LEPTOSPIRÆ IN NATURE

Has the presence of pathogenic leptospiræ been demonstrated in nature? Cases of Weil's disease caused by swimming, falling in the water, etc., would seem to indicate their presence. Further, APPELMAN claims to have produced a typical case of leptospirosis in a guinea-pig by immersing it in a puddle of water, after scarifying

its paws and abdomen (see also, for example, SAWERS' experiment at Ingham (see LUMLEY)).

Reference is also frequently made to BUCHANAN's experiment, in which he injected 4 c.c. of the slime covering the roof of a mine into two guinea-pigs, which subsequently died of typical leptospirosis with jaundice. It is true that the writer calls this a "direct inoculation of a water leptospira". In the light of subsequent investigations, however, we think it may be accepted that he demonstrated by means of an animal experiment the presence in nature of pathogenic leptospiræ originating from a rat.

As far as we know, a pathogenic leptospira in nature has never yet been isolated by culture.

That this is possible would appear to be borne out to a certain extent, though only very inconclusively, by an animal experiment of HINDLE's and another of FLETCHER's. Guinea-pigs inoculated with leptospiræ cultivated from water showed, on post-mortem examination, certain pathological changes: in the first series, hæmorrhages and slight jaundice; in the second, "spotted lungs" in one out of ten guinea-pigs. HINDLE emphasises the fact that the cultures were not pure. It is possible that ETCHEGOIN's culture obtained from a swimming-bath (where cases of leptospirosis had occurred), which reacted with the serum of a cured patient, in dilutions up to 1:2,000, was a pathogenic leptospira.

CAN SAPROPHYTIC WATER LEPTOSPIRÆ HAVE A PATHOGENIC EFFECT ON HUMAN BEINGS ?

Some investigators are not satisfied with the rat theory. According to them, the saprophytic water leptospiræ (*L. biflexa*, WOLBACH & BINGER) can become pathogenic for man. UHLENHUTH & ZUELZER found that, after prolonged culture on animal protein, some of their water strains assumed properties of the classical *L. icterohæmorrhagicæ*. They became so similar serologically that they could, for example, be as highly affected by icterohæmorrhagic anti-serum as the genuine strain and *vice versa*. Furthermore, one strain had a pathogenic effect on guinea-pigs after the 70th passage in serum containing media.

UHLENHUTH & HERMANN, UHLENHUTH & GROSZMANN, BAERMANN & ZUELZER (the last two in Sumatra) obtained similar results.

BAERMANN & ZUELZER succeeded in rendering various water strains virulent by passing them through guinea-pigs, in some cases even at the first inoculation. They were also able to do this, for example, with the water strain Wa A from Amsterdam, though it could not be made virulent in the laboratory there. In Germany, ZUELZER also obtained positive results with the "Leiden" water strain by inoculating exceptionally large quantities of culture into the experimental animal in every possible way.

On the other hand, certain investigators were quite unable to alter the serological properties of water leptospiræ in any way, or to change them from saprophytic into pathogenic strains.

To this category belong the experiments of SARDJITO & ZUELZER himself, who failed to make their water strains virulent in Java, and those of KAGAYA, who tried various methods on all kinds of experimental animals, in conjunction with inadequate feeding, etc., but failed to obtain a virulent culture of water strains even after the seventy-two passages. The experiments of DIMITROV, VAN THIEL, GARDNER, SJOEIB PROEHOEMAN, KIRSCHNER and ZIMMERMAN were likewise unsuccessful.

Certain objections of a theoretical nature also exist. In the first place, if the variability of a strain is to be demonstrated, there must be no doubt that the guinea-pig has no latent infection which is activated by the injected leptospiræ; such spontaneous infections have been noted in Amsterdam (SJOEIB PROEHOEMAN). There is also the fact that the first strain described by UHLENHUTH & ZUELZER, which, according to them, changed into a pathogenic strain, reacted like a *L. icterohæmorrhagiæ*—that is, like a strain occurring in Europe. Another strain which had become pathogenic reacted, however, like the "Rachmat" strain, so it seemed, in Amsterdam. The latter is a pathogenic strain occurring in the Netherlands Indies which has never been found in Europe, though it was present in the laboratory where the modification of the water strain is stated to have taken place. This can only be explained through an unobserved infection with the Rachmat strain. Such a laboratory infection had already occurred previously in Amsterdam, when it was possible to observe how easily the Rachmat strain could be transmitted to other experimental animals under conditions of inadequate isolation.

Besides, water leptospiræ are present everywhere, whereas cases of leptospirosis only occur in certain districts.

Furthermore, it is difficult to see why the longer a strain is cultivated the more virulent it becomes. Our experience has been just the opposite. The constant sub-culturing of an originally virulent strain has the effect of reducing the virulence until the strain finally becomes entirely avirulent. No further culture passages can restore its virulence (see also ALSTON & BROWN). Furthermore, we never observed a change in the antigenic structure such as UHLENHUTH & ZUELZER report.

Finally, it may be wondered whether, in order to demonstrate the variability of the water leptospiræ, cultures from a single organism should not be used, particularly in cases where saprophytic and pathogenic leptospiræ may occur side by side in the same water.

Thus, although, given our knowledge of changes in *B. proteus* and vibrios, we cannot rule out the possibility of saprophytic water leptospiræ being able to change into pathogenic ones, the fact remains that such a change has not yet been demonstrated.

2. CLINICAL FEATURES OF LEPTOSPIROSIS ICTEROHÆMORRHAGICA

In 1886, when WEIL described the disease which has been named after him, he mentioned as the principal symptoms (after an acute onset with fever) jaundice, nephritis and swelling of the spleen. Though these symptoms had been known previously and it was realised that some of them, such as jaundice, might be absent, this description led many investigators to make a further detailed study of the disease and to differentiate it from other febrile diseases with jaundice.

In France, in particular, the division of the symptoms into various groups (syndromes) has shown the variable appearance which the disease may present.

A summary of the symptoms is given here, together with various details observed in cases investigated in the Netherlands. Some of the cases were bacteriologically and serologically examined at the Institute of Tropical Hygiene in Amsterdam.¹

¹ The Institute sends to doctors who forward blood or serum for examination a questionnaire on the clinical symptoms of the case. The present information is derived from their replies. We should like to take this opportunity to express our thanks to them for their help.

Incubation Period.

According to INADA, the incubation period was 5 to 7 days (on rare occasions as much as 13). Subsequently, opportunities occurred for determining its length in a number of cases in Europe, *inter alia* when laboratory workers contracted the disease by accident. The duration of the incubation period was ascertained in 56 of the serologically examined cases in Amsterdam (Table 3). The average proved to be 9.6 days, the most frequently recorded figure being 10. The duration was about the same in icteric and anicteric cases ; it was not appreciably shorter in fatal cases.

Table 3.—LENGTH OF PERIOD OF INCUBATION OF WEIL'S DISEASE

	Period of incubation in days														Mean Period of incuba- tion in days		
	4	5	6	7	8	9	10	11	12	13	14	15	16	17		18	19
(a) Total number of cases (56) ...	2	—	2	4	9	6	17	4	2	6	1	1	—	—	1	1	9.6
(b) Cases with jaundice (24) ..	1	—	1	3	4	4	4	1	1	3	—	—	—	—	1	1	9.9
(c) Cases without jaundice (36) ..	1	—	1	1	5	2	13	3	1	3	1	1	—	—	—	—	9.5
(d) Fatal cases (9).	—	—	1	1	2	2	—	1	1	1	—	—	—	—	—	—	9.2

CLINICAL SYMPTOMS

The course of the disease can be divided into several stages (INADA, MARTIN & PETTIT) :

1. The *first stage* is the *septicæmic*, during which the spirochetes circulate in the blood and are found in many internal organs (KANEKO & OKUDA).

The onset is usually acute with a high temperature, assuming the form of *febris continua* during the first few days, and accompanied by a sensation of severe illness.

Among the cases studied at the Institute for Tropical Hygiene, there were, however, some (including, indeed, one fatal case) in which the beginning of the disease was neither acute nor accompanied by severe symptoms.

The patient experiences a sense of fatigue, apathy and depression ; he may, however, feel restless ; in some cases, he becomes delirious (hence the former name of bilious typhoid : GRIESINGER, VLASSOPOULO).

In most cases, there is severe headache. The first symptoms are often vomiting and sometimes diarrhoea. Thirst and lack of appetite are common. The tongue is dry and thickly coated ; its tip or edges may be red, a characteristic of the disease ; erosions, necrosis and ulcers may even appear on the edge of the tongue and in the mucous membrane of the mouth. The whole face is often red and puffy. The tonsils are frequently red and swollen, causing difficulty in swallowing ; this, combined with the swollen lymph nodes in the neck, makes the whole picture suggest septic sore throat.¹ The disease is not infrequently diagnosed as bronchitis or pneumonia. One of the outstanding symptoms is severe muscular pains occurring spontaneously and especially when pressure is applied, particularly in the calves and thighs, but also in the back, neck, arms and legs. Among the Amsterdam patients, the symptom is recorded in 272 out of 319 cases. The conjunctivæ are injected. Even this symptom, though characteristic of Weil's disease, may not be present. Out of 234 patients in the Netherlands, 46 (= 19%) did not have the symptom. DAVIDSON did not observe it among his patients (19), though PETZETAKIS did.

BAERMANN & SMITS, and subsequently MULDER, gave a very detailed description of these conjunctivæ. They found that the vessels in the conjunctiva, bulbi and sclera were enlarged ; the swelling was greatest at the line of reflexion and decreased towards the cornea. The symptom may sometimes only be noticed when the eyelid is turned up, so that the line of reflexion can be seen. As the vessels of the sclera and the conjunctiva do not lie in one plane, this places them over one another so that two superimposed net-like layers can be seen. This, together with the lacklustre appearance and peculiar tint of the sclera (icteric, sub-icteric or almost untinged), gives a very characteristic picture. These characteristics of the cases of leptospirosis in Sumatra also apply without a doubt to leptospirosis icterohæmorrhagica in Europe. It is not conjunctivitis, though the latter may also be present.

¹ Owing to this symptom, it has sometimes been supposed that the tonsils might be the point of entry for the disease.

If severe headache and vomiting is accompanied by pains in the neck and Kernig's sign, the clinical picture may be one of meningitis as COSTA & TROISIÈRE first pointed out. This will be referred to later on.

The *kidney* symptoms are very important ; all gradations may be observed from a light febrile albuminuria (or not even that) to severe hæmorrhagic nephritis with anuria. In severe cases, chlorides and urea accumulate in the blood and may cause uremia, and subsequently coma and exitus letalis. The remarkable number of renal casts is sometimes a characteristic (MARTIN & PETTIT). The elimination of renal casts may continue for a long time during convalescence. Ambard's constant is considerably increased but soon becomes normal again in favourable cases. Urobilin is nearly always found in the urine, often in large quantities ; and, when jaundice is present, bilirubin. Hay's reaction may be positive even when no jaundice is present. FIESSINGER & LEROY also found biliary salts in the urine in cases without jaundice. Boiling with acetic acid sometimes produces a green colour, apparently due to the instability of the bile pigments which oxidise more easily than usual. This reaction, which has been described by PAGNIEZ, was also subsequently observed in the Netherlands, among others by CLEYNDERT & GOUDSMIT, HAMMER & WOLFF, and by ZAINAL in the Netherlands Indies. Edema is rare.

Of the Amsterdam patients, 41 out of 232 (17.5%) showed no symptoms of nephritis ; so far, at least, as can be ascertained from the data, which in some cases record only one examination of the urine. Nephritis occurs less frequently in cases without jaundice than in those with jaundice ; thus :

Of 123 cases with jaundice, 13, or 11%, showed no nephritis ;
Of 109 cases without jaundice, 29, or 25%, showed no nephritis.

Moreover, the nephritis was frequently more severe in icteric than in anicteric cases. This is also borne out by another symptom—namely, the presence of oliguria :

Out of 106 patients with jaundice, 38, or 35%, had oliguria (10 with anuria) ;
Of 34 patients who died, in this group, 29 had oliguria (10 with anuria) ;
Of 95 patients without jaundice, only 5 had oliguria = 5% (none with anuria).

These results are born out by the figures for the blood urea content ; thus :

In 19 fatal cases, the urea content was 2 to 6 grammes per litre ;

In 17 icteric cases (with a favourable issue), the content was 0.3 to 3.6 grammes per litre (the figure varying according to the day on which the patient was examined and the presence or absence of oliguria) ;

In 13 anicteric cases, the content was 1.3 gramme in 1 case only ; in the others it was less than 1 gramme per litre.

The urea content increased during the course of the disease, in a few cases even though diuresis was restored. It was wondered, therefore, whether the urea is entirely due to the reduced action of the kidney and whether it might not also be partly the result of increased disintegration of body proteins. Some cases also occurred in which diuresis again increased and the urea content fell, but the outcome was none the less fatal.

The above considerations indicate that the prognosis is often, though not always, dependent on the urea content of the blood, as GARNIER & GERBER have already shown.

In conclusion, reference may be made to a fact already recorded by MERKLEN & LIOUST—namely, that the retention of urea may precede the jaundice. This is an important point in diagnosis, and it may be added that DAVIDSON & SMITH emphasise as diagnostic signs : an acute onset of the disease with high temperature, muscular pains, nephritis, sudden increase of the blood urea without œdema or hypertension.

2. The *second stage* begins with the appearance of *jaundice*, and may be described as the *toxic stage*. The leptospiræ disappear from the blood, but agglutinins and lysins begin to appear in the serum.

JAUNDICE

Day of Inception of Jaundice.

According to INADA, jaundice appears in the middle of the first week. STRASBURGER gives from the 3rd to the 9th day inclusive, MARTIN & PETTIT from the 3rd to the 8th day. The day of inception of jaundice was determined in 132 cases recorded by the Institute of Tropical Hygiene.

	Day of inception of jaundice							
	Second	Third	Fourth	Fifth	Sixth	Seventh	Eighth	Ninth
Number of cases	1	17	27	35	26	12	8	3

It will be seen that here, too, jaundice usually appeared between the 3rd and the 6th day inclusive, most frequently on the 5th day.

A relapse caused jaundice to appear in one instance, and aggravated it in several others. In the case of one patient, the jaundice was described as intermittent, as it became intensified with each rise in temperature.

The intensity may vary between a light yellow colour of the scleræ and a dark orange spreading over the whole body. The latter is characteristic of Weil's disease, as MARTIN & PETTIT pointed out. The number of cases without jaundice is given for the various epidemics. The figures, particularly those for hospital cases, may be very divergent, and are difficult to compare owing to the different methods of collecting data. It is particularly evident from ROMIJN and KRAMER's cases (see table below) that, provided consideration is not limited exclusively to severe hospital cases, the percentage of cases with jaundice will not prove so very high.

	Number of cases	Number with jaundice	Percentage with jaundice
Ido, Wani	56	23	41
Stokes, Ryle, Tytler	100	60	60
Strasburger	26	23	88.5
Thurner	27	27	
Lorando	35	(12 marked, 13 subicteric)	71
Netherlands : Institute of Tropical Hygiene	342	205	60.7
Netherlands : Romijn (Dordrecht).	45	15	33
Netherlands : Kramer (Rotterdam)	73	28	38.3
Davidson, Campbell, Rae, Smith..	15	11	73.3

The following facts should be noticed in connection with the figures for the Institute of Tropical Hygiene (Table 4) :

Whilst the first cases recorded in the Netherlands were all icteric, once interest in the disease had been aroused, anicteric cases were detected in increasing numbers. It can, moreover, be seen from Table 4 that the proportion of cases without jaundice rises as the total number of cases grows larger—*e.g.*, in 1932, when an equal number of cases with and without jaundice were reported. Though the number of anicteric cases (and the total number) subsequently fell, more than half the cases in 1937 were anicteric. That year, however, owing to the great interest which was aroused among the medical profession, a number of cases of meningitis leptospirosa (anicteric) were also recorded in Amsterdam. It is this, in reality, which accounts for the apparently special characteristics of the disease at that time.

Table 4.—NUMBER OF CASES WITH AND WITHOUT JAUNDICE

Years	Total	Fatal cases	Jaundice	No jaundice	Unknown
1924	14	4	11	3	
1925					
1926	12	3	7	5	
1927	9	2	8	1	
1928	8	0	4	2	2
1929	13	2	6	1	6
1930	20	4	12	7	1
1931	18	2	10	6	2
1932	84	5	39	38	7
1933	55	4	30	22	3
1934	45	8	24	15	6
1935	26	1	19	6	1
1936	30	4	16	11	3
1937	40	5	19	20	1
Total	374	44	205	137	32

Though cases without jaundice have a favourable issue however severe the disease may be in the first stages, those with jaundice are generally more serious. Thus, in the Netherlands, only one fatal anicteric case has been reported, and even in this, death was due to a complication.

No evidence could be found at the Institute of Tropical Hygiene to show that certain symptoms of Weil's disease such as rash, iritis, etc., occurred only in association with jaundice as stated by STRASBURGER.

The Causes of Jaundice.

That the jaundice in Weil's disease is not merely due to a simple obstruction of the bile ducts is evident from the fact that the jaundice may be severe in cases where the fæces are not colourless, or that urine tests for bilirubin may occasionally prove negative, even when jaundice is present to a certain degree.

These facts show that the jaundice may also be hæmolytic in origin and this is confirmed by :

- (a) Pathological findings, and
- (b) The results of Hijmans van den Bergh's test.

A. Pathological Findings.

The occurrence of jaundice may be due to the following causes :

- (1) Degeneration of the liver ;
- (2) Mechanical causes ;
- (3) Increased hæmolysis.

Attention had already been drawn to the changes in the liver cells by BRULÉ & MOREAU (granular degeneration, vacuolation, pycnosis and caryolysis), which were confirmed by McNEE, who also described the occurrence of cells with two nuclei and mitotic figures. SNIJDERS, who compared the liver in cases of Weil's disease and yellow fever, even considers these mitotic figures to be very characteristic of leptospirosis icterohæmorrhagica, so characteristic, in fact, that, on the strength of the pathological liver findings, he diagnosed as "leptospirosis" the cases of some patients who had died a few years before. The diagnosis was confirmed by LEVADITI who by staining of the same liver sections showed the presence of leptospiræ.

That the mechanical causes must not be ignored was evident from cases in which inflammation of the bile ducts could be demonstrated (KRAMER), or where the bile, after passing through the liver, was prevented from discharging into the intestine owing to the

swelling of the liver cells or was discharged directly into the blood as the result of ruptured bile ducts (KOUWENAAR). KANEKO draws attention to another mechanical cause of jaundice—namely, the separation of the liver cells, owing to the loosening of the intercellular connective tissue. He noticed the bile had penetrated between the parenchymatous cells and had spread into the oedematous fluid around the small blood vessels. Erythrorrhesis has been described by various authors, including LEPEHNE, who observed it in the cells of the reticulo-endothelial system in the liver, spleen and lymph glands (see also KOUWENAAR and SNIJDERS). The latter has drawn special attention to the signs of very extensive disintegration of red corpuscles in the spleen.

B. *Hijmans van den Bergh's Reaction.*

A positive and direct H.v.d.B. reaction indicates hepatogenic bilirubin and a positive indirect reaction hematogenic bilirubin.

The information supplied to us concerning a number of patients yields the following findings :

Group	Number of patients	Direct H.v.d.B.	Indirect H.v.d.B.	Bilirubin in the urine	Urobilin in the urine
I. Jaundice	44	44 +	30 +, 14 unknown	44 +	44 +
II. Jaundice	6	5 +, 1 —	3 +, 3 unknown	6 —	6 +
III. No jaundice .	28	20 —, 8 slightly +	16 — or not increased 12 increased	22 — 1 traces 5 unknown	20 + 4 — 4 unknown

I. The direct reaction of this group, and, as far as could be determined, the indirect reaction also, was positive and quantitatively high. In some cases, there were two phases. Bilirubin and urobilin were present in the urine. In these cases, jaundice was hepatogenous and could be partly hematogenous as well.

II. The positive direct and indirect reactions (the latter were, however, few in number) show that jaundice was hematogenous and also partly hepatogenous in these cases. On one occasion, even the direct reaction failed to occur and the jaundice could be considered as exclusively hematogenous. In this group H.v.d.B.'s

test gave a more sensitive result than the urine test for bilirubin, for the latter was negative.

III. No jaundice and practically no bilirubin, but chiefly urobilin. The indirect H.v.d.B. test reaction in some cases slightly intensified, indicating blood disintegration products in the serum ; there even appeared (in 8 instances) to be traces of hepatogenous bilirubin in the blood. The H.v.d.B. reaction was thus an even more sensitive diagnostic sign than the jaundice itself.

These examples show that where jaundice is present the H.v.d.B. test may be a better indicator than the bilirubin reaction in the urine, apart from the fact that the first gives an indication of the origin of the jaundice. In cases where there was no jaundice and bilirubinuria was absent, the H.v.d.B. test sometimes showed that hæmolysis alone had increased or that the function of the liver was disturbed ; which could be a sign of developing jaundice, an important prognostic point.

The following changes in the *blood picture* are reported :

(1) A marked anæmia, which may even be considerable and last for a long time, is held to be characteristic of Weil's disease (RENAUX, GARNIER & REILLY, THÖRNER).

(2) Leucocytosis with an eosinophilia.

(3) A deviation towards the left as far as myelocytes (RENAUX, MARTIN & PETTIT, POSTMUS), which may also be described as typical of the disease. In the Netherlands, 2% to 2.5% of myelocytes or metamyelocytes have repeatedly been reported. Even myeloblasts (0.5% to 1%) have occasionally been observed. It would appear that the degree of deviation to the left does not depend on the severity of the case as marked deviation to the left also occurred in a mild case.

(4) Toxic changes in the leucocytes (toxic granules, Doehle's inclusions, vacuolisation).

(5) Retarded coagulation through the reduction or disappearance of contraction in the blood clots (PAGNIEZ) and a reduced number of blood platelets which would partly account for hæmorrhages. This reduction in the number of platelets is a characteristic symptom which may appear even if there is no apparent change in regard to

erythrocytes or leucocytes. This might be of importance for the diagnosis in the pre-icteric stage.

(6) GARNIER & REILLY and STRASBURGER found that the resistance of the erythrocytes to physiological saline solutions increased at first and in later stages decreased.

(7) Increased sedimentation rate. In our cases also, this symptom is constantly reported—*e.g.* :

Patient No. 335 :

Day of illness	Rate of sedimentation Millimetres	Day of illness	Rate of sedimentation Millimetres
12th	54	51st	47
23rd	67	58th	44
30th	90	65th	40
35th	109	72nd	28
44th	90		

The above figures show the length of time it may take before the rate of sedimentation is again normal.

Hæmorrhages are a further symptom at this stage. Their frequency and extent vary considerably in different epidemics.

In Japan, hæmorrhages were so numerous that the disease took its name from the symptom. They were also frequent in Egypt (VESSOPOULO) but were more rarely reported in European epidemics. In the Netherlands, they were absent in 32 out of 132 cases known to us (24 %). They were mainly nasal and often occurred at the very beginning of the disease ; skin hæmorrhages were also reported. Occasionally, there was sub-conjunctival—and more rarely intestinal—bleeding. Of the latter, there were 10 cases in some of which blood recognisable as such was eliminated, whilst, in others, the classical tarry discharge occurred. The nephritis frequently assumed an hæmorrhagic form ; macroscopic hæmaturia was rare (6 cases) and there was even less hæmorrhage in the stomach (1 case) ; in 5 cases, the sputum contained blood ; there was 1 case of hæmorrhage from herpes and 1 case of severe and prolonged bleeding from a finger wound made for the blood test. As was to be expected, serious hæmorrhage occurred chiefly in fatal cases. In fatal cases, death usually occurs during this period : INADA noted of 18 fatal cases, 16 terminated between the 8th and the 16th day ; while in Holland, of 40 patients who died, 36 died between the 8th and the 16th day.

Heart weakness and nephritis are conditions on which much depends in this second period. In unfavourable cases, oliguria may develop into complete retention, the urea content may increase and the patient may succumb with symptoms of uræmia. Even if diuresis increases, however, it is not always certain that the patient will make favourable progress ; as the evidence, 1 Dutch case and LISSNER's case in the Philippines, indicates. Notwithstanding improved urine secretion and a fall in the urea content of the blood, the patient may die with symptoms of a heart weakness or cholæmia. Owing to the latter, cases of Weil's disease were often diagnosed in the past as acute yellow atrophy of the liver.

If the disease does not take a fatal turn, then, other symptoms may appear, such as *iritis* or *iridocyclitis*, which may assume a very mild form, though some severe cases are known. GOEBEL first observed bilateral iridocyclitis in 1916. It also occurs in forms of leptospirosis other than icterohæmorrhagic (in Japan, in cases of "Hasamiyami" ; in Australia, etc.). Reports concerning the incidence of *iridocyclitis* vary a great deal ; the more it is looked for, however, the more it is found (VAN DRIEL). STRASBURGER observed it in 44% of the cases, including the very mild ones ; KAHANER & CORTI, in 3 cases out of 16. In the Netherlands, it was observed in 13 out of 128 patients, though all available means of detection were not brought to bear. This figure of 10% is therefore a minimum. Iritis occurred in the Netherlands in mild and severe cases, with and without jaundice (5 with, 12 without, thus more frequently without jaundice). It was unilateral or bilateral, was sometimes defined as slight and sometimes also as severe (iridocyclitis with hypertension, puncture contemplated) : a patient had already been nearly blind for fourteen days when removed to hospital. As far as can be ascertained, all cases of iritis were cured.

In some cases, the exact day of inception is recorded—viz., 16th, 22nd, 24th, 25th, 32nd, 36th and 42nd days and even later ; it is therefore late in appearing. This obviously leads to the supposition that iritis may be connected with a relapse. In the case of one patient, it was specially stated that the iritis was to be regarded as a symptom of relapse. In some instances, however, though iritis appeared, there was no question of a relapse.

Neuritis optica was also observed several times among patients in the Netherlands. ROMIJN found it at Dordrecht, in as many

as 3 out of his 45 cases, whereas it was seldom reported among the Amsterdam patients.

Should the leptospiræ themselves or their toxins be held responsible for the appearance of iritis? In some cases the former would seem probable, as, in a case of uveitis, HERTEL found leptospiræ in the anterior chamber of the eye, the uvea and the sheath of the optic nerve; furthermore, leptospiræ were even found in the body during a relapse (*e.g.*, in the cerebro-spinal fluid). Elective localisation of leptospiræ in the uvea is thus a possibility to be contemplated. The very mild iritis, which would appear to be more frequent than is indicated by our case records, suggests the affection may perhaps also be of toxic origin.

A rash was observed in a number of cases; it is sometimes described as having the appearance of measles or scarlet fever, at other times as resembling large patches or papulo-macules, occasionally as an erythema; it may be urticarial, in which case it is pruritic. It may also be hæmorrhagic.

This symptom was reported 23 times among our patients; including 17 times among the last 168 cases, which were systematically investigated on this point. It occurred both when jaundice was present and—even though seldom (4 cases)—when it was not. In 5 other cases, the rash was ascribed to the injection of serum a few days previously. In one or two instances, the day of inception was reported. In the Netherlands, the rash was found to appear between the 10th and the 30th day. STRASBURGER observed it in 36% of the cases, a much higher proportion than in the Netherlands. Nearly all his cases were icteric, however. NOLF & FIRKET, on the other hand, report a rash in 10% of their cases, usually on the 7th or 8th day, or on the 13th or 14th day, just before the relapse. In the Netherlands, however, half of the patients thus affected had no relapse.

Herpes is observed chiefly on the lips and nose. Its presence may be explained in the same way as in the case of malaria and other diseases—namely, the virus was previously in the body but unable, until the development of leptospirosis, to exert its nosogenic properties. The frequency of herpes varies in different epidemics.

INADA makes no reference to it; both THÖRNER and TROISIÈRE observed it in 25% of their cases. Of 365 cases examined in the Institute for Tropical Hygiene, 55, or 15%, had herpes. Of these, some (38 cases) also had jaundice, some (17 cases), had not.

The ratio of icteric to anicteric cases for the whole group being 205 to 137, the incidence of herpes may thus be regarded as higher among the former than among the latter. The figures should, however, be considered minimum values, since the absence of herpes is not expressly mentioned in every instance. Among 42 persons whose symptoms were for special reasons reported in great detail, there were 9 cases of herpes. If these figures are anything to go by, herpes occurs in nearly a fifth of the cases in the Netherlands.

The date of inception is rarely given ; where it is stated, it ranges from the 4th to the 9th day inclusive.

According to the earlier evidence available, *leptospiræ* begin to appear *in the urine* about the end of the second week ; in 17% of his cases, INADA found them as early as the 10th day (and claims indeed that, in these particular instances, they can be detected during the first few days). They occur so regularly that KORTHOFF was always able to obtain a culture by injecting the urine of the same patient into guinea-pigs daily from the 9th to the 16th day of sickness. We have little information as to the duration of leptospiruria. SLOT & VAN DEN WALLE recorded its persistence in one patient for five months, and in Australia it was observed after eleven months (JOHNSON). In most cases, leptospiruria would seem to disappear after a few weeks.

3. With the improvement of the general symptoms (decrease or disappearance of headaches, muscular pains, feeling of illness, etc.), the *third stage*, that of *convalescence*, begins. Blood pressure grows normal, oliguria, if it has occurred, comes to an end, and the patient passes large quantities of urine (" *crise urinaire* ") still containing much urea. Convalescence is often protracted by a *relapse*, usually after the second and at the beginning of the third week ; the relapse takes the form mainly of a recrudescence of temperature, which may be accompanied by the return of a few symptoms such as headache and muscular pains. The relapse may continue for a few days or longer. It may be followed by a long sub-febrile period, with occasional rises of temperature which give the temperature chart an undulating appearance (STRASBURGER).

Evidence concerning relapse rate is very conflicting.

INADA gives the rate as 28%. MARTIN & PETTIT consider that a relapse occurs fairly regularly, though sometimes only in the form

of a slight increase of temperature. TROISIER observed it in 70%. STRASBURGER in at least two-thirds of the icteric cases and THÖRNER in 70% to 75%.

In our records, the number of cases in which a relapse is recorded is 182 out of 342 patients (or 53%); the relapse occurred during the second week in 46, during the third week in 80, and during the fourth week in 18 cases, whilst in 4 others it occurred later; no information was available on this point in 34 cases. Of the cases relapsing during the second week, there were 8 in which another relapse occurred; of those relapsing in the third week, 11; and of those relapsing in the fourth week, 4.

Some patients even had 3 relapses; a few, 4. Relapses were at least as frequent in anicteric as in icteric cases; thus 137 anicteric produced 78 relapses (57%); and 205 icteric cases, 104 relapses (51%). These values are similar to those recorded in other spirochætal diseases such as syphilis and relapsing fever.

Relapses were not originally regarded as such by INADA, but rather as secondary infection, since the recurrence of the main symptoms (hyperæmia of the eye-balls, jaundice, hæmorrhages, etc.) was not observed and since leptospiræ were never found in the blood. What was observed was a rise of temperature, accompanied sometimes by headache and aggravation of the muscular pains.

Subsequently, however, COSTA & TROISIER cultivated the leptospira from cerebro-spinal fluid tapped during relapses (1916) and GARNIER, NICAUD and MAISLER (1931) succeeded similarly with a meningitis case. Though it is therefore possible that a relapse may be the effect of toxic influences, the leptospira itself may sometimes be the cause.

In the Netherlands, a recurrence of old (and sometimes even the appearance of new) symptoms forming part of the syndrome was frequently observed during relapses. Thus it was noticed in one instance that jaundice only occurred during this period. Other cases presented a recrudescence of jaundice which, in one patient, recurred at successive rises of temperature, thus suggesting intermittent jaundice. Other observed symptoms include skin hæmorrhage, urobilinuria, pancreatic signs, and psychoses.

One of the patients, who had a slight relapse on the 16th day, developed neuritis of the brachial nerve on the beginning of the 18th day. Another developed herpes during a relapse,

and a third iritis. Since both these affections may also occur without a relapse, it remains doubtful whether they were symptoms of the relapse, or mere coincidences.

After this, the patient definitely improves ; it usually takes some considerable time, however, before recovery is complete. Renal casts and traces of albumin in the urine may continue for several weeks. THÖRNER and RENAUX, among others, have drawn attention to the long persistence of anæmia, the blood picture containing leucocytes in the same proportion as lymphocytes, with an increase of monocytes and eosinophils. Headaches occasionally continue for a long time. Loss of hair, and even of the nails, are sometimes mentioned.

COMPLICATIONS WITH OTHER DISEASES

Apart from pneumonia or gastro-enteritis, which may occur immediately after a fall in the water and cannot be described as complications, various other diseases are known which may occur as genuine complications—for example, typhoid and paratyphoid fevers (GARNIER & REILLY, LEDOUX & RÉTEL, TROISIER, ERBER, etc.).

Cases in which infection with both diseases has occurred at the same moment are particularly noteworthy—*e.g.*, through a fall in the water. As the incubation period for leptospirosis is about 8 days and for typhoid fever 14, Weil's disease appears first and the typhoid symptoms a week later, then the roseola, etc.

INADA, IDO, HOKI, ITO & WANI already noticed, as a complication, purulent meningitis and other suppurative processes, which caused the death of two of their patients (1916). In other countries, too, it was repeatedly noticed how the skin lost its resistance to infection with cocci (*e.g.*, virulent furuncles).

Other microbes besides cocci may cause meningitis in the course of Weil's disease. Thus CLEYNDERT observed tuberculous meningitis as a complication in 1933, and, on another occasion, malaria.

MARTIN & PETTIT mention sub-acute leukæmia as a very rare complication.

Certain other affections are obviously caused by the leptospira itself. Two cases of acute endocarditis in which leptospira

were found (DRÄGERT, 1934) are an example. Myocarditis, which caused the death of a patient of MOLLARET & FERROIR (1935), must also be included in this category, as well as cases of neuritis and myelitis during Weil's disease. KLIENEBERGER observed neuritis as far back as 1918 ; it usually developed late in the disease and had a good prognosis.

Cases were also observed in the Netherlands—*e.g.*, neuritis of the brachial plexus (KRAMER), and of the axillary nerves (ERKELENS), polyneuritis (JOOSTEN). Myelitis may also occur, with consequent paralysis (HEGLER). LUYKE RÖSKOTT observed a case of progressive paralysis in the Netherlands Indies.

The slight anatomical changes that have been observed in the central and peripheral nervous system (KANeko & OKUDA, DRÄGERT, etc.) are quite in keeping with the occurrence of such symptoms.

Finally, parotitis has occasionally been observed in cases of leptospirosis [one case in the Netherlands and two in Lisbon (JORGE)]; it is difficult to decide whether parotitis is a complication due to another virus or a rare symptom of leptospirosis.

DIAGNOSIS

Though in typical cases the diagnosis may be fairly accurately determined from the clinical and epidemiological symptoms, it can hardly be regarded as completely reliable unless it is borne out by a laboratory examination. Though it may be possible in epidemics to recognise mild and atypical cases through their connection with the others, in sporadic cases such examination is essential. There are, in particular, certain syndromes such as mild influenza or serous meningitis which cannot be adequately differentiated, clinically, even by the most experienced doctor. As the immune bodies persist in the blood, it is still possible after many years to determine by serological test whether a person has had Weil's disease.

The clinical symptoms of diagnostic significance are :

1. Those of an acute infectious disease, acute onset, fever, headache, feeling of severe illness.

2. Typical muscular pains, occurring spontaneously and when pressure is applied; localised in the thighs, calves and back; also characteristic redness of the conjunctivæ.

3. Above all liver symptoms: Jaundice, bilirubinuria and severe urobilinuria; sometimes symptoms of cholæmia.

It has already been noted that where no jaundice is present the Hijmans van den Bergh test nevertheless occasionally shows an increased bilirubin content of the serum, by giving either a positive indirect or a weakly positive direct reaction, thus indicating, even in anicteric cases, an increased destruction of red blood corpuscles and participation of the liver in the morbid process.

4. Kidney symptoms.—While mild or severe nephritis is observed in many infectious diseases, it is characteristic of leptospirosis that symptoms of hæmorrhagic nephritis should be frequent and that, in severe cases, the urea content of the serum should be dangerously increased, without œdema and hypertension as a rule.

5. Low blood pressure with a weak and rapid pulse are also symptoms appearing during the first week, which should be noted for the diagnosis.

6. Marked deviation to the left of Arneth's formula is already apparent at the beginning of the disease, accompanied by a great decrease of blood platelets.

7. Leptospirosis should now always be borne in mind in cases progressing as a typical serous meningitis.

Sometimes all symptoms suggesting Weil's disease are absent. If the patient's medical history gives no clue (no swimming, dog or occupation bringing him into contact with rats), a laboratory investigation is the only means of revealing the true nature of the disease.

8. Epidemiological information (swimming, fishing, working in sewers, falling in the water, etc.) may clearly be of great importance. In the course of the last few years, evidence has come to light that dogs are a possible source of infection and therefore also deserve special attention.

Accurate diagnosis, whether at the time or retrospectively, is also of social importance. Thus if the disease is contracted during work, as in the case of sewer-men, fishermen, bath attendants, etc.,

it is regarded as an occupational accident and comes under the occupational accident compensation laws. In some countries—*e.g.*, in Australia, France, Japan, the Netherlands, Scotland and some districts in Germany (Hamburg)—the disease is compulsorily notifiable. In some districts in Japan, the disease even comes under the law on infectious diseases (TSURUMI).

PROGNOSIS

Many factors are important in establishing the prognosis, among them are :

1. The age of the patient.

It has already been noted that old age is a highly unfavourable factor (INADA, THÖRNER, JORGE, Amsterdam patients).

2. The presence or absence of jaundice. Cases without jaundice always progress favourably. In this connection, the Hijmans van den Bergh test is important, as it can demonstrate incipient jaundice.

3. The function of the heart.

4. Uræmia. It has been noted that complete anuria and a rapidly increasing urea content of the blood are unfavourable symptoms, though a high urea content need not always point to a fatal issue.

An increase in urine secretion and a fall of the urea content are favourable symptoms, though cholæmia and heart weakness may still cause death.

Though the prognosis may be favourable so far as the final outcome of the disease is concerned, the course of the disease may yet be severe. In some cases, the patient remains weak for months on end and frequently complains of headache, etc. Prolonged anæmia has repeatedly been observed. Cases involving a stay of two months or more in hospital are quite common in the Netherlands.

TREATMENT

Only a few indications on general and symptomatic therapy will be given ; for further information, the reader is referred to the various text-books.

Severe cases require appropriate nursing ; care of the skin and mouth is important. The diet must depend on the functioning of the liver and kidneys and must include much fluid. Frequently, physiological saline solution—and in the Netherlands even more frequently glucose solution (*e.g.*, 25%)—is injected intravenously, in order to promote diuresis. In some cases, insulin is added. The other methods for the treatment of uræmia (venesection, etc.) are also indicated.

With regard to medicinal therapy, the chief remedies are cardiac drugs and stimulants ; while sedatives are used where there is severe pain or great restlessness.

In cases with meningitis, lumbar puncture is frequently followed by alleviation of the headache, a fall in temperature, and general improvement.

Attempts have been made to reduce the excretion of leptospiræ in the urine by means of chemicals. Several experiments with urotropin and prontosil on dogs gave no definite result (Institute for Tropical Hygiene). A diet causing an acid reaction in the urine (ketogenic diet) may be recommended on theoretical grounds. We must point out, however, that we have found leptospiræ living in acid urine.

We have no experience of hydrocyanic acid.

According to THIRY (1930), gold thiosulphate administered to mice had a good effect on the elimination of leptospiræ. Both in the spontaneously contracted disease and after inoculation with *L. icterohæmorrhagiæ*, excretion ceased after three days. THIRY was of the opinion that this method should also be tried in human beings.

CHEMOTHERAPY

At an early date, needless to say, attempts were made to kill the leptospiræ in the body by specific substances, in particular arsphenamine (INADA, UHLENHUTH & FROMME, etc.), but without success. Furthermore, owing to the condition of the liver and the kidneys, great care must be exercised in the administration of such toxic substances (MARTIN & PETTIT). Numerous other preparations were shown by animal tests to be of little or no value in experimental leptospirosis. Bismuth preparations were the only exception.

SAZERAC and NAKAMURA first drew attention in 1927 to the beneficial effect of sodium bismuth tartrate, which is so little toxic that it is not injurious to guinea-pigs.

It impeded the development of the disease as soon as it had been applied, or promoted recovery. The guinea-pigs which survived had become immune.

UHLENHUTH & SEIFFERT drew attention to the beneficial effect obtained with other bismuth preparations, after numerous chemical substances (such as antimony, arsenic compounds, etc.) had been tried without result. They obtained good results with colloidal bismuth and even better results with a bismuth-yatrene A mixture. As far as we know, this has not yet been applied to human beings. Since necrosis may be produced, the substance must always be administered intravenously.

Whereas UHLENHUTH & SEIFFERT consider that the preparation does not act directly upon the leptospiræ but stimulates a defensive reaction against the infection, KRITSCHIEWSKI, basing his deductions, *inter alia*, on his experiments with *Sp. obermeieri* on mice (and those of UHLENHUTH with *L. icterohæmorrhagiæ*), takes the view that such a direct action is exerted. Although opinions still differ as to the way in which bismuth preparations act, animal experiments generally confirm their beneficial effect.

Sodium ricinoleate has so far only been tested *in vitro* by VIOLLE (1934); even in a solution of 1 : 1,000 and in albuminous fluids, it killed various forms of spirochætes, such as *Sp. recurrentis*, *Sp. gallinarum*, water spirochætes and *L. icterohæmorrhagiæ*. Its action in the animal organism is not yet known.

While it is true that, on the strength of animal experiments, good results may be expected from bismuth and possibly other chemotherapeutic agents (though nothing can, as yet, be said concerning their action on human beings), serological has reached a more advanced stage than chemical treatment, having been applied to human beings ever since the ætiology of the disease began to be known.

SERUM THERAPY

After a leptospira had been found to be the cause of infectious jaundice, protective substances against the disease were looked for

in the blood of convalescents. Experimental research on guinea-pigs then developed in all countries.

When the presence of immune bodies was demonstrated, convalescents' serum and immune serum prepared *ad hoc* were administered as curative agents. This was first accomplished in Japan, where INADA, IDO, HOKI, ITO & WANI began to inject the serum in August 1915, and published a report which appeared in October 1915. In 1916, a few publications on the subject followed in English. By that time, they had not only convalescent serum, but serum of immunised goats and horses, able to resist an inoculation of 800 c.c. of pure culture. The strength of the serum was assessed by the determination of the quantity necessary to protect the guinea-pig against a lethal dose of the infectious material.

I. *Preparation of the Curative Serum.*

In Europe, HUEBENER & REITER, and almost at the same time UHLENHUTH & FROMME, demonstrated the presence of immune bodies in the convalescent serum, and were able to protect a guinea-pig against infection with that serum.

By producing a high degree of immunity in rabbits, a serum with curative properties was obtained. In addition to this, UHLENHUTH & FROMME also had soon more than 25 convalescent sera. They showed, in a series of experiments, that the immune serum was effective until the sixth day. Soon, a number of firms in Germany were producing it.

In France, after the serum had acted satisfactorily on guinea-pigs, MARTIN & PETTIT prepared rabbit immune serum and a horse serum, which had a preventive and curative effect on guinea-pigs up to the third day. STOKES, RYLE & TYTLER also secured good results with convalescent serum in other animal experiments (1917).

Horses were also immunised by NICOLLE & LEBAILLY (1918), by Stanley GRIFFITH in England (where the serum may now be obtained from pharmacies), and in the United States (NOGUCHI), the Netherlands Indies and the Netherlands.

In the Netherlands, convalescent serum has been, and continues to be, administered. The State Serological Institute at Utrecht also made dog and goat serum available, but the most commonly used preparation is horse immune serum, which is supplied by the central laboratory at Utrecht and the State serum Institute at

Rotterdam. As this horse serum was prepared in collaboration with the Institute for Tropical Hygiene, a short account of the immunising of a horse and of the progress of the serological reaction may be given here.

The horse was immunised with two strains (*L. icterohæmorrhagiæ* and *L. canicola*), first with avirulent and then with virulent cultures. Apart from certain symptoms due to an intercurrent disease, the horse showed signs of a marked anaphylactic reaction (the cultures had been grown on a rabbit serum medium), from which it recovered.

The titre finally rose to 1 : 100,000 four months after immunisation against both strains was begun. At that time a considerable amount of blood was collected from the horse. Six months later, in September, the titre was 1 : 30,000 ; in December 1936, it was still 1 : 3,000. In May 1938, two and a half years after immunisation was begun, a few inoculations of *L. icterohæmorrhagiæ* and *L. canicola* culture again raised the titre against both to 1 : 100,000.

II. *Strength of the Immune Serum.*

At first, the strength of the immune serum was calculated on the amount necessary to enable a guinea-pig to resist a, normally, lethal dose of infectious material. In the case of leptospiræ, however, the method has its pitfalls. Just as there are difficulties in differentiating strains, so there are difficulties in determining the minimum lethal dose, owing to the pronounced variations in the virulence of the strains and the individual differences in the sensitivity of the guinea-pig. Nowadays, it is often considered sufficient to mention the agglutination and lysis titre. This does not, it is true, express the protective values, but it is assumed on good grounds that both values go together (ZIMMERMANN & ARJONA).

For curative purposes, the practitioner should, if possible, use a serum of high agglutinating and lytic titre. Our experience shows that this affords the highest probability of administering serum of real protective value.

III. *Results.*

Owing to the variety in cases during an epidemic and the differences between the epidemics themselves, it is very difficult to obtain an objective opinion of the value of serum therapy. Furthermore, one investigator may work among patients who are all, or nearly

all, jaundiced, while another may be dealing with an epidemic with a jaundice incidence of only 60% or even less, and, consequently, a higher proportion of mild cases.

The protective action of the immune sera used may, perhaps, also vary considerably, and the results may also depend to a great extent on the day on which the serum is administered (INADA, ZIMMERMANN & ARJONA). Furthermore, it is sometimes impossible to say at the beginning of the disease whether it will be mild or severe. Many patients are seriously ill for a few days and then improve rapidly, even without serum. If serum had been administered in these cases, the cure would probably have been ascribed to it. The reverse often happens. In Amsterdam, a few cases occurred in which the symptoms were slight and which yet proved fatal (KRAMER, Amsterdam patients).

In the circumstances, it is very difficult to compare the results obtained by different investigators, and it is understandable that opinions regarding the value of serum therapy should vary so widely.

The literature on the subject gives some information concerning the effect of serum therapy. This information is partly a matter of subjective impressions and partly based on objectively observed facts.

Thus, INADA, ITO, HOKI, IDO & WANI report that the serum appeared to reduce the mortality rate. A rate of 30.6% fell to 18.3% in the case of a group of 23 serum treated patients. The serum caused the leptospiræ to disappear from the blood stream at an earlier stage; this was demonstrated by inoculation to guinea-pigs. The development of immune bodies also appeared to be accelerated, though this could not be confirmed in Amsterdam. The serum was even more effective when it was injected intravenously. Given early, it had a beneficial effect on the symptoms, such as hæmorrhages, and reduced the duration of the disease. Relapses were not prevented, as appears from the data supplied by WILMAERS & RENAUX, as well as from Amsterdam. The dose required was large, 10 c.c. to 20 c.c. being inadequate. They recommended 60 c.c. spread over 5 or 6 hours, or 40 c.c. in one dose and 20 c.c. the next day.

Their results were in one respect confirmed by the investigation made by KANEKO & OKUDA into the dissemination of leptospiræ in the various organs of patients who had died of Weil's disease. They compared 8 cases with, and 4 cases without, serum treatment,

and found that, in the first 8 cases, leptospiræ did not occur in the internal organs as abundantly as in the other 4, or had even completely disappeared. The kidneys were an exception, the organisms were found in these in both groups.

Satisfactory results were also reported as a result of the treatment of 41 patients with Griffith's serum, the mortality rate being reduced. When the serum was given early, the disease took a mild form and its duration was reduced. The serum also had a beneficial effect on the hæmorrhages and on the heart.

RENAUX & WILMAERS were of opinion that the general condition of 6 patients was improved as a result of the serum. Their headache disappeared and the blood pressure became normal. The serum did not affect the elimination of leptospiræ, which began as usual on the fifteenth day. Relapses were not prevented.

NICAUD, HERSBACH, UHLENHUTH & ZIMMERMANN also reported a beneficial action of the serum. KLIENEBERGER, on the other hand, and GARNIER, who experimented on 13 patients, were less satisfied;¹ KRAMER, too, did not find the results entirely satisfactory.

The following results of serum treatment were obtained in the case of several patients who were serologically examined at the Institute of Tropical Hygiene :

Serum was given to 36 patients with jaundice, who recovered ; 5 with jaundice, who died ; and 7 without jaundice.

The days on which serum was given for the first time were :

	Day of first injection									
	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	?
Number of patients with jaundice				2	6	11	12	7	2	1
Number of patients without jaundice	1		1	1	1			1	1	1
Total number of patients (48)	1		1	3	7	11	12	8	3	2

¹ We do not know on which day the serum was given

In most cases, several injections were made ; in one, as many as five. The total quantity of serum was generally very large, usually more than 100 c.c. The smallest quantity was 20 c.c. and the largest 240 c.c.

Influence of the Serum on the Frequency of Relapses.

1. In order to gain some idea of the action of the serum, the percentage of relapses among the serum treated and untreated patients was compared, a distinction being made between icteric and non-icteric patients. Fatal cases were omitted.

Of 34 patients with jaundice who received serum, 24 had a relapse = 67%.

Of 34 with jaundice who did not receive serum, 15 had a relapse = 44%.

Of 7 without jaundice who were given serum, 6 had a relapse.

Of 64 without jaundice who were not given serum, 34 had a relapse = 53%.

If the patients who received serum at an early stage (1st, 3rd, 4th and 5th days) are excluded, then :

1 patient to whom serum was given on the 1st day had a relapse ;

1 patient to whom serum was given on the 3rd day had a relapse ;

Of 3 patients to whom serum was given on the 4th day, only 1 had a relapse ;

Of 7 patients to whom serum was given on the 5th day, 3 had a relapse and 4 did not (including 1 given serum on the 5th, 6th, 7th and 8th days).

The group which was given serum had, if anything, more relapses than the other group. Furthermore, the proportion of patients who had a relapse appears to be the same in icteric and non-icteric cases.

Duration of the Febrile Period with and without Serum Treatment.

2. The duration of the febrile period in both groups was compared as accurately as possible, including the first period with fever and also the number of days that elapsed before the final disappearance of fever.

The first febrile period was as follows :

	Days	Duration of the total febrile period Days
In 23 cases with jaundice which were treated with serum	8.1	34.1
In 14 cases with jaundice without serum treatment	8.3	34
In 6 cases without jaundice and with serum treatment	8	25
In 35 cases without jaundice and without serum treatment	8.8	23.4

There was therefore no significant reduction of fever as a result of serum treatment.

3. It was observed on several occasions that, after a serum injection had been made, the temperature dropped suddenly on the same day or on the day after. The question arises whether this was due to the serum. The drop sometimes followed so quickly on the injection, that the serum appears to have been the cause (see results given below).

Patient N°	Days on which jaundice appeared	Dayson which serum was injected	Day on which temperature dropped
124	5th	6th, 7th	6th
137	6th	7th, 8th, 9th	7th
182	4th	4th, 5th, 6th	5th
223	6th	7th, 8th,	9th
285	6th	6th, 7th	8th
306	5th	5th, 6th, 7th, 8th	6th
330	3rd	6th, 7th	7th
165	—	5th	5th

It cannot be said with any degree of certainty that the temperature decreases after and on account of the injection of serum, since it very frequently begins to return to normal from the 7th to the 9th day (the average duration of the first febrile period at Amsterdam was 8 days). It is also obvious from the following figures that care must be exercised in attributing the drop in temperature to the effect of the serum.

LEPTOSPIROSES

Number of patient	Day on which Jaundice appeared	Days on which serum was injected	Drop in temperature
312	7th	7th, 9th, 11th	5th
103	6th	No serum	10th
111	6th	No serum	8th
147	6th	No serum	8th
212	6th	No serum	8th

It will be seen that the sudden drop occurred in one case before the serum was injected, and there were four other cases of rapid defervescence in which no serum had been given. It is true, however, that in all four cases the drop did not occur until the 8th day or later, whereas it is remarkable that in the previous table six of the cases had a shorter febrile period.

Serum was also injected in a number of cases treated by the Institute of Tropical Hygiene, which proved fatal. In several of these, the serum was administered at an early stage (5th and 6th days) and, so far as could be observed, it did not seem to affect the temperature in any marked degree :

In one case (No. 275 ; serum given on the 5th and 6th days), the temperature declined on the 5th day, and rose again on the 6th day. In another (No. 259), the temperature being already normal on the 5th day, serum was given on the 5th and 6th days, and the temperature rose again on the 7th day.

Diuresis sometimes increased again a day or two after serum had been injected, but this took place at a stage at which the increase normally occurs if it occurs at all. Diuresis was furthermore ascribed by the attending physicians to intravenous glucose solutions injections, euphyllin, venesection, etc.

KRAMER reports a case which proved fatal, although serum was twice administered, and another fatal case in which serum had been injected on the 5th day.

Can it be said then that serum has no demonstrable beneficial effect ? The question can only be answered by those who inject the serum and watch their patients. RENAUX, who was also unable to prove the beneficial effect of serum objectively, noticed such an improvement in the general condition of the patient after injection that he did not feel justified in discontinuing serum treatment.

In the Netherlands, too, cases were observed in which the serum was injected at an early stage, and which left the doctor in no doubt

as to the beneficial effect of the serum treatment on the general subjective and objective condition of the patient.

In Amsterdam, the effect of the serum given at a very early stage was observed on one occasion in a case of laboratory injection.

On September 24th, 1931, at 9 o'clock in the morning, D.S. suddenly felt ill with rigors, vomiting, and severe pain in the calves, thighs, and loins. Within half an hour, her temperature had risen to 39.1°. An examination for malaria parasites in the blood gave negative results, but leptospiræ were found in the plasma. A week earlier, she had broken a test-tube containing a culture of virulent leptospiræ, and had made a slight cut in her finger.

The patient received her first injection of serum (50 c.c. horse serum) five hours after the onset of the disease. In the meantime, the temperature had risen to 40.2°, and the patient was severely ill. The effect of the serum treatment was remarkable; the temperature declined in the evening, and was normal on the following day. She felt well, but had no appetite, and a furry tongue.

The next day, September 26th, the patient's condition grew worse again, the temperature rising a little, and the subjective symptoms increasing, so that the case soon assumed the same appearance as at the onset. A second injection (50 c.c. of convalescent serum) was immediately given, and had a beneficial effect on the course of the disease. On the 5th and 6th days, the condition once more became acute. This time, the patient received 15 c.c., which was all that remained. Fortunately, this was enough to curb the disease completely, and from that day onwards the improvement was maintained, save for a slight relapse, which occurred on the 17th day (a rise in temperature, with subjective symptoms). It was noteworthy that everybody, including the patient, had the impression that the convalescent serum was even more effective than the horse serum.

Seldom does an opportunity occur to administer serum treatment at so early a stage; at a later stage, its effect is less striking.

UHLÉNHTH also records an improvement in subjective symptoms after administration of serum in a case of laboratory infection.

At the Institute of Tropical Hygiene, ESSEVELD investigated, the variation of the titre of serological reactions of patients suffering

from leptospirosis icterohæmorrhagica, noting the day on which the serum was administered, the day on which jaundice appeared, etc. He collected data on :

- 40 patients who had jaundice and had received serum ;
- 46 patients who had jaundice and had not received serum ;
- 58 patients who had not jaundice and had received no serum ;
- 7 patients who had not jaundice and had received serum.

In the upshot, there was found to be no appreciable difference in the strength of the reactions.

The group of seven serologically treated patients who had no jaundice call for the following remarks :

Two of them did not receive their first injection until the 8th and 9th day respectively—that is to say, at a time at which jaundice usually no longer appears. The position was otherwise with the remaining five cases. Of these, three were injected before the 4th day of sickness, one on the 4th day and one on the 5th. In these cases, therefore, jaundice might still have occurred.

Though it cannot be established from so small a number of cases that early serotherapy prevents the occurrence of jaundice, the evidence thus afforded is of sufficient importance to deserve attention, for it would be very strange if all five cases happened to have the mild anicteric form of the disease. These observations do suggest, therefore, that the serum has a very real effect upon one of the most important symptoms.

Although the evidence as a whole does not conclusively demonstrate that the serum exerts any specific action upon the pathogenic organism, it seems clear that it has a beneficial effect when administered within four days of the onset of the disease. RENAUX' conclusions may therefore be regarded as substantiated.

At what Time should the Serum be administered, and in what Quantity ?

Agreement may be said to exist on the following points : serum should be administered as early as possible, and in not too small quantities—for instance, 30 c.c. to 60 c.c., the dose to be repeated as necessary. These indications are based in the main upon animal tests and upon a number of very striking observations—such as these made by ourselves—on human beings.

Now it is known that the disease always takes a favourable course in anicteric cases, in which serotherapy might accordingly be dispensed with.

It will be difficult in practice, however, to determine whether a case of Weil's disease recognised at the very outset will become icteric or not. Furthermore, cases which begin with comparatively mild symptoms may take a turn for the worse. Although, in cases in which no jaundice is present, H.v.d.B.'s test may act as a danger signal, it is best, in any case, to administer serum as soon as the disease has been definitely diagnosed, even though it may not appear severe. Only in this way can the striking effect of the serum be made evident and the grave disappointment of failure through belated action be avoided.

Serum Prophylaxis.

The question whether serum should be administered for preventive purposes comes up occasionally—for example, when a person incurs the risk of a leptospiral infection through falling in the water. That the serum also exerts a beneficial prophylactic action has been shown in animal experiments by various research workers (*e.g.*, & NOGUCHI, MARTIN & PETTIT, ZIMMERMANN). The use of serum as a prophylactic does not appear necessary in human cases, however. The most heavily infected water in the Netherlands is that found in the Amsterdam canals, and even there only 1 in 75 persons falling in contracts the disease. Moreover, all such persons are kept under observation. If, after 8 or 9 days any one of them has attacks of cold shivering followed by a high temperature and a sensation of severe illness, the serum will be immediately administered and at such an early stage that good results may be expected.

The same applies to accidental laboratory infections, in which the risk of infection is even greater. In such cases, too, it is better to postpone the use of serum and observe the patient, rather than to administer the serum at once.

3. CLINICAL FORMS OF LEPTOSPIROSIS IN MAN

A. Meningitis leptospirosa

In 1916, COSTA & TROISIER drew attention to a meningitic form of leptospirosis icterohæmorrhagica existing side by side with the classical icteric form of the disease. Not only were they able to show that a number of cases among those recognised as leptospirosis presented meningitic symptoms, but also that a few of the acute cases of meningitis of unknown origin, without jaundice, were caused by *L. icterohæmorrhagiæ*. They named this form of the disease "spirochétose méningée pure". Various cases in France were described by BLOCH, HÉBERT, GARNIER, NICAUD, MAISLER, etc. In 1935, twenty such cases were already known, seven of which were slightly icteric.

Distribution of Meningitis Leptospirosa.

The presence of the meningitic syndrome was confirmed in other countries—*e.g.*, in Greece, the Netherlands Indies, the Netherlands, Portugal, CochinChina, Tonking, Scotland (1934), the Argentine, Germany and Sweden, though the cases were by no means all "spirochétose méningée pure". In some (*e.g.*, in the Netherlands Indies), the syndrome was probably not caused by the classical strain (*L. icterohæmorrhagiæ*) but by another leptospira. This has certainly been the case on several occasions in the Netherlands, particularly where *L. canicola* infection was concerned.

In the Netherlands, now that attention has been attracted to the disease, more and more cases are being discovered, as is evident from Table 5. Of 129 cases without jaundice, there were 20 of pure meningitis. In the last two years, among 25 anicteric cases, there were as many as 8 with meningitis. A fairly high proportion had only slight or indistinct meningeal symptoms. The chances that the meningeal form of the disease will occur in cases without jaundice are therefore considerable.

LAVERGNE & ACOYER have stated that in France, too, the incidence of pure meningitis was comparatively high, in 1935.

Table 6.—NUMBER OF CASES OF LEPTOSPIROSIS ICTEROHÆMORRHAGIÆ BACTERIOLOGICALLY EXAMINED IN THE INSTITUTE OF TROPICAL HYGIENE, AND NUMBER WITH MENINGITIC SYMPTOMS

	Number of cases of leptospirosis examined	Number of cases in which the presence or absence of jaundice is recorded	With jaundice				Without jaundice			
			Number	Number with meningitic symptoms	Of these		Number	Number with meningitic symptoms	Of these	
					Marked meningitis	Slight or indistinct meningitis			Marked meningitis	Slight or indistinct meningitis
Up to the end of 1935 ...	304	274	170	8	5	3	104	17	12	5
In 1936 and 1937	61	53	28	2	0	2	25	13	8	5
	365	327	198	10	5	5	129	30	20	10

They considered this to be a special epidemic phenomenon, on the ground that the total number of infections with *L. icterohæmorrhagiæ* was probably no greater than in other years and the cases of meningitis appeared to be concentrated in several districts. We are, in the Netherlands, inclined to regard the discovery of so many cases last year as evidence of the special interest which some doctors have taken in the disease.

It is remarkable, and at the same time characteristic of the typical meningeal form, that in some cases there is nothing to suggest Weil's disease, and a bacteriological examination for leptospirosis is requested only because of a previous fall in the water, or because the patient is a regular swimmer. Even then the positive result may come as a complete surprise. Formerly, such cases were often diagnosed as *meningitis serosa*, from which they are clinically difficult to distinguish. The way the diagnosis has developed, as is apparent in our own country, may briefly be stated as follows : meningitis was first found to be a symptom of leptospirosis, and leptospirosis was then found to be a cause of meningitis.

Ætiology of Meningitis Leptospirosa.

The cases of infection reported in France in 1935 were caused by bathing (LAVERGNE & ACOYER). Infection in the Netherlands was due to the following causes :

- 4 cases were due to a fall into the water ;
- 26 cases were due to swimming ;
- 5 cases were due to the person's occupation, which either brought him into contact with water (fisherman, seaman, etc.) or with rats (agricultural labourer, etc.) ;
- 4 cases were due to a dog ;
- In 1 case, the cause was unknown.

As will be seen from the above figures, the number of infections caused by the canine *L. canicola* strain is relatively large. Only 12 cases of infection caused by the strain were observed in the Netherlands. It is impossible to say as yet whether this is a mere coincidence or whether the canicola strain really has a greater tendency to cause a meningitic syndrome.

Sex and Age of the Patients.

Meningitis patients comprised 28 men, 9 women and 3 whose sex is not recorded. As in France, they were mostly young people, though not all very young.

- 2 were under 10 years of age ;
- 23 were from 10 to 20 years of age (11 were not over 15) ;
- 6 were from 20 to 30 years of age ;
- 6 were from 30 to 40 years of age ;

Clinical Symptoms of Meningitis Leptospirosa.

The actual meningitic syndrome (stiffness of the neck, Kernig's sign, Brudzinsky's sign, hyperæsthesia of the skin, vasomotor disturbances, changes in the tendon reflexes, headache, vomiting, etc.) can, as TROISIER pointed out, vary greatly in intensity and may hence be more or less conspicuous. Occasionally, every suggestion of leptospirosis is absent, even episcleral injection or muscular pains.

TROISIER also described various forms in which the disease is present though other symptoms are very prominent—*e.g.*, the meningo-subicteric form, meningo-renal form, etc. As regards the nature and frequency of the other symptoms, the Netherlands case records tally on the whole with TROISIER's descriptions.

When such Weil symptoms occur, the line of demarcation between meningitis leptospirosa and the classical Weil's disease is not always sharply defined. On the other hand, meningitis, though "pure", may be so slight (*e.g.*, ephemeral meningism) that a diagnosis of meningitis would be an over statement. At the same time, there are undoubtedly a number of cases in which the disease presents such a typical meningitic appearance, at any rate for several days, that it may, for example, be confused with tuberculous meningitis.

Cerebro-spinal Fluid in Cases of Meningitis Leptospirosa.

According to TROISIER, the cerebro-spinal fluid is usually under increased pressure ; it is nearly always clear and gives a weak positive albumin reaction, while the number of cells is increased. The number of cells depends on the duration of the disease ; hardly any

Table 6.—CEREBRO-SPINAL FLUID IN LEPTOSPIROSIS CASES WITH AND WITHOUT MENINGITIS

Part (a)

Number of patient	Meningitis	Jaundice	Day of disease	Pressure	Clearness and colour	Nonne test	Pandy test	Sugar content in milligrammes (%)	Number of cells	Polymorph. or mononuclear	Leptospiræ in C.-S.F. (animal inoculation)
327 ...	+	—	7th	250		±	+	74	30 /3	Mostly polymorph.	—
347 ...	+	—	7th	180	Very light, cloudy	+	+	36	99 per cub. mm.	polymorph.	
378 ...	+	—	7th	150	Rather cloudy, and grey	+	6.5	62	3,200 /3		
377 ...	+	—	7th	180	Clear	—	6.5	60	560 /3	40 % lymphocytes	
338 ...	±	—	7th	100	Clear and colourless	±	±	68	A few	80 % lymphocytes	
354 ...	+	—	4th	180	Clear	±	+	++	2 /3		
360 ...	±	—	4th			Normal			Normal	80 % lymphocytes	
361 ...	+	—	7th	Slightly raised	Gossamer	—	6.5	63	2,800 /3		
351 ...	+	—	5th	150	Clear	—	—	71			
294 ...	+	—	5th	Raised	Clear	±					
201 ...	+	—	4th	Raised		±					
207 ...	+	—	6th	Raised		±					
256 ...	+	—	14th	Raised	Clear	—	—	375			
282 ...	+	—	12th								
142 ...	+	—	5th		Clear		+		2 /3		
			7th		Cloudy		+		1,000 /3		
			10th		Less cloudy		+				
			12th				+		30 /3		
370 ...	+	—	7th		Clear	+	4	45	175 /3	50 % polymorph.	
168 ...	+	±	5th			±			6	Many epithel. cells. 70 % lymphoc. 30 % polymorph.	
133 ...	+	±	6th			±		Increased	Increased		

Part (b)

379 ...	—	+	7th			+	6.5	69	264 /3	38 % polymorph.	—
371 ...	—	+	7th	Normal	Yellow	+	6.5		27 /3	polymorph.	
330 ...	—	+	12th								+
355 ...	—	+	7th			+	6.5	63	103 /3	60 % polymorph.	
369 ...	—	+	9th	Normal		+	6.5	68	586 /3	90 % polymorph.	—
328 ...	—	+	6th			±	±		30 /3		
346 ...	—	+	Unknown		Deep yellow	+			No abnormal cells		
357 ...	—	+	8th			+	6.5		70 /3		+

cells can be noticed during the first four days, but from the 5th day onwards the number increases up to an average of 200 to 300 per cubic millimetre ; from the 15th day onwards, the number declines to less than 75, sometimes increasing again if a relapse occurs. There are also large daily variations in the differential blood-count. During the first few days, polymorphonuclears are frequently found ; lymphocytes, which as a rule only become prominent after a few days, are sometimes present from the onset (at least mononuclear cells). The chloride content is lower, while the glucose content is sometimes slightly increased. KRAMER suggested that the latter symptom was not necessarily connected with meningitis but might sometimes indicate that the pancreas was concerned in the morbid process.

We obtained details of the condition of the cerebro-spinal fluid collected by means of lumbar puncture from 18 patients in the Netherlands. The results generally corresponded with those of TROISIER (see Table 6(a)).

In this case, too, the fluid was occasionally cloudy, a fact also reported by LAIGNEL-LAVASTINE & BOQUIEN.

In two cases (351 and 260), there was no change at the onset of the disease —*i.e.*, at the stage when the number of cells has not yet necessarily increased. Nevertheless, the meningitic symptoms were already very distinct at that stage.

Cerebro-spinal Fluid in the Classical Form of the Disease.

Equally remarkable is the result of an examination of the cerebro-spinal fluid of patients suffering from the classical form of leptospirosis with jaundice and hæmorrhages but without meningeal symptoms, in which a positive albumin reaction and an increased number of cells are nevertheless found in the cerebro-spinal fluid (Table 6(b)).

COSTA & TROISIER are of opinion that the deviations in the cerebro-spinal fluid are nearly always present. GARNIER and REILLY observed them in 11 severe and moderately severe cases of *Leptospirosis icterohæmorrhagica*, of which only 1 had meningeal symptoms. The albumin and cytological reactions did not differ from those in cases of meningitis ; the only difference was the frequent absence of hypertension in classical Weil cases.

CUSHING also described a case with jaundice and hæmorrhages without typical meningeal symptoms, in which the cerebro-spinal fluid gave a positive albumin reaction and contained an increased number of cells. MINKENHOF observed changes in the albumin and sugar contents and in the cell count of 7 out of 8 patients suffering from the classical form of *Leptospirosis icterohæmorrhagica*, changes which were at least as marked as in the cases with meningitis (see Table 6(b)).

It remains to be seen how inflammation products such as albumin and cells can be present in the cerebro-spinal fluid in cases without meningitic symptoms.

It is possible that certain chemical substances produce such a reaction in the cerebro-spinal fluid. Thus, albumin and cytological reactions may be observed in cases of uræmia (DEMME), of acute and chronic nephritis, and after injections of serum or biliary acid salts (GARNIER & REILLY) into the spinal cavity, without the presence of meningeal symptoms. It does not appear that clinical meningitis caused simply by the presence of the leptospiræ in the meninges, as leptospiræ can be cultivated in both meningitic and non-meningitic cases (COSTA & TROISIER, GARNIER & REILLY, MANINE, CRISTAU & PLAZY, OKUDA, CUSHING, Institut of Tropical Hygiene). It is not clear, therefore, why meningitic symptoms should be present in one case and not in another. According to TROISIER, the cerebro-spinal fluid remains infectious for a longer time than the blood; he attributes this to the fact that only minute quantities of immune bodies are present in the fluid. He even succeeded in obtaining cultures from the fluid during relapses. An examination of the fluid, particularly in the later stages of the disease, thus increases the chances of detecting leptospiræ.

On two occasions in Amsterdam, the leptospira strain was isolated from the cerebro-spinal fluid when it could not be obtained from the blood (see Table 7—*e.g.*, 294 and 357). In contrast with TROISIER's findings, however, cultures were obtained more often from the blood than from the cerebro-spinal fluid (354, 360, 330).

Agglutination-lysis Test of the Cerebro-spinal Fluid.

In the Netherlands, at all events, the number of cerebro-spinal fluids tested is limited, for lumbar puncture is not performed without

good reason. The agglutination-lysis test was performed as on blood serum. Table 8 shows that none of the tests gave a positive result, whereas the blood serum gave a clear result in more than half the cases. The last case is particularly remarkable, the blood having a titre of 1 : 3,000 on the 23rd day, while

Table 7.—LEPTOSPIRÆ IN BLOOD AND CEREBRO-SPINAL FLUID IN CASES WITH AND WITHOUT MENINGITIS

Patient number	Day of disease	Strain from blood	Strain from cerebro-spinal fluid	Menin- gitis	Jaundice
294	5th	—	+	+	—
338	7th	—	—	+	—
354	4th	+	—	+	—
361	7th	—	—	+	—
370	7th	Not taken	—	+	—
377	4th	+	—	+	—
378	23rd (relapse)	—	—	+	—
360	4th	4	—	—	—
330	5th	+	—	—	+
355	7th	+	+	—	+
357	8th	—	+	—	+
369	9th	—	—	—	+
371	7th	—	8	—	+
379	5th	+	7	—	+

the cerebro-spinal fluid remained negative. Other investigators have occasionally observed a reaction in the fluid. Thus, TROISIER & BOQUIEN found the values of 1 : 3,000 with the blood and 1 : 200 with the cerebro-spinal fluid in a case of *Leptospirosis icterohæmorrhagica*. MOLLARET & FERROIR recorded values of 1 : 10,000 with the blood and 1 : 100 with the cerebro-spinal fluid.

Agglutination-lysis Test of the Serum.

Apart from the clinical symptoms, the diagnosis is always based either on the serological reaction coupled with the cultivation of the

leptospira or on the agglutination-lysis test alone. In the latter case, the test is always repeated several times, in order to confirm increase of titre without which the diagnosis cannot be established.

Table 3.—AGGLUTINATION-LYSIS REACTION IN CASES WITH AND WITHOUT MENINGITIS.

Number of patient	Day of disease	Se- rum ¹	Cerebro- spinal fluid ²	Day of disease	Se- rum	Meningitis
354.....	4th	0	0	14th	1,000	+
360.....	4th	0	0	14th	1,000	+
355.....	7th	0	0	14th	1,000	—
361.....	7th	0	0	14th	1,000	+
377.....	7th	Trace	0	13th	300	+
379.....	7th	10	0	55th	3,000	— Strain cultivated from blood
357.....	8th	10	0	14th	1,000	—
371.....	8th	100	0	64th	10,000	— fatal case
369.....	9th	100	0	17th	3,000	— fatal case
338.....	7th	300	0	23rd	30,000	+
378.....	23rd	1,000	0	87th	3,000	+

¹ First dilution 1 : 10. The strength of the reaction is expressed as the reciprocal of the dilution.

² Undiluted.

Lumbar Puncture.

In the interests of the patient, lumbar puncture should be used as little as possible. It may, however, be therapeutically and diagnostically indicated ; therapeutically, because the patient's condition is often found to improve rapidly after the puncture has been performed ; headache decreases, the temperature goes down and the meningeal symptoms are alleviated.

As regards its diagnostic use, lumbar puncture is nowadays performed in all suspicious cases of meningitis, for the purpose of detecting tuberculous or serous meningitis, and the like. One advantage of lumbar puncture is that the leptospira can sometimes be isolated in this way, while the blood remains negative. By the time, however, the pathogenic agent can be identified in this manner, it should already have been possible to make a diagnosis on the strength of the serological reaction and clinical symptoms.

Meningitis Leptospirosa with "L. Canicola" Infection.

In the Netherlands, 4 cases of meningitis leptospirosa were recorded among 12 patients, presenting a *L. canicola* infection. Two of the patients were young women whose symptoms, together with the previous medical history, suggested meningitis tuberculosa. In both cases, a dog in the house was responsible and cultures of *L. canicola* were obtained from the urine both of the patients and of the dogs.

The third case concerned a man who had contracted severe meningitis without any obvious cause, such as swimming, etc. After a fortnight, a serious relapse occurred with the recurrence—after complete disappearance—of severe meningeal symptoms. The serological reaction pointed to *L. canicola*, and the strain cultivated from the urine proved to be a genuine canicola.

The fourth patient, who was only diagnosed serologically, owned a dog which exhibited some symptoms of disease. When the patient's seroreaction pointed to *L. canicola*, the dog's blood was also examined and gave a positive canicola reaction.

Pathological Alterations in the Meninges.

Little is known of the pathological alterations in the meninges in cases of pure leptospiral meningitis, as this form of the disease is not fatal.

A few data concerning the other form of the disease may, however, be of value. KANEKO & OKUDA describe the presence of leptospiræ in the spinal meninges, and less frequently in the tissue of the central and peripheral nervous system, in the white matter, the grey matter and in the neuroglia.

DRÄGERT noticed small infiltrations of round cells in the spinal ganglia and peripheral nerves of 6 cases of Weil's disease, and BINGEL noticed slight changes, such as ependymal granulations and meningeal infiltrations with macrophages in a case with marked meningism.

Experimental Meningitis Leptospirosa.

According to TROISIÈRE, it is very easy to produce acute meningitis in the guinea-pig by injecting 0.2 to 0.3 c.c. of a moderately virulent

culture under the *dura mater*. The diagnosis is, however, not established clinically, but chiefly by microscopy of the meninges (infiltration of mononuclear and polynuclear cells under the arachnoid membrane). *Leptospiræ* are present, sometimes in clumps, between the cells, particularly the perivascular cellinterstices. They are not present, however, in the cerebral parenchyma. TROISIER was also able to produce this anatomical picture in young rabbits, accompanied by a few clinical symptoms (cramp), while in the case of dogs and monkeys the clinical symptoms were less characteristic. Microscopic examination of the meninges revealed inflammation, however.

Terminology.

The question also arises whether it is justifiable to speak of a "leptospirose méningée pure", an expression suggesting a form of the disease in which the leptospiræ are localised, chiefly, if not exclusively, in the meninges, and absent from the rest of the body.

From the standpoint of bacteriology and serology, this term is open to objection, since the leptospiræ may be cultivated from the blood and, when the disease has lasted somewhat longer, from the urine. Furthermore, leptospiræ may also be shown to be present in the cerebro-spinal fluid of patients suffering from the non-meningeal form of the disease.

The agglutinins and the lysins appear sooner and attain a much higher titre in the blood than in the meningeal fluid, even in this form of the disease a fact which MOLLARET & ERBER quote as proof of the oneness of all these syndromes, whether they be with or without meningitis. Guinea-pigs successfully infected with the meningeal fluid of a patient suffering from meningitis die of the classical form of the disease. These leptospiræ are therefore as virulent as those which cause the classical form of Weil's disease. In both forms, the meninges are impervious to fuchsin. It is also improbable that the meninges of certain persons are specially sensitive, were it the case it would be difficult to understand why cases of meningitis should occur in large numbers in certain epidemics (LAVERGNE).

Nor has it been proved that we are concerned here with a leptospira having some special neurotropism.¹ We are, however,

¹ PETTIT & MOLLARET consider that neurotropism occurs but very seldom, if ever, whereas meningotropism occurs regularly. As we have only seen a

concerned with a form of disease which differs so much from what Weil's disease is supposed to be, that the doctor in charge is apt to diagnose it as acute meningitis ; and is only induced to ask for a serological test for Weil's disease, because the patient went swimming before he fell ill, or because of the occurrence of episcleral injection. We think, however, that " meningitis leptospirosa " is the appropriate name for this disease, by analogy with meningitis tuberculosa, pneumococcus meningitis, etc.

B. " Mud fever "
due to *Leptospira Grippytyphosa*

In some flooded districts there have been epidemics of a non-fatal disease, known as " summer influenza " (GLASER), " mud fever " or " water fever " (BASCHENIN), etc. It occurs among harvesters during floods, when they are forced to work while standing in the water. Such epidemics were reported, *inter alia*, in Bavaria (1926), Brandenburg, Saxony, Silesia (for example, in 1891)—that is, in the regions of the Danube, Elbe and Oder which are liable to floods (PRAUSNITZ & LUBINSKY, BRILL, KATHE, RIMPAU)—as well as in Russia, particularly in the province of Moscow, where it was specially investigated in 1927, 1928 and 1929 (BASCHENIN, EPSTEIN & TARASSOFF). It was also described in riverside military camps (SEMENENKO and BRILL). It is also known as " harvest fever " (RIMPAU) and is not necessarily connected with flooded districts. It has been supposed that some decomposition products of manure, such as protein derivatives and H₂S promote the growth of the micro-organisms which, as will be explained, are considered to be the cause of some, at any rate, of these diseases.

The outbreak of an epidemic may depend on the degree of immunity possessed by the population at that moment, and on the time of the year during which the floods occur. Thus, if the population

report of their article, we are unable to discover whether they mean that the meninges are affected in all cases of leptospirosis, which would be in entire agreement with the evidence set forth above concerning the presence of leptospiræ and inflammation products in the cerebro-spinal fluid in meningeal and non-meningeal forms alike.

retains a certain degree of immunity from a former epidemic, or if the harvest has been brought in when the land becomes flooded, no epidemic will break out. There are, of course, sporadic cases from time to time. It is also not impossible that some epidemics may be in fact simultaneous outbreaks of several different diseases (*e.g.*, the epidemic described by KATHE). It has often been suspected that some connection with *Leptospirosis icterohæmorrhagica* existed, but, up till now, no transmitter has been found.

CLINICAL SYMPTOMS OF MUD FEVER

The onset of the disease is acute, after an incubation period of a minimum of one or two, and a maximum of ten days (PRAUSNITZ & LUBINSKY), with fever, headache, muscular pains, injection of the conjunctiva, mild and transient kidney symptoms, sometimes a rash or herpes, frequent relapses, vomiting, other intestinal symptoms, stomach pains and swelling of the lymph glands. The patient's condition sometimes becomes serious, with somnolence and delirium. The blood picture shows a left deviation with degenerative changes in the leucocytes (MURATOWA & JABLOKOV). Most investigators observed no jaundice, or practically none (PRAUSNITZ, LUBINSKY, BASCHENIN & TARASSOFF). One important point is that, according to nearly all investigators, the disease is not fatal, for, in the two fatal cases mentioned by KATHE, the clinical symptoms and the pathological findings suggest the classical form of Weil's disease. (The organism isolated and grown in culture was presumably *L. icterohæmorrhagiæ*.) Some epidemics are mistaken for influenza.

ÆTIOLOGICAL AGENT OF MUD FEVER

In 1926, PRAUSNITZ & LUBINSKY found spirochætes in the serum and blood cultures of two patients, in Constantinowa. Further cultures and subcultures remained negative and could not be transmitted to experimental animals.

Though these two investigators thus certainly isolated spirochætes from patients, they were unable to prove that these were the cause

of the disease, and that they were a separate strain and not, for example, *L. icterohæmorrhagiæ*.

In the 1928 epidemic in Stromyn, TARASSOFF was able to obtain cultures of leptospiræ from three patients and subsequently from 8 out of 15 patients in Constantinowa. They were of the so-called Weil leptospira type, but from an examination of the strain and from the clinical symptoms of the disease and serological tests, for which he also used *L. hebdomadis*, *L. autumnalis* A and B, and *L. icterohæmorrhagiæ*, he realised that he was dealing with a separate, independent strain. Its virulence for man was thoroughly established by a laboratory infection, which caused the same clinical symptoms as in the epidemic. He named the new strain *L. grippotyphosa*.

In 1937, an infection with *L. grippotyphosa* was also identified in Bavaria by serological tests performed on patients suffering from harvest fever (RIMPAU).

Finally, KORTHOFF was even able to prove that *L. grippotyphosa* could cause a disease in men resembling mud fever in a region where this never occurs—namely, the Netherlands. He injected 0.3-1 c.c. of a culture of *L. grippotyphosa* into eleven chronic but strong patients, in order to secure a marked rise of temperature for a while, and presented the same symptoms as in the natural disease. All developed a positive serological titre of 1 : 3,200-1 : 24,000 against *L. grippotyphosa*. During the period of incubation and up to the 4th day of the disease, KORTHOFF was able to recover and culture the strain from the blood.

CLASSIFICATION OF *L. grippotyphosa*

In 1929, a culture of *L. grippotyphosa* (Moscow V), isolated by TERSKICH, was received in Amsterdam from KRICHEVSKI, and, in 1937, the strain Moscow VIII was received from SCHLOSSBERGER. From Table 9, which shows the reactions with various sera of these strains, as well as these of the strain Andaman B,¹ it is clear that *L. grippotyphosa* occupies a special place of its own.

¹ The Andaman B strain is included in the grippotyphosa group on account of its serological reactions.

Not many paraspecific reactions occur, apart from a few very low ones of 10, except in the case of the Rachmat group where such reactions may yield values as high as 100, 300, or 1,000. Table 10 shows the reactions of various strains with an anti-Moscow V serum

Table 9.—REACTIONS OF STRAINS OF THE GRIPPOTYPHOSA GROUP WITH VARIOUS SERA

Serum	Titre of serum ¹	Strains		
		Moscow V	Moscow VIII	Andaman B
Moscow V	30,000	30,000	30,000	30,000
Andaman B	100,000	10,000 30,000	100,000	100,000
<i>L. icterohæmorrhagiæ</i> group ...	10,000	0		
	100,000	0		0
<i>Canicola</i> group	30,000	0		0
	10,000			
Salinem	5,000	0		
	10,000	0		
Soworino	30,000		10	10
Zanoni	10,000	0		
Rachmat	30,000	300	1,000	100
	300,000	30		
Jaw Jit	30,000	30	100	
Akiyami A	100,000	1,000		100
	10,000			
Swart v. Tienen group	30,000	0		0
	25,000			
H.C. group	30,000	0		0
<i>L. hebdomadis</i>	30,000	0		0
Ballico	30,000			
Pomona	30,000	0		0
Andaman A	10,000	0		0
Wa A (<i>L. biflexa</i>) ²	10,000	0		
Wa O (<i>L. biflexa</i>) ²	50,000	0		

¹ Titre of the reaction expressed as the reciprocal of the serum dilution.

² "Wa A" and "Wa O" are water strains (*L. biflexa*) from Amsterdam.

and with an anti-Andaman B serum. In these cases, too, the paraspecific reactions generally attain but low values, though, here again, the strongest and most numerous reactions, occur with the Rachmat strains.

GUINEA-PIG INOCULATION WITH *L. grippotyphosa*

The strain is not very pathogenic to guinea-pigs causing only fever and loss of weight ; virulence did not increase in thirteen

passages. At the end of the second week, the guinea-pig has a positive serological reaction which lasts for about six months. Pfeiffer's test also gives a positive result (TARASSOFF).

The low virulence for guinea-pigs, was also demonstrated at Amsterdam (DINGER & VERSCHAFFELT) where NICOLAI was also

Table 10.—REACTIONS OF SERA OF THE GRIPPOTYPHOSA GROUP WITH VARIOUS LEPTOSPIRA STRAINS

Strains	Serum ¹	
	Anti-Moscow V Titre : 30,000 10,000	Anti-Andaman B 100,000
Grippotyphosa group :		
Moscow V	30,000	30,000
Moscow VIII	30,000	100,000
Andaman B	30,000	100,000
<i>L. icterohæmorrhagiæ</i> group	0 — 30	0 — 10
<i>L. canicola</i> group	0	0 — 30
Salinem group	0	0
Rachmat group	30 — 300	30 — 1,000
Swart v. Tienen group	0	0
H.C. group	0	0
<i>L. hebdomadis</i> group	0	0
Ballico group	0	30
Pomona	0	0
Andaman A	0	0

¹ Titre of the reaction expressed as the reciprocal of the serum dilution.

able to demonstrate a positive serological reaction of the experimental animal against *L. grippotyphosa* three weeks after infection (Table 9).

STUDY OF CROSS-IMMUNITY THROUGH ANIMAL INOCULATION

Five guinea-pigs infected with *L. grippotyphosa* were injected on the thirty-fourth day with the liver emulsion of a guinea-pig which had succumbed to a virulent culture of *L. icterohæmorrhagiæ* (NICOLAI).

Leptospiræ were present for several days in their peritoneal fluid and urine ; three died after 7, 8 and 9 days respectively lung hæmorrhages and leptospiræ in the liver. Two of the three had jaundice (Table 11). Two also had a few focal lesions in the liver.

Whether the survival of two animals is to be ascribed to the protective action of the previous infection of the Moscow V strain

Table 11.—INJECTION WITH *L. grippotyphosa* (Moscow V) ;
SUBSEQUENT INJECTION WITH *L. icterohæmorrhagiæ* (Kok)

Guinea-pig 2916	Wt. 120 grm. Inj. 0.5 c.c. strain Moscow V.P.200
After 2 days	Peritoneal fluid +
After 3-9 days	Blood +
After 7, 22, 28 days	Urine —
After 22 days	<i>Serological reaction :</i> With Moscow V : 3,000 With <i>L. icterohæmorrhagiæ</i> . : 0
After 34 days	<i>Further injection</i> (wt. 185 grm.) : With 0.5 emulsion of liver of guinea-pig — Kok strain
After 2-4 days	Peritoneal fluid +
After 5-6 days	Blood +
After 8 days	<i>Death</i> icterus + hæmorrhages + leptospiræ in liver +
Guinea-pig 2919	Wt. 110 grm. Inj. 0.5 c.c. strain Moscow V.P.200
After 2 days	Peritoneal fluid +
After 3 days	Blood +
After 8, 21, 28 days	Urine —
After 22 days	<i>Serological reaction :</i> With Moscow V : 3,000 With <i>L. icterohæmorrhagiæ</i> : 0
After 34 days	<i>Further injection</i> (wt. 140 grm.) : With 0.5 emulsion of liver of guinea-pig — Kok strain
After 2-5 days	Peritoneal fluid +
After 3-5 days	Blood —
After 7 days	<i>Death</i> icterus — hæmorrhages + leptospiræ in liver +
Guinea-pig 2920	Wt. 125 grm. Inj. 0.5 c.c. strain Moscow V.P.200
After 2-3 days	Peritoneal fluid +
After 3-4 days	Blood —
After 22 days	<i>Serological reaction :</i> With Moscow V : 3,000 With <i>L. icterohæmorrhagiæ</i> : 0
After 34 days	<i>Further injection</i> (wt. 160 grm.) : With 0.5 emulsion of liver of guinea-pig — Kok strain
After 2-6 days	Peritoneal fluid +
After 6-7 days	Blood +
After 9 days	<i>Death</i> jaundice slight hæmorrhages + leptospiræ in liver +

Table 11 (continued).

Guinea-pig 2917	Wt. 125 grm. Inj. 0.5 c.c. strain Moscow V.P.200
After 2-3 days	Peritoneal fluid +
After 3-9 days	Blood —
After 7-12 days	Urine —
After 22 days	<i>Serological reaction :</i> With Moscow V : 1,000 With <i>L. icterohæmorrhagiæ</i> : 0
After 34 days	<i>Further injection (wt. 210 grm.) :</i> With 0.5 emulsion of liver of guinea-pig — Kok strain.
After 2-6 days	Peritoneal fluid +
After 3 days	Blood + <i>Survived</i>
Guinea-pig 2918	Wt. 160 grm. Inj. 0.5 c.c. strain Moscow V.P.200
After 2 days	Peritoneal fluid +
After 3-9 days	Blood —
After 7-20 days	Urine —
After 22 days	<i>Serological reaction :</i> With Moscow V : 300 With <i>L. icterohæmorrhagiæ</i> : 0
After 34 days	<i>Further injection (wt. 285 grm.) :</i> With 0.5 emulsion of liver of guinea-pig — Kok strain
After 2-4 days	Peritoneal fluid +
After 3-5 days	Blood —
After 14-25 days	Urine + <i>Survived</i>

is uncertain, for the animals in question were the heaviest of the batch.

These experiments do not, therefore, constitute positive proof of the protective action of a previous infection with *L. grippotyphosa* against a subsequent inoculation with the classical strain. This type of experiment would be well worth repeating, since any such proof would be of great value in connection with a possible *L. grippotyphosa* vaccination against the dangerous classical strain.

WHERE IS *L. grippotyphosa* FOUND OUTSIDE THE HUMAN BODY ?

TARASSOFF isolated a leptospira, which bore a striking resemblance to *L. grippotyphosa*, from numerous lakes, ponds, marshy meadows and wells in Stromyn and Constantinowa. Owing to the

morphological resemblance and also for epidemiological reasons (he was, for example, able to find these organisms in large numbers in districts where the disease occurred), he concludes that these leptospiræ may cause leptospirosis in man. Since it is possible to isolate from water of all kinds (as BASILEVSKY did in Kieff), water leptospiræ (*L. biflexa*) which are quite different from *L. grippolyphosa* in respect of antigenic structure, and are not pathogenic to man, it still remains to be demonstrated by laboratory experiment that such leptospiræ are the cause of "mud fever".

BASILEVSKY also drew attention to the fact that although he was able to obtain leptospiræ in water from various wells in Kieff, for instance, and grow them in culture, no leptospirosis could be attributed to this water.

BRILL, on the other hand, thought that field-mice might transmit the disease. As far as we know, this possibility has not yet been investigated.

Although the problem of transmission still requires further elucidation, there is no doubt that there occurs in Europe, as a disease *sui generis*, an anicteric (epidemic and endemic leptospirosis) the specific cause of which is *L. grippolyphosa*, an organism clearly differentiated from other known forms of leptospiræ by its antigenic structure and its effect on guinea-pigs.

C. Leptospiroses in Japan

Besides *Leptospirosis icterohæmorrhagica*, several leptospiral diseases are found among human beings in Japan :

(1) *Nanukayami*, or seven-day fever in Fukuoka, which occurs chiefly in autumn, in the rural districts but not in the towns.—The usual symptoms of leptospiral infections are present (fever, muscular pains, hyperemia of the conjunctiva, albuminuria, swelling of the glands, etc.) and as a sequel, opacification of the vitreous humour, but no jaundice occurs and no fatal cases are known (IDO, ITO, WANI, OKUDA & HOKI). The cause is a leptospira which is found in blood films and urine and is called *L. hebdomadis*; it differs serologically and immunologically from the classical strain (KANEKO & MORIHANA, OBA) and has little or no virulence for

guinea-pigs ; the symptoms in guinea-pigs resemble those shown by human beings. The carrier is *Microtus montebelloi*. Laboratory infections (one in Japan and one described by BEGER) showed definitely that the strain could cause the disease in man.

(2) *Akiyami*, which occurs in Shizuoka during the period August to October.—The mortality recorded is 0.3%. KITAMURA thought he could distinguish two kinds of leptospira. This was confirmed by KOSHINA, SHIOZAWA & KITAYAMA, who found that the two kinds differed in respect of their virulence for guinea-pigs. They called the more virulent strain *L. akiyami* A and the less virulent *L. akiyami* B. The Pfeiffer test, agglutination by Oba's method, etc., showed that both strains differ from *L. icterohæmorrhagiæ*. *L. akiyami* B was not a new strain, but appeared to be identical with *L. hebdomadis*. The carrier of *L. akiyami* A was *Microtus montebelloi*.

ANIOFF & SHIOZAWA also investigated other properties of *L. hebdomadis*, *L. akiyami* A and B, the classical *L. icterohæmorrhagiæ* strain, water strains and strains from the Netherlands Indies, particularly their resistance to various influences such as saponin, bile, alkalies, acids, salts, the oligodynamic action of metals, symbiosis with bacteria, etc. Both of them demonstrated that the pathogenic strains are less resistant than the water strains, but more resistant than *L. icterohæmorrhagiæ*.

L. akiyami A was found by FLETCHER in the Federated Malay States in human beings, dogs and rats.

(3) In Hasami, a riverside village in Nagasaki, a form of leptospirosis called *hasamiyami* was found to occur among men and women, school-children, and particularly among the peasantry. It caused more jaundice than *nanukayami* (about half the cases were icteric) ; hæmorrhages were more frequent, whereas swellings of the glands were clearly less so. Opacification of the vitreous humour was frequent (KANeko, KOTORII and AOKI). No relapses were observed. *Hasamiyami* is rather closely related to the classical *Leptospirosis icterohæmorrhagica*, but differs from it particularly in having a low mortality rate (1.9%).

There were 418 cases observed (69.6% men and 30.4% women) (KOTORII). The agent appeared to be identical with *L. akiyami* A

(TOSHIO, ABE); it was called *L. autumnalis* and proved fairly virulent for guinea-pigs, causing jaundice in twenty out of thirty-eight animals; all those which contracted jaundice succumbed. The reservoir is reported to be *Apodemus speciosus* (out of 210 specimens of this species examined, 11 % were positive).

The forms of leptospirosis here described as occurring in Japan, which are all less or much less dangerous than the classical Weil's disease, differ, not only in the serological properties of their pathogenic agents, but also in that the carriers of those agents are mainly field-mice and not rats.¹ Whether the environment has so affected the leptospiræ that their effect on man has become less virulent than that of *L. icterohæmorrhagiæ* is a question that remains to be studied (SNIJDERS).

CAN THE VARIOUS JAPANESE LEPTOSPIRÆ BECOME IDENTICAL BY BEING PASSED THROUGH GUINEA-PIGS ?

KANEKO attempted to discover how far the virulence and serological properties of the various leptospiræ could be changed by passage and whether they could thus be made more similar.

He performed various experiments in which he gave guinea-pigs intra-testicular, intraperitoneal and sub-arachnoidal injections of *L. icterohæmorrhagiæ*, *L. autumnalis* and *L. hebdomadis* cultures or painted them into the rectum, into the nasal cavities, etc. He observed on the whole an increase in the virulence up to the sixth passage, in the sense that the time elapsing between the inoculation of the pathogenic strains and death grew shorter. He noted, in particular, that more pathological changes appeared in the 7th passage. In the case of *L. icterohæmorrhagiæ*, agglutinability also increased. There was also a slight group agglutination in the case of *L. autumnalis*. He was unable to prove, however, that any one of the three strains became identical with another.

¹ Though one of these strains was occasionally found in the rat (*e.g.*, *L. akiyami* A, by FLETCHER : see chapter E on Leptospiroses in the Federated Malay States).

SOME INVESTIGATIONS OF THE JAPANESE STRAINS IN THE
INSTITUTE OF TROPICAL HYGIENE IN AMSTERDAM

Agglutination-lysis tests of *L. hebdomadis* strains and their sera with other sera and other leptospiral strains conducted in the Institute of Tropical Hygiene showed that the strains belonging to the hebdomadis group could easily be differentiated from all other kinds with one exception. Control tests with other strains or sera seldom gave any reaction at all, or at best a weak one. The exception was the H.C. group, consisting of dog strains from Deli, which gave very high paraspecific reactions with the hebdomadis group. Since, however, no reaction of an H.C. strain with hebdomadis serum and no reaction of a hebdomadis strain with an H.C. serum ever attained the titre of the respective specific reactions, one may consider the two groups as distinct.

According to their serological reactions, four other Deli dog strains (Hd₂-Hd₁₂) belong to the hebdomadis group. The hebdomadis strain which occurs in the Netherlands Indies in dogs has not yet been observed in man.

Five guinea-pigs, which survived inoculation with *L. hebdomadis* culture, were reinoculated after 17 to 19 days with a virulent *L. icterohæmorrhagiæ* strain; four died of leptospirosis and one survived. The preliminary inoculation with *L. hebdomadis* did not therefore protect the four which died against the subsequent infection with the virulent pathogenic leptospiræ.

An akiyami A strain received in Amsterdam via Batavia appeared to belong to the Rachmat group, judging by its serological reaction with Rachmat antisera (Table 15, A and B). Leptospiræ of the akiyami A group would appear to be spread over a large territory in Japan and the Netherlands Indies, while FLETCHER has also found akiyami A in human beings, dogs and rats in the Federated Malay States.

An autumnalis A strain, however, which should be identical with akiyami A and was recently received from Copenhagen (which it had reached from Japan via Berlin) gave a very strong reaction with Rachmat antisera, though not as high in titre as the specific reaction (see Table 15 A). When tested against an akiyami A serum, neither the autumnalis strain nor any of the Rachmat strains gave a reaction of quite so high a titre as did the akiyami A strain itself,

Table 12.—REACTIONS OF STRAINS OF THE HEBDOMADIS AND H.C. GROUPS WITH VARIOUS SERA

Sera	Hebdomadis Group									H.C. Group			
	Titre of sera	Hebd.P.	Hebd.	Aut.B.	Aut.P.	Hd ₁	Hd ₇	Hd ₁₀	Hd ₁₁	H.C.	Hd ₁	Hd ₉	
Hebdomadis group :													
Hebdomadis	10,000 30,000	30,000	30,000	30,000	30,000	30,000	30,000	100,000	30,000	3,000	100 3,000		
Hd ₇	30,000		30,000	30,000	30,000	30,000	30,000	10,000	10,000				
Hd ₁₀	100,000		30,000	30,000	30,000	30,000	30,000	30,000	100,000				30,000
							100,000	100,000	30,000				
H.C. group :													
H.C.	30,000		3,000	1,000	1,000	1,000	1,000	3,000	1,000	30,000	30,000	100,000	
Hd ₁	30,000		3,000			3,000	3,000	10,000 3,000	3,000 1,000	30,000	30,000	100,000 30,000	
Icterohaemorrhagiae group	10,000 300,000		0 25	0	0	0	0	0	0	0	0	0	
Canicola group	25,000 30,000		30	0	0	0	0	0	0	0	10	0	
Salinem group :													
Salinem	10,000		0	30	0	0	0	0	0	0	0	0	
Zanoni	30,000		30							0			
Rachmat group :													
Rachmat	30,000 10,000		0	0	0	0	0	0	0	10	0	0	
Jaw Jit	300,000 100,000		0 1,000			0	0	0	0				
Akiyami A.	100,000		0			0	0	0	0	0	0	0	
Swart v. Tienen	30,000		10	0	0	0	0	0	0	0	0	0	
Grippotyphosa group ..	30,000 100,000		0	0	0	0	0	0	0	0	0		
Pomona	30,000		0	0	0	0	0	0	0	0			
Andaman A.	10,000		0	0	0	0	0	0	0	0			
Ballico	30,000		0	0	0	0	0	0	0	0			

Hebd.P., Hebd., Aut.B., Aut.P. are hebdomadis and autumnalis strains, belonging to the hebdomadis group.
Hd₇ and Hd₁₁ are Deli dog strains, belonging to the hebdomadis group.
H.C., Hd₁ and Hd₉ are Deli dog strains, not belonging to the hebdomadis group.

though another Rachmat strain, Kartomonawi, did react nearly up to the same level (Table 15 B). Some preliminary experiments

Table 13.—REACTIONS OF SERA OF THE HEBDOMADIS GROUP AND H.C. GROUP WITH VARIOUS LEPTOSPIRA STRAINS

Strain	Hebdomadis group			H.C. group	
	Hebd.	Hd ₇	Hd ₁₀	H.C.	Hd ₁
Hebdomadis group :					
Hd ₁	30,000	30,000		1,000	3,000
Hd ₇	30,000	30,000	100,000	1,000	3,000
Hd ₁₀	100,000	10,000	100,000	3,000	10,000
Hd ₁₂	30,000	10,000	30,000	1,000	3,000
Hebdomadis	50,000	30,000		3,000	3,000
	10,000				
Hebd.P.	30,000				
Autumnalis B.	30,000	30,000		1,000	
Autumnalis	30,000	30,000		1,000	
H.C. group :					
H.C.		3,000	3,000	25,000	30,000
				30,000	30,000
Hd ₁	100	3,000		30,000	30,000
Hd ₀				100,000	100,000
<i>L. icteroh.</i> group	0			0	0
	10-50				
Canicola group	0	0		0	0
Salinem group	0			0	0
Rachmat group	0	0		0	0
Swart v. T. group.....	0			0	0
	300	0			
Grippotyphosa group	0			0	0
Ballico group	0	0		0	
Pomona	0			0	
Andaman A.	0			0	
<i>L. biflexa</i>	25-50				

recently made by CASTELLANI showed that akiyami A, autumnalis and Rachmat have part of their antigenic structure in common but are by no means identical.

It still remains to be decided, therefore, whether the relationship between the Rachmat, akiyami and autumnalis strains is sufficient to justify their inclusion in one group.

Table 14. — INVESTIGATION OF CROSS-IMMUNITY IN THE GUINEA-PIG ;
 INOCULATION OF *L. hebdomadis* AND FURTHER
 INOCULATION WITH VIRULENT LEPTOSPIRÆ

Guinea-pig 1284	Weight 170 gm. Injec. 0.5 c.c. <i>Hebdomadis</i> culture
After 7 days	Peritoneal fluid +
After 19 days	Further injection : 1 c.c. of liver emulsion guinea-pig, Jaw Jit strain
After 3 days	Died : jaundice — blood — leptospiræ in liver +
Guinea-pig 1317	Weight ... Injec. 1 c.c. <i>Hebdomadis</i> culture
After 2 days	Peritoneal fluid +
After 3 days	Blood +
After 9 days	Further injection : 1 c.c. of liver emulsion guinea-pig, Jaw Jit strain
After 2 days	Peritoneal fluid +
After 3 days	Blood +
After 5 days	Died : jaundice + blood + leptospiræ in liver +
Guinea-pig 2989	Weight 145 gm. Injec. 0.5 c.c. <i>Hebdomadis</i> culture
After 2 days	Peritoneal fluid + Blood —
After 17 days	Serum reaction : <i>Hebdomadis</i> > 300 Wijnberg 0
After 17 days	Further injection (weight 170 gm.) : ‡ c.c. liver emulsion guinea-pig, R. Oostenburg strain
After 6 days	Peritoneal fluid. + Died : jaundice — blood — lept. in liver —
Guinea-pig 2991	Weight 140 gm. Injec. 0.5 c.c. <i>Hebdomadis</i> culture
After 2-3 days	Peritoneal fluid —
After 17 days	Serum reaction : <i>Hebdomadis</i> 1,000 Wijnberg 0
After 17 days	Further injection : (weight 170 gm.) ‡ c.c. liver emulsion guinea-pig, R. Oostenburg strain
After 2 days	Peritoneal fluid +
After 3 days	Blood +
After 6 days	Died : jaundice + blood + lept. in liver +

Table 14 (continued).

Guinea-pig 2986	Weight 150 gm. Injec. 0.5 c.c. Hebdomadis culture
After 2-3 days	Peritoneal fluid + Blood —
After 17 days	Serum reaction : Hebdomadis 300 Wijnberg 9
After 17 days	Further infection (weight 180 gm.) ‡ c.c. liver emulsion guinea-pig, R. Oostenburg strain
After 32 days	Urine + Survived

Table 15A.

Sera	Titre of sera	Strains			
		Akiyami A (Neth. Indies)		Autumnalis (Copenhagen)	
Rachmat	30,000	30,000	t	10,000	t/3
Kartomonawi 3701	30,000	100,000	t +	10,000	t/3
Akiyami	100,000	100,000	t	30,000	t/3
Hebdomadis	30,000	0		0	

Table 15B.

Strains	Serum Akiyami A 100,000	
Rachmat	10,000	t/10
Kartomonawi	100,000	t
Akiyami A	100,000	t
Autumnalis	30,000	t/3

t = Reaction giving a titre equal to that of the specific reaction.
t/3 = Titre equal to one-third that of the specific reaction.
t/10 = Titre equal to one-tenth that of the specific reaction.

D. LEPTOSPIROSIS IN THE NETHERLANDS INDIES

A few sporadic cases of Weil's disease had occurred in the Netherlands Indies since 1892. The first case was described in 1892 in Batavia by VAN DEN SCHEER and comprised all the classical

symptoms. After that, SCHÜFFNER found the first leptospiræ, together with a few malaria parasites, in the blood of a patient who died with symptoms of blackwater fever.

In 1922, as a result of an investigation into fevers of short duration of unknown origin (some of them with jaundice), VERVOORT discovered the leptospira as a specific cause and named it *L. pyrogenes*. The leptospira bore a striking resemblance morphologically to that found in the classical Weil's disease. The question therefore arose whether both leptospiræ, and perhaps also the diseases they caused, were not identical. As VERVOORT discovered a culture medium with which it was easy to cultivate the leptospira, further research became possible on this point.

CASES OF LEPTOSPIROSIS DEMONSTRATED SINCE 1922

After this, cases of leptospirosis, occurring as epidemics or sporadically, were discovered in various places in the archipelago.

The incidence in the various islands varies a great deal. Whereas hundreds of cases occur in Sumatra and many in Tarakan, only a few are found in places like Batavia, Semarang, Soerabaya and Macassar. The places where many cases are recorded, however, are those inhabited by plantation coolies in which all the sick (including mild cases) are sent to hospital, whereas in Java and the Celebes, where the population is independent, only the serious cases are reported and the slight ones ignored. It is thus possible that the great difference in frequency may be (partly, at any rate) only apparent.

CLINICAL SYMPTOMS OF LEPTOSPIROSES IN THE NETHERLANDS INDIES

Table 16 shows the frequency of jaundice and death among recorded cases. Generally speaking such data are sufficient in Europe to distinguish between epidemics of the various types (*e.g.*, mud fever and Weil's disease). This is not so easy in the Netherlands Indies, for it will be seen that, there, jaundice is liable to occur everywhere, and if, in any particular place, the data appear as first sight to suggest the contrary (VAN LINGEN, Borneo), there

is always evidence of some previous case which was at once clinically certain, icteric and fatal.

Jaundice is, however, proportionately more frequent in certain districts. Generally speaking, a high incidence of jaundice usually goes hand in hand with a high death rate, whilst a low incidence is associated with a low death rate, as was, indeed, to be expected.

The problems arising for consideration are hence these :

Are the mild cases caused by another strain than the severe cases ?

Must the difference in the incidence of disease be attributed to a difference in the pathogenic agent, or to social factors ?

BACTERIOLOGY AND SEROLOGY OF LEPTOSPIROSES IN THE NETHERLANDS INDIES

Table 17 reproduces graphically the reactions with the Indies strains examined at Amsterdam. It shows that the strains can be divided into eight groups,¹ which can be differentiated serologically.

The strength of the reaction is expressed in fractions of the full specific titre of the serum ; thus a reaction can go up to the specific titre of the serum, or to one-third, one-tenth, etc., of the titre, as is shown graphically in the manner explained in the footnotes to the table.

The reactions which reach one-third or one-tenth of the specific titre can be, in fact, either specific or aspecific in character. The manner in which this is determined is explained in the section on the classification of *L. icterohæmorrhagiæ* (Section II on Leptospiroses in Rats). The table explains that such a specific reaction must be connected with the reaction which reaches the full specific titre, for the strain which gave a lower reaction always produced a reaction of the full specific titre with another serum.

STRAINS FOUND IN HUMAN BEINGS

The first group comprises the classical *L. icterohæmorrhagiæ*. The strain was found in human beings in Sumatra and Java and was also isolated from rats in Java. Rachmat and the Salinem

¹ Some new strains recently discovered have not been included, as they have not been fully compared with one another.

Table 16.—JAUNDICE AND FATALITY IN CASES OF LEPTOSPIROSIS
RECORDED IN THE NETHERLANDS INDIES

	Number of cases ¹	Jaundice	Death
<i>Sumatra :</i>			
VERVOORT, 1922	5	1 +	0
VERVOORT, 1923	90	8 +	2
VAN DER VELDE, 1922	4	4 +	1
KOUWENAAR, 1923 ..	164	21 + = 13.5%	5
BAERMANN, 1923	8	5 + 2 —	1
earlier	5 Europeans		5
KOUWENAAR, 1925 ..	?	10%	without icterus : 0 with icterus : 20%
BAERMANN & SMITS, 1925	196	17%	1%
	150*		
WOLFF, 1931	224**		8.5%
1932	212**		6.7%
MULDER, BONNE, SARDJITO, 1931 ...	50	4 + = 8%	2
SLOT & VAN DEN WALLE, 1932	1 * 4 Chinese 17	1 + 2 + 1 —, 1? 8 + = 47%	0
<i>Banka :</i>			
SLOT, 1929	4	3 + 1 —	2
FISCHER, 1930	2	2 +	1
SLOT, 1931	5	1 + 4 —	0
<i>Billiton :</i>			
LUYKE, ROSKOTT, 1934	2	1 + 1 —	0
<i>Java :</i>			
WALCH, 1926	1	1 +	1
BOON VAN OSTADE, 1933	1	1 +	1
DINGER, 1933		1 +	
MOCHTAR, 1933	8 incl. 2*	8 +	1
ZAINAL, 1937	1	1 +	0
SOEMADJONO, 1937..	1	1 +	0
HOEKSTRA & SARD- JITO, 1938	1	1 ±	0
<i>Borneo :</i>			
SMITS, 1932	26	Sporadic	3
VAN LINGEN, 1933 ...	1* European 7**	1 + 7 —	1
VAN DEN SCHROEF, 1934	1	0	0
BESSEM, 1936	1* European 1 European 6 Chinese	1 + 1 —	1
<i>Celebes :</i>			
BEZEMER 1934.....	5	5 +	2

¹ Unless stated otherwise all cases concerned natives and were confirmed bacteriologically.

* Clinical diagnosis only.

** Bacteriological confirmation of a part only of the cases.

strains were among the first to be isolated in Sumatra and were sent in 1923 and 1925 by BAERMANN to Amsterdam ; subsequently, however, strains were received on various occasions which appeared to belong to one of these groups. The Salinem strain was also found in a *Mus rattus brevicaudatus* in Java by MOCHTAR & ESSEVELD and was also identified in Amsterdam. The Rachmat group includes some strains which do not give reactions equal to the full specific titre with all sera, values of only one-tenth of that titre being even obtained. A few Rachmat strains also react up to the full titre with akiyami A serum but a larger proportion failed to do so. Certain differences would therefore appear to exist between the various Rachmat strains. This matter hence calls for further investigation by means of Castellani's test, etc., in order to determine, for example, the relationship between akiyami strains and the Rachmat group.

The Swart van Tienen strain (Batavia type) was isolated by WALCH in Batavia in 1926 and studied by WALCH & SOESILO, who also found that some rat strains belonged to this group. The same strain was subsequently also demonstrated in other patients in the neighbourhood of Batavia, and was also found in Borneo, as well as in Celebes, where it was also present in rats (BEZEMER). Shortly afterwards, cats in Batavia were found to be infected with this strain (ESSEVELD & COLLIER).

STRAINS FOUND IN DOGS

The dogs were also found to be carriers of leptospiræ (WOLFF & KOUWENAAR). Strains isolated from dogs appear so far to belong to two groups : H.C. and hebdomadis (Amsterdam) which can be clearly differentiated, but show close affinity in that H.C. gives high paraspecific reactions with hebdomadis serum and vice versa. No infection of a human being with any of the dog strains known in the Netherlands Indies has been demonstrated so far.

STRAINS FOUND IN RATS AND FIELD-RATS

Table 18 shows where—together with the place of discovery—the species of rats in which leptospiral infection has been

LEPTOSPIROSES

Table 17. — REACTION OF STRAINS FROM 7

Strains	<i>L. icterohæm.</i>	<i>L. canicola</i>	Salinem	Rachmat	Akya-mi A.	Swart v.T.	Pomona
<i>L. icterohæmorrhagæ</i> 2 strains	■■■■	■■	☐	☐ ☐ ☐☐			
<i>Salinem</i> 10 strains	■ ■ ■ ■ ■ ▨ ▨ ▨ ▨ ▨ ▨	▨ ▨ ▨ ▨ ▨	■ ■ ■	▨ ▨ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐	☐ ☐ ☐ ☐ ☐	☐ ☐
<i>Rachmat</i> 8 strains	▨ ▨ ▨ ▨ ▨ ▨ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	▨ ☐ ☐ ☐ ☐ ☐ ☐	■ ■ ■ ■ ■ ■ ■ ■ ■ ■ ■ ■	■ ■ ■ ■ ■ ■ ■ ■		▨ ▨ ▨ ▨
<i>Swart v. Tienen</i> 3 strains	☐ ☐ ☐ ☐	☐ ☐ ☐	☐ ☐	☐ ☐ ☐ ☐	☐	■ ■ ■	☐ ☐
<i>Hd 2, 7, 10, 12</i> 4 strains	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐	☐ ☐ ☐ ☐	☐
<i>H.C.</i> 2 strains	☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	▨ ☐ ☐ ☐ ☐ ☐	☐	☐ ☐ ☐	☐
<i>Field rat Semarang 173</i> 1 strain	▨	☐	☐	☐		☐	☐
<i>Javanica</i> 1 strain	▨	☐	☐	▨		☐	☐

Reaction ■ up to the full specific titre and higher ;
 ■ up to 1/3 of the specific titre and higher ;
 ▨ up to 1/10 of the specific titre and higher ;
 ☐ from 1/30th to 1/100th of the specific titre and higher ;

NETHERLANDS INDIES WITH VARIOUS SERA

Moscow	Andaman 31	H.d.7-H.d.10	Hebdom.	H.C.	Ballico	Andaman 11	Field rat Semarang 173
							□
□□ □□□	□		□□□□	□□□ □□□□	□□	□□	□
☒ ☒ □□□ □□□	☒ □ □□□ □□□	□	□□□□	□□□□	□□	□□	□
□□□	□	☒ □	☒ □□	□□□□	□	□□	□
□□□□		■ ■ ■ ■ ■	■ ■ ■ ■ ■	■ ■ ■ ■ ■ ■ ■ ■ ■ ■ ■	□	□	□
□□□	□	■ ☒	☒	■ ■ ■ ■ ■ ■ ■ ■ ■ ■		□	□
□	□		□	□	□		■
□			□	□	□		□

SDN 8624

- Reaction ☒ from 1/300th to 1/1,000th of the specific titre and higher ;
 □ from 1/3,000th to 1/10,000th of the specific titre and higher ;
 □ negative ;
 ■ reaction of 1 strain with 2 sera, 1 up to the full specific titre, and 1 up to 1/3 of the titre.

Table 18.—INFECTION OF VARIOUS RATS IN THE NETHERLANDS INDIES¹

Investigator	Place	Date	<i>Mus norvegicus</i>	<i>Mus rattus diardii</i>	<i>Mus rattus brevicaudatus</i>	Number +	Method of investigation	Remarks
HOKSEN	Batavia	1919	<i>M. norv.</i>			1	A + P	
FLU	Batavia	1920	35			2	A	
KOUWENAAR ...	Sumatra, east coast	1924		30		2	P	
SARDJITO & POSTMUS	Sumatra, east coast	1927	23			17%	C + A + MR	2 strains. Type Batavia ² (WALCH & SOESILO)
FISCHER	Panakal Pinang, Banka	1929						
FISCHER	Panakal Pinang, Banka	1929		89		6		
MERTENS	Batavia	?				+		Strain Rat G.J. not Batavia type (DINDER)
SARDJITO	Macassar, Celebes	1930	350 216 adults 134 young			7% 12% 0%	C	4 strains Batavia type
SLOT	Belinfoo, Banka	1930	108			0	0	
BOELENB	Semarang, Java	1931				30%	C	
KIRSCHNER	Bandoeng, Java	1931		260		? +	A + C	
SLOT & VAN DEN WALLE	Bangkinang, Sumatra	1932		40 (house rats)		0		
MOCHTAR	Semarang, Java	1933	20			40%	C	2 strains <i>L. icterohæmorrhagiæ</i>
SARDJITO, MOCHTAR & WIRASMO	Ambarawa, Java	1936			104 12 adults 42 young	21% 50% 7%	C	1st strain Salinem, 2nd strain <i>L. Javanica</i> (MOCHTAR & ESSEVELD)
SARDJITO, MOCHTAR & WIRASMO	Ambarawa, Java	1936		9		0		
SARDJITO	Semarang	1938				1		Strain, field rat 173, Semarang (SARDJITO)

¹ Taken from the table of SARDJITO, MOCHTAR and WIRASMO, except for the last column.

² Batavia type—Swart van Tieneen strain.

A = Animal inoculation.

C = Culture of liquid expressed from kidney.

M.R. = Microscopic examination with dark field illumination of renal tissue.

P = Post mortem findings.

demonstrated in the Netherlands Indies. It also indicates as far as is known, the strains concerned. The strains *L. javanica* and field-rat Semarang 173 were isolated from field-rats ; the former has not yet been found in man, while an infection with the latter has only been established serologically on one occasion (SARDJITO).

STRAINS FOUND IN CATS

The following strains have so far been found in cats (ESSEVELD & COLLIER) :

- (1) The Swart van Tienen (Batavia type), and
- (2) The *L. javanica* (new strain).

The fact that the first of these has caused infections in human beings should be an inducement to further investigation of the part which cats may play in spreading the various forms of leptospirosis.

So far, in the Netherlands, the Rachmat strain has only been found in human beings.

In the Netherlands Indies, the Rachmat strain has so far only been found in human beings, the H.C. and hebdomadis group in dogs, whereas the classical strain and the Swart van Tienen (Batavia type) and Salinem strains have been found both in rats and in human beings ; the Swart van Tienen strain has also been found in cats ; the *L. javanica* strain has been found in field-rats and cats, and the Semarang 173 field-rat strain in field-rats and (serologically) in human beings (Table 19).

SYMPTOMS OF THE DISEASE CAUSED BY THE VARIOUS NETHERLANDS INDIES STRAINS

Table 20 contains what is known about the occurrence of jaundice and the mortality among cases due to the various strains. The data rest upon the isolation of well-defined strains from clinically identified cases.

A few patients were included from two places where only a serological test had been made, since they belonged to a group from which certain definite strains had been isolated, which were in keeping with these patients' serological reactions.

Table 19.—OCCURRENCE OF LEPTOSPIRÆ OF THE VARIOUS GROUPS AND THEIR RESERVOIR SPECIES IN THE NETHERLANDS INDIES

	Strains isolated from man	Presence in man indicated by the serological reaction	Strains from rats	Strains from dogs	Strains from cats
Classical <i>L. icterohæmorrhagiæ</i> group...	East coast, Sumatra	Probably at Poeroektjaoe, Borneo	Semarang, Java (<i>M. norvegicus</i>)		
	Benkoelen, Sumatra	Benkoelen, Sumatra			
Salinem group	Semarang, Java		Albarawa, Java (<i>Mus rattus brevicaudatus</i>)		
	East coast, Sumatra				
	Atjeh, Sumatra				
Rachmat group	East coast, Sumatra	Probably at Pemangkat, Borneo			
	Bangkinang, Sumatra	Probably at Benkoelen, Sumatra			Batavia
Swart v. Tienen group (Batavia group)	Batavia and neighbourhood	Magelang, Central. Java	Batavia, W. Java (<i>M. norvegicus</i>)		
	W. Java	Kandangang, Borneo (S.W.)			
	Kandangan, Borneo	Macassar, Celebes	Macassar, Celebes (<i>M. norvegicus</i>)		
	Macassar, Celebes	Probably at Benkoelen		Deli, Sumatra	
	Billiton	Sumatra		Deli, Sumatra	
H. C. group (dog)			Ambarawa, Java (<i>Mus rattus brevicaudatus</i>)		Batavia
Hebdomadis group ..			Semarang, Centr. Java (<i>Mus rattus brevicaudatus</i>)		
<i>L. javanica</i> group					
Field-rat strain		Semarang			
Semarang 173					

Table 20.—COURSE OF THE DISEASE IN INFECTIONS WITH DIFFERENT NETHERLAND INDIES STRAINS

	Jaundice	No jaundice	Survival	Death	
Classical group. <i>L. icterohæmorrhagiae</i> : 8 cases, Semarang .	8		7	1	8 cases 4 strains
	8		7	1	
Salinem group :					
Sanidjojo		1	1		
Sowirono		1	1		
Parlo		1	1		6 cases 6 strains
Kamidi		1	1		
Polhaupessy	1		1		
Imoen	1			1	
	2	4	5	1	
Rachmat group :					
Rachmat		1	1		5 cases 5 strains
W. D. A.	1		1		
Lie Soey	±		1		
Jaw Jit		1	1		
Kartomonawie	1			1	
	2 — 3	2	4	1	
Swart van Tienen (Batavia) group :					
Swart van Tienen .	1			1	
Macassar	1				14 cases 6 strains
Billiton (Chinese girl)	5	1	3	2	
Asi, Borneo		1	1		
Other cases Borneo.		5	5		
	7	7	11	3	

The classical type gave rise to severe icteric cases which were sometimes fatal. The Batavia type (Swart van Tienen) caused severe cases in Java and Celebes with jaundice and a large mortality rate ; in Billiton and Borneo, it gave rise to slight and very slight anicteric cases. The Rachmat and Salinem strains generally caused mild and very mild cases—*e.g.*, sometimes entailing only fever and conjunctival injection. In both groups, a typical Weil case occurs from time to time and we recently obtained a new strain from each group, both being isolated from fatal cases (WOLFF).

The case records give the impression that the classical and Batavia strains are more dangerous than Salinem and Rachmat, that they are more prone, for instance, to cause jaundice. Apart from the influence of small figures, this difference may, however, be due entirely (or nearly so) to differences in social conditions.

The Rachmat and Salinem strains are found in districts where leptospirosis is epidemic or endemic, particularly in plantation districts—i.e., in communities where even slight cases occurring among the workers are removed to hospital. The Swart van Tienen and classical strains in Java occur sporadically in districts where the population is independent, so that patients having a mild form of the disease are probably never detected.

Even if the Rachmat and Salinem strains gave rise to a large number of mild cases, it is quite impossible that they should be so different from the classical Weil form as, for example, "mud-fever" and nanukayami. The difference between the syndromes engendered by these four groups is rather of a quantitative character.

GUINEA-PIG INOCULATIONS WITH NETHERLANDS INDIES LEPTOSPIRÆ

Experiments were made both in the Netherlands Indies and in Amsterdam on guinea-pigs with human leptospiræ; in the Netherlands Indies, the blood and urine of the patients were chiefly used; in the Institute of Tropical Hygiene in Amsterdam, only cultures were used.

Guinea-pig inoculation showed that the strains which were virulent for man were at least as virulent for guinea-pigs (e.g., Swart van Tienen) and that Rachmat, in particular, though apparently not very dangerous to human beings, acted like a classical strain on guinea-pigs. This has made us exercise even more caution before making a pronouncement concerning the virulence of the various strains.

RAPID DECREASE IN THE SEROLOGICAL TITRE

Another point which must be mentioned concerns serology. It is known in the Netherlands, for example, that the serum of patients who have had Weil's disease contains lysins and sometimes also

agglutinins against *L. icterohæmorrhagiæ* many years after recovery. POSTMUS proved that titres of 1 : 300 persist for years. Later, cases were noticed in which the titre declined to 1 : 100 within a year. In the Netherlands Indies, on the other hand, BAERMANN & ZUELZER found that the titre decreased rapidly so that, in many cases, it had dwindled to zero after one year ; BAERMANN & SMITS found that though, in some instances, the titre was still 1 : 300 after three years, 30% of their cases were negative after 200 days. This rapid decline was confirmed by WOLFF (1936). A curve made by WOLFF showed that the average titre was 1 : 1,000 after four months, somewhat higher than 1 : 300 after six months and negative after a year.

It is not yet certain whether this applies to all or, as some think, only some of the strains, excluding *L. icterohæmorrhagiæ*. On the other hand, a case is known of infection at Amsterdam with the Netherlands Indies strain Rachmat, in which the titre was 1 : 300 after nine years as it would normally have been with *L. icterohæmorrhagiæ*. Another possibility is therefore that the immune substances disappear more rapidly from the body in the Indies than in Europe.

EPIDEMIOLOGY OF LEPTOSPIROSES IN THE NETHERLANDS INDIES

In the Netherlands Indies, as in other countries, evidence of the part played by water in the spread of leptospirosis is constantly coming to light. But here, as elsewhere, this factor is occasionally absent and a more direct contact with the rat can be clearly established. The connection with water was easily demonstrable in the cases recorded by BAERMANN, who observed sporadic infections every year, usually after bathing and swimming in the river, and epidemics caused by work in marshy or boggy districts. In Benkoelen, too, cases occurred after bathing, as well as in Borneo (LINGEN, VAN DEN SCHROEF), where the river was locally polluted by the waste of a military kitchen, and therefore infested with rats. Men also fell sick after patrol work in boggy districts (Borneo and Atjeh) and work in damp mine galleries (Benkoelen). In some other districts—*e.g.*, in Banka, where tin ore was washed—however, much work was done in the water without cases of the disease

occurring as a result, although FISCHER demonstrated infection among rats on that island. MOCHTAR attributes the disease among his patients in Semarang to contact with water, which was certainly infected by rats.

There is no doubt that the outbreak which BESSEM observed in Pemangkat (Borneo) was due to the newly opened swimming-bath which had been used by all the patients, some of whom had a few skin abrasions. It is also certain that this water (surface water from a pool) could have been contaminated by rats.

In the Netherlands Indies, the connection between the infection in rats and human beings is even more striking seeing that, in some districts, the same strain of leptospiræ is found in both.

Thus, in Batavia, the Swart van Tienen strain is found both in man and, in rats. This is also true of this same strain in Macassar and of a *L. icterohæmorrhagiæ* strain in Semarang.

CAN THE SAPROPHYTIC WATER LEPTOSPIRA BE CHANGED INTO A STRAIN PATHOGENIC TO MAN ?

As has already been stated (see Chapter I. 1. "Epidemiology") some investigators are not satisfied with the rat theory and consider that, in certain circumstances, saprophytic water leptospiræ (*L. biflexa*) can be pathogenic to man. This opinion is also held by BAERMANN & ZUELZER, who made numerous experiments in Sumatra which they considered demonstrated the metamorphosis of water leptospiræ into pathogenic leptospiræ. The grounds on which they base their claim and the objections which can be raised against it have been dealt with in the above chapter, to which we would refer the reader.

CAUSES OF THE DIFFERENCES IN THE FREQUENCY OF CASES IN DIFFERENT DISTRICTS

To what must the differences in the incidence of cases in Sumatra and Java, for example, be attributed ? They cannot be due to differences in the specific agent but may partly be attributed to social factors such as those which have been mentioned (communities

of plantation coolies where removal to hospital is compulsory and free communities), though there may be other causes as well.

SARDJITO & ZUELZER have made a special study of this point. While ZUELZER found water spirochætes in all kinds of water in Sumatra she and SARDJITO were seldom able to find them in Java. They discovered that the reason was that in West Java, which consists of young volcanic rock, the water gives an acid reaction pH. (5.7-6.7), whereas, in Sumatra, it is neutral or alkaline. Another difference was that the water in Sumatra was harder, as it contained more calcium, and the soil was richer in alkalis (Na and Mg) than in West Java. The water in Sumatra was, moreover, more turbid, owing to floating particles of clay to which the leptospiræ tended to cling.

SARDJITO & ZUELZER also found that leptospiræ occur in nature in a pH of about 7 ; they cannot live in a pH of under 6.8-6.6. The optimum conditions for them are at a pH of 7.3-8, but they grow in the laboratory in a pH of 6.9-8.6. ZUELZER's theory that human beings can be infected by saprophytic water spirochætes would thus explain why there is so much less infection in Java than in Sumatra.

SARDJITO subsequently pointed out that the pH of rivers, etc., is not so important, since the connection in Java with bathing, swimming, etc., has not really been proved. The pH in the washing places near the kitchens in the kampongs (villages) is of great importance, however, as many infections must have been caused through the close contact of human beings and rats with such water.

SEX DISTRIBUTION OF LEPTOSPIROSES

On this aspect of the question, the findings in the Netherlands and in the Netherlands Indies are concordant. More cases were observed among men than among women (on the east coast of Sumatra by BAERMANN, and in Benkoelen by BONNE, MULDER and SARDJITO). Though it may be true that, in some districts, certain social factors affecting the man in particular may be adduced to account for this phenomenon, this in other districts is not so.

Whereas, in Benkoelen, the ratio of men to women was 4 : 1, the corresponding proportion among the patients was 50 : 1, though

the number of infections among mine-workers was not large. In the Netherlands, too, this difference in the infection index among men and women remains to some extent unexplained. The few patients treated by MOCHTAR in Semarang included one or two women, however.

E. Leptospiroses in the Federated Malay States

In 1927, FLETCHER described thirty-two cases of leptospirosis observed by him in the Federated Malay States. The disease was most frequent among coolies, and sometimes occurred among Government clerks and police officials. Now these are groups of persons who are immediately removed to hospital whenever they are too ill to work. The consequence is that a fairly accurate picture can be obtained of the disease, in all the forms in which it occurs, whereas, in a population whose sick need only go to hospital when they choose, the mild cases will not be brought to light.

CLINICAL SYMPTOMS IN THE FEDERATED MALAY STATES

The onset of the disease was acute, with fever, frequent vomiting, severe muscular pains, headache, injection of the conjunctivæ ; occasionally there were hæmorrhages and a rash ; albuminuria was nearly always a symptom. Jaundice was clearly marked, in seven cases, and very slight in another seven. One patient out of 32 died with jaundice, hæmorrhage and black vomiting. In 75% of the cases, the fever lasted longer than seven days.

F.M.S. STRAINS

The diagnosis of leptospirosis was performed as follows :

- (1) By making smears of the patient's blood : leptospiræ were found in this way in 3 out of the 32 cases ;
- (2) By making cultures of patients' blood on the special Noguchi medium : these culture tests always gave a positive result if the blood used was taken not later than the 7th day of sickness ;

(3) By guinea-pig inoculation : the guinea-pigs died with jaundice and hæmorrhage when they were inoculated with blood obtained before the 8th day of the disease.

By inoculation in passage, the strain acquired a fixed virulence, and the guinea-pig died regularly on the 5th or 6th day. A smear of its blood was nearly always positive (Fontana stain). FLETCHER was able to distinguish seven groups among the leptospiral strains by carrying out serological tests and by performing Pfeiffer's test with a guinea-pig culture or liver emulsion. One patient, who died, showed the classical *L. icterohæmorrhagiæ* strain, 6 *L. akiyami* A, and the remainder other strains.¹ It has already been noted that many of these strains are virulent for guinea-pigs. We do not know, however, the results of guinea-pig inoculation with all the strains.

EPIDEMIOLOGY OF LEPTOSPIROSES IN THE F.M.S.

Five of the patients had bathed in a muddy stream on a rubber plantation. Many other patients lived along the banks of the same river ; others, however, were widely scattered. FLETCHER rightly points out, however, that most of the inhabitants of the country come into constant contact with water in one way or another. Only black rats are found ; there are no brown rats. 26% of *M. rattus*

¹ Most of them (thirteen) came under the appellation *L. pyrogenes*. We now know that this covers a number of very different strains which do not belong to one group. It is hence impossible to tell which *L. pyrogenes* strain FLETCHER used in his examination. Nor do we know how far the three other strains (Nallathambey, Eruthyan and Klemens) resemble those occurring in the Netherlands Indies.

Now that so many strains have been discovered, at any rate in the Far East, all laboratories should possess one culture of every one that has been clearly defined. Or a complete collection should be held available in one particular laboratory. It seems that occasion will naturally arise to use FLETCHER's strains for serological reactions in the Netherlands Indies where they are not known, and the Rachmat, Salinem, Swart van Tienen, etc., strains in the Federated Malay States. Even Australian strains ought to be included together with *L. grippotyphosa*, *L. andaman*, C.H.₁₁, etc.

EDITOR'S NOTE.

Since this article was received for publication the special laboratory suggested for the identification of leptospiral strains has been set up in the Central Medical Laboratory of the Netherlands Indies Public Health Service at Batavia and is to serve the Far East ; as the article itself shows : Prof. Schüffner's Laboratory at the Institute of Tropical Hygiene, Amsterdam, has served the same purpose in Europe.

diardii were found to be positive (cultures). The town rat, *M. rattus griseiventer*, was negative, however. The strain obtained from rats was mostly *L. akiyami* A. This strain, oddly enough, was also found among young dogs who were ill with jaundice, and frequently died. Young dogs and guinea-pigs could be infected by organ emulsions from these dogs, but fully grown dogs were relatively immune. *L. akiyami* A is thus seen to behave otherwise than the *canicola* strain, which is also found in both human beings and dogs, but not in rats. The characteristics of the disease in the Federated Malay States are thus in many ways similar to those found in the Netherlands Indies—*i.e.*, marked differences in the strain and a relatively small mortality rate. On the other hand, the social conditions are such that the milder cases also come to light. Here, too, *L. icterohæmorrhagiæ* strain infections proved fatal.

F. Leptospiroses in the Andaman Islands

Cases of leptospirosis had already been observed on many occasions in the Andamans before BARKER diagnosed the disease for the first time in 1926 by demonstrating leptospiræ in stained preparations of urine, etc. In 1928, BROWN found a positive adhesion reaction in the blood of a patient. The epidemic which occurred in 1929, chiefly among convicts and British troops, was observed and described by TAYLOR & GOYLE.

CLINICAL SYMPTOMS OF LEPTOSPIROSES IN THE ANDAMAN ISLANDS

64 cases were observed, 42 with jaundice (of which 8 were light cases, however). Hæmorrhage occurred in 14 cases and albuminuria in 29. 12 patients relapsed. The blood picture showed leucocytosis, at times a certain amount of lymphocytosis with left deviation (myelocytes), and anæmia. The resistance of the erythrocytes was normal or reduced. There were, in all, 12 fatal cases, all of which were icteric.

The above account of the symptoms conveys the impression of a disease as severe as leptospirosis icterohæmorrhagica. But an investigation in regard to the pathogenic agent showed that there

were two of these, each differing from *L. icterohæmorrhagæ*, and causing sickness with different symptoms.

The leptospiræ which appeared to be responsible for the disease were demonstrated by blood cultures on Noguchi's medium, or Fletcher's modification of that medium. Blood from the 4th or 5th day of the disease was positive in as many as 60-85% of the cases ; after the 7th day, however, it was impossible to make any cultures.

Leptospiræ were observed in the urine from the 9th to the 44th day.

ANDAMAN STRAINS

Altogether TAYLOR & GOYLE obtained twenty-eight cultures : four strains were isolated from mild anicteric cases (group CH₃₁) and twenty-four from severe and moderately severe cases, nineteen of them with and five without jaundice. The last group also included fatal cases (group CH₆, CH₁₁, CH₆₂). TAYLOR & GOYLE compared their strains with others by means of serological tests—agglutination-lysis reactions and the adhesion phenomenon. It was found that the CH₁₁ strain was an entirely new type (Andaman A). Strain CH₃₁ (Andaman B) appeared to be more or less similar to *L. akiyami* A.

The Andaman A and B strains were received in Amsterdam from the National Collection of Type Cultures in London. Sera were made with both strains, and the strains and sera examined in the usual way.

Tables 21 and 22 which show various reactions of the Andaman strains with their sera indicate that the Andaman A is an entirely separate strain and very easy to distinguish from all others. On the other hand, Andaman B reacted up to the full specific titre with the anti-Moscow V serum, and its serum also reacted with the Moscow strains up to the full specific titre or one-third of that titre. On the strength of these serological reactions, it is accordingly to be assigned to this group. This classification is further confirmed by its para-specific reactions with the Rachmat sera and the paraspecific reactions of its serum with the Rachmat strains, as well as by its pathogenic properties, as a genuine *L. grippotyphosa* for, it caused only four slight cases.

Table 21.—REACTIONS OF THE ANDAMAN A AND B STRAINS WITH VARIOUS SERA

Serum	Titre of the serum	Strain	
		Andaman A	Andaman B
Andaman A	10,000	10,000	0
Grippotyphosa group :			
Andaman B	100,000	0	100,000
Moscow V	30,000	0	30,000
Ictero-hæmorrhagiæ group :			
Wijnberg	10,000	0	0
Canicola group :			
Resoort	30,000	0	0
Salnem	10,000	0	0
Zanoni	30,000	10	10
Rachmat group :			
Rachmat	30,000	0	100
Akyami A	100,000	0	100
Swart v. Tienen group :			
Swart v. Tienen	10,000	0	0
Dog. H.C.	30,000	0	0
Hebdomadis group :			
Hebdomadis	30,000	0	0
Pomona	30,000	0	0
Ballico	30,000	0	0

Table 22.—REACTIONS OF THE SERA OF THE ANDAMAN A AND B STRAINS WITH VARIOUS STRAINS OF LEPTOSPIRÆ

Strain	Serum	
	Andaman A Titre 10,000	Andaman B Titre 100,000
Andaman A	10,000	0
Grippotyphosa group :		
Andaman B	0	100,000
Moscow V	0	30,000
Moscow VIII		100,000
Ictero-hæmorrhagiæ group :		
Wijnberg	0	30
Rat 219	0	10
J.J.D.	0	0
M. 210	0	
H.Zw.	0	
Canicola group :		
H. Utrecht IV	0	0
Resoort		0
Salnem	0	0
Rachmat group :		
Rachmat	0	1,000
Kartomonawi	0	30
Akiyami A	0	
Swart v. Tienen group :		
Swart v. Tienen	0	0
Cat M.	0	0
Dog H.C.	0	0
Hebdomadis group :		
Hebdomadis	0	0
Hd 7	0	0
Autumnalis B.	0	
Pomona	0	10
Ballico	0	30

¹ See note to table 9.

GUINEA-PIG INOCULATION OF ANDAMAN STRAINS

Very few of the guinea-pigs inoculated with patients' blood or urine died (2 out of 22 and 1 out of 19 respectively). A few had jaundice or hæmorrhage, while leptospiræ were found in the blood or kidneys of a few others. Cultures of Andaman A strain also showed little virulence for guinea-pigs; they did, however, infect young guinea-pigs (120 grammes) and their virulence increased rapidly in successive passages. The other strain, CH₃₁, also had no pathogenic effect on young guinea-pigs.

EPIDEMIOLOGY OF LEPTOSPIROSES IN THE ANDAMAN ISLANDS

The disease occurred chiefly among adults working in mud or in marshy districts in the autumn. Thus, 18 cases occurred in one place where a dam was being built. There were also many victims among soldiers who tramped a great deal through mud.

The pH of the water, 6.9 or more, was favourable to the growth of leptospiræ, which were therefore easily demonstrated by the investigators. The examination of rats did not give such satisfactory results. To begin with, rats, were scarce at the time. Moreover, no leptospiræ could be demonstrated in the seven house-rats and 22 field-rats which were obtained. TAYLOR & GOYLE think it possible, however, that pathogenic leptospiræ are passed out with human and animal urine into the water, where they remain pathogenic for some time. Though the investigators recognise various kinds of leptospiræ serologically, and differences in their virulence, evidenced by the varying severity of the disease caused, they are inclined to wonder whether it is worth while to do more than describe all cases as "leptospirosis" instead of distinguishing between Weil's disease, seven-day fever, mud fever, etc. We shall revert to this matter further on.

G. LEPTOSPIROSES IN AUSTRALIA

1. Cases of leptospirosis have been reported in three places : in Queensland : at Brisbane, at Pomona 86 miles to the north, and in the district of Ingham 500 miles further north.

In each of these places, both the syndrome and the agent were different.

(a) *Ingham district* (COTTER & SAWERS, MORISSEY, LUMLEY).—Here the disease occurs in an endemic form, sometimes developing into an epidemic. Mild and severe cases have been described, with and without jaundice. Only icteric cases were fatal.

	Number of cases	Number with jaundice	Deaths
October 1933-February 1934	40	16	4
June 1934	32	4	2
August 1934	80	0	0
September 1934	1	1	1
Subsequently	5		
	158	21	7

The disease chiefly occurs among cane-cutters and cane-farmers who work in the fields, while the women and children, who remain indoors, are not attacked by it. It breaks out at the beginning of dry spells after heavy rains. The pools which remain, and in which people walk without protecting their feet, can easily be infected by rats. The infection may also be contracted through touching cane which has been fouled by rats. Two different strains of leptospira were found, Ballico and Zanoni (*L. australis* A and B). Both are pathogenic to guinea-pigs. In experiments made with the Zanoni strain, 10 out of 11 died ; and of a series of 5 injected with the Ballico strain every one died, despite the fact that, in this case, the organism had been grown in culture for a whole year. Agglutination-lysis tests applied to the sera of numerous patients gave a specific reaction in every instance with one or other of these strains. Both were found in rats. Of 60 specimens of *Mus norvegicus*, *Mus rattus* and *Mus alexandrinus*, 30% were carriers, while the bandicoot (*Bandicota malabarica*) was also found to be infected. *M. culnorum* was subsequently reported as being similarly a carrier of leptospiræ.

(b) In *Pomona* (CLAYTON, DERRICK & CILENTO), conditions were quite different. Only a few cases of a fever lasting for about 8 days occur each year in dairy farms (30 cases in five years).

The disease is not fatal. Its mildness and the tendency to opacification of the vitreous humour made the disease suggest a certain resemblance to Japanese nanukayami from which it appears, however, to differ in certain clinical particulars. Thus it lasts eight days or more instead of seven, and produces no swelling of the glands. In any case, the pathogenic agent is a different one.

A strain was isolated in one of these cases.¹ It appeared to be entirely new, and to have little pathogenicity for guinea-pigs, for only 2 out of 22 guinea-pigs died of leptospirosis (with jaundice). No virus reservoir has yet been found.

(c) In *Brisbane* (JOHNSON, BROWN & DERRICK), three cases have so far been described, which all exhibit the classical symptoms of leptospirosis icterohæmorrhagica. One patient, who had contracted the disease in North Queensland, died. The other two had worked at Brisbane, in the same sewer, but with a time interval of seventeen months. The diagnosis of the first cases was made retrospectively. The strain was cultivated from the third patient, and strains were also obtained from rats. They were all *L. icterohæmorrhagiæ*. The human strain J.J.D. was the only one which gave a high paraspecific reaction with anti-Andaman strain serum, while the serum of the patient concerned also reacted with the Andaman strains.

SEROLOGICAL REACTIONS WITH THE AUSTRALIAN STRAINS IN AMSTERDAM

Various strains and human sera were sent to us,² and sera were produced in Amsterdam with the Ballico, Zanoni and Pomona strains. These Australian strains and sera were tested with various leptospira group sera and strains at present available at Amsterdam.

¹ In the other cases, the diagnosis was therefore exclusively clinical.

² The Pomona and Ballico strains sent by Dr. E. H. DERRICK (Laboratory of Microbiology and Pathology, Brisbane); the Zanoni strains, Rat 144, Rat 145, Halifax and De Primo by Dr. W. C. SAWERS (School of Public Health and Tropical Medicine, Sydney) on behalf of Professor SUTTON.

1. The Ballico strain was found to belong to a separate group comprising several other strains isolated in the same district and to be an entirely new type of strain which did not react with other sera, with the exception of a slight paraspecific reaction with Rachmat and Andaman B (Table 23). The Rachmat and Moscow V strains were also the only ones to give a paraspecific reaction with anti-Ballico serum (Table 24).

2. Pomona was similarly a new and easily distinguishable strain, which gave a fairly high paraspecific reaction with Rachmat and akiyami A serum, and a lower reaction with *L. icterohæmorrhagiæ*, and Andaman B serum (Table 23). Conversely, Pomona serum always reacted with the Rachmat strains, but gave little reaction, if any, with others. (Table 24).

3. The classification of the Zanoni strain offered some difficulties.

(a) The Zanoni serum gave a very high paraspecific reaction with a few classical strains, though not up to the limit of the specific titre.

This and tests against Zanoni sera made with heated antigen, in which the classical strains gave a lower reaction (Table 25), together with Castellani's test, showed, however, that Zanoni was not a classical strain.

(b) The Zanoni and Salinem strains gave a high reaction with each other's serum (the Zanoni strain even gave a reaction up to the specific titre with a somewhat unreliable Salinem serum). There again, reactions with sera prepared by means of heated antigen and Castellani's test showed Zanoni and Salinem to be different (Table 26). Notwithstanding the high paraspecific reaction of each strain with the serum of the other, which, in any case, indicates some degree of similarity in antigenic structure, we are of the opinion that the Zanoni strain should, for the present at any rate, be called by the name LUMLEY gave it—i.e., *L. australis* B. A further investigation will still have to show whether the strains have so much affinity that they should be classified in a single group (the Salinem group).

4. Judging by its reaction up to the specific titre limit with icterohæmorrhagiæ serum, the strain J.J.D. (from Brisbane) appears to belong to the classical group; such a classification is also in keeping with its paraspecific reaction with Canicola and Salinem (Table 23).

The high paraspecific reactions of J.J.D. with anti-Andaman sera which have been described in Australia were not obtained

in Amsterdam. This shows that a single strain inoculated into two rabbits, one in Australia and one in Amsterdam, can produce sera which differ greatly in respect of their paraspecific reactions. J.J.D. belongs to the classical strains which, as has been said above, give with anti-Zanoni serum a high reaction, which appears to be non-specific (Table 25).

4. SUMMARY OF THE DIFFERENTIAL CHARACTERS OF SOME OF THE KNOWN FORMS OF LEPTOSPIROSIS IN MAN

Table 27 gives in a summarised form the main characteristics of the various forms of leptospirosis occurring in man, which are caused by clearly-defined types of leptospiræ and present a definite clinical picture. The table does not include any details relating to endemic and epidemic manifestations of leptospiral infections due to two or more pathogenic agents as yet undefined, or for which there is as yet no definitely established connection between the clinical picture and the type of leptospira involved (*e.g.*, the akiyami disease, the cases in the Federated Malay States, the epidemic in Ingham, etc.).

Where the number of cases is small, the information given concerning them must be treated with great caution.

The forms of disease mentioned in Table 27 are listed in order of increasing virulence for human beings, virulence for man goes hand in hand with the severity of the jaundice and virulence for guinea-pigs.

The various forms of leptospirosis can be fairly easily classified into four or five clinical groups. It is true that even in severe epidemics light and very light cases also occur which cannot be distinguished on mere clinical grounds from those of milder forms of leptospirosis. If, however, the distinction is difficult to make for individual cases, it is far easier when one deals with epidemics.

1. The first four diseases ["mud fever" (autumn fever), Andaman B, nanukayami and Pomona fevers] do not cause jaundice and are never fatal.

Clinically, they are not quite identical; thus there may be differences between nanukayami and Pomona fever, as regards swelling of the lymph glands.

Table 23.—SEROLOGICAL REACTIONS OF THE STRAINS FROM AUSTRALIA WITH VARIOUS MONOVALENT SERA

Strains	Ballico Titre ¹ : 30,000	Pomona 30,000	Saltnem 10,000	Icteroh. 10,000 100,000	Canicola 30,000	Rachmat 30,000 Andam. A. 100,000	Swart v. Tienen 10,000	Hebdo- madis 30,000	Grip- typhosa 30,000 And. B. 100,000	Andam. A 10,000	H.C. 30,000
Ballico	t ²	0	0	0	0	t/100 And.A. t/300	0	0	0 Andam. B. t/3,000	0	0
de Primo ...	t	0	0	0	0	0	0	0	0		
Halifax	t	0	0	0	0	0	0	0	0		
R.145	t	0	0	0	0	t/100	0	0	0		
Pomona	0	t	0	t/300	0	t/10 And.A. t/100	0	0	0 Andam. B. t/10,000	0	0
Rat.144	0	0	t	t/100	t/300	0	0	0	0		
Zanoni I	0	0	t	t/10 t/30	t/100	0	0	0	0		0
Zanoni II ...	0	0	t								
J.J.D.	0	0	t/300	t	t/10	0 t/3,000	t/300	0	0 0	0	0

¹ See note to Table 9.² See note to Table 15.

Table 24.—SEROLOGICAL REACTIONS OF STRAINS OF VARIOUS GROUPS OF LEPTOSPIRÆ WITH SERA FROM AUSTRALIAN STRAINS

Strain	Sera					
	Ballico (titre ¹ 30,000)		Pomona (titre ¹ 30,000)		Zanoni (titre ¹ 30,000)	
<i>Icterohæmorrhagæ</i> group :						
Wijnberg	10	t/3,000	30	t/1,000	3,000	t/10
Wismar						t/10
J.J.D.	0		0		10,000	t/3
Kantorowicz .					10,000	t/3
Rat 219	0		30	t/1,000		
<i>L. canicola</i> group:						
H Utrecht IV.	0		0		300	t/100
Ballico group :						
Ballico	30,000	t	0			
De Primo	30,000	t	0			
Halifax	30,000	t	0			
Rat 145	30,000	t	0			
Zanoni group :						
Zanoni	0		0		30,000	} t
					100,000	
					30,000	
Rat 144	0		0		30,000	t
Salinem group :						
Salinem	0		0		10,000	t/3
Polhaupessy .	0				10,000	t/3
Rat 148					10,000	t/3
Sowirono					3,000	t/10
Imoen	0				10,000	t/3
Pomona group :						
Pomona	0		100,000	t		
			30,000	t		
Rachmat group :						
Rachmat	30	t/1,000	30	t/1,000		
Jaw Jit			100	t/300		
Baermann	0		30	t/1,000		
Bangkinang ..	0					
3701	0		300	t/100		
Akiyami A	0		300	t/100	0	
Swart v. Tienen group :						
Swart v. Tienen			0			
Cat M.	0		0			
Hebdomadis group :						
Hebdomadis .	0		0		30	t/1,000
Autumnalis B.	0		0		30	t/1,000
Hd ₁	0					
Dog H.C. group :						
Dog H.C.			0			
Andaman A. group :						
Andaman A ..	0		0		10	t/3,000
Grippotyphosa group :						
Moscow V	30	t/1,000	0		10	t/3,000
Andaman B ..	0		0		10	t/3,000

¹ See note to Table 9.

² See note to Table 15.

Table 25.—PARASPECIFIC REACTIONS OF CERTAIN CLASSICAL STRAINS WITH ZANONI SERA

Strains	Sera				Sera of classical strains									
	Zanoni I ¹ Titre ² 30,000		Zanoni 0 ³ 3,000		Wismar 100,000 30,000		Wijnberg 30,000		Lishon 10,000		Ila 50,000		Flte 50,000	
	³	⁴	³	⁴	³	⁴	³	⁴	³	⁴	³	⁴	³	⁴
Wijnberg	3,000	t/10	>30	t/100			30,000	t			50,000	t	50,000	t
Wismar	3,000	t/10			30,000	t			10,000	t				
J.J.D.	10,000	t/3	30	t/100	30,000	t								

- ¹ Zanoni I = first serum prepared with a Zanoni strain.
- ² Zanoni 0 = Zanoni serum prepared with heated antigen.
- ³ Reaction expressed by the reciprocal of the serum dilution.
- ⁴ Reaction expressed as the proportion to the titre of the full specific reaction.

Table 26.—SEROLOGICAL REACTIONS OF STRAINS FROM THE ZANONI AND THE SALINEM GROUP WITH SERA OF BOTH GROUPS

Strains	Sera											
	Salinem I ¹ Titre ² 10,000		Salinem II ³ 100,000		Salinem 0 ⁴ 10,000		Zanoni I ⁵ 100,000 > 30,000		Zanoni II ⁶ 30,000		Zanoni 0 ⁷ 3,000	
	⁷	⁸	⁷	⁸	⁷	⁸	⁷	⁸	⁷	⁸	⁷	⁸
(a) Zanoni group :												
Zanoni	10,000	t	30,000	t/3	3,000	t/3	> 30,000	t	> 30,000	t	3,000	t
Rat 144 (Australia)	10,000	t			3,000	t/3	> 30,000	t			1,000	t/3
(b) Salinem group :												
Salinem	10,000	t	100,000	t	10,000	t	10,000	t/3	> 10,000	t/3	> 300	t/10
Polhaupessy	10,000	t			3,000	t/3	10,000	t/10			300	t/10
Rat 148 (Semarang)	30,000	t+			3,000	t/3	> 10,000	t/3			> 300	t/10
Sowirano	10,000	t					> 3,000	t/10				
Djalio			300,000	t+	3,000	t/3			3,000	t/10	300	t/10

- ¹ Salinem I = old serum not fully reliable.
- ² Salinem II = freshly prepared serum.
- ³ Salinem 0 = Salinem serum made with heated antigen.
- ⁴ Zanoni I = first Zanoni serum.
- ⁵ Zanoni II = second Zanoni serum.
- ⁶ Zanoni 0 = Zanoni serum made with heated antigen.
- ⁷ Reaction expressed by the reciprocal of the serum dilution.
- ⁸ Reaction expressed as the proportion to the titre of the full specific reaction.

There are undoubted etiological differences between them, as the *L. grippityphosa*, *L. hebdomadis* and the Pomona strains are not in the least alike in antigenic structure. The Andaman B strain, on the other hand, appears to be the same as Moscow V (*L. grippityphosa*), since the reaction of each strain gives with the serum of the other a reaction to the full specific titre of the serum. Epidemiologically, there would also appear to be more similarity between the Andaman B and Moscow V forms of the disease than between these two and the Pomona and *hebdomadis* (nanukayami) forms. Though "mud fever" is not necessarily connected with floods (sporadic cases also occur among persons not working in mud or water), the fact remains that the great majority of the known epidemics is so connected, while the cases in the Andaman Islands occurred among people working in, or patrolling in, the mud. No connection has, however, been demonstrated between the Pomona disease and mud or water, and nanukayami, too, can seemingly occur without their presence.

It is not yet known whether the various types of leptospiræ are carried by different animal species. *Microtus montebelloi* has been found to be a carrier of *L. hebdomadis* in Japan. As all three other forms of the disease are also contracted in the countryside, the field-mouse (field-rat) is suspected of transmitting these also, but up till now none of the three infections (*L. grippityphosa* Andaman B and Pomona) has been found in rats, mice or field-mice.

2. The *L. canicola* infection is the next in the table. It does not cause either jaundice or death in the Netherlands (12 cases). A case with jaundice has, however, been reported in San Francisco and another in Denmark (verbal information from BORG PETERSEN), though it is believed that, in the latter, there was liver trouble of long standing. Before we can gain any idea of the proportion between icteric and non-icteric cases, we must therefore wait until a large number of cases have become known. Judging by the evidence of the Netherlands, jaundice should seldom or hardly ever occur. The pathogenic agent differs from all the others in antigenic structure, but is more closely related to *L. icterohæmorrhagiæ* than the four strains mentioned above, and can sometimes only be distinguished from it after a thorough examination.

Epidemiologically also, the *canicola* infection differs entirely from those already discussed (and those which follow), for the

source of infection is the dog, the only known carrier. Not only is *canicola* not found in rats, but so far it has proved impossible to infect the rat with it experimentally.

3. We now come to some forms of disease in which jaundice is of more frequent occurrence, and which can prove fatal—viz., the Rachmat, Salinem and Swart van Tienen infections.*

The number of cases in which both the clinical symptoms and the strain are known is so few, however, that it is impossible to say with certainty which of the three is most dangerous and most liable to cause jaundice. The information available would seem to show that the Swart van Tienen strain is the most dangerous, but this strain has been isolated from cases occurring among independent population, in which mild attacks of a disease remain undetected, whereas Rachmat and Salinem infections come from a region in which plantation coolies are removed to hospital even for mild affections (Deli, Sumatra). Not until further data have been collected will it be possible to say whether these three strains differ in their pathogenicity for man, and if so, to what extent.

The Rachmat and Salinem infections were frequent among persons working in damp places, and also occur, now and again, among soldiers on patrol (Atjeh). The Swart van Tienen cases did not appear to be so definitely connected with damp places (Java), but also occurred after bathing in the river or patrol duty (Borneo). It is therefore unlikely that great epidemiological differences exist between the three infections. The three leptospiral strains differ clearly from each other, however, and from all other known leptospiral strains in their antigenic structure.**

The Salinem strain, like *L. canicola*, is, however, closely related to the classical *L. icterohæmorrhagiæ*, in so far that strains of this type always give a paraspecific reaction with the latter, sometimes even a high one.

* This group probably includes the Ballico and Zanoni forms of the infection in Ingham (*L. australis* A and B). Cases with jaundice occurred, though not so frequently as with *L. icterohæmorrhagiæ* infections. The case mortality was 5%, but we do not know to what extent the Ballico and Zanoni forms were severally responsible. Both strains are virulent for the guinea-pig and both are found in rats. (*M. norvegicus*, *Bardicola*, etc.)

** Apart from the fact that, serologically, the Rachmat strain appears to fall into the same group as *L. akiyami* A, or, at any rate, bears a close resemblance to it.

The Swart van Tienen strain has been found in *Mus norvegicus* in Java and the Celebes, and also in cats in Batavia.

The Rachmat animal reservoir is not yet known. True, the Salinem strain was found in a *M. rattus brevicaudatus*, but only in Java, and therefore far from the district where the Salinem strain was prevalent.

This group also includes the Andaman A strain, which was isolated from 24 patients, of whom 19 had jaundice and a few died. The disease occurs among convicts working in the mud and is only found among men, which may be due to the fact that only convicts and soldiers were exposed to the environmental conditions concerned. No animal reservoir was found.

To sum up, it may be said that the forms of disease in this third group either resemble each other clinically or differ but quantitatively. It is possible that when information is available on a large scale it will appear that part of them should belong to the fourth or even fifth group. The pathogenic agents differed serologically; further they differed with regard to animal reservoirs since one of the strains (Swart van Tienen) was found in rats and cats; another (Salinem), in field rats.

The last two forms of the disease are :

(4) the Hasami, which is clinically very similar to leptospirosis icterohæmorrhagica and

(5) leptospirosis icterohæmorrhagia itself.

The Hasami disease is often accompanied by jaundice (according to KOTORII in half the cases), though frequently only of the sclera. It differs from nanukayami inasmuch as it produced more jaundice and hæmorrhage and less gland swelling, and from Weil's disease inasmuch as the fatality rate was decidedly lower—i.e., 1.9% as compared with a leptospirosis icterohæmorrhagica death rate as high as 30% in Japan itself.

These figures have since changed, as have the number of cases, as a result of compulsory notification, health education, the extermination of rats, the use of calcium cyanide as a manure and the introduction of vaccination in some districts. TSURUMI also states that in 1933 the mortality among 1,636 cases of Spirochætosis icterohæmorrhagica was only 4.6%, which, however is still well above that for Hasami fever. Furthermore, the case mortality figure for leptospirosis icterohæmorrhagica has remained high in some

districts in Japan. Thus, during the last few years, 1,237 cases occurred in the Haraki prefecture with a mortality rate ranging between 16.9 and 29.4%. We do not know the incidence of jaundice in cases of leptospirosis icterohæmorrhagica during the last few years in Japan. In the Netherlands the incidence is 40-50% while the case mortality rate for the past few years has fluctuated between 8 and 13%.

Thus the Hasami fever as an *epidemic* appears to be clinically separable from leptospirosis icterohæmorrhagica, though this may not be true of individual cases. There is, furthermore, a clear difference as regards the antigenic properties of the responsible leptospiræ.*

The animal reservoir also is different. *Apodemus speciosus* carries *L. autumnalis*, the cause of Hasami, while *M. norvegicus*, *M. rattus* and *M. rattus alexandrinus* carry *L. icterohæmorrhagiæ***

Table 28 sets forth in somewhat summarised form the strains held in the laboratory at Amsterdam and their reactions with various sera. It is clear that they are all sharply defined strains with marked differences in their antigenic structure.

If the various leptospiræ are examined from the point of view of their action on guinea-pigs, it will be found that they too can fall into a few groups which correspond to the clinical classification.

(1) Strains which are but slightly virulent for man did not seriously affect the guinea-pigs—namely, *L. grippotyphosa*, Andaman B, *L. hebdomadis* and Pomona.

(2) The *canicola* strain, however, which can attain sufficient virulence for man to cause jaundice (one such case is known), does not normally affect the guinea-pig. It proves fatal now and then, but only after several passages and in animals which develop jaundice. Furthermore, few *canicola* strains were, it is true, so virulent for guinea-pigs that they killed half of them in the first passage.

* It is quite possible that *Autumnalis A* may prove to belong to the same group as the Akiyami A and Rachmat strains; serologically, at all events they appear to be related, for tests performed at Amsterdam show them to have much in common as regards antigenic structure. The investigation of the strains for purposes of classification has not yet been completed.

** It is possible, however, that the *Apodemus* can also harbour other strains, and that the same leptospiræ may be transmitted through more than one carrier (e.g., *L. icterohæmorrhagiæ* may be carried by *M. norvegicus* and *Microtus montebelloi* [MITYAJIMA]).

(3) The Salinem strain causes jaundice and kills some of the guinea-pigs in the first passage. The Swart van Tienen strain, though it may be more virulent for man, affected guinea-pigs in more or less the same way as Salinem.

The two strains which are somewhat exceptional are Rachmat and Andaman A.

The latter appears to have been but slightly virulent for guinea-pigs, but this may have been due to their size, as young guinea-pigs were readily infected with it and its virulence increased in the later passages. The Rachmat strain, on the other hand, proved highly virulent for guinea-pigs, little less so, indeed, than the classical strain (Rachmat inoculated with patients' blood killed five guinea-pigs out of six ; a culture of it killed 36 guinea-pigs out of 38 in the first passage).*

The strains of the third group are, therefore, in general more virulent for the guinea-pig than those of the first and second group ; some of them are equal in this respect to the classical strain.

As was to be expected,

4. *L. autumnalis*, and

5. *L. icterohæmorrhagiæ*

are both dangerous strains, but whereas *L. icterohæmorrhagiæ* killed more than 90% (102 out of 106) of the experimental animals at Amsterdam, *L. autumnalis*, though it always infected, only produced icterus (which was invariably fatal) in a certain proportion of the cases—namely, 20 out of 38.

To sum up, it may therefore be said that substantial clinical differences exist between various forms of leptospirosis ; in many cases there is an epidemiological difference as well, for example, between " mud-fever " (occurring after floods), Pomona, which appears to have no connection with floods, and *L. canicola* infection, which is spread by dogs. Finally, the various leptospiræ have totally different animal reservoirs—*e.g.*, *L. canicola*, *L. icterohæmorrhagiæ*, and *L. hebdomadis* are carried by the dog, rat, and *Microtus montebelloi* respectively. So far it has not even been possible experimentally to make the rat a *canicola* carrier, which it is not in nature, whereas it is nearly always possible to infect it with

* *L. australis* A and B which, to judge by the clinical symptoms produced, are very probably similar to the Rachmat strain, are also virulent for guinea-pigs.

Table 27.—SUMMARY OF THE KNOWN HUMAN FORMS OF LEPTOSPIROSIS

<i>Leptospirosis</i>	<i>Clinical symptoms</i>	<i>Epidemiological characteristics</i>	<i>Strain</i>	<i>Animal inoculation</i>	<i>Carrier</i>
<p>"Mud-fever". Thousands of cases. One strain cultivated from various cases.</p>	<p>Practically : <i>no jaundice</i> (except sometimes in the sclera), <i>no mortality</i>, gastro-intestinal symptoms.</p>	<p>Epidemic, endemic and sporadic ; chiefly after floods, among people working on the land ; also women ; sometimes without contact with water (Russia, Germany).</p>	<p><i>L. grippotyphosa.</i></p>	<p><i>Not virulent</i> or only <i>moderately virulent</i> for guinea-pigs ; <i>infects</i> mice, killing them in the 3rd passage.</p>	<p>Unknown.</p>
<p>Nanukayami. Many cases. One strain cultivated from various cases.</p>	<p>Practically : <i>no jaundice, no mortality</i>, swelling of the lymph glands. Sequellæ : <i>opacification of the vitreous humour.</i></p>	<p>In the autumn in Fukuoka and other districts of Japan in rural areas only.</p>	<p><i>L. hebdomadis.</i></p>	<p><i>Not virulent</i> or <i>moderately virulent</i> for guinea-pigs ; still <i>less virulent</i> for rabbits ; <i>not virulent</i> for rats or mice.</p>	<p><i>Microtus montebellii.</i></p>
<p>Pomona fever (7-day fever of Australia). 30 clinical cases. Strain cultivated from one case.</p>	<p><i>No jaundice, no mortality.</i> Sequellæ : <i>opacification of the vitreous humour.</i></p>	<p>Pomona (Queensland, Australia), 30 cases in 5 years, in summer and early autumn. Men aged 16-40, dairy-farmers.</p>	<p>Pomona.</p>	<p><i>Hardly virulent</i> for guinea-pigs ; of 22 guinea-pigs in various stages, 2 died of jaundice and hæmorrhages.</p>	<p>Unknown.</p>

<p>Andaman B fever. 4 cases. One strain cultivated from 4 cases.</p>	<p>4 light cases : <i>no jaundice, no mortality.</i></p>	<p>Found among convicts and soldiers working or patrolling in mud. Chiefly in autumn.</p>	<p>Andaman B agglutination-lysis test shows it to belong to the <i>grippotyphosa</i> group.</p>	<p><i>Not virulent</i> for guinea-pigs.</p>	<p>Unknown.</p>
<p><i>L. canicola</i> fever. 12 cases in the Netherlands. One strain cultivated from 4 cases. The remainder serologically determined.</p>	<p>In the Netherlands, practically <i>no jaundice</i>. One case in San Francisco and Denmark respectively with <i>jaundice, no mortality</i>, a fair proportion (4) with meningeal symptoms.</p>	<p>The dog has been demonstrated to be the source in many cases (in the Netherlands and San Francisco). Men and women.</p>	<p><i>L. canicola.</i></p>	<p>Virulence for guinea-pigs in 1st passage <i>very small</i> ; increased in the course of later passages. Of the guinea-pigs which died : the following showed leptospiræ : 4+, 5 ±, 21— ; In the 1st passage, 5 out of 27 guinea-pigs died ; in later passages, 25 out of 32 died.</p>	<p>Dog ; it was impossible experimentally to make the rat a carrier.</p>
<p>Rachmat infection. 5 cases. Cultures of strains obtained from the 5 cases.</p>	<p>Of 5 patients : 2 <i>no jaundice</i>, 3 <i>jaundice</i> (very light in 1), 1 died.</p>	<p>Endemic in Sumatra, mostly in plantations, etc.</p>	<p>Rachmat.</p>	<p><i>Virulent</i> for guinea-pigs ; 5 guinea-pigs out of 6 had <i>jaundice</i>.</p>	<p>Unknown.</p>

Table 27 (continued)

<i>Leptospirosis</i>	<i>Clinical symptoms</i>	<i>Epidemiological characteristics</i>	<i>Strain</i>	<i>Animal inoculation</i>	<i>Carrier</i>
Salinem infection. 6 cases. Cultures of strains obtained from the 6 cases.	Of 6 patients : 4 no jaundice, 2 with jaundice, 1 died.	Endemic in Sumatra, mostly in plantations, etc.	Salinem.	Moderately virulent for guinea-pigs ; at least 2 guinea-pigs out of 4 had jaundice.	<i>M. rattus brevicaudatus.</i>
Swart v. Tienen infection. 14 cases. Strains cultivated from 9 cases. 5 serologically determined.	Of 14 patients : 7 no jaundice, 7 with jaundice, 3 died. Certain cases are severe, others mild.	Sporadic in Batavia, Macassar, Borneo, Banka, etc. Widely disseminated; men and women.	Swart van Tienen.	Moderately virulent, even in the second passage. In the first passage, 1 guinea-pig out of 5 died ; 3 had jaundice.	<i>M. norvegicus.</i>
Andaman A fever. 24 cases. Strains cultivated from 24 cases.	Of 24 patients : 5 no jaundice, 19 with jaundice, a few died.	Found among convicts and soldiers working or patrolling in mud. Chiefly in autumn.	Andaman A.	Virulence for old guinea-pigs small ; young guinea-pigs can be infected ; virulence increases in successive passages.	Unknown.

<p>Hasami fever. 418 cases. One strain cultivated from various cases.</p>	<p>Half the patients : of 18 patients who were re-examined after a few months, 8 had eye trouble : <i>jaundice</i>, only of the sclera. Case <i>fatality</i> rate very low (1.9%). <i>Opacification</i> of the <i>vitreous humour</i> in perhaps 90% of the cases. Inflammation of the glands in 20%.</p>	<p>Endemic in Nagasaki during the autumn ; found among peasants, school-boys, potters, etc. Women, 30.4%; men, 69.6%; sometimes after falling in the water or fishing ; no connection with the situation of the dwelling in a hilly or flat region and no special connection with water.</p>	<p><i>L. autumnalis</i> Akiyami A ; the agglutination - lysis test shows that this strain belongs to the same group as Rachmat.</p>	<p>Fairly virulent for guinea-pigs, all of which were infected ; those who contracted jaundice died ; 20 contracted jaundice out of a total of 38.</p>	<p>Akiyami A was first found in <i>Microtus montebelloi</i> ; <i>L. autumnalis</i> was subsequently discovered in <i>Apodemus speciosus</i>. Of 210 field-rats, 11% were positive.</p>
<p>Leptospirosis icterohæmorrhagica.</p>	<p>Netherlands : <i>jaundice</i>, 40-60% ; case <i>fatality</i>, about 10%. Japan : 1,636 cases : case <i>fatality</i>, 4.6%. In Haraki : 1,237 cases : case <i>fatality</i>, 16% to 29.4%.</p>	<p>More men than women ; contracted through falling in the water, swimming or occupation that brings the person in contact with water, and through contact with rats. In Japan, usually along rivers, in marshland and by the seaside ; seldom in high and dry districts ; frequently in coal mines, agriculture.</p>	<p><i>L. icterohæmorrhagiæ</i>.</p>	<p>Virulent ; kills guinea-pigs in nearly 100% of cases with jaundice.</p>	<p><i>M. norvegicus</i>. <i>M. rattus alexandrinus</i>. <i>Microtus montebelloi</i>.</p>

L. icterohæmorrhagiæ. These differences in animal reservoirs may prove to be very important. Another important point, and a clear differential feature distinguishing the various epidemics, is the serological properties of the leptospiral strains. A further difference is the degree of virulence for guinea-pigs.

Now it may well be asked whether these diseases, which differ clinically and epidemiologically, and in respect of the carriers of the pathogenic agents and the serological properties of the latter, should be regarded as one disease under the name, for example, of Weil's disease. This would appear to be quite unjustifiable. Even leptospirosis icterohæmorrhagica, as now known, differs so much from what was originally called Weil's disease that the latter name would no longer describe it, let alone "mud-fever", nanukayami, etc. To assume, as is sometimes done in the Netherlands Indies, that there are two diseases—Weil's disease and leptospirosis febrilis—seems even less logical, for there is no reason why Weil's disease should be taken separately and all other forms arbitrarily grouped together. Names like "seven-day fever" also create confusion. Is the seven-day fever observed at Pomona in Queensland, the same as the one occurring in Japan? Clinically speaking, such does not appear to be the case, and it certainly is not the case bacteriologically, since the Pomona and the *L. hebdomadis* strains are plainly different.

If all forms are to be classified under a single item, we would recommend one name, that of leptospirosis, which is appropriate to all forms and indicates what they have in common. To indicate the differences which are so characteristic in some cases, the name of the strain could be added in some form or another—*e.g.*, leptospirosis grippotyphosa, leptospirosis Rachmat, Salinem, etc. (or Rachmat fever, canicola fever, etc.). If a report then came in from some hitherto unaffected district that an outbreak of leptospirosis Pomona or Rachmat had occurred, exact conclusions could immediately be drawn as to the clinical symptoms and the prognosis (assuming that the properties of each strain were accurately known), just as in the case of an outbreak of paratyphoid or typhoid fever. Table 27 indicates that such a stage has not yet been reached, but the blanks on the chart of leptospirosis are steadily decreasing.

Table 28.—AGGLUTINATION-LYSIS REACTION OF THE STRAINS

Strain or group	Sera										
	L. grippotyphosa Titre 30,000 ¹	Andaman B 100,000	Hebdomadis group 30,000	Pomona 30,000	L. canicola group 10,000	Andaman A 10,000	Salinem group 30,000	Swart v. T. group 30,000	Rachmat group 30,000 100,000	Akiyami A 100,000	Icterohæmorrhagie group 10,000 30,000 100,000
<i>L. grippotyphosa</i> ..	30,000	30,000 100,000	0	0	0	0	0	0	30-1,000	1,000	0
Andaman B	30,000	100,000	0	0	0	0	0-10	0	100	100	0
<i>L. hebdomadis</i> group	0	0	30,000	0	30	0	0	10	0-1,000	0	0-25
Pomona	0	10	0	30,000	0	0	0	0	3,000	1,000	100
<i>L. canicola</i> group	0	0	0-30	0	10,000 30,000	0	0	0	0	0	300-3,000
Andaman A.	0	0	0	0	0	10,000	0	0	0	0	0
Salinem group	0	0	0	0	300-1,000	0	30,000	0	0-1,000	30	100-25,000
Swart v. Tienen group	0	0	0-300	0	0	0	0	10,000 100,000	0	0	0
Rachmat group ...	0-300	10-1,000	0	30-300	0	0	0-100	0	30,000 10,000	10,000 100,000	0-300
<i>L. Akiyami A.</i>	30	10	0	300	0	0	0	0	30,000	10,000	300
<i>L. autumnalis</i>			0						10,000	30,000	
<i>L. icterohæmorrhagie</i> group	0-30	10-30	0-50	10-30	30-10,000	0	30-2,500	0-300	0-2,500	1,000	10,000 30,000 100,000

LEPTOSPIROSES

253

¹ The intensity of the reaction is expressed by the reciprocal of the serum dilution.

II

LEPTOSPIROSES OF RATS AND OTHER RODENTS

A. LEPTOSPIRAL INFECTION IN RATS

The first scientific worker to discover spirochætes resembling *L. icterohæmorrhagiæ* in a rodent was MIYAJIMA. He found them, in 1915, in the kidneys of *Microtus montebelloi* and subsequently in an *Epimys* (he examined *M. rattus alexandrinus* and *M. norvegicus*).

Feeling still uncertain in the matter, he took the opportunity, in 1916, when he again discovered a spirochæte in a *Microtus montebelloi*, to inoculate a guinea-pig with infected material. The guinea-pig developed fever and hæmorrhages and, in the later stages, jaundice, while *L. icterohæmorrhagiæ* immune serum killed the detected spirochæte. MIYAJIMA thereupon concluded that he was indeed dealing with a genuine *Leptospira icterohæmorrhagiæ*. In the accessible Japanese literature on the subject, *Microtus montebelloi* is subsequently mentioned only as a carrier of *L. hebdomadis* and *L. Akiyami A.* Thus this single instance of a classical leptospira in the *Microtus* appears to be a unique case.

Subsequently IDO, HOKI, ITO & WANI found the same spirochæte, this time regularly, in *Mus norvegicus* and *Mus rattus alexandrinus* (1916 and 1917). A systematic examination of the organs of the rat appeared to show that leptospiræ were only present in the kidneys.

In Europe, MARTIN & PETTIT were the first to report the discovery of the leptospira in one of a group of five *Mus norvegicus* rats in January 1917.

Shortly afterwards COURMONT & DURAND found infected rats at Lyons; STOKES, RYLE & TYTLER discovered them on the British front in January 1917, while in the same year RENAUX found them on the Belgian front, and MONTI came across an infected rat in Bergamo, whilst GRASSO also discovered one in Genoa in 1918. In 1918, FROMME published an article on a positive rat found in

the German lines, and UHLENHUTH & ZUELZER followed with an article on the infection-index of 110 rats in Berlin. After this, the rat was gradually shown to be a carrier of leptospira in all parts of the world.

The annexed Table 29 shows, as far as we know, where and in what year rats were found to be infected with leptospiræ. It will be seen later on that all the organisms are not the genuine *L. icterohæmorrhagiæ*. For instance, in Japan, the Netherlands, the Netherlands Indies, the Federated Malay States, the Andaman Islands and Queensland, rats were found to be infected with other strains of leptospiræ.

1. METHOD OF INVESTIGATION

The following methods of investigation are used :

A. *Direct Examination of the Kidneys, Other Organs or Urine.*

1. Dark-ground microscopic examination of tissue or urine (IDO, HOKI, ITO & WANI) ;
2. Staining of the kidney substance or urine sediment, with Giemsa, Fontana-Tribondeau, Burri stains, etc.) ;
3. Sections of organs stained by Levaditi's process ;
4. Dark-ground microscopic examination of the mucous membrane of the bladder (SCHWETZ, SCHWETZ & KADANER).

B. *Serological Tests of the Rats' Serum.*

1. Determination of the titre of agglutinins and lysins (methods of Martin, Pettit and Vaudremer, Schüffner and others) ;
2. Rieckenberg's adhesion-test as adapted by Brown & Davis, and others, or complement deviation.

C. *Animal Inoculation.* The experimental animal usually chosen is the guinea-pig ; mice may be used for special purposes (BESSEMANS & THIRY). The experiments can if necessary be completed by testing the immunity of the surviving experimental animals (NICOLLE & LEBAILLY).

Table 29.—INFECTION INDEX OF RATS IN VARIOUS PLACES

				Number exa- mined	Number +	% +	Method of investigation
America							
1917	NOGUCHI	New York	Sewer rat			7 to 8	
"	JOBLING & EGGSTEIN	Nashville, Tenn.		100 ?	+	10	
"	BEAUREPAIRE, ARAGÃO	Rio de Janeiro		6	1		
1918	NEILL	Washington			+		
"	RIBEYRO	Lima (Peru)	<i>M. rattus</i> fully-grown, young	6	2		
				8	0		
1919	NOGUCHI	Guayaquil		24		67	
"	A. OTTERAAN	Chicago		30	1		dark-ground
1920	CARINI	São Paulo		1			inoc.
"	SMILLIE	" "		41	4		inoc.
"	MCDOWELL	Rio de Janeiro			+		inoc.
1921	GUITERAS, LEBREDO & HOFFMANN	Havana					
1922	WADSWORTH, LANGWORTHY, STEWART, MOORE, COLEMAN	Albany, N.Y.		128	22	17.2	
1924	ROBINSON	Baltimore	<i>M. norvegicus</i>	100		7	dark-ground
1926	CAMERON	Toronto			25		inoc.
1927	WALCH	Baltimore	<i>M. norvegicus</i>	51	17	33	dark-ground and inoc.
"	LANGWORTHY & MOORE	Albany, N.Y.				40	dark-ground and
						44	inoc. serol.
1928	ITURBE & GONZALES	Caracas				frequent	
1930	M. DOWELL, B. DE CARVALHO, G. TRAVASSOS	Rio de Janeiro			+		
1931	J. R. RIDLON	San Francisco	<i>M. norvegicus</i> (fully- grown)	50	17	34	dark-ground
			<i>M. rattus alexandrinus</i>	64	2	3	dark-ground

LEPTOSPIROSES

..	L. J. PAWAN	Trinidad	Chiefly old rats	120	32	26.6	
1932	CARBO NOBOA	Guayaquil				2	
1934	E. CHIODI	Buenos Aires				2	inoc.
..	R. PAEZ	Santiago, Chile	<i>M. norvegicus</i>			25	inoc.
			<i>M. rattus</i>				
1935	"	"		253		37	serol.
1937	MEYER, EDDIE & ANDERSON	San Francisco	<i>M. norvegicus</i>	420	139	33	
			<i>M. r. alexandrinus</i>				
			<i>M. rattus rattus</i>				
Africa							
1917	NICOLLE & BLANC	Tunis	Rats	119	0		
..	NICOLLE & LEBAILLY	Tunis	<i>M. norvegicus</i> (slaughter-house)	34		20	inoc.
			<i>M. norvegicus</i> (outside the town)	8		0	inoc.
			<i>M. rattus alexandrinus</i>	3		0	inoc.
						28.5	immunity test
1918	L'HÉRITIER	Algiers	<i>M. norvegicus</i>				
			Summer ; in suburb			3	
			Winter ; in suburb			6	
			Harbour			0.5	inoc.
..	LÉGER & CERTAIN	Dakar	<i>M. rattus alexandrinus</i>				
			<i>M. rattus</i>	120	0		
			<i>M. norvegicus</i>				
1919	G. BLANC	Tunis		107	12	11.2	
			Slaughter-house			15.7	
			Harbour			9.9	
			Town			6.6	
1930	FORSYTH & GOHAR	Cairo	<i>M. rattus alexandrinus</i>	64	2		dark-ground ; without inoculation.

Table 29 (continued)

				Number exa- mined	Number +	%+	Method of Investigation
1934	J. SCHWETZ	Stanleyville	Rats	190	0		
			Mice	136	0		
"	SCHWETZ & KADANER	"	Rats	50	10		dark-ground
Asia							
1915	MIYAJIMA	Japan :			1+		
1916	IDO, HOKI, ITO, WANI	Kyushu	<i>Microtus montebelloi</i>			39.5	micr. 32.4%
		"	<i>M. rattus alexandrinus</i>	86			Inoc. 7%
		"	<i>M. norvegicus</i>				
1917	IDO, KOKI, ITO, WANI	"	<i>M. norvegicus</i>	149		40.2	
			<i>M. rattus alexandrinus</i>	24		8 ?	
"	SAITO	Kyoto				50	
1918	IDO, ITO, WANI	Fukuoka	<i>Microtus montebelloi</i>			5.3	
1922	MATZUSAKI	Kyoto		110		40	
1925	KOSHINA, SHIAZAWA, KITAYAMA	Shizuoka	<i>Microtus montebelloi</i>	10	1	10	
1930	INOUE		<i>M. norvegicus</i>	71	12	17	Rieckenberg
			<i>M. rattus</i>	43	5	12	
1933	ABE & colleagues	Hasami district (Nagasaki)	926 wild rats (in particular <i>Apodemus</i> <i>sp.sp.</i>)		71	7.7	dark-ground
1935	KANEKO, KOTORII, AOKI and previous investigators	Hasami district	<i>Field rats :</i>				
			<i>M. norvegicus</i>	722	0	0	
			<i>M. rattus alexandrinus</i>	103	1	1	
			<i>Apodemus sp.</i>	1668	238	14.3	
			<i>Microtus montebelloi</i>	25	1	4	

		town of Nagasaki	<i>House rats:</i>				
			<i>M. norvegicus</i>	40	0		
			<i>M. rattus alexandrinus</i>	291	0		
			<i>Sunc. caerul</i>	6	0		
			var. <i>riutsuanus</i>				
..	AOKI, KANEKO, MORIMOTO	Hasami district	Field rats	50	14	28	dark-ground
					16	32	+ animal inocul.
					20	40	culture
					18	36	aggl.-lysis test
					42	84	Rieckenberg test
1927-	FLETCHER	F.M.S.	<i>M. rattus diardii</i>			26	
1928			<i>M. rattus griseiventer</i>			0	
1931	TAYLOR & GOYLE	Andaman Is.	House rats	7	0		
			Field rats	22	0		
..	.. (according to						
	ALSTON & BROWN)	Rangoon	<i>Nesobia bengalensis</i>	31		43	
1928	EARL B. Mc.KINLEY	Philippines	Wild rats			1	
1931	R. KNOWLES	Calcutta	<i>M. norvegicus</i>	193			dark-ground or
			<i>Nesobia sp.</i>		2		culture
1934	FARINAUD	Cochin-China				high	
1935	HASLÉ, TOULLEC, VAUCÉL	Hanoi		142	4	2.7	inoc.
1937	ANDERSON (letter to Taylor)	Bombay	<i>M. norvegicus</i>	100	32	32	kidney
	(according to ALSTON & BROWN)		<i>Gunomys varius</i>	100	7	7	
			<i>M. rattus rattus</i>	100	0		
1922	MENDELSON	Siam	?	1483	8	0.54	
		Netherlands Indies:					
1919	HOESEN	Batavia	<i>M. norvegicus</i>		1		inoc. post mor-
							tem
1920	FLU	Batavia	<i>M. norvegicus</i>	35	2		inoc.
1924	KOUWENAAR	S.O.K. Deli	<i>M. rattus diardii</i>	30	2		post mortem
1927	SARDJITO & POSTMUS	Batavia	<i>M. norvegicus</i>	23		17	cult. inoc. dark-
			<i>M. rattus</i>	17		0	ground

Table 29 (continued)

				Number ex- amined	Number +	%+	Method of Investigation
1929	FISCHER	Pinang	<i>M. norvegicus</i>	111		20	dark-ground
"	"	"	<i>M. rattus diardii</i>	89	6	6.5	dark-ground
?	MERTENS	Weltevreden			+		
				350		7	cult.
				216		12	
1930	SARDJITO	Macassar	<i>M. norvegicus</i>	adult			
				134		0	
				young			
"	SLOT	Belinjoe	<i>M. norvegicus</i>	?		0	dark-ground
1931	BOELENS	Semarang				30	cult.
"	KIRSCHNER	Bandoeng	<i>M. rattus diardii</i>	260	+		cult. inoc.
1932	SLOT & v. d. WALLE	Bangkinang	House-rats	40		0	
1933	MOCHTAR	Semarang	<i>M. norvegicus</i>	20		40	cult.
1936	SARDJITO, MOCHTAR, WIRASMO	Ambarawa	<i>M. rattus brevicaudatus</i>	104		21	
				12 adult		50	cult.
				42		7	
				young			
"	"	"	<i>M. rattus diardii</i>	9		0	
Europe							
1917	COURMONT & DURAND	Lyons	<i>M. norvegicus</i>	50	5	10	inoc.
"	MARTIN & PETTIT	Riquebourg	<i>M. norvegicus</i>	5	1		inoc.
"	MARTIN & PETTIT	Lorient	<i>M. norvegicus</i>	12	1		inoc.
"	MARTIN & PETTIT	Rennes	<i>M. norvegicus</i>	1	1		inoc.
"	MONTI	Bergamo			+		
"	RENAUX	Belgian army			1		

..	STOKES, RYLE & TYTLER	British army		9	5		
1918	COLES	Bournemouth	<i>M. norvegicus</i>	100	9	9	microscope
..	FROMME	German army		67	1		
..	GRASSO	Genoa	sewer-rat		2		inoc.
1917	MARTIN & PETTIT	Marseilles	<i>M. norvegicus</i>	30	0		inoc.
			a few black rats				
1918	<i>M. norvegicus</i>	30	at least		
					2		
1919	DALMAU & BALTA	Barcelona		15	13		.
..	FOULERTON	London	<i>M. norvegicus</i>	116	43		
..			<i>M. rattus</i>	7	2		
..	UHLENHUTH & ZUELZER	Berlin		101	10	10	dark-ground and inoc.
1920	STEFANOPOULO	Paris (Bièvre)	<i>M. norvegicus</i>	10	3		inoc.
1922	A. BALFOUR	London	<i>M. norvegicus</i>	154		13.6	urine
			<i>M. rattus</i>	15	0	22.6	kidney
..	CARRIEU & SOLLIER	Montpellier		20	1		
..	PEREIRA DA SILVA	Portugal	<i>M. norvegicus.</i>	12	1		inoc.
1922	SIGALAS & PIROT	Bordeaux		3	2		
..	STEVENSON	London		100	30	30	
1923	ANIGSTEIN	Poland		42	4		dark-ground
..	Slaughter-house	47	9		
..	Town	23	0		
..	GHETTI	Faenza		13	2		
..	MAGGIORA	Bologna		?	+		
..	SCHÜFFNER & KUENEN	Amsterdam	<i>M. norvegicus</i>	207	58	28	dark-ground and inoc.
..	..	Amsterdam	<i>M. rattus</i>	29	1	3	
1924	G. BUCHANAN	Scotland	Rats, field-mice				
..	ETCHEGOIN	La Valette	Slaughter-house	53	4	7.5	inoc.
..	FISCHER	Amsterdam	<i>M. norvegicus</i>	182	38	21	
..	J. SMITH	Aberdeen				24	

Table 29 (continued)

				Number exa- mined	Number +	% +	Method of investigation, etc.
1925	SOESILO	Amsterdam	<i>M. norvegicus</i>	401	45	10	
"	TAKAKI	Vienna		8	2		dark-ground.
1926	CERRUTTI & REITANO	Turin		100	0		inoc.
"	UHLENHUTH & GROSSMANN	Freiburg in Breisgau		51		15.7	dark-ground and inoc.
1927				54		10	"
"	BROWN & DAVIS	London		100	36	36	
"	BUCHANAN	Scotland	<i>M. norvegicus</i> Field-mouse	166	61	36.7	
					1 +		
1929	A. MIDDLETON	Oxford				41.7	
"	SSINJUSCHINA	Moscow		60		8	
1930	SJOEIB PROEHOEMAN		<i>M. norvegicus</i>	64	32	50	
			<i>M. rattus</i>	16	0		
1931	J. P. BIJL & G. KORTHOF	Utrecht	Rats	167		20	
"	LAVERGNE & STUMPF	Nancy	<i>M. norvegicus</i>	100	14	14	
1932	CAMINOPETROS	Athens		146	40	27.3	
		Piraeus		120	0		
"	ERBER	Paris		26	2		
"	JORGE	Lisbon		9	9		
				70	2	3	
"	KUNSTEIN	Freiburg	<i>M. norvegicus</i>	19	8		
"	LÉPINE	Piraeus	<i>M. norvegicus</i>	120	—		
"		Athens	<i>M. norvegicus</i>	13	—		
		Syra	<i>M. norvegicus</i>	6	4		
"	PETZETAKIS	Syra	<i>M. norvegicus</i>	5	5		inoc.
"	H. LOREY	Germany		32	8	25	
"	PETZETAKIS & KYRIAZIDES	Athens		90	3	3	

1933	G. BASILEWSKI	Kiev		91		30.7	
..	BESSEMANS, THIRY	Brüssels	Sewer rats	57	22	39	
			Canal rats	84	27	32	
			House rats	46	0		
			White laboratory rats	50			
			Rats from attics				
			House mice	17	0		
..	BESSEMANS, THIRY, TIELLIEU		Sewer rats	84	27	32	
..	KISTER	Hamburg				9.6	
..	SPINELLI & MARCHESI	Rome	<i>M. norvegicus</i>	53	2	3.7	
..	UHLENHUTH & ZIMMERMANN		Tame white	33	17		serol. inoc.
1934	OLIN	Stockholm	1931 <i>M. norvegicus</i> (Stockholm)	7	3		inoc.
			1934 <i>M. norvegicus</i> (Stockholm)	26	0		
			1934 <i>M. rattus</i> (Stockholm)	92	6	6	inoc.
				11	0		
..	REITER	Hamburg				14	
1935	J. v. d. HOEDEN	Utrecht	Wild rats	11	6		serol.
..	SPINELLI & MARCHESI	Rome			3		
1935	SANDUS, BAYARRI, MONTOLIN- VOLANT, SABINA	Valence	<i>M. norvegicus</i>	33	1		
..	M. ZUELZER	Denmark	<i>M. rattus alexandrinus</i>	2	0		
			<i>M. norvegicus</i>	91	23	45	
			<i>M. rattus</i>	2			
1937	BROWN (ALSTON & BROWN, 1937)	Oxford (England)	<i>Apodemus sylvaticus</i>	36	0		
..	MALMGREN	Sweden			+		
..	WIRTH	Vienna	<i>M. norvegicus</i>	166	9	35.5	
			<i>Arvicola arvicola</i>	45	6	13.3	
			<i>M. musculus</i>	24	4	16.6	
1937	ADAMSKI	Kattowice				10	

Table 29 (continued)

				Number exa- mined	Number +	% +	Method of Investigation, etc.	
Oceania								
1934	COTTER & SAWERS	Queensland (Ingham)	<i>M. norvegicus</i>	60	20	33	dark-ground	
			<i>M. rattus rattus</i>					
			<i>M. rattus alexandrinus</i>		7			+
			<i>Bandicota Sp.</i>					
	" "		<i>R. culmorum</i>		heavily infected			
1937	JOHNSON, BROWN & DERRICK	Brisbane	Wild rats	85	2	2.3	microsc.	

D. *Cultures.* Cultures can be made by setting pieces of tissue or a loopful of the material in a culture medium. For the composition of the various culture media, see among others MARTIN & PETTIT, and UHLENHUTH & FROMME.

Many investigators, however, combine various techniques, usually animal inoculations followed by one or several other tests.

Observations on Methods.

A. At Amsterdam, kidney substance is microscopically examined with dark-field illumination in a drop of water on a cover-slip, objective D, eye-piece IV, Zeiss. If leptospiræ are detected some of the kidney emulsion is injected into a guinea-pig, so that the strain can be isolated and identified. The advantage of this method is that the preparation of the slide and examination take little time. It is necessary to scrape off a good deal of the surface of the kidney (only of the cortex, however), as the leptospiræ are only found in foci in the convoluted tubules. Owing to this localisation, it is advisable to examine both kidneys. Even then, positive rats may not be detected if very few leptospiræ are present. Some of the latter may be detected, however, if substance from all the kidneys which are negative under the microscope are inoculated into guinea-pigs. Even greater completeness can be attained by making cultures from the renal cortex and by serological testing.

The microscopical examination of urine or urine sediment with dark-field illumination, though very easy does not yield any better results, as leptospiræ may not be present in every sample of urine. Besides, they die relatively quickly in acid urine and are then sometimes difficult to detect. In any case, the urine must be examined while it is still as fresh as possible.

B. Various research workers have demonstrated infection in wild rats serologically (BROWN & DAVIS, 1927, LANGWORTHY & MOORE, 1927, ZIMMERMANN, 1930, ERBER & PROEHOEMAN, 1934, REITANO & MORSELLI, 1935) some of them reporting the titre obtained, which appears at times to be very high. Thus ZIMMERMANN found that 37 out of 85 *Mus norvegicus* rats yielded a titre of 1:400-1:5,000 ; there was even a case of 1:12,000. SJOEIB PROEHOEMAN, at Amsterdam, found that one out of 12 carriers gave a negative reaction and the others gave values of 1:50-1:2,500,

while 21 out of 22 non-carriers gave a negative reaction and one gave a value of 1:25. BESSEMANS & THIRY found that some sewer rats in the Brussels district had a titre of 1:2,000-1:5,000, while PAEZ (Santiago, Chile) obtained positive reactions with 37 out of 253 rat sera the titres ranging from 1:20 to 1:3,500. As will be seen later on, the serological method gives many positive results, more, for example, than animal inoculations. There are, however, also objections to this method :

1. With very low titres it is difficult or almost impossible to say which reactions are specific and which aspecific ;

2. It is not known for certain whether the rat serum can lose its reacting properties after a while, as has, for example, been shown to be the case after human infections in the Netherlands Indies. This would appear to be true of rats also, as some of them are found to be leptospiræ-carriers without giving a positive serum reaction (PROEHOEMAN, ZIMMERMANN). Whilst serological tests may thus, on the one hand, fail to detect certain infected rats, they may, on the other, occasionally give a positive result in the case of rats which do not harbour the leptospira (ZIMMERMANN).

C. Injections into guinea-pigs of organic substance finely ground up in saline solution or of a culture, may be given subcutaneously, intraperitoneally, intracordially (UHLENHUTH) or into the liver (v. D. VELDE). The material may be instilled in the eye, or it may be mixed with food or sniffed.

In this way, only strains which are pathogenic to the guinea-pig can be detected. It should be noted, however, that when only a few leptospiræ are present in the kidney, they are sometimes not detected by examination with dark-field illumination or staining, whereas they are brought to light by animal inoculation. Furthermore, strains which are scarcely, if at all, pathogenic can still be detected in the guinea-pig, if it is systematically examined, even though it may not appear to be ill. For this purpose, peritoneal fluid or blood should be examined daily with the dark-field illumination and the urine similarly controlled after about ten days. At Amsterdam, 109 out of 121 rats which were microscopically examined and found positive in the course of the past three years were also shown to be positive by animal inoculation. In 106 of these cases, the leptospiræ killed the guinea-pig ; only 3 guinea-pigs recovered.

This indicates a high degree of virulence. The remaining 12 showed no trace of disease. The reason for non-infection was not investigated; it may have been the small quantity injected, the lack of virulence or the presence of a variety of leptospira other than the classical one.

When other leptospiræ—*e.g.*, *L. canicola*—are used, it frequently happens that all the experimental animals remain alive after the first inoculation, though they are all infected, as an examination of the peritoneal fluid, blood or urine or a subsequent inoculation with a virulent strain will show.

It would appear that not only should small guinea-pigs be used for the test but that, in addition to this, not every guinea-pig is receptive.

D. Renal cortex cultures give very good results (AOKI, MOCHTAR, SARDJITO and many others). Here again, both kidneys should be used. MOCHTAR, for example, found in Semarang that, among 20 rats, 40% were positive; SARDJITO, MOCHTAR & WIRASMO found that 21% of 104 rats from the Rewa Pening district were infected. Figures comparing this method with the others are furnished by AOKI, among others (see Table 30 A). From one point of view, this method of examination is not as satisfactory as the dark-field method, as several days or weeks must elapse before results are obtained. The result is sometimes obscured through mixed bacterial infections often found in rats.

Table 30 A shows that animal inoculation gives the smallest number of positive results. The largest number is obtained by serological tests and cultures. The dark-field method of investigation yields results which are half way between those of the serological method and animal inoculation, but it has the great advantage that results are obtained within ten minutes. Thus, it is obviously advisable to combine the various methods as is strikingly shown by Table 30 B.

2. DIFFERENCE IN THE INFECTION-INDEX OF OLD AND YOUNG RATS

The difference in the infection-index of old and young rats has been noticed by various investigators (MARTIN & PETTIT, RIBEYRO,

Table 30.—COMPARISON OF RESULTS OBTAINED WITH DIFFERENT METHODS OF INVESTIGATION FOR DETECTING LEPTOSPIRAL INFECTION
A.

		Number of rats examined	Microscopically (dark-field; kidney substance) %	Serologically %	Animal inoculation %	Cultures %	DF + A %	A + I %	
IDO, HOKI, ITO & WANI	1916	86	32.4		7				DF + A
NICOLLE & LEBAILLY	1918	34			20			25	A + I
SMILLIE	1920	41			10			75	A + I
ROBINSON	1924	100	7		4				DF + A
WALCH	1926	51	28		12		33		DF + A
LANGWORTHY & MOORE	1927	?	40	60					serol. direct
FORSYTH & GOHAR	1930	64	2		0				DF + A
ZIMMERMANN	1930	85		46	40				serol. + A
INOUE	1930	114	2	18	15	8			serol. DF + A. culture.
REITANO & MORSELLI	1935	?		44	40				serol. + A
AOKI, KANEKO, MORIMOTO . .	1935	50	28	36		40	32		serol. DF mostly cultures.

DF = dark-field illumination. A = animal experiment. I = investigation of immunity.

B.

			Urine microsc.	Kidney microsc.	Animal experiments	Cultures
SJOEIB, PROEHOEMAN	1930	43	17 + 26 -, of these	8 + 18 -, of these	5 + 13 -, of these	1 + 12 -
			17 +	8 +	5 +	1 = 31 positive = 72%.

SMILLIE, etc.). SCHÜFFNER & KUENEN investigated the proportions, using a large number of rats and adopting the length of the rat as their standard, those longer than 20 cm. (excluding the tail) being classed as adults, and those less than 20 cm. in length as young rats. Of 207 *Mus norvegicus* rats, 28% were found to be infected ; the infection index was 45% among those longer than 20 cm. and only 2.4% among those shorter than 20 cm. Subsequent investigations by various workers in the Institute confirmed these results (see Table 31).

The results were also confirmed by MIDDLETON (who found that 41.7% of the total number of rats were infected, whereas the figure for fully grown rats was 56%, SARDJITO, KUNSTEIN, COTTER & SAWERS, KANEKO, KOTORII, AOKI, and also ALSTON & BROWN.

3. WHAT RATS ARE THE MAIN LEPTOSPIRA RESERVOIRS ?

Table 32 gives a brief outline of the extent to which certain rats (field-mice and mice) are found to be infected.

These figures cannot, however, be compared without certain qualifications. The composition of the groups from which they are calculated is not always the same in respect of age, and is in some cases unknown. Furthermore, different investigators have used different methods.

The frequent difference in the infection-index of *Mus norvegicus* and *Mus rattus* noted by the same investigator deserves, however, to be noted (e.g., IDO and his collaborators, NICOLLE & LEBAILLY, SCHÜFFNER & KUENEN, SARDJITO & POSTMUS). The place at which the rat is caught should also be borne in mind (see Table 33).

4. DEPENDENCE OF THE DEGREE OF INFECTION ON THE PLACE OF CAPTURE

It has sometimes even been reported that infection among rats is confined to special groups ("clans", "lots"). Thus, LAVERGNE & STUMPF found in 1931 that, of 24 rats caught in a sewer at Nancy, 7 were carriers, whereas there were no carriers among 12 rats caught in the Medical School. Rats caught in cage traps, were,

Table 31.—INFECTION-INDEX OF *M. norvegicus*

		Total number of rats			Fully-grown specimens over 20 cms.			Young specimens under 20 cms.		
		Examined	Positive	Positive %	Examined	Positive	Positive %	Examined	Positive	Positive %
SCHÜFFNER & KUENEN..	1923	207	58	28	124	56	45	83	2	2.4
FISCHER	1924	182	38	21	134	36	26	48	2	4
SOESILO	1925	401	45	10	231	40	17	170	5	3
SJOEIB	1930	64	32	50	47	31	66	17	1	6
1933-1937		521	154	29.5	383	144	37.6	138	10	6
		1,375	327	23.8	919	307	33.4	456	20	4.4

INFECTION-INDEX OF *M. rattus*

SCHÜFFNER & KUENEN	29	1	3
SOESILO	15	1	
SJOEIB PROEHOEMAN	16	0	
1933-1937	9 small 1 large	0 1	
	70	3	

moreover either all carriers or all free from infection. This is accounted for by the fact that rats in a cage infect one another (TROISIER & BOQUIEN, UHLENHUTH & ZIMMERMANN). It also seems very probable that rats infect their immediate environment most heavily and most readily.

5. CORRELATION BETWEEN MURINE AND HUMAN LEPTOSPIROSES

IDO and his collaborators were able to prove that the districts and mines in Japan where rats showed a high infection index were also those in which most cases of leptospirosis icterohæmorrhagica occurred. The same was established in Rotterdam, in the neighbourhood of the Tiber and Aniene (MARCHESI), in Leipzig (SEIFFARDT), etc.

Another kind of concomitance (which cannot be expressed in figures) has been observed in some districts in which infection among human beings was found to be caused by some particular strain of leptospiræ, which is also found in the local rats. Thus in Japan *L. hebdomadis* was detected in both human beings and *Microtus montebelloi* and the Swart van Tienen strain among both human beings and rats in Batavia.

Examples are plentiful, however, to show that a strong infection among rats need not cause an epidemic of the disease among human beings.

In Genoa, where GRASSO found infected rats, the disease was unknown among human beings. The same is true of New York State, where the infection-index among rats is very high (40% direct, 60% serological), of Baltimore (LANGWORTHY & MOORE), and of Trinidad (PAWAN). KANEKO, KOTORII & AOKI were similarly unable to establish any connection between infection in rats and in human beings. In Amsterdam, with its 800,000 inhabitants, where the rats are strongly infected, only about 4-12 cases occur every year.

It has been wondered whether these inconsistencies might not be due to the fact that, in such cases, the strains are not virulent, but this is not borne out by facts. LANGWORTHY & MOORE found that all the strains in the New York State were virulent, and this is also the case in Amsterdam. In Trinidad, of 32 isolated strains, 30 were pathogenic to guinea-pigs.

Table 32.—VARIETIES OF RATS, ETC., FOUND INFECTED WITH LEPTOSPIRÆ

			<i>M. norvegicus</i>		<i>M. rattus</i>		<i>M. rattus alexandrinus</i>		<i>M. rattus dardii</i>	
			Number	%	Number	%	Number	%	Number	%
1917..	IDO, HOKI, IDO & WANI	Japan	149	40.2			24	87		
1918..	NICOLLE & LEBAILLY	Tunis	34	20			7	0		
1919..	FOULERTON	London	116	37	7	28.5				
1920..	FLU	Batavia	35	5.7						
1922..	BALFOUR	England	154	13.6	15	0				
1923..	SCHÜFFNER & KUENEN	Amsterdam	207	28						
1924..	FISCHER	Amsterdam	124 a.	45	29	3				
			182	21						
			134 a.	26						
1924..	ROBERTSON	Baltimore	100	7						
1924..	BUCHANAN	Scotland	166	36.7						
1924..	KOUWENAAR	Dell							30	6.7
1925..	SOESILO	Amsterdam ¹	401	10	15	6.7				
1925..	KOSHINA, SHIOZAWA, KITAYAMA	Japan								
1927..	FLETCHER	Federated Malay States ²							Country	26
1927..	SARDJITO & POSTMUS	Batavia	23	17	17	0				
1929..	FISCHER	P. Pinung	111	20						
1930..	SARDJITO	Macassar	350	7						
			216 a.	12						
1930..	SJOEIB PROEHOEMAN	Amsterdam	64	50	16	0				
1930..	INOUE	Japan	71	16.7	43	11.6				

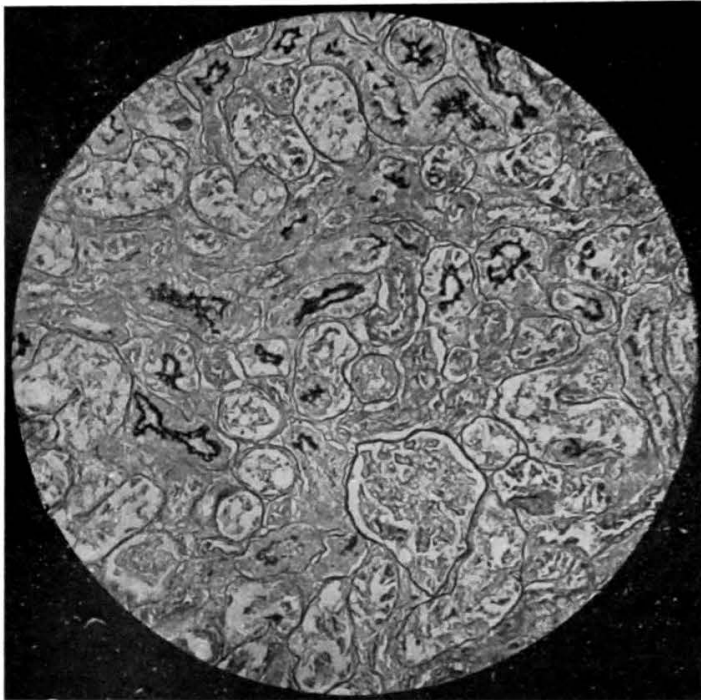
1930..	FORSYTH & GOHAR	Cairo					64	3		
1931..	TAYLOR & GOYLE	Rangoon ^a								
1931..	RIDLON	San Francisco	50	34						
1931..	LAVERGNE & STUMPF	Nancy	100	14						
1931..	R. KNOWLES	Calcutta ^a	193	0						
1933..	BESSEMANS & THIRY	Belgium	37	59	46	0				
			84	32						
1933..	MOCHTAR	Semarang	20	40						
1935..	KANEKO, KOTORII, AOKI	Hasami District ^a	f. 722	0			f. 103	1		
			h. 40	0			h. 291	0		
1937..	SARDJITO, MOCHTAR, WIRASMO	Ambarawa ^a							9	0
1937..	ANDERSON	Bombay ⁷	100	32	100	0				
1937..	COTTER	Queensland ^a								
1937..	CLAYTON, DERRICK, CILENTO	„ ^a								
1937..	WIRTH	Vienna ¹⁰								

a. = adult.
f. = field.
h. = house.

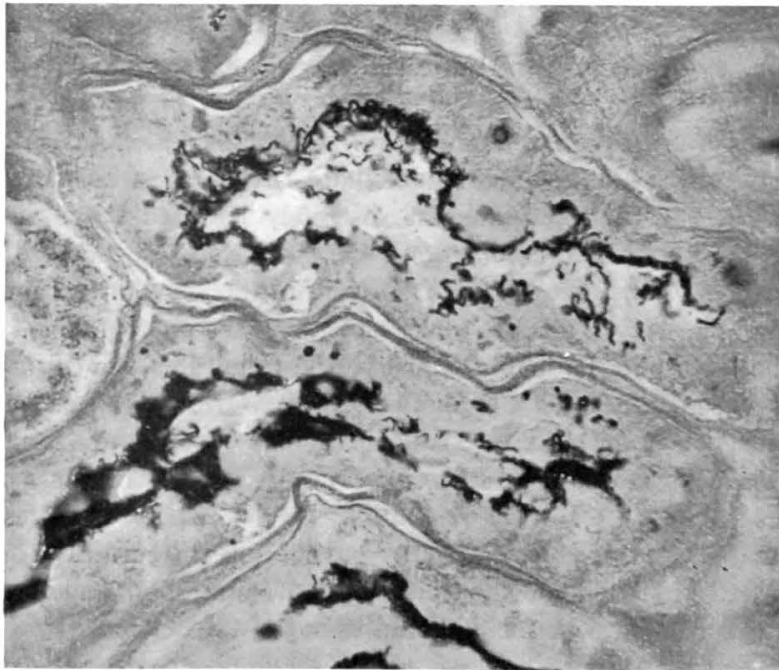
- ¹ et *Microtus montebellii*, 10, 10% ;
² *M. griseiventer* ?, 0 + % ;
³ *Nesobia bengalensis*, 31, 43% ;
⁴ *Nesobia bengalensis* 7, 2 + ;
⁵ *Sunc. caerul. var. riutsuanus*, 6, 0% ;
Microtus montebellii, 25, 4% ; *Apodemus sp.*, 1668, 14.3% ;
⁶ *M. r. brevicaudatus*, 104, 21% ; *M. r. brevicaudatus* (adultes), 12, 50% ;
⁷ *Gunomys varius*, 100, 7% ;
⁸ *M. norvegicus*, *M. rattus rattus*, *M. rattus alexandrinus* : 60, 30% ;
Bandicota : 7, 100% ;
⁹ *R. culmorum*, strongly infected.
¹⁰ *Arvicola arvicola* : 45, 13.3% ; *Mus musculus* : 24, 16.7%.

Table 33.—DIFFERENCES IN INFECTION-INDEX ACCORDING TO PLACE WHERE FOUND

				Place where found	Infection-index
1917.....	NICOLLE & BLANC	Tunis	91 <i>M. norvegicus</i>	In native quarter	0 Feb. March
	NICOLLE & LEBAILLY	Tunis	34 <i>M. norvegicus</i>	Slaughter-house	20/25% Oct. Nov.
1918.....	LHÉRITIER	Algiers	159 <i>M. norvegicus</i>	Suburb	3.8%
			50 <i>M. norvegicus</i>	Harbour	0.5%
1923.....	SCHÜFFNER & KUENEN	Amsterdam	35 <i>M. norvegicus</i>	Slaughter-house	26% Only adults
			65 <i>M. norvegicus</i>	Zoological Garden	51% Only adults
1923.....	ANIGSTEIN	Warsaw	47	Slaughter-house	19%
			23	Town	0
1932.....	CAMINOPETROS	Athens	146	Generally	27.3%
			56	Themistocles street	41%
			40	In outlying part of town	5%



LEPTOSPIRAL LESIONS OF THE KIDNEY IN THE RAT



It is possible, however, that, in one case, the pH of the surface water, its organic matter content, etc., is more favourable to the existence of the leptospiræ than it is in another, and that the risk of human infection varies accordingly.

Furthermore, the habits of the population also affect the frequency with which leptospiræ can infect man (consider, for instance, the foci of leptospirosis which develop among human beings in Syra and Lisbon through the drinking of infected water, and among fishworkers in Aberdeen, etc.). Finally, discrepancies may be due to failure to recognise the disease.

6. HOW LONG CAN RATS BE CARRIERS ?

During the first years of investigation, in Japan, the maximum period was found to be 63 days (IDO and his colleagues, November 1916) ; GARNIER & REILLY found the period to be 103 days, and ROBINSON noted that white rats were carriers for at least 4 months. In Amsterdam, wild rats were kept under observation for as long as two and a half years, during which period they regularly passed out leptospiræ in varying quantities.

7. LOCALISATION OF LEPTOSPIRÆ IN THE RAT'S KIDNEY

SCHÜFFNER & KUENEN, among others, examined Levaditi stained sections of the kidneys, and found what STEVENSON had depicted—namely, that the leptospiræ are discretely localised. The whole section must therefore sometimes be examined for them to be discovered. They are found exclusively in the convoluted tubules of the renal cortex and only here and there (see photographs).

The leptospiræ lie in the lumen of the tubules on the epithelial surface, sometimes in a close network pattern which projects somewhat between the cells, so that star-shaped patterns are formed. They are never found in the tissue proper, except in the acute stages ; when the disease is chronic, the leptospiræ are already eliminated, and are hence actually outside (on the surface of) the body cells. Living on the epithelium, it multiplies, and passes with the urine into the bladder and so out of the body.

Leptospiræ are found in such large quantities in the urine that their appearance is that of a dense culture. Then abundance may vary, however, in one and the same animal. The results depend *inter alia* on the degree of acidity of the urine. According to ZUELZER, the leptospiræ die more rapidly in acid than in alkaline urine. In the latter, they can remain alive for 24 hours (observed at Amsterdam).

Similar conditions in the kidneys were described by KLARENBECK in dogs and by DINGER in tame mice.

8. PATHOGENICITY OF LEPTOSPIRÆ FOR THE RAT

It was first thought that the rat though infected with leptospiræ, did not actually become ill from the infection. MARTIN & PETTIT observed, it is true, that rats with leptospiræ frequently had an enlarged spleen, but as old rats often show such organic lesions, they did not feel justified in drawing any conclusions from this.

When, however, as frequently occurs, leptospira-carrying rats give a strong serological reaction it is fair to assume that they have had a general infection. Finally, experiments have shown that the young sewer-rat is easily infected, presents leptospiræ in the circulating blood, and sometimes even has jaundice (Amsterdam). In nature we are usually unable to observe this stage of the disease, and we only see the after effects of acute infection in the form of leptospiræ in the kidneys.

The animals generally appear quite healthy, though it is possible, if the morbid process is widespread, for the kidney epithelium to be so severely affected that it may no longer function satisfactorily. Whether these symptoms, which were first described by STEVENSON in 1922 (dilatation of the tubules, formation of casts, infiltrations with lymphocytes, or with polymorphonuclears), are due to the action of the leptospiræ is doubtful, having regard to the bacterial infections frequently found in the kidneys of old rats (see further WIRTH's description of pathological alterations in the rat's kidney).

The rat's natural resistance to leptospiral infection, far greater than that of the guinea-pig, for example, should, according to CORRALIS, be ascribed in part to the definitely destructive action of the peritoneal fluid. Like MARTIN & PETTIT, he also observed

strong active phagocytosis. There would also appear to be a resistance of the tissue cells themselves. HIGUCHI is of the opinion that the rat produces large quantities of anti-bodies. The importance to be attached to these several factors can, however, only be determined by experiment.

9. MANNER IN WHICH RATS ARE INFECTED

There being no direct observations, it must be assumed that rats in nature are infected either through food which has been contaminated by the urine of a carrier, or else by bodily contact or by contact with infected material, particularly if the animal has any open skin lesions. It is not improbable that a mother rat which is a carrier infects her offspring. In such a case, the infection cannot be spread otherwise than through food or direct contact, particularly in the genital tract.

The hypothesis put forward in 1923 by KUENEN & SCHUFFNER that an ascending infection of the urinary system was the normal route for contamination was abandoned by these authors. It could not be held from the moment that *L. icterohæmorrhagiæ* was recognised to be pathogenic for rats. On first entering the urinary passages, the leptospiræ go through the epithelium causing a general infection, and only after the latter do they then return to the kidney and get localised on its epithelium.

The theory that rats and human beings can become infected through *L. biflexa*, a saprophytic water leptospira, which would acquire pathogenic properties in special circumstances, is examined in the chapter on epidemiology.

10. HOW ARE LEPTOSPIRÆ TRANSMITTED FROM RATS TO MAN ?

(i) Direct infection is caused by the use of food or drinking-water which has been contaminated with rat urine (as observed in epidemics in Syria and Lisbon), through handling of infected material in slaughter-houses and fish markets and through working in sewers, working with reeds, etc., in the course of which small skin abrasions enable infection to enter the body. Such contact may also cause

infection among laboratory workers, already observed on two occasions in Holland.

(ii) Contact with water containing rat urine with leptospiræ, through bathing, swimming, falling in the water, etc., is the commonest mode of infection. By dilution, the urine loses its adverse properties, and the leptospiræ can, accordingly, live in it much longer. The danger of infection is thus correspondingly prolonged. It has been emphasised that, in swimming, the mucous membranes, which are easily penetrated by leptospiræ, come into contact with the water such as those of the nose in the crawl stroke and of the deeper air passages in diving, with consequent absorption of water. VAN THIEL demonstrated experimentally that guinea-pigs are more easily infected through the nasal mucous membrane than through the mouth.

(iii) A special and very rare method of infection is through rat bite. Two such cases were, however, already known in Japan in 1916 (INADA, IDO), and UHLENHUTH described a case in which a laboratory assistant contracted a disease resembling Weil's, through the bite of a rat, which was only identified fifteen months later through a positive serum reaction. It cannot be said for certain whether the infection was transmitted through the saliva, whether the bite merely produced a portal of entry for the leptospiræ in the urine, or whether the infection was accidental.

11. RAT INOCULATION

Both tame and wild rats have been used for experimental purposes, and it has been found that both could be infected. The results of some of the inoculations are shown in succinct form in Table 34. The table shows that it is very rare for the animal to die as a result of the inoculation (IDO, HOKI, ITO, WANI and BALFOUR) ; whilst the rat that died at Amsterdam also showed symptoms of salmonella infection. Symptoms of illness, such as fever and jaundice, are sometimes noted (BALFOUR, HIGUCHI), while a few investigators showed that immune bodies appeared in the blood (BROWN & DAVIS, SJOEIB, PROEHOEMAN, ZIMMERMANN). Leptospiræ were shown in many instances to be present in the internal organs, particularly

Table 34.—INOCULATION OF RATS WITH LEPTOSPIRÆ

	Rats used	Infecting material	Results	
			Died	Surviving
IDO, HOKI, ITO, WANI	4 white rats	Blood or liver emulsion of infected guinea-pigs	1 with jaundice and L. in kidney	
NICOLLE & LEBAIL- LY	3 grey rats from slaugh- ter-houses. 1 <i>M. rattus alexandrinus</i>	L. of rats through guinea- pigs		5, 29 and 69 days after inoculation, L. were demonstrated in internal organs 102 " " "
HAENDEL, UNGER- MANN & JAENISCH	Rats	Liver emulsion of infected guinea-pigs		L. demonstrated in peritoneal fluid and blood
BALFOUR	7	Food with liver emulsion of infected guinea-pigs; by means of catheter	1 killed sub fi- nem	2 fever and jaundice : both killed after 7 and 10 days respec- tively Post mortem : symptoms of the disease L. in urine after 14 days Antibodies found in blood with adhesion test
ROBINSON	White rats	Virulent culture		
BROWN & DAVIS ...	White rats	3 injections with different cultures		
SJOEIB PROEHOE- MAN	Wild rats	Inoculation of culture or food mixed with it		
	2 already carriers (positive serum reac- tion)	" " " "		Serum titre increased from 250 to 2,500
	8 non-carriers	" " " "		
	4 non-carriers	" " " "		Serum titres obtained : before inocula- tion 0 ; after inoculation 10-1,000 Of the 4, 2 became carriers
HIRUCHI	Wild rats	Inoculation <i>per os</i> Through scarified skin Intra-peritoneal		70% successful 80% successful 79% after 2-5 days, L. in circulation after 4-8 days, nearly all L. in urine

UHLENHUTH & ZIMMERMANN	21 white rats	In same cage with wild rats Only tame rats together		Bilirubin content of half the number increased in blood After 3 days, L. in many organs After 6 days, L. in kidneys, liver and myocardium After 9 days, L. in kidneys only 16 positive serum reactions, 6 carriers
KANEKO, KOTORII, AOKI	12 white rats	Together in 1 cage		1 positive serum reaction, 2 carriers
Amsterdam	{ 3 <i>M. rattus</i> 3 young <i>M. rattus</i> II. { 4 <i>M. norvegicus</i> 4 white rats 1 young rat I. { 3 <i>M. rattus</i> 4 white rats	Culture of <i>L. canicola</i>		Percentage of infected rats the longer they were kept together in one cage 3 L. in peritoneal fluid, 2 serum reactions 1/30 3 L. in peritoneal fluid, 3 serum reactions 1/300 1 L. in urine (1 day) 4 L. in peritoneal fluid, 3 died after 42 days and 4 months respectively 4 L. in peritoneal fluid, 4 serum reactions 1/100 L. in peritoneal fluid and in blood
CLAYTON, DERRICK & CILENTO	2 <i>M. norvegicus</i>	Liver emulsion of guinea-pigs with classical <i>L. icteroh.</i>	Died after 5 days (salmon.) with L. in kidney (inocul.)	2 L. in peritoneal fluid ; 2 serum reactions 1/1,000 2 L. in urine 3 L. in peritoneal fluid ; 3 serum reactions 1/100-1/1,000 3 L. in urine
		Culture of <i>L. icteroh.</i>		
		Culture of <i>L. icteroh.</i>		
		Liver emulsion of guinea-pigs infected with Pomona strain		1 killed after 8 days } L. in internal organs demonstrated through inoculation 1 killed after 20 days }
VAN THIEL	Young rats	<i>L. canicola</i>		Did not become carriers

LEPTOSPIROSES

in the kidneys (IDO and collaborators, HAENDEL, UNGERMANN, JAENISCH, ROBINSON, PROEHOEMAN, NOGUCHI, UHLENHUTH & ZIMMERMANN, Institute for Tropical Hygiene, Amsterdam, CLAYTON, DERRICK & CILENTO).

UHLENHUTH & ZIMMERMANN pointed out that the infection of tame rats by wild rats which were carriers appeared to occur as easily as the spreading of infection from one wild rat to another in nature. KANEKO and his collaborators adduced evidence of the spread of infection among wild rats in a cage in the sense that the percentage of infected rats was found to increase the longer the animals were kept together.

At Amsterdam, not only were wild and white rats infected with *L. icterohæmorrhagiæ*, but it proved possible to infect rats with another strain (*L. canicola*) though only transiently (for these experiments, see Section 13). Two *M. norvegicus* rats were also infected in Australia with the Pomona strain obtained from a seven-day-fever patient.

The experiments with rats made by IDO and his collaborators should also be mentioned. After they had established two cases of Weil's disease caused in man by the bite of a rat, they attempted to produce the disease in guinea-pigs by causing them to be bitten in their hind-paw by a rat. One of the 50 bitten guinea-pigs fell ill, and died on the 11th day with jaundice and hæmorrhages, leptospiræ being found in its blood and liver. INADA, however, offers another explanation of this single case of infection in which we concur.

12. STRAINS OF LEPTOSPIRÆ WHICH HAVE SO FAR BEEN FOUND IN RATS AND SOME OTHER RODENTS

As has already been pointed out, *L. icterohæmorrhagiæ* is not the only strain found in rats. Table 35 gives the strains which, so far as our information goes, have been observed in the various kinds of rats. A few strains are known to occur in man but have not yet been discovered in rats (*e.g.*, Rachmat, *L. canicola*, *L. grippolyphosa*, etc.). This may be due to the fact that the rat has great powers of resistance to certain strains. As this might be of epidemiological importance in the Netherlands, in connection

Table 35.—DATA REGARDING VARIOUS STRAINS OF LEPTOSPIRÆ FOUND IN RATS

			Name of carrier	Name of strain
1915.....	MIYAJIMA	Japan	<i>Microtus montebelloi</i> <i>M. norvegicus</i> and <i>M. rattus alexandrinus</i>	<i>L. icterohæmorrhagiæ</i>
1916.....	IDO, HOKI, ITO, WANI	Japan	<i>M. norvegicus</i>	<i>L. icterohæmorrhagiæ</i>
1918.....	IDO, ITO, WANI	Japan	<i>M. rattus alexandrinus</i> <i>Microtus montebelloi</i>	<i>L. icterohæmorrhagiæ</i> <i>L. hebdomadis</i>
1925.....	KOSHINA, SHIOZAWA, KITAYAMA	Japan	<i>Microtus montebelloi</i>	<i>L. akiyami A</i> and <i>B</i> (<i>L. autumnalis</i> and <i>L. hebdomadis</i>)
1927.....	Isolated by SARDJITO & POSTMUS, agglutinated by WALCH & SOESILO	Batavia	<i>M. norvegicus</i>	Swart van Tienen strain (Batavia type)
1927-1928...	FLETCHER	Federated Malay States	<i>M. rattus diardii</i>	Mostly <i>L. akiyami A</i> .
1928.....	BESSEMANS & THIRY	Ghent	Mouse (laboratory)	S.S. ("Muis Gent") (Ghent mouse)
1934.....	COTTER & SAWERS	Ingham, Queensland	<i>M. norvegicus</i> <i>M. r. alexandrinus Bandicola</i>	Among others Ballico strain Zanoni strain (Salinem)
1935.....	KANEKO	Japan	<i>Apodemus speciosus</i>	<i>L. autumnalis</i>
1938.....	Isolated by MOCHTAR and collaborators, agglutinated by ESSEVELD & COLLIER	Java	<i>M. r. brevicaudatus</i>	<i>L. javanica</i>
1938.....	Isolated by MOCHTAR and collaborators, aggl. ESSEVELD & COLLIER. Inst. Trop. Hyg.	Java	<i>M. r. brevicaudatus</i>	<i>L. Salinem</i>
1938.....	SARDJITO	Java	<i>M. r. brevicaudatus</i>	Semarang field-rat strain 173

Table 36.—EXPERIMENTS ON RATS IN AMSTERDAM WITH *L. Ictero-hæmorrhagizæ* AND *L. canicola*

	No. of rat	Inoculated with	Lept. in peritoneal fluid	No. of days after inocul.	Lept. in blood	No. of days after inocul.	Lept. in urine	No. of days after inocul.	Serum reaction with strains :				Day and cause of death	
									II. Utr. IV		Wijnberg			
									Day	Ti-tre	Day	Ti-tre		
<i>L. canicola</i>	Rat 1	0.2 cc. urine of guinea-pig, 1st passage Res. strain	—		—									
	2	"	—		—									
	<i>M. rattus</i> 3	0.5 cc. cult. II. Utr. IV	+	1	—		—		48		30	0	48 (killed) kidney	
	4	"	+	1	—		—		48		30	0	" "	
	9	"	+	3	—		—						26 (eaten)	
	<i>M. norveg.</i> young 18	0.5 cc. cult. Res. P. I.	+	2	—		—							42 (died)
	" 19		+	2	—		—							42 (died)
	" 20		+	3	—		—							after 4 months (died) kidney —
	" 21		+	1	—		—							
	<i>M. rattus</i> young 25	0.5 cc. cult. IIa.	+	3	—		observed after 104 days		1	49	300		0	
	" 26	"	+	3	—		—			49	300		0	
	" 27	"	+	3	—		—			49	300		0	

LEPTOSPIROSES

	28	0.7 c.c. cult. We.	+	1	—	—		14	300	0	25 (died)	
	29	0.7 c.c. cult. We.	+	1	—	—		14	300	100	26 (killed) urine neg.	
	30	0.5 c.c. cult. We.	+	3	—	—					29 (died) urine — kidney —	
	31	0.5 c.c. cult. We.	+	3	—	—					” ”	
	32	0.5 c.c. cult. We.	+	3	—	—					23 (died) urine — kidney —	
	White rat V	0.5 c.c. cult. Ha.	+	2	—	—		71	100	0	3 months (killed)	
	” VI	”	+	3	—	—		71	100	0	”	
	” VII	”	+	3	—	—		71	100	0	”	
	” VIII	”	+	2	—	—		71	100	0	”	
<i>L. icterohæ-</i> <i>morrhagiæ</i>	Young rat	0.5 c.c. liver emulsion of guinea-pig infected with <i>L. icteroh.</i>	+	1	+	1	—	Kidney + (animal inocul.) at least 108				5 months (died) with spots in the liver suggesting salmonellosis
	<i>M. rattus</i> young	0.5 Kok. cult.	+	4	—		+	49	0	1,000		
	”	”	+	4	—		+	49	0	1,000		
	<i>M. rattus</i> older	”	—		—		—					10 (died) kidney —
	White rat	0.5 c.c. Coster cult.	+	2	—		+	at least 64	71	0	1,000	
	”	”	—		—		+	”	71	0	300	
	”	”	”	+	1	—		”	71	0	100	Died of bites

with *L. canicola*, the following experiments were made at Amsterdam:

13. INOCULATION OF RATS WITH *L. icterohæmorrhagiæ*
AND WITH *L. canicola*

Various rats (*M. rattus*, *M. norvegicus* and white rats), preferably young ones, were inoculated with virulent *L. icterohæmorrhagiæ* and *L. canicola*, after which their peritoneal fluid and blood were examined for a few days and their urine for several weeks. There was some difficulty in obtaining live, and especially young, rats, so that part of the experiments were performed with adult rats and the total number of rats used was small. The rats were not noticeably affected, except those which died of an intercurrent disease.

Table 36 gives details of the rats and of the inoculated material as well as the number of days during which leptospiræ were found in the peritoneal fluid, blood, etc.

α. When *L. canicola* was inoculated, leptospiræ could always be demonstrated in the peritoneal fluid during the first few days, even though but transiently, but not in the blood. They were not passed out with the urine, save in one exceptional case (25), in which they appeared in the urine for one day only. VAN THIEL also failed to make rats carry *L. canicola*; this fits in with the fact that *L. canicola* has not been found in the kidneys of the rat in nature, either in the Netherlands or in San Francisco, where *L. canicola* infection occurs among dogs.

β. The results of inoculation with *L. icterohæmorrhagiæ* are in some respects similar. It was found in nearly every case in the peritoneal liquid, and only once in the blood. On the other hand, it was always present in the urine or kidneys (save in the case of an old *M. rattus*, which died of an intercurrent disease on the 10th day).

There was therefore a remarkable difference between the two strains as regards elimination; whereas the rat hardly ever became a carrier of *L. canicola*, it nearly always became a carrier of *L. icterohæmorrhagiæ*.

Even if the rat becomes infected with *L. canicola*, it does not, as is apparent from these data, pass it into water, whereas it

disseminates *L. icterohæmorrhagiæ* profusely. This may be one of the reasons why the *canicola* infection is so rarely found in man.

That the infection left its mark in other ways was evident from tests of the serum of 9 rats, performed some time after their inoculation with *L. canicola*, and of the serum of five other rats after their inoculation with *L. icterohæmorrhagiæ*. Both strains caused the production of anti-bodies ; for the titres, see Table 36.

The *L. icterohæmorrhagiæ* anti-bodies are excreted with the urine (V. D. HOEDEN). V. D. HOEDEN found that some of the wild rats only gave positive reactions against *L. icterohæmorrhagiæ* and not against *L. canicola*.

In Queensland, where a leptospira was found, causing a mild 7-day disease (the strain was sent to Amsterdam under the name of Pomona), CLAYTON, DERRICK & CILENTO succeeded in infecting two *M. norvegicus* rats. They killed them on the 9th and 14th day respectively, but were unable to find leptospiræ in the liver or urine under the microscope, though they did discover them by means of guinea-pig inoculation. Thus, this strain, which was not very pathogenic for human beings and guinea-pigs, scarcely affected rats at all, though it appeared to be able to turn them into carriers.

14. SOME PROPERTIES OF THE STRAINS OF LEPTOSPIRÆ ISOLATED FROM RATS AT AMSTERDAM*

Classification of Strains according to Serological Reactions.

It was formerly held to be by no means certain that the varieties of *L. icterohæmorrhagiæ* found in various countries, and in human beings or rats, were all identical. INADA and his colleagues were undecided in 1916 as to whether Japanese and German leptospiræ were identical, and so were GONDER & GROSZ in 1918.

The identity of many strains was later established by various investigators (INADA, MATZUSAKI, various rat strains, SHIOZAWA & ANJOW, KAGAYA,† UHLENHUTH, ZUELZER, human and rat strains).

* The particulars of other rat strains isolated in tropical and sub-tropical regions are discussed in chapters where the forms of leptospirosis found in these regions are dealt with.

† For the Japanese literature on the subject, see KITAOKA, *Zentr. Bl. f. Bakt.*, 138, 1937, page 163.

Table 37a.—CLASSIFICATION OF *L. Icterohæmorrhagiæ* OF VARIOUS ORIGINS

Strains of <i>L. icterohæmorrhagiæ</i>	Sera against								
	I. <i>L. icterohæmorrhagiæ</i> from : —						II Salinem	III Canicola	
	Nether- lands 10,000 100,000	Ame- rica 50,000	Ger- many 10,000 50,000	France 300,000	Por- tugal 10,000	Rat 25,000	Dog 10,000	25,000	10,000 30,000
I. Human strains :									
68 Netherlands	6 t+ ² 80 t 23 t/3	4 t 4 t 4 t/3	7 t	3 t	2 t/3	2 t+	4 t	1 t/3 2 t/10 2 t/30 9 t/100 1 t/300	1 t/3 13 t/10 22 t/30 16 t/100 8 t/300 1 t/1,000
7 America	1 t+ 3 t 8 t/3	9 t 1 t/3	2 t				1 t		1 t/10
6 Germany	7 t 5 t/3	1 t+ 1 t/3	3 t 1 t/3	1 t+ 1 t	1 t 1 t/3			2 t/30 2 t/100	
3 England	2 t 4 t/3	1 t+			1 t+ 1 t	Hickey 1 t		1 t/100 1 t/1,000	1 t/3,000 5 t/30 2 t/100
2 Denmark	1 t 1 t/3				1 t				
1 Norway					1 t				1 t/10 1 t/30 1 t/10
1 Sweden	1 t/3		1 t+	1 t/3	1 t	Hickey 1 t			1 t/3 1 t/30 1 t/100
1 France	3 t		1 t	1 t	1 t			1 t/300	1 t/10
1 Portugal	1 t+ 3 t		1 t	1 t/3	1 t				1 t/30

Strains of <i>L. icterohæmorrhagiæ</i>	Sera against								
	I <i>L. icterohæmorrhagiæ</i> from : —						II Salinem	III Canicola	
	Nether-lands 10,000 100,000	Ame-rica 50,000	Ger-many 10,000 50,000	France 300,000	Por-tugal 10,000	Rat 25,000	Dog 10,000	25,000	10,000 30,000
Titre ¹ →									
1 Portugal			1 t					1 t 3	1 t 10
1 Australia							1 t 300		
2 Netherlands	1 t 2 t						1 t /1,000	2 t 10	
93 Strains									
II. Rat strains :									
104 Netherlands	27 t+ 67 t 10 t/3	1 t+		5 t 6 t/3		Rat 2 t+ 2 t 1 t/3	1 t/3	6 t 30 6 t /100	7 t 10 32 t 30 54 t 100 12 t 300 2 t /1,000
10 America	6 t+ 4 t								2 t 3 3 t 10 3 t 30 2 t 1,000
7 Copenhagen	1 t								1 t 30 1 t /100 6 t 300

Table 37c

Strains of <i>L. icterohæmorrhagiæ</i>	Sera against							
	I <i>L. icterohæmorrhagiæ</i> from : —						II Salinem	III Canicola
	Nether-lands 10,000 100,000	Ame-rica 50,000	Ger-many 10,000 50,000	France 300,000	Por-tugal 10,000	Rat 25,000	Dog 10,000	25,000 10,000 30,000
2 Germany	1 t+ 1 t/3	1 t						1 t/10
1 Vienna	2 t+			1 t/3			1 t/30	1 t/30
1 Antwerp	1 t+ 1 t/3							1 t/10
126 strains								
III. Dog strains :								
4 Netherlands	5 t 1 t/3	1 t					2 t	1 t/10*
1 Denmark	1 t+							1 t/30 1 t/100
1 Sweden	1 t/3		1 t+	1 t/3	1 t	Hickey 1 t		1 t/30 1 t/30 1 t/300
6 strains								
IV. Sucking-pig strains :								
1 Netherlands	2 t		1 t	1 t				1 t/10
1 strain								

* See table 9.

* See table 15.

The figure on the left in each column indicates the number of test performed, the figure on the right the strength of the reaction.

(continued)

strains of :

IV Rachmat	V Swart v. Tienen	VI Pomona	VII <i>Hebdo- madis</i>	VIII <i>Grippo- typhosa</i>	IX Ballico	X Dog H.C.	XI Andaman C.H.	XII Field rat 173 Se- marang
10,000 25,000 30,000	10,000 30,000 100,000	30,000	25,000 30,000	30,000 10,000	30,000	25,000 30,000	10,000	10,000
		1 0						
1 0	1 t/100	1 0	1 0	1 0	1 0	1 0	1 0	

* The serum used for this had a titre of 1/5,000. We do not feel justified in attaching to tests with so weak a serum the same value as to tests with sera of high titre. The figures have only been inserted in this case in order to indicate that the strain does react with a Salinem serum.

Table 37b.—CLASSIFICATION OF *L. Ictero-hæmorrhagiæ* BY MEANS

Sera

Strains	Ictero-hæmorrhagiæ	Salinem Zanoni	Canicola	Rachmat
From man 93 strains				
From rats 126 strains				
From dogs 6 strains				
From young pigs 1 strain				

- = Reaction yielding a value equal to the full titre of the specific reaction.
- = Reaction yielding a value equal to 1/3 of the specific reaction.
- = Reaction yielding a value equal to 1/10 of the specific reaction.
- = Reaction yielding a value equal to 1/30-1/100 of the specific reaction.
- = Reaction yielding a value equal to 1/300-1/1,000 of the specific reaction.
- = Reaction yielding a value equal to 1/3,000-1/10,000 of the specific reaction.
- = Negative.

OF AGGLUTINATION-LYSES TESTS WITH MONOVALENT SERA

Sera

Swart van Tienen	Pomona	Hebdomadis	Grippotyphosa	Ballico	H. C.	Andaman A	Muklis Se-marang 173
☒							
☒ ☒	☒	☒ ☒	☒				
☐		☐ ☐	☐	☐			
☐ ☐	☐ ☐	☐ ☐ ☐	☐ ☐ ☐ ☐ ☐	☐ ☐	☐ ☐ ☐	☐ ☐ ☐	☐
☒	☒	☒ ☒					
		☐ ☐ ☐ ☐ ☐	☐ ☐	☐		☐	
☒							
	☐	☐	☐	☐	☐	☐	

SDN9145

☒ = Reactions of the same strain up to the value of the full titre and also up to 1/3rd. of that value.

☐ = 1 reaction.

☐ = 10 reactions.

☐ = 50 reactions.

NOGUCHI compared strains from Japan and Belgium with American rat strains, and found only insignificant differences.

In the same way, the Verdun human strain appeared to be identical with the French rat strain (MARTIN & PETTIT) and with strains from Catalonia (DALMAU & BALTA), Warsaw (ANIGSTEIN) and Amsterdam (BONNE). A rat strain from Baltimore proved to be identical with a strain isolated from human beings in the Netherlands (WALCH & SOESILO), while HIGUCHI found that certain human and rat strains were identical with a German strain. We do not know whether the Japanese and German strains of *L. icterohæmorrhagiæ* compared by KANEKO & MORIHANA and pronounced to be either a single strain or closely related strains comprise both rat and human strains.

KITAOKA found, by using various reactions (agglutination-lysis test, adhesion phenomenon, Pfeiffer's test, etc.), that all rat and human strains of *L. icterohæmorrhagiæ* were the same, though there were individual differences, in respect of their agglutinability.

Tables 37a and 37b give a review of the serological reactions of *L. icterohæmorrhagiæ* strains isolated at Amsterdam or obtained from other places, the group of rat strains being the largest.

In order to compare the behaviour of *L. icterohæmorrhagiæ* isolated from human beings and from rats, and also to compare the strains from various countries, the strains have been classified in the table according to whether they are obtained from human beings, rats, dogs or a young pig, and also according to their place of origin.

As regards anti-sera (all monovalent) the country of origin of the strains with which they were produced is given. In addition to being tested with the sera against various strains of *L. icterohæmorrhagiæ*, a rat strain serum and a dog strain serum, some of the strains were also tested with sera made with the other groups of leptospiræ at present known to us.¹

Table 37a should therefore be read as follows :

The figures on the left side of each column give the number of tests ; the figures on the right side give the strength of the reaction.

¹ The reactions of three newly established strains from the Netherlands Indies have not been included in the present table.

The strength of the reaction is expressed in fractions of the full specific titre of the serum used ;

Table 37*b* reproduces the same details graphically in more condensed form. All the sera relating to the same strain—*e.g.*, *L. icterohæmorrhagiæ*—are grouped together in a single column regardless of their country of origin, but are subdivided into four groups according to their human or animal origin.

Thus with one or more *L. icterohæmorrhagiæ* sera, these 225 strains all gave reactions of a value equal to or exceeding the specific titre, while some also gave a reaction of 1/3 of this value with another serum from the same group.¹ No strain gave a single reaction below one-third of the full titre with a serum of its own group, and none reacted up to the value of the full specific titre with a serum of another group. There was therefore no difficulty in distinguishing all these strains.

So far as the main reactions are concerned (*i.e.*, with *L. icterohæmorrhagiæ* serum), the rat strains generally differed little from human strains. The rat strains generally differed little from human strains. The rat strains seemed, however, to yield very high values more easily than human strains. Thus of 215 reactions with 92 human strains, 147 were up to the level of the full titre, 15 were higher and 53 lower, and of 148 reactions with 126 rat strains, 87 were up to that level, 40 were higher and 21 lower.

We think this may be attributed to the fact that the rat strains had all only just been isolated, and were therefore examined while still young, and then discarded. Various human strains, however, were preserved and used repeatedly for tests, some of them being now 15 or 20 years old. Now it frequently happens that young strains are more easily affected by the antiserum than old ones.

There were, however, also great similarities between rat and human strains as regards paraspecific reactions.

Thus both of them always gave a paraspecific reaction with *canicola* and with Salinem serum and usually (though not always) with Rachmat serum, while, with the antisera of the remaining groups,

¹ The fact that each strain which had yielded such a value of one-third had also given a value equal to the full specific titre with at least one other serum has been presented in the graph in such a way that reactions of a strength of one-third are not shown separately, but always coupled with the corresponding full-strength reaction.

the reaction was low or nil. The paraspecific reaction of *L. icterohæmorrhagiæ* with *canicola* antiserum was sometimes very marked, yielding a value up to 1/3 of the specific titre. That the strain concerned was definitely *L. icterohæmorrhagiæ* could be deduced first and foremost from the fact that reaction reached the level of the full specific titre with one or more icterohæmorrhagiæ antisera, but did not do so with *canicola* antiserum, and also from the fact that paraspecific reaction was apt to turn out weaker when the test was repeated or when a serum produced with heated antigen was used (Table 37c).

Two very strong reactions with a serum of the Salinem group (Zanoni serum¹) were obtained with two human strains. For the reasons mentioned, these were judged to be paraspecific reactions.

Leaving aside these strong paraspecific reactions of a few strains with *canicola* and Salinem serum, there was no difficulty in distinguishing *L. icterohæmorrhagiæ*, whether derived from human beings, rats, dogs or a young pig. The reactions with other sera were lower or even negative.

KITAOKA frequently noticed that some young rat strains were difficult to agglutinate by means of anti-human-strains sera and human convalescent serum. Our experience at Amsterdam has been different. In this table, all the sera except two (one from a rat strain and one from a dog strain) are made from human strains, and three convalescent sera are also included in the column "Sera from the Netherlands". The titres attained by the rat strains show that they give a rapid reaction with all immune sera, including those obtained with the Netherlands strains.

To sum up, it can be said that the strains of *L. icterohæmorrhagiæ* can be classed serologically in one group, whether they are isolated from human beings, or from rats or other animals, and regardless of their country of origin. There are, it is true, certain small individual differences, such as the degree of the paraspecific reactions with heterologous sera.

¹ The Zanoni serum was grouped with the Salinem sera, though it differs somewhat from them (see strains from Australia).

Table 37c.—REACTIONS OF THE FIVE STRAINS OF *L. icterohæmorrhagiæ* WHICH GAVE A REACTION WITH CANICOLA SERUM OF A STRENGTH EQUIVALENT TO ONE-THIRD OF THE SPECIFIC TITRE

	<i>L. icterohæmorrhagiæ</i> serum						<i>L. canicola</i> serum											
	Wijnberg 30,000		Verdun 100,000		Lisbon 10,000		Wismar 10,000 30,000		Hickey 10,000		H Utrecht IV. 30,000		Resoort 30,000		Alarik*** 10,000			
Ar	*	**																
Ar	30,000	t																
M. Sweden	10,000	t/3	30,000	t/3	10,000	t	30,000	t	10,000	t	10,000	t/3	10,000	t/3	1,000	t/30	100	t/100
H. Sweden	10,000	t/3	30,000	t/3	10,000	t	30,000	t	10,000	t	10,000	t/3	10,000	t/3	1,000	t/30	30	t/300
Rat 219	30,000	t																
Rat 219															10,000	t/3		
Rat 219															3,000	t/10		
Rat City D.	30,000	t													10,000	t/3		
Rat City D.															3,000	t/10		

* See note to Table 9.

** See note to Table 15.

*** Canicola serum produced with heated antigen:

15. GUINEA-PIG INOCULATIONS

Of the rat strains in the Netherlands between the years 1933 and 1937, 109 had already been identified by the end of 1936. The kidney substance of 12 other rats, which showed leptospiræ under the dark-field microscope, caused no symptoms in the guinea-pigs, so that no cultures of the strain could be obtained.

Of the kidneys of 109 rats which successfully infected the guinea-pigs, all but 2 caused death. In the 2 cases mentioned, however, the strain was recovered and cultivated from the heart blood. In one of the two cases, jaundice did not occur in the 1st passage, but did so in the second. When the strain was determined, it could not be serologically distinguished from other strains of *L. icterohæmorrhagiæ*.

Table 38 shows, for purposes of comparison, the results of experiments in which guinea-pigs had been inoculated with material from patients. This material consisted of blood or urine, which are here classed together, though they appeared to differ, particularly as regards the virulence of the leptospiræ they contained. The matter will be referred to again later (see "Leptospirosis in Dogs").

The table gives the number of cases in which leptospiræ were found in the peritoneal fluid and in the blood of guinea-pigs, as well as certain other, post-mortem, findings.

In point of virulence, there is no noticeable difference between the murine and human strains; both if they gained a foothold were very virulent in the 1st passage; thus, of 108 and 106 animals, 106 and 102 respectively died. It does not appear that the virulence, which was so high in the 1st passage, was further increased in the second. KANEKO observed an increase in the virulence of his *L. icterohæmorrhagiæ*, as reflected in the shortening of the period before death, but only after the 7th passage.

Jaundice.

In the first passage, 77 guinea-pigs inoculated with a rat strain, had jaundice, 16 had not (Table 38). With human strains, the numbers were respectively 82 and 7. The jaundice was usually

Table 38.—DEGREE TO WHICH *L. icterohæmorrhagiæ* OBTAINED FROM HUMAN BEINGS AND RATS IS VIRULENT FOR THE GUINEA-PIG AND CAPABLE OF CAUSING JAUNDICE

Number of guinea-pigs inoculated with :	Number Infected	Lept. peritoneal fluid		Lept. in in blood		Alive	Died	Jaundice		Hæmorrhages		Lept. in internal organs		
		+	-	+	-			+	-	+	-	+	-	
<i>1st. Passage</i>														
(a) Blood or urine of patients	117	106	103	2	75	3	4	102	82	7	89	2	75	2
(b) Kidney emulsion of rat	121	109	96	5	67	10	2	106	77	16	92	2	80	3
<i>2nd Passage</i>														
(a) Blood or urine of patients		44	8		17	1	4	40	32		28		27	1
(b) Kidney emulsion of rat		26	18		14	2	1	25	21	2	22		17	3

LEPTOSPIROSES

very clearly marked ; for example, of the 77 guinea-pigs only 5 were slightly affected. Sometimes jaundice was only noticeable in the second or later passages. This was the case with seven strains, four of which produced but slight symptoms of jaundice in the second passage, and with one strain which did not kill guinea-pigs though, serologically, it could not be distinguished from *L. icterohæmorrhagiæ*. Another strain, however, produced jaundice in the first passage but not in the second.

It has been supposed that jaundice might not occur in cases where the animal died at an early stage, too early, as it were, for jaundicè to develop. In the cases here considered, there was not always any correlation, however, between the duration of the disease and the occurrence of jaundice, and, from the results of later passages, the strains in question would all appear to be capable of producing jaundice. With rat strains, there was no jaundice in the first passage in 17% of the cases ; with human strains, the figure was 8%. The difference is not statistically significant ($9\% \pm 3.3$) ; moreover, the two series of guinea-pigs were not inoculated with exactly the same material.

No importance can therefore be attached to this relatively small difference in icterogenic properties, and it must be concluded that both the serological and the guinea-pig tests show the rat and human strains of *L. icterohæmorrhagiæ* (in the laboratory at Amsterdam) to be identical.

Finally a laboratory infection proved that the rat strain could cause the typical Weil's disease in human beings (ADAMSKI).

B. LEPTOSPIRAL INFECTION IN MICE AND FIELD-MICE

1. OBSERVATIONS OF INFECTION IN NATURE

(a) *Mice.*

In Europe, and in a few countries outside Europe, it was thought that the mouse seldom, if ever, played a part in spreading leptospiræ.

For example, NICOLLE & LEBAILLY (1919), LOREY (1927), ERBER (1932), SCHWETZ (1933), BESSEMANS & THIRY (1933), could find no

leptospiræ in mice, nor were they found in the laboratory at Amsterdam. Generally speaking, however, the number of mice investigated, except in the case of SCHWETZ (136 mice), was not large (16, 52, 10, 136, 17 and 36).

WIRTH, on the other hand, was able to demonstrate a leptospiral infection among mice in Vienna (out of 24 house mice (*M. musculus*), 4 or 16.7% were infected in the natural state). White mice were also found to be spontaneously infected (see BESSEMANS & THIRY). PACKCHANIAN, in the laboratory, also found the *Mus musculus* naturally infected.

(b) *Field-mice.*

In Japan, however, at an early stage leptospiræ were found in some field-mice, and *Microtus montebelloi* was detected as a carrier of *L. icterohæmorrhagiæ* (MIYAJIMA, 1915), of *L. hebdomadis* (IDO, ITO & WANI, 1918) and of *L. akiyami* (KOSHINA, SHIOZAWA & KITAYAMA, 1925). It was later shown that *Apodemus speciosus* played a predominant part as a carrier and disseminator of leptospiræ, particularly of *L. autumnalis* (KOTORII, AOKI, KANEKO, & AOKI, KANEKO & MORIMOTO, 1935).¹

In Scotland, BUCHANAN found that a considerable percentage of field-mice (he does not specify their species) was infected. BROWN, on the other hand, in England, failed to demonstrate infection in 36 field-mice (*Apodemus sylvaticus*) (see ALSTON & BROWN, 1937). In Austria, field-mice (*Arvicola arvalis*) appeared to be carriers of leptospiræ. WIRTH found them in 6 out of 45 (13.3%).

The field-mouse has sometimes been suspected of being partly responsible for the spread of mud fever, but, as far as we know, no detailed investigation of this possibility has yet been made.

2. INOCULATION OF MICE AND FIELD-MICE (see Table 39)

The following details concerning inoculation of mice with various strains of leptospiræ may be mentioned :

Some investigators found that *L. icterohæmorrhagiæ* was fatal to a number of mice (IDO and his collaborators, DINGER &

¹ *M. rattus brevicaudatus*, which has been found to be infected with various strains in India, is usually included among field-rats rather than field-mice.

Table 39.—EXPERIMENTS ON MICE WITH VARIOUS PATHOGENIC STRAINS OF LEPTOSPIRÆ

Strain used	Investigator	Substance inoculated	Number of mice	Leptospiræ in :				Died	Remarks
				Peritoneal fluid	Blood	Urine	Organs		
<i>L. icterohæmorrhagiæ</i>	IDO, ITO, WANI	Liver emulsion of guinea-pig	14				Kidneys +	4	4 died of jaundice ; 10 survived
"	NICOLLE & LEBAILLY	Blood of guinea-pig	?				+		
"	HAENDEL, UNGERMANN, JAENISCH	Liver emulsion of guinea-pig	A few	+	+		0		
"	"	Peritoneal fluid of mouse 5th passage						A few	Lung hæmorrhages in later passages Also jaundice ; thus increase of virulence through the passage
"	DINGER & VERSCHAFFELT	Culture	7	2		5		2	A few died with hæmorrhages and jaundice
"	"	Culture obtained after numerous passages	4	2 neg.		1		1 after 49 days 1 " 8 "	Hæmorrhages. No visible increase of virulence
"	"	Highly virulent culture from guinea-pigs	2				Liver +	1 " 3 " 1 " 8 "	Lung hæmorrhages Lung hæmorrhages and jaundice
"	BESSEMANS, THIRY & TIELLIEU	3 strains 2 strains	3 groups 2 groups			+		Many	3 groups died after a long period of cachexia These 2 groups contracted : 1stly Weil (hæmorrhage and jaundice) or 2ndly only hæmorrhage or 3rdly extensive œdema

..	APPELMAN & VAN THIEL	Liver of guinea-pig (virulent rat strain) Virulent lept.	6 passages 7 groups of 2 mice 1st gr. with 1 L 2nd 10 L 3rd 100 L 4th 1,000 L 5th 10,000 L 6th 100,000 L 7th 1,000,000 L				0	It was impossible to increase the virulence for the mouse through 6 passages
				+		Kidneys+	0	1 mouse died, 1 negative ; in the second case the strain was obtained from a kidney culture
				+			0	
				—			0	
				+			0	
				+			0	
				+			0	Positive seroreaction 1/10,000.
..	..	Avir. lept. mouse strain 0.25 " 1 c.c.		+				Positive seroreaction
<i>L. icteroh. ?</i>	HIRANO	Culture from urine of patient	?			A few	0	Virulent in the 2nd passage
<i>L. hebdomadis</i>	IDO, ITO, WANI	Strain	Mice 3 Field-mice 10		+		0	
						5 +	0	
Swart v. Tienen (Java)	DINGER	Strain	2			2	0	
SS. Ghent.	BESSEMANS & THIRY	Culture	?	+	Sometimes	Usually	2	A few died of paralysis
		Peritoneal fluid of mouse						
		Blood of guinea-pig	?	+		+	0	
		Liver emulsion of guinea-pig						
	DINGER & VERSCHAFFELT	Culture	6			6	Kidneys +	after 110 days
		" from mouse passage 1st	4			3	Kidneys +	2 ,, 9 ,,
		" " " 2nd	5			3	" +	1 ,, 7 ,,
		" " " 3rd	3			2+1 neg		

Table 39 (continued)

Strain used	Investigator	Substance inoculated	Number of mice	Leptospiræ in :				Died	Remarks	
				Peritoneal fluid	Blood	Urine	Organs			
<i>L. canicola</i>	Institute of Tropical Hygiene	Urine of guinea-pig Res.	4	3	1	3		0	Only observed for 14 days	
		Urine of dog Wubb.	4	2		neg.		0		
<i>L. grippotyphosa</i>	DINGER & VERSCHAFFELT	Urine H. Kl.	4	0	0			0	.	
		1 c.c. culture	1	1	1			0		
		Blood 1st passage	4	1		1				
		Blood 2nd passage	3	3 neg.			Kidneys+	1		
<i>L. Pomona</i>	CLAYTON, DERRICK & CILENTO	Pomona culture	4 white mice			2 neg.	2 liver 2 kidneys	2 killed on 4th and 9th days respectively	Guinea-pig inoculation also negative	

VERSCHAFFELT); others found that it was not (APPELMAN & VAN THIEL, HIRANO). This may have depended on the virulence of the original strain. APPELMAN & VAN THIEL, and DINGER & VERSCHAFFELT failed through 6 passages to increase this virulence; HÄENDEL, UNGERMANN & JAENISCH did succeed, however, the peritoneal fluid of a mouse in the 5th passage killing the following mouse. Some of the mice which died had lung hæmorrhages and jaundice, while leptospiruria was frequent among the survivors.

BESSEMANS, THIRY & TIELLIEU, who injected five groups of mice with various strains and obtained varying results (see table 39) concluded that the mouse, as an experimental animal, could sometimes show differences in virulence which are not evident in guinea-pigs. APPELMAN & VAN THIEL also found that the mouse reacts even to very small quantities of virulent culture.

The Swart van Tienen (Java) strain, which caused both mild and fatal cases with jaundice in human beings, was found in a single experiment performed with mice to have no virulence for these animals (DINGER).

L. hebdomadis did not affect the mice's health in Ido, Iro & WANI's experiments and could only be demonstrated in the peritoneal fluid. 5 out of 10 field-mice, however, had leptospiruria. It was also a field-mouse (*Microtus montebelloi*) which was found to be a carrier of *L. hebdomadis* in nature.

The SS. Ghent strain occurred spontaneously in mice which had been fed with bread and water from Ghent. For the results of the experiments with the mice, reference may be had to Table 39. The culture caused a disease in the guinea-pig, with leptospiræ in the peritoneal fluid, blood and liver. Further passages were made, and resulted in such an increase of virulence that the latter approximated that of *L. icterohæmorrhagiæ* (BESSEMANS & THIRY). Surviving guinea-pigs however did not prove immune to *L. icterohæmorrhagiæ* and the special serological properties of the strain remained unchanged.

The experiments with the strain SS. Ghent on mice were confirmed in a general way by DINGER & VERSCHAFFELT. The cultures obtained from the later passages did not display any increased virulence for mice. BESSEMANS & THIRY therefore recommend passing the strain alternately through guinea-pigs and mice to preserve its virulence.

L. canicola appeared to infect mice to the extent that leptospiræ could be recovered from the peritoneal fluid (blood). They were, however, also excreted in urine, which is not the case with the rat. It should be noted that the experiments were few in number and the period of observation was too short (Institute of Tropical Hygiene).

The culture of *L. grippolyphosa*, which infected the mouse, but did not kill it, could become fatal to the mouse when its virulence was increased by passage (DINGER & VERSCHAFFELT).

Pomona, a strain isolated from a patient suffering from a mild form of leptospirosis in Queensland, which was not very virulent for human beings and guinea-pigs, did not even infect four white mice (CLAYTON, DERRICK & CILENTO).

All these experiments show that the mouse, though not an important carrier of leptospiræ in nature, may become one in certain circumstances, since it can be infected experimentally with many kinds of leptospiræ. The mouse was not always killed by the infectious material. Experiments with mice in which widely differing strains of leptospiræ were used showed that all strains except Pomona (which has, up till now, only been tested on 4 white mice) can infect mice and very frequently cause leptospirosis.

PACKCHANIAN reported that the American deer mouse (genus *Peromys*) is very sensitive to *L. icterohæmorrhagiæ* and a suitable experimental animal to demonstrate leptospirosis in human beings.

3. INOCULATION OF FIELD-MICE

So far, only a few experiments have been made, the reason in the Netherlands being that the field-mouse is so difficult to obtain.

As the field-mouse (field-rat) is found to be infected by so many strains in nature, it may be assumed that this fact will be easily demonstrated experimentally.

IDO, ITO & WANI's experiments with *L. hebdomadis* have already been noted. PETZETAKIS found that the field-mouse was very sensitive and that a large dose of virulent material caused swiftly fatal septicæmia, so that there was not even time for jaundice to develop. When a small dose was injected, the disease progressed more slowly with fever and jaundice as in the case of the guinea-pig.

III. LEPTOSPIROSIS IN DOGS

1. THE OCCURRENCE OF LEPTOSPIRAL DISEASE IN DOGS

Epidemic or Infectious Jaundice (Weil's Disease) in Dogs.

The possibility of Weil's disease occurring in dogs was suspected once KRUMBEIN & FRIELING had observed a case of jaundice in a dog followed, a few weeks later by Weil's disease in the two persons who came into close contact with it. This suspicion was strengthened when UHLENHUTH & FROMME noticed a case of jaundice in a dog at the front during the great war. They found "spirochætes" in the dog's liver, and a guinea-pig which was inoculated with material from the liver died after 37 days and was found to have a considerable number of "spirochætes" in its kidneys.

Infection Experiments on Dogs with a Classical L. icterohæmorrhagiæ Strain.

By inoculating virulent liver substance into young dogs, COURMONT & DURAND showed that dogs could be infected with *L. icterohæmorrhagiæ*, and contracted a disease which resembled the human Weil's disease. This invariably caused a fatal form of jaundice with vomiting, bloody diarrhœa. They also described the pathological findings in such cases.

These experiments were confirmed in a general way by MONTI, MARTIN & PETTIT, and GHETTI, while MARIO LEBREDO infected both old and young dogs with a *L. icterohæmorrhagiæ* strain (Merida). KORTHOFF & KLARENBECK, and WINSSER were frequently able to produce an icteric disease in young dogs by means of an *L. icterohæmorrhagiæ* strain, while WIRTH (1935) also showed that young dogs and guinea-pigs could be made to develop icterus gravis.

L. icterohæmorrhagiæ Infections of the Dog in Nature.

OKELL, DALLING & PUGH proved that the infectious jaundice occurring naturally in dogs was caused by a spirochæte. They

isolated a leptospiral strain in three out of ten cases of "enzootic jaundice", which corresponded in every way to the classical *L. icterohæmorrhagiæ* strain obtained from rats. With this strain, they were able to produce the typical form of the disease in dogs and guinea-pigs. They also described a peracute form of the disease particularly with hæmorrhages (stomach, intestine, etc.) to which we shall refer later.

Stuttgart Dog Disease (Stuttgarter Hundeseuche).

Another disease also occurred among dogs however, the so-called Stuttgarter Hundeseuche also called dog typhus, stomatitis ulcerosa, gastro-enteritis hæmorrhagica, etc., the etiology of which was unknown. The nephritic symptoms played a prominent part in the clinical picture of the disease (thirst, polydipsia, polyuria, stomatitis ulcerosa, gastro-enteritis, melæna, etc.).

Sp. melanogenes canis.

In 1922, LUKEŠ was able, by means of Levaditi stained sections, to demonstrate the presence, in the kidneys and other organs of 9 dogs, of a leptospira which he called *Sp. melanogenes canis*. In 1924, KRIVÁČEK found it in 17 dogs suffering from Stuttgart dog disease.

LUKEŠ & DERBECK also inoculated 13 guinea-pigs, 1 rabbit and a few dogs with these canine spirochætes (probably in the form of an emulsion of the organ), as a result of which their experimental animals generally caught the same disease. LUKEŠ has also recorded post mortem findings in regard to the animals which died of Stuttgart dog disease.

The question arises whether LUKEŠ was not working with the leptospira which now goes by the name of *L. canicola*, though it appears to have been more virulent for the guinea-pig than the latter. The strain was not a pure one, and was lost after a short time.

In 1937, WIRTH described yet another form of Stuttgart dog disease, which took a peracute course and caused numerous hæmorrhages.

This raises the question whether the peracute form observed by OKELL, DALLING & PUGH in the case of enzootic jaundice differs from the above, and whether both are caused by the same strain.

As far as we know, neither OKELL and his colleagues nor WIRTH have succeeded in obtaining a strain from this form of the disease.

For the moment, the evidence adduced by LUKEŠ and his colleagues was not conclusive. Moreover, there was another disease, azotemic uremia, the symptoms of which tallied in every way with those of Stuttgart dog disease. In 1925, however, KLARENBECK was also able to find spirochaetes in the kidney of a dog suffering from azotemic uremia. The Stuttgart dog disease, which resembles azotemic uremia but is caused by a leptospira, must therefore be distinguished from azotemic uremia due to other causes (kidney trouble).

The same symptoms can also be produced by foreign bodies obturating the intestine. The etiology of this syndrome must therefore always be ascertained.

The difference between Stuttgart dog disease and Weil's disease was not always as clear, however. Transition forms between the two diseases were observed, and WIRTH's experiments (1937) among others showed a connection between the two, as he succeeded in producing the symptoms of the Stuttgart dog disease in young dogs by means of leptospiræ from rats (*i.e.*, *L. icterohæmorrhagiæ*); furthermore, by infecting them with Stuttgart virus by means of a kidney or liver emulsion, he found that 9 out of 10 dogs exhibit the symptoms of infectious jaundice. WIRTH therefore thinks that the Stuttgart dog disease is the anicteric form of the latter disease.

The Canicola Strain.

The matter is not quite so simple, however. It was shown in 1931 that all leptospiral strains cultivated from dogs were not identical; KLARENBECK & SCHÜFFNER found a strain which gave a titre of 1:10,000 with its own anti-serum, whereas with a serum against *L. icterohæmorrhagiæ* its reaction was 1:25. The new strain known as *L. canicola* is morphologically identical with *L. icterohæmorrhagiæ*, and can be cultivated on the same culture medium. Serologically and in its action on guinea-pigs, however, it is clearly different, and, as was subsequently ascertained, it does not occur in rats.

KLARENBECK & WINSSER have now also infected small puppies with this strain (after passing it through a dog). The dogs exhibited more or less marked symptoms of jaundice, while one of the animals

appeared to be completely unaffected, though leptospiræ were later demonstrated in its urine. It may therefore be said that according to circumstances *L. icterohæmorrhagiæ* and *L. canicola* may produce forms of the disease with or without jaundice.

2. SOME CLINICAL FACTS CONCERNING NATURAL *L. icterohæmorrhagiæ* AND *L. canicola* INFECTIONS AMONG DOGS

It is important to know whether both strains naturally produce a separate and typical picture—*e.g.*, whether *L. icterohæmorrhagiæ* produces Weil's disease, *L. canicola* the Stuttgart dog disease—even though experiments by KORTHOF, KLARENBECK & WINSSER, and WIRTH show that, experimentally, this is not always the case.

A survey of the material collected in KLARENBECK's veterinary policlinic in Utrecht in 1934 (see DHONT, KLARENBECK, SCHÜFFNER & VOET) and a further survey from the same policlinic in 1938 (KLARENBECK, WINSSER) provide information concerning the symptoms which each strain produces in dogs in the natural state. Some of the particulars given in the second survey have been summarised in the table below.

In the case of these dogs, the form of infection was determined serologically or by cultivation and identification of the strain.

	Number			Infected with		
	Number	Male	Female	<i>L. icter.</i>	<i>L. canic.</i>	Unknown
Jaundice	12	9	3	9	2	1
No jaundice	27	22	5	1	23	3
Total	39	31	8	10	25	4

Outcome			Leptospiuria
Died	Cured	Unknown	
8	2	2	2 (in icteroh. cases)
9	10	8	17 (14 in canicola cases 3 unknown)
17	12	10	19

It will be seen that, in these cases, the canicola infection was more frequent than the *L. icterohæmorrhagiæ*. The dogs infected with *L. canicola* usually had no jaundice, though 2 out of 25 did ; those infected with *L. icterohæmorrhagiæ*, on the other hand, nearly all had jaundice (only 1 out of 10 did not). The case mortality was high in both infections, though *L. icterohæmorrhagiæ* would appear to be the more fatal of the two strains.¹

The fatal cases in the canicola group were usually due to uremia. Leptospiruria occurred after both infections, though much more frequently in canicola cases. Whilst allowing for the greater frequency of canicola, this may be due to the high mortality rate of the classical group. Only 2 animals out of 12 survived.

It was often possible to tell from the clinical picture whether one dealt with a *L. icterohæmorrhagiæ* or *L. canicola* infection. Slight or indistinct cases were, however, often misleading ; in such cases, the nature of the infection could only be ascertained by laboratory investigation.

Though *L. icterohæmorrhagiæ* and *L. canicola* both produce a typical syndrome (jaundice being marked in the first case and uremia in the second) a number of cases occur in which these symptoms overlap. Epidemic jaundice, however, may be said to be chiefly caused by *L. icterohæmorrhagiæ* and dog typhus by *L. canicola*.

When dogs are inoculated with " material obtained from Stuttgart dog disease ", as it is described in the literature on the subject, it is impossible, without further information to know whether *L. canicola* or *L. icterohæmorrhagiæ* is actually inoculated ; the same remark applies to " material obtained from infectious jaundice " of dogs.

Localisation of Leptospiræ in the Kidneys.

The localisation of the leptospiræ in the kidneys is not the same for the two diseases. In 4 cases of icterus gravis, KLARENBECK observed leptospiræ with dark-field illumination in the blood and

¹ According to KLARENBECK's latest investigations, which we have just received :

L. canicola caused jaundice in 3% of the (94) cases.

L. icterohæmorrhagiæ caused jaundice in 82% of the (57) cases ;

The case fatality rate for *L. canicola* was 41% ;

The case fatality rate for *L. icterohæmorrhagiæ* was 51%.

fluid expressed from the kidney, and also in Levaditi stained sections of the kidney. They were situated outside the lumen of the tubuli in the interstitial tissue and occasionally in the epithelium of the tubuli. In the uremic form of the disease, they were chiefly found in the lumen of the kidney tubes, which were covered with a black fringe similar to that demonstrated by SCHÜFFNER & KUENEN in rats' kidneys. The position of the leptospiræ in the kidney therefore probably depends on the duration of the case whether Weil's or Stuttgart disease.

Thus KOUWENAAR & WOLFF observed among street dogs—*i.e.*, in cases where the acute stage of leptospirosis would not be found—the leptospiræ in the convoluted tubules but never interstitially. They were grouped together in clusters and were few in number. Dogs can therefore carry and excrete leptospiræ as well as rats. KLARENBECK & VOET considered however that leptospiruria in dogs differs from that in rats as the latter continue to excrete leptospiræ in the urine for the rest of their lives, the former only for a limited period.

3. DISTRIBUTION OF LEPTOSPIROSIS IN DOGS

Geographical Distribution.—Infection of dogs with leptospiræ has been shown to occur in many European countries and has also been described in many other places including the Netherlands Indies, the Federated Malay States, Madras, San Francisco.

Whilst in the Netherlands Indies and the Federated Malay States, strains of leptospiræ are found which are not encountered in Europe (in the Netherlands Indies—the H.C. group and another group which must be classed with *L. hebdomadis*; in the Federated Malay States—Akiyami A), canicola infection has been traced in various countries. Apart from the Netherlands, where it has been found in human beings and dogs, it exists in Denmark (BORG PETERSEN); in Germany (UHLENHUTH & ZIMMERMANN). WIRTH cultivated the strain in Vienna and VAN DER WALLE in Antwerp, and serologically positive dog serum has been found in Sweden (reported by MALMGREN). In San Francisco, the canicola infection was found in human beings and dogs, and strangely enough the strain was cultivated from five jaundiced dogs.

It is difficult to determine how frequent the leptospiral infection among dogs is. The results obtained by various investigators (collected in Table 40) are not always comparable as the material is not always obtained in the same way and investigators differ in their methods.

KORTHOF, KOUWENAAR & WOLFF, REITANO and MORSELLI, and PETER DAHR had dogs which were normal or not specially selected, while others received non-selected material from a veterinary polyclinic (Amsterdam—50 dogs examined) or received some of their material from veterinary surgeons (UHLENHUTH).

All investigators were, however, able to demonstrate a leptospiral infection in some of their dogs, either by cultivating leptospiræ from the kidneys in Vervoort's culture medium (KOUWENAAR & WOLFF found 6 cases among 106 dogs) or by animal inoculation (KRISHNAMURTI—one case), or again by means of serological tests, which was the method most used (KORTHOF, ERBER, Institute of Tropical Hygiene, REITANO & MORSELLI, UHLENHUTH & ZIMMERMANN, DAHR).

Serological reactions are difficult to interpret when the titres are low. The question whether such low titres in dogs are specific or not is even more difficult to decide than in the case of human beings. Furthermore it is impossible in tropical countries and elsewhere to determine whether a low reaction may not be due to paraspecific agglutination while the real strain concerned has not yet been discovered. If a titre of more than 1:100 is accepted as proof of infection, the percentage of positive reactions among the dogs examined would be between 4 and 15%.

Age Distribution of Infection in Dogs.—Young dogs sometimes gave no serological reaction (Amsterdam) or their reaction was low (KORTHOF, who considered such reactions to be negative). UHLENHUTH also observed few infections in young dogs. Other investigators have shown, however, that young dogs may be infected. Thus, in Rotterdam, a whole litter was found to be infected, while, in KLARENBEK's clinic, there were 81 dogs with leptospirosis (1934 and 1937) of which 13 were less than a year old, 51 1 to 5 years old, and 17 over 5 years old.

Proportion of L. icterohæmorrhagiæ and L. canicola Infections in Dogs.—During the two years for which a survey appeared, 52 dogs

Table 40.—OCCURRENCE OF LEPTOSPIRAL INFECTIONS AMONG DOGS FROM VARIOUS PLACES

	Number of dogs	1 year	1 year or over	Serological reaction	Culture	Animal test	
KOUWENAAR & WOLFF (Dell), 1930	106 dogs, not sick				Kidney in nutrient medium of Verwoort 6 + 2 of 1 year 3 of 2 years 2 of 8 years	Virulence low ; no guinea-pig died	
G. KORTHOF : 1930	39 normal dogs	18	21	16 < 100 2 1,000-2,500 7 < 100 10 100-900 4 1,000-25,000			Age had a distinct effect on the serological titre
1930	123 street dogs taken at random	13 ^a	110	11 < 100 2 200 67 < 100 36 100-800 7 1,600-12,800			Sex had no noticeable influence
B. ERBER, 1932	12			6+ 200-1,000			
KRISHNAMURTI, 1932	?					1	
Inst. of Tropical Hygiene, Amsterdam, 1932	50 dogs taken at random from a veter. polyclinic	11	39	11 negative 17 negative			Serological reaction with both <i>L. icteroh.</i> and <i>L. canicola</i>

				<p>Highest reaction with <i>L. icteroh.</i> :</p> <p>4 10</p> <p>2 30</p> <p>2 300</p> <p>1 1,000</p> <p>1 3,000</p>	<p>Highest reaction with <i>L. canicola</i> :</p> <p>1 10</p> <p>2 30</p> <p>2 100</p> <p>3 300</p> <p>2 1,000</p> <p>2 10,000</p> <p>1 30,000</p>		Age had a distinct effect on the serological titre
REITANO & MORSELLI, 1935	112 street dogs		4 positive	400-800			
UHLENHUTH & ZIMMERMANN, 1936	42		37 negative				Serological tests with <i>L. icteroh.</i> only
	48		5 positive	200-800			
			38 negative				
			<p>Highest reaction with <i>L. icteroh.</i> :</p> <p>1 640</p> <p>1 1,200</p> <p>1 5,000</p>	<p>Highest reaction with <i>L. canicola</i> :</p> <p>1 300</p> <p>2 1,200</p> <p>1 5,000</p>			with <i>L. icteroh.</i> and <i>L. canicola</i>
			and 1 at 71 200 with <i>L. icteroh</i> and <i>L. canicola</i> alike				Only one among the positives was 1 year old, all the others were older
P. DAHR, 1937	200 normal dogs		190 negative				
			<p>Highest reaction with <i>L. icteroh.</i> :</p> <p>1 100</p>	<p>Highest reaction with <i>L. canicola</i> :</p> <p>6 50-350</p>			
			3 with 40-50 for each				

in KLARENBEK'S policlinic were infected with *L. canicola* and 26 with *L. icterohæmorrhagiæ*. UHLENHUTH also reports twice as many infections with *L. canicola* as with *L. icterohæmorrhagiæ*. Furthermore, in the case of 50 dogs taken at random and examined in Amsterdam, very high titres (10,000 and 30,000) were obtained for *canicola* infections but not for *L. icterohæmorrhagiæ* infections. Diseased dogs also gave more high reactions with *canicola*. Owing to the small number of animals, it is impossible to say whether this is due to a characteristic property of the strain, or whether it is merely a matter of chance.

Sex Distribution of the Infection in Dogs.—The number of dogs infected was larger than that of bitches (KLARENBEK & WINSSER). Of 39 dogs mentioned above in the Utrecht policlinic, 31 were male and 8 female, whereas the number of dogs being treated at the time was 281 male and 188 female. This is presumably connected with the habit of male dogs licking or sniffing at the urine of other dogs. In this way, infection with leptospiræ may often be transmitted from one dog to another without water being necessary as a medium of infection. Owing to this fact, the occurrence of mixed infections may be less uncommon than in human beings; and the cases in which the serological reactions give an equally high titre for both strains may be of that kind.

4. LEPTOSPIROSIS IN DOGS AND PROPERTIES OF THE CANICOLA STRAIN (*Investigations in the Institute of Tropical Hygiene*)

When the *canicola* strain was first isolated it could not always be easily distinguished from the classical strain, since the two are in some ways similar. Tests with *L. canicola* were therefore included in all the routine work (examination of human and animal sera, and of unknown strains), so that its special properties were brought to light, and its claim to be regarded as a separate strain established. A summary of some of the results obtained in these investigations is given below:

(a) *Number of Dogs Examined.*

Altogether 414 sera of dogs believed to be suffering from leptospirosis were serologically examined from 1929 up to the end of

1937 ; 116 did not react with either of the leptospiral strains.¹ From 1929 to the beginning of 1932, 27 of the dogs were examined (Table 41). This examination was in so far unsatisfactory that *L. canicola* was not yet known, and infections with this strain may therefore have passed unrecognised.

From the middle of 1932 onwards, reactions with both the classical *L. icterohæmorrhagiæ* and *L. canicola* strains were introduced.

(b) *Serological Reactions in Dogs.*

The number of dogs infected with *L. canicola* was greater than that infected with *L. icterohæmorrhagiæ* (Table 41).

Table 41.—NUMBER OF SEROLOGICAL REACTIONS IN DOGS SUSPECTED OF LEPTOSPIROSIS
(*L. icterohæmorrhagiæ* AND *L. canicola*)

	Number of dogs examined	Number negative	Number of dogs with a positive reaction to <i>L. icteroh.</i> or <i>L. canicola</i>	Number reacting more strongly to <i>L. icteroh.</i>	Number reacting more strongly to <i>L. canicola</i>	Number reacting with equal intensity to both	Number of positive reactions
1929	16	6	10	10			13
1930	8	1	7	7			7
1931	1	0	1	1			1
1932	2	0	2	2			2
	27	7	20	20			23
1932	5	1	4	3	1		4
1933	71	13	53	23	30	5	66
1934	61	12	45	18	27	4	58
1935	64	18	41	15	26	5	50
1935	50	27	23	11	12		23
1936	63	22	36	12	21	5	47
1937	100	23	66	25	46	3	108
	414	116	268	107	166	22	356

¹ We have no clinical details concerning these dogs. It is even possible that the serum of a few dogs was investigated several times without our being informed. This was, however, of no importance for the details of the serological reaction discussed here.

Tables 42 and 43 show that the *canicola* strain gives a very high titre much more frequently than *L. icterohæmorrhagiæ*.

In the case of the former, 75 of the 186 reactions, or 43%, were as high as 10,000 or 30,000, whereas, for the latter, the number reaching this value was 15 out of 114, or 13%. This has already been mentioned in connection with the serological reactions of one group. The classical strain may give rise to an abundance of antibodies in the serum of dogs: a positive reaction being still

Table 42.—STRENGTH OF SPECIFIC AND PARASPECIFIC REACTIONS IN DOGS
(INFECTION WITH *L. canicola*)

Titre with <i>L. canicola</i> (specific)	Number	Titre with <i>L. icterohæmorrhagiæ</i> (paraspecific)								
		Neg.	10	30	100	300	1,000	3,000	10,000	30,000
10 ...	2	2								
30 ...	8	5	3							
100 ...	25	12	7	6						
300 ...	27	9	1	9	8					
1,000 ...	24	1	3	9	8	2	1			
3,000 ...	25	1	1	8	6	8	1			
10,000 ...	24	2	1	5	5	6	5			
30,000 ...	51				7	10	16	17	1	
	186	22	16	37	34	26	23	17	1	

Table 43.—STRENGTH OF SPECIFIC AND PARASPECIFIC REACTIONS IN DOGS
(INFECTION WITH *L. icterohæmorrhagiæ*)

Titre with <i>L. icterohæ-</i> <i>morrhagiæ</i> (specific)	Number	Titre with <i>L. canicola</i> (paraspecific)								
		Neg.	10	30	100	300	1,000	3,000	10,000	30,000
10 ...	10	10								
30 ...	16	14	2							
100 ...	9	6		3						
300 ...	23	8		5	6					
1,000 ...	29	11	4	3	4	7				
3,000 ...	12	3	4	1	2	3	1			
10,000 ...	11	0	2	2	1	3	2	1		
30,000 ...	4	1	2			3				
	114	53	14	14	13	16	3	1		

obtained at a dilution as high as 1:30,000, as shown by 4 cases reported in Table 43.

Very low reactions are difficult to interpret. They may be due to a recent or to a previous leptospiral infection, or they may be wholly aspecific. The question of the possible limits and frequency of these aspecific reactions in dogs, has not yet been investigated. The clinical symptoms, a repetition of the reaction with a later sample of serum, and, if necessary, the cultivation of the strain from blood or urine, may often put the investigator on the right track in such cases. There are, however, also cases in which the one serum reacts with the other strain in a manner which is termed paraspecific (associated reaction), since it rests upon the similarity of the two strains in respect of their antigenic structure. Those cases in which such a paraspecific reaction does not occur or is very slight, constitute, of course, valuable evidence of the independence of the *L. icterohæmorrhagiæ* and *L. canicola* strains. The subjoined Table gives some instances of this.

	<i>L. icterohæmorrhagiæ</i>	<i>L. canicola</i>
Serum dog 101	30,000	0
„ „ 198	3,000	0
„ „ W.H. 133	0	10,000
„ „ Jack	0	3,000

Distinction between Specific and Aspecific Reactions.

The titre generally serves to distinguish between these paraspecific reactions and the main (specific) reactions. If the difference is small, as sometimes happens at the outset of the disease, the test should be repeated after, say, one week, though this is not always possible in the case of dogs.

Whereas there were 300 reactions in which one of the two strains yielded a higher titre than the other, 22 had a titre which was identical for both strains, so that one reaction was not sufficient to show the strain responsible. This matter will be referred to further on.

Apart from the difference in titre, main and paraspecific reactions cannot be distinguished with certainty : retardation of the reaction of highly dilute sera was noted in both cases, and in either case

the reaction occurred just as well with the agglutinins as with the lysins, at any rate if the paraspecific reaction was sufficiently strong. In very low reactions (whether main or paraspecific), the agglutinins may indeed be absent.

Difference between L. icterohæmorrhagiæ and L. canicola as regards the Number of Paraspecific Reactions.

There would appear to be a difference between *L. canicola* and *L. icterohæmorrhagiæ* as regards the tendency to paraspecific reactions.

Of 186 sera from cases of *canicola* infection, only 32 (i.e., 17.2%) gave no reaction with *L. icterohæmorrhagiæ* (Table 42), and of 114 sera from cases of *L. icterohæmorrhagiæ* infection there were 53 (i.e., 46.5%) which gave no reaction with *L. canicola* (Table 43). As both groups were not composed in the same way, we made a special comparison of the sera of a titre of 1:1,000 and more, and noted that, of 124 giving a titre of 1,000 and over with *L. canicola*, 4 (i.e., 3%) were negative with *L. icterohæmorrhagiæ*, and out of 56 sera giving a titre of 1,000 or more with *L. icterohæmorrhagiæ*, 15 (i.e., 27%) were negative with *L. canicola*. Thus, in the case of these higher titres, too, there is a marked difference in the tendency of the respective strains to give paraspecific reactions. Though a paraspecific reaction is less frequent with a *canicola* serum, it is generally not lower, when it does occur, than reaction of *icterohæmorrhagiæ* serum with a *canicola* strain (see Tables 42 and 43). We have no explanation to offer for this phenomenon.

Reactions with Formalin Strains.

In testing dog sera with *L. icterohæmorrhagiæ* and *L. canicola*, not only living strains, but formalin-killed strains have been used in a number of instances. So far (end of 1937), the number of such formalin reactions performed with *canicola* strains is not large; they indicate, however, that a reaction with a formalin-killed *canicola* strain reaches about the same titre as the lysis of a living strain, or differs from it at most by one degree of dilution (above or below) (Tables 44 and 45). In this respect, *L. canicola* behaves exactly like *L. icterohæmorrhagiæ*.

With a formalin treated strain (for which consequently only the agglutination titre was recorded), positive results were obtained

equally well in regard to both specific and paraspecific reactions, as the following examples show. They show once again that a serum giving a paraspecific reaction does contain agglutinins against the heterologous strain.

Serum	<i>L. canicola</i>		<i>L. icterohæmorrhagiæ</i>	
	Living	Formalin killed	Living	Formalin killed
Dog 3869	10 (0)	30	300 (0)	100*
„ 28	100 (10)	300	1,000 (30)	3,000
„ C.E.	300 (0)	300	3,000 (100)	1,000
„ 466	100 (10)	100	10 (0)	10
„ 4862	10,000 (100)	3,000	300 (10)	300
„ 80	30,000 (30)	30,000	1,000 (0)	1,000

* The numbers between the parentheses for the reactions with living strains refer to the degree of agglutination; in the reactions with formalin-killed strains, only agglutination occurred, of course.

Equally High Reactions with L. canicola and L. icterohæmorrhagiæ.

In 22 cases, the reaction with *L. canicola* and *L. icterohæmorrhagiæ* was the same—viz., 1:30 in 5 cases, 1:100 in 5 cases, 1:300 in 4 cases, 1:1,000 in 4 cases, and 1:3,000 in 4 cases. In order to ascertain which of the two reactions is specific, the reactions should be repeated in order to determine how they stand in relation to

Table 44.—TITRE WITH LIVING AND WITH FORMALIN STRAINS
L. canicola.

Titre with living strains	Number of reactions	Titre with formalin strains								
		Neg.	10	30	100	300	1,000	3,000	10,000	30,000
0 ...	12	10	1	1						
10 ...	2		1	1						
30 ...	7		1	5	1					
100 ...	14		1	1	7	5				
300 ...	10				3	5	2			
1,000 ...	4					1	3			
3,000 ...	7						2	2	1	2
10,000 ...	7							3	3	1
30,000 ...	12								2	10
	75	10	4	8	11	11	8	5	6	13

LEPTOSPIROSES

Table 45.—TITRE WITH LIVING AND WITH FORMALIN STRAINS
L. icterohæmorrhagiæ.

Titre with living strains	Number of reactions	Titre with formalin strains								
		Neg.	10	30	100	300	1,000	3,000	10,000	30,000
0 ...	5	4			1					
10 ...	5		3	2						
30 ...	11		3	6	2					
100 ...	4			2	2					
300 ...	12				3	6	3			
1,000 ...	11					1		1		
3,000 ...	4						2	2		
10,000 ...	2							1	1	
30,000 ...	1									1
	55	4	6	10	8	7	14	4	1	1

each other as the disease progresses. We had little opportunity of doing this with dog sera, and even less with human sera.

An example of how a repetition of the test proved decisive in the case of a dog is given below :

Successive Seroreactions of Dog de R.

	Serum	Strains	
		<i>L. icterohæmorrhagiæ</i>	<i>L. canicola</i>
Dog de R. ...	First test	300	100
	One week later	3,000	3,000
	Two weeks later	3,000	30,000

(c) *Classification of the Strains.*

Table 46 reproduces graphically the classification of the strains of *L. canicola* found in dogs and human beings.¹ The classical strains from dogs are included in the table for all the classical strains in the chapter on rats ; they do not differ from other *L. icterohæmorrhagiæ* strains isolated from human beings or rats.

¹ 6 *canicola* dog strains were isolated at the Institute of Tropical Hygiene from urine ; we received 5 from Professor MEYER of San Francisco ; the others were given by Professor KLARENBECK. The 4 strains from human beings were all obtained in the Institute of Tropical Hygiene from the urine of patients.

Table 46.—CLASSIFICATION OF *L. canicola* BY AGGLUTINATION-LYSIS REACTIONS WITH MONOVALENT SERA
Sera against :

Strains	Canicola	Ictero-hæ- morrhagie	Salinem	Rachmat	Swart van Tienen	Pomona	Hebdo- madis	Grippe- typhosa	Ballico	H.C.	Anda- man A	Pleth-rat 178 Semarang
Dogs from Netherlands 18 strains	■ ■	■ ■ ■ ■ ■ ▨ ▨ ▨ ▨ ▨ ▨ ▨ ▨ ▨	▨ □	 □ □ □ □ □ □ □ □ □ □	□	□	▨ ▨ □	□ □	□	□	□	□
Dogs from San Fran- cisco 4 strains	■ ■ ■ ■ ■	■ ■ ▨ ▨		□ □ □ □ □								
	■	▨		□								
4 strains isolated from man. Netherlands	■ ■ ■ ■	■ ■ ▨ ▨ ▨ ▨ ▨ ▨ ▨ ▨ ▨		□ □	□		□ □	□ □ □		□		SDN 9144

- Reaction - ■ of a strength equal to the full specific titre.
 ▨ of a strength equal to 1/10 of the full specific titre.
 ▨ of a strength equal to 1/30-1/100 of the full specific titre.
 ▨ of a strength equal to 1/300-1/1,000 of the full specific titre.
 □ negative.

All the *canicola* strains gave, in addition to a reaction of full strength with the homologous serum, paraspecific reaction with the serum against *L. icterohæmorrhagiæ*. There were no instances, such as some we observed with human patients infected with *L. canicola*, whose serum, though yielding a titre of 30,000 when tested against the homologous strain failed to give any paraspecific agglutination at all with *L. icterohæmorrhagiæ*. In spite of the occasionally strong paraspecific reaction, it was always possible to decide whether one dealt with the *canicola* strain or the classical one.

Further, unlike *L. icterohæmorrhagiæ*, which very frequently reacts with Rachmat antiserum (see rat and human strains of *L. icterohæmorrhagiæ*) the *canicola* strain gave no paraspecific reaction (so far as the testing went) with the antisera of the Rachmat group. With the other antisera used, paraspecific reactions where present were weak.

Five of the classical strains, on the other hand, gave a very strong paraspecific reaction with *canicola* serum ; this is described in the section on the classification of *L. icterohæmorrhagiæ*, which also shows how these strains could always be differentiated from *canicola*. Our experience with some *canicola* antisera, prepared by the inoculation of heated cultures in rabbits, was different, the paraspecific reactions with *L. icterohæmorrhagiæ* being weaker or disappearing entirely (see chapter on rats).

(d) *Animal Experiments with L. canicola.*

Experiments with Guinea-pigs.

Manner of Infection.

Our first inoculations of guinea-pigs were nearly always made with patients' urine containing leptospiræ. Only 2 guinea-pigs were inoculated with patients' blood. It soon became evident that the infection was not easily transmitted by intraperitoneal inoculation or by instillation into the eye. We therefore had recourse to intra-cardiac inoculation as recommended by ZUELZER. Thus did the leptospiræ prove to be somewhat more abundantly present in the peritoneal fluid.

The *canicola* strain also displayed certain characteristic properties in guinea-pig infections, particularly as regards the generally low virulence on 1st inoculation.

Table 47. — VIRULENCE OF *L. icteroh.* AND *L. canicola* FOR THE GUINEA-PIG

	1st passage			2nd passage			3rd passage			4th and further passages		
	Number of guinea-pigs			Number of guinea-pigs			Number of guinea-pigs			Number of guinea-pigs		
	Inocu- lated	Survi- vors	Dead	Inocu- lated	Survi- vors	Dead	Inocu- lated	Survi- vors	Dead	Inocu- lated	Survi- vors	Dead
<i>L. icterohæmorrhagiæ</i> from blood :				p.s.em.			p.s.em.			em.		
Infection	85	1	74 (10c.)	37	3	32 (2c.)	16	1	14 (1c.)	20	0	20
No infection	5	5										
Total	90	6	74 (10c.)	37	3	32 (2c.)	16	1	14 (1c.)	20	0	20
<i>L. icterohæmorrhagiæ</i> from urine :				p. s.			p. s.					
Infection	21	3	16 (2c.)	7	1	6	4	0	4			
No infection	6	6										
Total	27	9	16 (2c.)	7	1	6	4	0	4			
<i>L. canicola</i> from urine :												
Infection	27	22	5	14	4	10	5	0	4 (1c.)	17	3	11 (1c.)
No infection	10	10		3	3							(2 interc.)
Total	37	32	5	17	7	10	5	0	4 (1c.)	17	3	11 (1c.) (1 interc.)

p. = peritoneal fluid. s. = blood. em. = liver emulsion. interc. = intercurrent. c. = cardiac puncture.

Guinea-pigs marked (c), who had heart puncture died the same day, but not from this cause, for they were already very ill.

Virulence of L. canicola for Guinea-pigs.

The bottom part of Table 47 shows, for example, that, of 37 guinea-pigs inoculated with canine or human urine containing living leptospiræ, only 27 became infected; 22 of which survived the 1st passage, only 5 dying of leptospirosis. 10 out of 17 died in the 2nd passage, and more in the subsequent passages. After the 3rd passage, the period between inoculation and death did not appear to be definitely reduced any further.

There is a possibility that the medium from which *L. canicola* was regularly obtained—*i.e.*, the urine—influenced the inoculation experiments and was one of the reasons for the mild effect of the first inoculation. It is hence interesting to compare the effect of inoculating guinea-pigs with human blood or with human urine, containing *L. icterohæmorrhagiæ*, or else with *L. canicola* obtained from the urine of dogs or human beings as shown in Table 47. From this table, there does indeed seem to be some difference according to whether the guinea-pigs are infected with the urine or the blood of human patients suffering from *Leptospira icterohaemorrhagiæ* infection.

In the first group, 1 out of 85 (= 1%) of the guinea-pigs infected with *L. icterohæmorrhagiæ* survived the 1st passage; in that infected with urine, 3 survived out of 21 (= 14%); this may be due to the fact that, at the stage at which the urine is taken for inoculation, the disease has already been progressing for some time and more immune bodies have been formed, or to the reduced activity of the leptospiræ in the urine, as a result of its acid reaction. In the case of *canicola*, 22 out of 27 (81%) survived.

The pathogenicity of *L. icterohæmorrhagiæ* and *L. canicola* inoculated with urine would therefore appear to be very different.

In the 2nd passage, when the guinea-pigs are given an injection of blood or liver emulsion, the difference in the virulence is much less, but, even in further passages, the *canicola* strain continues for a long time to be somewhat less deadly.

Moreover, in the 1st passage, at any rate, the virulence of the various *canicola* strains also appeared to differ.

The strains from patient Ha and the dogs concerned already killed 5 out of 7 guinea-pigs in the 1st passage, though, of 7 other strains, none caused death in any one of the 20 guinea-pigs tested.

In the 2nd passage, all the strains appear to be more virulent and the differences do not persist.

Although, particularly in the 1st passage, the guinea-pigs did not all die, the number of infections was higher than the small number of fatal cases would have suggested. Thus leptospiræ were found in the peritoneum in several non-fatal cases. Leptospiræ were, furthermore, found in the urine of many of the surviving animals after 2 or 3 weeks, where they sometimes persisted for some considerable time.

In other experiments, infection was demonstrated by the fact that the guinea-pigs were able to resist a subsequent infection by a virulent strain, whereas the control guinea-pigs succumbed. For example, 6 guinea-pigs inoculated with urine from Dog W all survived (see table subjoined). Leptospiræ were, however, demonstrated in :

No. of guinea-pigs inoculated with urine of dog W.	Peritoneal fluid	Blood	Urine	Reinoculation
2897	—	—	+	
2911	—	—	+	
2923	—	—	+	
2924	+	+	15th day—	
2927	+		+	+ died after seven days of pseudo tubercul.
2928	+		+	+ survived

The examination of the peritoneal fluid, blood, urine, etc., showed, in these cases, that none of the animals had escaped the infection. The examination of the urine therefore deserves special attention.

Jaundice in L. canicola Infection of the Guinea-pig.

L. canicola caused little jaundice in guinea-pigs in the Netherlands ; when it did occur, it was nearly always slight, and occurred in all passages (see Table 48). Material taken from one guinea-pig not suffering from jaundice and infected into another may cause jaundice, while material from a guinea-pig with jaundice may infect an animal in the next passage without producing jaundice.

The table also shows the great difference in the frequency of jaundice caused by *L. icterohæmorrhagiæ* and *L. canicola*.

Experiments on Dogs with an L. canicola Strain.

Soon after the *canicola* strain was first isolated at the Institute of Tropical Hygiene, 4 dogs were inoculated with *L. canicola*; 2 by injection, while 1 was given food mixed with the strain and the other was put in a cage with one infected dog. All 4 became infected, as was shown by examination of the peritoneal fluid, blood and urine, and also by the serological reaction.

As soon as the presence of leptospiræ in the peritoneal fluid showed that the experimental infection had succeeded, the dogs were given 5 c.c. of anti-serum. Three showed no signs of illness, while the fourth which was already ailing before died with jaundice and hæmorrhages; the autopsy revealed, however, that it had a very large intussusception of the intestine, so that its death could not be attributed solely to the leptospiræ.

By injecting the *canicola* strain into very young dogs, KLARENBECK & WINSSER produced jaundice in 10 out of 11 cases, some slight and others marked. As these puppies were killed after a few days, it is impossible to say in how many cases the infection would have proved fatal.

Inoculation of L. canicola to Rats and Mice.

Experiments on this subject are described in the sections dealing with leptospirosis in rats. All that need be recalled here is that inoculation of *L. canicola* affected rats very little. The leptospiræ could be found for a while in the peritoneum but could not be found in the blood or in the urine (except in 1 rat out of 14, and on one day only). It may therefore be said that the rat cannot be made a carrier. In the case of mice only, some were temporarily infected. Only one strain, which had already been passed through a guinea-pig and had become more virulent as a result, was recovered from the peritoneal fluid and blood of mice, and had therefore turned them into carriers.

Inoculation of L. icterohæmorrhagiæ and L. canicola to Cats.

Both *L. canicola* and *L. icterohæmorrhagiæ* appeared equally able to infect cats. 3 cats and 2 kittens were inoculated with each of the two strains, which were virulent for guinea-pigs. The first

Table 18.—JAUNDICE IN GUINEA-PIGS INOCULATED WITH *L. icteroh.* OR *L. canicola* AND DYING THEREFROM

	1st passage			2nd passage			3rd passage			4th and further passages			Total		
	Ict +	Ict ±	Ict —	Ict +	Ict ±	Ict —	Ict +	Ict ±	Ict —	Ict +	Ict ±	Ict —	Ict +	Ict ±	Ict —
<i>L. icterohæmorrhagiæ</i> from blood	66	1	5	24	2		6		1	17		1	113	3	7
<i>L. icterohæmorrhagiæ</i> from urine	15		2	6			4			4			29		2
Total	81	1	7	30	2		10		1	21		1	142	3	9
<i>L. canicola</i>	1	1	3	2		7		2	2	1	2	9	4	5	21

Ict + = jaundice.
 Ict ± = doubtful.
 Ict — = no jaundice.

received 18-21 c.c. in 4 and 7 injections respectively ; the second 6.5 c.c. in 4 injections. No pathological symptoms were observed.

After 14 days all the cats injected with *L. icterohæmorrhagiæ* had a serological titre between 1:100 and 1:1,000 against the homologous strain, while those injected with *L. canicola* had a titre of 1:300 to 1:3,000. The titre was usually 1:1,000. Leptospiræ were found in the peritoneal fluid of the kittens, and one kitten in each group became a carrier. There was thus no fundamental difference in the symptoms caused by the injections of the two strains.

5. *L. canicola* INFECTION IN HUMAN BEINGS

Up to now, the *canicola* infection has been demonstrated in 12 patients in the Netherlands ; a strain has already been isolated from human beings in Denmark (BORG PETERSEN), and infections in San Francisco and Berlin have been discovered serologically.

Clinical Symptoms (Cases in the Netherlands).

Though it is certainly not possible to distinguish the *canicola* infection in human beings from the classical *L. icterohæmorrhagiæ* infection by clinical criteria, the *canicola* disease has certain special characteristics.

Up till now, it has caused no deaths, though the disease is by no means always mild or of short duration. The 12 cases included some very slight ones (v.d.K., R., which were accidentally discovered); but others were very protracted (Res., Kl., Wubb., We.) lasting more than 30 days, as compared with an average of 24 days for anicteric cases of Weil's disease in the Netherlands. One or more relapses occurred in all but 3 cases, or else the temperature curve went up and down. On one occasion, the febrile period was very long (more than 20 days).

Severe symptoms were not always recorded, jaundice hardly ever.

Sub-icterus of the scleræ was reported in only 2 cases, and lasted for so short a time that it was not entered in the hospital record. Hijmans van den Bergh's test gave a weak positive direct reaction, however, in 2 out of 3 anicteric cases examined, and the indirect test gave values of $1\frac{3}{4}$ and $1\frac{1}{4}$ respectively ; this indicates the presence

of bile pigments in the blood serum, though in insufficient quantities to cause jaundice.¹ In some cases, the changes in the urine did not amount to much more than those which occur in febrile albuminuria coupled with urobilinuria. A sediment of renal casts, leucocytes, and erythrocytes, was present in some instances, but this generally lasted only a few days. In a few cases, the albuminuria and elimination of casts went on for a somewhat longer period. Even muscular pains, headache and episcleral infection were not always present.

On the other hand, it is remarkable how often the meningitis symptoms or at least symptoms of meningismus occurred (in 4 out of 12 patients).

The blood picture showed the same deviations as are found in the classical form of the disease. A feeling of great weakness was repeatedly noted in the convalescent stage. In one case, a patient was reported to have grown new nails during his period of recovery.

The typical syndrome produced by *L. canicola* in dogs is not found in human beings. It is true that, in both cases, there is no jaundice, and the course of the disease tends to be protracted. But the serious renal symptoms and uræmic condition which are so typical for the infection in dogs have not been found in the human cases so far observed.

Relationship between Human Cases and Canine Infections.

Most of the patients had a dog, and, in several cases, the dog was also reported to have been ill. The doctor dealing with the case was usually able to have the serum or urine of the dog examined. In some cases, the dog itself was sent to the laboratory for examination. Thanks to this co-operation between the owners and doctors, serological reaction tests or cultivation of the strain from urine showed on 6 occasions that the dog had had a *canicola* infection, and could therefore be presumed to have transmitted the disease to the human patient.²

¹ The case described in San Francisco was clearly accompanied by jaundice, and one of the patients in Denmark also had jaundice. In the latter case, it may have been due to pre-existing liver trouble.

² Kl., So., Wu., Ha., v.d.K., R., (the last three patients were infected by two dogs).

Table 49.—SEROLOGICAL REACTIONS OF PATIENTS WITH CANICOLA INFECTION AND OF THEIR DOGS

Name of patient	Day of illness	Serological reaction of :				Canicola strain cultivated from :	
		Patient with		Dog with		Patient's urine	Dog's urine
		<i>L. icteroh.</i>	<i>L. canicola</i>	<i>L. icteroh.</i>	<i>L. canicola</i>		
Oh.	11	30	1,000				
	30	0	1,000-3,000	1,000	1,000		
	8	0	100				
Child, S.	20	1,000	10,000				
Father, S.	20	0	10,000				
Res.	13	100	3,000			+	
	109	100	1,000				
	190	10	300				
KL	34	100	30,000				
	54	30	10,000	{ 30 100	{ 10,000 30,000		+ Same infection stated to have been found in dog.
J.	± 70	10	300				

Sa.	22	300	1,000				
	28	300	3,000				
	40	100	3,000	100	300 at least		Dog also ill.
Wu.	9	0	100				
	15	30	300			+	+ <i>do.</i>
	29	300	10,000	0	30,000		
Ha.	13	0	1,000	Dog S 10	10,000	+	Dog S + and sick
	21	0	3,000	Dog B 100	30,000		Dog B +
	35	10	3,000				
	51	50	10,000				
V.d.K.	40	10	1,000	Dog S			Dog S +
R.	16	100	1,000	Dog B			Dog B +
We.	12	3,000	1,000			+	
	23	3,000	1,000				
	61	1,000	30,000				
	87	300	3,000				

In one case (dog 01), in which only one serological test could be performed, and gave 1:1,000 with both strains, it remained uncertain whether the dog had been infected by *L. canicola* or *L. icterohæmorrhagiæ*, or by both.

Bacteriological and Serological Diagnosis of Patients and their Dogs.

Table 49 gives the summary of the serological reactions of patients and their dogs carried out at the same time, and also indicates whether a strain was cultivated from the human beings or the dogs. In nearly every case, a paraspecific agglutination of *L. icterohæmorrhagiæ* occurred.

The reaction was, naturally, read as *canicola*-positive, when it was higher than that with *L. icterohæmorrhagiæ*. The diagnosis could often be confirmed by the fact that the reaction increased during the course of the disease (Wu., Ha., So., We.). In some cases, the test was only performed once, but the titre immediately became so high that a *canicola* infection could certainly be assumed (01, Schl., Kl., v.d.K.).

In four of the cases (Res., Wu., Ha. and We.), it was possible to cultivate the leptospira from the urine and to identify it as *L. canicola*.

An interesting serological reaction was that of the father and child S., who had both swum on the same day and fallen ill on the same day; the reaction (both 1:10,000 with *canicola*) showed they were infected with a *canicola* strain. The child's serum gave a paraspecific reaction up to (1:1,000) with a classical strain, not so the father, though both infections were presumably due to the same cause.

The patient We.'s reaction was peculiar. There was no doubt that he was infected with *L. canicola*, as was shown by the high reaction which his serum gave with this strain, but, during the first weeks, he gave a higher reaction with *L. icterohæmorrhagiæ* than with *L. canicola*. Arguing by analogy from other similar cases in which Castellani's test indicated a single infection, we presume that, in this case too, the patient was only infected with *L. canicola*, a view which is borne out by the fact that the *L. canicola* but not *L. icterohæmorrhagiæ* was cultivated from the urine.

The history of three cases (H., v.d.K. and R.) is sufficiently remarkable to be briefly given here. The first of these patients

was removed to a hospital in Rotterdam with a diagnosis of " meningitis ", and leptospirosis was first suspected when a sudden marked improvement was noted after a lumbar puncture. She seemed to have been infected by a young Samoyed belonging to a litter of which the animals, with one exception, were apparently infected with *L. canicola*. All the dogs and their parents, seven in all, were examined as a result of this case, as well as all the members of the various families owning the dogs. 2 more of the 25 persons in contact appear to have had a *canicola* infection judging by their serological reactions. They had been slightly unwell during an epidemic of influenza, one of them for only 3 or 4 days. Evidence was available to show that this had happened after a whole day's contact with an infected dog. A contact dog was also found to be infected with *L. canicola*.¹

By the strength of the serological reactions, it was possible to determine the probable order of infection ; the dog had infected the bitch who had infected the litter ; the pups and another dog had infected the three persons. The fact that so much infection had been caused among human beings was due to special circumstances :

- (1) The dogs had been in very close contact with the human beings ;
- (2) They were eliminating an exceptionally large number of leptospiræ ;
- (3) The strain appeared to be more than usually virulent for guinea-pigs.

It was remarkable that the dogs had only been very slightly sick, if at all, so that none of the owners had thought it necessary to call the veterinary surgeon. It will thus be seen that there are mild cases which are not recognised in normal circumstances and this shows that the *canicola* fatality rates in dog clinics are apt to be misleading, just as the fatality figure for Weil's disease among human beings appears larger than it actually is owing to the fact that a number of slight cases pass unnoticed.

Half these dogs were still carriers when examined.

¹ Table 49 only gives the serological reactions of the two dogs who were responsible for the three cases among human beings.

Thus, without arousing suspicion, and without their owners even realising that they have been ill, dogs may excrete leptospiræ. The above instances show what the consequences may be for human beings. We do not think, however, that there is any reason to regard the dog as a particularly dangerous source of infection. In the above cases, there were special reasons for so much infection. The few cases of *canicola* infection in human beings (only 12 in five years, though some may admittedly have escaped notice) shows that the risk of infection from dogs is indeed very small.

IV.

PREVENTION OF LEPTOSPIROSES

Measures for the prevention of leptospirosis have been chiefly applied in countries where the disease is very prevalent, such as Japan, and also in countries where it is not frequent but causes local epidemics in slaughter-houses, swimming-baths, and among sewer-men (H. FAIRLEY), sugar-cane cutters, etc. A great variety of measures have been recommended, some of which are considered below.

1. *Measures to prevent Contamination of Ground and Surface Water with Rat Urine.*

(a) The most important of these measures is the *extermination of rats*. For this purpose, the Amsterdam Health Service uses the so-called Hora gun, firing a cartridge which releases CO and H₂S into the rat-holes. In a test, 44 dead rats were found in one hole. Scilla preparations are also used as rat poison, extracts being made in the form of a paste or liquid which is mixed with bread and a very small quantity of aniseed oil. These methods are applied wherever complaints are made about rats, and also at the beginning of the swimming season in swimming-baths and the immediate neighbourhood, in boat-houses, etc., and in places where cases have occurred.

Other preparations (Zelios, Spyx) are used in the slaughter-house in Amsterdam, where campaigns against rats are periodically

conducted. This appears to be sufficient to keep the meat stores free of rats, but the rats do not disappear for good, as they eventually return from other districts in the neighbourhood. SMITH & DAVIDSON point out that deratisation is most effective when conducted on a very large scale.

(b) Another method consists in *ratproofing buildings* which are liable to be overrun with rats (bakeries, slaughter-houses, fish-mongers' shops, swimming-baths). The method must be economical, particularly in small concerns which cannot afford additional expenditure. Though complete efficiency cannot everywhere be attained, great improvements can be effected given careful and systematic application of simple methods (SMITH & DAVIDSON). These include closing the rats' access to sewers where they go to drink, particularly at night (ALSTON & BROWN)—*e.g.*, by covering the openings with gratings, etc. In some swimming-baths in Amsterdam, a railing is placed under water, going down to a depth of a foot and a half. New swimming-baths are built in the form of cemented pools, and are filled from the water mains.

(c) *Strict cleanliness* and the elimination of anything that attracts rats.

It was noticed in the Netherlands that the infections ceased after the swimming-baths had been thoroughly cleaned. Furthermore, under the terms of a Decree of 1934, every swimming-bath must be approved by the authorities, and such approval is only given if the baths conform to certain standards. Thus, waste matter must be kept in places inaccessible to rats, particular attention being paid to food wastes.

SMITH & DAVIDSON recommend the following measures in the buildings in Aberdeen, where fish is cleaned, cured and packed: the floors, benches, etc., should be washed with a disinfectant not only in the evening when the premises are cleaned up, but also again in the morning, as the floors, etc., might be polluted by rats during the night; no articles should be kept on the floor, but should be washed and hung on wooden frameworks; garbage bins should be closed with tightly fitting lids and removed daily; water should be used straight from the tap and not kept in tubs, as is the custom.

(d) It should be borne in mind that human beings who are recovering from Weil's disease for a time pass out leptospiræ in

their urine, though this method of dissemination has not yet been proved to spread the disease. The urine should be disinfected as long as leptospiræ are found in it. Attention has already been drawn to this by INADA, and MARTIN & PETTIT.

Leptospiuria does not usually persist for very long ; INADA mentions about 63 days ; SLOT & VAN DER WALLE, however, found leptospiræ in the urine of a patient after 5 months, while JOHNSON in Australia observed them after one year. Patients who have been cured of Weil's disease cannot, however—in the Netherlands, at all events—be legally compelled to submit to supervision.

More importance must be attached to dogs as carriers. There is no doubt that they are able to pass out leptospiræ in the urine for a long time, and that human beings can be infected by dogs. In Amsterdam, leptospiuria was found, in some dogs, to persist for 4 months.

As it is very difficult to disinfect dogs' urine in practice, dogs which have been cured should be isolated for as long as they have leptospiuria. To solve this difficulty, attempts have been made to disinfect the urine by giving dogs prontosil, hydrocyanic acid, or a ketogenic diet. Such experiments have not yet given any results in our laboratory.

2. Measures for the Destruction of Leptospiræ in Nature

A second group of measures concerns the leptospiræ disseminated in nature. Endeavours have been made to make the surroundings as unfavourable as possible to the existence and development of these organisms. Thus, in Japan, where cases only occurred in damp mines, drainage and disinfection of the soil have proved particularly successful (INADA, and also IDO, IIOKI, ITO & WANI). Drainage is also of great importance in agricultural districts (rice-fields, etc.). A special measure which has been recommended in such cases is the fertiliser calcium cyanamide (CaC_2N_2), which effected a great reduction in the number of infections, as it kills leptospiræ.

Drainage cannot, however, be resorted to in every case, for example at Ingham (Australia), which is only intermittently boggy, and where the region is such that drainage is not possible (COTTER and SAWERS). The possibility of burning the sugar-cane and

disinfecting the stubble and soil was considered, but proved both impracticable and economically impossible.

DAVIDSON & SMITH have recommended hypochlorite as a disinfectant in Aberdeen. The highest dilution of their preparation which, added to cultures of leptospiræ, would render the latter innocuous to guinea-pigs, was found to be 1:4,000, but in practice a solution of 1:64 was used to ensure that sufficient free chlorine was available to disinfect substances rich in protein.

3. *Protection of Workers exposed to the Infection.*

The protection of workers in infected districts by preventing the organisms from penetrating through the skin or mouth. If such protection is used, it should consist of water-tight boots and, if necessary, hand and arm coverings. Thus, sewer men are provided with impervious boots (FAIRLEY). It may sometimes be impossible to apply such measures, owing to the climate. This was the case in Australia. The quick cleansing and bandaging of small wounds, including skin abrasions, so that leptospiræ cannot penetrate into the body, also come under this heading (ALSTON & BROWN), though these measures are not sufficient in themselves, even if they are performed quickly and thoroughly, as was proved by a laboratory infection in Amsterdam.

In some laboratories (UHLENHUTH & ZIMMERMANN), rubber gloves are used, but this is considered unnecessary in Amsterdam.

4. *Protection by Means of Active Immunisation.*

Where drainage and other measures are impossible, or where the infected district is too large for disinfection to be effective, vaccination should be resorted to (INADA), for example in factories, mines, slaughterhouses, etc., and in cases where the ratproofing of buildings is too costly or deratisation ineffective; also on sugar-plantations in Australia where the annual incidence of the disease among canecutters sometimes reaches 18% (MORISSEY), among sewer-workers (FAIRLEY), etc. In Leipzig, several cases of Weil's disease occurred among sewer men; when the risk of infection is thus limited to an occupational group, vaccination becomes practical. Elsewhere, however—*e.g.*, in the Netherlands—where

not a single person working in sewers or having a similar occupation has contracted the disease in a year or more, vaccination would be unnecessary. It would be called for only in laboratories, whether they are working in leptospiræ or not, for contact with rats is, in any case, frequent. In this way, laboratory infections, which sometimes prove fatal, may be avoided.

Preparation of the Vaccine.

The vaccine may be prepared in various ways :

- (1) By heating, followed if necessary by
- (2) The addition of carbolic acid (IDO, HOKI, ITO & WANI),
or by
- (3) The addition to the cultures of a small piece of copper
which has cooled after being heated to glowing point (BEGER).

Immunisation is used on a large scale in Japan, both in coal-mines (WANI) and in some rural districts.

To immunise miners, WANI used cultures from Noguchi's medium, which he heated twice for half an hour at a temperature of 56° with an interval of 24 hours ; he then added 0.25-0.5% of carbolic acid to the cultures, and kept them for one week in a refrigerator. The immunisation was performed in two stages by inter-capular injections with 2 c.c. and 3 c.c. of vaccine respectively. WANI mentions that he inoculated 10,268 miners in a coal-mine in Fukuoka, 2,259 of whom only received one injection.

The vaccination generally caused only slight discomfort : 50% were able to continue working, 33% had to break off for 1 to 2 days (more than 4 days was rare), 30-40% developed a slight temperature or at least complained of a local feeling of warmth.

Results of Vaccination.

As regards results, WANI calculated *inter alia* that in one mine and during the same period :

5 cases occurred among 3,655 vaccinated workers = 0.13%
70 cases occurred among 6,266 non-vaccinated workers =
1.12%

MAYIMA later continued this work (1919-1926) and observed 673 further cases among non-vaccinated individuals and only 21 cases among the vaccinated although they were the majority.

TSURUMI mentions that, in 1925, 10,617 persons were vaccinated in the prefecture of Toyama, which was strongly infected. According to the local health service, the vaccination proved effective. No cases among those vaccinated had been reported.

After a laboratory infection, UHLENHUTH & ZIMMERMANN immunised three of their staff, by means of two injections at a week's interval ; 14 days after the second injection the serological titre in two of the cases was 1:100 and 1:50 respectively, but the serum of these two persons did not protect the guinea-pig against a fatal dose of virulent culture.

In Amsterdam, 20 persons were vaccinated in two laboratories. The culture used as vaccine was twice heated up to 70° with an interval of twenty-four hours.

When preparing vaccine by heating, it is advisable to close the test-tubes containing culture by fusing the glass so that they can be completely immersed in the warming water ; otherwise quite a number of germs may survive. It was found in Amsterdam that 25 minutes' warming at 50° was sufficient to kill *L. icterohæmorrhagiæ*. Heating at 70°, therefore, left no room for doubt that the vaccine was killed.

The first 5 persons were given 3 doses. The first 2 consisted of inter-scapular injections of 2 c.c. and 3 c.c. respectively given with an interval of 1 week. The third dose (3 c.c.) was injected intravenously a month later, when it appeared that the titre of their serum was not high.

12 persons received 2 intravenous injections with an interval of one week.

3 persons received one single intravenous injection.

The inter-scapular injections caused only local discomfort. The intravenous injections were somewhat more troublesome.

When the intravenous injection was first given most patients exhibited no symptoms, a few had headache, giddiness and a sensation of cold, which soon disappeared. The second injection was more disturbing, though the symptoms were also slight. Only one person showed a somewhat stronger reaction (rigour and a raised temperature) ; another person vomited. Both persons were at work again the next day, however.

After the 3rd injection one of the immunised persons showed symptoms which must, in this case, be attributed to anaphylaxis

(rigour, temperature and headache). It is better, therefore, not to give a 3rd injection and to give the first two in rapid succession.

One person, who had received one injection, and another, who had received two, developed no demonstrable serological titre ; all the others had titres of at least 1:100, some having 1:300 and 3—1:1,000 (8 days after the last inoculation). The titre of 2 was again tested after 9 months and proved to have fallen from 1:300 to 1:100 or 1:10. VAN THIEL has shown that even when showing a very low titre guinea-pigs were protected against a subsequent inoculation. He also demonstrated that 1 c.c. of the serum of the immunised guinea-pigs (titre 1:1,000) afforded protection against simultaneous inoculation with virulent leptospiræ (of which control animals died). The results may therefore be described as very satisfactory, although conclusions based on animal experiments cannot automatically be applied to human beings.

The use of *live leptospiræ* for vaccine, was an idea that suggested itself readily by analogy with a similar use of bacteria. The strains used were those which had lost their virulence, at any rate for guinea-pigs, through continuous cultivation in artificial culture media. VAN THIEL made tests with the "Franken" strain which no longer infected guinea-pigs. As a result of inoculation, one of the persons thus inoculated experimentally did contract Weil's disease without jaundice but with a very high temperature and feeling of sickness, so that the experiments were discontinued. A virulence in regard to guinea-pigs did not thus imply a sufficient loss of pathogenicity for man. In other words, human beings may remain sensitive to a strain which is no longer pathogenic to guinea-pigs. It may be that other laboratory strains will be found which have lost their virulence to a still greater extent but, as long as these are not available, live vaccines must not be used.

Inoculation with other kinds of leptospiræ which are not in themselves dangerous to life, such as the leptospiræ of "mud fever" or nanukayami, is of no value, as their immunising properties, if any, are insignificant against the genuine Weil's infection. Furthermore, these kinds of leptospiræ produce pathological conditions, which are undesirable accompaniments of preventive inoculation. It is therefore preferable, even essential, only to vaccinate with killed-cultures.

In this connection, *vaccination of dogs and silver foxes* may be mentioned as a means of preventing the death of valuable animals. Though the same precautions need not be exercised in such cases and attenuated live strains might be used, the killed vaccine is necessary in this case too, in order to avoid creating a new leptospira carrier who would further disseminate the disease. We still lack information on this subject, however.

5. *Health Education and Propaganda. (Films, Lectures, etc.).*

These methods have been particularly employed in Japan. In the Netherlands, knowledge of the mode of infection, the rat danger, etc., is also steadily percolating through the population, just as the diagnostic knowledge has penetrated the medical profession.

6. *Compulsory Notification.*

Notification is already compulsory in Australia, the United Kingdom, France, Japan, the Netherlands, Scotland and parts of Germany. In Japan, the disease is legally classed in some districts as an infectious disease.

The advantages of the latter methods (5, 6) are obvious for an earlier recognition of cases as well as the stamping-out of epidemic outbreaks.

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TECHNICAL STUDY OF THE COMPARATIVE
EFFECTS OF MORPHINE AND OF CERTAIN
HABIT-FORMING DRUGS : EUCODAL,
DICODIDE, DILAUDIDE¹, ACEDICONE

FOREWORD

In its session held in May-June 1937, the Advisory Committee on Traffic in Opium and Other Dangerous Drugs discussed the comparative pharmaco-dynamic properties of certain drugs which were being used as substitutes for morphine—namely, eucodal, dicodide, dilaudide and acedicone—and decided to ask the Secretariat to prepare a memorandum for the information of the Committee. The Health Section, at the request of the Health Committee, had thereupon the following bibliographical study prepared.

¹ The question of dilaudide has been studied with great care by M. R. B. KING, C. K. HIMMELSBACH and B. S. SANDERS (supplement No. 113 of the *United States Public Health Reports*, 1935). No special chapter has therefore been devoted to dilaudide, but a great deal of its bibliography is included and comparative matter will be found in this study generally and in its last chapter in particular.

INTRODUCTION

A thorough and exact study of the different properties of opiates—analgesic, cough-relieving, hypnotic, etc.—is always a matter of some difficulty, and this difficulty is greatly increased if account is taken of the individual's constitution and condition, the special reaction of his autonomic nervous system and the nature of his endocrine formula.

Appraisal of the value of new opiates calls for a comparative examination of the different pharmacological and clinical effects. Research on these lines will indicate the group of opiates to which the new drug should be assigned and show its peculiar reactions in the human body. Where drugs of the morphine group are concerned, this work of systematic comparison is the more needful, since those who prescribe or generally recommend them are taking a serious responsibility. It must be acknowledged, however, that the clinical examination, which is usually of primary importance, is particularly difficult in the case of these various substances, which are very similar in nearly all respects.

The effects on the respiratory centre are difficult to judge by experiment. The real value of a medicament as a cough-relieving agent can be tested only on the human body, because the animals which are habitually used for these experiments are not subject to coughs and no experimental condition can be produced in them which would be really equivalent to the chronic irritation associated with a cough in the human patient.

Furthermore, there is no way of objectively measuring the influence of any remedy on a cough. Hence, the physician must fall back on observations carried out with the utmost care, and on the evidence of the patient. It follows that, if optimum conditions are to be ensured, the research here contemplated can only be reliably conducted on intelligent patients and in hospital. Failing this, the basis of comparison would be different, as is evidenced by the well-known fact that out-patients usually cough much more; indeed, quietness is *per se* a good method of combating the cough.

The influence of new opiates on pain and sleep is relatively easier to assess, but here also we have to take into consideration individual response, and depend for our evidence on the intelligence and goodwill of the patient. To measure the intensity of pain in a patient, we have no objective scale, and none either for the degree of alleviation of pain. Account must further be taken of the possibility of suggestive influence on pain of different kinds. Furthermore, it is impossible to compare absolutely equal intensities of pain to assess the analgesic strength of two drugs. Finally, and this is specially true of opiates, one can never be quite sure whether the patient's own judgment of the pain-stilling power of a drug is unaffected by any euphoric influence.

Whether a new drug is really habit-forming or not may be easier to judge. This we can do, it is true, only after we have collected all the necessary facts, but if, having done so, we pronounce a drug to be habit-forming, we can speak with some confidence. Whenever a new opiate comes on the market, it is usually claimed to be non-habit-forming and not to have the undesirable by-effects commonly associated with the older drugs of the same group. One particularly famous example of this kind is that of a drug put on the market several decades ago—heroin—but there are other instances in more recent times. The great difficulty in estimating the degree of euphoria arises from the observation, repeated time and time again, that individuals vary in their reactions to these drugs. Some of them feel, say, unpleasant by-effects of morphine to a very high degree, and to such persons it would, hence, be almost impossible to administer morphine in an emergency. Others, with the same substance, feel the typical effects of euphoria, delightful sensations, etc., and they return to the doctor to try to obtain more. These facts, known to every experienced physician, afford the best proof of the difficulties entailed in judging the comparative value of opiates. Thus, opiates in the wider sense of the term, afford an apt illustration of the English proverb: "One man's meat is another man's poison".

If, therefore, in the light of all the above factors, we address ourselves to the task of comparing the effects of morphine on the one hand, and eucodal, dicodide, dilaudide and acedicone on the other, we may well, in so intricate a matter, be guided by the precept of David HUME in *An Enquiry concerning Human*

Understanding: "In general, there is a degree of doubt and caution and modesty, which, in all kinds of scrutiny and decision, ought for ever to accompany a just reasoner."

* * *

In the study which follows, the different drugs in question will be taken in the order of their appearance on the market—that is to say, eucodal, dicodide, dilaudide¹ and acedicone. The drugs will be considered in relation to morphine as a basis of comparison. The final chapter will be devoted to a more general comparison in which several of these drugs will be taken together.

This is only a study of literature. The data which have been set forth as to comparative effects are those furnished by the different authors. Beyond these limits it did not seem wise to go, the more so as some clinical authors do not always adduce sufficiently precise evidence in support of their judgment.

EUCODAL

PHARMACOLOGICAL OBSERVATIONS

The oldest of the four habit-forming drugs discussed in this paper is eucodal, which has been known since 1917.²

Eucodal is regarded as a derivative of thebaine, but it has no longer the characteristics of this substance. It does not cause convulsions; on the contrary, it is as narcotic as morphine (and codeine). Its action is also based on a central effect, and, generally speaking, is not only much more powerful than that of codeine but may sometimes surpass even that of morphine.

The first pharmacological findings of HEINZ and FALK are rather meagre, and hence of no great value for the purpose of our study.

¹ See footnote in the foreword.

² Besides eucodal, there are other salts of dihydrohydroxycodone—for instance, the French preparation eubine and the Czech dinarkon. The great majority of papers published on the effect of this substance relate to eucodal, and a very few papers to other preparations. The same applies to dicodide.

HEINZ detected morphine-like effects in eucodal, as regards susceptibility, narcosis and respiration. FALK found in his experiments on animals that it has no harmful effects on the heart. According to the observations of VEHRER, eucodal in small doses has a soothing effect on the central nervous system, especially the cerebrum (sensitiveness is decreased, sleep is produced, but not unintermittently); the frequency of the pulse—and mostly that of the respiration—is diminished. Larger doses cause, not sleep, but giddiness, restlessness and convulsions; cats and dogs, on the contrary, show only symptoms of excitement—in a few cases only was a distinct contraction of the pupils observed. The general effect is quite similar to that of morphine, but the initial symptoms of restlessness are always less marked and do not appear in some cases. Somnolence and sleep, with more or less diminished sensitiveness, appear more quickly, on the average, with eucodal than with morphine. Recovery takes less time than with morphine.

In the experiments of BIBERFELD, the sedative action on the cerebrum of rabbits was also quite powerful and induced sleep. The effect was sometimes four times as intense as that of morphine. The influence on the sensitiveness of the respiratory centre is also much more marked than with morphine, and resembles more that of heroin, although heroin is still more effective than eucodal (about five times). With eucodal, general narcosis is also stronger than with morphine, but it is more transient. The lower limit (*dosis minima*) of effectiveness of morphine and eucodal is about the same.

As regards intestinal function, no constipation was observed in the experiments of VEHRER, but BIBERFELD found that eucodal influences the tonus of the intestines at least as strongly as morphine.

No habituation was noticed in rabbits after seven injections of 0.01 gramme. Dogs quickly grew accustomed to the sedative action (the same as with codeine), whilst the stimulating effect of larger doses was unaffected by repeated injections. It is therefore true to say that a drug habit was created in dogs; but, after twenty-five days, this habit completely disappeared, and the dogs reacted as at the beginning (BIBERFELD).

The toxicity in animals differs according to species. It is well known that cats are specially sensitive to morphine and that morphine only creates a state of intense excitement, although KOBERT found that the toxicity of eucodal on cats is about four

times less than that of morphine. But eucodal is not as dangerous as heroin. Rabbits tolerate about five times as much eucodal as heroin. The general symptoms with the same doses of eucodal or morphine (0.05) disappeared much more quickly after eucodal (BIBERFELD). On horses, the toxicity of eucodal is much less than that of morphine (DÖENECKE).

A more general pharmacological study has been made by WIKI and his pupil TEYSSEIRE¹ in which eucodal is compared with several other previously known opiates. After these experiments on different animals, guinea-pigs, rabbits, cats and dogs (as well as frogs), WIKI came to the following conclusions. The hypnotic properties of eucodal are about equivalent to those of morphine. The following order could be established, starting with the most potent substance : morphine, eucodal, heroin, codeine, dionine.

As an analgesic, eucodal is superior to morphine. Order of decreasing strength : eucodal, morphine, heroin, codeine, dionine.

As a cough cure, eucodal is, according to these observations, less potent than codeine and dionine. It seems that eucodal, like morphine, effects a reduction of the sensitiveness of the respiratory tract commensurate with the degree of narcosis produced. Order of decreasing strength : codeine, dionine, heroin, eucodal, morphine. Its ability to create euphoria is less pronounced than with morphine. Order of decreasing strength : morphine, heroin and eucodal, codeine, dionine.

The toxicity in the rabbit is reflected in the convulsive power. Order of decreasing strength : heroin, dionine and eucodal, codeine, morphine.

The toxicity for man is inferred from the depressing effect on the respiratory function of the rabbit. According to these observations, eucodal seems to be slightly more dangerous than morphine but less to be feared than heroin. Order of decreasing strength : heroin, eucodal, morphine, codeine, dionine.

¹ Reference may be made here to the pharmacological experiments on tissue cultures (pigmented epithelium cells of the iris) carried out by SANJO to determine the influence of codeine, dionine, heroin and eucodal on the growth of these cultures. The effect of eucodal was the most potent of these four, then follow dionine, codeine and heroin. No conclusions can be drawn from these observations for the purpose of this study.

WIKI takes the view that the clinical observations seem to be in full agreement with the laboratory experiments. The observations in clinical and medical practice will now be examined in detail.

CLINICAL AND PRACTICAL OBSERVATIONS

The *dosage* of eucodal is on the average : orally 0.005 gramme, which corresponds in potency generally to 0.01 gramme of morphine ; subcutaneously 0.01-0.02 gramme. In most cases, 0.01 gramme is sufficient (FALK), but other observers prefer doses of 0.02 gramme on the ground that the analgesic effect of 0.01 gramme has been shown to be insufficient (ROTHSCHILD).

It seems that 0.005 gramme of eucodal corresponds in effect to about 0.03 gramme of codeine (DREYFUS).

Toxicity.

One case of over-dosage has been described, in which 0.12 gramme was given without harmful results (FELDHEIM). But there are also known cases of over-dosage of morphine likewise not followed by harmful consequences.

If we try to assign eucodal to its appropriate place in the opiate group, we have to put it between morphine and codeine ; but it is closer to morphine in type of its effect. Its fundamental characteristics are very similar to those of morphine, but perhaps less pronounced, especially in the matter of concomitant effects, addiction properties, etc. (KLEINSCHMIDT).¹

Eucodal frequently proves superior to morphine in swiftness of action and intensity of the effect, but the duration of the latter is generally shorter—on the average 6 hours, instead of 12 with 0.02 gramme of morphine (PFEILER). Other authors have not observed this shortness of effect—*e.g.*, WOHLGEMUTH. In many cases, eucodal seems at least equivalent to morphine, and in some even superior (BAUMM).

¹ W. E. DIXON is of opinion that eucodal is more similar to heroin than to morphine.

Respiration.

The sedative effect on the respiration is generally judged to be more powerful than that of morphine or codeine in corresponding doses (DREYFUS, HESSE). LEICHTWEISS found the sedative effect on the respiration more intense and more durable than that of codeine or pantopon or heroin. Only one author holds this effect to be less potent than that of morphine (R. F. MAYER). Eucodal is generally regarded as a good remedy against coughs (BAUMM) and hence of value in this respect in cases of tuberculosis and asthma (SCHRÖDER). Morphine has not the same effect, and the analgesia it produces has been found to be of shorter duration and not so complete as with eucodal (BAUMM). When given alternatively with morphine and codeine in lung affections, eucodal has repeatedly proved more active and safer than morphine or codeine in corresponding doses (HESSE).

The respiratory centre is more influenced by eucodal than by morphine (FALK); in major operations on the thorax and the lungs, the sedative effect on the respiratory centre persisted much longer than that of morphine (ZBIRAL).

Finally, on the whole, eucodal acts better on whooping-cough than codeine (only a few cases observed) (FRANK and GLASER).

Circulation.

It has been found in the above-mentioned experiments on animals that eucodal has no adverse effect on the circulation.

The evidence of clinical experiments is generally to the same effect. Eucodal does not impair heart function even in persons with cardiac defects, but the lowering of the blood pressure may, in certain circumstances, be quite considerable (FALK, ROTHSCHILD). Other authors have observed no unfavourable influence on the heart, vessels or blood pressure (BAUMM, PFEILER). An authority on heart diseases, E. VON ROMBERG, explicitly states that eucodal is well tolerated, especially in the case of hypertony.

JACOBI, too, observed no harmful action on the function of the heart and respiration, his observations being especially concerned with cases of melancholia where eucodal was given for longer

periods. With morphine, on the contrary, great care must often be taken in cases of chronic heart disease (E. VON ROMBERG).

Analgesia.

The main purpose for which eucodal is used is as an analgesic. As such it is at least equal to morphine. The analgesic effect often appears more rapidly than with morphine (after 3, 4, 5 minutes) and lasts as long or longer (R. F. MAYER, LEICHTWEISS, FALK, BAUMM, WOHLGEMUTH).

There is no need, here, to stress the fact that in so difficult a question as the relieving of pain, in which the objective effect is overlaid with a host of personal factors and reactions, the conclusions and observations of different authors obviously cannot be congruent. It is not surprising therefore that we should have to make allowance for fluctuations of individual response, and that the effect should, in some cases (but very few), have been judged even shorter than that of morphine. The action of eucodal was quick and powerful in most cases, including some in which morphine failed in its effect. On the showing of the experience of four years, eucodal is not inferior to morphine ; 0.005-0.01 gramme is, on the average, sufficient, but 0.02 gramme may have to be given on occasion (BECK). It is frequently more efficient in its analgesic effect than morphine when subcutaneously injected in the same dose (HESSE), and lacks the exciting action of morphine (SIEGFRIED). In many instances, it is without doubt superior to morphine (WOHLGEMUTH).

There are, however, a few papers in the literature on the subject in which morphine is preferred to eudocal for severe and lasting pain. KEIM found eucodal in the same doses as morphine less analgesic. SPENGLER observed a prompt effect, but one of shorter duration (see the contrary findings quoted above).

ROTHSCHILD gives particulars of a series of patients who reacted but partially or not at all to eudocal, whilst, in others, the effect was quite good (whereas morphine did not act). According to the observations of the same author, the effects of eucodal on cancer patients were at least equivalent to those of morphine, and in many cases even better, especially if morphine or pantopon were badly tolerated previously.

FALK himself, who—as the author of the first paper—introduced eucodal into therapeutics, is of opinion that it is not suitable for

use in the initial phases of confinement because it creates a distinct attenuation of labour.

That there is a certain difference between the effects of morphine and eucodal can also be seen from the observations of BECK. He found eucodal equivalent, on the average, to morphine, but, in cases of seriously injured men of good muscular development, morphine was superior to eucodal.

Præ operationem, the same observation was made by this author with both these opiates. The pre-anæsthetic period of excitement is shortened ; the necessary amount of narcotic for narcosis is diminished ; vomiting occurs but rarely if at all—much less, at all events, than with morphine ; the function of the heart is not weakened (ZBIRAL, BECK, WOHLGEMUTH). In ophthalmological treatment, it was found equivalent, before an operation, to morphine, and without undesirable effects (HANKE).

BECK recommends eucodal also as a good analgesic *after operations* ; the effect (with 0.01-0.02 gramme) is obtained more rapidly and lasts as long as that of morphine (ZBIRAL). On the other hand, ROTHSCHILD found that 0.01 gramme was ineffectual ; nor indeed was 0.02 gramme quite effective in many cases ; the drug had therefore to be replaced by morphine or pantopon, etc.

Eucodal—in small doses—is regarded as a good analgesic remedy for children (0.0025-0.005 gramme) (WEISE), and has also proved successful, in the same doses, given in the form of tablets, for coughs in children. This is interesting to note, considering the rather high toxicity of morphine for children.

We may mention here some observations on dentistry, perhaps a little outside of the usual run of experience. The healthy pulp of teeth reacts to electrical faradic excitation in a different way. HEINROTH found that the sensitiveness of the pulp to pain is greatly diminished by morphine and to a lesser, yet considerable, degree by paracodine, and that there are no effects worth mentioning with codeine and eucodal and dicodide. In this case, eucodal is on a level with codeine and not with morphine, a fact which is at variance with current experience in medicine.

Veterinary Medicine.—On horses, the analgesic effect of therapeutic doses was found to be considerably higher than that of morphine (DENECKE).

It is recommended for colic in horses : it acts at once more swiftly and more powerfully than morphine (BRAUN, RIETHUS).

Narcotic and Hypnotic Effects.

The narcotic effect of eucodal is described as being more potent than that of morphine. It is sometimes possible to achieve shorter narcosis with eucodal alone (FALK). The narcotic effect developed not less rapidly than that of morphine and on some occasions, even better (LEICHTWEISS). It was not, however, really superior as regards duration (HESSE). The diminution in the state of excitement at the beginning of narcosis was striking—*e.g.*, on inebriates. One case appears instructive as an example : a strong young man in whom eucodal produced no excitement displayed it in some considerable degree in later morphine narcoses (SIEGFRIED).

It is hardly necessary to say that eucodal is not a real hypnotic, just as it would be not indicated and indeed quite wrong to give morphine, for instance, to induce sleep (if sleep is not prevented by pain). In those cases in which the underlying reasons for insomnia are nervous, eucodal is as contra-indicated as morphine, for the medical prescription of an opiate in such circumstances means running the risk of creating a habit without any justification.

In its power to induce sleep, eucodal is about equivalent to morphine but has the advantage of causing less disagreeable by-effects (R. F. MAYER). The same author points out that, if eucodal is not effective as a hypnotic, other opiates may also not be so. Sleep is sometimes obtained better and more quickly than with morphine, a fact that has been observed in a surgical clinic by ROTHSCHILD. Through large doses, it is possible to force even very excited patients to sleep, but, in these cases, the respiratory centre is affected too and the respiration considerably diminished. For use in this way, eucodal therefore does not seem preferable to older opiates (FALK).

In veterinary medicine, the dosage of eucodal for dogs is the same as that of morphine to induce sleep (0.05 gramme per kilogramme). Larger doses serve only to lengthen the duration of the sleep and not its intensity. Eucodal appears to take effect a little more slowly than morphine. Recovery from the effect produced usually proceeds more rapidly with eucodal than with morphine. The

sleep caused by eucodal is always calm. That induced by morphine is restless. During deep sleep induced by morphine, dogs often whine for hours ; they never whine when eucodal is used (BLOSS).

Not a great deal has been published about the administration of eucodal in *neurology* and *psychiatry*, but JACOBI gives a case of melancholia in which he resorted to eucodal rather than to the usual opium cure ; the therapeutic effect was at least equivalent to that of opium.

Intestinal Tract.

There are a few statements extant as to good analgesic and anti-spasmodic effects exerted by eucodal on several intestinal diseases (KEIM, HIRSCHBERG), but no comparison with morphine is made. Many observations are recorded concerning the influence of eucodal on peristalsis as compared with that of morphine : they point to the general conclusion that constipation is less severe than with other opiates, especially morphine. Peristalsis is reduced and constipation, or at least retarded function of the gut, may occur if eucodal is used for a longer period (SPENGLER, FALK, BECK). In the treatment of melancholia also, less constipation was observed than with opium (JACOBI).

Veterinary Medicine.—In dogs, after a certain period, peristalsis is undoubtedly retarded through morphine, whilst eucodal has no such influence (BLOSS). On horses, no constipating effect is experienced if analgesic doses are administered. On colic in horses the drug is more effective than, and superior to, morphine (BRAUN, BLOSS, REISMAN). Since eucodal does not cause constipation in horses if analgesic doses are administered, it can also be used to treat colic arising from constipation, whereas for this purpose, morphine is directly contra-indicated (RIETHUS).

Secondary Effects.

The most important and undesirable secondary effects of opiates are excitement, dizziness and giddiness, headaches and vomiting. In this direction, the experience of the various authors with eucodal has not been wholly concordant, but most of them report that the

by-effects are less accentuated than those of morphine. Some of the observers deny the occurrence of secondary effects like those experienced after the administration of morphine (PFEILER, SCHRÖEDER), whilst others state that they generally saw none if the dosage administered was not too high (WOHLGEMUTH). The seedy feeling so frequent after morphine is absent (STERN). In lung diseases and operations, these disagreeable phenomena are less pronounced than with morphine (NICOLESCU); they did not appear at all in several cases in which they had been produced by morphine (SPENGLER, SIEGFRIED, FALK). If eucodal was given before narcosis as well as after operations, there was no vomiting and no other unpleasant effect (ZBIRAL) (as regards the absence of excitement, see chapter on analgesia). If the dosage is carefully selected, eucodal is regarded as certain not to cause nausea (OSTERMAIER). When, also, it was administered for longer periods in cases of melancholia, the usual concomitant effects were scarcely observed at all, whereas trouble of this kind is more frequently experienced when opium is given (JACOBI).

According to other observers, however, these accompanying disturbances can become more severe. FALK, the first to observe the effects to eucodal, has already given a warning only to use eucodal in small doses (0.05 gramme) to anæmic, neurasthenic young girls, because it may cause exhaustion and giddiness and a desire for sleep. ALEXANDER describes a state of excitement of some considerable intensity, coupled with paresthesia in the arms and legs, after small doses of eucodal *per os*. In one case, he found that vomiting occurred infallibly after administration of eucodal, whilst, at an earlier stage, morphine had been tolerated for an appreciable length of time without any difficulty. EIBUSCHITZ describes two cases of somewhat severe effects of the kind mentioned above. ROTHSCHILD utters a warning against eucodal *per os* in out-patients, since fairly grave disturbances may be entailed. Sometimes he was confronted with such a violent outbreak of perspiration that eucodal had to be abandoned. In another case, however, he observed vomiting after morphine but not after eucodal, which only created increased perspiration and was therefore the drug to be preferred. LEICHTWEISS says that eucodal was well tolerated by most of his twenty-eight patients, and that, in particular, no serious trouble was experienced with the circulation. Only in one case did

collapse occur after the second injection. In all the other cases, no unpleasant results ensued when eucodal was administered over a period of several weeks.

Some few skin rashes are also described—*i.e.*, urticaria (or itching of the skin) (ALEXANDER, BECK) or roseola-like eruptions (KEUTZER).

Veterinary Medicine.—In dogs, the appetite is completely suppressed by the use of eucodal, as it is by morphine, but for shorter periods. Morphine gives rise in most dogs to extensive retching movements and finally vomiting, whether the stomach be full or empty. Eucodal, on the contrary, never causes vomiting or the retching movements (BLOSS). The undesirable morphine-engendered state of excitement is completely absent in dogs after the administration of therapeutic doses of eucodal (DENECKE).

Horses do not vomit after eucodal (RIETHUS). Cattle also tolerate eucodal well, as distinct from morphine (RÖMER).

Addiction.

If one reviews the publications on eucodalism, it would seem that this kind of addiction is relatively rare (so far as published papers are concerned), considering that the drug has existed for twenty years.

Nevertheless, eucodal offers a striking example of the necessity for international and national control.

The very first observations or impressions recorded as to the habit-forming effect of eucodal can only justify the warning given at the outset, on the strength of past experience, as to the addiction properties of new opiates. The earlier publications and prospectuses concerning eucodal asserted that no habit developed through using this drug. In the last years of the great war, eucodal achieved considerable popularity because the demand for narcotics was rather large and because nothing was known to the medical corps in general about the danger of creating a habit. But already in the earlier years of its existence, during which eucodal was not brought under the German Opium Law, cases of addiction to this drug were not rare, especially in the neighbourhood of its place of manufacture (P. WOLFF). But these observations were not published.

Eucodal was therefore regarded as a suitable and real substitute for morphine. But, a short time after the war came the first

warnings : KÖENIG, who described the first cases of eucodalism, found that the symptoms are difficult to differentiate from those of morphinism, and ALEXANDER observed typical abstinence symptoms in a case in which addiction was established after a fortnight's administration of the drug.

True, FALK and BAUMM, among others, could find no symptoms of habit. Others stated that the danger of addiction is considerably less than with morphine (PFEILER, LEICHTWEISS, SPENGLER), especially if the doses administered are not larger than is absolutely necessary, and if they are administered in the right way.

There are, however, several cases published in which the description of the symptoms are not in keeping with this view and in which eucodal has been able to create a real drug addiction. The euphoric state of mind may, as HANKE says, develop rather quickly. Other observers describe a distinct euphoria after administration of eucodal for a short time (see, *e.g.*, FALK). Morphinists, says F. H. MUELLER, prefer eucodal to morphine. It is also certain that addiction to morphine can be continued by means of the substance in question (*e.g.*, DUPOUY, with the French preparation eubine). The impression of a less severe kind of addiction through eucodal (than through morphine) which is conveyed in several observations may be explainable by the fact that the euphoria after eucodal is perhaps less strong than that after morphine (WIKI).

Since that time, a number of further cases of eucodalism have been published, among which may be mentioned those of MAX MEYER, LEMPERG, MENNINGER-LERCHENTHAL, MEGGENDORFER, BERLINER, FRENSDORF, EIBUSCHITZ. Some of these cases are secondary ones—that is to say, that the addicts first became morphinists and then turned over to eucodal. On the whole, they do not seem to differ very much from cases of morphinism as regards symptoms during both addiction and abstinence.

MEGGENDORFER, however, refers specially to mobility of ideas and lack of ability to concentrate during the fully developed state of eucodalism, as well as other symptoms of neurotic origin. During the abstinence period, there is also a strange failure on the patient's part to appreciate his position (MEGGENDORFER, P. WOLFF).

There are only about ten cases which can be regarded as primary, of addicts who used eucodal as the first and only opiate (if the

assertions of the addicts are true).¹ The latter cases seem to be more important as evidence on which to judge of any special characteristics of eucodal addiction and withdrawal. Some were not found to display any features essentially different from those of morphinism, others, however, showed during abstinence symptoms not usually observed in morphinists : a feeling of fear and suffocation resembling the sensations of angina pectoris (MENNINGER-LERCHENTHAL), to which some reference is also made in other descriptions (FRENSDORF). LEMPERG also describes a noteworthy case of a doctor aged 33 who took up to 9 grammes of eucodal per day. He grew very irritable and rather threatening to his patients ; during the abstinence period (gradual method) he became definitely atactic and died on the thirteenth day of the course of treatment.

LEISCHNER, who, in 1938, thoroughly analysed a recently observed case from the psychic side, detected some strange characteristics closely resembling the behaviour of an epileptic, which he describes in detail. It is interesting to note that this patient had no mental fixation in regard to this opiate, and that eucodal was easy to withdraw from the first day without any strong abstinence symptoms being noticed. The strange mental symptoms mentioned above appeared after one week. LEISCHNER comes to the conclusion that the habit-forming effect of eucodal differs in some of its major features from the usual "unpleasant" picture of morphinism. This description tallies with some others previously published ; SPENGLER, for instance, found withdrawal to be quick and easy, even after the drug had been taken for some appreciable time, and so did BECK, dealing with patients who had been addicted to eucodal for periods up to six months ; JACOBI too, treating cases of melancholia in which courses of eucodal treatment were given instead of the usual opium, had the same experience.

If one should try to sum up in a general way the addiction properties of eucodal, one would say that the danger of contracting a habit through taking eucodal should not be thought to be a less serious matter than the risk of morphine addiction, a conclusion

¹ Cf. what is said about the differentiation of primary and secondary cases in the paper on "The Significance of Codeine as a Habit-forming Drug". *Bull. Health Org.*, 1938, 7, 548-549.

which is borne out by the evidence collected by means of a questionnaire and published in 1928 (P. WOLFF).

DICODIDE

PHARMACOLOGICAL OBSERVATIONS

The second of the four newer habit-forming drugs under consideration; dicodide, has been known since 1923.

Dicodide is really a derivative of codeine, but with some of the characteristics changed, and occupying in the sequence of the opiates a position somewhat different from that of codeine.

The main pharmacological research on this product was carried out by GOTTIEB. We shall pass over the observations on frogs, because cold-blooded animals are of minor importance for the purposes of this study. In cats, dicodide produced excitement in every way comparable to that caused by morphine. Dogs are not anaesthetised by the administration of dicodide, but are restless and show accelerated respiration. Their sensation of pain is not affected. In rabbits, as distinct from dogs and cats, a definite calming action is exerted on the respiration after quite small doses. Large doses produce a more complete narcosis, but, at the same time, the reflexes are increased and convulsions may occur.

BADRUTT also found this distinctive slowing-down effect on the respiration of rabbits, and it may be added that the rhythm of respiration is less emphatic than with eucodal or heroin. The artificial cough of rabbits is also soothed by dicodide, but less than by codeine or dionine (a result which does not agree with those obtained on man).

BELLI also found that dicodide had a favourable influence upon the respiration of guinea-pigs, rabbits and dogs; better than morphine and codeine (details are not given).

To test the analgesic effect of dicodide, HESSE and KUEGLER made some experiments on healthy and inflamed parts of the body (abscesses with croton oil). They found :

	Normal part (Mice)	Inflamed part (Rabbits)
Morphine	++	+
Dicodide	+	++
Codeine	(+)	+

Dicodide thus acted more strongly on an inflamed part than morphine.

The blood sugar of rabbits is raised by 2 milligrammes per kilogramme of dicodide, which is the same dose as for morphine, whereas 5 milligrammes of codeine and 0.2 milligramme of heroin are needed to yield a like increase. With morphine, the blood-sugar curve is first decreased and then increased ; but with dicodide this two-phase effect is not observed. When the addiction develops, the rise of the blood sugar stops earlier or later (AKIMOTO).

GOTTLIEB came to the conclusion, in the light of his experiments on different animals, that dicodide should be placed—in respect of pharmacological character—between morphine and codeine. EDDY and REID also judged that dicodide is more effective than codeine, but less so than morphine.

CLINICAL AND PRACTICAL OBSERVATIONS

The dosage must be selected individually, as is always recommended with opiates. On the average, it seems sufficient to give small amounts *per os*—*e.g.*, 0.005 gramme or, if necessary, 0.01 gramme. It is not recommended to exceed 0.02 gramme in a single dose, in order to avoid undesirable accompanying effects.

The majority of statements on dosage have reference to the effect on coughing. 0.005 gramme dicodide corresponds in its effect to 0.03 gramme codeine or 0.01 gramme heroin (STANGANELLI, KENNER, BING, SAMETINGER). ZEMMIN found that dicodide administered *per os* had at least double the effect of morphine, and sometimes more.

According to the experience gained by RIPPENA in a hospital ward for lung diseases, a 0.4% solution of dicodide corresponded in its effect to a 2% solution of codeine.

The work carried out on children may be specially emphasised. Naturally, dicodide must be given with great caution, as is done with morphine and codeine, because children, especially little children, are more susceptible to dicodide than adults.

As with all opiates, the doses for babies and small children should not be those calculated in direct proportion to the weight of the child, but should be smaller. On the other hand, there is no reason

why dicodide should not be given to children in suitable doses (SAMETINGER, KAUPE, ZISCHINSKY).

It is always recommended to avoid the administration of dicodide on an empty stomach : many of the by-effects which have been described can thus be averted.

Dose for dose, the duration of the effect of dicodide and morphine is about the same, so far as the available evidence can be relied upon (CASTELHUN).

Toxicity.

In two cases observed by SAMETINGER, in which the persons concerned took 10 tablets of dicodide (= 0.1 gramme) and 50 tablets (= 0.5 gramme) respectively, no harm was done. The second of the two had a very slight habit, taking up to 0.06 gramme per day. Both were cured after 1 and 5 days respectively. On a further 28 cases of overdose, only one case proved fatal (a child of two years with heart weakness who had been given five times too much in a single dose). It is remarkable that men who had an overdose of 0.08-0.2 gramme should have shown no serious symptoms of giddiness or desire for sleep, whilst the latter symptoms were more perceptible in women. Children, as already mentioned, also tolerated overdosing without any danger, but less readily.

From these observations, it is concluded that the margin between the therapeutic and lethal doses of dicodide is extraordinarily great, even where no habit exists. SAMETINGER is of the opinion that it would not be easy to poison an adult fatally with dicodide.

On the strength of pharmacological observations, it is held that dicodide should be placed between morphine and codeine. Clinical and practical experience (BING, HECHT, RICKMANN) suggest a like classification. It is better tolerated than morphine (BING) and is superior to codeine in every indication ; it is relatively innocuous for adults, and able to replace morphine in many directions (SAMETINGER). The effect on coughs is more powerful than the narcotic effect (A. FRAENKEL, HECHT), but diminution of the irritation set up by the cough is associated with a general soothing effect and decrease of the central perception of pain without impairment of the other sensations, or the bringing on of sleep (RICKMANN, SCHWAB, GUTTMANN).

These general statements will be further elaborated in the following sections.

Respiration.

The main effect of dicodide, as already mentioned, is its sedative action on coughs. This is easy to understand, considering its close relationship to codeine (although that would not be an absolutely necessary consequence ; the changes in the chemical structure could have produced a more far-reaching alteration of effect).

It is generally recognised that the effect of dicodide on the respiratory centre is elective and stronger than that of codeine, and indeed, without any need for large doses (as with codeine), sometimes superior to that of morphine, whilst free from the unwelcome concomitant effects of the latter (SAMETINGER, FURLAN, BELLI, BERRETTA). In some observations, dicodide surpassed even heroin in the sureness with which it acted upon the respiratory centre (WEHL). It seems, further, that the respiratory centre is less endangered by dicodide than by morphine (SCHINDLER). This elective action of dicodide with its calming effect upon the cough reflex invariably takes place whatever may be the cause of the cough (SCHUBERTH). Dicodide also acts more quickly than codeine (PAVESI) and its effects last longer (STANGANELLI).

Other observations claim that suppositories of opium or morphine may, if administered to children, produce somewhat dangerous respiratory trouble which calls for preventive measures. Two years experience in the use of dicodide suppositories, has shown, however, that these precautions are superfluous. For, in spite of the decided sedative influence of dicodide on the respiratory centre, in no case were these ill-effects observed (OBADALEK).

For catarrhal symptoms of the upper respiratory tract, dicodide is equivalent to codeine (REHFELDT). In influenza and pneumonia, dicodide is usually more effective than codeine and heroin and, in particular, is better tolerated than heroin, which often causes loss of appetite and nausea (SCHINDLER).

In cases of acute bronchitis, tablets of dicodide of 0.005 or 0.01 gramme act more powerfully than 0.05 of codeine.

In very small doses, dicodide will calm the night attacks of whooping-cough in cases in which codeine fails (even in babies) without causing unpleasant symptoms (KEIM, KAUPE).

In cases of dyspnoea, from various causes (cardiac defects, bronchial asthma, emphysema ; always associated with nervous trouble) excellent results were recorded in clinical observations (WEINBERG). In the treatment of bronchial asthma, dicodide was in several cases superior to morphine, whilst in others it failed and had to be replaced by pantopon (SCHINDLER). It will be readily understood that the greater part of the observations belonging to this section are concerned with the sedative effects on tuberculosis of the respiratory tract. The results recorded by different authors are unanimously good. The drug is regarded as reliable in its action, being more effective than codeine or dionine, and, according to some authors, equivalent or superior to paracodeine, morphine, eucodal or even heroin (*e.g.*, LÆWENTHAL, SCHWAB, ACHILLES). It is considered as effective in its action on coughs as dilaudide (see also the next chapter) (RADY). If sleeplessness in tuberculosis is caused by cough or pain, dicodide is preferable to codeine (BING). Only in a few cases had it to be replaced by morphine. The sleep induced was better than with codeine (RIES). If the administration of codeine or dicodide *per os* did not prove satisfactory, good results could be obtained with injections of the latter substance (STERN). Where hæmoptysis occurred, calmness and, at the same time, mental tranquillity were obtained with dicodide, but without the deafening and sleep-inducing effects of morphine. This is important in view of the danger of aspiration of blood and dissemination of germs, or even of suffocation, an ever-present contingency when morphine is administered in such cases (KENNER).

In a general way, expectoration is checked less with dicodide than with codeine (BERNHEIM, RICKMANN, STANGANELLI).

Analgesia.

The analgesic effect of dicodide is also described as quite definite and satisfactory. A great many observations have been published on this subject ; it must be recognised, however, that since the appearance of dilaudide on the market, the latter drug has replaced dicodide for this purpose in very many cases. Nevertheless, the analgesic effect of dicodide is real and must be mentioned in this comparative study. Its action is quite sure and prompt. Moreover, several authors specially mention the fact that, while relieving pain, it does not induce sleep if administered in doses up to 0.01 gramme

subcutaneously. The sensation of pain is relieved to the same degree as by morphine (R. F. MAYER, SAMETINGER, RICKMANN), and sleep may therefore be induced and continue, because the painful sensations have ceased (GERBER and REMBOLD). In some cases, dicodide was found to be superior to morphine and without undesirable effects (FREUNDLICH) ; it also had this anti-pain action where morphine failed (SCHINDLER, HERZ, SCHWAB). It is also stated that the duration of the analgesic action is longer than that of morphine (CASTELHUN).

On the other hand, there are some observations in which the analgesic action of dicodide was not judged to be as perfect as that of morphine. The reason may be too small a dose (0.01 gramme) or the administration *per os*, yet even in these cases there was at least some alleviation of pain (WEINBERG). Larger doses should not be recommended ; the analgesia does not last longer, but there may be undesirable accompaniments (LUNZ).

Children tolerate dicodide without ill effects in correspondingly smaller doses, given *per os*, or, if necessary, subcutaneously (DÆRFLER).

As already mentioned in the section on respiration, dicodide suppositories are preferable, where children are concerned, to those of pantopon or morphine, because there is no risk of dangerous consequences. The analgesic effect is quite the same. After operations, coughing and vomiting, etc., occur less violently, if at all (OBADALEK).

In adults, the post-operative effect of dicodide is equivalent, or even superior to that of morphine (HEUSSLER, K. SCHMIDT, DÆRFLER) ; there are no undesirable concomitant effects as with morphine (ROSENBERG). KLEINSCHMIDT also recommends dicodide for post-operative pain : the effect seemed to last longer than that of morphine.

Narcotic and Hypnotic Effects.

The sedative effect of dicodide on the brain is similar to that of morphine, and much more distinct than that of codeine (RICKMANN). In comparison with morphine, the general narcotic effect of dicodide is considerably less (SAMETINGER), whilst the soothing action on the respiration is more powerful than that of codeine, and the narcotic effect on the sensation of pain equal to that of morphine.

For the preparation of narcosis, dicodide is therefore useful only in children and in quiet patients who are not accustomed to narcotics. It is a striking fact that general sensory function other than pain is not diminished (DÆRFLER), but the stronger sensory stimuli are weakened.

In the usual doses of 0.015 gramme, subcutaneously, dicodide does not produce deep, uninterrupted sleep, but it promotes sleep to the same degree as 0.02 gramme of morphine (HEUSSLER). Patients afflicted with a cough sleep better when given dicodide than when given codeine (STANGANELLI). In any case, dicodide is not a real hypnotic.

The excitability of the reflexes of the mucous membrane is diminished in the preparation of a gastroscopy ; if 0.01 gramme dicodide is given, only half the amount of cocaine which would be required after the administration of 0.01-0.02 gramme of morphine is necessary (SCHINDLER).

Corresponding courses of codeine and dicodide *per os* were compared to the opium treatment in depression and melancholia. In 80% of the cases, the results favoured dicodide, which had a quicker and more lasting effect on the depression, although relatively smaller doses were administered (BUFE). WEINBERG also obtained satisfactory results in cases of depression and anxiety ; HERZ too, dealing with the latter type of case, had a similar experience, though he did not find dicodide any better than opium for the treatment of melancholia. Dicodide was also used for its sedative and anaphrodisiac effects in acute gonorrhœa, against painful erections (SIMON), and its effect is said to have been better than that of heroin.

Intestinal Tract.

Dicodide did not cause pylorospasms where morphine did not produce them ; but in the great majority of cases in which morphine produced pylorospasms, dicodide did so too. In some, however, especially men, it did not (CASTELHUN).

The constipating effect which is typical with morphine and also with eucodal is not found to occur with the usual therapeutic doses of dicodide, a fact which is vouched for by many authors (SCHUBERTH, SAMETINGER, BOEHNCKE, WEHL, SCHINDLER, ROLLER, MARTIN and WOLFF). This is regarded as a considerable advantage after operations (K. SCHMIDT). Flatulence during the resumption of

intestinal function after operations is not as considerable as with morphine (DÖRFLER). Furthermore, suppositories given to children after abdominal operations did not produce constipation (OBADALEK).

Secondary Effects.

Whether these concomitant effects occur, and if so, to what degree, is a matter of some importance in judging and extending the range of utilisation of a new opiate. Many authors have published their observations on this point in relation to dicodide, but they are not in full agreement, and the statements made are occasionally somewhat contradictory. The main symptoms under this heading are the same as mentioned in the chapter on eucodal—that is to say, excitement, giddiness, dizziness, headache and vomiting.

Some authors assert that dicodide is able to replace other opiates like morphine without producing the familiar and somewhat powerful secondary effects of the latter. These disagreeable by-effects of other opiates are seldom if ever found with dicodide if the dosage is chosen reasonably—viz., 0.01–0.015 gramme *per os*, or 0.015 gramme subcutaneously (CASTELHUN, ROLLER, STANGANELLI, SCHINDLER, KLEINSCHMIDT, PAVESI and others)—but 0.02 gramme subcutaneously may give rise to a certain amount of apathy, desire for sleep, excitement, giddiness or vomiting (LUNZ). These general statements, which recur repeatedly in papers published on dicodide, may be illustrated by some examples.

FELSENFELD found, among 200 cases, only a few who had nausea or vomiting, but they took the dicodide on an empty stomach, which is not advisable. In almost every case, it was possible to avoid hyper-sensitiveness of the sensory nerves of the stomach by taking dicodide *after* meals. PAVESI also found slight giddiness and dizziness and headache, but only after too high a dose, and not with 0.015 gramme *per os*. Similar observations as to the relationship between dosage and undesirable concomitant effects have been made in numerous cases of tuberculosis, etc., by SCHWERMANN, SCHUBERTH and others.

SCHELENZ found that, in hundreds of cases, no such unpleasant effects were complained of, but they occurred suddenly in four

cases (the cause is not known). It seems reasonable to expect that trouble of this kind should be experienced occasionally, even though somewhat rarely, having regard to the potency of the drug.

Several authors state that if dicodide is given in a dose of 0.015 gramme subcutaneously after operations, the by-effects of the kind which is familiar after the administration of morphine appear very seldom. There is no excitement, vomiting or giddiness (HEUSSLER, DÆRFLER, K. SCHMIDT).

In regard to children, the experience of different observers does not fully agree. LUST, for instance, in his textbook on pediatrics, advises caution in the use of dicodide for children, and prefers to give it only to older ones, in order to avoid such effects. ZISCHINSKY and also KAUPÉ failed, however, to observe any in a large number of children. ZISCHINSKY, at all events, favours the careful administration of dicodide on children.

In comparison with these mainly favourable results, others must be quoted which were less so. Among out-patients treated with 0.005-0.01 gramme *per os*, WEINBERG found six who showed symptoms of nausea, and this to such a degree that the treatment with dicodide had to be abandoned. Dicodide given *per os* regularly produced in two women a general urticarial rash which disappeared on the day when this treatment was suspended (KENNER).

Much general interest attaches to the psychological observations on the effects of dicodide which were carried out by MEYER and PFAFFENHOLZ in experiments on themselves. They found by objective tests that the usual doses produced a certain reduction of working capacity, both quantitative and qualitative. Subjectively they experienced a decrease in concentration and a disinclination for work. The reaction is therefore quite different from that of codeine, which does not produce these mental symptoms.

The same authors made similar observations on out-patients, some of whom preferred in consequence not to take codeine in order to avoid being disturbed in their work. On the other hand, these authors never observed these secondary effects in patients under clinical treatment, when dicodide was given after meals. (It is a well-known fact that sick persons who are working are often more sensitive than patients in bed.)

These findings regarding working capacity are in agreement with experiments conducted on himself by ROEMMELT, who also felt

this lack of energy ; it should be said, however, that his is the case of a highly sensitive and vasomotorially excitable man.

Addiction.

It is well known and recognised that dicodide creates euphoria and addiction, but the degree to which this is the case will now be explained more fully.

There is no question but that dicodide is able to create euphoria (SAMETINGER, WEHL, SIMON and others) ; it seems, however, that the euphoria is less intense than with morphine (ROLLER, CASTELHUN). R. F. MAYER states, on the other hand, that euphoria seemed to endure longer in his observations than that of morphine, because it does not have the same sleep-inducing effect as the latter. This slighter degree of euphoria may explain why the danger of contracting a habit seems to be less strong (CASTELHUN, WEINBERG, HECHT, BING). FURLAND and SCHELENZ state, accordingly, that the effect on coughs is not diminished by the administration of dicodide over a longer period. With dicodide, therefore, the danger of misuse seems to be considerably less than it is with morphine, even when dicodide is administered over lengthy periods (SAMETINGER). But there is no doubt, as has been said before, that cases of addiction to dicodide are known (SAMETINGER, MUELLER DE LA FUENTE). In their replies to the questionnaire of P. WOLFF, 17 observers report that they have noticed cases of addiction ; but one has the impression that the degree of addiction is relatively slight—a fact which tallies with observations of SAMETINGER and MUELLER DE LA FUENTE. Dicodide has not been found to be an equivalent substitute for morphine (CASTELHUN). Abstinence symptoms are described as being relatively slight, passing off quickly (R. F. MAYER). The drug could always be withdrawn without great difficulty (RIES, SAMETINGER), even in cases of depression (RICHTZENHAIN). Abstinence symptoms are less pronounced than with morphine or dilaudide (EDDY and REID).

Addiction to dicodide seems to be rarer and easier to combat than that of morphine or eucodal.

ACEDICONE

PHARMACOLOGICAL OBSERVATIONS

The newest of the drugs reviewed in this study is acedicone, which was introduced on the market in 1929. The basic report on the pharmacology of this drug was published by WIELAND and BEHRENS. They came to the following comparative conclusions : they adduced, as the most important result of their study, the fact that acedicone differs in its effects from morphine and codeine. According to the results of their experiments on mice, they placed this substance between thebaine and codeine, whereas, according to their experiments on rabbits and dogs, it should come between codeine and morphine. They considered that, for human beings, acedicone should be placed between morphine and codeine.

In rabbits, there is a slowing-down effect on the respiration, or, to speak more accurately, a diminution of the sensitiveness of the mucous membrane of the respiratory tract (JICHLINSKI). This author concludes that acedicone is closer, in its respiratory effects, to dilaudide, codeine and dionine than to morphine, eucodal or heroin.

Other pharmacological experiments followed a different line of approach. It is known through observations of STENDER and AMSLER that morphine and pantopon are able to prolong the anæsthetic effect of cocaine on warm-blooded animals. These experiments were carried out on the eyes. In equivalent doses, the normal duration of the effect of cocaine exceeds three or four times that of morphine and ten times that of pantopon. Further, certain doses of cocaine which, by themselves, are insufficient to influence the reflex serving as a standard, become fully effective through the addition of the said opiates. (It may be noted that the superiority of pantopon over morphine in this connection is due not to the influence of several other alkaloids contained in it, but to a complex interaction (JUERGENSEN-STENDER).)

Continuing this research, MATSCHULAN found that acedicone is similarly able to prolong the local cocaine anæsthesia of the cornea as much as $2\frac{1}{2}$ -5 times. The prolongation is therefore about as great as that effected by morphine.

WIELAND and BEHRENS further concluded that dogs do not become habituated to acedicone, or at least not so easily as to morphine.

CLINICAL AND PRACTICAL OBSERVATIONS

The dosage of acedicone is 0.005-0.01 gramme *per os* or subcutaneously, and, in the latter case, the dose may be increased to 0.02 gramme. Later practice has been to reduce by half the doses given by the mouth in order to avoid distressing secondary effects (see chapter on this subject).

According to the clinical observations of NONNENBRUCH, 0.01 gramme of acedicone corresponds to about four times the dose of codeine in its cough-alleviating effect; the analgesic and hypnotic effects of acedicone are considerably greater than that of codeine. REHFELD is of opinion that the effective doses correspond to those of morphine.

According to NONNENBRUCH, acedicone usually acts much less powerfully when orally administered than when injected subcutaneously; but BERTRAM and STOLTENBERG found the effect to be the same by either method of administration, that on the cough being perhaps even slightly stronger when the drug was taken by the mouth. According to the same authors, the analgesic effect of morphine and acedicone thus administered is about equal.

PAULA also is of opinion that the effect of acedicone given by the mouth is satisfactory and adequate.

It may be concluded that acedicone should rank between morphine and codeine. The claim of the manufacturing firm that acedicone is better tolerated than pure morphine is not quite correct. Enough has been published to show that acedicone is, on the contrary, badly tolerated on occasion if small doses are exceeded.

Some case records have been published in which acedicone was administered by the mouth, and a collapse-like state was observed; in one of these patients, this did not occur after the administration of dicodide or morphine (NONNENBRUCH). This was the reason for diminishing the therapeutic doses as mentioned above.

On the other hand, acedicone was tolerated without difficulty by patients with circulatory diseases, whilst morphine and other opiates often created dizziness and vomiting in the same patients

(NONNENBRUCH). The blood-pressure was not immediately influenced by therapeutic doses (in which respect, acedicone behaves like morphine); larger doses reduce the number of pulsations through the central stimulation of the vagus (PAULA).

Children of all ages, including babies, tolerated acedicone well (ZISCHINSKY).

Respiration.

The effect of acedicone on the respiratory tract is quite a distinctive one. Like other similar opiates, it greatly reduces coughing without decreasing the amount of expectoration. When the drug is subcutaneously administered, its action in this respect is about as powerful as that of morphine, and perhaps even of longer duration (NONNENBRUCH). Similarly, it acts promptly when orally administered (PAULA). Furthermore, it is quite sufficient as a calming agent in more severe cases of irritation of the respiratory tract (REHFELDT), as well as after tonsillectomy (HALASZ).

According to the experiments of BERTRAM and STOLTENBERG, it is, in both reliability and duration, superior to similar drugs like morphine, codeine, heroin or dicodide in acute affections of the upper respiratory tract. In cases of acute bronchitis or tracheitis, 0.01 gramme of acedicone by the mouth had a better effect than 0.03 gramme of codeine. Similar observations were made by BUSSOW. BERTRAM and STOLTENBERG also found that acedicone acted promptly when similar preparations no longer succeeded, and that the converse was usually true. REINWEIN and BERTHOLD recommend acedicone as a good and reliable remedy for coughs. For post-influenzal coughs, according to some observations, acedicone proved highly useful (DALAL).

If the cough is due to cardiac congestion, the administration of acedicone may be continued, and need not be suspended (as, for instance, treatment with morphine and codeine) owing to subsidiary effects on the respiratory centre, the circulations and the intestinal tract. Acedicone is similarly effective in the case of coughs due to serious bronchiectasis, whereas codeine fails where secretion is abundant. BERTRAM and STOLTENBERG conclude that, as a remedy for coughs, acedicone is superior to codeine and related drugs in reliability, potency and duration of effect, and that this holds equally good for chronic conditions.

Again, acedicone is frequently effective in cases of metastasis of tumours in the lung or the bronchi which are liable, if severe, to develop a convulsive cough (CURSCHMANN).

In tuberculosis of the lungs, codeine was, in many instances, as effective as acedicone. Administration *per os* is usually sufficient (CROHN). In serious cases in which acedicone no longer acted, the desired result could be obtained with pantopon, dilaudide or morphine (BUSSOW).

In cases of hæmoptysis, acedicone can be administered without the hesitation which is usually felt in prescribing morphine, for its narcotic effect is less intense (NONNENBRUCH). HOLDHEIM also holds this view.

ZISCHINSKY is of opinion that acedicone is the most effective remedy for coughs in children on account of its sedative effect, which means that the injections of morphine can be avoided.

On the other hand, there are some statements which are not entirely positive; thus, NARBESHUBER found acedicone sometimes more favourable and sometimes less favourable than morphine or codeine in its action.

Analgesia.

The analgesic effect of 0.01 gramme of acedicone given subcutaneously corresponds to that of roughly the same amount of morphine (NONNENBRUCH). Its action is as swift as that of morphine but is less powerful and usually of shorter duration; BERTRAM and STOLTENBERG estimate that, for analgesic action, 0.01 gramme of acedicone subcutaneously corresponds to about 0.007 gramme of morphine; they believe, at the same time, that acedicone is better tolerated. BUSSOW also considers that acedicone is equivalent to morphine in alleviating pain due to a variety of causes, but inferior where the pain is caused by spasms; in the latter cases, pantopon or morphine are preferable and their effect lasts longer.

To eliminate post-operative pain, acedicone is sometimes preferred because it has not the sleep-inducing effect of morphine (HALASZ).

Narcotic and Hypnotic Effects.

As already explained, the narcotic effect of acedicone is less strong than that of morphine. The hypnotic effect is about half as intense as that obtained with the same doses of morphine (NONNENBRUCH).

Sleep is also induced without pain in about half of the cases if 0.01 gramme or more is given. PAULA found that a pleasant sleep ensued, the patient awakening refreshed. There are some cases, on the other hand, in which excitement was produced instead of sleep (BERTRAM and STOLTENBERG). BUSSOW, too, found the sleep effect uncertain and not to be compared with the more reliable action of pantopon or morphine.

Intestinal Tract.

The severe constipation which is very distressing with some other opiates is not produced by acedicone, or is at any rate much less serious, especially if the drug, even though administered over an appreciable period of time, is given in small doses (BERTRAM and STOLTENBERG, HOLDHEIM, NONNENBRUCH, HEGLER, PAULA, CROHN).

Secondary Effects.

As already mentioned, larger doses of acedicone occasionally cause giddiness to an uncomfortable degree, as well as dizziness and vomiting—especially, it would seem, when given by the mouth. If the doses are halved, these symptoms appear much less often. On the other hand, some patients who were hypersensitive to morphine, tolerated acedicone better (BERTRAM and STOLTENBERG).

Addiction.

As it is the rule, we venture to say, for the first clinical observations not to bring real addiction to light, NONNENBRUCH could not find real cases, but his observations proved already that acedicone has secondary addiction properties, for he was able to replace morphine by acedicone in dealing with real morphinists. In the same year, 1929, PAULA found typical euphoria and therefore took care to use acedicone only for serious cases of advanced tuberculosis of the lungs.

Although the consumption of acedicone is relatively insignificant, some cases of addiction to this drug became known quite soon after it was put on the market. BERTRAM and STOLTENBERG found in some of a batch of 1,200 cases—mostly diseases of the respiratory tract, especially tuberculosis—a certain degree of habituation (attenuation of the effect) as well as euphoria, but not decided addiction.

One of the first cases is fully described by E. WENGER, a primary one. The author found that the withdrawal treatment severely taxed the patient, whose symptoms and persistent complaining were reminiscent of those of heroinists. It may be interesting to note that this addict tried several times to take eucodal instead of acedicone, but with each dose of eucodal he realised that it was inferior in its effect, and unable to replace acedicone in corresponding doses. In another case, observed by BIELING, the abstinence symptoms were specially serious, affecting sensory as well as motor function, the circulatory apparatus, etc. It is not known if this case was a primary one. Similar symptoms, but not so grave, were observed by UNVERRICHT.

It can therefore be concluded that the statements affirming that acedicone does not create addiction (ZISCHINSKY) are erroneous.

COMPARATIVE STUDIES OF GENERAL DRUGS

In this chapter, the various subjects will be taken, so far as possible in the same order as in the chapters which precede. This, of course, will not always be possible, because the research work mentioned sometimes has a more general bearing, and the picture will be more complete if the different parts of one and the same study are not separated from each other.

Special attention may be drawn to the general comparison of the drugs in question contained in the Memorandum of the United States Public Health Service, document O.C./Confidential/29, May 19th, 1938, and also to document O.C.1605(c), of August 23rd, 1937, in which a comparative table is given.

PHARMACOLOGICAL OBSERVATIONS

In the first place, a study of MYERS may be mentioned, in which he compares eucodal, dicodide and dilaudide. According to his statements, eucodal differs from dicodide and dilaudide in the following way : It does not cause convulsions in mice and rabbits as do dicodide and dilaudide when given in suitably large doses. Eucodal exerts a weaker effect than either dicodide or dilaudide on the movements of the intestinal tract, and does not increase

spinal reflexes, but the effect on the respiration is as powerful as that of morphine or dilaudide. To kill animals, very large doses of eucodal are necessary : the toxicity is therefore less.

Order of Increasing Toxicity.

Eucodal—Dicodide—Dilaudide.

All these three are very similar to morphine but more toxic.

According to JICHLINSKI, the lethal dose for guinea-pigs (deep, intra-cerebral injections) under certain conditions is as follows :

	Milligrammes
Morphine	0.25
Codeine	1
Dicodide	1.25
Heroin	1.5
Eucodal	2 (approximately)
Acedicone	3
Dionine	4

Respiration.

Dicodide, dilaudide and eucodal all three act most powerfully on the respiration of cats, even in small doses. Respiration slows down and becomes deeper ; the general effect on the respiration resembles that of morphine. Toxic doses of these three substances create serious progressive depression of the respiratory centre ; finally, respiration is arrested before the heart is seriously injured. In therapeutic as well as toxic doses, these three substances behave in a manner similar to morphine and heroin. Dicodide, dilaudide and eucodal have little or no effect on the bronchioles of cats (MYERS).

The action on experimental coughs of cats was examined by ERNST. According to his observations, the minimum effective doses which suppress coughs are as follows :

	<i>a</i> Minimum dose which suppresses (Milligrammes per kilogramme)	<i>b</i> Maximum dose which can be given without subsidiary effects on the ciliated epithelium (Milligrammes per kilogramme)	$\frac{b}{a}$
Morphine	0.5	0.25	0.5
Codeine	3	15	5
Dicodide	0.25	0.25	1
Acedicone	0.5	0.25	0.5
			3

Codeine takes first place so far as secondary effects are concerned ; then follow dicodide, morphine and acedicone. This classification, however, is of value for guidance only in so far as no other reactions (habituation, etc.) intervene below the level at which the function of the ciliated epithelium is inhibited. ERNST concludes from his observations that codeine is still the best remedy for coughs.

The minimum effective dose affecting the respiratory rate and minute volume of rabbits is, for :

Morphine, approximately 0.5 milligrammes per kilogramme ;
Dilaudide, approximately 0.03 milligrammes per kilogramme ;
Dicodide, less than 0.3 milligrammes per kilogramme.

Larger doses give correspondingly intense effects.

Therefore dicodide acts more powerfully on the respiratory centre than morphine, and dilaudide more powerfully than dicodide (WRIGHT and BARBOUR).

Other extensive research work led to the following results : the effect on respiration of the substances investigated was tested according to the method of DRESER, that dosage being selected which diminishes the respiratory volume by 40%-50%. This dosage is called the effective respiratory dosage : on the average, KEIL and POEHL found :

	Analgesic dose	Effective respiratory dose	Ratio
Morphine	3.6	2.8	1.28
Pantopon	7.2	4.8	1.50
Laudanone	6.0	4.0	1.50
Narcophine	4.0	3.0	1.33
Dilaudide	0.225	0.175	1.29
Dicodide	2.0	1.8	1.10
Heroin	0.45	0.225	2.0

The respiratory effect is thus obtained with smaller doses than the analgesic effect, but the two sets of figures run parallel ; heroin alone is characterised by a special respiratory effect, a finding which is in agreement with all past observations. So far as dilaudide is concerned, the alleged weakness of the respiratory relatively to analgesic effect which has been mentioned in the literature on the subject, could not be confirmed.

The following table indicates the number of respiratory movements in rabbits, expressed as a percentage of the initial value, at the moment of the maximum slowing down (JICHLINSKI) :

	%		%
Dionine	85	Morphine	15
Codeine	58	Dilaudide	12
Dicodide	38	Eucodal	11
Acedicone	30	Heroin	5

GÖTTLIEB made a number of experiments on the habituation of the respiratory centre by some of the substances in question. For some weeks, rabbits received morphine, dicodide and dilaudide subcutaneously without any increase in the dose. The influence on the respiration was controlled every week just after the injection. Outside influences were eliminated as far as possible. The doses were the minimum which had an effect on the respiratory centre :

	Milligrammes per kilogramme
Morphine	1
Dicodide	0.5
Dilaudide	0.3

After four weeks he found :

Morphine : The sedative effect on the respiration was reduced to nil.

Dicodide : The influence on the respiration remained about the same (on other rabbits, a certain habituation was observed if the doses remained stationary, but in no case was the drug completely robbed of its effect).

Dilaudide : The sensitiveness of the respiratory centre remained unchanged. Therefore dilaudide gives rise to but very little habituation so far as the respiratory centre of rabbits is concerned.

COMPARISONS OF ANALGESIC AND MORE GENERAL PROPERTIES

HILDEBRANDT tested pain on guinea-pigs through changes of temperature ; the effect of dicodide and dilaudide was superior to that of morphine. This agrees with clinical experience. The effect of dicodide and dilaudide was about the same ; codeine, too, was effective if the dose was about ten times that of morphine.

For comparison of the analgesic effect of opiates, the so-called novocaine-morphine methods have been worked out ; the first by A. WEISS and the second by W. WEISS. These methods consist (as already explained in the chapter on acedicone) in increasing the local anæsthetic effect produced on the eyes of rabbits by morphine injections ; they permit a comparison of the analgesic power of morphine derivatives in terms of figures. These two measures did not give absolutely the same values. The method of A. WEISS determines the duration of the analgesic effect : the method of W. WEISS the immediate effect of morphine in the first minutes.

Pharmacological methods do not always agree with the experiments on human beings. Another method therefore was sought whereby the effect could be evaluated. KEIL and KLUGE chose as a suitable criterion the so-called tail phenomenon of mice, which was discovered by STRAUB. If morphine is injected in white mice they react with the characteristic spasm, erecting the tail in an S-like curve. According to the experiments of HERRMANN, this method is useful for comparisons in the opiate series. It was therefore used by KEIL and KLUGE.

On the basis of these experiments, KEIL and KLUGE tried to draw up a table of the strength of the effect of opiates in comparison

Preparations	Quantity yielding the effect of the standard morphine dose (1/55 milligramme).	Percentage analgesic value as measured by the mouse-tail test (morphine = 100).	Percentage analgesic value as measured by the test of A. Weiss (morphine = 100).	Therapeutic dose for man, corresponding to 0.01 gramme of morphine.	Percentage analgesic value for man (morphine = 100).
Pantopon	1/34	64	65	0.03 = 0.02 morphine	Commensurate with morphine content
Laudanone ...	1/36	65	65	0.02 = 0.01 morphine	
Narcophine ...	1/53	96	32	0.03 = 0.01 morphine	
Heroin	1/130	234	280	0.005	200
Dilaudide	1/165	300	500	0.002	500
Eucodal	1/48	142	—	0.01	100
Dicodide	1/31	56	—	0.015	66

with morphine : the standard was an average value of morphine of $1/55$ milligramme for the tail phenomenon. The same table contains for comparison the analgesic value according to the method of A. WEISS and also the analgesic value of therapeutic doses in man.

KEIL and KLUGE came to the conclusion that the figures at which they arrived agreed almost exactly with those of A WEISS, except for narcophine. There is therefore a general parallelism between the tail reaction and the analgesic effect.

The result of this research may be easier to understand if morphine is taken as equal 100 ; the analgesic values are then (KEIL and POEHLIS) :

Method	Morphine	Pan-topon	Laudanone	Narcophine	Dilaudide	Dicodide	Heroin
A. WEISS	100	65	65	32	500	—	280
W. WEISS by KEIL and KLUGE	100	50	60	90	1,600	180	800
KEIL and KLUGE	100	64	65	96	300	56	234

In themselves, these methods reveal an increase of the strength of the effect under certain conditions which have nothing to do with the problem under review ; nevertheless, they do warrant certain conclusions in connection with the present study. One somewhat striking point is the difference in the values of dilaudide, which has a specially powerful analgesic effect, but this effect seems to wear off rather quickly. This is evidenced by the fact that the method of W. WEISS, which indicates the immediate effect, yielded a value of 1,600%, whereas the two other methods gave respectively 500% and 300% (the method of A. WEISS has reference to the duration of the effect as already stated).

This research has yielded a good deal of evidence of that characteristic analgesic action of dilaudide which is frequently mentioned in medical papers. The effect of heroin, for instance, in this respect, is much less great, whilst its toxicity is five times that of morphine (DRESER, IMPENS). It can therefore be concluded that, to use heroin in lieu of morphine for analgesic purposes (A. WEISS), is a retrograde step.

Another method of comparison is based on observations of the increase of convulsions. Convulsions produced in white rats by cocaine are intensified by morphine. This is also true of other opiates, the equivalences between these and morphine being : (EICHHOLTZ and KRAUTH) :

5 milligrammes of morphine correspond to :

5 milligrammes of pantopon	2.5 milligrammes of dicodide
5 milligrammes of laudanone	1.5 milligramme of eucodal
7.5 milligrammes of narcophine	5 milligrammes of acedicone
0.6 milligramme of heroin	15 milligrammes of codeine
0.6 milligramme of dilaudide	25 milligrammes of dionine)

If all the methods mentioned above are compared, the following table can be compiled (morphine = 100) (EICHHOLTZ and KRAUTH) :

	EICHHOLTZ and KRAUTH	KEIL and KLUGE	A. WEISS	KEIL and POEHLS
Morphine	100	100	100	100
Laudanone	100	65	65	60
Narcophine	100	96	32	90
Heroin	800	234	280	800
Dilaudide	800	300	500	1,600
Acedicone	100	—	—	—
Dicodide	200	56	—	180
Eudocal	330	142	—	—
Codeine	33	—	10	—
Dionine	25	—	—	—

OBSERVATIONS ON THE NERVOUS SYSTEM

The sensitivity of the vagus centre is much increased in cats by small doses of dilaudide, but with larger doses there is at first a brief increase followed by a decrease. Similar observations were made with dicodide. Eucodal, on the contrary, seems to depress this centre from the outset even in small doses. Morphine increases the reflex excitability of the vagus centre ; dilaudide and dicodide therefore resemble morphine in this respect (MYERS). Larger dose of dilaudide and dicodide administered to cats exert a marked action on the spinal reflexes, twitchings, convulsions, etc. These reactions are more easily produced by dilaudide, whilst larger doses of dicodide are required for the same effect. However, these phenomena are not caused by therapeutic doses but only by much larger doses. Similar effects can be observed with morphine or heroin, but these

drugs are much more active in this respect. Eucodal on the contrary has not this effect, not even with large doses (MYERS).

Intestinal Tract.

In experiments on intestines *in situ* or isolated, the effect of dilaudide and dicodide is roughly the same as that of morphine and heroin, but the influence of heroin on the tonus is stronger. Smaller doses increased tonus and peristalsis : larger doses decreased these functions. Eucodal behaved differently : it had little effect in small doses, and increased tonus and peristalsis in larger doses. The stomach and the sphincter pylori of cats are distinctly influenced by dilaudide, as they are by morphine ; the movements of the sphincter are increased, as well as those of the stomach. The effects of dicodide and eucodal in this connection are very slight and can be ignored.

The tonus of the ileo-colic sphincter of the cat is appreciably increased by dilaudide, dicodide and eucodal, which, in this respect, resemble morphine and heroin ; but to produce the same effect, eucodal must be given in larger doses than dicodide and dilaudide (MYERS).

Addiction.

The observations on habituation of the respiratory centre have already been mentioned.

Reference may, however, be made to a statement by KEIL and POEHLS : a rabbit which became insensitive to morphine reacted but slightly to dilaudide and dicodide. It is therefore concluded that morphine habituation extends over the whole morphine group.



Finally, mention should be made of a table summarising the pharmacological research of JICHLINSKI, which starts with the most active substance in each group :

Soporific :

Dilaudide		Heroin	Codeine
1	2 Eucodal	3 Dicodide	4 Dionine
Morphine		Acedicone	

426 COMPARATIVE EFFECTS OF CERTAIN HABIT-FORMING DRUGS

Analgesic :

1 Dilaudide
2 Eucodal
3 Dicodide

4 Morphine
5 Acedicone

6 Heroin
7 Codeine
8 Dionine

Cough-relieving :

Dilaudide
Codeine

Dionine
Acedicone

Heroin
Dicodide

Morphine
Eucodal

Eupnæic (toxic for man) :

Heroin

Eucodal

Dilaudide

Morphine

Acedicone

Dicodide

Codeine

Dionine

Euphoric :

Morphine

Heroin

Eucodal

Dicodide

Dilaudide

Acedicone

Codeine

Dionine

CLINICAL AND PRACTICAL OBSERVATIONS

The clinical and practical observations relating to comparisons of the drugs here considered are not numerous.

Respiration.

In regard to their action in slowing-up and deepening respiration, these drugs may be classed as follows, in ascending order of potency : dicodide—morphine—eucodal. For the purpose of relieving coughing, eucodal seems superior to the others. The reduction of the secretion seems to be somewhat greater with dicodide than with the other drugs (R. F. MAYER).

As a cough-alleviating agent, dicodide, given in much smaller doses and especially in subcutaneous injections, has a better and more protracted effect than morphine. Eucodal, for its part, is less efficacious in this respect than either dicodide or codeine. It acts, generally speaking, more like morphine than like codeine. If a certain degree of habituation to subcutaneously administered dicodide already exists, more powerful general effects can be obtained with eucodal. Compared with morphine and preparations

containing morphine, dicodide seems to be endowed with a particularly high cough-relieving potency relatively to its general sedative properties.

In morphine, the narcotic effect is more prominent ; in dicodide, the effect on coughs (HECHT).

In dyspnoea of circulatory origin, it is recommended to give dicodide during the day but morphine or eucodal during the night on account of the sleep-inducing effect of the latter drugs (R. F. MAYER).

Circulation.

The dilating effect on the cutaneous vessels is followed by a feeling of warmth, which is small with all the opiates. The most intense effect of this kind is usually produced by eucodal, which gives a stronger reaction in this respect than dicodide or morphine (R. F. MAYER).

Analgesia.

The effect on the cutaneous sensation of pain varies with the different morphine-like preparations. In the course of research extending over some appreciable length of time, it has been found that the milliamperage which is necessary to produce the pain falls ; the effects of a drug hence wear off (MOEHRKE). GRUENTHAL and HOEFER found in their research work on the effect of opiates on the quality of cutaneous sensation that morphine exercised an acute deadening effect on the sensation of pressure and pain on the skin, but not on its sensitiveness to temperature (cold and warmth).

If morphine is given for a long period, the influence on pressure and temperature sensation remains unchanged, but the threshold of pain is raised little by little ; finally, larger doses of morphine are necessary than in the beginning in order to exert any perceptible influence on the pain ; these are apparently symptoms of habituation. Pantopon, dicodide and eucodal have the same effect in this respect as morphine. Similar observations were made on a case of dicodide addiction and on another of eucodal addiction (HOEFER, GRUENTHAL and HOEFER).

R. F. MAYER found that, when tested on patients for pain-deadening properties, these drugs ranked in the following ascending

order : dicodide, eucodal, morphine (dilaudide had not yet been examined at the time).

Mental Symptoms.

A state of intense excitement instead of the usual calming effect of opiates, which occurs in persons of special constitution, was observed after eucodal as well as after dicodide and morphine (R. F. MAYER).

Intestinal Tract.

R. F. MAYER found that the increase of tonus is least marked with codeine and heroin and greatest with opium ; morphine and dicodide occupy roughly a middle position, and eucodal is slightly less strong than morphine. In regard to constipation, the differences between the drugs are not very great. Nevertheless, the constipation seemed to be slightly less with eucodal and dicodide (dilaudide had not yet been examined).

MYERS & DAVIDSON investigated in detail the effects of the drugs in question upon the passage of food along the alimentary tract of human beings. From observations involving the use of the barium meal and X-ray methods, they came to the conclusion that the effect of dilaudide closely resembles that of morphine. Dilaudide produces a condition of increased tonus in the pyloric and ileo-colic sphincters, resulting in delayed emptying of the stomach contents into the duodenum, and a delayed passage of the intestinal contents into the cæcum. Dicodide has a much weaker action upon the pyloric and ileo-colic sphincters than morphine, heroin, dilaudide or eucodal. It causes only a negligible delay in the passage of food. Eucodal has an action resembling that of morphine.

Smooth Muscle.

The increase of the tonus of the vesical sphincter which induces retention of the urine was greatest with morphine ; relatively small with dicodide and slightly less with eucodal (R. F. MAYER).

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Abbreviations :

A.E.P.P.	=	<i>Arch. j. exp. Path. u. Pharm.</i>
B.Kl.W.	=	<i>Berliner Klin. Wschr.</i>
D.M.W.	=	<i>Deutsche Med. Wschr.</i>
J.A.M.A.	=	<i>Journal of the Amer. Med. Assoc.</i>
J.Ph.Th.	=	<i>Journal of Pharm. and Exp. Ther.</i>
Kl.W.	=	<i>Klinische Wschr.</i>
M.Kl.	=	<i>Medizinische Klinik.</i>
M.M.W.	=	<i>Münchener Med. Wschr.</i>
Schw.M.W.	=	<i>Schweiz. Med. Wschr.</i>
W.Kl.W.	=	<i>Wiener Klinische Wschr.</i>
W.M.W.	=	<i>Wiener Med. Wschr.</i>

430 COMPARATIVE EFFECTS OF CERTAIN HABIT-FORMING DRUGS

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436 COMPARATIVE EFFECTS OF CERTAIN HABIT-FORMING DRUGS

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438 COMPARATIVE EFFECTS OF CERTAIN HABIT-FORMING DRUGS

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DOPING :
**A Study of the Means employed to raise
the Level of Performance in Sport**

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The term "doping" was originally used to describe certain methods designed to augment the functional efficiency of athletes by means of highly active drugs. It is now used in a general sense to describe any method of improving athletic performance temporarily, either during training or in connection with competitive events.

Apart from actual drugs, such as benzedrine, cocaine, caffeine, coramine and others, the agents used for "doping" also include dietetic preparations, glucose, vitamins and various non-toxic salts such as phosphates, which are also normally consumed in food.

The term also covers the inhalation of pure oxygen and ultra-violet irradiation ; indeed, even massage and the encouragement shouted to competitors in athletic contests can be regarded as falling within the concept.

According to Hans SEEL, anything which involves a departure from the normal mode of life is to be looked upon as a form of "doping". For my part, I consider this standpoint difficult to justify ; for any strict special training, and, indeed, every athletic contest as such, would, if it were accepted, have to be regarded as entailing a departure from the normal mode of life.

There can be no doubt that stimulants are to-day widely used by athletes participating in competitions ; the record-breaking craze

and the desire to satisfy an exacting public play a more and more prominent rôle, and take higher rank than the health of the competitors itself.

The large number of papers published in the past few years on the question of "doping" shows how much this question is now to the fore. But resort to means designed to enhance the physical powers of athletes is no new thing; even in antiquity, it was known that certain substances could give competitors added strength.

The Samoyeds, for example, ate fly-agaric (*Amanita muscaria*), a mushroom containing muscarine, to rouse themselves to the required pitch of combativeness; and the celebrated Berserkers of Rolf Krake's time are said also to have had recourse to the same stimulant. Again, it is common knowledge that the Red Indians used to chew coca-leaves when a particularly strenuous or protracted effort was required of them.

In sports in which animals took part, the use of stimulants was so widespread that several countries introduced legislation to forbid it on the ground of its cruelty to the animals. Equal attention ought also to be paid to human beings participating in sports. The responsible authorities should be told what means can legitimately be employed to increase physical output; their effect should be explained and the use of harmful substances should be strictly forbidden.

Most sports leaders and doctors who have expressed themselves publicly on the subject hold the same view; but, in discussions of this type, the ethical and medical aspects are so intermingled that the problem as a whole becomes most confused.

By the ethical aspect is meant here the question whether it is truly consistent with good sportsmanship to have recourse to special stimulants. This is a matter on which sports leaders have to make up their minds, but it has no more connection with the medical aspect of the problem than has the amount of the prizes.

Medical advice, on the other hand, must be based strictly on the known harmful or beneficial effects of the various substances in use, though it must, of course, be realised that any sort of artificial stimulus to exceptional performance (prizes, etc.) is liable to react very unfavourably upon health.

In the following pages, an attempt is made to describe the various agents for increasing physical efficiency which can be used in

connection with sports, and to indicate their harmful or beneficial effects. It must, however, be made clear at the outset that, despite the existence of copious literature on the subject, the available knowledge is still extremely limited. This is due in part to the number and variety of the factors which must be taken into consideration in determining whether a particular substance increases functional output or not ; again, it is often extremely difficult to decide whether a given substance is, in itself, deleterious, for it is not enough merely to ascertain that it is non-toxic. The mere fact that some agent—perhaps not toxic in itself—renders the organism capable of exceeding its normal maximum output of energy—*e.g.*, because it influences in a non-physiological manner the natural regulator represented by the sensation of fatigue—may involve a serious menace to health.

In theory, there are many ways of raising the level of performance of an athlete. Substances, such as concentrated foods, salts, vitamins and oxygen, used up by the organism in muscular effort can, for example, be administered. Again, such a result can be achieved by acting upon the nervous system with stimulating or sedative agents—*e.g.*, cocaine, caffeine, benzedrine and various sedatives.

Another group of substances consists of those which stimulate the circulation of the blood by acting on the vasomotor centre, the heart and the vascular system. Lastly, as is shown by experiments on isolated muscles, there are other substances that can increase the efficiency of muscular function directly. For all these substances, however, it remains true that evidence of single effects cannot be translated without further ado into terms of the organism as a whole. The existence of any given influence must be verified by an investigation of its effect in various forms of sport, and by systematic tests based on the performance of work and carried out in exactly defined experimental conditions. Frequently, these experiments prove to be extremely difficult, since many other factors can come into play besides the drug under investigation.

In order to obtain a clearer notion of the action of the various substances, it will be convenient to divide them into a number of groups according to their nature and mode of action, although, in some cases, any such classification is bound to be quite arbitrary.

1. FOOD PREPARATIONS

It is proposed to deal, in the first place, with substances the action of which is to provide calories in a readily accessible or otherwise suitable form. In order not to include the whole question of nutrition under the heading of "doping", consideration will be limited, in this survey, to special artificial foods intended for consumption immediately before or during athletic performances, and from which a favourable effect upon the performance of muscular work is expected.

It is, of course, impossible to draw any hard-and-fast line between such foods and special forms of diet. *Carbohydrates* may be looked upon as the most appropriate fuel for muscular effort, and it has long been thought that performance could be improved if they were absorbed in a readily absorbable form immediately before or during muscular work. This idea was all the more natural, in that many experiments show that a drop in the sugar content of the blood, due to the strain upon the reserves of carbohydrates in the organism, may bring about a condition of exhaustion.

BURGESS and his collaborators, DILL and his collaborators, TALBOTT and his collaborators, BØJE, and others, have found that protracted muscular work causes such acute hypoglycœmia that the work may have to be interrupted.

When, however, *glucose* is supplied to the body, the physical capacity to perform protracted muscular work is increased. As examples may be quoted a series of tests in which the author put a number of subjects through spells of work with Krogh's cycle-ergometer—pursued until complete exhaustion with a low sugar content in the blood. By the administration of glucose or cane-sugar, the condition of exhaustion was relieved without the necessity of a pause, and the effort could be continued in satisfactory conditions for a full hour more. These observations confirm numerous findings of athletes themselves.

In the case of a brief period of muscular work, entailing no carbohydrate deficiency, no appreciable result is to be expected from the ingestion of glucose. In a series of weight-lifting tests, PAMPE and others have arrived at similar findings. In certain circumstances, indeed, a large intake of glucose can even limit physical output.

If physical work is started after the ingestion of a considerable quantity of glucose and at the moment when the post-prandial hyperglycoemia curve begins to fall, a sudden and considerable drop in the sugar content of the blood may sometimes hamper the performance of the work (as shown by experiments of my own, the results of which have not yet been published). If glucose is to be used for the purpose of increasing efficiency, the medical advisers of the individuals concerned should bear this fact in mind. Medically speaking, there is no objection to the use of this substance in connection with sports.

My own experiments show that cane-sugar, though cheaper, gives just as good results as glucose. Many strength-giving preparations with high-sounding names, which increase their cost, contain glucose ; but beyond the psychological effect invariably caused by a high-priced product, they offer no particular advantages.

In various quarters, particularly invigorating effects are ascribed to preparations containing *lecithin*. Eggs, for instance, have always been in high favour as a means of enhancing the capacity for muscular work and other forms of exertion. Since, however, lecithin is completely decomposed in the intestinal tract, and since the substance is only built up in the cell itself, it appears unlikely, *a priori*, to serve any very useful purpose. ATZLER and LEHMANN have investigated the effects of soya-bean lecithin on the output of work of 5 persons. They found that when 44 grm. of this substance was administered daily for several days, a greater amount of work than would otherwise have been needed was required to produce a particular degree of increased pulmonary ventilation ; lecithin is also said to produce greater manual strength and skill.

These tests show, however, that it is extremely difficult to determine which of the observed effects was due to lecithin and which to suggestion and training. I therefore consider that there is no experimental tendency to justify the use of lecithin as an agent for improving athletic performances, and there is no reason why it should be recommended to athletes. The same applies to certain preparations, which are strenuously urged upon athletes, but which are only calories in a very expensive form.

Turning to *vitamins*, special mention should here be made of vitamin B₁, which plays a part in the carbohydrate metabolism. BICKEL and COLLAZO have observed a considerable increase in the

glycogen content of the liver and the muscles after administration of yeast extract ; basing themselves on the work of EMBDEN and HAB, who found a higher glycogen content in muscles which had undergone training, they conclude that a substantial intake of yeast is favourable to muscular effort.

AIDA observed, after administration of dried yeast and small quantities of glucose, the accumulation of larger glycogen reserves in the liver than when glucose alone was administered. On the other hand, the glycogen storage resulting from the intake of glucose in large amounts appeared to be independent of the simultaneous ingestion of yeast.

According to PI-SUNER and LISS, yeast taken once causes a considerable increase in the glycogen deposit of the liver, whereas, taken regularly, it merely acts on the fat storage in that organ. CSIK and BENCSIK investigated the effect of the vitamin B preparation " Arnea " on the capacity for work of two students using Mosso's ergograph and dynamometer and applying a series of weight-lifting tests. They believed that they could detect an increase, but from the results of the tests it would appear that the changes observed were due merely to training and practice. There is therefore no experimental basis upon which to recommend the use of yeast or similar preparations to athletes. This, of course, does not mean that participants in sports should not, like everyone else, see that their diet contains a sufficient quantity of vitamin B₁. KINNERSBERG and PETERS have found, for instance, that a deficiency of B₁ leads to the accumulation of lactic acid in the blood and organs. But until further proof is adduced, an excess of B₁ can in no circumstances be looked upon as specifically raising functional capacity. On the other hand, I have not so far been able to detect any deleterious secondary effect due to this group of preparations.

The position is similar in regard to *vitamin C*, of which the athlete's diet should, of course, contain an adequate allowance. Here again no direct increase in physical efficiency is to be expected from an excess.

In general surveys of the problem of " doping ", the experiments of C. MÜLLER on the influence of *liver* preparations on muscular work are frequently quoted. According to MÜLLER, the daily administration of 25 to 30 grm. of *Hepatrat. liquid.* (Normal), or 5 cubes of " Heparglandol " (Roche), causes an appreciable rise of

efficiency in the performance of a six-minute spell of work equal to 3,600 kilogrammetres on the cycle-ergometer. But his experiments are in no sense conclusive, for the tests were made at irregular intervals, a highly unsatisfactory circumstance in connection with such investigations, since unforeseen changes in the state of training can occur—sometimes very suddenly—during the rest periods.

Moreover, in those experiments, the net efficiency was abnormally low : even after the preparations in question began to exert their good effects, it hardly reached the level usually found in subjects in a medium condition of training. The amount of work which formed the basis of the tests was, moreover, so small that conclusions applicable to really heavy strains such as those entailed by sporting contests cannot be drawn from them.

If the above tests have been described in some detail, although they do not justify any conclusion favourable to the use of preparations containing liver as conducive to increased physical efficiency, the chief reason is that these and similar investigations continue to be quoted unchallenged with the object of inducing athletes to purchase a whole series of preparations, the scientific basis of which is more apparent than real.

As regards the effects of *phosphates*, a series of investigations, beginning with the work of EMBDEN and his collaborators on the part played by phosphates in muscle metabolism, can be referred to. Tests carried out on soldiers, some of whom turned an ergometer to which a brake was applied, whilst others carried out long marches, showed that the effect of an intake of phosphates was to increase the total output of work by more than 20%.

To eliminate the influence of suggestion, tartaric acid was substituted for phosphates in some of the tests. Both in these, and in most of the other similar tests with phosphates, the latter were administered in the form of primary sodium phosphate ("Recresal"). EMBDEN's practice was to give from 5 to 7.5 g. daily, four or five hours before the test. The results were also found to be favourable in the case of soldiers on the march ; despite strenuous physical effort, they were in a much fresher condition when phosphates had been administered.

Phosphates can often cause a purely subjective feeling of freshness and zest for exertion, which may amount to a condition of euphoria ;

nevertheless, large quantities can cause sleeplessness and diarrhoea. HERXHEIMER has carried out similar tests on police officers, and found in those who had been given phosphates a considerable increase in weight and an improvement in various types of physical performance.

In experiments of this type, however, it is extremely difficult to delimit clearly the effect produced by each of the various factors which can influence physical capacity ; and I consider that none of the investigations of which the results are yet available allows of the definite conclusion that phosphates increase in fact the standard of athletic achievement. Nor does the work of ATZLER and his collaborators support the view that such a result can be secured. According to MARBE, the effect of " Recresal " is purely suggestive. His experiments with an expander and a dynamometer, and also a series of arithmetical tests, showed that one drop of congo-red in distilled water or a solution of bicarbonate of soda was just as effective in increasing physical output as a dose of 3.5 g. of " Recresal " dissolved in water.

Reference should finally be made to POPPELREUTER's experiments, pursued over several years on himself with daily doses of 3-20 g. of " Recresal ". He felt much better both physically and mentally whilst taking the drug. After prolonged administration, however, sudden discontinuance caused abstinence symptoms in the form of a reduced capacity for work and a sense of discomfort. In further investigations carried out on female workers, POPPELREUTER found that the effect of " Recresal " was chiefly noticeable in arithmetical calculations and similar work, and was practically non-existent in the case of strenuous physical effort.

It would therefore seem that phosphates act principally upon the nervous system, but even from these experiments it is difficult to determine whether this is a matter of suggestion, or whether phosphates can increase the powers of the organism in other ways. The chief result of POPPELREUTER's observations is the finding that even a dose repeated daily over a period of years has no deleterious effect—a reassuring discovery, since phosphates are in great demand in athletic circles, particularly in Germany, owing to intensive advertising of their beneficial properties.

The conclusion appears to be justified that phosphates, taken in quantities exceeding the amounts found in a normally varied diet,

can probably increase the output of the organism, although it is by no means certain that the whole effect is not due to suggestion.

Of other non-toxic salts, *calcium* also has been credited with the property of increasing athletic powers. RIESSER found that the output of isolated muscles could be improved in this way. Here again, however, the experimental data are insufficiently definite to justify recommending the administration of calcium in amounts exceeding those found in a rationally varied diet. The position is, of course, different when the diet is unbalanced ; but discussion of that aspect of the question lies beyond the scope of this survey.

Heavy physical effort in great heat entails a loss of salts, especially sodium chloride, so considerable as to cause a complex of symptoms variously described as miners' cramp or heat cramp (see, *e.g.*, TALBOTT and MICHELSEN). In such cases, an additional ration of salt becomes essential. Doses of sodium chloride could therefore be used with advantage as "dope" in connection with protracted athletic trials. But, for short sporting events, the same will seldom be true ; only in prolonged contests will signs of salt deficiency reduce the standard of performance, especially as the salt content of the participants' diet is generally cut down to prevent thirst.

Frequent endeavours have been made to stimulate the physical aptitudes of persons undergoing heavy physical strains by the administration of *alkalis* in the shape of sodium carbonate, on the ground that the fall in the blood alkaline reserves, caused by the increased acid production associated with muscular effort, is thereby compensated. DILL and his collaborators found, in experiments on man, that a condition of alkalosis allows the organism, before it reaches exhaustion, to incur a heavier oxygen debt, hence to perform a greater amount of muscular work than is normally the case. A subsequent and more extensive series of tests, however, showed no increase in physical efficiency, although the same changes in the blood composition were observed. DENNIG and his co-workers found, in treadmill tests, that an intake of ammonium chloride reduced physical efficiency, whereas alkalosis caused by drugs increased it.

It is, however, not easy to settle the question of the value of *alkalis* as "doping" agents, because, to begin with, it is uncertain how far the formation of lactic acid is a limiting factor in the performance

of work, or how far a sharp fall in the alkali reserve in the blood would reduce the output of work. Before deciding to administer alkalis, regard should be had to the fact that the change produced by exertion in the pH of the blood and in its CO₂ tension influences, among other things, the regulation of respiration. The administration of alkali *per os* constitutes such a violent interference with the whole pH regulatory system that it is as likely to be detrimental to the maximum physical output as the reverse.

It may be of interest to aviators and mountaineers frequenting high altitudes to learn of the favourable effects of *ammonium chloride*, discovered by HALDANE in the course of research into acclimatisation to low oxygen pressures. His findings were confirmed by two members of the expedition to Mount Kamet, which rises to a height of 8,000 metres.

DOUGLAS, GREEN and KERGIN made a series of six similar tests on a subject placed in a low-pressure chamber and working on a cycle-ergometer. In two of the tests, ammonium chloride was administered. Working capacity was found to be greater than in the control tests, the rise in the pulse rate was less, alveolar oxygen pressure was higher, the carbonic acid tension was lower and the feeling of strain and exhaustion less acute than under the corresponding normal conditions.

CHRISTENSEN and SMITH carried out experiments on six subjects in a low-pressure chamber, with and without administration of ammonium chloride in gelatine capsules. Five of the subjects were aviators used to high altitudes ; the tests took the form of reducing the oxygen pressure gradually to the lowest degree which each subject could stand. After administration of ammonium chloride, five of the six subjects were able to withstand reduced oxygen pressures equivalent to altitudes 1,000 to 2,000 metres higher than those reached in the control tests.

According to HALDANE, the beneficial effect of ammonium chloride is due to the following cause : a low oxygen pressure causes increased respiration, and thus causes the amount of carbonic acid expelled by the lungs to rise ; the consequent alkalosis then inhibits any further increase of pulmonary ventilation. The administration of ammonium chloride retards the development of alkalosis ; the degree of ventilation can therefore rise further, and the alveolar oxygen pressure can increase.

Aviators and mountaineers can therefore look upon ammonium chloride as an agent capable of increasing functional capacity. In the doses specified, the drug should have no harmful secondary effects ; though larger quantities, or a sensitive stomach, may bring about slight local irritation.

Medically speaking, there can be no objection to the use of this agent ; but, in practice, the question will seldom arise.

2. OXYGEN

The use of pure oxygen as "dope" has been discussed from time to time in Press articles. At the time of the Olympic games, for example, it was stated that the Japanese swimmers were "pumped full of oxygen" in their dressing-rooms, and there followed a discussion of the possible influence of this practice on athletic performance.

It can safely be asserted that, in this instance, the level of achievement was no better and no worse, the oxygen having been used up long before the competitors had covered the distance between their dressing-rooms and the starting-line. Only if oxygen were to be administered immediately before the start, especially in the case of under-water swimming, could some favourable effect be expected.

A whole series of tests have been made to determine the effect of inhaling oxygen (or air with an oxygen content higher than the normal of 20.96%) on athletic performances and other forms of strenuous muscular effort. L. HILL and FLACK, and also MIYAMA, in tests carried out on boxers and sprinters, found that, when air containing extra oxygen was inhaled just before the start, speed and physical efficiency were improved. They state that the pulse rate rises less sharply and that shortness of breath is less distressing. They also found that the breathing-in of oxygen after physical effort shortened the time of recovery.

These experiments are open to the same objection as those carried out with numerous other stimulating agents : it is extremely difficult to establish whether the improvement in physical performance is really due to the agent under investigation or not.

No surprise need therefore be felt if other workers—*e.g.*, SIMONSON and his co-workers—reach quite different conclusions as regards

the inhalation of oxygen. These investigators timed seven subjects over 100 metres, first without and then with previous inhalation for 10 minutes of a mixture containing 45% oxygen and 5% carbon dioxide. Although there was a subjective illusion of greater physical power, the actual times were not improved.

In order to establish definitely whether the inhalation of air with a high oxygen content improves physical ability in competitions, it is important to know whether cases actually exist in which the output of work is really limited by a shortage of the supply of oxygen to the lungs, and whether this output can be increased by the supply of extra oxygen. A number of workers have investigated this question, among them A. V. HILL and, later, NIELSEN and HANSEN. The research work of the last-named is particularly comprehensive and shows the effect of air with a high oxygen content on severe muscular effort. Two subjects in well-trained condition were given air with a high oxygen content and tested in the performance of work of varying intensity on the Krogh cycle-ergometer. It was found that exertion for which the oxygen content of normal air was adequate did not lead to any appreciable variation in the oxygen intake when the oxygen content was raised to 45-47%. With more strenuous efforts, however, there was a reduction in the pulmonary ventilation and respiratory quotient. When the effort became exceptionally strenuous and the oxygen requirements exceeded the rate of oxygen absorption compatible with the breathing of normal air, the inhaling of air containing 45% of oxygen led to an increased oxygen absorption and to an improvement in physical efficiency.

That improvement does not depend wholly upon the more abundant intake of oxygen, but also upon an easing of the labour of breathing as a result of reduced pulmonary ventilation.

A series of "final spurt" tests with the oxygen content of the inspired air at 22.8%—*i.e.*, at a level at which the diffusion properties of the gas are already substantially increased—gave results in respect of capacity for exertion, oxygen absorption and pulmonary ventilation which differed in no wise from those of similar tests performed in an ordinary atmosphere. Under normal conditions, therefore, oxygen absorption cannot be increased even by considerably improving the conditions of diffusion, and this means that greater pulmonary ventilation has no effect.

The increase in oxygen absorption and the higher physical output obtained by inhaling air with 45% oxygen must be due either to the fact that the minute volume of the heart can be still further increased under such conditions, or to the raising of the oxygen content of the arterial blood stream. The increase in the intake of oxygen being about $\frac{1}{2}$ litre per minute, the additional quantity actually absorbed cannot account for the whole of it. The tests carried out with air containing 22.8% of oxygen showed that there was no increase in the consumption of O_2 , and therefore destroy the argument that the blood content is raised. The only probable explanation is that the increase in oxygen absorption and in energy output is due to a specific circulatory effect of increased oxygen tension. I have gone into some detail in connection with these tests, because they illustrate clearly the basic physiological factors which determine the character and magnitude of the effect produced upon physical efficiency by breathing air with a high oxygen content.

My feeling is that most athletes and sports leaders have the most fanciful and confused ideas about the meaning of "oxygen priming". To put it briefly, it is highly questionable whether the inhalation of oxygen is of any advantage in ordinary sports events.

Whilst in those forms of athletics which call for prolonged exertion the supply of oxygen through the lungs will certainly not prove a limiting factor, some advantage might be expected in theory from the inhalation of air of high oxygen content in athletic sports requiring only a brief effort, but the administration of such air would scarcely be practicable during a contest and quite useless before.

The importance of oxygen at high altitudes is not under discussion here, as it falls outside the scope of this survey. In any case, there can be no question of oxygen inhalation producing any deleterious effect; and no objection need therefore be made, on this ground, to the alleged "oxygen-doping" practised by the Japanese swimmers.

3. ARTIFICIAL SUNLIGHT

A great deal has been said in recent years about the value of ultra-violet rays in connection with athletic training. In particular,

the question how this practice is unsportsmanlike in spirit has aroused much attention, although no general agreement has been reached. The record of these controversies shows the futility of discussions on "doping" on any but a medical basis. Little will be said here about that aspect of the problem, for, in my opinion, the athlete's health adviser should be exclusively guided in his counsel by the evidence available as to the effects of the substances concerned. The most important question for us is therefore whether artificial sunlight can increase the physical efficiency of the organism and whether its use is attended by any deleterious effects. Although much research has been carried out, it is, in my opinion, impossible as yet to give a definite answer.

A large number of experiments showing that irradiation can raise the standard of athletic performance rely on a purely subjective feeling of well-being or of increased functional capacity ; but, in the majority of cases, no acceptable evidence by which these results could be checked is available.

In considering this matter, I shall refer only to the exhaustive investigations of LEHMANN and SZAKÁLL on the influence of ultra-violet rays on metabolism during physical effort, and on the capacities of the organism for work. These workers carried out a series of tests on six male subjects, aged from 24 to 31 years, using Krogh's cycle-ergometer with and without irradiation with a mercury quartz lamp.

Briefly put, the results were the following : repeated exposure to the lamp caused a drop in the rate of metabolism when the subject was resting, and an increase of the respiratory quotient. The neutrophile leucocyte count fell while lymphocytes appeared in large numbers. During irradiation, 1,836 kilogrammetres of work was performed in two minutes with greater efficiency and a smaller oxygen debt ; in addition, an increase in the capacity of fixation of CO_2 in the blood was observed.

These findings would tend to show that exposure to ultra-violet rays endows the organism with capacity for work. To determine whether the irradiated organism is really capable of a greater output of work, the subject under investigation must pursue his effort on the ergometer until complete exhaustion. After a while, an output of 180,000 kilogrammetres of work in three hours can be achieved.

The experiments did not show, however whether the increased capacity for work was due to ultra-violet radiation or was the effect of training. In the final series, therefore, the method was altered to determine what amount of work could be performed whilst allowing the pulmonary ventilation to be the same during the minute following the end of the test, this being taken as a measure for the oxygen debt. In this experimental series, an increase of working capacity of about 60% has been observed ; but no attempt was made to determine whether irradiation could also raise the maximum output.

According to LEHMANN and SZAKÁLL'S experiments, it can be assumed that, where a moderate amount of work is being performed, the use of ultra-violet rays brings about changes in the organism which result in improved efficiency.

If administered in suitable doses and kept within moderate limits, ultra-violet radiation should not present any dangers. Signs of marked fatigue may follow the first sittings, and only after some time will an improved zest for exertion and a greater sense of well-being make their appearance. Athletes who are not used to ultra-violet rays should therefore refrain from this practice immediately before taking part in competitions.

4. PHARMACEUTICAL SUBSTANCES

In this section, we shall first consider a series of substances the use of which in connection with athletics is based mainly on their influence upon the *nervous system*, either as stimulants or as soothing agents. Substances capable of acting upon the *heart* and the *circulation* will next be considered. This chapter deals with a series of drugs, which are in part very poisonous, and are usually the substances referred to when the term " doping " is used.

The toxic action of *alcohol* so overshadows its other effects that this, and not the part it plays as a source of energy, is of importance here. Every athlete knows that, taken in large quantities, alcohol lowers the standard of performance ; this is fully confirmed by many experimental tests. The possibility that, when taken in small doses and at the appropriate time, alcohol may act as a stimulant by removing inhibitions and by lessening the sense of fatigue cannot,

it is true, be dismissed out of hand. Both in the case of very prolonged athletic exertion, such as six-day races and long-distance swimming-tests, and in contests calling for a brief effort, such as boxing-matches, etc., even the most experienced trainers often administer a small glass of wine or a tot of brandy as a stimulant.

Before deciding whether this practice is justified or not, we must briefly review the results of the chief experiments carried out to determine the effect of alcohol on the performance of various kinds of work. Using an ergometer of the Johannson type, HELLSTEEN showed that the administration of 80 grammes of alcohol thirty minutes before the work is started diminishes the total output. On the other hand, small doses of alcohol taken five or ten minutes before the beginning of the work increase the output during the first part of the test, but reduce it in the later stages. DURIG found that an intake of 30 c.c. of alcohol lowers efficiency on mountain climbs, and attributed this to a deterioration of the quality of muscular function and co-ordination and to the climber's loss of skill in picking his way. TIGEGSTEDT and KALLIOINEN's ergographic tests show that a given quantity of alcohol administered in a 40% concentration reduces output of work more markedly than the same quantity administered in an 8% concentration.

GRAF, after an exhaustive series of investigations into the ability of motor-drivers under the influence of alcohol, has shown that every type of physical work associated with simultaneous mental activity is unfavourably influenced by alcohol. TIGEGSTEDT reached the same conclusions after a series of tests in which the criterion consisted in threading needles before and after consumption of two litres of beer with an alcohol content of 2.74%.

Lastly, reference may be made to ATZLER and MEYER's interesting experiments to determine the effect of strong doses of alcohol (210 c.c. in beer or brandy) on rough muscular work carried out by an habitual drunkard.

Work was continued to the point of exhaustion on the cycle-ergometer, no particular pace being prescribed, so that variations of intensity could be observed. The experiments show that both the intensity of work and the total output are much reduced when alcohol is consumed the evening before the test. If it is taken four hours previously there is no change in the intensity of work; and the aggregate output is, if anything, somewhat greater.

Alcohol taken immediately before a test does not exert any certain effect on the output of work, but during the test, the intensity of the effort is slightly enhanced, although markedly irregular.

Since the intensity of work is patently much greater if the performer has a feeling of ease while making it, these authors conclude that the immediate influence of alcohol is to be found in the good humour and mood which it engenders. Though alcohol taken on the previous evening reduces the output of work, it cannot be concluded from this that it is due to a direct influence on muscular vigour. Here again we are faced with a psychological factor ; the depressing after-effects kill all zest for exertion, thereby lowering endurance.

MEYER has investigated energy expenditure and efficiency after taking alcohol. He detected no change in efficiency when the alcohol was consumed immediately before the beginning of the test, but a reduction of efficiency if an interval of twelve hours had been allowed to elapse. The amount of the oxygen debt was not affected by alcohol.

There can be no doubt as to the effect of large doses of alcohol in reducing output in the case of heavy muscular work and in forms of muscular activity which require delicate co-ordination and ability to react quickly. The influence of small doses of alcohol is, however, quite different. This raises the important question whether alcohol merely has an inhibitory effect on the central nervous system, or whether it exerts first a stimulating and then a paralysing action. Up to the present, nothing conclusive can be said on this subject, but KRAEPELIN's investigations may perhaps indicate that, unlike the sensory and intellectual processes, motor processes are first facilitated and only later impeded. This was confirmed by subsequent observations.

There can, on the other hand, be no doubt that an inhibitory effect exerted, for instance, on the feeling of fatigue and on starting "nerves" can help the organism to greater effort. It might, therefore, be deduced that in any type of athletic exertion which depends upon sheer muscular strength and staying power, small doses of alcohol could raise the standard of performance, whereas in all cases in which the central nervous system is required to effect a nicer co-ordination of movements, the ingestion of

even small quantities of alcohol definitely reduces functional efficiency.

As alcohol is a toxic substance, its use in connection with sport obviously cannot be recommended. If participants in six-day races and long-distance swimmers—for whom the health aspect of the matter is relegated to the background—resort to spirits as a stimulant, that is quite another matter.

It would be extremely difficult, in practice, to enforce a prohibition to use alcohol in such small doses. This need not, however, cause any concern, since the quantities involved are quite certainly harmless and since larger amounts are automatically ruled out by the object to be achieved—namely, the attainment of the highest level of achievement.

SEEL and other workers include *ether* as a “doping” agent. As far as I am aware, it is, however, very little used by athletes. For the most part it is taken in the form of Hoffmann’s drops consisting of one part of ether to three parts of alcohol. This practice does not appear likely to assume any real importance in connection with sports.

Smelling-salts, particularly favoured by boxers in the intervals between rounds, consist of a *solution of ammonia* and of *ammonium carbonate* combined, in most cases, with *ethereal oils*. They influence the central nervous system by exciting the nasal mucous membrane, and thus act as a stimulant. The use of these salts can be pronounced harmless, and there is no reason for depriving trainers and “seconds” of their greatly prized smelling-bottles.

Cocaine is one of the oldest known forms of “dope” and TSCHUDI’s accounts of the muscular performance of Indians while under the influence of coca-leaves would turn a modern six-day racing cyclist green with envy. TSCHUDI states: “An Indian did extremely trying excavation work for me for five consecutive days and nights without touching food at any moment or taking more than two hours of sleep each night; every two and a half or three hours he chewed about half an ounce of coca-leaf, and kept the ‘quid’ in his mouth in the intervals. I was standing over him throughout and was thus able to observe him continuously. After completing this work, he accompanied me on a two-day ride across twenty-three leguas (about 140 kilometres) of high plateau country, padding along by the side of my fast-stepping mule and resting

only when he felt the need for coca. Upon leaving me, he assured me that he was quite prepared to undertake the same work again without food, provided only I supplied him with enough coca-leaf."

Cocaine is still consumed in large quantities in South America to-day by persons performing heavy physical labour in difficult conditions. CHRISTENSEN relates that the mine-workers in the Chilian mountains, whose arduous work is performed at an altitude of 5,000 metres, use large quantities of coca-leaf, to which they attribute the property of accustoming the body to low oxygen pressure and low temperatures. The use of this poisonous substance is, as a matter of fact, officially forbidden, but the prohibition is not strictly enforced, since work would at once cease if it were.

It is not an easy matter to determine to what extent cocaine is resorted to by athletes ; but no one acquainted with the position would gainsay that they are far from ignorant of its uses. WORRINGEN states that, in the earlier six-day cycle races in America, the participants were so intoxicated with cocaine that their bearing after the race was like that of lunatics.

Some research has been done on cocaine and muscular work. Mosso's experiments with the finger-ergograph are no doubt the most comprehensive ; they show that small doses of cocaine (0.1 gramme) attenuate the sensation of fatigue. The capacity of the subjects tested for work was much higher when they had taken cocaine than when they had not. Large doses of the substance, on the other hand, created a feeling of fatigue and of distaste for work.

THIEL and ESSIG investigated the effect of 0.1 gramme of cocaine hydrochloride on metabolism during physical exertion ; they found that the maximum output of work was appreciably raised, that the efficiency was much greater and that the oxygen debt was smaller when this substance was employed. The scope of these investigations was, however, restricted and the findings are hence uncertain ; the duration of the physical effort is not shown, and I do not feel that any definite conclusions regarding the influence of cocaine on metabolism in the course of muscular work are justified.

In tests involving the performance of 2,100 kilogrammetres of work in two and a half minutes, HERBST and SCHNELLENBERG were

unable to detect any certain effect of cocaine on metabolism, although they suggest that recovery may have been more rapid.

Leaving aside entirely the question whether cocaine affects metabolism favourably or not, its influence upon the central nervous system, which constitutes the motive for its use as a stimulant, cannot be questioned. The drug acts first as a stimulus and later as a inhibitory agent. A stage of mental exhilaration soon makes its appearance, accompanied by a feeling of well-being and the rapid disappearance of any sensation of fatigue. These effects, in association with an anæsthetic influence upon the mucous membrane of the stomach, allows the subject to enable work to be performed for long periods without symptoms of fatigue or sensation of hunger. Cocaine does not reduce metabolism at rest. As for the other properties of the substance, such as its habit-forming tendencies, these need not be discussed here.

The real point about cocaine in connection with athletics is that it is effective in removing the sensation of fatigue and can thus undoubtedly raise the level of performance in the course of prolonged effort. This putting out of action of fatigue—the normal safety-valve—is most assuredly not without its dangers. A warning must also be uttered as regards the acute intoxicating effects of this substance when used in large doses, as well as its chronic action which engenders addiction. Cocaine should hence never be used in connection with athletics and every infringement of this prohibition should be severely punished.

It is well known that *caffeine* and other *purine derivatives* are widely used as stimulants in connection with physical and intellectual effort. They are used either in the pure state or in the form of coffee, tea, cola or chocolate. Caffeine stimulates the central nervous system ; it increases the reflex responsiveness of the motor areas of the cortex, and exerts a favourable influence upon mental functions, especially under conditions of intellectual strain. It also shortens the reaction time to tactile and visual sensory stimuli, and accelerates the normal process of association (CHENEY).

The action of caffeine on the heart is chiefly manifested in an increase of the absolute strength of that organ and in a dilatation of the coronary vessels. Breathing is intensified as a result of the stimulation of the respiratory centre ; and ergographic tests performed in particular groups of muscles have shown that caffeine,

and products containing that substance, can improve the efficiency of the muscles (HOCH, KRAEPELIN and others).

In view of its known pharmacological properties, caffeine might be expected to improve athletic performance in certain circumstances, although it would be unjustified to apply findings arrived at by tests on individual muscle groups to the complex process of an athletic contest.

Caffeine would not appear to have any effects in connection with brief physical efforts. HERXHEIMER, after administering caffeine to 46 subjects before a 100-metre race, found that the time recorded was no better. Work tests on the cycle-ergometer show, on the other hand, that, when caffeine is administered, a larger aggregate amount of work can be performed before exhaustion sets in. In tests involving an output of 825 kilogrammetres of work per minute, SCHIRLITZ found that, after the administration of caffeine (0.2 gm. of caffeine sodio-salicylate), the total time during which the exercise could be continued was extended by a few minutes and that efficiency was somewhat greater. No definite conclusions can, however, be derived from these few experiments, owing to the wide dispersion of the values obtained.

GRAF carried out an extensive series of very thorough tests to investigate the influence of *cola-nuts* on muscular work ; his first object was to see how far that influence was different from that of caffeine. He used for his tests either chocolate with or without the addition of caffeine, or chocolate with dried cola-nut and a little coffee ; there was no question of suggestion, since all the chocolate preparations were identical in taste, and the two subjects under test were quite unaware of the different admixtures to the chocolate they consumed. The first stage of the tests consisted in establishing a certain degree of preliminary fatigue by means of a carefully measured amount of work performed on the bicycle-ergometer or by riding along the roads. An interval of one hour was then allowed, during which a small meal was taken including—except on certain specified days—one of the chocolate preparations. A test pursued until complete exhaustion was then given, the brake-power of the ergometer being increased every ten minutes until the subject was totally unable to continue. Notes were taken of any departure from the prescribed pace during the test, and of the pulse rate in the minute before the end ; the pulmonary ventilation

was also measured during the first ten minutes after the end of the test, and the general condition of each subject was noted. The total daily output of work exceeded 300,000 kilogrammetres.

The output was greater whenever either ordinary chocolate, caffeine-chocolate or coca-chocolate had been administered, but by far the greatest increase (from 20 to 30%) was produced by the chocolate with cola, whereas improvement recorded after giving chocolate with caffeine was scarcely greater than that brought about by ordinary chocolate. Since these tests were planned and executed with the utmost care, the influence of the two factors which normally hamper the interpretation of such experimental findings—*i.e.*, suggestion and training effect—can be discounted and it may be concluded with certainty that in any event, preparations containing cola are capable of increasing the capacity for muscular work in the case of protracted athletic exercise.

It is very difficult to gauge how far pure caffeine, or caffeine in the form of coffee, chocolate and cola, given to athletes in normal therapeutic doses as a physical stimulant, can endanger their health. But it seems likely that any substance capable of stimulating the body to exertion beyond the limits set by the normal sensation of fatigue will prove injurious.

MATTHIAS measured the influence of ordinary coffee and of "Hag" coffee, on the blood circulation—by measuring the pulse rate and blood pressure—before and after an 800-metre run ; he believes he can demonstrate that coffee from which caffeine has not been removed lays an additional burden upon the heart. As, however, he does not state whether the times taken to cover the distance were identical in all cases, and as the tests with ordinary coffee were carried out between June 8th and June 20th, whereas those with "Hag" coffee between June 22nd and July 4th, it is quite impossible to draw from these experiments any conclusions regarding the effect of caffeine. Nevertheless, and although we have no direct proof, we must expect the use of caffeine as a "doping" agent to be, in some measure, dangerous. It would therefore appear that, in any event, the use of pure caffeine or of preparations with a high caffeine content should be prohibited in connection with sports competitions. There is, of course, no need to overdo things by forbidding coffee, tea and chocolate altogether.

Even more than caffeine, it would appear that *benzedrine* (β -phenylisopropylamine) is capable of eliminating the sensation of fatigue. Tests with intellectual work have shown, it is true, that only in some 30% of the cases studied was the capacity for work increased by these substances when the subjects were sleepy and tired. Up to the present, no investigations have been made into the possible effect of this product upon muscular work ; participants in six-day cycle races have, indeed, used benzedrine, but I have no information as to the results.

The tonic influence of this substance is frequently accompanied by unpleasant secondary symptoms such as palpitation of the heart, vertigo, a dry mouth, a feeling of coldness, hypertonia, restlessness and insomnia. The available literature also records various instances of ill-effects in the form of persistent hypertonia and cases of circulatory collapse.

Moreover, it is not definitely established that performance is improved. Consequently, this substance should not be used in connection with athletics, all the more since the application of extra stimuli, or a weakening of natural powers of resistance in organisms undergoing a severe strain, must certainly involve risks.

How far substances exerting a calming influence on the nerves, such as *valerian*, *bromides* and preparations with a basis of *barbituric acid* can be included among "doping" agents is a moot point. Nervous disturbances of the heart, starting "nerves" and functional disturbance of the gastro-intestinal tract are frequent occurrences among athletes. According to WORRINGEN and SCHWARTZ, a preparation containing valerian is an excellent remedy for such troubles. The removal of these distressing nervous disturbances no doubt enables a higher standard of performance to be reached. Since, however, the symptoms described above present themselves in individuals who are not perfectly healthy, it does not appear justifiable to class such substances as "dope". There appears to be no danger of abuse among athletes, since every one of these substances has powerful fatigue-producing properties. Preparations with a basis of barbituric acid or hyoscyamus could be used in sailing contests to prevent sea-sickness, but whether this should be regarded as "doping" is an open question.

We now turn to a series of substances which are generally used for their effect upon the circulation. Since the circulatory system often sets a limit to athletic performance, it will be readily understood that efforts have been made to push back this limit by the use of stimulating agents.

From time to time, athletes who had heard something of the tonic action of *digitalis* in connection with heart complaints have experimented with this substance. WORRINGEN quotes a case observed by WIENER, in which a young competitor in bicycle races consulted him because he feared that he was over-trained. He had thought that he should strengthen his heart with a cardiac drug and was, in fact, suffering only from severe *digitalis* poisoning. It is consoling to think that such occurrences are extremely infrequent.

In the view of pharmacologists, *digitalis* has no stimulating action upon a healthy circulation. On the contrary, all the available experimental evidence on the subject points to a considerable diminution of the minute volume (STEWART and COHN, NEUKIRCH). This in itself is a sufficient reason for not using this substance in connection with sport. It might perhaps be argued (RUSSE) that, as far as sport is concerned, the heart, when it has been subjected to heavy strain, must be considered hypodynamic ; the administration at the appropriate time of *digitalis* or *strophanthus* would then raise the functional level. Leaving aside, however, the fact that there is no reason to take this view of a heart which is subjected to exertion, it is to be hoped that such arguments will not gain currency in practice, as it is well known that preparations containing *digitalis* are far from innocuous.

Nitroglycerine is sometimes used in bicycle races, and racing cyclists claim that they suffer less from shortness of breath after a violent sprint if they have first taken a 0.5 mgrm. tablet. This practice was resorted to by competitors in the six-day races at Copenhagen ; apart from this instance, there is no evidence of misuse of this product in athletic contests. Therapeutically, *nitroglycerine* is commonly used for spasms of the coronary vessels ; its alleged effect in connection with strenuous muscular exertion may perhaps be brought about by vascular dilatation. *Nitroglycerine* is not harmless, and may cause unpleasant secondary effects, such as vertigo, headache, palpitation, vomiting, a fall in the blood pressure and even circulatory collapse. Its continued use may lead to a

dangerous degree of methæmoglobinæmia, and it goes without saying that it should not be used in connection with sport.

Much has been written in the past few years on the use by athletes of *coramine* and *cardiazol*, and the question has been debated how far the use of such substances by athletes in good health is justified. It is not proposed to consider here the action of coramine, cardiazol and similar products when administered to remedy defective circulation, whether that defect is due to athletic strain or to some other cause.

Both substances act as stimulants of the central nervous system (and of the cerebral cortex); reflex responsiveness is enhanced, the respiratory centre is stimulated, and the administration of large doses may give rise to muscular spasm. The action on the circulatory system is chiefly due to stimulation of the vaso-motor centre. Minute volume determinations have shown in all cases an increased pulse volume. It has also been claimed that cardiazol eliminates symptoms of fatigue in the muscles of frogs and warm-blooded animals. This is probably due to peripheral action, since it also occurs after the peripheral nerves have been cut through (FISCHER).

The chief reason why athletes have resorted to this substance lies in its stimulating influence on the circulation and the central nervous system, which produces a definite subjective feeling of freshness in the tired organism.

It was doubtless for purely prophylactic reasons that MAJDRAKOFF first began to administer cardiazol to large numbers of athletes to prevent the appearance of circulatory disturbances due to violent physical effort. He performed some four hundred tests and investigated the effects of this substance on two groups of subjects, one of which was subjected to slight but protracted physical effort, whilst the other underwent short but very heavy strains. Cardiazol was administered as soon as the first signs of fatigue appeared in the course of walking-tours and ski-runs. It was also administered to competitors in bicycle races in the first third of each race, and to footballers at the beginning of the second half of each match. The effect of the drug was checked by observation of the pulse, the blood pressure and the subjective condition of the subjects. Whenever cardiazol was administered, the pulse rate and blood pressure rose less after exertion and reverted sooner to the value which is

normal when the body is at rest; endurance was also greater and subjective symptoms of fatigue less marked. As, however, the amount of work was not measured exactly in these experiments, and as some measure of suggestion cannot be ruled out, the results must be accepted with some reservations. The same applies to further experiments of the same type—*e.g.*, those carried out by MARTINS—on the influence of coramine in connection with light athletics.

SCHÖNHOLZER has published a report on experiments with coramine on himself; on ski-runs, he observed a striking increase in staying power on some occasions, whereas no effect was produced on others. He also mentions one case of acute muscular cramp occurring in a highly trained athlete during a mountain skiing competition; this cramp yielded at once to administration of calcio-coramine.

To sum up, it can be said of both coramine and cardiazol that they can probably raise the level of muscular performance in cases of protracted effort, although definite evidence on the point is not yet available. As regards deleterious effects, special attention must be drawn to the convulsive properties of both substances, though it would no doubt be a difficult matter to determine whether there is any connection between local muscular cramp and the administration of these drugs.

There is no other evidence of any harmful effects when therapeutic doses are used, and this applies in all important respects to all the other substances having similar properties, such as veritol, sympatol, preparations with a basis of camphor, etc. The effect sought in administering these drugs to athletes may be taken to be the elimination or attenuation of the normal regulative action of fatigue; there is, however, nothing to show that recovery is improved. For this reason, the use of such products by athletes should be definitely avoided. This is also the advice given by STAHELIN.

Quite recently, the newspapers announced that the remarkable performances of the Wolverhampton Wanderers football team were due to gland extract treatment provided for the players by their manager, Major Buckley. The Portsmouth team consequently decided to follow their example. Such cases show that, nowadays, no hesitation is felt in administering even *hormone* treatment as a

method of improving athletic performance. I do not know what hormones the English footballers use to score their goals, but this, presumably, is irrelevant, as we are probably dealing with a purely subjective phenomenon.

Theoretically, it is conceivable that the administration of sex hormones or of preparations of adrenal cortex might increase physical output even if, as is the case in the athletic world, the subjects are young men whose internal secretions are intact. Any functional failure of the adrenal cortex induces a condition of marked fatigue, accompanied, among other symptoms, by a lowering of muscular tonus. It is therefore not surprising that attempts should have been made to determine whether the use of preparations containing extract of adrenal cortex could raise the physical output of persons in good health.

Reference may be made in this connection to the experiments of EAGLE, BRITTON and KLINES, who observed marked improvement in the capacity for muscular work in three dogs in good physical condition treated with intra-peritoneal injections of steril protein-free extract of adrenal cortex.

In rats performing treadmill tests, INDOWINA and BAENA found an appreciable increase of the capacity for work after injecting adrenocortical hormone. MISSIURO, DILL and EDWARDS administered from $\frac{1}{2}$ to 1 c.c. of an adrenocortical preparation, during three to five days, to subjects who then showed slightly improved efficiency in easy walking-tests. Capacity for work in a confined atmosphere was not increased, however. It is impossible to decide as yet whether an improvement in physical output can be achieved by the administration of adrenocortical hormone.

In special cases among women athletes, hormone treatment has been found to be of assistance in attaining the highest level of performance. In particular, the administration of oestrus-producing substances may delay the onset of menstruation if this should coincide with the date of the contest.

After the Los Angeles Olympic Games, when it was observed that some of the best women athletes lost because of menstruation, OKAMOTO and his collaborators endeavoured to retard the menstrual process by means of a follicular product called "Pelanin". In about half the cases (29 subjects, of whom 19 engaged in athletic sports), they found that "Pelanin" administered *per os* could

retard menstruation. This effect was practically invariable in the younger women, whereas the older ones reacted less regularly.

The hormone treatment must be applied immediately before the day on which menstruation is expected to begin. Only in a few cases was any influence observed upon the following menstrual period, which, in these instances, began a little earlier. The intensity and duration of menstruation was, on the other hand, not affected, and, in some cases, previously existing menstrual trouble is said to have disappeared. No exact information can be given as to dosage.

Even though there may be cases in which the use of hormones has enabled athletes to improve their performance, nevertheless, it goes without saying that their use should definitely be avoided, since it may involve dangers the extent of which cannot be entirely gauged.

This more or less completes the list of "doping" agents, but it is not denied that a large number of substances of which no mention has been made here have also been tried. The evidence on the subject is, however, so flimsy that it is hardly worth while to examine it in any detail.

Mention may be made, by way of example, of the investigations of SCHREIBER and VILLINGER into the properties of "Zetton", a tonic with a gold basis. A few wholly valueless work-tests leads these workers to conclude that the substance produces a definite improvement of muscular tonus.

It is occasionally reported that athletes resort to morphine, atropin, strychnine or arsenic, but such cases are so rare, and research into the action of these drugs on the muscular work is so limited, that they need not be considered here. Reference must also be made to the voluminous literature on *tobacco* and athletics. That question also need not detain us, since it is now unanimously agreed that tobacco is more likely to lower than to raise the level of athletic performance.

This brief survey shows that there exists a whole series of substances which, rightly used, may render improved athletic performances possible. In addition, there are a considerable number of substances which athletes actually use, or which are urged upon them, the efficacy of which has not been conclusively demonstrated. In some cases, their use does not endanger health ; in others,

they are assuredly injurious, or this cannot be definitely proved. Heavy doses of hormones, cocaine, benzedrine, nitroglycerine, digitalis, strophanthin and caffeine may be definitely asserted to be detrimental to health.

On the other hand, it is impossible to adduce definite data regarding the possible toxicity of small doses of coramine, cardiazol, caffeine and various salts, as also of the moderate use of ultra-violet rays and alcohol. Medical advisers called upon to guide athletes must naturally strictly forbid the use of any agent suspected of being in any manner deleterious. To summarise the position, it may be asserted that it is essential to avoid the use of any artificial stimulants whose action is associated *directly* with risks of intoxication, or *indirectly* with the danger of whipping up the organism to extreme exertion. Medically speaking, there can be little objection to the use of nutrient preparations, of vitamins and of oxygen. Nevertheless, the medical adviser will naturally do everything he can to discourage the use of costly and ineffectual substances.

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DOPING

469

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RURAL DIETARIES IN EUROPE¹

I. GENERAL FEATURES

The dietaries of rural populations of European countries, as contrasted with urban dietaries, show certain main characteristics in common. In each country—or, more exactly, in each geographical area of Europe—there are, of course, special features and peculiarities in the peasants' food habits, but, in spite of this, there emerge from the scattered surveys made in different parts of Europe certain main principles.

The chief characteristic of rural dietaries is monotony, since the average peasant household uses only a limited number of foodstuffs. This is a disadvantage from a nutritional point of view, since, in a more varied diet, there is less danger of shortage of one or more essential food factors, particularly certain minerals and vitamins. There may be, as we shall see later, considerable seasonal variation in rural dietaries, but the day-to-day dietary, during the greater part of the year, usually lacks variety.

The first requirement of the average European peasant is to produce, with the greatest economy of land and of labour, foodstuffs which will supply the maximum energy value which he needs for hard physical work. For this reason, cereals, which are the cheapest form of energy-providing foodstuffs to produce, form the basis of

"This note was prepared by Dr. E. J. McDOUGALL on the basis of the documentary material collected by the Secretariat and supplemented by the author during her studies of the dietary aspects of bread consumption in various countries (see page 498)."

most peasant dietaries. The type of cereal used varies from wheat in Western Europe and the Danube Basin, to rye in Northern Europe, and maize and barley in parts of Eastern and South-eastern Europe ; but whether the cereal grown (or bought) is wheat, rye, barley, oats or maize, it is used in the great majority of peasant households throughout Europe as the basis of every meal. There are certain exceptions, as for example certain mountainous regions of the Balkan Peninsula, Sub-Carpathian Russia and Scandinavia, where cereals cannot be grown, and where the diet is made up of what vegetables can be produced (such as potatoes, beans, etc.) and of animal foodstuffs. Since these foods are less economical to produce than are cereals, the population of such regions are usually underfed, unless either some subsidiary source of income is found, or, as in Yugoslavia and Sub-Carpathian Russia, State relief in the form of wagon-loads of wheat or maize is provided.

The preponderance of cereals in the rural dietary is most marked in Central, Eastern and South-eastern Europe, where cereal foods often provide 80% or 90% of the energy value of the diet. This very high proportion of cereals in the diet decreases as the peasant population becomes more prosperous, and is very much less in Western or Northern Europe. In the more primitive rural areas of Europe, cereals are not always eaten as bread, but are often simply ground to a rough meal and cooked with water as groats, porridge or polenta, or made into hard unleavened cakes.

After cereals, some vegetable of high energy-providing value is usually the second most important foodstuff. In Ireland, in Poland and in parts of Germany, potatoes are even more important than cereals in providing the energy value of the diet. In most parts of the Balkans and Central Europe, beans are second only to cereals as a regular source of calories in the rural dietary.

The amount of meat eaten by rural populations varies greatly from one region to another. On the whole, the consumption of meat depends on the prosperity of the peasant. The poorer agricultural worker and small farmer in Central and South-eastern Europe may eat meat only on feast days (*i.e.*, a few times a year) while the more prosperous peasant may eat it once or twice a week. In Western Europe, the poorest peasants generally eat meat once a week, while the most prosperous farmers often have two or even three meat meals daily.

The consumption of milk also varies enormously from one part of Europe to another. In Finland and Latvia, the rural population is reported to drink a litre of milk per head per day, while in Hungary, Roumania and Yugoslavia there are districts where the peasant families drink practically no milk at all.

The level of milk consumption in rural households does not depend entirely on the level of milk production in that area. The tendency is for peasants who produce milk, butter or cheese, to regard these products primarily as articles for the market and not as essential foodstuffs for their own families. A striking example is the Danish farmer who produces butter for export and buys margarine for himself and his family.

It is sometimes a nutritional disadvantage when improved means of transport enable a primitive rural area to sell its produce to the towns, for then the milk, butter and eggs, which the peasant families used to consume themselves, are zealously kept for sale to the towns. For this reason, some of the most primitive parts of Europe have a higher level of consumption of animal foodstuffs than the more highly developed neighbouring areas. In some of the poorest mountainous districts of Greece, Yugoslavia and Slovakia, for instance, goat- or sheep-milk cheese is eaten regularly, whereas, in the less remote districts, the peasants who produce cheese sell it to the towns and go short of animal foodstuffs themselves.

Thus, apart from certain isolated areas where meat, fish or milk products are the most abundant foodstuffs, and where lack of transport facilities prevents a profitable sale of these products, the great majority of rural people sell most of the animal foodstuffs which they produce, and live on a diet largely composed of cereals and vegetables.

It is usually economic necessity rather than ignorance that prevents the peasant from consuming an abundant amount of the meat, eggs and milk which he produces. These foods are regarded as luxuries, and if a peasant family becomes prosperous, it will eat more meat and more eggs (and perhaps more milk, though, in many parts of Europe, milk is not considered as a normal food for adults). But, to a certain extent, ignorance is also involved; such valuable foodstuffs as whey and blood are wasted in some countries and consumed in others.

Another special feature of rural dietaries is the fact that there tends to be a much greater seasonal variation than in urban dietaries. Most rural dietaries depend on the supply of foodstuffs which are grown locally at any one time, and the diet is usually at its best in late summer and autumn when fruits are available and the supply of cereals, vegetables, and also of eggs and milk products, is most abundant. In the spring, the opposite is true, and, in the poorer rural communities in Central and South-eastern Europe, the diet may become drastically reduced as the supply of cereals, meat and vegetables runs out. It is at this time of the year that most ill-health due to deficient diet is seen, in the form of pellagra, scurvy, night-blindness, rickets and other deficiency diseases.

In most parts of Europe, the diet of the peasants in late summer and autumn tends to approach an ideal diet, especially in regions where milk is abundantly drunk. Fruits and fresh green vegetables are often eaten in adequate amounts during this short season of plenty, and eggs, cheese, milk and meat may be eaten regularly, especially during the harvesting season ; but, during the rest of the year, rural diets tend to be markedly deficient in fruit and in fresh green vegetables, as well as in animal foodstuffs.

In Balkan countries, the rural dietaries are still further impoverished during winter and spring by long religious fasts, amounting to 206 days in the year when strictly observed, when no animal foodstuffs are eaten.

There is one special advantage of rural dietaries over urban dietaries, and that is that rural people usually eat their food in a fresh and natural state. This is particularly important with regard to cereals, which are usually eaten as highly refined white flour in the towns, while, in most parts of Europe, the rural populations still eat whole-grain cereals.

The difference between refined flour and wholemeal flour (whether of wheat, rye or barley) is undoubtedly of considerable nutritional significance, especially in the case of the Central and South-east European peasants, for whom bread (or other forms of cereal food) forms the basis of the diet. Whole-grain wheat or rye flour provides at least twice as much minerals and vitamins as refined white flour, and these are the very factors in which most peasant diets are deficient. The loss of these essential substances during milling is less important in the case of abundant and varied dietaries, but it

would certainly be of grave significance in the more restricted rural diets.

Probably the worst feature of rural nutrition is the feeding of infants and young children, and of pregnant and nursing mothers. Infants are usually fed at the breast in rural areas for a longer period than in the towns, but in spite of this, rickets is found to be very widespread in most rural regions, whether in the Balkans, Central Europe, Scandinavia or Western Europe. This paradox seems to be due to deficiencies in the mother's diet, which is too poor to enable her to provide the child with sufficient minerals and vitamins. This may often be due to ignorance of the nutritional needs of pregnancy and lactation, so that even when milk, eggs, meat and vegetables are available, the mother does not know how important it is that she should have a more abundant share of these foods than usual. Amongst the slightly older children also, wrong feeding is probably more common in the country districts than in the towns, due to greater ignorance, as well as to lower purchasing power.

II. DEFICIENCY DISEASES

In most parts of Europe, too few exact dietary surveys of the peasant's dietary have yet been made to estimate directly whether the average intake of vitamins and minerals is sufficient to meet physiological requirements ; but manifestations of definite shortage of one or more vitamins are seen in the symptoms of deficiency disease which are frequently reported amongst the rural populations in many different parts of Europe. Cases of night-blindness and skin affections attributable to vitamin-A deficiency have been reported amongst rural communities in parts of Sweden, Norway, Finland, Czecho-Slovakia and Yugoslavia. This is seen particularly in the spring, when the diet is at its poorest. At the same time of the year, scurvy is often reported—for instance, in villages in Yugoslavia and Czecho-Slovakia—showing a deficiency of vitamin C in the diet.

Rickets is very widespread amongst rural children in South-eastern and Central Europe, and is probably due, not only to a shortage of vitamin D, but also of calcium and fats in the diet. It

has been found in Greece and Yugoslavia that the prolonged breast-feeding, which is the usual practice of peasant mothers, rather increases than prevents the amount of rickets in the children, showing that the diet of the nursing mother is seriously deficient.

In parts of Yugoslavia, where the women of the Mussulman communities live the traditional secluded life, cases of osteomalacia and osteoporosis are reported, indicating a very serious shortage of vitamin D and calcium in the diet, but these cases are probably most common in the towns.

Pellagra is found every spring amongst the peasants of certain large areas of Roumania, where maize is the staple foodstuff, and to a lesser extent it is reported in Yugoslavia and in Czecho-Slovakia. It has been shown in Roumania that it can be prevented by improving the dietary, and it therefore represents a condition of dietary deficiency.

In Hungary, where white bread is eaten by the peasants instead of wholemeal bread as in the Balkan countries, sporadic cases of beriberi have been reported amongst peasants, and it seems probable that some degree of vitamin-B₁ shortage is a common feature of the poorer Hungarian peasant's diet.

III. METHODS OF IMPROVING RURAL DIETARIES

There is no doubt that the nutritive value of rural dietaries could often be improved by education. The majority of rural housewives in Europe know little or nothing of the principles of nutrition, and they might frequently be able to feed their families more adequately if they knew the relative value of different foodstuffs. The importance attached to certain foods varies considerably in different countries. For instance, in Scandinavia, Finland and Latvia milk is known to be a valuable food and is drunk by old and young ; but in Greece and many parts of the Balkans milk is not regarded as a food for adults and is only given to very young children and invalids. Again, the Roumanian peasants do not usually bother to grow vegetables for their own use, while, in the same regions, Bulgarian peasants will cultivate and consume a variety of vegetables and thereby escape the pellagra from which their Roumanian neighbours suffer.

Through ignorance, there is often a serious wastage of potential foodstuffs in rural communities. For instance, in cheese-making districts in Britain the whey, if not required for pig-feeding, is often thrown away, while in some countries the peasants take home whey from the village dairies to use for cooking purposes, thus adding valuable minerals to their diet. In Hungary, the village abattoirs throw away the blood after slaughtering, whereas in parts of Czecho-Slovakia blood is made into sausages or consumed as blood soup. By education, such wastages of valuable foodstuffs could be prevented.

The consumption of fruits and vegetables could probably be increased considerably in most countries (with very great advantage to the nutritional value of the diet) by education in methods of growing and preserving them. Many rural communities have abundant supplies of fruit and vegetables at their disposal for a short season, and, having no knowledge of how to preserve them for winter use, they leave much of the crop to waste. For instance, in Latvia, the teaching of methods of preserving fruit and vegetables has enriched the winter dietary in many farm households, and, in Bulgaria, the Ministry of Agriculture has started a campaign for demonstrating in the villages very cheap methods of canning surplus fruit and vegetables for home consumption in winter. Education in the feeding of infants and growing children would also be of immense value in most villages of Europe, for it is here that ignorance is the greatest danger to health.

Many European countries have realised the urgent need for education with regard to rural nutrition, and a beginning has been made to instruct the rural housewife as to the dietary needs of her family, even in several of the relatively backward agricultural countries.

Apart from any improvement in the peasant dietaries which can be achieved by greater knowledge, there are whole areas in Europe where the peasants have not sufficient land to produce either all the foods their family ought to have or sufficient of a cash crop to enable them to buy an adequate diet. In such cases, some sort of planned assistance from the State is necessary if the nutrition of the peasants is to be made adequate for health. There are, for instance, parts of Yugoslavia and Sub-Carpathian Russia to which wagon-loads of cereals have to be brought each year to feed the

population, and paid work has to be provided in the form of road-making or some such State undertaking.

The methods used to help the peasant must depend on the individual State. In some cases, agricultural credit is given to enable the farmer to buy equipment to increase production ; in other cases, the agricultural producer may get relief from taxes, direct subsidies, family allowances, or free seed or stock from the State.

Relief is often given to destitute families in rural areas in the form of food, and many countries provide village children with free or cheap meals at school. But these relief measures only touch the fringe of the problem and offer no real solution. This can only be found in agricultural and economic readjustments, both national and international. This aspect of the problem of nutrition is very complex and has been dealt with elsewhere, as, for instance, in the Final Report of the Mixed Committee on Nutrition in 1937, which considered nutrition in relation to agriculture and economic policy.

IV. STUDIES OF RURAL DIETARY WHICH ARE BEING MADE BUT ARE NOT YET AVAILABLE

Great Britain.

(a) Ministry of Health survey : 500 families in rural districts in England and Scotland.

(b) Carnegie Trust Research survey, in urban and rural areas in all parts of the country.

Belgium.

Dietary surveys have been combined with tests for vitamin deficiency made on school-children in urban areas, and it is hoped to extend these studies to rural areas.

Finland.

Survey, giving some information on nutrition of 3,682 of poorest and largest families, made in 1936 (to be published shortly).

France.

(a) Family enquiry of 250 families in all regions.

(b) Survey of food habits of seventy groups in different classes and regions.

Hungary.

A survey is being made on the state of nutrition and the economic conditions in a village, with special reference to the inter-relation between the two.

Norway.

Dietary and state of nutrition survey in 250 families, some of which are in two small fishing districts, the rest in Oslo or neighbouring towns (to be published shortly).

Sweden.

(a) Study of vitamin-A intake in northern Sweden (to be published shortly).

(b) An investigation into diets of school-children will be made.

Yugoslavia.

(a) Nutrition diaries kept for one year in Vráčár (not yet published).

(b) Dietary surveys in six villages undertaken by Institutes of Hygiene of Belgrade and Zagreb.

(c) A study of nutrition of infants in rural areas was started at the beginning of 1938.

V. COUNTRIES IN WHICH DIETARY SURVEYS IN RURAL AREAS HAVE BEEN MADE

BELGIUM

A nutrition survey of school-children has been made by Dr. Madvan't Hof in the Liège district. Some of the children were from rural homes, some from coal-mining districts. Altogether 1,200 children, between the ages of 6 and 10 years, were medically examined and at the same time approximate knowledge of their home diets gained by questionnaires.

The diet of the children was found to be extremely ill-balanced. The intake of energy-providing foods was adequate, there being an excess of bread and potatoes, but the consumption of milk, milk products, eggs, vegetables and fresh fruit was markedly deficient. An interesting point was the excessive consumption of chocolate, which was given to the children to appease hunger.

The state of nutrition of these children was highly defective. Their weights were definitely below normal, so that compared with children of normal growth they were from one to one and a half years behind. Dental decay, rachitic symptoms and chronic infections of the nose and throat were frequent.

The survey is being continued, with special reference to vitamin-C pre-deficiency.

BULGARIA

It is estimated by the Institute of Agriculture of Sofia from studies made in 1935/36 that the average intake of the peasant is 3,400 calories, which is thought to be insufficient during heavy manual labour, such as harvesting.

The diet is usually very monotonous and consists chiefly of bread, the percentage of the total calories derived from flour being estimated as 72%, from meat and fats 10%, dairy products and eggs 6%, vegetables 5%, fruits 4%, alcohol 2%, and sugar and rice 1%. The result is that 76.6% of the proteins of the diet and 46.9% of the fats are of vegetable origin.

The average annual *per caput* consumption of foodstuffs in rural areas is given by the Institute of Agriculture as follows :

	Kilogrammes		Kilogrammes
Flour (or bread)	352.7	Preserved meat	1.3
(or nearly 1 kg. per day)		Fish	0.5
Rice	2.7	Lard	4.8
Macaroni, etc.	0.3	Vegetable oils	5.7
Sugar	2.0	Vegetables	109.3
Milk	67.6	Dried vegetables.....	13.3
Cheese	9.5	Potatoes	17.5
Butter	1.1	Fruit	24.0
Eggs (number)	71	Grapes	70.7
Meat	21.9	Wine	39.9
Poultry	4.3	Brandy	1.5

FINLAND

A dietary survey was made by Dr. A. I. Virtanen¹ on fifty-four families, comprising 375 persons of poorer class in nine communities,

¹ Report of Finnish National Nutrition Committee, 1938.

of which two were urban and seven rural, for ten days in spring 1936 and again for five days in autumn 1936.

Foodstuffs were weighed and samples were analysed at the Biochemical Institute of Helsinki. The state of health was also examined, enquiries were made as to previous ailments, and the subjects were measured, tested for vitamin-C adequacy by the Göthlin method (*i.e.*, capillary resistance test) and the hæmoglobin content of their blood was determined. The personnel consisted of advanced medical students and household instructors.

The energy, calcium, phosphorus, protein and vitamins A, C and B₁ contents of diets were calculated.

In January and February 1937, a similar survey was made of forty families of rather more well-to-do manual workers in sixteen different communities.

Results.—The investigation showed that the diet consisted of practically the same foodstuffs all over the country. The relative amounts of the different foodstuffs eaten averaged as follows : cereals 43%, milk and milk products 25%, potatoes 11%, meat 9%, fish 1%, sugar 6%, margarine 2.3%, vegetables, roots and fruits 1%, peas 1%. The following main points were noted :

1. The amount of food eaten was often too low in the poorest families.
2. When the calorific value was adequate, the protein intake was almost without exception sufficient, and of very good quality, since generally half was animal protein, and this mostly from milk.
3. The fat content was generally adequate, fat providing about 20% of the total calories.
4. Calcium and phosphorous intakes were regularly quite adequate (0.7 gramme calcium and 1.3 grammes phosphorus being taken as the daily requirement).
5. The vitamin-A content of the diet was generally adequate in summer (4,000 international units being taken as the adult requirement), due to liberal use of milk and butter, which supplied 50%-70% of the vitamin-A intake. From November till the end of May, however, the vitamin-A intake was inadequate, and it was found that the vitamin-A content of the winter milk and butter was only about a third of the summer content, due to stable-feeding

of cattle. (Analyses showed cow's milk to contain 2,000 international units of vitamin A per litre in summer, and only 700 international units during stable-feeding in winter.)

An attempt to remedy this defect in winter milk is already being made by changing the cattle feed by a method which preserves the carotene content of the fodder.

6. The vitamin-C intake was considerably better throughout the year than the vitamin-A intake, due to the use of fresh milk and potatoes. If 1,000 international units is taken as the adult daily requirement for vitamin C, then only 8% of the families had an intake of less than half of this in the spring, 2% in autumn and 3% in winter. In autumn, 87% of the families reached or exceeded the normal requirement; in winter, 70%; and, in spring, 50% (the decrease in vitamin-C intake in spring is due to lack of potatoes at that time).

The capillary resistance tests for vitamin-C adequacy were "in fairly good agreement with the nutrition investigations"—*i.e.*, probable vitamin-C shortage was seen in 11% of families in spring, 2% in autumn and 7% in winter.

7. For vitamin B₁ a standard requirement of 250 international units for both adults and children was taken, and the intake was found to be almost without exception sufficient. This is due to the fact that the bread is mostly wholemeal rye bread. As long as the consumption of sugar does not increase sufficiently to replace potatoes and bread, there is no fear of a vitamin-B₁ deficiency in the Finnish diet.

8. Vitamin-D deficiency is indicated by the prevalence of rickets in infants, and Baltic herrings and eggs are being recommended for pregnant and nursing mothers.

In general, it is interesting that, in spite of the very low consumption of green vegetables and fruits during half the year at least, the diet is sound, owing to the liberal use of milk and potatoes and whole-grain bread.

The chief defect to remedy is the low vitamin-A content of winter milk, and it would be valuable also to encourage the use of carrots in winter to increase the intake of pro-vitamin A.

Amongst the town people, milk and milk products have retained their important position in the diet. For example, in Helsinki, the

per caput milk consumption is 0.65 litre, compared with about 1 litre in the whole country. The butter consumption is about 10 kilogrammes per year and could be increased.

HUNGARY

The Hungarian National Committee on Nutrition, in its report for the year 1937/38, draws certain conclusions as to the dietary of the peasant population, based on considerations of some twenty dietary surveys made by different workers since 1926. These surveys cover 40,500 people, and, although in most cases the surveys were not made to give exact quantitative information, the indications which they give agree with those shown by the statistical estimations of food consumption.

From these two types of estimation, it appears that the rural dietary consists mainly of highly-milled white wheat flour and of legumes. The consumption of milk, eggs and meat is very low, and the diet of the poorer peasants and landworkers is markedly deficient in energy value, animal proteins, minerals and vitamins. The chief mineral deficiencies seem to be of calcium and possibly of iron, while, in the case of vitamins, a general polyhypovitaminosis is very probable with an especial shortage of vitamin-B complex, and of vitamins C and D during the winter months. A substantial increase in the production and consumption of milk, eggs, meat, green vegetables and fruit is needed to make the average peasant's diet adequate to meet his nutritional requirements.

Only two exact dietary surveys have been made amongst rural families, one in the district of Gödöllő (near Budapest) and the other in Komlo in the Comitatus Baranya. The former was made in 1928/29 on seven families, and the following values were found for the intake of different food factors—calories from 1,878 to 4,467 per head per day, protein from 61.7 grammes to 138 grammes (of which, animal protein from 4.6 grammes to 63.7 grammes), fat from 37 to 88 grammes and carbohydrate from 288 to 766 grammes. It is obvious that the minimum values found are grossly inadequate, and these represent the diet of the poorer agricultural labourers.

In this survey, it was found that from 62%-81% of the carbohydrates of the diet was provided by bread and flour, only 3%-14%

by potatoes, and 2%-5% by green vegetables, 1%-4% by dry vegetables and 4%-21% by fruit in the fruit season. The consumption of fruit was in proportion to the family income, while that of green vegetables was very low in all seven families. Bread formed the chief foodstuff in all families, but the average daily consumption was only 277 to 375 grammes per head, so that even the energy value of the diet was too low.

It seems that the consumption even of bread is not sufficiently high to ensure an adequate calorie intake except amongst the richer peasants, where 750 to 1,000 grammes are eaten daily.

From the Komlo survey, it appears that the labourers' families investigated had a better diet than those in Gödöllő, the calorie, protein and fat intake being adequate in all cases. This difference may have been due to the time of year at which the surveys were made or to a difference in the degree of poverty of the families investigated, which varies greatly with the number of children in the family. The greatest difference in the diets of the poorer and more well-to-do rural families appears to be in the fat and animal protein intake (and probably in the mineral and vitamin intakes, which were not estimated).

Less exact surveys of peasants' diets have been made on much larger numbers of families. The largest of these wider surveys, made by the questionnaire method, was carried out in May and June of 1934 on 5,215 families (80% of which were agricultural) in the Comitat Csongrad.¹ This survey showed that there was a great deficiency of milk in certain parts of the country and not in others, while a complete lack of fresh vegetables and fruit was found in other parts. Thus 16% of the families had practically no milk at all and 19% were short of it; 18% had no meat at all, 45% had no vegetables and 43% no fruit.

An investigation was made in Békés in 1936, as a result of the occurrence of some cases of beriberi, to estimate the vitamin-B₁ intake of the average peasant family.² The average dietary was found to consist of 84%-87% of carbohydrate, 3%-4% of fat and 11%-12% of protein, only 1% of which was animal protein. The daily vitamin-B₁ intake in relation to the calorie intake was estimated

¹ MÉSZAROS, G. : *Népegészségügy*, 1936, No. 4.

² GARAMVÖLGYI, K. : *Népegészségügy*, 1936, Nos. 10 and 15.

to be insufficient (according to Cowgill's standard) to afford protection against vitamin-B₁ deficiency.

The consumption of sugar in the villages has been the object of a special study, and it was found to depend on the amount of land owned by the peasant, the landless workers or owners of less than 5 acres consuming only 1.2-1.3 kilogrammes a year (in 1934/35) and those with 30-50 acres consuming 3.7 kilogrammes a year.¹

It seems certain that the diet of the children of agricultural workers in Hungary is gravely deficient, as the following two surveys show. In December 1935, the food of 1,186 school-children of 6 or 7 years old was recorded on two consecutive weekdays and one Sunday in a rural area of the county Fejér.² The diets were found to be not only qualitatively but also quantitatively inadequate. The percentage of children whose diet might be considered as adequate was 32% of the children of agricultural labourers with a one-year contract, only 8% of those of labourers without long-term employment, 27% of those of small-holders, and 23% and 25% respectively of children of labourers with some land of their own or artisans.

In February 1936, an investigation was made of the diets of 151 school-children of 6-12 years of age in the village of Csabacsüd.³ Only nine of the children were judged to be adequately fed, while forty-three had a diet which supplied sufficient calories but was deficient in quality, and the rest (ninety-nine children out of 151) had a diet which was both quantitatively and qualitatively inadequate. Of this last group, 40% were anæmic. Of all the children, 41% received no milk at all.

In general, it appears from the different surveys made¹ that most of the rural population consumes a very inadequate amount of all the protective foods. The consumption of vegetables and fruit is much too low throughout the country ; that of meat, eggs and animal fat is in proportion to the income of the peasant and is quite inadequate in the majority of families. The milk consumption

¹ DABIS, L. : Report to Hungarian National Committee for Public Nutrition, 1938.

² KELLER, A. : *Népégeszégügy*, 1936, 17, 455.

³ KRAJCSOVICH, P. : *Népégeszégügy*, 1936, 17, 906.

varies considerably from one part of the country to another, and in many parts is practically nil.

The basis of the diet, even of the more well-to-do peasants, is white bread and refined wheat flour, and, in the case of the poorer families, even the consumption of bread is insufficient to give the diet an adequate energy value. These poorer diets show a marked deficiency of calories, animal proteins, fats, minerals and vitamins, and, even in the better diets of the richer peasants, it is probable that the intake of minerals and vitamins is inadequate.

Relief work in the form of distribution of milk and sugar to the poorest mothers and children in rural districts is being extended. During 1937 and 1938, 23,000 children up to 2 years of age were supplied with 500 grammes of sugar a fortnight, the distribution being made by the health centres.

In 1939, it is intended to extend this distribution of sugar to the pregnant and nursing mothers of the landless agricultural and small farmer class.

In 1937, the Village Association of Farmers and Landworkers introduced a milk distribution campaign, and, with a grant from the Government and an equal sum from private sources, 123,000 litres of milk were distributed to 10,226 children in ninety-two villages, each child receiving 200 c.c. of milk for the first three months of the year. In 1938, this work is being continued and extended.

Distribution of free milk is planned to begin in October 1938 in 240 villages, where 23,000 children will receive 250 c.c. of free milk in the schools at 10 a.m. The children of slightly more well-to-do farmers can also receive milk for 3 fillér, and it is hoped that at least as many will buy milk as are given free milk. The cost of the free milk is borne half by the Government and half by local contributors.

For 1939, the Government has granted 2,500,000 pengö for milk relief, and the Secretary of State for Health has announced the following plan of distribution :

- (1) 32,000 pregnant and nursing women (from fourth month of pregnancy till sixth month of nursing)—half a litre a day ;
- (2) 34,000 infants up to 3 years—half a litre a day ;

- (3) 40,000 children from 3 to 5 years— a quarter of a litre a day.
- (4) 80,000 children from 6 to 11 years—a quarter of a litre a day for five months of the year.

The recipients of this free milk will be from families whose earnings are *less than 400 pengő a year*, and it is reckoned that 10 % of all such families will be thus supplied.

The Committee is aware that these relief schemes do not solve the problem of under-consumption of milk in Hungary. To do this, the production of milk must be increased at least 130%.

The distribution of free meals to 4,050 children of very poor families for seventy-five days in winter was organised by the Green Cross Public Health Organisation in eleven rural districts. The meals consisted of 300 c.c. of milk in the morning and a lunch at school of thick soup, a vegetable dish (occasionally with meat) and a dish made with flour.

A feeding experiment has also been started in the county of Békés where 130 village children will receive free meals for several years and the effect on the state of health will be studied.

LATVIA

Although no dietary surveys have been made in rural areas in Latvia, the rural dietary may be judged from the figures of the State Statistical Bureau given in a report of the Latvian National Nutrition Committee, which are based on 128 farm account books. It is seen to be exceptionally rich in animal foodstuffs, especially in milk. The average consumption for 128 farms in 1936/37 was 356 kilogrammes of whole milk and 325 kilogrammes of skim-milk per consumption unit per year. This means a consumption of about a litre per day per consumption unit of both skim-milk and whole milk. Much of the milk is taken in the form of milk soups and of curds, and at every meal, in the summer especially, some form of milk is taken.

The consumption of meat is also much higher in farm households in Latvia than in most other agricultural countries. For 1936/37, the average annual *per caput* consumption is given as 61.3 kilogrammes per consumption unit for the whole country, and for the

different provinces, the figures are : 82.3 kilogrammes in Vidzeme, 97.2 kilogrammes in Kurzeme, 102.5 kilogrammes in Zemgale and 59 kilogrammes in Latgale. The consumption of butter is about 11 kilogrammes per head per year, and the consumption of white cheese is also said to be high, although no figures were given in the report mentioned.

The rest of the diet is made up of black rye bread, of which $\frac{1}{2}$ to 1 kilogramme per head is eaten daily in the farms, with wheat bread once or twice a week, and with a high consumption of potatoes. Peas, beans and cabbage are also eaten regularly and tomatoes are becoming increasingly popular in summer. The consumption of fruits is said to be increasing rapidly but no reliable figures are available as to the present level of consumption. The rural dietary appears to have improved considerably in the past ten years, and it is now at a level far above that of most agricultural countries. The steady consumption of milk and milk products, meat, black rye bread, potatoes and other vegetables may be expected to ensure a diet which meets the physiological requirements of the population. It is not yet known, however, to what extent all farm households in Latvia reach this high standard of nutrition.

Furthermore, to safeguard the health of children of agricultural workers, the Government has recently allotted to each agricultural worker's family a monthly grant for each child up to the age of 10 years.

The Ministry of Agriculture has initiated another practical measure to improve rural nutrition by organising the transport, in State-owned lorries, of sea-fish from the coast to inland regions to enable the whole population to consume more fresh fish.

The feeding of children in schools is also organised, so that, in all schools, the children have a hot lunch every day. In the schools in Riga, the price of the lunch is only 16-17 centimes and it is given free to children of poor families.

Agricultural production of all kinds has increased considerably since 1929/30. The Government has done everything to stimulate production by protecting the home market from foreign competition, by fixing prices, by supplying farm machinery and fertilisers at low prices, and, finally, by organising courses of instruction for farmers.

NETHERLANDS

From surveys made in the Netherlands, the following facts are reported :¹

1. There are 234,145 farms of which 110,646 have less than 5 hectares. The measures which are required to assist them are financial credit in case of farms able to support a family, and the provision of supplementary employment for those which are too small to support a family.

2. As the number of consumption units per family falls, the amount spent per head on food rises and the intake of animal protein, fat, carbohydrate, carotene and vitamin C also rises, due to increased consumption of milk, cheese, eggs, meat, fish, animal fats, vegetables and fruits. The consumption of bread, beans, potatoes and plant fats and oils is almost constant in all families.

3. The level of the general death rate for the whole country is very satisfactory, being only 9.5 per thousand in 1925-1934, but the death rate is slightly higher in rural areas than in towns.

4. The rural dietary is more monotonous than the urban, and may contain too little vitamin A. Less fruit is eaten in many rural communities than in the towns, but potatoes provide ample vitamin C. Rickets is frequent in rural areas, perhaps because preventive treatment for children is less well organised in the country than in the towns. There may also be a shortage of iodine in some parts.

5. From a survey of forty-two persons for twenty-eight days in Westzaan in 1931, it was found that a Westzaan peasant stockbreeder consumes 1 litre of milk, 355 grammes of bread, 334 grammes of potatoes, 149 grammes of vegetables, 79 grammes of meat, 59 grammes of butter, 43 grammes of other fats, 33 grammes of cheese, 48 grammes of eggs and 70 grammes of sugar per day. From a study of eighty-six peasants in Groningen, which is a crop-growing region, a peasant was found to eat more potatoes (579 grammes a day) and less milk (590 grammes) and less butter (7 grammes) a day than the stock-breeding peasant in Westzaan. The amount of

¹ Report of Netherlands National Nutrition Committee, 1938.

bread eaten in both town and country seems from this survey to be remarkably constant, being from 318 to 380 grammes per head daily.

NORWAY

In 1933, a survey was made of the diets of 301 families of small means for a period of four weeks in May and June. The families were mostly living in the country or in small industrial districts in South-east Norway; sixty-five were self-supporting, 132 received some relief and 104 were dependent on relief. The diet was very monotonous, especially in families on relief when it consisted of skim-milk, salt bacon, salted herring, cereals, potatoes and sugar.

The family coefficients of Cathcart and Murray are used to calculate calorie intake. The average for all families was 2,646 calories net (3,004 gross) with limits of 4,626 and 1,223. For ninety-two families on full relief, it was 2,282 calories; for 129 on part relief, 2,646 calories; and for sixty-two self-supporting families, 3,110 calories per man daily.

Of the families on full relief, those which received the lowest grant absorbed only 1,760 calories and those with the highest grant 2,920 calories per man value.

Families with the secondary occupation of potato-growing consumed 300 calories per man value more than others; those which kept a cow consumed 600 calories more than the rest.

When thirty-two families on relief became self-supporting, their expenditure on food increased 23% and the calorie intake by 12%. The average daily protein fat and carbohydrate intake of all families was 64.9 grammes of protein (of which 32.2 grammes were animal protein), 79.1 grammes of fat and 401.1 grammes of carbohydrate per man value. (This is poorer in animal protein and fat and richer in carbohydrates than in previous Norwegian surveys.)

The intakes of total protein, fat and carbohydrates all rose with the incomes of the families in about the same proportion, while the proportion of animal protein rose more sharply with increase in income. Where relief grants were higher, much more fat was eaten and slightly more protein and less carbohydrate.

The average mineral intakes per person per day were 0.86 gramme of calcium, 1.10 grammes of phosphorus, and 5.38 milligrammes

of iron. The values were considerably higher for the self-supporting families, and somewhat higher for those on partial relief than for those on full relief.

The calcium intake was considerably greater amongst families which kept a cow, because more milk was drunk.

With increase in relief grants there was a distinct increase in phosphorus and iron intake, and to a lesser extent in calcium intake.

Milk intake averaged 314 c.c. whole milk and 211 c.c. skim-milk per man value per day with great variations ; fifty-three families had no whole milk at all in four weeks.

Meat and fish intakes were 27.1 grammes and 41.8 grammes respectively per man value per day, which is very low. The variations were great : eighty-one families used no meat in four weeks and thirty families no fish.

Fat intake averages 73 grammes per man value, but in the families which received relief in kind, it was much lower, fats only supplying 12.1% of the calories.

The consumption of eggs averaged 14 grammes per day, but the fluctuations were great : 118 families used no eggs during four weeks, and others ate more eggs than fresh meat and fish.

Almost all the families showed an extremely low consumption of fresh vegetables and fruit. Potato consumption was fairly high though variable, the average being about 391 grammes per man value per day.

The bread consumption was very low, averaging only 69.6 grammes per man value per day, while that of flour and groats was high, 313 grammes daily.

Sugar intake averaged 51 grammes, which is below the national average consumption of about 94 grammes.

Animal foods supplied only 21.2% of the gross calories of the diet. Margarine supplied 14.3%.

The foods which increased in consumption as the family income rose were whole milk, cream, butter, cheese, fresh meat, blood and glandular organs, fish, bacon, eggs and dried peas and beans. Increase in the number of children in the poorer families caused increase in consumption of flour and potatoes and groats, and a fall in that of fish, bacon, margarine, bread, fresh vegetables, sugar, syrup and coffee.

The families which received relief in cash bought more protective foods than those on relief in kind, but the intake of calories and of the different food factors was too low. It is clear that relief, whether in cash or in kind, is not enough for a satisfactory diet. The grants allowed for extra children are also insufficient, so that the larger the family, the more deficient the dietary.

ROUMANIA

A dietary survey was made¹ in 1936 on fifty families of agricultural workers in Dragus and twelve families in Cornova. It was found that 83% of the total calories of the diet came from vegetable foodstuffs, of which 75% came from cereals (32% from wheat and rye and 43% from maize). Only 17% of the total calories came from animal foodstuffs, 11% from meat and 6% from milk and milk products and eggs. The proteins from animal origin were about 22% of the total proteins, while 35% of the total protein was from maize and 34% from wheat and rye. Of the total fat eaten, 79% was of animal origin, 38% from meat and 21% from milk and milk products and eggs.

The diet was very monotonous, and although more milk was drunk in these villages than in many parts of Roumania, the diet consisted mostly of cereals. The consumption of sugar was very small, providing less than 1% of the total calories.

The peasants eat very little meat, but, at Christmas, nearly every family kills a pig. As they do not as a rule take the trouble to salt or to smoke the meat, it is quickly eaten. The lard is used to a certain extent together with vegetable oils (sunflower) in the preparation of plain dishes. Those peasants who live near rivers also eat a certain amount of fish.

In the report of a dietary survey made in Moldavia in 1935,² it is said that "the basis of the diet of the Moldavian peasant is whole-grain yellow maize. The maize is ground between two revolving stones, often in primitive hand-driven mills, and subsequently put through a fine sieve, to remove gritty particles, and

¹ GEORGESCO, D. C. : Institut social roumain of Bucharest.

² AYKROYD, W. R., ALEXA, I., and NITZULESCU, J. : *Arch. roum. de path. expér. et de microbiol.*, 1935, 8, 407.

made into a pudding, usually eaten hot, called "mamaliga". The rest of the diet is largely made up of small quantities of green and root vegetables, beans and cheese. Wheat bread is rarely eaten.

For the rest, fish is eaten at certain seasons of the year, and a small amount of cheese. Milk consumption is very low, except for a short period in spring and summer, when the children drink rather more than usual. Very few vegetables are grown.

The religious fasts which are observed still further impoverish the diet. Every Wednesday and Friday are fast days, and no animal foods except fish may be eaten. During the Lent fast of seven weeks, animal foods are not eaten at all, except for fish on certain days. During Passion Week, even vegetable fats are not eaten. The six-week pre-Christmas fast is similar in severity, and the two summer fasts of two weeks each are less severe and not observed by all. Children under 10 do not usually fast, and indeed their diet tends to improve at these times as more milk and eggs are to spare for them. More than half the families studied, however, consumed no milk.

The energy value of the diet was high, even in winter, when the activity of the peasants is much reduced. The protein intake was in excess of 100 grammes per day, but 60% of this protein was derived from maize, and the proportion from animal foods was about 20% during most of the year and only 3%-4% during fasting seasons. The carbohydrate intake was high, but the fat intake low. The calcium intake was low, the phosphorus and iron intakes apparently adequate. There was a probable shortage of vitamins A, D and B₂ in the diet.

In a more recent survey¹ on four families, a similar picture of the peasants' diet was given. The average amount of maize eaten daily was 1½ kilogrammes, increasing to 3 kilogrammes in the summer, when very strenuous work was being performed. Bread was only eaten on special occasions, at the most on twenty days in the year. The food which was second in importance in the diet of all families was beans. Potatoes, carrots, cabbage and beetroots were also eaten, but to a lesser extent. The consumption of sugar was

¹ Dr. ENESCU and Dr. RADENSCHI : *Revista de igiena sociala*, 1937.

extremely low, only 1-1½ kilogrammes a year being consumed by a family of ten in two cases.

The milk consumption was from 400 to 600 litres per year for families of from five to ten persons, giving an average daily consumption of 240 c.c. in the smallest family and 115 c.c. in the largest. The meat consumption was from 30 to 78.5 kilogrammes a year per family, or 12 to 23 grammes of meat per day per person. Eggs were very rarely eaten.

The vitamin content of the diet appeared to be very low from November till Easter ; in summer and autumn, it was definitely better.

The younger children especially, were found to be very under-nourished, while the adults were shown to lose 10%-15% of their body weight during agricultural work.

SWEDEN

At the instigation of the Board of Health, investigations have been made¹ in Norrland to trace the connection between frequency of gastro-intestinal disorders and the diet of the coastal population who live on a lacto-cereal diet.

From examinations of 4,500 adults and 1,200 children in Umeå Hospital Clinic, and 2,500 regional examinations from Västerbotten and Norrbotten where whole villages were examined, achylia and anæmia were found to be more frequent in North Sweden (Norrland) where the diet is chiefly of cereals and milk, while ulcers and colitis were more common in Southern and Central Sweden, where the diet is predominantly of meat.

The achylia in men was often caused by chewing snuff rather than by diet. A reduced basal metabolism was also seen in these cases on lacto-cereal diet, and also " an increased tolerance to glucose tests as well as the ordinary pharmacodynamic tests with injections of adrenalin, pilocarpin, and atropin, pointing to a reduced activity of the endocrine apparatus ". On the other hand, the lacto-cereal diet seemed to produce considerably less gout and diabetes than the mixed meat diet, less heart complications and less obesity.

¹ *Acta Medica Scandinavica*, 1934, Suppl. LIX.

The diet was weighed in forty-five cases of patients in Umeå Hospital and the following values found :

	Men	Women	Children
Calories	2,226-3,647	1,509-1,863	1,124-2,829
Calories (kilogramme body weight per hour)	1.5-2.53	0.92-1.14	1.23-3.1
Protein	66.2-122.9	45.7-66.3	31.2-100.4
Milk (grammes per day) ...	697-1,398	488-769	450-1,289
Potatoes	30-278	87-189	23-299
Flour	204-588	178-300	92-525
Iron (milligrammes per day)	17.5	11	15

The low calorie intake is surprising since these people have the possibility of eating more food, and they are engaged in agricultural work. It may be due to the lowered basal metabolism. This undernutrition disappears if there is an increase of meat in the diet, hæmoglobin values rise, achylia disappears and basal metabolism increases to a normal rate. The anæmia improves even more rapidly up to a point, with iron administration, but iron alone does not cure achylia, undernutrition and reduced basal metabolism.

Amongst forest-workers who take food from home to the forests, hypovitaminosis C is found, but in the coastal population living on milk, cereals and potatoes, there is no lack of vitamin C in summer, although in winter it might be expected to occur (no clinical evidence was found).

There is some evidence that a slight deficiency in vitamin A is widespread. In North Sweden, most of the objects tested were short of this vitamin.

Rickets in children is, however, very frequent, symptoms being found in 33%-67% of children in Västerbotten. No adult rickets, osteoporosis or osteomalacia are found, but dental caries is frequent.

Some shortage of vitamin B₁ is very probable from consideration of the diet, since the flour used is refined. Indeed it is suggested this may account for the reduced basal metabolism, achylia and undernutrition. Both analysis of the diet and the clinical symptoms suggest a hypovitaminosis B.

This monotonous lacto-cereal diet consists of barley bread or wheat bread of refined flour, butter, milk, potatoes and salt herrings as a flavouring, gruels of barley or wheat meal, some fruit soups

on Sunday, *very* occasionally boiled meat, with very little vegetable or fruits.

This diet is in great contrast to that of forest-workers in the same part of the country who live on pork and other meat, milk and potatoes and some game meat—that is to say, a predominantly meat diet.

Investigations were also made at Skane in Southern Sweden amongst the agricultural population, where the diet is more varied, consisting of meat three times a week, pork twice, herring twice, other fish once, one egg a day, cheese, fruit two or three times a week, potatoes and cereal dishes daily.

The diet of the industrial population in Boras in Västergötland was also studied ; this is even more markedly animal, consisting of meat and fish seven or eight times a week, pork once a week, fruit and vegetables three times a week, eggs seven times, and bread—mostly fermented rye and wheat bread.

YUGOSLAVIA

While the latest dietary surveys in Yugoslavia are not yet finished, a few isolated surveys have been made in the past, and from these some idea of the rural dietary can be obtained.¹

In contrast to the dietary in the towns, where animal foodstuffs predominate, village dietaries consist mostly of vegetable foods. There is considerable variation between the winter and summer diet, the winter diet being particularly monotonous and very inadequate from a nutritional point of view. The basis of the diet at all seasons is bread (made from whole grain wheat, maize, barley or rye, and, in winter, there is little else to eat besides bread and dried beans, with meat on feast-days and on Sundays in varying amounts depending on the degree of poverty of the peasant family.

From Christmas onwards, there is frequently a shortage of wheat for bread, and the peasant has to buy small amounts of wheat or maize and to kill his remaining pigs, so that the diet at this period is often very reduced in amount and consists chiefly of pig-flesh and bread. Vegetables and fruit are usually not obtainable at

¹ From the Report of the National Nutrition Committee of Yugoslavia, 1938.

this season, and any winter reserves of them which have been made are exhausted. Milk and eggs are scarce at this time of year and are usually sent to market. The food is cut down to two restricted meals a day, or even in the case of the poorest peasants to one meal a day, and the peasant family sleeps much of the time.

In spring, the diet usually becomes even poorer, because the pig-meat is finished and there are still no fruits and vegetables. The diet now consists of little more than bread (frequently maize bread) and beans, and it is at this period that outbreaks of symptoms of deficiency diseases are most commonly seen. From all parts of Yugoslavia, cases of rickets, night-blindness, scurvy, pellagra and anæmia have been reported in the spring. The diet is clearly deficient in proteins, fats, minerals and all vitamins during late winter and spring, and it is further impoverished by two fasts of six weeks each before Christmas and Easter.

The summer diet restores the health of the rural population as soon as sufficient fruit and vegetables can be added to the diet. There is, however, still a shortage of animal proteins and fats.

In autumn, the dietary is most satisfactory. Milk is now usually added to the daily food, and fruit and vegetables are eaten more abundantly. Meat and cheese may become part of the daily diet, and the protein requirement is often exceeded during this season of plenty. This is the period of hardest physical work for the peasants, so that the energy value of the diet is also at its highest level in summer and autumn.

In general, the rural diet in Yugoslavia may be said to be gravely deficient in animal foodstuffs, fruits and fresh vegetables, and frequently even in energy value in the winter and spring, while in summer and autumn, it is usually much more satisfactory.

There is, however, considerable variation between the diets of different parts of the country. Economically, there are three main types of village :

- (1) Those in mountainous areas, in which the chief food is barley bread, with oats and maize as subsidiary cereal foods, with a good deal of milk or cheese and very little meat ;
- (2) Those in the plainlands, where wheat, maize or barley is grown, and where the milk may be either consumed in the home or sold ;

(3) The sea-coast villages or villages near to towns, where the villagers can market their produce and can obtain employment in the towns from time to time. In such villages, refined foodstuffs such as macaroni and white bread are often eaten instead of the more nutritious whole-grain bread of the villages farther from the towns.

Apart from these types of village, there are the non-self-supporting areas in Montenegro, Herzegovina, Dalmatia, Bosnia and to some extent in Croatia and Slovenia, where 50% of the peasants have not sufficient food of any kind to last them till the next harvest. These areas do not produce 1 kilogramme per head per day of all cereals taken together (including animal fodder), and although this shortage of cereals is partly compensated by the production of potatoes in some districts, this is not sufficient to feed the population throughout the year. Cattle-raising and the cultivation of vines, fruit and industrial plants are not enough to make good the shortage, and State assistance in the form of cereals in return for labour on roads, bridges, etc., has to be provided each year, while those who cannot work have to be given cereals free of charge.

In answer to a questionnaire sent out to doctors in rural areas, in all parts of Yugoslavia, 2,371 cases of deficiency diseases were reported, of which 1,870 were said to be due to vitamin-D deficiency, 154 to vitamin-C deficiency, 103 to vitamin-B deficiency, and fifty-three to vitamin-A deficiency. It seems clear that a general shortage of all the vitamins frequently occurs amongst rural dietaries, and the poorer peasants in all parts of the country seem to be in constant danger of suffering from serious dietary deficiencies, more particularly in late winter and spring.

REPORT ON BREAD IN SEVERAL EUROPEAN COUNTRIES

At its twenty-seventh session (February 1938), the Health Committee adopted the following resolution :

" The Health Committee,

" Realising that the composition, and consequently the nutritional value, of bread varies considerably from country to country and even within the same country, so that nutritional surveys give but imperfectly comparable results :

" Resolves to undertake comparative studies on this question. "

In accordance with this resolution, Dr. E. J. McDougall was entrusted with a study of the questions involved, and visited for this purpose a number of European countries (Bulgaria, Greece, Hungary, Latvia, Poland, Roumania, Sweden, Yugoslavia).

The following report was prepared on the basis of the studies thus made.

INTRODUCTION

Cereal foodstuffs are still the basis of the diet for the vast majority of the population of Europe and, of such foodstuffs, bread is infinitely the most important.

The practice of baking flour with some sort of leaven or crude yeast culture to make leavened bread seems to have been known since very early times in Asia, and the Romans knew both leavened and unleavened bread.

In Central Europe, bread-making seems to have been established at least as early as the eighth century ; Charles the Great, for instance, fixed the prices in his kingdom for wheat, rye and barley breads. In many towns, in the Middle Ages, the standard of baking for festival breads must have been quite high ; for instance, in Augsburg in 1276, the baking laws show that there were at least five sorts of bread in use : semmel bread, rye bread, mixed rye and barley bread and two kinds of brezeln. It is probable, however, that bread was not taken as an everyday food, except by the wealthy landlords, until much later. In the poorer man's house, cereals were cooked with water to form a gruel or porridge, or baked as flat dry cakes without leaven.¹

At the present time, the population of practically the whole of Europe eats its cereals chiefly in the form of bread, the only exception to this being in the maize-eating parts of Roumania, Italy, Yugoslavia and smaller areas of Bulgaria, Greece and eastern Czecho-Slovakia, where maize is eaten in the form of polenta, which is simply a stiff pudding of maize meal cooked with water.

In the Western countries of Europe—such as France, Britain, Belgium, Netherlands, Switzerland, Spain and Portugal—the bread is mostly wheat bread. In the countries of Northern and Central Europe, the bread is mostly rye bread or wheat and rye bread in about equal amounts. In the Baltic States and Poland and the western half of Czecho-Slovakia, rye is the chief bread cereal, and, in Scandinavia and Germany, wheat and rye breads are about equally important. In the Danubian Basin and most of Bulgaria, Greece and Turkey, wheat is the chief bread cereal.

TRENDS IN CEREAL CONSUMPTION

The trend of cereal consumption in Europe since 1918 seems to have followed certain principles. In the Western European countries as a whole, and in the towns of other European countries, the consumption of bread has decreased as the general purchasing power has increased.

¹ HINTZE, K. : *Geographie und Geschichte der Ernährung* (Leipzig, 1934).

There would seem to be several reasons for this decrease in the consumption of bread. First, the general increase in purchasing power has led to a greater consumption of the more expensive but more appetising foodstuffs—such as meat, fruit, dairy products, eggs, etc.—and thus less bread is needed to make up the energy value of the diet. The increase in consumption of such foodstuffs in Britain and other Western European countries since 1918 has been very striking, and a similar aspect of the same phenomenon is seen in the parallelism between rise in income and in consumption of meat, dairy produce, eggs, vegetables and fruit amongst industrial workers in Britain, Germany, Belgium, Sweden, Poland, Norway, Czechoslovakia and the United States of America.¹

Secondly, as more industrialised work takes the place of hard manual labour in Western European countries, the physiological need for energy foods is less than previously, and therefore the amount of energy food required has decreased.

A third reason for the decline in the consumption of bread in the industrialised parts of Europe, is the competition of sugar as a cheap energy foodstuff. The price of sugar has fallen to such an extent in the past fifty years that, instead of being a luxury for the few, sugar has become to be considered a necessity of life by even the poorest classes in the industrialised countries.

World production of cane sugar has risen from 9.8 million tons in 1893/94 to 29.2 million tons in 1930/31, and beet sugar has risen from 3.8 to 11.5 million tons in the same years.² The *per caput* consumption in France has risen from 1.33 kilogrammes in 1817-1821 to 24.6 kilogrammes in 1928/29; in Germany, it rose from 3 kilogrammes in 1850 to 26.1 kilogrammes in 1928/29 and, in Denmark, from 23.4 kilogrammes in 1900 to 56.1 kilogrammes in 1928/29. In Great Britain, it is estimated to have increased five times in the course of the past century.

This striking increase in sugar consumption must have effected adversely the consumption of bread, since both are essentially energy-providing foodstuffs whose function in the diet is to supply calories in an easily assimilated form.

¹ The Relation of Nutrition to Health, Agriculture and Economic Policy, page 240 (document A.13.1937.II.A).

² The Relation of Nutrition to Health, Agriculture and Economic Policy, page 108 (document A.13.1937.II.A).

Incidentally, it must be noted that this increase in the consumption of sugar at the expense of bread is to be deplored from the nutritional point of view. Sugar contributes no proteins, vitamins or minerals to the diet, while bread, even when it is white bread, supplies small but by no means negligible amounts of certain vitamins and minerals, as well as considerable amounts of protein.

A fourth reason for the decrease in bread consumption in the more advanced countries may be the propaganda in favour of the protective foodstuffs, and the spread of the idea that bread is a less valuable foodstuff than others which are richer in minerals and vitamins.

The decline in bread consumption is very little influenced by the retail price of bread.¹ In spite of fluctuations in price, bread remains the cheapest form of energy-providing food in most countries, so that the amount of bread which is eaten to make up the energy value of the diet depends on the amount of other foodstuffs which can be afforded, and therefore depends rather on the prices of other foodstuffs than on the price of bread itself. If the price of bread decreases, it is not more bread which is bought, but more of other foodstuffs such as meat, dairy produce, eggs, vegetables or fruit.

Apart from this tendency for the consumption of bread and cereals to decline as the standard of living rises, there is also a tendency in some of the countries in which the bread is made chiefly from rye to replace that rye more and more with wheat. This applies to the Scandinavian and Baltic countries, Poland, and, until the depression of 1924-1927, it applied also to Germany, Austria, Czecho-Slovakia and Finland. A similar replacement of maize (and other cereals) by wheat was taking place also in Roumania and Yugoslavia until the depression years, but, since then, there seems to have been a return to the cheaper cereals as the purchasing power of the peasants again decreased.²

In the Scandinavian countries, the consumption of rye has fallen more on the whole than that of wheat has risen, so that the tendency is for a decrease in the total amount of cereals eaten. The same is true of Finland and of Germany.

¹ Wheat Advisory Committee Report, 1938.

² The Relation of Nutrition to Health, Agriculture and Economic Policy, page 104 (document A.13.1937.II.A).

On the other hand, in certain poor agricultural countries such as Hungary, Bulgaria and Greece, the *per caput* consumption of wheat has risen steadily since 1914. This is probably due to a gradual increase in the number of peasants eating wheat who previously ate maize, and not to any increase in the total amount of cereals which the average peasant eats in these countries.

In general, therefore, it appears that the tendency is for a decrease in the amount of cereals eaten as the purchasing power increases and the possibilities for a wider choice of foodstuffs arises. This trend has been observable for from thirty to fifty years in the Western countries of Europe which have developed a higher standard of living. In the poorer agricultural countries of Central and Eastern Europe, the trend is already seen in the towns, but, amongst the rural population, a raising of the purchasing power would in many areas be more likely to increase than decrease the amount of cereals eaten (where this is below the optimal amount desired), or to increase the proportion of wheat used at the expense of maize, rye, barley or other cereals (oats, millet, buckwheat) which are at present the chief bread cereals of certain areas. In the poorest agricultural parts, a large improvement in standard of living would be necessary before any decrease in the amount of bread eaten might be expected.

THE NUTRITIVE SIGNIFICANCE OF BREAD IN THE DIETARY OF DIFFERENT COUNTRIES

The nutritional value of bread in the diet and the desirability of a higher or lower level of consumption of bread, depend entirely on the nature of the bread and the rest of the dietary. First, the actual cereal used is important in determining the nutritive value of the bread. Wheat and rye are about equal in food value, the average content of protein and of the different mineral elements in the whole grains being remarkably similar. Barley and oats are also very similar to wheat and rye in protein content and in the proportion of the different minerals, but maize has less minerals¹ and less

¹ SHERMAN, H. C. : *The Chemistry of Food and Nutrition*, 1933.

vitamin B₂ than wheat and rye,¹ and rice has distinctly less protein than the other cereals.²

The main function of bread and other cereal foods in the European diet is to provide cheap and easily assimilated energy value. Bread or some sort of cereal flour is the cheapest calorie-provider in most countries.³ In parts of Europe in which rye or maize is the chief cereal, wheat flour is often a relatively expensive foodstuff and may provide calories at greater cost than potatoes, sugar, legumes or other foodstuffs. But whatever cereal is grown in a country, that cereal is the cheapest energy foodstuff, whether it is wheat, rye, maize, barley or oats.

Besides being the cheapest source of energy value, bread and cereals are in many countries also one of the cheapest sources of vegetable protein. Furthermore, the proteins of cereals, although not of such high biological value as the proteins of milk, eggs, meat and fish, are of higher biological value than most other vegetable proteins; they are, for instance, superior to the proteins of legumes.⁴

There has been some discussion as to whether the biological value of maize protein is or is not inferior to that of wheat and rye, but, on the whole, experimental evidence seems to show no appreciable difference between the proteins of the three chief cereals of Europe.⁴

In the poorer agricultural countries of Europe, where bread is very much cheaper than other foods, and where bread or some form of flour forms at least 60% to 70% of the total diet of the peasant population, the proteins supplied by the cereal eaten are of great importance. In regions where very little milk or cheese is available, cereals provide the greater part of the total protein intake, the rest being supplied by beans and other vegetables and by what little meat or milk is consumed.

In the poorer families of the industrialised countries of Europe also, bread may become a very important provider of proteins. For example, in England the amount of protein provided by the bread and flour is about 20 grammes a day, which is 33% of the total

¹ AYKROYD, W. R. : *Biochemical Journal*, 1930, **24**, 1479.

² SHERMAN, H. C. : *The Chemistry of Food and Nutrition*, 1933.

³ The Relation of Nutrition to Health, Agriculture and Economic Policy, page 248 (document A.13.1937.II.A).

⁴ BOAS-FIXSEN, M. A. : *Nutrition Abstracts and Reviews*, 1935, **4**, 447.

that more of certain other foodstuffs would be bought and correspondingly less bread. In other words, the process of the replacement of part of the bread eaten by other more attractive foods is possibly complete in the well-to-do families, but is still continuing in the poorer households, which, of course, form the great majority in all countries.

In England,¹ however, it seems that this process of replacing bread by other foods has almost reached its limit, since the poorest sections of the population eat, on the whole, very little more bread than the higher income groups, although the consumption of other foodstuffs (notably of meat, eggs, butter, milk, fruit and green vegetables) in the wealthier groups is considerably greater. In the other industrialised European countries, the decline in bread consumption is likely to continue in the poorer sections of the population as the purchasing power increases further.

The bread of most of the industrialised countries of Western Europe is white wheaten bread. Since the introduction of roller milling in the past century made the production of white flour possible, it came to be taken as a sign of poverty to eat brown bread. Now, health propoganda in favour of brown bread is beginning to reverse the process, so that brown bread is becoming the bread of the wealthier classes ; but, in general, the great majority of people in the west of Europe still insist on white bread as a part of the modern raised standard of living.

This preference for refined white flour, which is devoid of the greater part of the vitamin and mineral content of the wheat grain, is greatly to be deplored from the nutritional point of view, and is believed by many nutrition experts to be the cause of much ill-health, principally as a result of a general sub-optimal intake of vitamin B₁.²

In spite of the nutritive deficiencies of white bread in comparison with brown, white bread does provide appreciable amounts of minerals and vitamin B₁ in a diet which is poor in these factors. For instance, it is estimated that bread and flour provide 18%–30.9%

¹ LLOYD, E. M. H. : " Food Supplies and Consumption at Different Income Levels ", *Agr. Economics Soc.*, 1936.

² STIEBELING, H. : *Diets of Urban and Village Families in U.S.A., 1914-1936*, 1936.

HARRIS, L. : *Vitamins in Theory and Practice*, London, 1935.

MULLER, H. : *Revue suisse d'hygiène*, 1935.

of the iron, 16%-30% of the phosphorus and 6%-15% of the calcium of the diets of different income groups in England.¹

In countries such as France and Belgium, in which the general consumption of bread is higher than in Britain, the proportion of minerals supplied by bread may be even higher.

It should also be noted that bread is often the cheapest source of protein as well as of carbohydrate,² and as such it is of great importance in the diets of the poorest sections of the population even in the Western European countries. The diets of the lowest income groups in many European countries have been shown by analysis to be deficient in proteins, minerals, vitamins and sometimes even in energy value,³ so that the fact that bread (even white bread) provides energy value, proteins, iron and vitamin B₁ cheaply and is of considerable value, in so far as it leaves more money to spend on foods rich in other essential factors.

Thus bread, in the countries with a relatively high standard of living, is primarily used as a source of carbohydrate, but secondarily also as a source of cheap proteins, minerals and vitamin B₁.

BELGIUM

Most of the bread eaten in Belgium is wheat bread. The annual human consumption of wheat is amongst the highest in Europe, being 7.16 bushels *per caput* in 1909-1914 and 5.97 in 1936/37.⁴ The average daily consumption of bread is said to be about 400 grammes.⁵

Belgian wheat is soft, with only 7%-9% protein, and only 10%-15% of the crop is used for human consumption, the rest being used for stock feeding or export. The law insists, however, that at least 10% of home-grown wheat be added in milling. The foreign wheats used are mostly from the United States of America, Canada, France and the Netherlands. Permits are required for importing grain or flour, and the imports are taxed.⁶

¹ ORR, J. B. : *Food, Health and Income*, 1936.

² HUTCHINSON & MOTTRAM : *Food and the Principles of Dietetics*, London, 1936.

³ The Relation of Nutrition to Health, Agriculture and Economic Policy (document A.13.1937.II.A).

⁴ Wheat Advisory Committee Report, 1938.

⁵ Information furnished by "La Maison du Peuple", Brussels. May 1938.

⁶ U.S. Dept. of Agriculture *Bulletin*, No. 535, 1936.

Milling is mostly done in large commercial mills. The chief grades milled are straight-grade flour of 70% extraction, long patent of 65% and short patent of 50% extraction ; about 80% of the flour is milled as straight-grade flour for ordinary bread-making, 15% is long patent for rolls and special breads, and 5% is short patent for cakes and pastries.¹

Bleaching, and the addition of chemicals to improve the baking quality or to make self-raising flour, is prohibited.²

At least 90% of the bread eaten is white wheaten bread. Some rye bread is made, but this constitutes not more than 5% of the total, while wholemeal wheat breads form only 1.4% of the total.³ The common breads contain no fat or milk, these materials being used only in fancy breads. Most of the baking is done in small shop bakeries with modern machinery. The quality and baking of the bread is amongst the best in Europe and it varies in form and texture in the different parts of the country.

FRANCE

Wheat is the chief crop in France and the principal bread cereal. A certain amount of rye is used in bread-making, but this is only of importance in a very few parts of the country.

The consumption of wheat in France is one of the highest in Europe, although it is decreasing steadily ; in 1909-1914, it was 8.07 bushels ; in 1930/31, 6.85 bushels, and, in 1936/37, 6.18 bushels³ *per caput* per annum.

The common bread is white wheat bread, but, except for rolls, extreme whiteness is not especially demanded. Bleaching was prohibited by law in 1933, and most of the bread is not absolutely white. In the country districts, it is usually greyer than in the towns.

French domestic wheats are deficient in baking strength with a low protein content averaging only 8%. They require the addition of strong American wheats ; but there has been a Government limitation for the past ten years on the amount of foreign wheat which can be milled, varying from 0% to 45% of the total. The

¹ U.S. Dept. of Agriculture Bulletin, No. 535, 1936.

² Information furnished by "La Maison du Peuple", Brussels, May 1938.

³ Wheat Advisory Committee Report, 1938.

usual mixture of wheats is 70% of domestic and 30% of foreign wheat. Durum wheat has also to be imported for the manufacture of alimentary pastes.

The degree of extraction to which flour can be milled is fixed by law—*e.g.*, in 1922, the maximum degree of extraction was 66%.¹

Milling is less standardised in France than in most other European countries. There were, in 1931, 5,482 roller mills (some very modern and many old and poorly equipped), 2,459 stone-buhr mills and 10,444 small wind- and water-power mills.

Baking is mostly done in commercial bakeries of the small shop type. Home baking is only practised in remote country districts. In many rural areas, the bakers exchange bread for wheat with the farmers and may give as much as 65 kilogrammes of bread for 80 kilogrammes of wheat. The small bakeries tend to be less sanitary than in Denmark and other Western European countries.¹

The French public demands very fresh bread and has a preference for long slender loaves. Most bakers use the same flours for pastries and for bread-making. Cake and pastry consumption is relatively high.

In smaller cities and in rural districts, bread is baked with sour dough instead of with yeast. Where yeast is used, the amount is usually 1%, the fermentation time three hours and the baking time thirty minutes at 250° C.

The retail prices of both common and fancy breads are fixed by councils in each district in which the milling and baking industries, the consumers and the Government are represented.

Alimentary pastes are used chiefly in the Mediterranean section of the country. Their consumption is said to have declined materially since 1930.¹

GREAT BRITAIN

The consumption of bread in Britain is not very high and has been decreasing steadily. In 1909-1914, the *per caput* consumption of wheat was 5.54 bushels ; in 1930/31, 4.86 and, in 1936/37, 4.69 bushels per annum.²

¹ U.S. Dept. of Agriculture Bulletin, No. 535, 1936.

² Wheat Advisory Committee Report, 1938.

The bread is practically all white wheat bread made from flour of 70%'-72%' extraction. The wheat is mostly imported, since British wheat is too soft to make good white bread. Milling is largely in the hands of a few large firms, and the industry has been rationalised to a great extent. Four classes of flour are milled :

- (1) Bread flour, from a mixture of strong and medium strength foreign wheats ;
- (2) Pastry and cake flour from soft home or foreign wheats ;
- (3) Biscuit flour almost wholly from British wheats, and
- (4) Household flour, either plain or self-raising, from soft wheats.

Within these classes of flour, there are different grades, or degrees of extraction, such as short and long patents of high extraction (60% and less), baker's grade, low grades and straight-run grades, the greater quantity of flour being milled to about 71% extraction.¹ A small amount of wholemeal flour is milled for brown and wholemeal breads.

It is a general practice in Britain to bleach the flour and to use various improving processes to improve the baking qualities. Bleaching is forbidden in many countries, but it has a certain advantage in a country in which the public insists on very white bread, as it allows a lower grade of flour (such as 72%) to be used and whitened, while otherwise a higher grade such as 64% extraction would be required. This has a nutritional significance, since 70% flour contains an appreciable amount of vitamin B₁, while 64% flour does not.² The bleaching processes (nitrogen peroxide trichloride, Beta gas or benzoyl peroxide) have been shown not to destroy the vitamin-B content of the flour.³

In most parts of Britain, bread is baked in bakeries rather than in the home, with the exception of Ireland and parts of Northern England where home baking is still the custom.

(It may be noted that the price of sugar in Britain is low and its consumption high, being 54.6 kilogrammes per head in 1935/36.)

¹ U.S. Dept. of Agriculture Bulletin, No. 535, 1936.

² SCHEUNERT, A. : *Ernährung*, 1936, 1, 53.

COPPING, A. M., & ROSCOE, M. : *Biochemical Journal*, 1937.

³ VELICH, H. : 1928 (quoted HRUCKA, F. : 1927), *Proc. First Internat. Congr. Flour and Bread Manufact.*, Prague, 317.

NETHERLANDS

The chief bread cereals are wheat and rye. Before the war, about three times as much rye as wheat was produced and about equal amounts of each were consumed. Subsequently, the production of wheat increased and that of rye decreased until, in 1934, more wheat than rye was produced, and, at the same time, the consumption of rye decreased, while that of wheat remained constant, so that nearly twice as much wheat as rye was used in 1929-1933.¹

Since 1931, the Government has adopted a policy of maintaining the price for domestic wheats considerably higher than the open market price for foreign wheats, restricting the use of imported flours, and, at the same time, legislating that a certain percentage (35% since 1933) of domestic wheat must be used in milling. This policy increased the wheat acreage to an extent not anticipated by the Government, and, as a restriction on production, the Government announced, in October 1932, that subsidies would only be paid when the area sown with wheat did not exceed 30% of the cultivable area of the farm.²

The domestic wheat is very soft, and needs the addition of hard foreign wheats for bread-making purposes. American wheats were mostly used up to 1932, but, since then, most of the foreign wheat used is from Canada and the Argentine, and, to a less extent, from Russia, Roumania and Australia.

The domestic wheat is good for biscuit-making and for wholemeal bread, owing to its excellent flavour.

Milling is done mostly in modern mills using German machinery. It is estimated that 27.7 million bushels of wheat and 2.1 million bushels of rye were milled in 1933 by the modern mills, while 1.3 million bushels of wheat were milled by the small country windmills, which make only wholemeal flour.

Chemical improving processes are widely practised.

Baking is mostly done in commercial bakeries and very rarely in the home. Most of the bakeries are of the small shop type and are widely distributed, so that practically every household in town or country is within reach of one.

¹ *U.S. Dept. of Agriculture Bulletin*, No. 535, 1936.

² *Wheat Advisory Committee Report*, 1938.

Since 1919, the sale of freshly made bread and rolls before 10 a.m. has been forbidden, and this restriction has led to the use in Rotterdam of a method of freezing bread, so that bread baked the day before can be sold in the morning before 10 a.m. This process, however, adds 20% to the cost of the bread and is therefore not likely to become general.¹

The baking mixtures used contain 1½% to 2% yeast, and for milk breads sufficient milk to give a fat content of 3% in the baked loaf. Fat is also added to some of the non-milk breads. The wheat bread is usually of excellent quality, much of it being milk bread.

The consumption of rye bread is about a sixth of the total bread consumption, while that of wheat bread amounts to a seventh.

PORTUGAL

The common bread is wheat bread, while rye bread is important in some provinces only. A considerable amount of wheat is also eaten in the form of alimentary pastes.

Most of the wheat and rye consumed is produced in Portugal. Since before the war, there has been a great increase in the production of wheat, from 11.8 million bushels in 1913 to 20.5 million bushels in 1934, while rye production has also increased from 2.3 million bushels in 1909-1913 to 4.8 million bushels in 1934.¹ The wheat is semi-hard and of medium baking quality. In recent years, an import duty on wheat has been fixed, and the quantity imported is controlled by the State. Imports of grain are only permitted when a deficit occurs, and the importation of wheat flour is entirely prohibited. Prices for domestic wheat are also fixed.

The level of consumption of wheat and rye together is very low.¹ *Per caput* wheat consumption was 2.01 bushels in 1936/37, which is lower than in 1922/23, when it was 2.41 bushels, but higher than 1909-1914, when it was 1.51 bushels.²

Milling is mostly done by modern roller milling. Bleaching and improving processes are forbidden by law.

The wheat bread is made from low-grade flours of 75%-80% extraction. The baking is mostly done in small bakery shops.

¹ U.S. Dept. of Agriculture Bulletin, No. 535, 1936.

² Wheat Advisory Committee Report, 1938.

The quality of flour to be used and the retail price of bread are fixed by the Government. The bread is usually baked with yeast, and is of greyish colour and frequently of very poor quality.¹

SPAIN

The bread in Spain is almost all wheat bread, but maize is eaten to a considerable extent in the form of porridge, especially in the north-eastern and southern provinces. Rye is also produced, but its production has been decreasing since the war, while the production of wheat has been increasing. About 20% of the home-grown wheat is durum wheat, and this gives the bread a good flavour but a hard compact character.¹

In the rural districts, old-fashioned stone-grinding mills grind most of the flour. In the towns, modern roller mills produce the bread flour, which is mostly low-grade flour of 75%-80% extraction. Bleaching is allowed, but is not much used.

The *per caput* consumption of wheat is high, although it has been decreasing since 1909-1914, when it was 5.62 bushels per year, till 1936/37, when it was 5.13 bushels per year.²

SWITZERLAND

Most of the bread is wheat bread with or without some rye in it. Pure rye bread is eaten regularly in only a few remote mountain villages (*e.g.*, Rhone valley) which are cut off by lack of roads from the baker's van. These villages are already decreasing in number.

The degree of extraction for wheat bread is fixed by law to be at least 70%, and, owing to the policy of taxing the production of offals, the extraction is usually kept up to 72%-74%.

The *per caput* human consumption of wheat is fairly high (5.02 bushels per annum in 1936/37) and has not decreased since 1922/23, when it was 4.54 bushels.² Since 1909-1913, the *per caput* utilisation of rye has decreased, while that of wheat has increased, so that the total consumption of bread has decreased.

Baking is mostly done in small shop types of bakery, and sour dough is used more than yeast in the smaller towns and country

¹ U.S. Dept. of Agriculture Bulletin, No. 535, 1936.

² Wheat Advisory Committee Report, 1938.

districts. Milk is used only for rolls and luxury breads. A considerable amount of durum wheat is milled to make semolina for alimentary pastes.

Switzerland produces 20% to 40% of the wheat required for home consumption, and imports hard wheats from other countries (chiefly Canada, the Argentine, the United States of America and the Union of Soviet Socialist Republics). The production of rye has decreased, while that of wheat has increased, since 1918, owing to the greater drop in the price of rye.¹

The Swiss Government is at present concerned in trying to ensure the consumption of all the rye produced, since, in many of the mountainous regions of Switzerland, rye is the only crop which can be grown successfully.

In order to prevent a rise in the cost of living, the Federal Council decided to put on the market a brown bread of good nutritive value of which the price should be in no case higher than the price of bread hitherto. The millers produced a so-called wholemeal flour of a mixture of four-fifths wheat and one-fifth rye, the degree of extraction being fixed at 82%-85%. A kilogramme loaf of bread made with this flour was sold at 5 to 10 centimes cheaper than ordinary bread. Although the Government had not made any special propaganda in favour of this bread, the consumption reached a level of 65% of the total bread consumption in the first month, falling however to 16.5% nine months later. At the beginning of 1938, its consumption was 15.8% and, at the end of the year, 11% of the total bread consumption. The new cheap brown bread has, in fact, only replaced the other brown breads previously eaten and has not replaced white bread to any appreciable extent.²

The consumption of sugar in Switzerland is high, but appears to be decreasing, being 47 kilogrammes *per caput* in 1933/34, 43 kilogrammes in 1934/35, and 36 kilogrammes in 1935/36. The retail price of sugar is lower in Switzerland than in most other countries, being 40 centimes per kilogramme in 1936.³

¹ Кӓсн : *Schw. Med. Wochenschr.*, 1937, 67, 394, 729.

² Verbal information from Dr. O. STINER, Federal Service of Health, Berne, 1936.

³ LICHT, F. O. : *Welt-Zucker-Statistik*, 1937.

The Northern European Countries.

In the Scandinavian countries, the common bread used to be rye bread, but there is a marked tendency for wheat bread more and more to replace rye bread. In Sweden, Norway, Finland, Latvia and Estonia, the increase in wheat consumption has continued steadily since 1909-1914, when it was 1.77 bushels per head per year, until 1936/37 when it was 2.55 bushels.¹ This increase in wheat consumption has been accompanied by a still greater decrease in rye consumption in Norway, Denmark, Finland and Latvia, so that the total consumption of bread in these countries is decreasing slightly. In Sweden, the decrease in rye consumption seems to have been balanced by the increase in wheat consumption.²

The consumption of sugar in the Scandinavian countries is, on the whole, high. Denmark has had the highest national *per caput* consumption in the world since 1931/32, when it was 56.2 kilogrammes, till 1935/36, when it was 55.9 kilogrammes. In Sweden, the consumption has been increasing steadily since 1930/31, when it was 41.2 kilogrammes, till the present time, when it is the third highest in Europe, 48.8 kilogrammes in 1935/36. In Norway, a level of 31.9 kilogrammes per head per year has been maintained since 1930/31. In Finland, the *per caput* consumption has increased from 24.5 kilogrammes in 1930/31 to 29.7 kilogrammes in 1935/36, while, in Estonia and Latvia, there has been a slight drop in consumption since 1930/31, from 29.2 to 25 kilogrammes and from 26.8 to 24.7 kilogrammes per head respectively. In all these countries, the retail price of sugar is relatively low, being equivalent in 1936 to between RM. 0.23 and RM. 0.36.³

DENMARK

Wheat and rye are the chief bread cereals. Before the war, rye consumption was greater than that of wheat but the two cereals

¹ Wheat Advisory Committee Report, 1938.

² "The Relation of Nutrition to Health, Agriculture and Economic Policy", document A.13.1937.II.A.

³ LICHT, F. O. : *Well-Zucker-Statistik, 1937.*

are now about equally important foodstuffs. The annual *per caput* apparent utilisation of wheat and rye was 4.7 and 9 bushels respectively in 1909-1913 and in 1929-1933 it was 6.4 and 5.6 bushels.¹ These figures do not represent human consumption, but they show the tendency for more wheat and less rye to be used. The *per caput* human consumption of wheat has been decreasing very slightly in the past twenty-five years ; in 1909-1914 it was 2.82 bushels per year and in 1936/37 2.46 bushels. Although no exact figures are available, it is probable, from the decline in *per caput* utilisation, that human consumption of rye has decreased even more than that of wheat. In 1934, the *per caput* consumption of wheat and rye flour was 45 and 43 kilogrammes respectively.²

The home production of wheat and rye is sufficient to supply about half of the requirements of the home market. The production of wheat increased 73% between 1909-1913 and 1929-1933, while rye production fell 42% in the same period, so that the production of the two cereals is now about equal—10.9 million bushels of wheat and 9.5 million bushels of rye yearly in 1929-1933.¹

Danish wheat is very soft, with a variable protein content and a high moisture content. Its baking qualities are poor, so that most of the home-grown wheat is used for stock-feeding ; in 1930, about 11% of the home crop was milled for human consumption and in 1931 about 4%.

There are at present no subsidies paid for wheat production and no fixing of wheat prices to encourage production, but, in 1933, the British and German import restrictions affected the Danish exports of dairy and live-stock products so seriously that import licences and tariffs on imported grain and flour were started in Denmark. It is possible that Denmark will have to increase her production of wheat and use more of her home crop for human consumption if her exports of other products decreases further.²

Wheat flour is milled as two general types, one for bread-making and the other for pastry-making and household use. The bread flour is made from a fairly strong mixture of wheats, such as 60%

¹ U.S. Dept. of Agriculture Bulletin, 535, 1936.

² "Workers' Nutrition and Social Policy", International Labour Office Report, 1936, page 225.

³ Wheat Advisory Committee Report, 1938.

Canadian Manitoba, 20% Argentine Plato and 20% Danish wheat, while the pastry and household flour is made from a mixture of soft and semi-hard wheats.

Wheat bread is more than three times as expensive as rye bread, the latter being the cheapest form of energy food in the Danish dietary.¹

Rye bread is mostly dark, compact, heavy and moist with a slightly sour taste.² It is made with rye flour of 90%-95% extraction, and it is often lightened by the addition of low-grade wheat flour. Fine rye breads are also made from flours of 85% and even of 70% extraction. All these rye breads are baked with leaven instead of yeast, with the exception of a malted rye bread (made of flour of about 90% extraction with malt extract added) which is baked with yeast.³

The wheat bread is mostly white bread made with high-grade flours of 60%-70% extraction. It is usually baked in the form of small loaves of light texture and very good quality. The baking mixture usually consists of 100 kilogrammes flour, 60-65 kilogrammes skim-milk, 1 kilogramme pure lard, $\frac{1}{2}$ -1 kilogramme salt, $\frac{1}{2}$ -1 kilogramme malt extract and 4 kilogrammes of compressed yeast.

A small quantity of Graham wheat bread and of whole-meal wheat bread is also made from flours of 85%-95% and of 100% respectively.

There is a fairly high consumption of pastries made with wheat flour, milk, egg-whites, sugar, butter, yeast and cardamom.⁴

The baking of rye bread in the cities is usually done in large co-operative bakeries, while, in the villages, it is baked in the same shop as wheat breads and pastries. The sanitary regulations are strict, and machines are used for preparing the dough, even in the smaller bakers' shops.⁴ Night labour between 8 p.m. and 4 a.m. is forbidden.

¹ "The Relation of Nutrition to Health, Agriculture and Economic Policy", document A.13.1937.II.A, page 249.

² Wheat Advisory Committee Report, 1938.

³ Information supplied by Professor FRIDERICIA, of the Institute of Hygiene, Copenhagen, June 1938.

⁴ U.S. Dept. of Agriculture Bulletin, 535, 1936.

NORWAY

Rye bread and mixed wheat and rye breads predominate in Norway, but there has been a steady decline in the production and utilisation of rye in favour of wheat during the past twenty-five years. In 1909-1913, the annual rye production was 973 thousand bushels and wheat production was 306 thousand bushels, and, in 1929-1933, the rye production had dropped to 486 thousand bushels and that of wheat had risen to 713 thousand bushels.¹ The annual *per caput* utilisation of rye in 1909-1913 was 4.9 bushels and of wheat 1.7 bushels, while, in 1929-1933, that of rye had fallen to 2.2 bushels and that of wheat had risen to 3.2 bushels.

Most of the wheat and rye consumed is imported, the home crop of both cereals in 1929-1933 constituted only about 8% of the total requirements.¹ The Norwegian wheats are fairly hard in texture but of low protein content and poor baking quality. Some work on variety improvement is being made by the State Grain Monopoly, which has had complete control of the cereal trade since 1928, but the climate is unsuited for the production of good quality wheat. Production is maintained, however, by the Monopoly fixing the price for domestic wheat considerably higher than that for foreign wheats, and guaranteeing to buy all wheat fit for human consumption offered by the farmers.

The flour-mills are obliged to accept the grain imported by the State Grain Monopoly, and to mill it according to instructions. The prices for mill products are fixed equally for the whole country, freight being paid by the Monopoly.

The State Grain Monopoly has an elaborate cereal-testing laboratory in Oslo to determine the best mixtures of wheats to suit the trade's needs. In 1931/32, the percentages of various types of foreign wheat purchased by Norway were as follows : Canadian hard red spring wheat 40%, Russian 28%, Argentine 19%, Danubian 8% and Australian 5%. These proportions vary with the price of the different varieties, and some of the wheat purchased is used for stock-feeding, so that these proportions do not exactly represent the milling blends for the production of flour.²

¹ U.S. Dept. of Agriculture Bulletin, 535, 1936.

² Statens Kornforretnings, *ing Beretning 3*, 1931/32, quoted by U.S. Dept. of Agriculture Bulletin, 535, 1936.

The relative amounts of the different grades of flour milled in 1931/32 were as follows : mixed wheat and rye (sifted rye flour of 67% extraction with 15% wheat), 209.6 million lb. ; wheat flours of 73% extraction, 157.2 million lb. ; unbolted wheat flours, 34.6 million lb. ; unbolted rye flours, 30.9 million lb. ; sifted rye flour of 60% extraction, 5.7 million lb. ; sifted rye flour of 65% extraction, 3.3 million lb. ; coarse flour (blend of 90% rye and 10% wheat), 7.6 million lb. The total amount of wheat and rye flour milled was about equal, 224.9 and 224 million lb. respectively.

These figures also show that the greater part of the flour used is milled to as high a degree of extraction as 67% in the case of rye and 73% in the case of wheat flour. The proportion of brown or wholemeal flours appears to be very small.

The bakers use these different grades of flour chiefly to make a mixed bread containing about 20%-45% of wheat flour and the rest rye flour. This is the type of bread most commonly eaten and it is half the price of pure wheat bread, the mixed bread cost 36 øre per kilogramme and wheat bread 78 øre per kilogramme on June 9th, 1933, in Oslo.¹

Hard cracker breads and flat breads made from rye meal are very popular, but sweetened breads, which are so popular in Sweden, are not much used in Norway.

Dietary surveys show a decrease in the amount of bread eaten by manual workers in Oslo from 1912/13 to 1927/28 from 162.3 kilogrammes to 135.7 kilogrammes per consumption unit per year, while the consumption of potatoes and sugar, the other two principal carbohydrate foodstuffs, rose from 79.5 kilogrammes to 98.8 kilogrammes and 20.4 kilogrammes to 25.4 kilogrammes respectively, and the consumption of meat, fish, eggs, vegetables and fruit all rose considerably.² It seems therefore that, in Norway, as in most European countries with a rising standard of living, the consumption of bread is decreasing as that of other foods increases.

The well-known "Oslo breakfast", which has been instituted in all board schools in Oslo, Bergen and Trondhjem for the school-children, consists of wholemeal wheat bread supplemented with

¹ *U.S. Dept. of Agriculture Bulletin*, 535, 1936.

² "Workers' Nutrition and Social Policy", International Labour Office Report, B. No. 23, 1936.

Until recently, much of the wheat and rye was imported, but, since about 1934, the wheat and rye crops are quite sufficient to supply the home market, and there is even an export surplus of wheat.¹

There is Government control of all imports and a milling quota for home-grown wheat has been fixed at about 90%. In 1935, the Government established a reserve of 100,000 tons of wheat, and, in 1937, some of this reserve was sold to lower the retail price. The prices for both wheat and rye are fixed.¹

The grades of wheat flour milled are generally the following : short patents of 45% extraction, long patents of 15% extraction, straight (0-74%), clear (50-74%) and low-grade of 70-74% extraction and " baker's " flour, which is a mixture of " clear " and " straight ". The proportions of the different grades produced by one of the largest flour-mills is reported to be as follows : for wheat—65% of patent flour, 5-8% of clear, 3.3% of low-grade, 4.6% of middling and 21.6% of bran ; for rye—52.2% of first quality flour, 19.9% of second quality flour and 25.8% of offals. Thus, most of the wheat flour is high-grade flour of up to 65% extraction. Clear and low-grade wheat flours are mixed with rye flour for mixed breads, clear flour being used with the lighter types of rye flour, and low-grade only with dark rye flour.²

The destination of the wheat flour is about the following : 66% of it is made into wheat breads, cakes and pastries, 25% of it is mixed with rye flour for the so-called rye breads, 8% is mixed with rye to make crisp breads and 1% goes into biscuit and wafer manufacture.²

The common breads are known as rye bread although they nearly always contain a considerable percentage of wheat flour, especially in the northern half of the country. Bakers are tending to add more and more clear or low-grade wheat flour to the common rye breads, and the proportion of wheat to rye in these so-called rye breads is now usually about 65% of wheat to 35% of rye flour.²

Baking is done in the home in country districts, but, in the towns, only the well-to-do households bake at home. The commercial bakeries are developing more and more on a factory scale. Most

¹ Wheat Advisory Committee Report, 1938.

² U.S. Dept. of Agriculture Bulletin, 535, 1936.

of the bread is hearth-baked, but pan-baking is increasing, owing to the higher percentage of weak home-grown wheat in the flour.

There is a considerable production of *knackebrod* or crisp-breads, some of which are exported. These crisp breads are made either from rye or from mixed wheat and rye flours containing some bran and germ.

Sweetened breads and Swedish pastries are very popular and their consumption is fairly high. White wheat breads are baked in long French loaves or in round loaves somewhat larger than an ordinary roll. Some black rye breads are also made. The general baking quality of all these breads is very good.

The trend in bread consumption is said to be downward, which may be due to the lowering of quality of the wheat breads owing to the restrictions on imports of foreign wheats, or to general economic circumstances.

It seems that the consumption of bread and flour amongst agricultural workers is higher than amongst manual workers in the towns, but, in both groups, the consumption has decreased from 1920 to 1933. For agricultural workers in 1920, the consumption per household of 3.3 consumption units was 562 kilogrammes (or 170.3 kilogrammes per consumption unit) and, in 1933, it was only 508.5 kilogrammes (or 154.1 kilogrammes per consumption unit).¹ Amongst manual workers, the annual consumption of bread and flour was 135.3 kilogrammes per consumption unit in 1914, 124.5 kilogrammes in 1923 and 100.5 kilogrammes in 1933, while the consumption of sugar, margarine, eggs, cheese and meat increased.²

LATVIA

Rye and wheat are the chief cereals of Latvia, and about twice as much rye as wheat is consumed. Up till 1930, Latvia imported about 30% of the cereals consumed; since 1932/33, it has been self-supporting. In 1930/31, after a very good harvest, the Government bought the whole rye and wheat crop at a fixed price and re-sold it to the flour-mills. This policy of fixed prices for wheat

¹ "Workers' Nutrition and Social Policy", International Labour Office Report, B. No. 23, 1936.

² "The Relation of Nutrition to Health, Agriculture and Economic Policy", document A.13.1937.II.A., page 135.

has been maintained, and has, in the past five years, so greatly increased the production of rye and wheat that Latvia has changed from a cereal-importing to a cereal-exporting country.¹

At the same time, there has been a steady increase in the consumption of wheat; the amount of white wheaten bread consumed, in relation to the total bread consumption, has especially increased both in towns and in the countryside in the past five years. The International Wheat Advisory Committee published the following figures for the consumption of wheat: 1922/23, 1 bushel, 1930/31, 2.67 bushels and 1936/37, 2.78 bushels per head of population per year. The total consumption of bread, taking wheat and rye bread together, has, on the other hand, been decreasing, especially in the towns, so that the proportion of wheat to rye is always increasing and is higher in the towns than in the countryside. The latest figures of the Ministry of Agriculture (1938)² show a consumption of 130 kilogrammes of rye and 65 kilogrammes of wheat per consumption unit for the rural population (1,239,939 people) and 60 kilogrammes of rye and 75 kilogrammes of wheat for the urban population (710,563 people). The rural population therefore eats twice as much rye as the town populations, but slightly less wheat. The retail price of rye bread is less than half that of wheat bread.

A certain amount of barley is also eaten in Latvia, but mostly not in the form of bread. An average figure of 70 kilogrammes per adult per year (or 200 grammes a day) for farm households in 1933/34 is given by the Government Statistical Office.¹

Rye and wheat flours are not mixed for bread-making. The bread which is most commonly eaten by the rural population is home-baked black rye bread made with flour of about 98% extraction. White wheat bread is baked once or twice a week in most farm households. This seems to be an established custom, so that farm workers expect white bread once a week.

In town bakeries, white wheat bread and breakfast rolls of the Viennese type are made with yeast, while the rye bread is made with leaven. Most of the rye bread made is black bread of about 98% extraction, and a small proportion is of the grey variety from

¹ Note from Latvian Government to the League of Nations Mixed Committee on Nutrition, 1936.

² Private communication of the Cereal Office of the Ministry of Agriculture, Riga, 1938.

flour of about 75% extraction. Since 1934, regulations have been issued as to the quality of flour and bread and it is forbidden to add bran and lower-grade flours in the making of bread.

The quantity of bread eaten in farm households varies from $\frac{1}{2}$ to 1 kilogramme per head per day; the average given by the Government Statistical Office for 1933/34,¹ from a large number of farm account books being about three-quarters of a kilogramme a day.

The general dietary of the rural population in Latvia is very much richer in animal products than the dietary of rural population in the South-eastern and Central European countries. It is particularly striking how much milk is consumed. In the larger farms, the usual summer allowance of whole and skim-milk is a litre a day per head for all farm workers. In some of these farms, at least one litre a day of whole milk was consumed; in others, half a litre of whole milk and half a litre of skim-milk or butter-milk. The average figures given by the Government Statistical Office for farm households for 1933/34 are 381 kilogrammes of whole milk per consumption unit per year and 317 kilogrammes of skim-milk. In children's homes and holiday colonies, nearly a litre a day of whole milk is allowed per child in the summer and in winter slightly more than half a litre per child. In a workmen's canteen, where 2,000 men working on a river-dam were fed, the consumption of milk was about half a litre of fresh whole milk per man per day.

As well as this exceptionally high consumption of milk, the farm workers of Latvia have a very much higher consumption of meat than Central and Eastern European peasants. The figure given by the Government Statistical Office for 1933/34 is 83 kilogrammes per adult per year (or 234 grammes a day). Meat is eaten two or three times a day in the more prosperous farm households.

The consumption of butter is also high, 30 grammes per head per day being an average figure for farm households. Cheese and sour curds are eaten frequently, and herrings are popular, although their consumption is tending to decrease as the consumption of meat rises.

¹ Private communication of the Cereal Office of the Ministry of Agriculture, Riga, 1938.

The consumption of potatoes is also fairly high, since they are eaten at nearly every meal. An average figure of about 760 grammes a day per adult is given by the Government Statistical Office for 1933/34. Peas, beans and cabbage are also eaten regularly, and tomatoes are fairly popular in summer. The consumption of fruit is said to be increasing steadily but there are no reliable figures for its present level.

The consumption of sugar per consumption unit for the whole country was 24.7 kilogrammes per annum¹ in 1935/36 (70 grammes a day), while, in 1927-1932, it was 28 kilogrammes. Sugar is a State monopoly and the Government is trying by propaganda to raise the sugar consumption.

Central and South-eastern Europe.

In the Central and South-eastern European countries, the proportion of cereals to other foodstuffs in the dietary of the rural population is on the average very much higher than in the west of Europe. In the Balkans and in Hungary, parts of Czechoslovakia and Poland, bread or other forms of cereal foodstuffs form the basis of every meal, and may supply as much as 90% of the carbohydrate content of the diet and 70% of the protein content. The daily consumption of bread in these countries is often 1 kilogramme or more.

The reason for this high proportion of cereals in the peasant dietaries is primarily poverty. Cereals are the cheapest food material, since more food value can be produced in the form of cereals (especially maize) per acre of land than in the form of other vegetable, or animal, products. The Balkan or Central European peasant, who has to keep himself and his family alive on the minimum of land, therefore lives chiefly on cereals, and the poorest live on maize, which is the cheapest of the cereals.

Another factor which has probably contributed to keep up the high consumption of cereals in all these countries is the very low consumption of sugar. As has been said before, in the more

¹ LICHT, F. O. : *Welt-Zucker-Statistik, 1937.*

industrialised countries, the price of sugar has fallen and the consumption risen enormously in the past fifty years, and this increased consumption of sugar must have contributed to the decrease in the consumption of cereals, since the need for carbohydrate foods has rather diminished than increased in recent years, as less manual work is performed.

In the Balkan and Central European countries, however, the price of sugar has been kept up artificially by the State to provide a source of revenue and to protect the home production of beet sugar. In Hungary, Yugoslavia, Roumania and Bulgaria, the retail prices of sugar are more than three times as much as in England, Switzerland, Belgium, Sweden and Denmark, where there is little or no tax on sugar. The *per caput* consumption and retail prices of the latter countries make an interesting comparison with those of the Central and South-eastern European countries. The following table gives the figures for 1935/36 (LICHT, F. O. : *Welt-Zucker-Statistik, 1937*) :

	<i>Per caput</i> consumption (raw value) Kilogrammes	Retail price per kilogramme (granulated sugar) in :	
		National currency	Reichsmarks
Great Britain	54.6	4½d.	0.22
Denmark	55.9	0.43 krone	0.24
Switzerland	36.1	0.40 franc	0.23
Hungary	12.1	1.28 pengö	0.94
Poland	11.2	1 zloty	0.47
Greece	11.2	16 drachmæ	0.38
Yugoslavia	5.4	13 dinars	0.74
Roumania	5.4	29 lei	0.72
Bulgaria	4.0	23 leva	0.70

There is therefore an obvious reason for the low consumption of sugar in the Central and South-eastern European countries. The price in these countries is too high for sugar seriously to compete with cereals as a source of carbohydrates in the dietary of the peasants, as it has done in the diets of the general population of the more industrialised Western European countries, where the price of sugar is lower and the purchasing power of the average worker is higher.

Apart from bread, the diet of the Balkan countries is usually very poor, consisting of beans, cabbage and small amounts of potato,

garlic or onions (and fresh vegetables and fruits only in summer), a certain amount of goat-milk cheese, very little meat, sometimes a small amount of milk, no butter and very rarely eggs. The diet is usually very monotonous and poorly cooked. It varies usually with the seasons, being much richer in fruits and vegetables and often in meat and milk in the autumn. In some parts, for instance in parts of Roumania and Yugoslavia, the amount of animal food-stuffs eaten during the short season of plenty in autumn may be even in excess of requirements with regard to proteins and fats, while, in the late winter and spring, the diet is practically devoid of animal foods. In the spring, the poorer peasants in these countries are often reduced to a diet of very low calorific value consisting only of a limited amount of cereal, dried beans and preserved cabbage. It is repeatedly stated that symptoms of dietary deficiencies—such as pellagra, rickets, scurvy and nutritional anæmia—are seen each spring amongst peasant families.

The energy value of the diet in the most parts of these countries is very much higher during summer and autumn, when heavy manual work has to be done, than in winter, when the diet is very reduced.

Another important dietary factor which the Balkan countries have in common, is the religious fasts which the Greek Orthodox peasants observe and during which no foods of animal origin may be eaten. The diet during the fasts usually consists of bread, beans, cabbage and perhaps potato, and vegetable oils, such as sunflower oil, for cooking. The fasts are very long and are usually very strictly kept; they consist of every Wednesday and Friday of the year, six to seven weeks fast before Easter, six weeks before Christmas, and four shorter fasts of eight or fourteen days during the year, when oil and fish are permitted. The fasts are kept even by quite young children and by pregnant and nursing mothers, and are almost certainly periods of deficient dietary and therefore a considerable physiological strain. During the fasts, the importance of the nutritive value of the bread eaten is even greater than at other times, since the other foods eaten are so limited in character.

The fact that certain symptoms of deficiency diseases are found amongst the peasant population of all these countries shows that the dietary is in some cases inadequate. It is probable that most of these peasant diets are just on the borderline of adequacy, so

that any slight decrease in the amount of food available in a household will result in deficiencies which produce visible symptoms. For instance, it is reported by the Institutes of Hygiene in Yugoslavia, Hungary, Czecho-Slovakia and Poland that rickets is prevalent amongst peasant children, which may well be due to inadequate amounts of calcium and fat in the dietary. Again, in Roumania and in parts of Yugoslavia, pellagra occurs in the spring amongst the peasant population of the maize-eating areas, and it has been shown (in Roumania) that this pellagra could be prevented by enriching the diet with wheat and animal foodstuffs. In the Bosnian villages, mild scurvy is often seen in the spring, indicating a lack of fresh foodstuffs in the winter dietary. In Serbia, night-blindness has been reported at Christmas time, and, in the spring-time, rickets, scurvy, nutritional anæmia amongst children and xerophthalmia and keratomalacia amongst new-born infants, showing deficiencies of vitamins A and C and of iron. In Hungary, cases of beriberi and also of nutritional anæmia have been reported from certain villages.

The general peasant dietary of these countries seems therefore to be inadequate (especially in late winter and spring) to give definite protection against certain deficiency diseases. Very few investigations of the state of health of peasants have been made, but when such symptoms of dietary deficiency diseases as rickets, scurvy, pellagra and nutritional anæmia are found in one region, it is probable that peasants living on very similar diets in other regions will also be in danger of suffering ill-health due to these same dietary deficiencies.

The general dietary conditions of peasants in Central and South-eastern Europe have, as we have seen, much in common, but although some form of cereal food is equally important as a source of carbohydrates (and also of proteins) in all these countries, the character of the cereal food varies from one country to another, and from one region to another within the same country. In most parts of Greece, Bulgaria and large areas of Roumania, Yugoslavia and Czecho-Slovakia, the cereal food is wheat bread made from wholemeal flour ground by stone mills and baked in earthenware ovens. Such primitive bread contains the whole nutritive value of the wheat grain, and must be a rich source of vitamin B₁, iron and phosphorus.

In other regions of Roumania, Yugoslavia, and to a lesser extent of Bulgaria, Greece and Czecho-Slovakia, the cereal food is maize, eaten either as leaven bread or as mamaliga or porridge. The maize grain is also crushed whole in stone mills, but the nutritive value of the whole maize grain is less than that of wheat as regards protein, minerals and vitamins.

A third type of bread, which is common in Czecho-Slovakia, Poland and parts of the Balkans is rye bread, which is usually made from stone-ground whole grain. Such wholemeal rye bread is very similar in nutritive value to wholemeal wheat bread.

In other parts of Yugoslavia, barley bread and bread made from a mixture of cereals is the common bread.

In all these countries, bread is made from the whole grain, whether of wheat, rye, maize or barley, but, in Hungary, the situation is quite different. The peasants have as poor a diet in Hungary as in any of the Central European countries, and yet the great majority use only white flour to make their bread. The resulting loss in minerals and vitamins is probably a very serious nutritional disadvantage, since there is little possibility for the poorer Hungarian peasants to compensate for this loss by eating sufficient of other foods containing these essential factors. The fact that the loss of vitamin B₁ does produce ill-health is indicated by the reports of beriberi in Hungarian villages.

BULGARIA

Wheat is the most important bread cereal in the country as a whole, but maize and rye are almost equally important in certain provinces. The relative amounts of each cereal eaten in the whole of Bulgaria are cited by the Ministry of Agriculture in a recent survey¹ as 74% of wheat flour, 8% of rye flour and 18% maize flour. In the mountainous provinces of Sofia and of Plovdiv (the southwest quarter of the country), there is a higher consumption of rye than in the other provinces; the proportion of wheat to rye flour consumed is 50% wheat to 36% rye (and 14% maize) in Sofia and 64% wheat to 28% rye (and 8% maize) in Plovdiv province. In the provinces of Burgas, St. Zagora and Shumen (the eastern half of

¹ Christina MOCHEVA : "The Bulgarian Village Agricultural Household during 1935/36", Sofia, 1938.

the country), the proportion of wheat flour consumed is 90% of total cereal consumption. In the provinces of Vratza and Pleven (the north-western quarter of Bulgaria) where the country is mostly plain-land, more maize is eaten than in the other provinces, while the consumption of rye is negligible (less than 0.2%); the proportion of wheat to maize flour consumed is 56% to 44% in Vratza and 76% to 24% in Pleven province.

Since 1934, the Government has had a monopoly of all cereals, and has fixed the retail price of bread and flour. The wheat prices are maintained above world prices but no attempt is being made to increase wheat production which is tending to decrease in favour of other crops, such as fruit and vegetables, cotton, hemp and flax. In spite of this the consumption of wheat in Bulgaria has increased considerably in the last 15 years. In 1922/23 the *per caput* consumption was 3.76 bushels and in 1936/37, 5.97 bushels.¹

The Directorate for the Purchase and Export of Cereals, which fixes the prices of cereals, has also established large granaries throughout the country, so that after a bad harvest the peasant can receive help in the form of cereals (either through the Agricultural and Co-operative Bank, or through the Public Calamities Fund).

The State is interested in improving the standard of bread, and the Ministry of Agriculture had a department for testing the bread-making qualities of new varieties of wheat which the State has introduced into the country.

The Government also largely controls the milling industry and has power to fix the degree of extraction of the flour milled. There are three principal grades of flour milled in the towns: No. 0, which is the most refined white flour and which consists of the first 8-10% of the content of the grain; No. 3 which consists of the next 10-60% of the grain; and No. 4 which consists of the last 5-6% of the grain. The highest grade flour, No. 0, is used for pastries, rolls, cakes, etc.; the No. 3 grade is used for white bread and No. 4 for brown bread. In Sofia, the relative amounts of these different grades milled by the largest flour-mills are as follows: 50% of No. 3 for white bread, 15% of No. 4 for brown bread and 10% of No. 0 for pastry.

¹ Wheat Advisory Committee Report, 1938.

It is clear from these figures that the majority of bread eaten in the towns is white bread. The Ministry of Agriculture estimates that 80%-90% of the city people eat white bread, and since the brown bread is cheaper, it is probably the poorest 10%-20% who eat brown bread. A small amount of pure rye bread is also made in the towns as a speciality.

Some of the very small towns eat white bread also, while others eat mostly the brown country bread.

In Sofia, the army bread is made in a special military bakery, and the flour used is brown wheat flour. The allowance per soldier is 1 kilogramme of bread per day.

The retail price of white bread in Sofia is 5 leva per kilogramme, and brown bread is slightly cheaper. Maize flour is about half the price of wheat flour. Sugar is 22 leva per kilogramme.

The common country bread of most parts of the country is brown or wholemeal wheat bread. The wheat is ground between millstones in primitive watermills in the villages, and the peasants pay the miller 5% of the grain he mills for them. The flour milled is either 100% wholemeal flour, or flour from which the bran is removed—*i.e.*, a flour of 85%-90% extraction. In the large villages, roller-mills are often used instead of the more primitive stone grinding mills, and the peasants' flour is then usually milled to 82%-85% extraction, 15%-18% being removed as bran. The flour is in any case brown flour, containing a fairly high proportion of the mineral and vitamin content of the whole grain.

In districts in which rye is grown extensively, such as parts of the provinces of Sofia and Plovdiv, the bread usually contains a mixture of wheat and rye flour. Around Sofia, the wheat and rye are frequently planted together as a mixed crop and are therefore milled together. In some of the mountainous regions, on the other hand, rye is the chief cereal crop and the bread is then made of rye flour, often mixed with barley or with potato flour.

Where maize is the principal cereal food, it is eaten in the form of bread, not as polenta as in Roumania. The poorest regions where cereals have to be imported generally eat maize, while, in the wheat- and rye-growing districts, maize is considered to be the poor man's food, which is eaten only if the family has not enough wheat and rye to last them through the season.

The level of consumption of bread amongst the rural population is very high. The recent survey¹ by the Ministry of Agriculture on 936 farm households from different parts of the country shows that an average of 72% of the energy value of the diet is provided by bread and flour. In contrast to this, meat provides only 10%, dairy produce and eggs 6%, vegetables 5%, fruits 4%, wine and spirits 2% and sugar and rice only 1%. The average quantities consumed per year per consumption unit are given as follows: bread and flour 352.7 kilogrammes, meat 27.5 kilogrammes, fish 0.5 kilogramme, lard 4.9 kilogrammes, butter 1.1 kilogramme, vegetable oils (sunflower oil and others) 5.7 litres, milk 67.6 litres, cheese 9.5 kilogrammes, eggs 71, sugar 2 kilogrammes, rice 2.7 kilogrammes, fresh vegetables 109.5 kilogrammes, legumes 13.3 kilogrammes, potatoes 17.5 kilogrammes, fresh fruits 24 kilogrammes, grapes 81.6 kilogrammes, wine 30.5 litres. Of these foods only about 17% (by value) were bought from the stores while 83% were home-grown.

It will be seen from these figures that bread is by far the most important foodstuff, and must provide a high proportion of the total proteins of the diet as well as supplying the greater part of the energy value. The milk consumption, which is about a fifth of a litre per day per consumption unit, is higher than in many parts of the Balkans. It is probable that much of this milk is drunk as sour milk or yoghurt. The meat consumption is low, but again it is higher than in many other parts of the Balkans; it is usually eaten once or twice a week. The yearly consumption of fresh vegetables (109.5 kilogrammes) and of fresh fruits and grapes (24 and 82 kilogrammes) is also relatively high, which means a higher average mineral and vitamin intake than many peasant dietaries. The potato consumption is unexpectedly low.

It is interesting to note the extremely low consumption of sugar, 2 kilogrammes a year. This is undoubtedly due to the very high price fixed by the State (22-24 leva per kilogramme), 70% of which is tax. In the village stores, sugar is usually bought at a few lumps at a time. This is considered by the nutrition experts of the Ministry of Agriculture to be a disadvantage from the physiological point of view, since the average peasant cannot buy enough sugar to preserve his fruits for winter use.

¹ C. MOCHEVA, *loc. cit.*

With regard to the winter dietary, it may be noted that the Ministry of Agriculture has started a scheme to introduce home-canning of tomatoes and other vegetables to provide the peasant family with vegetables for winter use.

In general, it seems that the Bulgarian peasants' diet may be adequate in spite of the very high proportion of bread which it contains. The tradition for cultivating vegetables seems to have kept the general dietary much richer in these protective foods than is the case in other Balkan countries. It is said in Roumania that in villages on the frontier between Bulgaria and Roumania, the Roumanian half of the population often develops pellagra, while the Bulgarians in the same village with the same cereal basis of the diet (maize) do not succumb, presumably because they grow and eat more vegetables.

GREECE

Greece is primarily a wheat-eating country, and, although largely agricultural, most of the wheat is imported, since the greater part of the country is too mountainous for growing wheat. Since the world war, the Greek Government has made special efforts to encourage the production of wheat both by increasing the area under cultivation and by increasing the yield per acre. Since 1929, when Greece first began to feel the effects of the world crisis, the Government has tried to regulate the production, trade and prices of wheat by pooling surpluses, and fixing stable and remunerative prices to counteract the fall in volume and value of Greek agricultural exports. Wheat production has been increased by guaranteeing fixed prices to producers above the world price level, by compulsory milling quotas, and by high tariffs and indirect aids to growers such as tax abatements.

The *per caput* consumption of wheat is estimated to have risen in Greece since 1914; the International Wheat Advisory Committee's report of 1938 gives the following figures 1909-1914, 2.86 bushels per head per year; 1930/31, 4.90; 1936/37, 5.17.

The consumption of other cereals, such as barley and rice, is of very minor importance in the Greek peasant's dietary.

The bread of Greece is wheat bread, white in the towns and wholemeal in the country, and, in the case of the peasants, it forms

a very important proportion of the diet. White bread is slightly more expensive, and, in some of the well-to-do villages, as well as the towns, white bread is eaten rather than wholemeal. For instance in Macedonia, the flour-mills of Salonika mill white flour (of over 70% extraction) for sale in Salonika and in some of the more prosperous villages near by, and wholemeal flour of about 92% extraction for sale in the majority of villages. Three times as much wholemeal as white flour is milled, and the millers reckon that, while Salonika uses practically only white flour, the majority of villages consume at least nine times as much wholemeal as white flour.

Apart from the flour bought from the mills, much of the bread of the peasants is made from wholemeal flour ground in the villages by primitive stone mills or even ground by hand. Whether or not the peasants grind their own grain, depends on the price of wheat at the moment. When the wheat prices are high, the peasants tend to sell their grain and buy flour from the mills. They buy mostly wholemeal flour, sometimes with a small proportion of white flour. When the wheat prices are low, they eat their own grain milled in the villages. Thus the villager's bread is sometimes 100% wholemeal bread containing all the germ and bran, and at other times it will be a brown bread made from brown flour of 92%-95% extraction containing less of the germ and bran.

The composition of the bread of the villages is further varied because the wheat flour is often mixed with maize or barley during bad seasons, and with a little white wheat flour in good seasons. In particularly bad seasons, maize bread may even be eaten instead of wheat bread for part of the year. To summarise, one may say that, in any study of the diet of the Greek peasant, it must be noted that the bread eaten will probably be wholemeal wheat bread, but may from time to time be a mixture of wholemeal wheat flour with some white wheat flour, with barley or with maize according to the relative cheapness of the different cereals at that particular time.

The bread of the Macedonian peasants (which is probably typical of most of Greece) is baked at home in earthen ovens. It is made with leaven rather than with a prepared yeast culture, baked for two hours, and made once a week. After two or three days, it often tastes sour, but, when fresh, may taste very good. The Greek

wheat is said to have poor milling and baking qualities,¹ but, for home-baked wholemeal bread, it appears to be adequate.

The general consumption of sugar is very low ; in grape-growing regions sweet grapes are used as a sweetening syrup in winter instead of sugar. The *per caput* consumption for the whole country was 11.3 kilogrammes in 1935/36,² but, in the poorer peasant households, it is certainly much lower than this.

The general dietary of the Greek peasant is typically a very simple one, bread being eaten at every meal and forming the basis of the diet. Beans are probably the second most important foodstuff, bean soup being the traditional soup of Greece. The potato consumption is not very high ; the chief fresh vegetables are garlic, onions and cabbage, with some tomatoes and fruits in season. Olives are an important item in certain parts of Greece.

Meat consumption is very low, meat being regarded chiefly as a luxury food for feast days, and milk is given only to young children and invalids. Cheese made from sheep's milk is the chief animal foodstuff in most parts—*e.g.*, in villages near Salonika—or fish in some coastal villages.

The dietary may be adequate when it contains sufficient wholemeal bread, cheese, garlic, onions and cabbage and fruits in summer, but it is likely to be deficient in winter when these foodstuffs become scarce. The level of nutrition is further lowered by the very long religious fasts which occur three times a year, and last, in the case of the Lent fast, for forty days. During the fasts, no animal foodstuff may be eaten, and the diet consists of bread, beans and other vegetables. It is probable that, during these periods, there is a deficiency of high-class proteins and fats, and that the diet becomes inadequate in energy value.

No dietary surveys or enquiries into the state of nutrition of the Greek peasants have yet been made, but dietary deficiencies are suspected in Macedonia on account of the widespread anæmia found in women—*e.g.*, in patients of the hospital at Salonika. It is of course impossible to say how far this anæmia may be due to malaria and how far to faulty diet. It is the custom in Macedonia and other parts of Greece for peasant women to nurse their children up to 2 or 3 years of age in the hope of preventing further pregnancy,

¹ Wheat Advisory Committee Report, 1938.

² LICHT, F. O. : *Welt-Zucker-Statistik*, 1937.

and this may be an excessive drain on the mineral reserves of the mother. It is found in the Salonika hospital that the anæmic condition of women patients often improves if the woman stops nursing her child, and returns if she recommences the practice.

HUNGARY

Wheat is the chief cereal and the chief export of Hungary, and the bread of the whole country is almost exclusively wheat bread. The Government has been constantly concerned in devising means of improving the quality of the wheat and assisting producers by reduced freightage rates, easy credit and so on. Hungarian wheat used to command the top price for European wheat, but has now to compete with the hard wheats of Canada, America and Australia.

The *per caput* consumption of wheat in the country as a whole has increased in the past twenty years, from 4.36 bushels per annum in 1909-1914 and in 1922/23 to 5.52 in 1936/37.¹

Milling is mostly done by large roller-mills which produce the following grades of flour : No. 0 of 0.34%-0.40% ash content (dry weight basis), No. 2 of 0.40%-0.45% ash, No. 4 of 0.53%-0.60% ash, No. 5 of 0.61%-0.70% ash, No. 6 of 0.80%-1.15% ash and No. 7 of 1.50%-1.90% ash.²

A number of intermediate grades such as : Nos. 6½, 7½, 7¾ are also made. Of the chief grades, Nos. 0-2 are used for the finest white bread, No. 4 is used for the common greyish-white bread, No. 5 is made into half-brown bread, and No. 6 into real brown bread, which is the cheapest bread, the price being regulated by the Government in the interests of the poorest people.

Both for towns and country districts, the flour which is produced in the greatest quantity is the grade No. 4, for the common greyish-white bread ; next in amount come Nos. 0-2, for fine white breads and rolls and pastries, while Nos. 5 and 6, for the half-brown and brown breads, are required in very much smaller quantities.³

The lower grades, Nos. 6½ and 7, are sometimes used for making so-called wholemeal bread, but this is very little consumed and is practically only made for certain institutions.³

¹ Wheat Advisory Committee Report, 1938.

² U.S. Dept. of Agriculture Bulletin, 35, 1936.

³ Information from large Budapest flour-mill, July 1938.

Bleaching or the addition of any chemicals to flour is strictly forbidden in Hungary.

Baking is generally of a high standard. The Hungarian wheats produce flour of a good baking quality, and the art of bread-making has been highly developed for hundreds of years (*e.g.*, in 1673, an English traveller reported the bread in Hungary to be the best in Europe).¹ The commercial baking technique has, in general, kept to the old traditions of home baking, and still produces the various distinct types of bread which are called after the towns or district of which they are characteristic.

In the larger towns, the bakeries of the modern factory type produce most of the bread, while, in the smaller towns and villages, most of the baking is done by the small type of shop bakery. In the country districts, home baking is usually practised, but the housewives sometimes bring their dough to the village bakery to be baked.

The usual baking procedure for the common greyish-white bread is a quick fermentation method with sour dough as leaven together with about 1% of yeast. The home-made bread in the villages is baked every week or every fortnight. It is made with sour dough and yeast, and is baked in the form of large loaves of 5 or 6 kilogrammes weight.

In certain parts of Hungary, it is the custom to add 20%-25% of boiled potatoes to the flour. This makes a good tasting bread which keeps moist longer than pure wheat bread, and although it reduces the calorie and protein nitrogen content of the bread, it is considered by some authorities to be an advantage as regards mineral vitamin and essential amino-acid content.¹

A certain percentage of mixed rye and wheat bread is also made, the mixture usually being one-third of rye to two-thirds of wheat flour. Such bread is popular with a small number of well-to-do people in the towns and in some of the villages of German origin, but, in the typical Hungarian villages, the addition of rye to the bread is taken to be a sign of poverty. Only when the supply of wheat is becoming scanty, either due to a bad crop or in cases of great poverty, will the peasants mix rye or maize flour into their bread.

¹ DABIS, L. : *Egészség*, 1937

Bread is unquestionably the basis of the Hungarian peasants' diet. It is eaten at every meal, and usually provides about 50% of the energy value of the diet. In a survey made near the Tisza, it was found that the percentage of calories derived from bread was the greater the less land the peasant owned; for those with one acre, bread provided 66% of the energy value of the diet, while for peasants with ten or twenty acres, only 22% of the calories were derived from bread.¹

In a dietary survey of five small farmers' families and two poor artisans' families in 1934,² it was found that bread and other flour dishes provided between 62% and 89% of the energy value of the diet, while potatoes provided from 3% to 18%, green vegetables up to 5%, dried vegetables up to 8%, and fruit up to 20%.

The actual quantity of bread consumed daily is about 750 grammes to 1 kilogramme in the relatively rich wheat-producing regions, and may amount to 1½ kilogrammes per day in the summer; but, in the poorer districts, the *per caput* consumption is more often ½ kilogramme or less, and, in Gödöllő, near Budapest, daily averages of 277 grammes and 375 grammes per head have been found, accompanied by low levels of calorie intake.³

The rest of the diet generally consists of vegetables such as potatoes, dried peas and beans, cabbage and onions, a small amount of very fat pork and a variety of flour dishes. In summer and autumn, the diet is greatly improved by the addition of fresh fruits, such as melons, grapes, cherries, pears, apples, etc., in regions where these grow abundantly, but in a survey in Csongrad (covering 26,363 people of whom 80% were agricultural), 45% of the families had no fresh vegetables and 43% no fruit during the months of May and June.⁴

Raw paprika and tomatoes are also important additions to the summer diet, and are sometimes also preserved in vinegar or in salt for winter use.

The consumption of milk is very low in most parts of the country, and meat is only eaten once or twice a week by the average peasant.

¹ DABIS, L. : *Egészség*, 1937.

² SCHEFF, DABIS, L., & IVANOVICS, G. : *Health Politics Review*, 1934, I, 295.

³ DABIS, L. : Report to Hungarian National Committee for Public Nutrition, 1938.

⁴ MÉSZAROS, G. : *Népegészségügy*, 1936, No. 4.

Eggs, butter and poultry are very rarely eaten, except on feast days.

The consumption of sugar for the whole country is about 12 kilogrammes per head per year,¹ but, in the villages, it is much less than this, and varies, with the amount of land owned by the peasant, from 1.3 kilogramme per head per year in the case of the landless peasants, farm-hands and those with less than five acres to 3.7 kilogrammes in the case of peasants with from ten to fifty acres.²

The general dietary appears similar in its limitations to the typical peasant dietaries of the Balkan countries, but there is one important difference, the bread eaten in Hungary is white bread, while that of the Balkan peasants is generally wholemeal bread, whether of wheat, rye, barley or a mixture of cereals. The Hungarian peasant is therefore likely to be provided with considerably less vitamin B₁ (and possibly iron) than the Greek or Bulgarian peasant who eats a similar diet with wholemeal wheat bread. A shortage of vitamin B₁ is to be expected from consideration of the Hungarian peasant diet, and the fact that a few cases of beriberi have been reported³ in villages in the Békés district suggests that there may be a latent state of B₁ hypovitaminosis amongst the peasant population. It has also been suggested for other parts of the country that much of the so-called rheumatism seen amongst peasants may be a mild form of B₁ hypovitaminosis,⁴ but it must be noted that definite cases of beriberi have very rarely been reported in Hungary, so that further research into the question is necessary before any general conclusion can be drawn as to the adequacy of the diet with regard to vitamin B₁.

LITHUANIA

In Lithuania, 85% of the population is engaged in agriculture, and about 64% of the arable land is devoted to cereals. The production of wheat and rye is usually sufficient for domestic consumption, with occasional surpluses and shortages.⁵ Rye is the predominating bread cereal.

¹ LICHT, F. O. : *Well-Zucker-Statistik, 1937.*

² DABIS, L. : Report to Hungarian National Committee for Public Nutrition, 1938.

³ GARAMVÖLGYI, DR. K. : *Népegészségügy, 1936, Nos. 10 and 15.*

⁴ DABIS, L. : *Egészség, 1937.*

⁵ Wheat Advisory Committee Report, 1938.

The production and utilisation of wheat is only about 30% of the total wheat and rye production and utilisation (1929-1933), but the proportion of wheat to rye is increasing.¹

The *per caput* human consumption of wheat has increased from 1.30 bushels *per annum* in 1924/25 to 2.61 bushels in 1936/37.²

In 1929, a system of fixed prices was introduced to prevent too sharp a rise in the domestic price of cereals following the poor harvest of 1929. Since 1930, the Government has purchased wheat and rye at fixed prices through the Central Society of Agricultural Co-operatives, and has established a grain reserve.³

POLAND

The principal bread cereal in Poland is rye, and wheat is the second most important ; barley, buckwheat and millet are also consumed to a much lesser extent, usually not in the form of bread. Official figures of consumption published by the Central Statistical Office in Warsaw³ show that three times as much rye as wheat is eaten, and that this proportion, and also the level of consumption of both cereals, has remained fairly constant in the past twenty years. The consumption of rye (159 kilogrammes *per caput* in 1934) is the highest in Europe, and the consumption of wheat (48 kilogrammes *per caput* in 1934) the lowest.

Poland is an exporter of rye and to a lesser extent of wheat, and the production of these cereals has been maintained by Government assistance in the form of reduction of indebtedness, of taxes, of transport rates, of industrial prices, and by protective tariffs on imported cereals. The price of bread, together with that of sugar, meat, fat and dairy produce, is controlled, and the milling extractions for flour are fixed by the Ministry of Agriculture each year or even two or three times in the year. The average extraction usually permitted is 70% to 80%.

The bread of the cities is mostly made from greyish rye flour of 65% extraction, with or without some admixture of wheat flour, and from dark rye flour of 95% extraction. A certain amount of white wheat bread is made from flours of 70%-75% extraction, and

¹ U.S. Dept. of Agriculture Bulletin, 535, 1936.

² Wheat Advisory Committee Report, 1938.

³ *Petit annuaire statistique de la Pologne, 1937, Warsaw.*

luxury rolls are made with more refined wheat flour of 65% extraction and with the addition of butter and sugar. In Warsaw, the large bakeries bake at least five times as much rye bread as white wheat bread. The city workers eat dark rye bread and coarse low-grade gruels, and the wealthier classes in the cities also eat a good deal of black bread. The army bread is made from rye flour of 82% extraction.

Dietary surveys have shown the level of consumption of bread and flour in the towns to be from 157 to 208 kilogrammes per head per year for workers and 103 to 195 kilogrammes for intellectual workers. Amongst the rural population, the consumption is certainly higher, but no figures are available.

Black rye bread is the typical bread of the rural population (which is 70% of the total population of Poland), and the flour for this home-baked bread is usually stone-ground in old-fashioned wind-driven flour-mills, so that it is 100% wholemeal flour.

Richer peasants may mix some white wheat flour in their bread, or have their rye milled to 65% extraction, but this is unusual, except in parts of western Poland, where 65% rye flour mixed with wheat flour is the common bread mixture. White wheaten bread is only baked three or four times a year for feast days in most parts of Poland. A little rice is eaten, and noodles, macaroni and other wheat flour dishes are used to a certain extent. Barley is used for soups and other dishes, and, in some less fertile parts of the country, buckwheat is eaten by the poorest peasants in the form of a stiff porridge. The country bread is usually made with leaven rather than yeast and is baked in the home every one or two weeks. There is a tendency now, however, for village bakeries to become more numerous.

Bread and other cereals constitute at least 60% of the diet of the rural population, and the second largest item is potatoes, the consumption of which is higher in Poland than in any other country of Europe—*e.g.*, 768 kilogrammes *per caput* in 1934.¹ The consumption of meat and animal fats is low, since these foodstuffs are exported, and the source of fat is usually a vegetable oil, such as rapeseed oil or sunflower oil. It seems that appreciable quantities of buttermilk and skim-milk are consumed in some parts, which

¹ *Petit annuaire statistique de la Pologne, 1937.*

would provide a good source of animal protein. Cheese may also be an important item in the diet. Green vegetables and fruits are not much eaten, but their consumption is said to be increasing as a result of the instruction and help in growing them given by agricultural instructors in the villages.¹ The diet may be adequate where sufficient skim-milk and cheese are consumed, but is probably very poor during the religious fasts and amongst those peasants who have no skim-milk and cheese.

The consumption of sugar is low, 11.5 kilogrammes *per caput* in 1935/36,² and no attempt is made, as in some Balkan countries, to increase it, although the sugar trade is under State control.

ROUMANIA

The chief cereals for human consumption in Roumania are maize and wheat. The production of maize is greater than the production of wheat in the old Kingdom and in Bukovina in the north, while, in Transylvania and Bessarabia, about equal amounts of each are produced.³ In Bessarabia, and in Dobruja in the south-east, there is also an extensive production of barley, but this is not used to any great extent for human consumption. Rye and oats are produced to a much lesser extent.

Since the world depression the Government has made great efforts to maintain the production of cereals by State aids such as price stabilisation, land improvement, reduction of railway rates and erection of storage elevators, etc. In 1936 and 1937, the Government purchased wheat at a fixed price, and, since 1931, export premiums on wheat have been paid.⁴

The *per caput* consumption of wheat has varied considerably since 1909-1914, when it was 4.25 bushels per year, to 1936/37, when it was 3.43 bushels.⁴

The milling of wheat flours is partly controlled by the Government, the proportions of the different grades of flour to be milled

¹ Information from Institute of Hygiene, Warsaw.

² LICHT, F. O. : *Welt-Zucker-Statistik*. 1937.

³ *Album statistique de l'agriculture en Roumanie*, Ministère de l'Agriculture et des Domaines, Bucharest, 1929.

⁴ Wheat Advisory Committee Report, 1938.

being specified. Bakeries are required to have an official permit and are subject to regulations of the Commission of Hygiene as to hours of work, machinery and cleanliness.

The retail price of bread is fixed by the municipal authorities in each town. It is relatively low, and is the cheapest energy foodstuff in both town and country districts. Brown bread is somewhat cheaper than white.

In the towns, every family with an average income uses white wheat bread. Brown bread is eaten by the poorest families and by the servants. Very little rye bread is made, except in southern Roumania, where mixed crops of rye and wheat are grown. Some of the wheat bread has an addition of potato starch, a custom which is very common in Transylvania.

The quantity of bread usually eaten is very high. The army ration allows 1,100 grammes of brown wheat bread (80% extraction) daily per man ; and the usual allowance for school-children of from 8 to 10 years is 250 grammes of bread for breakfast alone. In Bucharest, dietary questionnaires of poor families show that rather more than half a kilogramme of wheat bread is usually eaten per head per day, while about half the families studied ate 1 to 1½ kilogrammes of maize per head daily. The rest of the dietary in these families was made up mostly of potatoes, beans and cabbage, with meat once or twice a week, usually only a very little milk for children, and most frequently no fruit at all. The sugar consumption was very low, being of the order of a quarter to half a kilogramme a week for families of eight and ten persons.

Amongst the rural populations of most parts of Roumania, where maize forms the chief food, the dietary is very poor. The maize is ground at the village mills, which are usually water-driven stone-mills, of which there are about 14,000-15,000 in the country. The cornmeal is then simply cooked with water to form a stiff cornmush, "mamaliga", which is eaten at every meal. It seems that 1½ kilogrammes a day is a usual allowance, and during the strenuous work of harvesting, as much as 3 kilogrammes is often eaten. Wholemeal wheaten bread is baked for feast days a few times a year from wheat milled in the village mills. In the vicinity of a town, peasants may buy wheat bread once or twice a week ; this is usually brown bread but may occasionally be white bread.

It was found in a recent village survey¹ of fifty families that wheat and rye provided 37.7% of the carbohydrates and 34.1% of the proteins of the diet, while maize provided a further 51.5% of the carbohydrates and 35.3% of the proteins of the diet. Thus altogether cereals accounted for 89.2% of the carbohydrates, 69.4% of the proteins and 75% of the energy value of the total diet, and the diet consisted of 72.5% carbohydrates, 16.9% fats and 10.6% proteins (of which 22.3% only were animal proteins).

Sugar production is a State Trust, and owing to the high price set by the Government to encourage the production of beet sugar, the consumption of sugar is very low. The retail price in Roumania (32 lei a kilogramme) is about ten times the world price, and is much too high for the peasant population to buy what in Western European countries would be considered a normal amount of sugar. According to *Welt-Zucker-Statistik, 1937*, the consumption of sugar for the whole of Roumania is about 5½ kilogrammes per head per year. With Yugoslavia, this is amongst the lowest levels of sugar consumption in Europe—only Bulgaria, Turkey and Albania having lower levels.

The rest of the dietary usually consists chiefly of beans, some potatoes (especially in Transylvania), cabbage, beetroots, carrots, onions, and a certain amount of cheese with milk during certain periods of the year only. Meat and eggs are eaten very rarely, except for very small amounts of fat salted pork which is used more or less as a flavouring; a little fish is consumed at certain seasons. Vegetable oils are used for cooking, mostly sunflower and hempseed oil. Butter is very rarely eaten.

In the preparation of soups, the peasants fairly frequently use a product known in Roumania as "borch", which they prepare from a fermentation of bran. This preparation may provide vitamins B₁ and B₂.

The diet is further impoverished by the long religious fasts consisting of seven weeks before Easter, six weeks before Christmas and two weeks before St. Peter's and St. Mary's feasts, and, besides this, Wednesday and Friday of each week. The diet during the fast includes no food of animal origin and usually consists of maize and beans, with onions, peas, potatoes or prunes.

¹ GEORGESCO, D. C. : *L'Institut social roumain*, Bucharest, 1936.

The dietary varies considerably in nutritional value according to the season. From the point of view of calories, it is lowest in autumn, and highest in summer during harvest work. The animal protein and fat content is high only on feast days ; otherwise, very low. At other times, the vegetable protein content is fairly high, but the fat content very low. The main deficiencies of the diet are probably calcium, high-class proteins, fat and vitamin B₂.¹ The state of nutrition is certainly poor in the maize-eating regions, as the great frequency of pellagra is sufficient to show.

YUGOSLAVIA

In Yugoslavia, the chief cereals used for bread-making varies from one part of the country to another. Maize and wheat are the most important cereals of the greater part of the country, the plain lands of the north-eastern and the extreme south-eastern parts of the country being the chief wheat-growing areas, while the rest of the country mostly eats maize, with the exception of much of Herzegovina and the inland districts of Dalmatia, where barley is the chief cereal. Rye predominates in the extreme north-western parts of Slovenia and in certain other mountainous regions in the south-east. In some regions, a mixture of cereals is commonly used for bread-making, often including oats and millet as well as the four main cereals mentioned above. Wheat and maize are important exports, barley and rye are grown chiefly for home consumption.

The *per caput* consumption of wheat for the country as a whole has fluctuated considerably in the past twenty years. In 1909-1914, it was 4.61 bushels a year ; in 1922/23, only 2.98 bushels ; in 1930/31, it had risen to 4.69 and, in 1936/37, it was again down to 4.17 bushels.² It seems that a large portion of the peasant population eat wheat when they can afford it and maize when the wheat is scarce or expensive.

In 1930, the Government tried to maintain prices for domestic wheat above export market prices, and, in 1931, established complete monopoly of buying, selling and exporting of cereals to ensure a fixed price to producers. Since then, the home market (in 1932)

¹ АΥΚΡΟΥΔ : *Arch. roumaines de path. expér. et de microbiologie*, 1935, 8, 407.

² Wheat Advisory Committee Report, 1938.

and later the export market (1933) have been freed, but the Government still endeavours, through the Privileged Export Company, to keep prices sufficiently high for the peasants to sell their grain with profit.¹

There is also a law in force (since 1931) to authorise the police to fix maximum retail prices for foodstuffs to protect the consumer against excessive prices. The profit made by selling foodstuffs must not exceed 25%, and all measures taken to increase prices by withholding foodstuffs, speculating, etc., are punishable under this law.¹

The chief problem of the Government with regard to cereals is to provide sufficient cereals for the non self-supporting areas of Yugoslavia. These are mostly in Montenegro, Herzegovina, Dalmatia and, to a lesser extent also, in Bosnia, Croatia and Slovenia. These districts do not produce as much as 1 kilogramme of cereal per head per day for both human and animal food together, and the production of potatoes or of cattle, industrial plants, wine or fruit is not sufficient to compensate for this shortage of cereal crops. Such districts in which there is not sufficient land to support the population contain 2½ million people, and Government assistance has to be given in the form of free maize or wheat, and by reduced railway transport rates for cereals carried from the producing districts. In spite of these measures, the retail price of maize is 100% higher and of wheat 75% higher in Montenegro than in the producing areas in the north-east.

In the large towns, the bread is mostly made from low-grade wheat flours, which give either brown or whitish bread, usually baked in small bakeries. The army ration is 1 kilogramme of pure wheat bread per head per day.

In the plain-land north of Belgrade, which is the chief wheat-growing area, the peasants eat home-baked wheat bread, made either of low-grade whitish flour or of wholemeal flour, depending on their prosperity. The peasants take their wheat to the village mills, and where these are roller-mills the richer peasants will have their wheat milled to a whitish colour, while those with less wheat have it milled as wholemeal. Those peasants who have no wheat, bring maize to be ground to a coarse flour which they make into

¹ Note from Dr. Edo MARKOVIĆ (Head of the Privileged Export Company in Belgrade) to the Financial Section of the League of Nations, 1936.

bread. If the wheat crop is poor and the wheat does not last all the year, most of the peasants eat maize, while the few richer ones buy white wheaten bread. It is therefore impossible to conclude that the bread of any one village will be the same at all times of the year.

In a village (Ripanj) of about 6,000 people near Belgrade, the village bakery sells whitish bread of wheat flour, while, in the poorest houses, only home-made maize bread, and, in the richer houses, both maize bread and brown home-made wheat bread are eaten. The school-children of the village bring for their midday meal a large slice of maize bread in most cases, or whitish wheat bread in a few cases. In addition to this, some of the children, but by no means all, bring some sheep's milk cheese ; the others have only bread.

In the north-west, south-east and centre of the country, maize is the chief bread cereal. On the Croatian coast and in parts of Dalmatia, the maize is eaten as polenta rather than bread.

In the villages north of Zagreb, for instance, the bread is made of maize with 20%-30% of either wheat or rye added. But, during part of the year, if wheat is plentiful, a brown bread of mixed wheat and rye flours may be made instead.

In the more immediate vicinity of Zagreb, the bread is typically of maize with some rye added. This is a heavy bread, but quite good tasting. It is baked once or twice a week with leaven. White wheaten bread is bought from Zagreb occasionally as a luxury.

On some of the islands off the Croatian coast cereals have to be brought from the mainland, and many different sorts of bread are made, white wheat bread, hard wheat crisp bread, and half wheat and half maize bread. Maize in the form of polenta is eaten more than bread and macaroni is very popular. (It may be noted here that on some of the islands the teeth are said to be especially bad, rickets very prevalent and gall-stones frequent, indicating a bad diet. Little fish, meat or milk, and inadequate amounts of goat's cheese and vegetables are eaten.)

In the south-west of Croatia, an unleavened bread of wheat and maize is made.

In Slovenia, the bread is dark rye bread in the north, and a mixture of maize, oats, barley and millet near Ljubljana. Maize in the form of polenta is often also eaten at the morning meal.

In large areas of Bosnia and Herzegovina, either pure barley bread or a mixture of barley and wheat bread is made.

In the hilly country, near Banja Luka, where living conditions are extremely primitive, the bread is made of maize and millet. The rest of the diet consists of beans, sour cabbage, sheep's or goat's cheese, some milk and eggs, very rarely meat and no fruit. (Prunes are grown only for making spirits.)

In general, it seems that the dietary of the peasants throughout Yugoslavia is similar in character to that of the other Balkan countries. Bread and other cereal dishes form the basis of the diet, and beans, cabbages and potatoes are the other staple foodstuffs. Goat's-milk cheese, meat and fruits are eaten in varying amounts. In autumn, the diet is usually much richer in these foods than at other times, and the requirements of animal proteins may even be exceeded. In the spring, the diet is at its poorest, and the supplies of meat, cheese, fruit, potatoes and even wheat are often finished, so that the peasant family often lives on little more than maize in the late winter and spring.¹

In most parts, the consumption of milk and eggs is very low, except for a short period in the autumn, when the consumption may increase. The diet is therefore very poor in animal foods for the greater part of the year, and is further impoverished in Serbia by the long religious fasts, during which no animal food at all is allowed. These fasts consist of six weeks before Easter, six weeks at Advent, eight to thirty days for St. Peter's fast, and three shorter fasts in which oils and fish are allowed. Besides this, every Wednesday and Friday of the year are partial fast days, when no fat is eaten.

After the long Lent fast, symptoms of nutritional deficiencies are said to be prevalent amongst the peasant children. Dr. IVANIC¹ states that rickets, scurvy and nutritional anæmia in young children, and tetany, sclerophthalmia and keratomalacia in new-born infants are found in Serbia during the spring fasts. He also says that night-blindness is frequent amongst peasants around Christmas time. In the villages near Banja Luka, mild cases of scurvy and pellagra have also been seen in the spring; and near Zagreb rickets amongst peasant children is reported to be prevalent.

¹ Unpublished report by Dr. IVANIC, of the Ministry of Health, Belgrade, 1937.

In spite of these symptoms of deficiencies in the dietary, it is of interest that, in the maize-eating areas of Yugoslavia, there is not such a high incidence of pellagra as in the maize-eating regions of Roumania. It seems that the Yugoslav peasants' diet may contain more of other foods which supply the factors missing in maize than in the case of the Roumanian peasant.

The sugar consumption in Yugoslavia is very low, owing to the high retail price due to a State duty on sugar. The *per caput* sugar consumption for the whole country is one of the lowest in Europe and has decreased since 1930 from 7.2 kilogrammes to 5.4 kilogrammes in 1935/36.¹

¹ LICHT, F. O. : *Welt-Zucker-Statistik, 1937.*

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TUBERCULOSIS IN RURAL AREAS¹

CONTENTS

	Page
I. TUBERCULOSIS MORTALITY IN RURAL AREAS :	
Preliminary Reservations as regards Statistics	552
A. Total Tuberculosis Mortality	553
B. Tuberculosis Mortality by Age-groups and Sex	564
C. Interpretation of Tuberculosis Mortality Rates in Urban and Rural Areas	574
II. TUBERCULOSIS INFECTION AND MORBIDITY IN RURAL AREAS . .	580
A. Children	580
B. Adults	587
C. Conscripts and Soldiers	592
III. INFLUENCE OF THE RURAL EXODUS ON TUBERCULOSIS	595
IV. HUMAN TUBERCULOSIS DUE TO THE BOVINE BACILLUS	600
V. PROGRAMME FOR A SURVEY ON RURAL TUBERCULOSIS	604
VI. SUMMARY AND CONCLUSIONS	607
<i>Bibliography</i>	609

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I. TUBERCULOSIS MORTALITY IN RURAL AREAS

PRELIMINARY RESERVATIONS AS REGARDS STATISTICS

In the following pages, a comparative study is made of the evolution of tuberculosis mortality in towns and rural areas in a number of European countries.

For that purpose, use will be made of figures published both by official authorities and by private authors, but no attempt will be made to conceal the degree of error which those figures contain. The main cause of error is the variation—from one period to another, or from one country to another, or within the same country as between towns and rural areas—in the proportion of deaths the cause of which is determined competently and certified in a reliable manner.

The lack of medical attention and hence of expert diagnosis in certain forms of tuberculosis, particularly in small children and old people, results in a lowering of the recorded mortality rates due to tuberculosis.

A similar result follows from the reticent attitude of the medical profession in certain countries, especially in former times when, out of consideration for the feelings of the family, doctors refrained from diagnosing tuberculosis and entered some ordinary lung affection on the death certificate.

That particular cause of error, which was revealed by PARISOT in the Department of Meurthe-et-Moselle, may exist, and may particularly have existed in the past, in many other regions and countries.

A general survey of the various causes of error which may invalidate tuberculosis statistics was made in 1924 by S. ROSENFELD for the Health Committee of the League.¹ It is sufficient here to refer the reader to that interesting document.¹ The conclusion, however, deserves to be quoted in the present study :

“ It is still impossible to look upon statistics of tuberculosis mortality as in any way accurate. Nevertheless, they are greatly improved and much progress has been achieved. Such

¹ L.o.N. Documents C.H.284 and 284(1).

deficiencies as subsist need not discourage us from following the evolution of tuberculosis mortality, provided the necessary precautions, which are set out in this report, are taken. If they are analysed with the required knowledge and critical spirit, those statistics can reveal accurately the changes occurring in the various forms of tuberculosis mortality in the various countries for each age-group and sex.”¹

The absence of documentary material makes it impossible to determine the extent of the direct influence of alcohol and alcoholism on the course of tuberculosis infection, on its morbidity, or on its origins.

* * *

A. TOTAL TUBERCULOSIS MORTALITY

Tuberculosis mortality will be reviewed in turn in countries of Northern, Western, Central and South-Eastern Europe. It is much to be regretted that certain countries must be omitted from this survey, because their statistics make no distinction between urban and rural areas. The first country to be examined is *Finland*, whose statistics share with those of Sweden the honour of being the oldest in the world.

Table 1.—MORTALITY DUE TO PULMONARY TUBERCULOSIS IN TOWNS AND COUNTRY AREAS IN FINLAND, 1771-1929¹

Years	Towns	Rural communes	Whole country
1771-1780	288	157	160
1781-1790	292	152	157
1791-1800	332	153	158
1801-1810	430	171	184
1811-1820	430	190	202
1821-1830	437	195	209
1831-1840	448	214	229
1841-1850	418	204	218
1851-1860	472	249	263
1861-1870	459	284	296
1871-1880	442	266	280
1881-1890	353	242	252
1891-1900	304	250	260
1901-1910	295	274	277
1911-1920	264	253	255
1921-1929	212	204	205

¹ L.o.N. Document C.H.284(1), page 41.

² Except where otherwise shown, all mortality rates in this report are expressed per 100,000 inhabitants.

According to BACKMAN and SAVONEN, from whose work Table 1 is taken, pulmonary tuberculosis only made its appearance in Finland at a recent period. Towns were first affected, and in certain areas contagion reached its climax towards the beginning of the nineteenth century. Tuberculosis then spread first to the areas adjacent to towns and next to country districts. Between 1861 and 1880, tuberculosis mortality reached its maximum point in all the departments except two. Those two departments fell into line with the others between 1901 and 1910, but the general rate began to fall soon after. Finland is an instructive example of the spreading of tuberculosis first in towns and next in country areas, followed by an unequal decline in mortality rates in town and country.

In *Denmark*, although the figures do not go back many years, it is also possible to detect a lower rate in the country than in the towns. The statistical period only extends from 1930 to 1936.¹

Table 2.—TUBERCULOSIS MORTALITY IN TOWN AND COUNTRY
IN DENMARK, 1930-1936

Year	Town	Country
1930	78	65
1931	77	63
1932	75	63
1933	64	54
1934	60	51
1935	56	48
1936	51	43

K. FABER, who studied rural tuberculosis in Denmark in 1928, stresses the fact that the disease was then less prevalent than in towns. That rule was not invariable, however: in North-West Jutland, for example, the rate for the country areas was 123 per 100,000 as compared with only 94 at Copenhagen.

In *Sweden*, at any rate since the period 1911-1915, which is the first shown in Table 3 below, the incidence of tuberculosis is higher in country districts than in towns, although it gradually improves. But the total figures for "country areas" are in reality an average of the specific rates for provinces, in which mortality varies greatly

¹ Very detailed information on tuberculosis mortality in Denmark will be found in the report of OSTENFELD, HEITMANN and NEANDER (L.O.N. doc. C.H. 957). Unfortunately, the figures relate to the country as a whole, and to Copenhagen, and not to the rural population taken by itself.

because the stage reached in the evolution of the contagion differs widely from one to another (*cf.* NEANDER).

Table 3.—TUBERCULOSIS MORTALITY IN TOWNS AND COUNTRY AREAS IN SWEDEN, 1911-1936

Years	Towns	Country areas	Whole country
1911-1915	178	240	194
1916-1920	169	211	181
1921-1925	144	159	148
1926-1930	129	136	132
1931-1935	107	109	108
1934	103	102	103
1935	94	94	94
1936	94	87	92

The situation in *Norway* is similar, though here there is the advantage that statistics making a distinction between towns and country are available from 1886 onwards.

Table 4.—TUBERCULOSIS MORTALITY IN TOWNS AND RURAL AREAS IN NORWAY, 1886-1925

Years	Whole country	Rural areas	Towns	Oslo
1886-1890	258	220	387	356
1891-1895	283	250	376	350
1896-1900	310	287	370	346
1901-1905	282	268	319	298
1906-1910	260	249	287	259
1911-1915	236	230	251	225
1916-1920	226	220	239	201
1921-1925	203	203	202	178

As this table shows, tuberculosis mortality in Norway was at the outset very much higher in towns than in rural areas; gradually, however, the gap dwindled, until in the last five-year period the rates for the two categories became roughly similar. At Oslo, during the last three five-year periods, the rate has been lower than those both of rural areas and of the other towns.

It is to be noted that the mortality rate in rural areas has moved concurrently with that for the whole country, the majority of whose inhabitants are country-dwellers; in both cases, the peak was reached towards 1900, after which a decline set in. In the towns, the mortality rate began to drop much earlier than in the country, but the figures do not go sufficiently far back to allow us to decide when the drop began. In rural areas, the total fall, from the highest point

reached in 1896-1900 to that reached in 1921-1925, amounted to 29%. In the same interval, the drop in the towns was much more appreciable: 45% for all towns taken together and 49% at Oslo.

For *Prussia*, a post-war statistical study carried out by FLATZECK (*cf.* Table 5) reveals a lower rate in country areas than in towns. At the same time, the rate of fall in mortality was less marked for country areas than for towns.

Table 5.—TUBERCULOSIS MORTALITY IN TOWN AND COUNTRY IN PRUSSIA, 1923-1925

Year	Whole territory	Towns	Country areas
1923	153	183	118
1924	122	142	98
1925	109	125	90

In *England and Wales*, tuberculosis mortality has always been less in country areas than in towns, while—at any rate in recent times—the decline has also been more marked in the former. Although intensive industrialisation, which drew very large numbers of workers from country areas, caused a very sharp increase in the incidence of tuberculosis among country-dwellers, the return of those affected to the country did not take place on a sufficient scale to produce an appreciable effect upon the mortality rate in the latter.

Table 6.—TUBERCULOSIS MORTALITY IN URBAN AND RURAL AREAS IN ENGLAND AND WALES, 1891-1936 (for the periods 1891-1900 and 1901-1910, the rates are standardised in relation to the 1901 census population figures).

Years	Urban population	Rural population
1891-1900	218	179
1901-1910	176	149
1913	144	101
1930	95	69
1931	95	69
1932	88	65
1933	87	63
1934	80	59
1935	75	56
1936	73	53

It is interesting to compare the figures for England with those for *Scotland*, where, according to the 1921 census, the urban fraction of the population amounted to 77.3%, as compared with 79.3% in England.

Table 7.—TUBERCULOSIS MORTALITY IN LARGE AND SMALL TOWNS AND IN RURAL AREAS IN SCOTLAND, 1919-1926

Year	Large towns	Small towns	Rural districts
1919	141	117	108
1920	148	110	99
1921	134	106	99
1922	136	109	98
1923	135	109	98
1924	133	102	98
1925	128	99	91
1926	115	87	83

By large towns is meant, in Scotland, those with more than 30,000 inhabitants ; all others are classified as small towns.

In Scotland, the mortality rate is higher than in England ; but here again the situation is better in rural districts than in towns, although the difference is not considerable. In both cases, the rate falls only very slowly, though a trifle more rapidly in large towns.

In the *Irish Free State*, where nearly three-quarters of the population inhabit country areas, the tuberculosis rates are very much higher ; once again, however, the position is better in rural areas than in towns.

Table 8.—TUBERCULOSIS MORTALITY IN RURAL AND URBAN DISTRICTS IN THE IRISH FREE STATE, 1907-1930

Year	Town	Country	Year	Town	Country
1907	376	212	1919	261	160
1908	368	207	1920	222	143
1909	327	201	1921	203	138
1910	312	191	1922	201	134
1911	304	178	1923	207	125
1912	298	178	1924	206	131
1913	295	178	1925	205	137
1914	306	167	1926	187	160
1915	317	182	1927	196	125
1916	285	183	1928	175	121
1917	285	192	1929	180	111
1918	302	177	1930	176	110

The evolution of the rate is practically parallel for town and country ; there is a slow decline before the war, ceasing during the period of the war and resuming somewhat more rapidly afterwards ; the rate for rural areas is throughout below that for towns, but the two are gradually coming together.

In the *Netherlands*, tuberculosis mortality is actually higher in country districts than in towns, although that has not always been

the case. Before the war, the rate for the large towns was distinctly higher than that for country areas, while during the war the shortage of food caused a still wider gap, as it affected chiefly town-dwellers.

Table 9.—TUBERCULOSIS MORTALITY IN RURAL AND URBAN AREAS IN THE NETHERLANDS, 1917-1936

Year	Town	Country
1917	188	167
1931	71	82
1932	62	74
1933	59	64
1934	53	61
1935	50	62
1936	48	59

Only in 1921 did the mortality rate at Amsterdam, for example, fall below that for the country as a whole. It must not be overlooked that only 20% of the population of the Netherlands inhabits communes of less than 5,000 inhabitants, and that even the agricultural section of the population lives for the most part in built-up areas, when it is particularly liable to early contagion; while, on the other hand, the circumstances favour an early drop in the rural mortality due to tuberculosis.

In *France*, the latest statistics do not allow of a distinction between rural and urban populations. Nevertheless, the work of BERNARD and BIRAUD (1930) provides figures going back over a number of years for communes of less than 5,000 inhabitants, towns of over 30,000 inhabitants, and Paris.

Table 10.—TUBERCULOSIS MORTALITY IN FRANCE, 1891-1936

Year	Paris	Towns of over 30,000 inhabitants	Communes of less than 5,000 inhabitants	Whole country
1891	—	389	—	—
1896	509	385	—	—
1901	468	377	—	—
1906	448	376	197*	255*
1911	400	351	158*	231*
1913	390	343	163*	225*
1919	296	271*	134*	214*
1921	286	270*	139	194*
1926	279	—	—	164
1931	220	—	—	152
1934	176	—	—	126
1936	169	—	—	—

* Figures corrected by BERNARD and BIRAUD by an allocation of deaths due to unspecified causes.

These figures show clearly that, at the end of the nineteenth century, tuberculosis mortality was very high in large towns, high in small towns and relatively low elsewhere. Since then the rates have fallen throughout, but more markedly in the larger towns, although even here they have not yet fallen to the level of the mortality rates in rural areas.

In *Switzerland*, where the population is still largely rural—in 1930, communes of over 10,000 inhabitants accounted for only 29.5% of the total population—tuberculosis mortality in towns, after having been for long more considerable than that in rural areas, gradually diminished until it finally became less. This is due to the fact that the town rate has fallen more quickly than the country rate.

In certain cantons, the economic and health conditions of the peasant's life still leave much to be desired, especially in those households where alcohol still maintains its hold.

This fact, and the further fact that in certain isolated mountain villages tuberculosis is of recent origin, account for the high mortality found in certain places—*e.g.*, in such alpine communes as Emmetten (Unterwalden), Realp (Uri) and Soglio (Graubünden). As CHODZKO points out, favourable climatic conditions and a high altitude—the two last-mentioned communes are 1,542 and 1,088 metres above sea-level respectively—are not sufficient in themselves to ward off tuberculosis, which can, even in those circumstances, be a principal cause of death.

Table 11.—TUBERCULOSIS MORTALITY IN URBAN AND RURAL AREAS OF SWITZERLAND, 1901-1936

Year	Town	Country
1901	312	251
1913	208	197
1921	167	164
1922	160	155
1923	160	147
1924	158	151
1925	151	153
1930	123	125
1931	129	119
1932	119	114
1933	107	106
1934	100	102
1935	98	97
1936	92	96

In *Yugoslavia*, the evolution of tuberculosis in isolated villages, and the powers of resistance against the disease of inhabitants of mountainous regions, have been studied on several occasions. In his work on the reactions of the Yugoslav population to tuberculosis contagion, MALOJCIC reports that few of the inhabitants of the mountains of Bosnia, Herzegovina and Montenegro fall victim to the disease provided they remain in their native land ; but the situation is very different when they come into the towns as soldiers, workmen, etc. Unfortunately, there are no statistics enabling a survey to be made of the evolution of tuberculosis in the various rural areas of the country ; only MALOJCIC's sample investigations are available.

In *Hungary*, tuberculosis mortality is lower in country areas than in towns. Both the urban and the rural rates are tending to fall, the interval between them remaining constant. The rate of fall has become appreciably sharper during the post-war period.

Table 12.—TUBERCULOSIS MORTALITY IN URBAN AND RURAL DISTRICTS OF HUNGARY, 1897-1937. (Until 1912, the figures relate to the territory before the Treaty of Trianon.)

Year	Town	Country
1897	404	365
1900	433	370
1912	380	345
1930	226	191
1931	237	183
1932	222	180
1933	197	155
1934	183	144
1935	173	148
1936	174	140
1937	169	138

In *Roumania*, recorded mortality rates (shown in the table below) reveal such sharp annual fluctuations that it is not easy to interpret them ; they suggest, by their very extent, changes in the procedure of declaration and registration of causes of death.¹

¹ The first statistics of rural mortality in Roumania, relating to the year 1928, included 16,090 deaths due to tuberculosis, 55,659 due to old age and 52,915 due to congenital debility (!). (*Sanatalea Publica*, 1929, page 8.) These figures reveal that there was no reliable diagnosis of the cause of death in a great many cases.

Table 13.—TUBERCULOSIS MORTALITY IN URBAN AND RURAL DISTRICTS OF ROUMANIA, 1927-1936

Year	Town	Country
1927	208	86
1928	204	93
1929	215	103
1930	221	159
1931	245	190
1932	222	173
1933	206	156
1934	205	161
1935	215	170
1936	216	167
1937	224	179

The figures quoted by BANU (1933) appear to show, however, that various parts of the country, and especially a number of mountain villages, stand at different stages in the evolution of tuberculosis contagion and accordingly show widely varying mortality rates.

Fortunately, local studies are available to supplement the official statistics. Those of GHEORGHIU (1929) relate to the two villages of Gologan and Slobozia-Ciorasti, in the department of Ramnicu-Sarat, a mountainous district in Northern Wallachia. The populations were 2,400 and 2,200 respectively, and the deaths due to tuberculosis during the period 1921-1929 totalled 53 and 58, giving mortality rates of 223 and 284 per hundred thousand respectively; tuberculosis accounted for 9.4% and 12.7% of the total number of deaths. In the villages of the Tomesti district, according to CIUCA, BALTEANU and NASTA (1937), the mortality rate varied between 142 and 215 per 100,000 inhabitants.

NASTA (1938) found a number of rates exceeding 300 in small towns—*e.g.*, Ploesti 302, Bazargic 304, Buzau 316, Alexandria 331, Lugoj 393.

PROCA does not believe that there is any appreciable difference between town and country as regards tuberculosis mortality. RIMNEANTU considers that the mortality rate in rural areas is high and is roughly stationary, whereas the rate in towns shows a slight tendency to decline. This is also confirmed by the official figures reproduced in Table 13.

For *Czecho-Slovakia*, particularly valuable information is available through the work of HULKA (1922), PELC (1929) and KLIMA (1937). This information is summarised in Table 14 and shows

the evolution of tuberculosis mortality in the main sectors of the country.

Table 14(a).—TUBERCULOSIS MORTALITY IN CZECHO-SLOVAKIA (BY PROVINCES), 1875-1936

Year	Bohemia	Moravia	Silesia	Slovakia	Sub-Carpathian Ruthenia	Czecho-Slovakia
1875	381	388	332			
1880	386	412	364			
1885	427	466	439			
1890	425	464	470			
1895	370	444	482			
1900	361	406	482	372	371	378
1905	374	426	482	421	387	398
1910	286	341	370	328	328	313
1914	263	323	351	303	286	290
1918	362	378	560	329	308	359
1920	255	289		239	275	261
1925	176	201		215	257	195
1930	149	155		174	239	161
1931	155	160		182	261	168
1932	137	144		162	233	149
1933	131	136		157	232	143
1934	129	129		152	206	138
1935	125	127		143	210	134
1936	123	122		135	194	129

Despite certain variations, the curves are parallel for each province. It is interesting to note that a fall in rates first occurred in the more developed and industrialised regions such as Bohemia, Moravia and Silesia, where mortality rates are now the lowest of all. The present position is that the rate is highest in those provinces in which peasants account for the largest proportion of the population, a fact which Table 14(b) makes clear.

Table 14(b).—TUBERCULOSIS MORTALITY AND AGRICULTURAL CHARACTER OF VARIOUS DISTRICTS OF CZECHO-SLOVAKIA

	Bohemia	Moravia and Silesia	Slovakia	Sub-Carpathian Ruthenia	Czecho-Slovakia
Proportion of the active population engaged in agriculture, forestry, etc., according to census of 1930	24.1%	28.6%	56.8%	66.3%	38.2%
Tuberculosis mortality in 1936	123	122	135	194	129

The high incidence of tuberculosis in the agricultural districts is confirmed by Table 15, which relates to the country as a whole and not to its territorial units.

Table 15.—TUBERCULOSIS MORTALITY IN URBAN AND RURAL AREAS OF CZECHO-SLOVAKIA, 1923-1936

Year	Town	Country
1923	238	187
1930	150	164
1931	153	172
1932	135	154
1933	126	149
1934	121	143
1935	116	141
1936	108	136

Finally, the following table illustrates the situation in *Greece* during the period 1926-1935.

Table 16.—TUBERCULOSIS MORTALITY IN RURAL AND URBAN AREAS IN GREECE, 1926-1935

Year	Country	Town
1926	98	298
1927	109	301
1928	110	292
1929	114	295
1930	115	262
1931	115	264
1932	108	277
1933	101	266
1934	97	248
1935	91	236

It will be seen that mortality due to tuberculosis appears to be much higher in towns. At the same time, it is likely that more efficient registration of causes of death in rural areas would to some extent reduce the apparent gap.

There would seem to be a slight, though somewhat irregular, decline in the country areas and a somewhat more marked decline in the towns.

The figures given in the preceding pages as a whole show that, generally speaking, tuberculosis mortality, which was formerly higher in towns than in country areas, has decreased more markedly and earlier in the former. Hence the curve has moved nearer to that of the country areas and has indeed fallen below it in certain highly urbanised countries.

The possible interpretations of those facts are examined in the following pages.

B. TUBERCULOSIS MORTALITY BY AGE-GROUPS AND SEX

The recorded differences in the mortality curves for the two sexes and the various age-groups differ from one country to another and do not present the same general outline. There are differences of detail depending upon local circumstances and the period considered; these differences must be taken into account in any measures undertaken against tuberculosis.

BIRAUD, after analysing tuberculosis mortality rates according to age and sex in a large number of countries and towns, succeeded in reducing the curves for the two sexes according to age to three main types, which, although divergent in certain respects, possess a number of common features.

During the first year of life, there is in every case a higher mortality rate for the male sex than for the female; the difference varies between 20% and 25%, but sometimes reaches as much as 50% or 55%. Next, in the later stages of childhood up to the age of about 12 years, the rate is the same for both sexes and is relatively low. From the age of puberty until 25 years, on the other hand, the mortality rate for females is above that for males both in towns and in rural areas.

The three types of tuberculosis mortality curves which BIRAUD distinguishes emerge clearly after the age of 25. Under type A, the curve reaches its climax for both sexes between the ages of 20 and 30; it then falls slightly and remains constant until about 70 years of age. Type B has a single peak between the ages of 20 and 40—often round about the age of 25—and this peak is followed by a steady decline leading to a low mortality rate towards the end of the adult period and in old age. Finally, type C rises from puberty to the age of 25, and continues to ascend until it reaches its maximum towards the end of adult age and even sometimes in old age—that is, between 70 and 80 years.

Of course, mixed types of curve can also be found and the various features are subject to change. Nevertheless, these standard types provide an indication of the general tendencies and a form of guide which helps in the interpretation of the different specific curves often found in the various districts within each country.

* * *

MORGAN has studied the incidence of tuberculosis in England and Wales, particularly in rural areas, in relation to women. The following table is based upon his findings.

Table 17.—TUBERCULOSIS MORTALITY BY SEXES IN ENGLAND AND WALES

	England and Wales		London		County boroughs		Other urban districts		Rural districts	
	M.*	F.*	M.	F.	M.	F.	M.	F.	M.	F.
1911 a**	124	90	176	99	154	105	105	81	84	78
„ b	44	38	48	36	51	42	43	38	32	33
1914 a	120	86	184	101	150	101	99	76	77	71
„ b	37	30	43	32	45	36	35	28	24	25
1921 a	100	78	132	86	121	87	87	72	69	68
„ b	26	22	24	20	30	25	27	21	21	21
1926 a	90	65	116	64	113	76	78	61	60	56
„ b	21	17	17	13	25	20	21	17	17	16
1930 a	86	62	114	65	109	72	76	57	55	54
„ b	17	15	14	11	20	17	17	14	16	13

* M : males ; F : females.

** a : pulmonary tuberculosis ; b : other types of tuberculosis.

Mortality due to pulmonary tuberculosis is higher in towns than in rural areas, but it affects women less than men ; in other respects, there are no appreciable differences.

That information is supplemented by Table 18, which is divided into age-groups and distinguishes between large towns and rural areas ; it illustrates the behaviour of each sex at various ages.

The general tendency revealed by Table 18, as regards rural districts, is towards a climax occurring between 25 and 45 years of age. In 1911, men were more affected than women, but in that same age-group, the rôles had been reversed by 1930. On the whole, there is equality between the two sexes with a slight preponderance for men : in 1930, the female rate for all age-groups was 54 per 100,000 as compared with 55 for males.

Table 18.—MORTALITY DUE TO PULMONARY TUBERCULOSIS
ACCORDING TO AGE AND SEX IN ENGLAND AND WALES

Age-groups	Males				Females			
	County boroughs		Rural districts		County boroughs		Rural districts	
	1911	1930	1911	1930	1911	1930	1911	1930
0-5 years	34	17	16	6	37	16	16	6
5-15 „	19	9	12	4	38	16	24	12
15-25 „	125	99	85	58	127	120	109	96
25-35 „	203	131	151	88	142	118	145	101
35-45 „	266	157	134	98	171	83	109	72
45-55 „	312	213	123	88	134	67	81	48
55-65 „	286	173	122	59	102	57	77	40
65 years and over	154	103	78	33	64	35	50	25
Total	154	109	84	55	105	72	78	54

The following table shows the evolution of mortality rates by age and sex from 1911 to 1930.

Table 19.—MORTALITY DUE TO PULMONARY TUBERCULOSIS
BY AGE AND SEX IN ENGLAND

Year	Males			Females		
	County boroughs					
	5-15 years	15-25 years	25-35 years	5-15 years	15-25 years	25-35 years
1911	19	125	203	38	127	142
1914	21	124	186	33	122	139
1921	13	114	156	28	139	130
1926	12	104	141	21	124	116
1930	9	99	131	16	120	118
	Rural districts					
1911	12	85	151	24	109	145
1914	8	75	130	20	105	124
1921	9	81	123	19	122	120
1926	9	63	109	14	105	104
1930	4	58	88	12	96	101

It will be observed that after the great war there was a substantial increase in mortality in the 15-25 years' age-group; it related to both sexes in rural areas, but to females only in large towns. The general tendency towards lower rates soon reappeared, however, and is still in progress, especially in country areas. Nevertheless, the rate of diminution of mortality is still less marked in the case of young adults, and particularly young women, than in the case of the later age-groups.

Table 20.—TUBERCULOSIS MORTALITY BY AGE AND SEX
IN ENGLAND AND WALES IN 1936

Age-group	Urban population		Rural population	
	Men	Women	Men	Women
0-4 years	53.7	50.5	48.8	34.1
5-14 „	18.2	19.4	12.7	14.4
15-24 „	76.3	102.6	53.4	80.4
25-34 „	97.4	85.1	68.1	83.3
35-44 „	111.3	60.8	77.9	52.5
45-54 „	146.2	47.3	86.2	38.7
55-64 „	139.7	42.9	93.2	36.2
65-74 „	86.3	35.4	53.8	36.2
75 years and over	46.5	25.2	23.3	25.1
Total	88.1	58.8	58.1	48.4

According to Table 20, which provides the most recent available information, female mortality is doubtless lower than male in country districts. If, however, the position of the various age-groups is examined, it becomes clear that the position of women is most unfavourable up to the age of 34, after which the rates are relatively low.

High rates of tuberculosis mortality among young women have been detected in many countries. This is to some extent confirmed by the following table, which relates to Denmark.

Table 21.—TUBERCULOSIS MORTALITY IN MEN AND WOMEN
ACCORDING TO AGE-GROUPS IN DENMARK, 1920-1925

Age-group	Copenhagen		Total rural population		Rural population in North-West Jutland	
	M.	F.	M.	F.	M.	F.
0-4 years	146	127	69	59	83	73
5-9 „	50	54	33	37	47	49
10-14 „	36	59	34	52	49	78
15-19 „	106	163	67	137	102	202
20-24 „	151	153	113	173	183	267
25-34 „	133	125	106	161	138	237
35-44 „	142	93	77	114	101	161
45-54 „	162	85	85	107	115	134
55-64 „	138	73	104	135	144	166
65-74 „	196	82	129	149	138	153
75 years and over	139	83	75	89	66	98
Total	124	101	74	107	102	144

In Copenhagen, for most age-groups except that extending from 5 to 24 years, mortality is appreciably higher among men than among women. In the country, on the other hand, the figures for women are throughout higher, except as regards the first five years of life. In North-West Jutland, the difference is very marked : in the 20-24 years' age-group, the tuberculosis mortality amounts to 18.3 for men as compared with 26.7 for women.

OSTENFELD, HEITMANN and NEANDER, from whom the Danish statistics are borrowed, classify various parts of the country according to the degree of tuberculosis mortality ; in 1920-1925, they obtained the following results as regards the rural population :

<i>Islands :</i>		
Men	64	} Excess of mortality among women, 20 ;
Women	84	
<i>South-Eastern Jutland :</i>		
Men	68	} Excess of mortality among women, 37 ;
Women	105	
<i>North-Western Jutland :</i>		
Men	102	} Excess of mortality among women, 42.
Women	144	

The situation is entirely different as between towns and the countryside : in the former, the higher the mortality rate, the greater the excess of male deaths over female, whereas in rural districts, the preponderance of female deaths is in direct relation with the mortality rate.

According to RIJKELS, female mortality in almost all age-groups has diminished less than male mortality ; women aged 15-40 years are in the most favourable position. In the 15-19 years' age-group, male mortality had fallen between 1910 and 1930 by 46% and female mortality by 67% ; in the 20-29 years' age-group, the reductions were 43% and 53% respectively ; and in the 30-39 years' age-group, they were 45% and 53% respectively.

As is shown by Table 22, which relates to 1935, a high rate of tuberculosis mortality among women is still in existence in Denmark. For the two age-groups 15-19 years and 20-24 years, the female rates in country areas are almost double those for men ; in later age-groups, the position of women is still unfavourable, and the general rates for all age-groups amount to 57 for women as against only 39 for men.

Table 22.—TUBERCULOSIS MORTALITY BY AGE AND SEX IN DENMARK IN 1935

Age	Urban population		Rural population	
	Men	Women	Men	Women
Less than 1 year	56	75	78	93
1-4 years	66	42	39	36
5-9 "	12	14	11	21
10-14 "	6	14	9	13
15-19 "	38	65	28	49
20-24 "	90	77	48	93
25-29 "	68	88	51	88
30-34 "	68	47	39	63
35-39 "	88	38	42	48
40-44 "	48	56	64	66
45-49 "	50	60	61	85
50-54 "	52	66	35	56
55-59 "				
60-64 "				
65-69 "				
70-74 "				
75 years and over				
Total	58	54	39	57

In *Norway*, mortality among women in rural districts is relatively high, as Table 23, covering the period 1889-1922, shows :

This table, which is borrowed from OSTENFELD, HEITMANN and NEANDER, is very characteristic : there is little change in general tendencies throughout the period in question, and at every stage, women in country districts are more affected than men. Going back to the earliest period—namely, 1889-1892—the situation is very comparable with that obtaining to-day : in country districts, female mortality was higher, and in towns, lower than male mortality.

In *Belgium*, OLBRECHTS has shown that, as regards towns and villages of less than 5,000 inhabitants, female mortality was appreciably higher in 1867 than male mortality. The statistics for 1890, which are the earliest available after those for 1867, and all subsequent statistics, show practically identical mortality rates for both sexes. The disappearance of the wide gap between the two sexes existing in 1867 has been ascribed to a sharp fall in female mortality concurrently with an increase in male mortality. The transfer of the higher mortality rate from women to men as regards the country as a whole, which occurred between 1867 and 1890, is the visible sign of a change which, in reality, only affected towns and villages with less than 5,000 inhabitants.

TUBERCULOSIS IN RURAL AREAS

Table 23.—TUBERCULOSIS MORTALITY BY AGE AND SEX IN NORWAY

Age	Rural population				Urban population			
	1889-1892	1899-1902	1909-1912	1919-1922	1889-1892	1899-1902	1909-1912	1919-1922
Men								
0-1 year	626	553	299	205	821	803	433	250
1-4 years	186	194	122	83	440	353	221	158
5-9 "	117	118	90	62	244	205	128	88
10-14 "	108	127	89	73	182	178	105	70
15-19 "	211	312	262	239	350	307	282	262
20-24 "	436	563	527	492	594	505	426	405
25-29 "				402				364
30-39 "	305	337	300	253	465	405	324	261
40-49 "	211	348	210	184	414	364	306	206
50-59 "	206	224	191	159	437	391	267	182
60-69 "	203	252	196	167	440	409	307	227
70-79 "	154	194	181	136	280	262	187	122
80 years and over	79	104	68	107	131	83	97	23
Total	232	269	220	198	411	362	267	223
Women								
0-1 year	566	527	255	171	744	745	356	231
1-4 years	167	183	116	86	433	366	198	136
5-9 "	132	164	97	71	299	230	167	97
10-14 "	160	216	149	122	290	217	170	114
15-19 "	313	400	323	333	384	346	272	311
20-24 "				452				338
25-29 "	375	463	439	410	371	362	335	291
30-39 "	363	406	344	325	454	414	329	227
40-49 "	272	316	269	220	387	308	246	185
50-59 "	231	294	214	182	358	289	209	153
60-69 "	218	254	192	171	361	252	196	144
70-79 "	191	200	196	155	345	225	163	113
80 years and over	122	80	93	115	143	122	134	55
Total	259	302	241	224	382	329	249	205

OLBRECHTS has prepared tables covering the period 1910-1927 for three groups of villages and towns numbering less than 5,000 inhabitants, from 5,000 to 20,000 inhabitants, and over 20,000 inhabitants respectively. In the last category, the death rate is higher among men than among women, whereas in the two others, the rates are approximately similar for both sexes, any slight difference that may exist being in most cases to the disadvantage of women.

In the Netherlands, as in many other countries, the mortality rate for women is higher than that for men. JITTA's tables leave no possible doubt on this point.

Table 24.—TUBERCULOSIS MORTALITY BY SEXES IN THE NETHERLANDS

Year	Males			Females		
	Communes of			Communes of		
	100,000 inhabitants and over	5,001 to 100,000 inhabitants	5,000 inhabitants and less	100,000 inhabitants and over	5,001 to 100,000 inhabitants	5,000 inhabitants and less
<i>Pulmonary tuberculosis</i>						
1921	96	86	80	101	100	108
1925	72	61	65	75	74	81
1930	50	52	49	50	52	66
<i>All forms of tuberculosis</i>						
1921	126	120	111	131	131	145
1925	100	89	107	103	102	114
1930	66	70	70	69	75	89

According to the same author, from whose work the above table is taken, the incidence of tuberculosis fell between 1921 and 1930 by 50% in large towns and by 33% only in rural districts. In 1930, mortality was lower in towns of over 100,000 inhabitants (66 for males and 69 for females) than in the smaller towns (70 and 75 respectively), and was also lower in the latter than in the countryside (70 and 89). The excess of female deaths is demonstrated as follows by JITTA :

Table 25.—TUBERCULOSIS MORTALITY AMONG WOMEN AS COMPARED WITH MEN (MALE RATE = 100) IN THE NETHERLANDS

Year	Communes of		
	100,000 inhabitants and over	5,001 to 100,000 inhabitants	5,000 inhabitants and less
<i>Pulmonary tuberculosis</i>			
1921	105	116	135
1925	93	121	125
1930	108	106	135
<i>All forms of tuberculosis</i>			
1921	104	108	130
1925	93	115	106
1930	111	107	127

According to JITTA, the effects of an unhealthy mode of life are particularly marked among women who have to carry out work which is frequently arduous in their homes, while their men-folk work in the open air; their situation is made still worse by certain rooted customs and prejudices.

According to EYKEL, the death rate due to tuberculosis has, since the beginning of the century in the Netherlands, moved in a direction unfavourable to women as compared with men.

In the period 1901-1905, for the country as a whole, the tuberculosis mortality rate for women was 5% lower than that for men, whereas in the period 1926-1930 it was 14% higher. Hence between 1901-1905 and 1926-1930 the decrease had been slower in the case of women (90 per 100,000) than for men (113 per 100,000).

A comparison between groups of communes shows that the mortality rate is higher in the countryside and that the excess is wholly due to a heavier proportion of female deaths, due particularly to tuberculosis of the respiratory system.

Whereas the mortality rate from all causes, in both town and country, is lower for women than for men, the burden of domestic duties and heavy work in fields and on farms accounts, according to EYKEL, for a heavier tuberculosis mortality rate among women.

Table 26.—TUBERCULOSIS MORTALITY BY AGE AND SEX IN SWEDEN IN 1934

Age	Urban population		Rural population	
	Men	Women	Men	Women
Below 1 year *	89	60	105	64
1-4 years	63	63	53	61
5-9 "	29	28	29	25
10-14 "	36	30	33	52
15-19 "	90	116	94	133
20-24 "	143	159	152	219
25-29 "	127	170	137	201
30-34 "	118	108	124	146
35-39 "	129	90	120	127
40-44 "	107	77	105	122
45-49 "	129	83	103	89
50-54 "	175	72	94	93
55-59 "	127	63	101	99
60-64 "	104	88	121	97
65-69 "				
70-74 "				
75 years and over	115	84	83	84
Total	108	96	97	111

* Rate per 100,000 live births.

Table 26, which covers the whole population of Sweden, shows that peasant women are not less affected by tuberculosis than other categories.

Other studies more restricted in time or space lead to the same conclusions : DENIS, who has studied separately urban and rural areas in the department of Meurthe-et-Moselle, has shown that deaths due to tuberculosis occur at a younger age in the countryside than in towns, but that in both cases male deaths occur later than female, the latter being chiefly concentrated in the 20-29 years' age-group, which is the period of highest fertility.

QUEYROI believes, in the light of his experience as a practitioner in Dordogne, that in country areas the age of death occurs later for men than for women. He considers that deaths are most numerous among the male sex towards the age of 50, whereas in the case of females the highest rates apply to ages below 30.

The monograph prepared by MALOJCIC makes it clear that no exact information regarding mortality in villages in Yugoslavia can be obtained, since few villages have had a resident doctor for any appreciable period. He has therefore confined himself to data secured in one area where all the diagnoses were made by a doctor. Although that area was relatively advanced in education and culture, and although the levels of nutrition and housing were good, the mortality rate is nevertheless high ; moreover, it tends to increase, owing to the fact that sick persons remain in their own homes instead of being isolated and treated in accordance with modern practice.

Table 27.—TUBERCULOSIS MORTALITY ACCORDING TO AGE
IN ONE YUGOSLAV VILLAGE

Age	0-5 years	6-11 years	12-14 years	15-24 years	25-29 years	60 years and over	Total	Number of inha- bitants
1915-1924 ..	310	170	90	620	470	60	350	3,575
1925-1934 ..	270	200	600	770	550	70	450	3,641

MALOJCIC supplements this table with the following information : the tuberculosis death rate per 100,000 for the 15-24 years' age-group was, from 1915 to 1924, 490 for men and 770 for women ; from 1925 to 1934, 520 for men and 1,050 for women. For the

25-59 years' age-group, the rates were, from 1915 to 1924, 520 for men and 420 for women; from 1925 to 1934, 560 for men and 530 for women.

C. INTERPRETATION OF TUBERCULOSIS MORTALITY RATES IN URBAN AND RURAL AREAS

Tuberculosis mortality in rural areas cannot be considered as a phenomenon apart; it is to some extent bound up with the course of urban tuberculosis. "In countries of the usual type", says Y. BIRAUD—"that is to say, countries comprising both an agricultural and an urban population—the incidence of the disease, the degree of tuberculation and the mortality in town and country areas respectively react upon each other."

The cross currents of varying endemo-epidemic intensity between town and country call for thorough investigation, at least as regards their results. Are the high rates to be taken as proof of unsatisfactory living conditions among the peasant population?

In this connection, we cannot do better than reproduce the essential passages of Y. BIRAUD's report to the Tuberculosis Commission of the Health Organisation.

As regards high rates, it should be noted:

(a) That they may be due to an invasion by the disease of a "virgin" area, the population of which has not been immunised and where, in consequence, the most serious clinical forms of tuberculosis are met with. A high rate may also be the result of migrations and the first appearance of the disease in isolated areas. The greater the rapidity with which the disease is spread, the higher the mortality; but in such cases, the decline is also more rapid.

(b) That the rate remains at a fairly high level over a long period in infected rural areas where there is no appreciable migration. The rate is kept at a high level in the infected areas by bad housing conditions and under-nutrition.

(c) That in the towns the rate is kept at a high level through the immigration of non-immunised country-dwellers and the resultant infection and deaths.

Low mortality, on the other hand, is to be explained by the following three causes :

(a) An apparent low mortality may be due to incomplete notification of tuberculosis as a cause of death. Such is quite frequently the case and partly explains the differences between the rural and urban rates.

(b) A genuinely low mortality may be due to the absence or quasi-absence of the disease—*e.g.*, in the virgin territories of Africa and in rural areas which are isolated or remote from urban centres ; such is the case when the rate is low but increasing, the urban rates being then much higher than the rural rates.

(c) Low tuberculosis mortality may be due to the fact that, the disease having been very widespread in the past, the population has been rendered immune, and also to a higher standard of living among the people ; such is the case when tuberculosis mortality is declining in a largely urbanised country.

The author completes his analysis of the causes of low and high rates by the consideration of cases in which the rates are increasing or declining. In his opinion, an increasing tuberculosis mortality rate may be found :

(a) In countries where the system of registration of causes of death is being gradually improved ; an increase due to this cause will clearly not be long maintained.

(b) In rural areas, while the disease is spreading after being newly introduced or through migrations of population.

(c) In towns, when rural immigration is increasing.

(d) In both town and country areas when, though the conditions governing the transmission of the disease remain unchanged, the powers of resistance of the population are decreased by famine, anergising epidemics (*e.g.*, influenza or measles) or other factors.

A falling rate may be found :

(a) Both in town and country areas, when the disease has been so widespread as to render the population immune. The decline here is from a high to a moderate rate.

(b) In towns, when there is no extensive rural immigration to counterbalance the effects on mortality of the immunity gradually brought about among the urban population by the existence of the disease in an endemic state.

(c) In town and country areas, when the prevalence of the disease has reached its normal level and the powers of resistance of the population have been increased through improved living conditions.

(d) In both town and country areas, when the frequency of transmission of the disease has been decreased by anti-tuberculosis action (education of patients, hospital treatment of advanced cases, etc.).

Apart from rising and falling rates, the rate is found to be stationary :

(a) In country areas, while the tuberculisations of the population is still in progress. When the process is slow (in the absence of extensive migratory movements), the fall in the mortality rate among those newly immunised is offset by the high mortality among those who contract the disease before their tuberculisations is complete.

(b) In towns, where the decline in the mortality rate, consequent upon the progressive immunisation of the population, is offset by the higher mortality rate among rural immigrants who are less completely immunised.

(c) In country areas, at least in theory, when anti-tuberculosis action decreases the frequency of transmission during the process of tuberculisations.

(d) In towns, when the mortality rate has reached a " normal level " : here the mortality is due to the infection of new-born children, to the super-re-infection of adults and to the breakdown of their powers of resistance when there is no change in the standard of living or in the occupations in which the adult population is mainly engaged.

* * *

After showing, in the paragraphs quoted above, the causes of the various types of tuberculosis mortality rate, BIRAUD considers the results reached by comparison of urban and rural rates.

(1) An urban rate which is higher than the rural rate may be due to several causes :

(a) More reliable registration of causes of death in the towns ;

(b) Better hospital facilities in the towns, with the result that patients in country districts go there to die. This cause of error only operates when the rates are calculated in accordance with death certificates and when no distinction is made between permanent and casual residence ;

(c) The influence of occupational mortality among men when the higher urban rate is due to the mortality among males ;

(d) Generally speaking, a marked difference in the mortality rate of both sexes as between urban and rural areas means that the tuberculisation of the rural population is far from complete.

(2) An approximation of the mortality curves for urban and rural areas means thorough tuberculisation of the population when the rates are moderate and rapid development of tuberculosis in rural areas, and extensive migration to the towns when the rates are high.

(3) A rural mortality rate which is higher than the urban rate means the rapid dissemination of tuberculosis in rural areas with negligible migration to the towns, tuberculisation being complete in the towns and still incomplete in the country.

These hypotheses are verified by means of an imposing mass of statistical data. The countries with the highest proportion of country-dwellers now show the highest tuberculosis mortality. In the most highly urbanised countries, on the other hand, the tuberculosis mortality rates declined considerably and remarkably low levels were reached, first in England, Scotland, Belgium and the Netherlands and later in Germany, the north-eastern corner of the United States, Australia and New Zealand.

In countries which are partially urbanised or where urbanisation is slow, the mortality rate is more or less stationary : France, Spain, Austria, Ireland until the war, Sweden, Czecho-Slovakia and Japan.

In short, the first contact with civilisation and urban and industrial development tends to bring about an increase in tuberculosis mortality which makes itself felt first in the towns and later in the country. This increase is followed by a decline which also affects the towns before the country, the interval of time at which the rural rates follow the urban rates being in inverse proportion to the migrations of population and transport facilities in the country concerned.

On the basis of these theoretical considerations, BIRAUD is to some extent able to predict the future course of tuberculosis mortality in a given country when the past and present urban and rural rates are known. It is thus possible to avoid the disappointment which might be caused by the relative failure of a standard anti-tuberculosis organisation in an insufficiently tuberculised country, where the tuberculosis mortality was increasing.

The prevalence of tuberculosis in rural areas is not necessarily due to the practice of agriculture. It is difficult to determine its causes with any degree of certainty, and particularly to decide how far it is the rural environment and how far the practice of agriculture which is responsible. The assertions of writers not personally familiar with local conditions should therefore be treated with the greatest caution; we shall confine ourselves to reproducing DARANYI'S statistics for Hungary.

Table 28.—TUBERCULOSIS MORTALITY IN HUNGARY
AMONG THE CHIEF OCCUPATIONAL GROUPS

Occupational groups	1920-1923			1930		
	Men	Women	Total	Men	Women	Total
I. Agriculture	260	310	290	170	210	190
II. (a) Mining	330	360	350	140	180	160
(b) Industry	420	320	370	300	210	250
(c) Commerce	290	200	240	200	130	160
(d) Transport	310	300	300	190	160	170
Total	380	290	340	260	190	220
III. Officials, professions	310	240	270	210	170	190
IV. Army	110	210	130	70	180	90
V. Unskilled workers	920	770	830	720	480	580
VI. Domestic servants	280	320	300	170	140	140
VII. Various	280	220	230	210	180	120
Total	300	310	300	200	200	200

According to Table 28, it is the unskilled workers who pay the highest toll to tuberculosis, their figures being markedly higher than those of the agricultural classes. In 1930, it is curious to note, the latter showed exactly the same rate as officials and members of the professions.

From 1920-1923 to 1930, there was an improvement in regard to all occupational groups, but the decline in the rate was most pronounced among unskilled workers (from 830 to 580), whereas among the agricultural classes the difference was less pronounced, the rate being 190 in 1930 as against 290 in 1920-1923.

Analysis of the position in an agricultural area may be complicated by the fact that part of the population is engaged in non-agricultural occupations. Such is the case described by WADE in connection with the high pulmonary tuberculosis mortality rate observed among the slate-quarrymen in the rural area of Gwyrfai. This area is in Carnarvonshire, on the coast of Wales, and is bounded on the inland side by agricultural areas. It is made up partly of rolling land given over to agriculture and partly of a more mountainous district intersected by a number of valleys where slate is quarried both on the surface and below ground. The climate is severe, and as the subsoil is impermeable, the whole area is rather damp. Its area is 70,414 acres and in 1921 the comparatively sparse population comprised 9,405 males over 12 years of age; of these, 2,469 worked in the slate-quarries.

WADE's investigations show that the mortality from pulmonary tuberculosis is higher in Gwyrfai than in the whole of England and Wales. In the district itself, moreover, the pulmonary tuberculosis mortality rate among the slate-quarrymen is higher than among the rest of the population.

The variations in this rate among the different age-groups in the district were specially investigated for two five-year periods—1909-1913 and 1921-1925. The curve illustrating these variations in regard to male workers shows certain characteristics: a peak corresponding to early manhood (about the twentieth year), a depression in the years of middle age and a further peak towards old age. The first peak is not truly characteristic, as it is also found in the curve for the female sex, though virtually no girls or women are employed in the slate-quarries.

II. TUBERCULOSIS INFECTION AND MORBIDITY IN RURAL AREAS

An attempt has been made to gauge morbidity on the basis of the mortality figures. In spite of its ingenuity, the findings reached by this means do not always convince impartial observers, who know what a great difference often exists between theory and practice. Life destroys hypotheses in so many cases ; it either shows that those who formed the hypothesis were unduly pessimistic or reveals the unsuspected gravity of a wrongly diagnosed situation.

Until the notification of tuberculosis has been made compulsory and can be relied upon, thus furnishing the information required for rural areas, analysis has necessarily to be based on isolated researches of limited scope. Special attention has been paid to children of school or pre-school age, but unfortunately very few investigations have been made with regard to adults.

A. CHILDREN

Among the investigations covering a large number of children, special mention should be made of those of GILLARD based on more than 10,000 tuberculin tests performed on school-children in some 60 rural communes of the province of Liège. The children were not sorted out beforehand ; in view of the difficulty of carrying out the skin- or intradermal reaction, MORO's test was used.

Compared with the other two methods, this test is usually less sensitive or even quite inadequate in the case of adults.¹

On comparing the figures of Table 29 with other statistics, GILLARD concluded that the tuberculosis index was lower than it had been a few years earlier. As the number of negative reactions was steadily increasing, it would be possible to diagnose more accurately a number of affections resembling tuberculosis.

¹ For further details as to the value of the different tuberculin tests, see : P. D'ARCY HART : *The Value of Tuberculin Tests in Man*, Medical Research Council, His Majesty's Stationery Office, London, 1932, pp. 136-ix (N.D.L.R.).

Table 29.—RESULTS OF TUBERCULIN TESTS PERFORMED ON SCHOOL-CHILDREN IN RURAL COMMUNES OF THE PROVINCE OF LIÈGE (MORO'S method)

Age	Number of children examined	Number of positive reactions	Percentage of positive reactions
2 years	8	0	0
3 "	243	33	14
4 "	479	67	14
5 "	719	109	15.2
6 "	1,137	230	20.2
7 "	1,395	315	22.6
8 "	1,367	369	27
9 "	1,369	425	31
10 "	1,439	465	32.3
11 "	1,378	460	33.4
12 "	1,178	445	37.8
	10,712	2,918	27.3

In order to ascertain the reliability of the test when repeated, GILLARD carried out MORO'S test for a second time, in a commune containing nearly 700 school-children, on subjects who had given a negative reaction the first time—*i.e.*, on 400 pupils, 5.7% of the negative reactions became positive the second time, representing an increase in the total rate of 3.4%. OLBRECHTS found, under the same conditions but with the skin test, that 16% of negative reactions became positive—*i.e.*, nearly 5% of the total percentage.

In Belgium, F. DE POTTER employed PIRQUET'S skin test—scarification of the skin covered with tuberculin from the Pasteur Institute at Paris. These tests were performed on 1,663 children from 3 to 14 years of age; the total average of positive reactions was 25.5%. From 6 to 8 years, the average was 20.6%, and from 8 to 12 years, 29.2%; among children from 12 to 14, it rose to 38.2%.

Table 30.—RESULTS OF SKIN TESTS PERFORMED ON SCHOOL-CHILDREN IN CERTAIN BELGIAN TOWNS AND RURAL COMMUNES, 1936/37

Age of children	Antwerp		Brussels		Liège		Rural communes. Province of Liège		Ghent	
	Number	% positive	Number	% positive	Number	% positive	Number	% positive	Number	% positive
From 6 to 7	161	17	253	19	109	11.5	2,532	21.4	268	20.6
From 8 to 11	464	30	552	30	267	12.8	5,553	30.9	648	29.2
From 12 to 14	351	35	290	42	96	42	1,173	37.8	400	38.2

Table 30 shows that the percentage of positive reactions obtained among school-children of Ghent was practically the same for children from 8 to 12, and very nearly the same for children from 6 to 8 and 12 to 15, as the rate recorded at Antwerp, Brussels and in the rural communes of the province of Liège.

The repetition of the tuberculin test makes it possible to ascertain the moment at which sensitisation occurs, due to the child's having been infected, and has become a classical method of early systematic diagnosis. Out of 172 tests performed at a one-year interval on children from 3 to 14 years of age, DE POTTER found that negative reactions became positive in 15 cases.

Out of 82 tests performed at a two-year interval, 10 negative reactions became positive ; while out of 15 tests performed at a three-year interval, one negative test became positive. Lastly, out of 51 tests repeated at a four-year interval, 6 negative reactions became positive and one positive reaction became negative.

ROCHAT, on the basis of an enquiry carried out in 1935/36 among 450 school-children in the district of La Sarraz (Switzerland), thought that in time the repetition of the test would show which children were most liable to the risk of progressive tuberculosis : those who had been infected, who were in an allergic state and in whom tuberculosis was likely to reappear during adolescence, or those who were in an anergic state, who had not acquired immunity and had never suffered from tuberculosis. The author was surprised by the variation in positive reactions in the different villages : La Sarraz came first with 22% of " positives ", whereas in Eclépens, a densely populated village, the rate was only 3%. It should be noted that, from the point of view of the hygiene of dwellings, there is nothing to choose between La Sarraz and Eclépens, where, according to M. ROCHAT, conditions " leave much to be desired ", so that the very marked difference between these two places can only be explained by the presence of a large number of foci of infection at La Sarraz and their almost complete absence at Eclépens. According to the evidence of a local medical practitioner, Eclépens twenty years ago was full of tuberculosis patients, who have since died. In the other villages, the average of positive cases does not exceed 12%, except at Villars-Lussery, where it amounts to 20% for some unknown reason, probably the presence of undiagnosed cases.

According to ROCHAT, the " social class " factor is of no importance, as is probable during the epidemic stage of tuberculosis. The division of the 60 infected children into different classes according to the social position of their parents gives us the following figures, which are not, however, very significant :

Well-to-do farmers	12 cases (10 families) ;
Tradesmen	14 cases (10 families) ;
Officials, teachers, etc.	3 cases (2 families) ;
Well-paid workmen.....	4 cases (4 families),

making a total of 33 cases out of 60 among the middle class.

The rest of the population was divided into :

Poor farmers	5 cases (3 families) ;
Labourers	22 cases (21 families),

making a total of 27 cases among the poorer class.

As the poorer class is larger than the middle or well-to-do class, this leads to the curious finding that positive reactions are considerably less frequent in the poorer class, in spite of very defective housing conditions and of the fact that among this class of the population there are as many, if not more, tuberculosis foci than among middle-class people who are better housed.

ROCHAT asserts that a decisive factor in the dissemination of tuberculosis is the infectious patient. Tuberculosis is, it is true, a disease of the slums, but on condition that there are cases in those slums. Experience has shown the author that positive reactions are frequent, not among large families in poor circumstances, but in the hygienic homes of the middle class, where there is nothing to reveal infection apart from the skin test.

CUMMING has reported the frequency of rural tuberculosis in the United States. He regards the percentage of positive tuberculin reactions as an indication of the prevalence of tuberculosis and is of opinion that the percentage of positive reactions is in direct ratio to the number of persons suffering from open tuberculosis in the region under investigation. The figures vary according to the district from, for instance, 4.3% among children at Rexburg (Idaho) to 53% in the rural part of the State of Delaware.

The value of the results obtained by skin tests will be increased if they are supplemented by other examinations.

PAOLUCCI and BUSI employed X-rays for the detection of latent tuberculosis and primary lesions among children in a rural district of Italy, and draw attention to the results obtained by this method, provided it is applied by skilled operators.

These two Italian authors examined 300 children ; the number of tuberculous lesions detected by X-rays (primary foci, calcifications, mediastinal lymph gland enlargement) amounted to 6.5% ; and of suspect cases, to 4.1%.

GILLARD, who examined by X-rays more than 20,000 school-children coming from about a hundred different rural communes in the province of Liège, reported (Table 31) the incidence of the various pulmonary lesions observed among unselected children, and established the percentage of the different types of tuberculous lesions discovered.

Table 31.—RADIOLOGICAL TYPES OF LESIONS OBSERVED
AMONG SCHOOL-CHILDREN IN RURAL DISTRICTS OF BELGIUM, 1936

Radiological type	Number	Per 1,000 children examined	Percentage of the lesions observed
Calcified nodules	416	32	40.8
Non-calcified nodules	140	10.7	15.7
Interlobar pleuritis.....	88	6.8	9.8
Ill defined dark patches	65	5	7.3
Appearance of sub-acute or chronic basal broncho-pneumonia	57	4.4	6.4
Defined circular patches	48	3.7	5.4
Lymph gland shadows.....	18	1.4	2
Primary complexes	14	1.1	1.6
Exudative lobitis	12	0.9	1.4
Tuberculosis of the adult type	10	0.8	1.1
Pleurisy with effusion	7	0.5	0.8
Extensive sequelæ of pleurisy	7	0.5	0.8
Interlobar lesions	4	0.3	0.45
Broncho-pulmonary air cysts	1	0.3	0.45
Needle in the mediastinum	1		
Chronic pneumothorax	1		
Extensive atelectasis	1		
Totals	890	68.4	100

GILLARD points out that the classification he has adopted is based solely on the radiological aspect of the lesions. He examined them very closely and studied the selective value of the different radiological aspects observed among a group in which tuberculosis was not very prevalent and in which only 30% of the children had a positive tuberculin reaction. If, on the other hand, the proportion

of infected children had been as high as, say, 75%, the diagnostic significance of the various lesions would have been far less. As it was, he was able to bring out the relationship between the different radiological types and positive tuberculin reaction. Table 32 shows the percentage of positive tuberculin reactions for each type of lesion.

Table 32.—RADIOLOGICAL TYPES AND POSITIVE TUBERCULIN REACTIONS AMONG SCHOOL-CHILDREN IN RURAL DISTRICTS OF BELGIUM

Radiological type	Number	Positive tuberculin reactions	
		Number	Percentage
Tuberculosis of the adult type	10	10	100
Pleurisy with effusion	7	7	100
Primary complexes	14	14	100
Interlobar lesions	4	4	100
Exudative lobitis.....	12	11	92
Calcified nodules	415	369	89
Well defined circular patches	48	41	85
Lymph gland shadows	18	15	83
Interlobar pleuritis	88	68	77
Ill defined patches	65	50	77
Extensive sequelæ of pleurisy	7	4	57
Nodules	140	75	54
Appearance of sub-acute or chronic basal broncho-pneumonia	57	20	33
Totals	885	688	78

From Table 33, which deals with lesions, tuberculous or non-tuberculous, GILLARD inferred that :

(a) The proportion of children with lesions which are probably tuberculous, like that of infected children, increases as they grow older ;

(b) The curve of non-tuberculous lesions is very different : it reaches its peak between the ages of 3 and 5 and drops at the age of 6 to a level which remains practically the same until the age of 14 ;

(c) Non-tuberculous lesions are sequelæ of acute infections, particularly whooping-cough, which frequently attacks very young children ;

(d) As the aggregate proportion of lesions is affected by the partial rates, the peak is reached between the ages of 3 and 5 ;

the rate falls at the age of 6 and afterwards gradually rises until the age of 14, at which it is highest ;

(e) The ratio between tuberculous lesions and non-tuberculous lesions at the various ages may be summarised as follows : among very young children, 60% of the lesions are non-tuberculous ; as the children grow older, the proportion is reversed and from the age of 11 onwards 75% of the lesions are tuberculous.

Table 33.—LESIONS, TUBERCULOUS OR NON-TUBERCULOUS, OBSERVED AMONG SCHOOL-CHILDREN IN RURAL DISTRICTS OF BELGIUM

Age	Number of subjects examined	Lesions observed		Tuberculous lesions		Non-tuberculous lesions		Ratio between the two types of lesions	
		Number	Per mille	Number	Per mille	Number	Per mille	Non-tuberculous lesions	Tuberculous lesions
2 years	8	0	0	0	0	0	0	0	0
3 "	273	17	62	6	22	11	40	65	35
4 "	519	41	79	17	33	24	46	59	42
5 "	778	52	67	17	22	35	45	67	33
6 "	1,228	42	34	20	16	22	18	52	48
7 "	1,472	61	41	37	25	24	16	39	61
8 "	1,434	93	65	60	42	33	23	36	64
9 "	1,465	91	62	66	45	25	17	28	72
10 "	1,559	125	80	83	53	42	27	34	66
11 "	1,471	104	71	74	50	30	20	29	71
12 "	1,248	105	84	89	71	16	13	15	85
13 "	1,061	102	96	78	74	24	23	24	76
14 "	484	56	116	42	87	14	29	25	75
Totals	13,000	889	68	589	45	300	23	34	66

Investigations such as those carried out by GILLARD, which he was able to undertake with the help of the travelling prophylactic dispensary of the province of Liège, make it possible to obtain a tuberculosis map of a district.

Certain investigations carried out in the Union of Soviet Socialist Republics deal with populations that were for a long time deprived of any modern medical service. MASSINO obtained 26.5% of positive skin tests among the children of Bashkirs, a nomadic people living in the South Urals. KUDRJAVCEV examined the Buriats, a Mongol branch living in North Russia ; among children from 0-2 years, he obtained 16% ; among children from 3-7,

59% ; and among children from 8-14, 82% of positive skin tests (PIRQUET). Among the Yakuts, a Turanian people, inhabiting the Lena Basin, ISAKOV obtained positive reactions in 4% of subjects from 8-17 years of age. For the Kalmuks in the Astrachan region, METCHNIKOFF, BURNET and TARASSEVITCH before the war compiled the following figures : 0-5 years, 30% ; 6-10 years, 63% ; and 11-15 years, 83% of positive reactions.

Invasion by the *B. tuberculosis* knows no boundary.

B. ADULTS

A number of authors have attempted morbidity surveys among adults in rural districts by means of skin testing ; not all of them are satisfied with this method ; it is therefore preferable to regard these researches as isolated and provisional contributions to a study the general technique of which has still to be determined.

Among enquiries into skin tests of rural populations, that of PHELEBON covered 3,360 subjects from 0 to 25 years of age. The results are condensed in Table 34.

Table 34.—SKIN TESTS IN A RURAL DISTRICT OF TOURAINE, 1920-1926

Ages	Number of cases observed	Positive results	
		Number	Percentage
0 to 1 year	30	1	3.3
2, 3, 4 years	177	9	5.0
5, 6, 7 years	193	12	6.2
8, 9, 10 years	404	22	5.4
11, 12, 13 years	350	26	7.4
14, 15, 16 years	354	30	8.5
17 years	198	23	11.6
18	231	57	24.6
19	222	95	42.8
20	279	105	52.9
21	197	119	60.4
22	189	123	61.4
23	235	142	60.4
24	193	119	61.6

The first thing which strikes us is the very low percentage of positive tests and the very slight variation in the figures

below the age of 18. Later on, the percentage rises. From 19 to 20, it increases suddenly and afterward rises steadily until the age of 25.

One gathers the impression that the positive skin test appears among this rural population about the age of 19, as the result of inter-human contagion in the towns when they leave their villages more frequently and for longer periods. In order to supplement this enquiry, PHELEBON performed a certain number of skin tests on adults between the ages of 25 and 40. Out of 50 tests, he obtained 31 positive results—*i.e.*, 62%.

In the case of all young subjects with a positive reaction, the author endeavoured to ascertain the source of infection; in many cases, their families were unwilling to give him any information or withheld some of the facts. Nevertheless, he discovered that contagion was the chief cause of infection. It was usually due to living in the same house as someone suffering from tuberculosis :

The mother	in 18 cases.
The father	in 10 cases.
The grandmother	in 3 cases.
The grandfather	in 4 cases.
An uncle or aunt	in 7 cases.
A neighbour or friend	in 2 cases.

In ten cases measles and in fourteen cases whooping-cough appeared to have had an anergic effect as the test, which was negative before these infections, became positive during the weeks following convalescence.

In Roumania, TATARANU and PATROIANU studied, by means of skin testing, tuberculosis infection in the rural commune of Moroeni, department of Dambovita ; 1,103 persons—*i.e.*, 51.5% of the total population of the two villages—were examined (Table 35).

The highest percentage of positive reactions was obtained among women between 25 and 30 (82.7%) ; 75% of women of that age are engaged in the manufacture of woollen carpets. Among them the percentage of positive cases was 73.3, whereas among women of no occupation it was only 48. 80% of the men between 30 and 35 gave a positive reaction ; these were itinerant merchants who sold the carpets made by their wives.

The Roumanian study draws attention to the fact that "rural" does not always mean "agricultural" population. From an

epidemiological standpoint, it is important to know what the position is in so-called " agricultural " districts, whose inhabitants are engaged in various occupations ;¹ further light will be thrown on the matter by other studies now in progress at Gilau and Tomesti.

Table 35.—SKIN TESTS IN A RURAL COMMUNE OF ROUMANIA IN 1936

Age-group	Cases examined			Positive reactions			Percentages		
	M.	F.	Total	M.	F.	Total	M.	F.	Total
2 to 6 years	133	108	241	32	38	70	24.7	32.5	29.9
7 to 9 "	52	52	104	15	18	33	28.9	34.6	31.7
10 to 14 "	44	77	121	18	36	54	40.9	48.8	44.8
15 to 19 "	33	106	139	25	60	85	75.8	56.6	66.2
20 to 24 "	32	71	103	18	52	70	56.3	73.2	64.7
25 to 29 "	31	52	83	20	43	63	64.5	82.7	73.6
30 to 34 "	31	47	78	25	37	62	80.7	78.7	78.7
35 to 39 "	23	47	70	18	36	54	78.3	76.6	78.7
40 to 44 "	16	34	50	12	25	37	75	73.5	72.2
45 to 49 "	15	25	40	12	19	31	80	76	78
50 to 59 "	22	22	44	16	17	33	72.8	77.3	75
60 years and over	12	18	30	8	13	21	66.7	72.3	68.5
Totals	444	659	1,103	219	394	613	49.3	59.7	56.6

Since the sojourn of country-folk in the towns exposes them to the risk of infection, certain authors wondered whether this might affect the test. According to THORBERG HOLM, who examined 2,000 cases and obtained 54% positive reactions, these were particularly frequent among persons who had resided in a town.

DURAND, in an article entitled " What is the cause of the large number of deaths among young villagers transplanted to the towns? ", considers that persons with a positive skin test run less risk of serious infection than those with a negative one.

MOROZOWSKI summarised in a table (36) the position among the inhabitants of a Ukrainian village according to whether they had or had not resided in a town.

¹ In the United States, agriculturists and non-agriculturists were also found in certain communes studied by ARONSON in Michigan. His findings bring out in particular the difference between the whites and the Indians. Among the latter, the number of positive reactions was appreciably higher than among the whites.

Table 36.—POSITIVE SKIN TESTS AND MORBIDITY
IN A UKRAINIAN VILLAGE, 1926/27

Length of residence in a town	Cases examined			Positive skin tests (percentage)			Cases of tuberculosis (percentage)			Open tuberculosis—Totals		
	M.	F.	Total	M.	F.	Total	M.	F.	Total	M.	F.	Total
Less than one year..	103	51	154	65.0	62.7	64.3	1.9	13.7	5.8	—	1	1
One year or more	415	160	575	59.9	53.1	58.0	9.6	19.4	12.3	8	1	9
Total	518	211	729	60.9	55.4	59.3	8.1	18.0	11.0	8	2	10
Persons who have never lived in a town.	1,300	2,031	3,331	53.5	31.8	52.7	5.8	5.3	5.5	3	14	17

Women who had never lived in a town showed a comparatively low percentage of positive reactions ; they subsequently became infected and morbidity among them was greater than among men. An examination of the whole population of a village showed a lower percentage of positive reactions among women than among men (Table 37).

Table 37.—POSITIVE SKIN TESTS IN A UKRAINIAN VILLAGE, 1926/27.
PROPORTION PER 100 PERSONS EXAMINED

Sex	15-19 years	20-29 years	30-39 years	40-49 years	50-59 years	60 and over	Total
Male	62.9	77.6	81.0	81.3	69.6	65.5	73.8
Female	55.8	63.3	68.2	65.7	59.2	64.4	62.6
Total	58.9	69.6	73.4	72.3	63.2	64.9	67.4

A work by the same author covering seven villages gives particulars of the various forms of tuberculosis (Table 38). The peak for all forms of tuberculosis is reached from 20 to 49 years of age—*i.e.*, 6.9% of the total population. Pulmonary tuberculosis comes first and attacks persons of all ages, while the osseous and glandular forms show a predilection for young people.

Table 38.—VARIOUS FORMS OF TUBERCULOSIS IN SEVEN UKRAINIAN VILLAGES. PROPORTIONS PER 100 PERSONS EXAMINED, 1925/26

Form of tuberculosis		Under 14 years	15 to 19	20 to 49	50 to 59	60 and over	Total
Pulmonary tuberculosis .	Males	0.6	5.4	6.2	3.2	1.8	3.4
	Females	1.0	3.5	7.2	3.7	3.3	4.0
	Total	0.8	4.4	6.7	3.5	2.5	3.7
Glandular tuberculosis ..	Males	3.8	0.5	—	—	—	1.6
	Females	4.7	0.6	—	—	—	1.8
	Total	4.3	0.5	—	—	—	1.7
Tuberculosis of the bones	Males	0.3	—	0.08	—	—	0.1
	Females	0.4	0.2	0.1	—	—	0.2
	Total	0.3	0.1	0.1	—	—	0.2
Other organs	Males	0.07	—	0.08	—	—	0.05
	Females	0.5	—	—	—	—	0.2
	Total	0.3	—	0.04	—	—	0.1
Total number of cases ..	Males	4.8	5.9	6.3	3.2	1.8	5.2
	Females	6.7	4.3	7.3	3.7	3.3	6.2
	Total	5.7	5.0	6.9	3.5	2.5	5.7
Number examined	Males	1,453	406	1,300	187	219	3,565
	Females	1,384	508	1,455	267	215	3,829
	Total	2,837	914	2,755	454	434	7,394

* * *

While a study of the skin test is of undeniable importance, it is equally necessary to ascertain the number of cases of pronounced tuberculosis and the forms it takes, regarding which very little information is available.

After examining some 3,600 cases of tuberculosis among Polish peasants and the inhabitants of Lwow, TOMANEK reached the following conclusions :

- (1) Infiltrations were found in 99.7% of cases of tuberculosis among the peasants and in 54.9% of cases among the town-dwellers ;
- (2) Tuberculosis in both lungs was three times more prevalent among the peasants than among the town-dwellers (ratio 3.3 : 1) ;
- (3) " Old pulmonary tuberculosis " among old peasants was rarer than among the town-dwellers of the same age ;
- (4) Rural tuberculosis assumed more serious forms than tuberculosis among the town-dwellers ;

(5) Tuberculosis of the skin and mucous membranes was more prevalent among the peasants than among the town-dwellers ;

(6) Tuberculous laryngitis was much more prevalent among the peasants than among the urban population (ratio 3.5 : 2) ;

(7) The very rapid progress of tuberculosis was especially frequent among the peasants ;

(8) Rural tuberculosis was particularly marked by the tendency to produce destructive lesions ;

(9) Glandular tuberculosis was more frequent among agriculturists than among the urban population ;

(10) The actual constitution of the peasant appears to render him specially susceptible and vulnerable to tuberculosis infection.

Table 39, compiled by STOUMAN, summarises the new cases diagnosed in a rural district of Hungary, and confirms the heavy tribute paid by women.

Table 39.—NEW CASES OF PULMONARY TUBERCULOSIS DIAGNOSED IN THE DISTRICT OF SZENTISTVAN, JANUARY 1930-JUNE 1936

Age	Males	Females	Percentage of excess of the rate for females over the rate for males
Under 5 years	88	123	39.8
5-14 years	110	239	117.3
15-24 "	133	375	182.0
25-44 "	147	260	76.9
45-64 "	70	103	47.1
65 years and over	0	0	—
Totals	109	220	101.8

As STOUMAN points out, the most striking feature of Table 39 is the very heavy incidence of the disease among young women and the absence of a high incidence among middle-aged men, contrary to the findings in urban and industrial areas.

C. CONSCRIPTS AND SOLDIERS

The results of the medical examinations performed when the conscripts are called up and the incidence of tuberculosis among soldiers and reservists enable us to form an idea of the health of

rural populations. Unfortunately, however, these enquiries are not as yet conducted systematically and on a wide scale, and only a few isolated studies are available.

DUROZOY examined the findings of the Recruiting Boards from 1826 to 1835 and from 1887 to 1896 in the canton of Ribécourt (Oise). From 1826 to 1835, out of a total of 822 conscripts, only 505 were examined, the others being exempted because they had "drawn a lucky number". Out of these 505, the Recruiting Board rejected 209, including 4 for "chest disease", 9 for "scrofula" and 44 for "weak constitution".

Altogether, there were 57 young men who were probably suffering from tuberculosis at some stage or other of the disease, making 11 suspected cases of tuberculosis per 100 conscripts examined; tuberculosis was the cause of 27% of rejections.

During the period 1887-1896, all the 802 conscripts were examined, no exemptions being then allowed by the drawing of lots. Out of this number, only 38 were rejected, as against 209 during the earlier period; there were only 18 suspected cases of tuberculosis, as against 57.

In this same canton of Ribécourt, where in 1830 11 conscripts out of every 100 were suspected to be suffering from tuberculosis and were rejected on that account, in 1900 barely 2% (exactly 1.6%) were sent back to their homes.

Whatever may be the historical interest of DUROZOY's contribution, no final conclusion can be drawn from it, and we must turn our attention to more recent enquiries conducted on a large scale. DEBENEDETTI, in collaboration with FORET, communicated in 1934 the results of the skin tests performed on 165 French recruits the day after they joined their regiment. In order to establish the possible relationship between the reaction and the place of origin of recruits, these were divided into two groups: urban and rural. After careful enquiries, men living on isolated farms, in hamlets or villages with less than 1,000 inhabitants and who had spent their childhood and adolescence in the country without ever having lived in a town were placed in the rural group. The urban group comprised all men living in a place with more than 1,000 inhabitants.

Of the 165 young soldiers, 105—i.e., 64%—belonged to the rural group and 60—i.e., 36%—to the urban group. In the urban group,

40 tests were positive—*i.e.*, 67%—as against 46, or 44%, in the rural group.

A further communication from the same author (1935) covering 345 recruits and 500 reservists called up furnished more detailed particulars :

- (1) The percentage of negative tests for the whole group was 42 ;
- (2) The percentage of negative tests among the urban group was 33 and among the rural group 54 ;
- (3) The percentage of negative tests was 61 among recruits brought up in the country ;
- (4) The percentage of negative test was 49 among reservists brought up in the country ;
- (5) On the other hand, the percentage of negative tests was about the same among town-dwellers of the young recruit group and of the older reserve men ;
- (6) The proportion of negative test among urban reserve men was as high as 34%.

A change in the skin reaction during or after military service therefore occurs more frequently in the rural group, whereas in the urban group the proportion of negative tests remains practically the same when they enter and when they leave the service.

In 1936, DEBENEDETTI, OISEAU, BALGAIRIES and FORET described the variations in the tuberculin index according to the area. Out of 2,155 cutireactions performed when the men were enrolled, they obtained 34% of negative reactions among 1,529 men of urban origin ; whereas among 626 men of rural origin, the percentage was 54.

In a regiment on the outskirts of Paris, 1,219 tests were performed, 42% of negative tests being obtained ; the proportion of negative tests among soldiers of urban origin, nearly all of whom came from the Parisian area, was 31% ; and among the rural group coming mainly from Anjou, Touraine and Brittany, 56%. In a northern regiment, 936 tests were carried out, the percentage of negative reactions being 24 — 21% among the urban group coming from industrial and mining towns in the north and 46% among the rural group coming from the Pas-de-Calais or the Avesnois.

The authors lay stress on these variations in the tuberculin index according to the place of origin of the soldiers. No satisfactory interpretation appears to be possible at the present time.¹

A difference between the inhabitants of urban and rural areas has also been observed in Roumania. NASTA states that, out of 4,088 recruits and soldiers from the different garrisons, 60.4% gave a positive reaction to tuberculin during the first year of their military service. The proportion varied in different parts of the country and according to the place of origin of the recruits, but in every case it was lower among men coming from rural areas than among town-dwellers, as shown by the comparison made at the garrison of Galatz, where positive results were obtained in 73% of the 172 town-dwellers and in 61% of the 657 countrymen.

QUERANGAL DES ESSARTS studied primary tuberculosis infection in the navy and analysed the results of cutireactions with tuberculin carried out at Brest. The École des Pupilles takes boys between the ages of 13½ and 15. They chiefly come from nearby country districts or places on the coast. From 1929 to 1935, 246 skin tests were performed; the percentage of positive reactions was 42 for pupils examined on admission and 65 for those examined some time during their stay in the establishment.

On classifying the data according to the origin of the boys, we find that, out of 172 pupils coming from rural areas, 30% had positive reactions on admission and 46% later; out of 74 pupils of urban origin, 65% had positive reactions on admission and 72% later.

III. INFLUENCE OF THE RURAL EXODUS ON TUBERCULOSIS

Migration to the towns is bound to affect the trend of a social disease like tuberculosis. What happens to the persons transplanted, on the one hand as possible victims, and on the other as transmitters of the tuberculosis bacillus?

¹ According to LAURENS & GAUCH, the proportion of tuberculosis infection among soldiers coming from the towns is practically the same both in Morocco and in France; moreover, while the rural population is less exposed to contagion in Morocco than in France, the urban population may possibly run more risk of becoming infected. This confirms BIRAUD's theory described above.

The improvement of rural conditions has become a vital problem for the towns. A study by OLINESCU RADU brings out the high percentage of countryfolk among the patients of a Bucharest dispensary. Out of 507 persons suffering from pulmonary tuberculosis, 61% came from rural districts, most of them having left their homes between the ages of 15 and 25. In 15% of the cases, tuberculosis had already developed and they had hoped to be cured in the towns. Their rural origin appeared to predispose them to bilateral progressive forms of the disease. In most cases, the onset of the disease occurred after ten years of residence ; in 31% of cases, it had first appeared from one to five years after their arrival in the Roumanian capital.

E. SERGENT & F. GOUIN studied the relation between tuberculosis and the desertion of the countryside on the basis of the enquiries they had conducted among in-patients suffering from tuberculosis in the Paris hospitals. On questioning the latter systematically as to their origins, these authors were struck by the large number who had been born in the provinces. Comprehensive statistics covering 3,000 patients admitted to the wards of the Charité Hospital during the past few years have confirmed this impression ; two-thirds of the patients are in fact of provincial origin. But tuberculosis is not the only disease which presents this peculiarity ; a fair number of other diseases would no doubt be found to affect chiefly, although possibly to a less marked degree, men and women who have left the countryside in order to work in Paris. These hospital patients, however, are not a fair sample of the population as a whole, as they belong only to certain classes.

In order to ascertain the influence of the rural exodus on tuberculosis, SERGENT collected in 1928 data relating to 261 patients (144 women and 117 men) in his hospital ward ; 107 (59 women and 48 men) had been born in Paris and 154 (85 women and 69 men) in the provinces. Among patients born in Paris, there was a higher tuberculosis morbidity among women up to the age of 40—particularly between the ages of 20 and 30 ; this might be attributed to the strain of pregnancies, confinements, lactation, looking after young children, etc. In the case of men, morbidity was most marked after the age of 40 and was apparently due to the fatigue caused by their work and to excesses of all kinds, to syphilis, alcoholism, etc.

The very high morbidity among women during the years when genital life is most active was even more marked among patients born in the provinces than among those born in Paris. At other periods, when the factor of transplantation alone operates, morbidity was more or less the same for both sexes.

A study of the relation between this transplantation and the apparent onset of tuberculosis showed that it was chiefly during the first two years of residence in Paris that the disease made its appearance in persons transplanted before the age of 30 : 52 cases (28 women and 24 men). A further outbreak occurred later after the fifth year of residence.

The majority of the patients of rural origin were engaged in very arduous occupations, which those countryfolk coming to the towns chiefly follow. Among the women, by far the largest number were domestic servants, although there was also a fair sprinkling of clerks.

SERGEANT points out that the countryman who has become infected with tuberculosis is a menace to his birthplace. After a more or less lengthy stay in hospital, he returns to his native village, where he becomes a source of infection, which is all the more dangerous because rural dwellings are often defective as regards hygiene and cleanliness, and in certain districts at any rate there is only one room for all the members of the family.

Table 40.—INFLUENCE OF RESIDENCE IN THE TOWNS ON THE SPREAD OF TUBERCULOSIS AMONG PERSONS OVER 14 YEARS OF AGE, INHABITING 7 UKRAINIAN VILLAGES, 1926-27

Name of village	Persons who have resided in town									Persons who have never resided in a town		
	Total	Infected	Suffering from T.B.	Length of Stay						Total	Infected	Suffering from T.B.
				Under 1 year	Infected	Suffering from T.B.	Over 1 year	Infected	Suffering from T.B.			
1. Swinkowka.	141	86.6	6.3	32	93.8	3.1	109	84.5	7.3	299	76.6	4.3
2. Wassiljewka	170	68.8	8.2	35	74.3	5.7	135	67.4	8.9	387	61.5	2.3
3. Woinarowka	82	52.4	14.6	8	50.0	12.5	74	52.7	14.9	637	43.3	11.1
4. Nikitowka .	128	23.4	15.6	30	23.3	6.7	98	23.5	18.4	1,009	36.2	4.4
5. Tscherneschtschina ..	52	28.8	1.9	13	38.5	—	39	25.6	2.6	265	40.4	2.6
6. Scharowka .	57	80.7	15.8	14	100.0	—	43	74.4	20.9	378	83.3	5.0
7. Repki	99	59.6	15.2	22	59.1	13.6	77	59.7	15.6	356	60.7	5.6
Total	729	59.3	11.0	154	64.3	5.8	575	58.0	12.3	3,331	52.7	5.5

In the Ukraine, MOROZOWSKI examined the rural inhabitants who had lived in a town and who were a possible source of tuberculosis infection (Table 40).

The seven villages studied are typical of the Ukraine : Swinkowka, with 709 inhabitants, is 29 kilometres from Poltava ; Wassiljewka, with 1,086 inhabitants, is situated on the banks of the Dnieper, 30 kilometres from Dniepropetrowsk ; Woinarowka, with 1,335 inhabitants, is 60 kilometres away from the town of Bielaia Zerkow. The villages of Nikitowka (2,264 inhabitants), Tscherneschtschina (728 inhabitants), Scharowka (794 inhabitants) and Repki (760 inhabitants) are about 50 kilometres away from the town of Kharkov. The total population is 7,676, of whom 7,394—*i.e.* 96.3%—were medically examined.

The epidemiological enquiry was continued in 1926 and 1927 under the direction of the Kharkov Tuberculosis Institute, with the help of the local doctor. MANTOUX's test revealed the number of infected persons. The percentage of the latter suffering from a tuberculous lesion was then ascertained.

Table 40 shows, for the villages of Nikitowka and Tscherneschtschina, a higher proportion of infected persons among those who have never lived in a town. If these two places are left out of account, we find that among those who have lived in a town 71% had a positive MANTOUX reaction and were therefore infected. This proportion is lower among the rural population that remained at home, the percentage being 57%.

The morbidity statistics relating to cases of pronounced tuberculosis are somewhat striking, the proportion of patients being 11% among those who have lived in a town as against 5.5% among the others.

According to the Ukrainian investigations, women run a much greater risk than men. Most of them leave the villages before they are infected, but soon fall a prey to infection which may lead to a form of open tuberculosis.

Without knowing the exact state of health of these persons before they left home and their living conditions in the town, it is difficult to express any opinion as to the real causes of tuberculosis morbidity ; the resistance of the body and the risk to which it is exposed. This latter factor is important, even if the persons transplanted are in robust health. While some authors furnish observa-

tions relating to the exodus of persons suffering from or predisposed to tuberculosis, others state that it is the *élite*, those who are apparently strong and healthy, that emigrate.

The type of occupation plays a decisive part in bringing on tuberculosis, but the necessary statistics are lacking. We will merely reproduce a table (41) compiled by JITTA, concerning the influence of occupation on the incidence of tuberculosis.

Table 41.—DEATHS FROM TUBERCULOSIS OF THE LUNGS OR LARYNX IN THE NETHERLANDS IN VARIOUS TRADES (BASIS 100 FOR ALL TRADES COMBINED)

Trade	Mortality index
All persons following a trade	100
All persons engaged in industry	121
All persons engaged in agriculture	97
All persons engaged in sea fishing	65
All persons engaged in river fishing	81
Sailors on ocean-going ships	139
Sailors on ships engaged in inland navigation	89
Groups of trades carried on at a high temperature	83
Groups of trades carried on in the open air	97
Groups of trades entailing heavy muscular work	98
Groups of trades in which organic dust is inhaled	137
Groups of trades in which the worker is exposed to poison, gas or vapour.....	156
Groups of trades carried on in a factory	176
Groups of trades in which inorganic dust is inhaled	376

From the point of view of our enquiry, no definite conclusions can be drawn, because we do not know what trades are followed by the persons transplanted.

We can form some idea—subject to all the necessary reservations—of the tuberculation of the rural elements that have emigrated to the towns by interpreting the various statistics relating, on the one hand, to the annual rate of immigration and, on the other, to deaths from pulmonary tuberculosis. According to BIRAUD, migration to the towns of a rural element not tuberculated or only partly tuberculated may be accompanied by a high tuberculosis mortality due to sudden tuberculation. This author has correlated the annual rates of immigration and mortality due to pulmonary tuberculosis; the results he obtained are set forth in Table 42.

Table 42.—COEFFICIENTS OF CORRELATION BETWEEN THE ANNUAL RATES OF IMMIGRATION AND MORTALITY DUE TO PULMONARY TUBERCULOSIS

Town	Observation period	Time-lag between immigration and death from tuberculosis			
		No time-lag	One year	Two years	In 5-year periods without any time-lag
Amsterdam .	1875-1914	+ 0.596 ± 0.069		+ 0.699 ± 0.056	+ 0.701 ± 0.121
Stockholm ..	1877-1912	+ 0.595 ± 0.073	+ 0.443 ± 0.090	+ 0.515 ± 0.083	
Rotterdam..	1875-1913	+ 0.801 ± 0.039	+ 0.815 ± 0.036		

All these coefficients of correlation are positive ; they are significant because they are considerably more than three times higher than their probable degree of error. Lastly, there is no appreciable difference between the coefficients obtained by correlating the immigration and mortality rates for the same year and those calculated by shifting tuberculosis mortality in relation to immigration for one of two years. This shows that high immigration during one year is not immediately or necessarily followed by heavy tuberculosis mortality during that year or the following year, and that a period of heavy immigration tallies with a period of heavy tuberculosis mortality. The examination of the immigration and mortality curves for the three towns under consideration shows an appreciable and parallel decline—that is to say, during the period of 35 years covered by these observations, immigration and tuberculosis mortality have both decreased. A movement in the same direction of two variable factors is not an absolute proof that a relation of cause and effect exists between them, but it nevertheless suggests such a relation.

IV. HUMAN TUBERCULOSIS DUE TO THE BOVINE BACILLUS

In a report drawn up by the Board of Health for Scotland, stress is laid on the fact that, at the present time, the incidence of bovine tuberculosis in man is chiefly a rural problem.

Table 43.—INCIDENCE OF BOVINE INFECTION IN SCOTLAND

Form of the disease or origin of the product examined	Number of cases	Cases of bovine infection	
		Total	%
Pulmonary tuberculosis	1,087	50	4.6
Tuberculous meningitis	278	72	25.8
Cervical adenitis	211	139	65.7
Abdominal tuberculosis	83	67	80.7
Genito-urinary organs	54	15	27.7
Bones and joints	94	27	28.7
Stomach washings (children) ...	21	8	38.0
Tracheo-bronchial glands	50	12	24.0
Miscellaneous	43	4	9.3
Total	1,921	394	20.5

Table 43 shows that the bovine bacillus is a frequent cause of abdominal tuberculosis and cervical adenitis. The high percentage (38) of cases of bovine infection in children discovered after washing out the stomach is very striking, as is also the rate of 25.8% for tuberculous meningitis.

After studying the incidence and form of tuberculous affections in man caused by the bovine bacillus, LANGE asserts that there is no form of tuberculosis in which the bovine bacillus may not act as pathogenic agent; in his view, there are, broadly speaking, three categories of countries:

(1) Countries in which the bovine type of the bacillus plays no part or only a very small part in human tuberculosis, such as Japan, India and to some extent Norway;

(2) Countries with an average proportion of bovine bacilli, at the head of which comes Germany and possibly also Switzerland;

(3) Countries in which the bovine bacillus plays an extraordinarily large part: England and Scotland.

In France, to judge by a *Statistical Survey of Bovine Tuberculosis in Meurthe-et-Moselle*, by DESROZIERS, which has not yet been published,¹ the position is serious. It is estimated that at the present time from 20% to 30% of French cattle are infected. To

¹ Communicated by Professor PARIBOT.

mention only three departments—in Morbihan, the rate is 33.5%; in Drôme, it is 54.5%; and in Haute-Saône, 62.5%. According to the 1931 census, 78 out of every 100 inhabitants of Haute-Saône—i.e. 170,379 out of a total of 219,257—lived in rural districts. It should be added that, in France, the habit of boiling milk is general.

In the United States, thanks to the exhaustive investigations undertaken in connection with the "Health Demonstration", NELBACH states that in 1923 in Cattaraugus county, which has a population of 74,000—32,000 in urban areas—15% of the 80,000 cattle inspected were found to be infected with tuberculosis.

The infection of cattle must affect human health. According to RUYs, the possibility of human infection is greater in rural districts than in the towns, because the former consume more raw milk. The milk drunk by countryfolk often comes from a few cows only; if one of them is tuberculous, the risk of contamination is particularly great.

Table 44.—INCIDENCE OF BOVINE INFECTION IN SCOTLAND.
FORMS OF THE AFFECTION AND AGE OF THE PATIENTS

Form of tuberculosis	All ages			0 to 5 years			5 to 15 years			Over 15 years		
	A	B	C	A	B	C	A	B	C	A	B	C
Respiratory	166	6	3.6	140	6	4.3	26	0	0	—	—	—
Glandular	139	106	76.2	86	71	82.5	50	35	70	3	0	0
Abdominal	73	60	82.2	64	52	81.2	9	8	88.9	0	0	0
Bones and joints .	94	27	28.7	19	9	47.3	32	12	37.5	43	6	13.9
Genito-urinary .	54	15	27.7	—	—	—	24	5	20.8	20	10	50.0
Meningeal	278	72	25.9	212	61	28.8	51	8	15.7	15	3	20.0
	804	286	35.6	521	199	38.2	192	68	35.4	81	19	23.5

Note.—A = Total number of cases.
B = Number of cases of bovine infection.
C = Percentage of bovine infection.

Table 44 shows that in Scotland the proportion of cases of bovine origin decreases with age, since it is 38.2% in the first age-group and only 23.6% in the third. Apart from cases of genito-urinary tuberculosis, the number of which is very small among young subjects, this rule applies to all the clinical groups taken individually. It should be noted, however, that, among the comparatively small number of cases of meningeal tuberculosis, the figures are slightly

higher in the group over 15 than from 5 to 15, although much lower than in the 0 to 5 group.

The risk of infection by the bovine bacillus run by children has been confirmed by various authors. LANGE, on the basis of Netherlands statistics, states that the higher percentage of infection among Amsterdam children coincides with the fact that in the district from which Amsterdam obtains its milk-supply the number of cattle with a positive tuberculin reaction is twice as high as in other rural districts.

There is nothing surprising about these findings in regard to children, since they are little exposed to air borne human infection, but great consumers of milk, some of it from tuberculous cows.

Table 45.—AGE-GROUPS WITH THE HIGHEST PROPORTION OF BOVINE INFECTION—ENGLAND AND SCOTLAND

	England	Scotland
1. Cervical adenitis	a 85.7	a 84.9
2. Bones and joints	a 27.3	a 60.5
3. Genito-urinary organs	c 33.3	b 40.0
4. Lupus	a 37.3	a 100.0
5. Meningitis	a 34.8	a 6.7
6. Lungs	c 0.8	c 3.8
7. Post-mortem examinations	a 29.7	a 33.3
8. Miscellaneous	a 33.3	b 75.0

Note.—a = under 5.
b = 5 to 16 years.
c = over 16.

Table 45, relating to the age-groups with the highest percentage of bovine infection, shows that in England and Scotland, with only one exception—namely, pulmonary tuberculosis—it is nearly always among children under 5 that the largest number of cases occur. This proves that young children run the gravest risk.

What are the various conditions that encourage the outbreak of a tuberculous lesion? DESROZIERS condemns the insanitary condition of cowsheds and points out that :

“ Grooming, and choice and copious food are reserved exclusively for horses ; cattle receive what is left over. The food supply of milch cows is often inadequate because it is not based on their needs but approximately on the quantities of fodder available until the next harvest.”

Systematic studies, taking into account medical and veterinary findings, should be undertaken on this matter.

V. PROGRAMME FOR A SURVEY ON RURAL TUBERCULOSIS

Throughout this monograph, the imperfection of our knowledge in regard to tuberculosis in rural areas and the necessity for systematic, co-ordinated researches have been clearly revealed. This situation has not escaped the notice of the Health Organisation of the League of Nations.

We give below the conclusions of the Sub-Committee on Tuberculosis of the Conference of Directors of Institutes and Schools of Hygiene, held at Geneva in November 1937 ; without entering into all the details of a programme for a survey on rural tuberculosis, the Sub-Committee drew up eight paragraphs reading as follows :

I

It approves the general principle that antituberculosis action, both curative and preventive, should be adapted to local conditions—viz., to the local epidemiology of tuberculosis, the way in which the population is distributed, and the social and economic condition of the people.

II

It considers it necessary, to permit of such adaptation, to carry out regional field surveys relating, not only to the incidence and forms of tuberculosis itself, but also to the whole of the social, medical and sanitary conditions in which the population lives, for tuberculosis cannot be regarded as an isolated problem.

III

It considers that the geographical area taken for regional field surveys should coincide as closely as possible with both a natural region and an existing administrative division. In addition to

data, however, regarding the selected region, considered as a whole, full particulars should be collected in a few localities which are representative samples of the whole (intensive surveys), or which represent distinct factors, if the region is not homogeneous.

IV

For the general survey of the social, economic and health conditions of the population, the " Health Indices " system might with advantage be used. Regions in which these indices are to be used experimentally might also be selected for the tuberculosis surveys.

V

The Sub-Committee approved as a whole a detailed scheme for both regional (extensive) and local (intensive) surveys—one complementing the other—of the incidence of mortality, morbidity and tuberculosis infection. In order to determine morbidity, it is necessary, not only to question every inhabitant of one or more localities, but also to subject each to both tuberculin-testing and X-ray examination for pulmonary lesions. In the case of patients and suspects, the X-ray examination should be supplemented by clinical and bacteriological examinations.

VI

The Sub-Committee considered it desirable that a single well-defined method should be adopted everywhere for tuberculin-testing. It did not feel called upon to recommend one method in preference to another. The tuberculosis specialists entrusted with the surveys arranged by the institutes of hygiene should agree on a method beforehand. Agreement should similarly be reached as to the classification of clinical forms of tuberculosis for the purposes of the surveys.

VII

The Sub-Committee considers that the local tuberculosis survey should be supplemented by a detailed enquiry into the social factors

of tuberculosis (housing, general and hygienic education, nutrition, occupations and social position of the population), and into migratory movements of individuals which may influence the spread and evolution of tuberculosis. Consideration should also be devoted to the position as regards medical and social assistance.

VIII

The Sub-Committee considered that, apart from data on human tuberculosis, data on animal tuberculosis might usefully be collected by the competent veterinary services (tuberculin reactions, frequency of tuberculous lesions in slaughtered animals, sanitary conditions of sheds and relationship between human and bovine cases).

* * *

Since the carrying-out of the survey will consist to a large extent in the compilation of a series of statistics, the results obtained should not be either blindly accepted or treated with undue scepticism.

“ Statistical results ”, PARISOT writes, “ should not be taken at their face value, or hasty conclusions drawn from them; they must be studied and must stand the test of time. We usually turn to health statistics in order to verify the results of social activity in that field; actually, however, the information they furnish is, in many cases, inadequate. The data are too general to enable us to go into details, to discern the part played by various factors, without a knowledge of which it is impossible to draw up a rational programme of action or to appraise at their true value the results of the efforts made. These general data should now be supplemented by more exhaustive investigations. A survey should be made of a carefully selected community representative of the regional physiognomy, a parallel being drawn between all the common factors, both human and external, which may have a positive or negative influence on health, and all measures and improvements affecting those factors and the object of which is to raise the standard of living. A comparison of the facts and results will then enable us to form a truer and more accurate estimate of the situation and will provide us with indications which will be more reliable because they will have been taken from real life.”

VI. SUMMARY AND CONCLUSIONS

(1) Tuberculosis appears to be less widespread in rural than in urban districts, although there is a fair number of exceptions. It sometimes happens that in the same country certain rural areas are more affected than others.

(2) A decline in tuberculosis mortality has been observed both in rural districts and in the towns, but in the latter it began earlier and at the present time is more marked.

(3) As a rule, young women are more frequently attacked by tuberculosis in rural areas than in the towns.

(4) The data collected regarding tuberculosis mortality according to occupations are not as yet sufficient to enable any definite conclusion to be drawn, because they make no distinction between the influence of the rural environment and the agricultural occupation.

(5) Rural mortality due to tuberculosis cannot be regarded as an isolated phenomenon but must be examined to some extent in conjunction with urban tuberculosis, because there is a connection between the urban and rural incidence of the disease, the degree of tuberculation and mortality in the towns and in the countryside.

(6) Until such time as adequate and reliable notification of cases of tuberculosis in all countries, furnishes full information relating to morbidity, this can best be gauged by sample surveys dealing principally with children of school age. The investigations undertaken by means of the tuberculin test show that there are very wide variations in the number of positive cases from one village to another in districts only partly tuberculated.

(7) In the case of adults living in a rural district, the tuberculin reaction becomes positive as a result of inter-human contagion, especially when they first come in contact with a town.

(8) The examination of conscripts shows that the percentage of positive tuberculin reactions is lower among countrymen than

among town-dwellers. It is chiefly among countrymen that the tuberculin reaction changes from negative to positive during or after military service, whereas the proportion of negative tests appears to remain more or less the same in the case of town-dwellers when they enter and when they leave the service.

(9) The study of mortality by age and sex usually reveals in rural areas an exceptionally high incidence of tuberculosis among young women and a low incidence among middle-aged men, contrary to the data collected in urban areas.

(10) The rural exodus leads to an increase in the number of cases of tuberculosis. A study of the place of origin of tuberculosis patients—particularly women—in urban hospitals emphasises the importance of the problem of the rural exodus and furnishes valuable suggestions for the anti-tuberculosis campaign.

(11) Owing to the consumption of raw milk, which is particularly widespread in rural districts, the bovine bacillus appears to play a much more important part in the spread of tuberculosis in rural areas than in the towns, especially among children.

(12) A study of the information regarding rural tuberculosis to be gleaned from official sources or the publications of various authors shows that its multiple aspects and factors are not always taken into account as fully as they should be. The conclusions of the Sub-Committee on Tuberculosis of the Conference of Directors of Institutes and Schools of Hygiene held at Geneva in November 1937 should therefore be adopted and systematic and co-ordinated studies encouraged.

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THE ORGANISATION OF PUBLIC HEALTH IN THE RURAL AREAS OF BELGIUM

By

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I

INTRODUCTION

1. DEFINITION OF RURAL AREAS

Owing to the density of the population, which is higher than in any other country in the world, the expansion of industry, and the very close network of communications, there are now very few areas in Belgium that can be called purely rural.

In 1930, the population was distributed approximately as follows :

25% in the five large urban areas of Brussels, Antwerp, Charleroi, Liège, and Ghent ;

25% in the more scattered industrial areas ;

50% in the areas with a relatively dispersed population, containing few communes with more than 15,000 inhabitants. The average population of these communes is under 1,500. In these areas, every family, with very rare exceptions, has a house to itself ; often it has a kitchen-garden, and rears poultry or rabbits. But although 40% of the people of Belgium live in communes with a population of under 5,000, only 17% of the gainfully-occupied population are engaged in agriculture, horticulture, forestry, or fishing.

If the areas which present a rural appearance are taken as a whole, half their gainfully-occupied population consists of clerical and industrial workers who live in the village, but go to work every day in a neighbouring town or industrial region. This state of affairs is good for the public health, but makes it difficult to determine exactly who are the rural population.

The largest number of persons engaged in agriculture per square kilometre is to be found in the province of Antwerp and the two provinces of Flanders. It is, however, in Luxemburg, in the southern part of the province of Namur, and in the south-eastern part of the province of Hainault that—among a population much less dense than elsewhere—the proportion of agriculturists is highest.

If, therefore, we wish to find an agricultural area as characteristic as possible, our choice must fall on the province of Luxemburg—a hilly and in part wooded region—where practically the only mineral workings are stone- and slate-quarries. A certain number of so-called “ frontier ” workers go to work in the Grand-Duchy of Luxemburg ; but most of the population are engaged in agriculture, stock-raising and forestry.

In comparison with the other rural areas, Luxemburg has a poor soil, a harsh climate and customs that still belong to the patriarchal age. The population, isolated in small villages considerable distances apart, and relatively poorly served by means of communication, leads a frugal life. The strictest economy is the rule. In Flanders and the Walloon part of Brabant, the impression would be quite different ; but those are not purely agricultural areas.

Looking at the matter from another angle, we can gain some rough idea by contrasting all the communes in the country with a population of under 2,000 with all the communes with a population of over 25,000. The former group is obviously mainly rural ; and the latter, mainly urban.

It must, however, be borne in mind that, owing to the smallness of the country in proportion to its population, the density of the network of roads, canals, railways, tramways and motor-omnibus services, and the wide diffusion of broadcasting and newspapers, there are hardly any districts in Belgium that are out of touch with urban life. A village in which one man out of two goes to town every day, in which every family makes its more important purchases and seeks its entertainment in the town, knows nothing of

the physical and intellectual isolation that was for so long a feature of rural life. Such isolation, however, still prevails to a certain extent in the province of Luxemburg and in the northern parts of the provinces of Antwerp and Limburg.

2. CHARACTERISTICS OF BELGIAN AGRICULTURE

“ A soil made fertile, improved throughout the centuries, intensively cultivated and often industrialised, maintains a singularly dense agricultural population, and yet there is no overcrowding of the land.

	Agricultural population per square kilometre of arable land		Agricultural population per square kilometre of arable land
Poland	91	Belgium	71
Italy	90	Czecho-Slovakia ...	66
Yugoslavia	77	Germany	48
Roumania	74	France	45
Netherlands	72	Great Britain	19

	Quantity of fertilisers employed per hectare (in kilogrammes)		Quantity of fertilisers employed per hectare (in kilogrammes)
Netherlands	90.7	Great Britain	10.9
Belgium	78.2	Czecho-Slovakia ...	9.5
Germany	48.5	Poland	1.9
France	19.4	Yugoslavia	0.2
Italy	12.0	Roumania	0.1

“ Generally speaking, Belgian agriculture is still organised on a one-man or family basis ; 90% of the persons engaged in it are farmers (41% owners and 59% tenants) working alone or with members of their families (of whom 44.1% are women and 8.6% children under 18) . . . Small-holdings predominate ; 75% of the holdings contain less than 20 hectares, and 50% of them less than 10 hectares . . .

“ Belgium is a country of mixed farming and intensive cultivation . . . Waste land now accounts for only 5% of the total area ; and woods and forests, for about 22%.

“ According to conservative estimates, the agricultural capital of Belgium is between 44,000 and 58,000 million francs ; the

agricultural debt is little more than 1,000,000,000 francs. Through the application of intensive methods, agriculture in Belgium has become highly profitable. In the days of prosperity, the gross value of our agricultural production was estimated at 16,000,000,000 francs. In 1936, it had fallen to 10,000,000,000 francs. (These estimates cover only produce marketed by agriculturists themselves.)

“ The spirit of economy and the sober life our agriculturists lead have enabled them to make considerable savings and investments, even during the depression years.”¹

For 1934, the aggregate income from agriculture (including horticulture, stock-raising and poultry-farming) was estimated at 3,318,000,000 francs, and investments at 1,193,000,000, or 35.95% of the income. The capital employed in horticulture is estimated at 9,000,000,000 francs, and the gross yield at 1,600,000,000 (orchards and nurseries, market-gardens, flower-gardens, hothouses). The importance of stock-raising is attested by the fact that the sale of meat accounts for nearly a third of the total value of agricultural production. The capital sunk in poultry-farming is estimated at 550,000,000 francs ; and the gross yield, at 1,200,000,000.

3. GENERAL SURVEY OF PUBLIC ADMINISTRATION

Administrative organisation in Belgium is characterised by the extensive autonomy granted to the provinces and communes. The King² appoints the provincial governors and the mayors, but it is the provincial councils and the communal councils, elected by universal suffrage, that vote the budgets and appoint, the former the Permanent Deputation, and the latter the aldermen, who form a sort of permanent government for the province and commune respectively.

Communes with a population of under 5,000 are placed under the tutelage of the District Commissioner, who is appointed by the King (there are from three to eight districts in each province). Certain decisions of the mayor, aldermen and communal council can

¹ Michel DEUTCH : *L'Agriculture en Belgique*. Conférence mondiale de l'énergie (Vienna, 1938). Brussels, 1938.

² This expression, wherever met with, is to be understood as referring to a ministerial decision submitted to the King for signature.

be disallowed by the Permanent Deputation, subject to appeal to the King ; and certain decisions of the provincial authorities can be disallowed by the King. This applies chiefly to decisions involving taxation and expenditure ; the Minister of the Interior sees to it that no province or commune commits itself to excessive expenditure or imposes exorbitant taxes.

The provinces have certain duties in connection with roads and waterways ; but some of them have also taken action in regard to public health, medical care, public assistance, housing, physical training, technical and domestic training, social work and the employment of leisure.

The communes, in their turn, are responsible for maintaining and, where necessary, establishing local roads, and also elementary schools. The mayor has very wide powers to maintain order and hygiene.

4. GENERAL ORGANISATION OF PUBLIC HEALTH

The Central Health Administration forms, together with the Administrations of Public Assistance and Physical Training, the Public Health Section of the Ministry of the Interior and Public Health.

This Section has under it central services and the following inspection services ;

11 medical inspectors of health, each of whom has for his area a province (except in two provinces, where the area is half a province) and for his assistant a woman health adviser, with 1 or 2 disinfection officers ;

5 sanitary inspectors ;

11 inspectors of foodstuffs and 16 deputy inspectors ;

4 inspectors of pharmacies ;

1 controller of narcotics ;

4 inspectors of public assistance and 2 auxiliary social workers ;

3 inspectors of physical training ;

The port and Scheldt health services ;

A central laboratory of bacteriology and serology ;

An analytical laboratory for pharmaceutical products ;

An analytical laboratory for foodstuffs. (Other laboratories—university, provincial, inter-communal, or private—are officially approved) ;

The State Central Vaccine Office.

The Minister consults the Royal Academy of Medicine, the Central Health, Public Assistance, Physical Training, and Nursing-school Boards, and the Pharmacopœia, Alcoholism, Cancer, and Nutrition Commissions.

A Royal Commission has been set up to frame a general scheme for public health.

There is no general law on the subject of public health in Belgium. The laws that it is the duty of the Public Health Section of the Ministry to enforce are concerned with infectious diseases, toxic substances and narcotics, foodstuffs, the inspection of unhealthy establishments, the practice of the medical and kindred professions, school medical inspection and public assistance. The Ministry of Economic Affairs and Agriculture enforces the laws on the health inspection of domestic animals ; the Ministry of Justice enforces the lunacy laws ; the Ministry of Finance enforces the regulations governing drink-shops ; the Ministry of Labour enforces the legislation relating to factory inspection and social insurance, which is compulsory only for accidents, occupational diseases, old-age pensions and family allowances. Unemployment insurance and sickness and invalidity insurance are unofficial but subsidised.

The notification of infectious diseases, isolation and disinfection are not compulsory ; smallpox vaccination is general, and diphtheria vaccination is becoming more common.

The provinces have founded institutes of bacteriology (the sera and vaccines are made at the Pasteur Institute of Brabant), disinfection services, two sanatoria, three lying-in hospitals, one colony for mental cases, one ophthalmic institute, a number of clinics, three institutes for deaf, blind or abnormal children, six schools for nurses and six schools for midwives.

Fundamentally, however, the whole armoury of public health depends on the commune, which establishes—or does not establish, as it thinks fit—piped water-supplies, sewers, scavenging services, health bureaux, services for the inspection of foodstuffs (supplementing the State service), and so forth. Moreover, it is the

communal public assistance committee, elected by the communal council, that controls the public institutions (hospitals, homes, lying-in hospitals, orphanages, almshouses) and administers free medical assistance.

It will readily be grasped that, while the larger communes can acquit themselves honourably of these tasks, the smaller communes often lack the necessary resources, qualified personnel and initiative.

These deficiencies are only in part made good by the medical service of the mutual insurance societies (which covers three million people out of a total of eight millions); the National Child Welfare Association, a semi-official institution which makes grants to institutions established by the communes or by private initiative; the Red Cross, the National Association against Tuberculosis, the National League against Venereal Disease, the National League against Cancer, and the National League for Mental Hygiene, all of which are subsidised by the Government; and private organisations, whether neutral, political or denominational, or maintained by employers or workers.

5. PUBLIC HEALTH PROBLEMS AND VILLAGE RESPONSIBILITIES

It will be seen from what has been said above that the protection of the health of villagers depends entirely on the energies and capabilities of the communal council and private organisations.

Some villages, either independently or jointly with others, have established piped water-supply systems and hospitals. Every village has an elementary school, and many have a kindergarten and a public library; school medical inspection is universal, at all events in theory. All public assistance committees provide the elements of medical attendance for the poor. Some villages have infant consultation clinics. For all other social hygiene institutions, recourse must be had to the nearest town.

Co-operative societies, agricultural banks, farmers' clubs and women's institutes offer a variety of facilities to the village population. A beginning has been made on agricultural household training, but this is as yet confined to a minority. Very few agriculturists belong to mutual insurance societies. Every village is connected up with the electricity system, and wireless sets are

becoming very common in the countryside. There are numerous football clubs, musical and choral societies, and archery and pigeon-flying clubs.

Statistics to which we shall refer later show that the general death rate is somewhat lower in the villages than in the towns. On the other hand, the infant death rate is 25% higher than in the larger communes.

There is no question but that hygiene, maternal and child welfare, the detection of tuberculosis, venereal diseases, cancer, mental disease, and physical defects, dentistry, and preventive medicine are quite inadequate in the villages, and that through force of circumstances both diagnosis and treatment are less scientifically conducted than in the towns.

It may be observed that none of the general social laws, except the Workmen's Compensation Act, applies to agricultural labourers. In regard to their sleeping accommodation, however, the province of Hainault has issued regulations dated July 25th, 1924, and agricultural labourers' trade unions have concluded collective agreements in which that point is dealt with.

II

PUBLIC HEALTH

1. PUBLIC HEALTH PERSONNEL

There are few villages that have not established a health service or a health bureau. On the outbreak of an epidemic of scarlet fever, diphtheria, or typhoid fever, the local doctor notifies the provincial Medical Inspector of Health, who at once institutes an enquiry and arranges with the mayor for the necessary steps to be taken. The health adviser visits the patients and endeavours to make their families understand and observe the necessary precautions. She also informs the provincial disinfection service. The local practitioner applies to the provincial Institute of Hygiene for any necessary analyses.

As a general rule, there is at least one physician and one midwife in every village, or at all events in the next village.

The physician and midwife give free attendance to the poor, for which they receive a small fee from the public assistance committee. Members of mutual insurance societies are entitled, on payment of a quarter of the cost, to medical attendance and medicines for the whole family, including confinements, operations, sanatorium treatment, etc.

When a sick person has to be examined by a specialist or treated in hospital or at a maternity home, if he cannot himself pay the expenses and is not a member of a mutual insurance society, the public assistance committee will aid him, but often only to a very small extent. The committee applies to local specialists, to a public hospital, or to a private nursing-home.

Foodstuffs are inspected in the village by the inspectors of the Ministry, whose visits are necessarily few and far between.

Inspection is compulsory for meat offered for sale and derived from animals slaughtered locally or not bearing the stamp of an approved slaughterhouse ; the commune appoints and pays a veterinary surgeon for this service. Frequently, however, the butcher obtains his meat from the slaughterhouse in the neighbouring town, which is a safer method.

In the event of an accident, murder, or death in suspicious circumstances, the judicial authorities call in a medical expert from the town.

Births and deaths in the villages are not generally certified by a doctor.

The chief shortage among medical personnel is that of visiting nurses.

2. TRAINING OF PUBLIC HEALTH PERSONNEL

The course of study for the medical degree lasts seven years (including the preliminary courses in natural science) ; for the degree in pharmacy, five years ; and for the degree of licentiate in dentistry, five years. All these courses include laboratory work and practical work.

An Order-in-Council of October 29th, 1908, introduced the diploma of public health officer, and an Order-in-Council of April 30th, 1932, that of licentiate in physical education. These two diplomas are conferred after an additional year's theoretical and practical study. They are not compulsory for medical inspectors,

but there is an increasing tendency to require them for such appointments.

Courses for midwives last two years ; for bedside nurses, three years ; for visiting nurses, three years (to be extended to four years under an Order-in-Council now in preparation) ; and for social workers, three years. Here, too, practical work and probationary courses are required.

There is a Faculty of Medicine and Pharmacy in each of the four universities (the State Universities of Ghent and Liège, the Free University of Brussels, and the Catholic University of Louvain).

There are 19 schools for midwives, 40 schools for nurses, and 8 schools for social workers. The schools of nursing at Brussels and Louvain are under the supervision of the faculties of medicine of those universities. The remainder have been established by the provincial authorities, public assistance committees, or private initiative. The same is true of the schools for midwives. All the schools for social workers are the outcome of private initiative.

The free universities and the schools for midwives, nurses, and social workers are subsidised by the State.

There is a State veterinary school at Brussels, and another attached to the Faculty of Medicine of the State University of Ghent.

The inspectors of foodstuffs are either chemists, pharmacists, or agricultural engineers.

No person may practise medicine unless he holds the appropriate degree. Dentists who were in practice before the introduction of the degree of licentiate in dentistry may continue to practise. Many of the nuns serving in hospitals are not certificated nurses. It is also by no means rare for unqualified midwives to practise illegally, but in circumstances which make prosecution difficult.

There is no legal diploma for masseurs, physiotherapists, chiroprodists, and the like, but they are prohibited from diagnosing and treating. The courses and schools for their training are run privately.

3. PUBLIC HEALTH AND SOCIAL HYGIENE INSTITUTIONS IN RURAL AREAS

There is only one rural health centre—at Boitsfort, a commune adjoining Greater Brussels and containing, in addition to an

agricultural population, a large number of townspeople's country residences.

This centre, which has been established by the Red Cross with the help of a private donation, possesses a pre-natal clinic, three maternity wards, an infant consultation clinic, a school medical inspection department, a gymnasium, a tuberculosis dispensary and bathrooms and showers. Poor people are also admitted for medical consultation. There are three visiting nurses attached.

The province of Liège has set up a travelling radiological clinic to examine school-children. A doctor and a nurse tour the communes in a specially fitted-up motor-car, in order to carry out the tuberculin skin-test and radiosopic or radiographic examinations on school-children. These examinations reveal numerous defects of health, quite apart from pulmonary tuberculosis.

To protect the health of mothers and children, there are pre-natal clinics and infant consultation clinics which have been established by the communes or by private initiative ; these are subsidised and supervised by the National Child Welfare Association, a semi-official institution. Most of these clinics, however, are in the towns. For the rural areas, the Association has appointed a number of visiting nurses, whose work it is to educate mothers and weigh and measure their children in their homes. If they find anything wrong, they advise that the family doctor or a doctor attached to the National Association be called in. So far, this service exists only in one part of the country. We shall have more to say about it later on.

There are not many maternity homes or hospitals in the rural areas, because there is always a town in the near neighbourhood.

The holiday camps, preventoria and sanatoria are situated in the country or by the seaside, but are mainly patronised by the urban population. They do not form a part of the rural health machinery.

4. TREATMENT OF THE SICK IN RURAL AREAS

M. Willy Selleslags, attached to the Public Health Section of the Ministry of the Interior and Public Health, has compiled statistics of the health personnel in communes with a population of under 5,000.

" 87.4% of the communes in Belgium have a population of under 5,000. The percentage varies in different provinces, being lowest in the province of Antwerp (67.1) and highest in Luxemburg (98.7).

" All these rural localities combined contain about 40% of the total population.

" Their average population is only 1,357 ; it is particularly small (745) in the province of Namur."

Belgian Communes with Population under 5,000.

	Number	Percentage of total number	Population	Percentage of total population	Average population per commune
Antwerp	102	67.1	240,079	19.3	2,354
Brabant	297	85.3	490,939	27.8	1,653
West Flanders	201	79.4	360,203	37.5	1,792
East Flanders	242	81.5	458,057	38.5	1,893
Hainault	380	85.6	496,314	39.9	1,306
Liège	339	90.9	426,210	43.9	1,257
Limburg	188	91.3	234,866	57.3	1,249
Luxemburg	230	98.7	197,692	89.7	860
Namur	357	97.5	265,899	74.6	745
Belgium.....	2,336	87.4	3,170,259	37.9	1,357

Belgian Communes with Population under 5,000.

	Number of			
	Doctors	Dentists	Pharmacists	Midwives
Antwerp	79	2	3	71
Brabant	232	10	52	143
West Flanders	139	18	23	90
East Flanders	164	3	1	114
Hainault	315	28	134	268
Liège	259	26	147	230
Limburg	78	2	15	117
Luxemburg	107	6	32	114
Namur	161	10	73	145
Total	1,534	105	480	1,292
Communes with popula- tion over 5,000	4,921	1,002	1,994	1,684
Belgium.....	6,455	1,107	2,474	2,976

Belgian Communes with Population under 5,000.

	Number of communes served by each			
	Doctor	Dentist	Pharmacist	Midwife
Antwerp	1.29	51.0	34.0	1.44
Brabant	1.28	29.7	5.7	2.08
West Flanders	1.45	11.2	8.7	2.23
East Flanders	1.48	80.7	242.0	2.12
Hainault	1.21	13.6	2.8	1.42
Liège	1.31	13.0	2.3	1.47
Limburg	2.41	94.0	12.5	1.61
Luxemburg	2.15	38.3	7.2	2.02
Namur	2.22	35.7	4.9	2.46
Belgium	1.52	22.2	4.9	1.81

Belgian Communes with Population under 5,000.

	Average number of persons served by each			
	Doctor	Dentist	Pharmacist	Midwife
Antwerp	3,308	120,040	80,026	3,381
Brabant	2,116	49,094	19,441	3,433
West Flanders	2,591	20,011	15,661	4,002
East Flanders	2,793	152,685	458,057	4,018
Hainault	1,576	17,726	3,704	1,852
Liège	1,646	16,393	2,899	1,853
Limburg	3,011	117,433	15,658	2,007
Luxemburg	1,848	32,948	6,178	1,734
Namur	1,652	26,590	3,642	1,834
Total	2,067	30,193	6,605	2,454
Communes with population over 5,000	1,055	5,181	2,603	3,083

" These figures give no indication of the fact that the people of small communes often go to doctors, chemists and dentists in larger communes. The sole purpose of the foregoing statistics is to show the actual numbers of the health personnel properly belonging to rural areas, and to afford a comparison with the personnel available in bigger places."¹

¹ Willy SELLESLAGS : " Le personnel sanitaire dans les parties rurales de la Belgique (1938) " (*Archives de Médecine sociale*, Brussels, November 1938, I, 9, pp. 806-808).

The personal health book, the property of the patient, is coming into use, but not so much in the villages as in the towns and industrial districts.

Naturally, the country doctor is hardly in a position to employ the more subtle and complicated methods of diagnosis and treatment. Analyses, radiograms, electro-cardiograms and consultations with specialists mean a journey to the town, and are expensive. In most cases, the doctor has to do without them and, as one country doctor put it, "go by guesswork". Acute cases are properly looked after, but for the most part the weakly and chronically ailing do not receive special forms of treatment. Again, the villager has a tooth pulled out when it becomes too painful, and in due course buys a set of false ones; preventive dental hygiene and preservative treatment are almost unknown.

Most confinements in rural areas take place at home, under the care of the midwife, who calls in the doctor if necessary. The people of Luxemburg generally undergo their operations at home: there are commercial firms in Liège which have trained male nurses who bring the necessary material by motor and fit up a room in the house as an operating-theatre.

In other cases, the patient goes into a public or private hospital, either at his own expense, or at the expense of the mutual insurance society (though few people in the country districts belong to such societies), or at the expense of the public assistance committee.

Motor-ambulance services have been organised by various public assistance committees; but the largest service of this kind is operated by the Red Cross, which has 47 motor ambulances in 35 different centres, so that no house is more than 40 kilometres distant from an ambulance station.

It should be added that country doctors are allowed to dispense their own medicines.

There is never any shortage of medicines, which are partly manufactured in Belgium and partly imported.

5. HYGIENE OF ENVIRONMENT

Dust is not a problem in Belgium.

There are now few *marshes*. The *polders*—tilled or pasture land below sea-level—are well protected by dykes, as are the "water-

ingues " (areas exposed to river floods). Polders and wateringues cover 200,000 hectares—one-fifteenth of the area of the country.

In the matter of *housing*, out of 2,200,000 dwellings, 100,000 may be described as slum dwellings or overcrowded. Far too many dwellings in the countryside are still damp, dark, ill ventilated and overcrowded.

Local welfare committees can obtain loans at a small rate of interest from the savings bank to assist the poorer people to build houses and become owners.

There are also local and regional societies, affiliated to the National Cheap Housing Society, which build and sell or let cheap dwellings.

Some farms have manure-pits, but in most the manure is spread out and the liquid part escapes into the farmyard. Many cowsheds are still dark and ill kept. The milk is often of poor quality, owing to the uncleanliness of the shed, the cow, the milker's hands, and the pails and cans. The Ministry of Agriculture makes grants for the improvement of cowsheds.

Where there is no piped water-supply and no sewerage—which is the case in the majority of villages—human dejecta are received in watertight cesspools. These are periodically emptied, and the contents, both solid and liquid, are spread on the fields as manure. In a very few suburban communes (Herstal, Kinkempois, etc.), the people use buckets. Septic pits exist in some of the larger villages, either because there are no sewers or because there is no sewage-purification plant. In many communes, non watertight pits are forbidden. Where they are tolerated, they are classified and placed under the supervision of the Health Administration.

In Brabant, Hainault, and the province of Liège, the Provincial Leisure Commission concerns itself with the designing, hygiene and amenities of houses and gardens.

Few villages have a scavenging service.

Dead animals are removed free of charge and either cut up, buried or destroyed, as the case may be, by approved knackeries, each of which has a monopoly of this work in one particular area. The knackers' yards approved by the Ministry of Agriculture are classified establishments under the supervision of the Health Administration. The same applies to cowsheds, pigsties, stables, sheepfolds and goat-enclosures, when kept in the built-up part of a commune.

6. HYGIENE OF NUTRITION

We have already referred to the inspection of foodstuffs. Co-operative *dairies* are becoming common and influencing agriculturists to take greater care, because the price paid for their milk depends on its cleanliness and fat-content. These co-operative dairies also make butter. Little cheese is made.

Water-supplies are provided either by communes, by associations of communes, or by the National Water-supply Company, a semi-official institution which, at the request of the communes, plans, establishes and operates local or regional water-supplies. Works of this kind are subsidised by the Government. None-the-less, 3,200,000 people, or 40% of the whole population (1,788 communes out of 2,671), have not yet got water laid on, and this is chiefly the case in the villages, more especially in the low-lying part of the country, where the water-bearing stratum, being near the surface, is frequently polluted, whereas in the higher parts it lies deeper. In communes where there is a piped water-supply, there is no obligation to be connected to it, and the same applies to sewerage.

7. CAMPAIGN AGAINST INFECTIOUS DISEASES

Typhoid fever and the *paratyphoids* are responsible for a little under 100 deaths per annum in the whole country (0.12 per 10,000 of population). Minor epidemics still break out from time to time in some of the villages that have no proper water-supply and no sewers. In such cases, the State medical inspector of health at once intervenes and endeavours to have the necessary works carried out.

Dysentery is rare. A small epidemic, due to Flexner's bacillus, was recently observed in a crèche.

In 1936, 377 deaths from *diphtheria* were recorded (0.45 per 10,000 of population). Active propaganda is being carried on in favour of vaccination against diphtheria.

Scarlet fever is for the most part of a very mild type. It caused 124 deaths in 1936 (0.15 per 10,000 of population). No attempt at vaccination has been made.

Measles led to 336 deaths in 1936 (0.40 per 10,000 of population), and *whooping-cough* to 433 (0.52 per 10,000). Sero-prophylaxis for the former, and vaccination for the latter, are seldom employed.

Acute *poliomyelitis* caused only 25 deaths in 1936 (0.03 per 10,000 of population).

Typhus, malaria, trachoma and *rabies* no longer exist in Belgium. A few cases of *brucellosis* have been reported.

The medical inspector of health and his health adviser proceed to the spot as soon as an epidemic is reported by the local practitioner, the head master of the school, the communal authority, or any private person.

Such necessary measures as the exclusion of the patient's brothers and sisters from school, and the closing or disinfection of the school itself, are taken in accordance with instructions issued by the Government. The notification of infectious diseases is optional, however, and neither removal to hospital nor isolation at home can be enforced. None-the-less, for the most part, the people readily obey the directions of the local practitioner, the inspector of health and the nurse.

8. MORBIDITY AND MORTALITY STATISTICS

In his remarkable study entitled *La Mortalité en Belgique*,¹ M. Willy Selleslags has established a comparison for 1936 between communes with a population of under 2,000 and those with a population of over 25,000.

In the former, the birth rate is 15% *higher* than in the latter, the general death rate is 3% *lower*, the stillbirth rate is 12% *lower*, the infant death rate is 24% *higher*, the tuberculosis death rate is 27% *lower*, and the death rate from cardio-renal affections is 34% *lower*.

It is thus essentially in regard to the protection of early infancy that the health organisation in rural districts lags behind that of the towns.

9. PREVENTIVE HYGIENE AND SOCIAL WELFARE

As we have already explained, the National Child Welfare Association, a semi-official institution which draws some 25 million francs per annum from the Government, co-ordinates, supervises and subsidises the organisations set up by the communes and by

¹ Brussels : *Archives de Médecine sociale*, 1938.

private initiative. But the 279 *pre-natal clinics* deal with only 5,369 expectant mothers ; and the 1,180 *infant consultation clinics*, with 42,300 children under 1 year (out of 126,000 births). Most of these clinics are in the towns ; but 212 communes with a population of under 2,000 have an infant consultation clinic, and in some cases even two. Further, in 465 communes, most of them rural, the Association has established 140 centres for visiting nurses, who visit 10,600 infants under 1 year of age.

In all, 1,086 communes out of 2,671 have a consultation clinic or a supervision service for infants. Two infants out of every three are not covered by this organisation, and most of them live in the rural areas.

There is no medical supervision of children of *pre-school age*, except in the kindergartens and nursery schools. The National Child Welfare Association intends to introduce such supervision in the form of special clinics to carry on the work of the infant consultation clinics.

School medical inspection, like school attendance, is compulsory between the ages of 6 and 14. Each commune is required to organise it at its own expense, both for its own schools and for private schools (about 50% of the children attend private schools—nearly all Catholic—inspected and subsidised by the State). A certain number of communes have established an excellent school medical service ; but in the majority of cases, especially in the rural districts, it is still rudimentary.

The hygienic conditions to be fulfilled by school buildings and installations are laid down by Order-in-Council.

There is no medical inspection of teaching staff ; but when a teacher is found to be suffering from open tuberculosis or mental disease, he is granted sick-leave and required to undergo treatment at a clinic or sanatorium, as the case may be.

Physical training is compulsory in the schools. The teachers, however, are not always very well qualified to administer it, and in any case few village schools have a gymnasium, a playground, wash-basins, shower-baths, or a medical examination room.

Some communes have a *school dental service*, and, through the generosity of Mr. George Eastman, the Brussels Public Assistance Committee possesses a magnificent school dental institute. In the rural districts, however, there is no service of this kind.

The same applies to *vocational training*.

Agricultural training is thoroughly organised from beginning to end, but too little use is still made of these facilities.

The campaign against *tuberculosis* is carried on, under Government supervision and with Government subsidies (10 millions per annum), by a public utility institution known as the National Association for Defence against Tuberculosis. This Association manages or supports 29 sanatoria (with 3,613 beds, of which 384 were taken on November 14th, 1938, while the annual number of deaths from pulmonary tuberculosis is 4,700), 107 dispensaries, 10 preventoria, 1 nursery school and 3 homes. Doctors are tending to an increasing extent to send patients suffering from any suspicious lung trouble to the dispensary. All the dispensaries, however, are in the towns. If a period in a sanatorium is desirable, the expenses may be paid by the mutual insurance society or the public assistance committee, if the patient himself is unable to pay. Few agriculturists, however, belong to mutual insurance societies, and the public assistance committees, which in the rural areas are generally short of funds, hesitate to incur this expense, or cut short the patient's stay in the sanatorium.

Many peasants live a very stuffy life in the winter, huddling round the stove all day and sleeping with hermetically sealed windows.

Moreover, in comparatively poor rural areas, such as Luxemburg, they sell their milk, butter, cheese, eggs, meat, vegetables and fruit, and live mainly on bread, bacon and potatoes. Such a mode of life is favourable to the development and transmission of tuberculosis.

As regards *venereal disease*, the Ministry supplies anti-syphilitic remedies free of charge to anti-venereal clinics, and also, on request, to practitioners, provided the drugs are certified to be intended for patients who cannot afford to pay (no names required). The number of new syphilitic infections in Belgium has greatly declined. Gonorrhœa is still common. Venereal diseases are much less widespread in the country than in the towns; for fear of indiscretions, patients often go for treatment outside their own village.

On the subject of *alcoholism*, it is difficult to say anything definite. The law prohibits the retail sale of spirits,¹ but there are no

¹ Spirits can be bought by not less than two litres at a time, for consumption off the premises.

restrictions on the sale of beer, wine and appetisers. In the 100,000 drink-shops in Belgium, the consumption of beer is very high and, unfortunately, strong beer is coming more and more into favour ; the same tendency is beginning to show in regard to appetisers. Fraud is common in respect of spirits : many publicans—and other tradesmen as well—supply “ a little drop ” almost with impunity. None-the-less, few drunkards are to be seen, and alcoholic brutality and crime are becoming more rare.

Narcotics are under strict control, and their importance in the rural districts is negligible.

Rheumatism is common, and we are very ill equipped to do anything against it. We have no rheumatism centres or institutes. The physiotherapy departments of the hospitals in some of the large towns, and the baths at Ostend, Spa and Chaudfontaine are out of the reach of the rural population.

In cases of *cancer*, the doctor arranges for an operation or sends the patient to one of the four university centres at Brussels, Ghent, Liège and Louvain. Diagnosis often comes too late, and too little use is made of non-surgical treatments.

Mental diseases, and to a still greater extent mental backwardness and defects of character, are somewhat neglected in the countryside. Obvious mental cases are either “ interned at home ”—which is an undesirable solution, because the patient’s family generally shows little understanding, and it is impossible to arrange for proper care—or sent to an institution at the expense of the Common Fund.

The *occupational diseases* of agriculturists are generally ignored. Students are not taught about them, nor is the subject ever mentioned in the medical journals.

Preventive hygiene is far from occupying the place it deserves. We have already discussed housing and nutrition. The house is generally clean, and the linen well kept, but personal cleanliness is often confined to washing the face and hands. The use of a toothbrush is very rare. No farm has a bathroom or a shower-bath, and only a few go so far as to use a hip-bath. The only forms of physical exercise, other than those involved in agriculture and stock-raising, are cycling (which is very common), football (fairly common among the young men), archery and skittles.

The countryman’s usual way of spending his leisure is to sit indoors if the weather is bad, or outside the door if it is fine, or else—

too often—in the public-house. Youth groups, however, are beginning to be formed (boy scouts, youth hostels, etc.).

Insurance against industrial accidents and for old-age pensions is compulsory for wage-earners ; but, as we have already remarked, few countrypeople belong to mutual insurance societies.

10. PROPAGANDA IN FAVOUR OF PUBLIC HEALTH

Some lessons in hygiene are given in all schools. A certain number of the 200 Red Cross committees have been formed in large villages. In 1937/38, the National Health Crusade covered the whole country with its lectures and exhibitions of hygiene. The subject is discussed from time to time at the women's institutes, nor is it neglected in the agricultural domestic courses. Elementary ideas of hygiene are spread by the child welfare associations and by the visiting nurses. Much, however, has still to be done in this field.

The Junior Red Cross inculcates habits of everyday hygiene upon the 80,000 school-children of both sexes who belong to it. Many of these are from the country districts.

11. RELATIONS BETWEEN PUBLIC HEALTH AND SPECIAL WORKS IN RURAL AREAS

Since almost the whole of the soil is cultivated, since the network of roads, railways, canals and electric cables is very close, since irrigation is not lacking, and floods are rare and limited in scope, the only works required from the public health standpoint are piped water-supplies, sewers, the drainage of the few remaining marshes and arrangements for the burial or destruction of household refuse. Measures for preventing the pollution of water-courses, and for the destruction of sewage, are a matter that chiefly concerns the towns.

12. SHOULD PUBLIC HEALTH AND SOCIAL WELFARE BE CONTROLLED AND PROVIDED FOR BY PUBLIC INSTITUTIONS OR BY PRIVATE ORGANISATIONS ?

The traditional system in Belgium is that of communal autonomy and subsidised independence—*i.e.*, official support of organisations which are often political or religious in character. It is desirable,

however, that the governmental inspection of public health should be strengthened by an increase in the number of medical inspectors, each of whom should be responsible for an area with a population of not more than 100,000, instead of from 220,000 to 1,225,000, as is at present the case. It is essential, moreover, that the Government should have power to compel the communes to introduce a certain minimum of measures of hygiene, and the public assistance committees to organise a certain minimum medical and social service. The proper policy is to make certain services provincial, and to establish unions of communes. Our small communes, with a population of 5,000 or under, are obviously powerless.

13. GENERAL SURVEY OF HEALTH WORK IN BELGIUM

Public opinion, Parliament and the Government have never displayed as much concern for public health in Belgium as they have in other countries. The creation—late as it came—of a Ministry of Public Health was followed by a setback : after being in existence for less than two years, that Department was combined with the Ministry of the Interior. The appropriations voted are inadequate, the staff too small and the legislation rudimentary.

Several of the provinces, a few communes and the private organisations have made good these defects to a certain extent.

Other factors that have had a highly favourable influence on public health are the facts that the majority of families have a house and garden and that a large number of town-workers live in the country.

Indoor cleanliness is traditional.

Labour legislation, which developed rapidly after 1920, has greatly reduced the prevalence of occupational diseases. Real wages have risen. The unemployed, if insured, receive allowances. There has been a marked increase in the general standard of well-being.

Public health has thus been promoted more by indirect general and social measures than by health legislation or organisation.

These things, among others, still remain to be done :

- (a) The autonomy of the Ministry of Public Health should be restored and it should be provided with the necessary funds and staff.

(b) A general law on the organisation of public health should be enacted.

(c) 100,000 cheap dwellings should be built, the system of piped water-supplies and sewers should be enlarged, and rural hygiene should be organised.

(d) Provision should be made for the necessary extra nourishment for expectant and nursing mothers, children and adolescents, and the quality of foodstuffs, especially milk, should be better protected.

(e) Physical training should be made more general and properly organised.

(f) Steps should be taken to complete the organisation of the protection of mothers and children (including children of pre-school and school age) and of measures against tuberculosis, venereal disease, mental affections, cancer and rheumatism, more especially by co-ordinating the existing institutions in health centres and increasing the number of polyvalent visiting nurses.

Annex**PUBLIC HEALTH ORGANISATION
OF THE PROVINCE OF LUXEMBURG**

By

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Luxemburg is the largest and most sparsely populated province of Belgium. Its population of 222,153 is scattered over an area of 4,418 square kilometres. The density of the population in this province is thus 50 inhabitants per square kilometre, while that in the Kingdom as a whole is 272.

The Ardennes cover the greater part of the province ; it is a diversified and infertile area, with a frequently cold and damp climate. Large districts are covered by forests and waste land. The best land is used for pasturage and fodder crops, the rearing of cattle and horses being the peasants' principal source of livelihood. Here and there are small industries which maintain an inconsiderable working population : quarries, tanneries, white-cooperage workshops, tobacco industry. Emigration to the towns and to foreign countries keeps the population of the villages and small towns scattered in the valleys and over the plateaux approximately stationary.

The south is comparatively low-lying, the climate being milder, the soil more fertile and the population more dense than in the rest of the province.

The town of Arlon and the few communes in the metallurgical basin of Athus-Messancy help to give the south-eastern frontier zone a half-industrial, half-agricultural aspect. The proportion of the population living on industry is not, however, sufficiently great to alter the essentially rural character of the province as a whole.

The State, the provincial authorities and the communes share responsibility for public health measures in the area.

**I. HEALTH WORK OF THE STATE
AND THE PROVINCIAL AUTHORITIES**

The Ministry of the Interior and Public Health is represented in the province by a Food Inspector and a Medical Inspector of Health.

The duties of the latter are numerous. They may be summed up by saying that he is the highest supervisory health authority in the area. His powers are restricted by the autonomy of the communal administrations, in his dealings

with which persuasion is usually the only method open to him, and his work is also hampered by the size of the area under his supervision.

As there is no provincial Institute of Bacteriology, the Inspector of Health is also entrusted with the management of the State Laboratory, which carries out, for the medical profession and the local authorities, bacteriological research on the diagnosis of infectious diseases. Luxemburg is one of the three provinces which have no provincial health institute.

The provincial authorities have not organised an autonomous health service and have no hospital or other institution of a medical, social or educational nature. The only sanitary service which it has set up is the disinfection service, under the management of the Government Health Inspector. The cost of this service is borne by the private persons and communal authorities for whom disinfection work is done. The expense to the province is only 190 francs a year—the cost of insuring the agents employed. The result of this lack of initiative on the part of the provincial authorities is that the price of disinfection is too high and that the service is doing less and less ; in 1936, there was, in whole cantons, no single case of disinfection.

The province of Luxemburg keeps its sanitary and social expenditure down to a minimum. Provision was made in the 1936 budget for the following items of expenditure :

- (a) 68,000 francs for public relief and assistance to destitute persons ;
- (b) 59,250 francs for popular dwellings ;
- (c) 40,010 francs for the health services ; of this sum, 29,000 francs were used for completing the Institute of Hygiene—the property of an association not run for profit—and 10,800 francs were for a grant to the State Health Laboratory at Libramont ;
- (d) 323,450 francs for provincial social services and grants to private organisations and mutual insurance societies.

This makes in all 490,710 francs, or 2.21 francs a year per head of population.

In 1938, the refusal of the Permanent Deputation to vote the provincial budget reduced the health expenditure to nil.

In short, the provincial authorities do very little indeed to safeguard the health of the population.

II. HEALTH WORK OF THE COMMUNAL ADMINISTRATIONS

In Belgium, the commune is by centuries-old tradition the fundamental unit of local government, and is accorded a large measure of autonomy by the Constitution and its laws. The communal authorities are mainly responsible for the health of the locality. In point of fact, in the rural areas, the communal authorities contribute to a quite inadequate extent to the improvement of health conditions. There are many reasons for this. It may be attributed to red tape and the incompetence of the communal officials in matters of health, but still more to the political structure of the commune and the subdivision of rural areas into a great number of small government units too loosely held together.

It must as a rule be physically impossible for a small commune, left to its own resources, to find the competent staff so indispensable to efficient public health administration.

This state of affairs applies particularly to Luxemburg, where the communes are very sparsely populated. The province has only one town with a population of 12,000 (Arlon), and two communes of 5,000 (Athus and Bastogne). Of the 233 communes in the province, 211 have under 2,000 inhabitants ; and 169, under 1,000.

A perusal of the communal budgets will give a general idea of the work done by the administrative departments in the health and social fields.

In 1936, the communes of Luxemburg spent on an average 77.57 francs per head of population on public health, assistance and education.¹ Of this sum, 21.57 francs were devoted to education and 45.49 francs to water-supply, sewerage, etc. ; 53% of the expenditure which we are considering was for the creation of fresh water-supply systems or the extension of existing systems. The rural communes have made considerable efforts during the past few years to modernise their drinking-water supply systems. We may mention, incidentally, that this work was greatly encouraged by the policy of grants pursued by the Ministry of Public Health and the Economic Reconstruction Office.

Unfortunately, however, it must be admitted that the communes do not, on an average, devote to other sanitary and social services more than 10.31 francs per year per head of population, as follows :

- (a) 6.60 francs as a contribution to the public assistance budget ;
- (b) 0.03 franc for the improvement of popular dwellings ;
- (c) 0.01 franc for the encouragement of physical training ;
- (d) 3.12 francs for communal health services, including school medical inspection, maternal and child welfare, etc. ;
- (e) 0.55 franc for communal social services and grants to private social organisations and mutual insurance institutions.

From these figures may be deduced what will be shown in greater detail below—namely, that, apart from the water-supply services, communal work in the sanitary and social field simply does not exist in most of the villages of Luxemburg.

1. WATER-SUPPLY AND SEWERAGE SYSTEMS

Owing to the configuration of the land and the comparative facility with which water can be brought up, the position with regard to water-supply is fairly satisfactory. In 1936, the system extended to 158 communes with a population of 168,673, or 75.9% of the population of the province. It should, however, be pointed out that a number of these supply systems are rudimentary and insufficient to supply the whole population of the commune. It is impossible

¹ The average expenditure per head of population has been calculated on the basis of the total of the ordinary and extraordinary budgets minus the corresponding receipts.

to establish the exact number of persons really served. Since 1936, the communes have still further improved and extended the water-supply system.

The position is much less favourable in regard to sewerage. 53 communes, with a population of 87,459, are provided with sewerage. Some 20 of these systems are out of date and rudimentary, but here again it is impossible to estimate with any degree of accuracy the number of persons served.

2. REMOVAL OF HOUSEHOLD REFUSE AND SCAVENGING

37 communes have organised services for the removal of refuse, which benefit 76,924 persons, or 34.1% of the population of the province; 6 of these communal services function at least 3 times a week; 17, once a week; and 14, less than once a week. On an average, they cost the communes 3.88 francs a year per head of population.

There is a communal scavenging service in 98 localities in the province; 43 of these services function at least once a week. The population served is 108,793, or 48.9% of the total population of the province.

The problem of the removal of refuse and scavenging is connected with drainage. Stagnant waste water and small heaps of refuse left by private persons also constitute a dangerous source of ill-health, which must be abolished. The Government Health Inspector states that only too often dung-heaps, without pits, some of which are much too big, are to be found by the roadside. It would be well if the numerous local authorities who have hitherto neglected these important problems were to give more attention to them. All communes with a population of more than 1,000, and especially tourist centres, ought to organise an adequate service for the removal of household refuse and arrange for the construction of a proper drainage system. In the rural districts, the local authorities ought to control and supervise more closely the placing of manure-heaps by the roadsides.

3. DWELLINGS, OVERCROWDED DWELLINGS AND SLUMS

The communal authorities have been requested to state the total number of dwellings, and the number of overcrowded dwellings (with the number of persons inhabiting them), slum-dwellings, and cheap healthy dwellings in their areas, but apparently many of them are unable to supply all this information.

The figures for the total number of dwellings are serviceable: 169 communes, with a population of 174,812, have reported the number of dwellings in their areas. These figures are sufficiently high to enable us safely to apply to the province as a whole the data for these 169 districts. There are 49,542 dwellings on their territory, one dwelling sheltering 3.52 persons on an average.

On the other hand, we know the number of overcrowded dwellings in 20 districts only, and the number of slum-dwellings in 35 communes. It is, however, certain that there are innumerable unhealthy dwellings in the province, both in the country districts and in the small towns. The Health Inspector's reports mention a large number of slum-dwellings in centres such as Arlon, Athus, Bastogne, Marche, etc.

4. COMMUNAL SWIMMING-BATH

Barvaux-sur-Ourthe is the only commune with a swimming-bath. This is an open-air bath, and is only used during fine weather.

No place in the province of Luxemburg has a public sports ground.

5. LOCAL MEDICAL COMMITTEES. PUBLIC HEALTH COMMITTEES AND COMMUNAL HEALTH SERVICES

The Order-in-Council of May 31st, 1880, authorises the setting-up, by communal authorities, of local medical committees in all towns where there are at least three doctors in practice. These committees are entrusted with the local supervision of the medical and kindred professions, and with the duty of advising the communal authorities as to the best means of improving the health conditions of the commune. In addition, the communal authorities have been encouraged to set up public health committees whose duty it is to advise them on all questions affecting public health.

Of the 233 communes in the province of Luxemburg, 16 have appointed a local medical committee or a public health committee.

Only 22 communes have a health bureau. None of these have adequate premises or are managed by a qualified hygienist. 6 communal authorities have engaged nurses, and 1 commune has engaged a social worker. Some 20 communal authorities regularly employ the services of medical practitioners and midwives ; 12 communes have a staff for the registration of births and deaths.

8 communal authorities inspect housing, and 5 the food trades, while only 1 commune has a service for the supervision of prostitution. At the request of 43 communal authorities, 111 buildings were disinfected in 1936. There are whole cantons where not a single building was disinfected.

In the whole of the province, there is only 1 communal pre-natal clinic and 4 communal infant consultation clinics ; there is not a single communal maternity home, maternity canteen, or crèche.

151 communal authorities had 2,366 persons vaccinated against smallpox in 1936. As both medical practitioners and private organisations carry out vaccinations, the work of the communes in this respect is relatively satisfactory. This does not, however, apply to vaccination against diphtheria : 833 children were vaccinated at the request of 11 communal authorities. The number of vaccinations is clearly too small to be able appreciably to influence the diphtheria morbidity rate.

6. COMMUNAL SCHOOLS AND SCHOOL MEDICAL INSPECTION

All communes are bound by law to organise school medical inspection.

In 1936, of the 227 communes in the province of Luxemburg which possess schools, 173 had organised a school medical inspection service, employing 180 doctors. In most of the communes, however, there is inadequate inspection,

with poor results. There are many reasons for this : lack of material, lack of suitable premises, and negligence and carelessness on the part of the responsible authorities, doctors and parents.

The fresh measures recommended by the Public Health Department may perhaps do something to remedy this state of affairs. The Government Health Inspector reports that there are already signs of substantial improvement.

7. SUMMARY

Of the 233 communes in the province of Luxemburg, 158 have a water-supply system, 173 have organised a school medical inspection service (for the most part rather inefficient), and 151 have carried out vaccinations against smallpox.

As for the other health work devolving upon the public authorities, we are bound to admit that it is conspicuous for its absence in the case of most of the communal authorities in the province.

III. WORK OF PUBLIC ASSISTANCE COMMITTEES

The communal authorities are assisted by public assistance committees, whose members are appointed by the communal council. These committees enjoy legal personality ; they may receive donations and legacies and own property. It is their duty to assist indigent persons residing in the commune and to provide them with medical attendance. Public assistance committees must organise a home medico-pharmaceutical service and bear the hospital expenses of the aged, orphans, women in childbed and the sick poor.

The public assistance committees in Luxemburg spent 3,243,564 francs in 1936, or, on an average, 14.60 francs per head of population. It may be of some interest to compare this with the corresponding expenditure of public assistance committees in an industrial region—namely, the district (arrondissement) of Liège : 70.88 francs a year per head of population.

The expenditure of the Luxemburg committees is as follows :

- (a) 42.5% for administration, upkeep of institutions and hospital expenses of poor persons ;
- (b) 25% medico-pharmaceutical assistance at home ;
- (c) 12% for poor-relief in cash or in kind ;
- (d) 0.45% for preventive assistance.

The last item comprises the contributions of poor persons belonging to mutual sickness or invalidity insurance societies. Assistance to one chronic invalid suffering from a serious disease is sometimes sufficient to ruin the budget of a village assistance committee. In order to avoid such disasters, the higher authorities have advised the public assistance committees to have their indigent people made members of mutual insurance societies and to make themselves responsible for the payment of their contributions. It is a pity that this practice has not had more success.

The committees' receipts were, in 1936, considerably less than their expenses—only 2,485,335 francs, of which 15% was derived from donations and legacies, 27% from income from property and 58% from communal grants.

Many public assistance committees were unable to give exact figures for the number of patients treated in their homes. 104 committees gave medical treatment at home to 896 indigent persons. This medical attendance involved an annual average expenditure of 271 francs per patient.

175 committees gave relief in cash or in kind to 1,547 indigent persons. The average expenditure per indigent person was 453 francs. Clearly, relief on such a small scale can only palliate the poverty of these unfortunate people. Relief as practised by most of these committees has the effect of preserving poverty instead of abolishing it.

140 public assistance committees sent to hospital at their expense 771 indigent persons, including 294 aged persons, 207 orphans, and 270 persons suffering from various diseases.

438 persons, including 195 doctors, were remunerated in 1936 by the public assistance committees for services rendered.

In short, the work of the public assistance committees in the province of Luxemburg does not amount to very much. It would be a mistake to conclude that the province is particularly prosperous or that poverty is rare. As a matter of fact, the reasons for inefficiency mentioned in the preceding chapter are to be found again here—namely, lack of social sense on the part of some local authorities, and especially the excessive subdivision of the territory. Like the communes themselves, the public assistance committees are independent of one another. This system leads to really shocking results: certain committees are so rich that they hoard their incomes or use them for road-construction, while those in neighbouring villages have only some few hundred francs to spend annually. The Government has long been aware of the drawbacks of this state of affairs and has attempted to remedy them by recommending the public assistance committees to insure indigent persons against disease. It has also recommended the formation of inter-communal assistance committees. This advice has, for the most part, been ignored. The care of mental patients has been made a charge on provincial public funds. This reform has done a great deal of good, but has not been sufficient to correct the serious defects inherent in the system. Up to the present, parochialism and the force of tradition have prevented the adoption of more radical measures.

9 public assistance committees have hospitals or similar institutions—8 hospices for old people, 2 orphanages, and 2 mixed institutions for old people and orphans. A small surgical clinic is attached to the hospice at Bastogne. Several of these institutions are out of date and badly kept.

88% of the 274 beds for old people were occupied in 1936. 69% of the 122 beds for orphans were occupied, and, of the 14 beds in the Bastogne clinic, only 25%.

The assistance committees place in public hospices most of the old people for whose institutional care they are responsible. On the other hand, they entrust to private institutions a large number of orphans and nearly all their sick.

The daily cost of maintenance for an old person or an orphan is 10.18 francs on an average. The smallness of this sum shows how economically these

institutions are run, but it must also be admitted that it shows how little comfort the inmates enjoy. Reports by inspectors show that this absence of comfort is too often accompanied by a regrettable lack of hygiene.

IV. PRIVATE INSTITUTIONS AND CHARITABLE ORGANISATIONS

(a) CLINICS AND HOSPITALS

Besides the Bastogne Assistance Committee's clinic, mentioned above, there are in this province some private clinics, the largest of which is at Arlon, the others being at Aye, Bertrix, Fosse-sur-Salm, Libramont, Longlier and Saint-Mard. The construction of a clinic is contemplated by the public assistance committee of Bouillon. There is no maternity home in the province, but women can go to the clinics for their confinements.

In the opinion of the Government Health Inspector, the present system in regard to clinics is largely satisfactory, inasmuch as they are fairly evenly distributed over a large, sparsely populated province. For this system to give entire satisfaction, it would be necessary to set up two or three small clinics in the areas which still have none, modernise those clinics whose equipment is too old and strengthen the connection between the clinics on the one hand and the mutual insurance societies and public assistance committees on the other, with a view to providing the members of the former, and the poor, with the care which they require. The problem of maternity homes could be solved fairly easily by organising a maternity ward in every clinic, and perhaps building maternity homes in the more important centres.

(b) HOSPICES AND ORPHANAGES

The private hospices at Bertrix and Saint-Mard contain 122 beds. It may be pointed out that the public hospices of the province have altogether 274 beds. It does not appear necessary to increase the number of beds for old people, but out-of-date and unhygienic institutions should be modernised.

Apart from the three public orphanages, there are private orphanages at Durbuy, Guirsch, Longlier, and My, a large institution for weakly children at Amberloup, and two children's homes at Laroche and Strumont.

(c) MATERNAL AND CHILD WELFARE

The ten infant consultation clinics in the province are managed or subsidised by the National Child Welfare Association. In 1936, only 627 out of the 3,330 children born were brought to these clinics. It is inevitable that they should be frequented by a small proportion only of the children of suitable age for medical examination. The population is so scattered, and the communications so poor, that, except in a few of the larger places, the system of fixed consultation clinics cannot give good results. Either travelling teams of consultants will have to be introduced, or, better still, the number of preventive examinations

carried out by local doctors in their consulting-rooms or in the patients' homes will have to be increased. It will also be necessary to increase supervision at home by the visiting nurse, not only of all children brought to the clinics, but also of those who live too far out to be taken there.

(d) CAMPAIGN AGAINST TUBERCULOSIS

The province has no sanatorium, but a large and very well-appointed preventorium was recently opened at Amberloup (Institut Saint-Ode).

The National Anti-Tuberculosis Society has set up tuberculosis dispensaries at Arlon, Bastogne, Marche, Neufchâteau and Virton. Only one of these—that at Arlon—has the necessary equipment for X-ray examinations. A sixth dispensary is to be opened at Athus.

Anti-tuberculosis equipment in this area will be completed when a sanatorium has been opened and when the six dispensaries have been fitted with X-ray equipment.

(e) CAMPAIGN AGAINST VENEREAL DISEASE

There is only one anti-venereal dispensary in the province, but doctors can prescribe syphilis remedies at Government expense if the patients cannot afford to pay.

(f) DOCTORS AND MEDICAL AUXILIARIES

138 doctors practise in the province. There are in Luxemburg 62.6 doctors per 100,000 of population. For the whole of the country, the proportion is 77.4.

There are 44 pharmacists, 123 certificated midwives and 13 dentists in the province. The shortage of dentists is the consequence rather than the cause of the reluctance of the rural population to practise dental hygiene.

Appendix.**Application of the Health Indices selected for Rural Districts
to the Province of Luxemburg (Belgium)**

By

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Civil Engineer, Inspector in the Ministry of Public Health, Brussels.

I. INDICES OF VITALITY AND HEALTH¹**(1) DEMOGRAPHY****1. Population.**

Last census (December 31st, 1930) number : 220,920.

Last estimate (December 31st, 1936) number : 222,153.

Percentage distribution at the last population census into :

(i) Urban (population over 5,000)	7.7 (60.5)
(ii) Rural (population under 5,000)	92.3 (39.5)

2. Density of Population (1930).

Population per square kilometre :

(i) In "urban" communes	1,448 (848)
(ii) In "rural" communes	46 (129)
(iii) In the whole district	50 (265)

3. Composition of Population (1930).

Sex and age distribution of population at last census :

¹ The indices for the whole country are given in brackets.

RURAL HEALTH IN BELGIUM

Age-group	Males	Females
0-4	9,767, or 8.8% (8.4)	9,654, or 8.7% (8.1)
5-9	9,936 ,, 8.9% (8.7)	9,796 ,, 8.8% (8.4)
10-14	7,790 ,, 7.0% (6.3)	7,819 ,, 7.1% (6.1)
15-19	9,711 ,, 8.8% (8.1)	9,076 ,, 8.2% (7.9)
20-24	9,475 ,, 8.5% (8.9)	8,857 ,, 8.0% (8.5)
25-29	8,805 ,, 7.9% (9.1)	8,541 ,, 7.7% (8.7)
30-34	7,824 ,, 7.0% (8.4)	7,837 ,, 7.1% (8.2)
35-39	6,773 ,, 6.1% (7.1)	7,222 ,, 6.5% (7.4)
40-44	6,764 ,, 6.1% (6.6)	6,906 ,, 6.2% (6.7)
45-49	6,835 ,, 6.1% (6.4)	6,871 ,, 6.2% (6.4)
50-54	6,709 ,, 6.0% (5.8)	6,601 ,, 5.9% (5.9)
55-59	5,742 ,, 5.1% (5.1)	5,655 ,, 5.1% (5.2)
60-64	4,994 ,, 4.5% (4.1)	4,847 ,, 4.4% (4.3)
65-69	3,863 ,, 3.4% (3.1)	4,140 ,, 3.7% (3.4)
70-74	3,037 ,, 2.7% (2.1)	3,086 ,, 2.8% (2.4)
75-79	1,643 ,, 1.4% (1.1)	1,838 ,, 1.6% (1.4)
80-84	820 ,, 0.7% (0.5)	934 ,, 0.8% (0.7)
85-89	257	375
90-94	46 } ,, 0.3% (0.2)	64 } ,, 0.4% (0.3)
95-99	3 }	7 }
100 +	—	—
	110,794, or 50.1% (49.52)	110,126, or 49.9% (50.48)

4. *Birth Rate (1936).*

Live births per 1,000 population : 15.9 (15.33 for the whole country—13.83 in communes with population 25,000 and over).

Illegitimate live births per 100 live births : 1.7 (2.68 for the whole country, 5.45 for communes with population over 25,000).

5. *Fertility (1930).*

Number of live births for the last census year per 1,000 women at ages 15-49 : 75.7 (69.5).

(2) *MORTALITY (1936)*6. *Maternal Mortality.*

Deaths from diseases or accidents due to pregnancy, childbirth, and the puerperal condition per 1,000 live births : 4.74 (4.57).

7. *Stillbirths.¹*

Number of stillbirths per 1,000 live births : 40.6 (32.3).

¹ Children born dead after six months' gestation.

8. *Infant Mortality.*

Infant mortality under 1 year per 1,000 live births : 81.5 (86.1).

Infant deaths per 1,000 live births from :

(a) Diarrhoea and enteritis	6.2 ¹	(7.0) ^a
(b) Bronchitis and pneumonia	9.8 ¹	(16.9) ^a
(c) Other causes	55.1 ¹	(54.7) ^a

9. *Neo-natal Mortality.*

Mortality under one month per 1,000 live births : 40.3 (31.8).

10. *Mortality due to Communicable Diseases.*

1. Deaths per 100,000 population due to :

(a) Typhoid affections	1.8	(1.2)
(b) Tuberculosis	61.1	(71.9)
(i) Respiratory tuberculosis	35.8	(56.2)
(ii) Other forms	25.3	(15.7)
(c) Influenza, bronchitis, pneumonia	162.0	(138.8)
(d) Other important diseases : chronic rheumatism and gout	25.3	(6.5)

2. Deaths per 100,000 children under 15 years from diphtheria : 2 (20).

11. *Other Specified Causes of Mortality.*

Deaths per 100,000 of persons 50 years and over :

(a) Cancer and other tumours	349	(447)
(b) Diseases of the heart and circulation	744	(972)
(c) Cerebral hæmorrhage	271	(406)

12. *Declaration of Causes of Death.*

(a) Percentage of deaths from unknown or ill-defined causes : 9.8 (6.4) (senility excluded) ; 29.0 (16.8) (senility included).

(b) Percentage of deaths not medically certified : ...

13. *General Mortality.*

Number of deaths per 1,000 population : 13.35 (12.75).

¹ Not including 35 deaths after less than 3 days' life.

^a Not including 1,041 deaths after less than 3 days' life.

(3) MORBIDITY

14. *Morbidity and Case-fatality from Communicable Diseases.*

	Per 100,000 population Cases	population Deaths	Apparent case- fatality rate (deaths as percentage of cases)
Typhoid fever	1.8 (1.2)	...
Diphtheria	0.4 (4.5)	...
Scarlet fever	0.4 (1.5)	...
Measles	0.9 (4.0)	...
Whooping-cough	8.6 (5.2)	...
Influenza	50.9 (23.0)	...
Tuberculosis, respiratory	35.8 (56.2)	...
Tuberculosis, other forms	25.3 (15.7)	...
Malaria	0 (0.1)	...
Trachoma

15. *Tuberculosis.*

- (a) Number of cases of open tuberculosis (Tb. bacillus test positive) newly registered or reported :
- (i) Per 100,000 population
- (ii) Per 100 deaths caused by tuberculosis (all forms) ..
- (b) Tuberculin skin-testing : percentage of positive reactions according to age (in years) among certain groups of the population (school-children, factory-workers, recruits, etc.)

16. *Veneral Diseases.*

- (a) Syphilis :
- (i) Number of contagious primary or secondary cases reported, registered or otherwise discovered per annum per 100,000 population
- (ii) Percentage of positive sero-reactions among certain groups of the population (pregnant women, etc.)...
- (b) Gonorrhœa : Number of cases reported, registered, or otherwise discovered per 100,000 population

17. *Mental Disease.*

Number of mental cases admitted to institutions or placed in families, per 100,000 population : 198 (295).

18. *Blindness.*

Number of blind persons per 100,000 population : ... (41).

Blindness due to :

- (a) Trachoma
- (b) Other causes

II. INDICES OF ENVIRONMENT

EXTERNAL ENVIRONMENT

(1) METEOROLOGY (1936)

19. *Meteorological Information.*

(a) Temperature :

(Temperature Centigrade.)

	January	February	March	April	May	June	July	August	September	October	November	December	Whole year
Average maximum	6·1	4·6	11·2	10·4	20·7	23·7	23·2	23·7	19·1	10·8	7·9	4·4	13·8
Average minimum	1·1	-4·3	-0·5	0·9	5·6	8·7	10·9	9·6	7·2	1·2	1·8	-1·7	3·6
Mean	3·8	0·1	5·3	5·6	13·7	16·2	17·1	16·7	13·2	6·0	4·8	1·3	8·7
Absolute maximum	11·5	11·0	19·1	17·2	29·4	35·8	30·7	32·2	27·1	15·8	13·0	11·8	35·8
Absolute minimum	-5·5	-12·9	-5·6	-5·5	-1·6	-1·3	4·9	4·5	-1·4	-7·1	-6·5	-8·6	-12·9

(b) Rainfall :

- (i) Annual (in millimetres) 999
- (ii) Number of days with rainfall 197

(c) Relative humidity (annual mean) : 77% at 1 p.m.

(d) Average hours of sunshine per day : 3.8 hours.

Houffalize station, 330 metres above sea-level, at the north-eastern extremity of the province.

(2) HOUSING

20. *Type of Dwelling.*

Percentage of population in one-family houses : Practically the whole.

21. *Overcrowding.*

(a) Percentage (at last census) of the population which is lodged as follows :

1 person per room
2 persons ,, ,,
3 ,, ,, ,,
4 ,, ,, ,,
5 ,, ,, ,,
6 ,, or more per room

(b) In the absence of such information, percentage of the population living in dwellings with more than two persons per room : ...

(c) In the absence of indices (a) and (b), percentage of dwellings containing (at the last census) :

1 room	5 rooms
2 rooms	6 or more rooms
3 ,,		—
4 ,,		100

22. *Newly-built or Improved Dwellings.*

(a) Percentage of newly-built houses : ...

(b) Percentage of improved houses : ...

(3) SANITATION

23. *Disposal of Excreta.*

A. Percentage of total population (or if this figure is not available, percentage of dwellings) :

(a) With closets
(i) Connected with sewerage system. About 30	
(ii) With watertight cesspit
(iii) With non-watertight arrangements
(b) Without closets

B. Percentage of manure-heaps (containing solid and liquid stable manure) with watertight bottom : ...

24. *Water-supply.*(a) *Type of supply.*

	Number of sources	Percentage of population served
A. Public :		
(i) Piped water-supply		About 60
(ii) Common wells, springs and cisterns
B. Private sources

(b) <i>Inspection of water.</i>		
	Number of analyses of water and inspections of water- supply	Percentage of satisfactory samples
A. Public supply :		
(i) Piped water-supply
(ii) Common wells, springs and cisterns
B. Private sources
(c) <i>Improvements.</i>		
	Percentage of sources condemned	Percentage of sources improved
A. Public supply :		
(i) Piped water-supply
(ii) Common wells, springs and cisterns
B. Private sources

(4) CONSUMPTION

25. *Food Consumption.*

.....

26. *Alcohol Consumption* : Belgium, 1936.Consumption *per capita* per annum :

(a) Beer (in litres of alcohol at 50° Gay-Lussac)	5.21 ¹
(b) Spirits (in litres of alcohol at 50° Gay-Lussac)	1.17

SOCIAL ENVIRONMENT

(1) OCCUPATIONAL ENVIRONMENT

27. *Occupations (December 31st, 1930).*

Gainfully-occupied population engaged in :

	Number	Percentage
(a) Agriculture, forestry and fishing	36,674	40.4 (17)
(b) Industry	32,146	35.5 (54.6)
(c) Commerce	8,148	9.0 (14.5)
(d) Public administration and national defence	4,983	5.5 (4.5)
(e) Liberal professions	3,168	3.5 (3.7)
(f) Domestic and personal services	3,602	4.0 (4.9)
(g) Others	1,951	2.1 (0.8)
Total	90,672	100 (100)

¹ The alcohol content of beer is assumed to average 3%.

28. *Forms of Farming (December 31st, 1929).*

A. <i>Farmers.</i>		%	
(a) Owners		62.2	(48.2)
(b) Tenants		37.8	(51.8)
		100	(100)
B. <i>Labour.</i>			
(a) Farmers and members of their families		96.2	(90.0)
(b) Agricultural labourers		3.8	(10.0)
		100	(100)

29. *Utilisation of the Soil (1929).*

Total area of the district : 441,918 ha. 58 a.

Percentage of above area cultivated	44.7	(62.5)
Percentage of above area forest	40.9	(17.8)
Percentage of above area waste land	3.2	(3.0)
	88.8	(83.3)

30. *Size of Holdings (1929).*

(a) Distribution of agricultural holdings according to area :

	(i) Holdings			
	Number	Percentage		Area
		Number	Area	
0-1 hectare	20,099	42.9	(74.2)	2.8 (6.6)
1-4 hectares	14,724	31.4	(17.2)	20.4 (26.0)
5-9 "	6,811	14.5	(5.0)	24.2 (20.7)
10-19 "	3,690	7.9	(2.5)	25.4 (19.9)
20-29 "	856	1.8	(0.6)	10.0 (8.7)
30-49 "	432	0.9	(0.3)	8.1 (7.2)
50-99 "	222	0.5	(0.2)	7.3 (7.1)
100 + "	26	0.1	(0.0)	1.8 (3.8)
		100	(100)	100 (100)

	(ii) Agricultural population ¹	
	Number	Percentage
0-1 hectare	205 (27,051)	0.4 (4.1)
1-4 hectares	19,608 (293,684)	34.2 (44.3)
5-9 "	17,208 (159,786)	30.1 (24.1)
10-19 "	12,695 (106,856)	22.2 (16.1)
20-29 "	3,553 (34,269)	6.2 (5.2)
30-49 "	2,202 (20,749)	3.8 (3.1)
50-99 "	1,546 (14,773)	2.7 (2.2)
100 + "	240 (5,214)	0.4 (0.8)
		100 (100)

¹ Agriculturists and members of their families.

31. *Crops (1929).*

Principal crops	Area cultivated (hectares)	Percentage
(a) Wheat	4,318.06	2.2 (8.1)
(b) Rye	8,212.73	4.2 (9.7)
(c) Oats	29,140.94	14.8 (12.1)
(d) Other cereals ¹	7,672.45	3.9 (1.0)
(e) Potatoes	12,021.19	6.1 (8.0)
(f) Hay and fodder	128,235.13	64.9 (43.4)
(g) Sugar-beet	14.39	0.0 (2.8)
(h) Tobacco	141.39	0.1 (0.1)
(i) Fruit	2,286.92	1.2 (3.7)
(j) Grapes (hothouse)	0.56	0.0 (0.0)
(k) Vegetables	1,314.77	0.7 (2.4)
(l) Other crops (flax)	4,114.08	2.1 (7.4)
		(1.3)
	197,472.61	100 (100)

32. *Livestock (1929).*

Number of animals per 100 population :

A : (a) Cattle	63.8 (20.8)
(b) Horses	10.5 (4.0)
(c) Pigs	30.4 (12.3)
(d) Sheep	4.9 (2.3)
(e) Goats	3.6 (2.0)
B : Poultry	365.4 (269)
Rabbits	19.3 (19.0)

(2) COMMUNICATIONS AND ELECTRIFICATION

33. *Means of Communication (1936).*

(a) Roads : number of kilometres permanently fit for vehicular traffic :	
(i) Per 100 square kilometres	30.5 (34.2)
(ii) Per 1,000 population	6.1 (1.3)
(b) Motor vehicles : number per 1,000 population	26.8 (24.8)
(c) Public passenger transport :	
Percentage of the population whose communes are crossed and served by a regular railway or omni- bus service	97.4

¹ Spelt, barley, meslin.

(d) Telephones :

(i) Number of telephones per 1,000 population	29	(43)
(ii) Percentage of the population living in built-up areas not connected to the telephone system	0	

34. *Electrification.*

(a) Percentage of dwellings provided with electricity ..	75.8	
(b) Number of kilowatt-hours per head of population per annum	49	(279)

(3) EDUCATION

35. *Cultural Level.*

School attendance :

(a) Percentage of children of school age regularly attending school	99.6	
(b) Percentage of children between the ages of 10 and 14 years earning wages	0	
(c) Post-school education : percentage of young people beyond compulsory school age attending educational institutions	
(d) Illiteracy (1930) : percentage of illiteracy among persons aged 15 years and over	1.9	(6.0)

III. INDICES OF PUBLIC HEALTH ACTIVITY

(1) PERSONNEL AND EQUIPMENT

36. *Medical and Auxiliary Professions.*

A. Number per 100,000 population of :

(a) Doctors	62.6
(b) Pharmacists	19.8
(c) Licensed midwives	55.4
(d) Nurses (all classes)	?
(e) Dentists	5.9

B. Staff of health services and other public medico-social services	Full-time staff engaged in		Part-time staff engaged in	
	Preventive medicine	Curative medicine	Preventive medicine	Curative medicine
(i) Medical officers ¹	1		30	
(ii) Nurses	6		0	
(iii) Public health nurses ¹	1		0	
(iv) Sanitary inspectors	0		20	
(v) Others ²	0		0	

37. Clinics and Health Centres.

	Number	Number per 100,000 population
(a) <i>Independent specialised clinics :</i>		
(i) Pre-natal	1	0.5
(ii) Infant	10	4.6
(iii) Pre-school	0	0
(iv) School	0	0
(v) Tuberculosis	5	2.3
(vi) Venereal disease	1	0.5
(vii) Mental	0	0
(viii) Others ³	0	0
(b) <i>Health centres representing a total number of consultation services</i>	0	0
(c) <i>Total number of clinics independent or in health centres (a + b) :</i>		
(i) Pre-natal	1	0.5
(ii) Infant	10	4.6
(iii) Pre-school	0	0
(iv) School	0	0
(v) Tuberculosis	5	2.3
(vi) Venereal disease	1	0.5
(vii) Mental	0	0
(viii) Others ³	0	0

38. Hospital Institutions.

(a) Hospitals (not including asylums, mental hospitals and sanatoria) :

	Number of institutions	Number of beds	Number of beds per 1,000 population
Number of institutions	6	210	9
			% per 100 beds
(i) For communicable diseases	0	0	0
(ii) For maternity cases	0	0	0
(iii) For children	0	0	0
(iv) Others	6	210	100

¹ This does not include those *exclusively* engaged in curative medicine.² Specify.³ Cf. comments.

(b) Tuberculosis institutions :	Number of beds	Number of beds per 100,000 population
(i) In special hospital wards	0	0
(ii) In sanatorium-hospitals	0	0
(iii) In sanatoria.....	0	0
 (c) Other institutions :		
(i) Services for chronic diseases	0	0
(ii) Mental disease institutions	0	0

(2) MEDICO-SOCIAL ACTIVITY

39. Maternal and Infant Health Services.

(a) Number of pregnant women per 100 live births :		
(i) Attending pre-natal clinics		3
(ii) Visited at home by nurses ¹
 (b) Number of infants under 1 year per 100 live births :		
(i) Attending infant clinics
(ii) Visited at home by nurses ¹

40. Health Services for Children.

(a) <i>Pre-school age.</i> Percentages of children of pre-school age :		
(i) Attending childrens' clinics
(ii) Visited at home by nurses ¹
 (b) <i>School age.</i> Percentage of school-children :		
(i) Medically examined during the year
(ii) Visited at home by nurses
(iii) Suffering from malnutrition ¹
(iv) Attending schools at which supplementary feeding is supplied
(v) Receiving adequate treatment after medical inspection
(vi) Diagnosed as mentally deficient, mentally backward, etc.

41. Control of Tuberculosis.

(a) Cases of open tuberculosis (Tb. bacillus test positive) expressed as a percentage of total cases on registers in dispensaries
---	-----

¹ Cf. comments.

- (b) Number of dispensary consultations per registered person per year
- (c) Number of home visits by public health nurses per registered person per year

42. *Active Immunisation.*

Percentage of persons vaccinated during the year by diseases and ages :

- (a) Smallpox (first vaccinations) % births
- (b) Tuberculosis (B.C.G.) (first vaccinations) . % births
- (c) Diphtheria per 100 children under 10 years
- (d) Typhoid fever (specify age-groups, contacts, etc.)
- (e) Other diseases (specify)

43. *Laboratory Work.*

Number of samples examined per known case of infection :

- (a) Typhoid affections 146, positive 24%
- (b) Diphtheria 1,402, positive 17%
- (c) Tuberculosis 971, positive 21%
- (d) Syphilis (number of samples examined per 100,000 population) 346, positive 9%



THE RECENT TREND OF MEDICO-SOCIAL POLICY IN EUROPE¹

CONTENTS

	Page
I. INTRODUCTION :	
<i>Historical Retrospect :</i>	
The European Conference on Rural Hygiene of 1931 . . .	664
The European Conference on Rural Life of 1939 . . .	665
II. PROBLEMS :	
1. Definition of Medical Assistance	666
2. Number of Doctors	669
3. Number of Pharmacists	670
4. Number of Auxiliary Personnel	671
Nurses	671
Midwives	672
5. First Aid	673
6. Centres of Diagnosis	673
7. Hospitals	674
8. Laboratories	677
9. Specialists	678
10. Means of Realisation :	
(a) Principles of Collaboration	679
(b) Public Authorities	679
(c) Health Insurance	679
(d) Public Assistance	679
III. PUBLIC HEALTH SERVICES :	
A. General Considerations :	
1. General Administrative Considerations	685
2. Medical Officers of Health	687

¹ This report was drafted in September 1938, by Dr. R. H. HAZEMANN, after his return from a tour of enquiry in various countries of Europe.

MEDICO-SOCIAL POLICY IN EUROPE 663

	Page
3. Size of the Public Health District	689
4. Unity of Direction	690
5. Minimum Personnel	691
Family Social Workers	692
Sanitary Inspectors	695
6. Sanitary Engineers	696
7. Programme of Services :	
(a) Branches of Work	697
(b) Notifiable Diseases	699
(c) Statistics on Social and Economic Conditions .	701
8. Co-ordination	702
9. Budget	703
10. Local Financial Contributions	705

B. *Rural Health Centres :*

1. Definition	706
2. Relationship of the Health Centre to the Health Services.	708
3. Diversity of Types of Health Centre	710
4. Primary and Secondary Health Centres	710
(a) Functions of the Health Centre	714
1. Maternal and Child Welfare	714
2. Tuberculosis	716
3. Venereal Diseases	717
4. Epidemic Diseases	718
5. Domestic Sanitation	721
6. Education and Propaganda	722
7. Laboratory Analyses	724
8. First Aid	724
(b) Buildings and Equipment	725
(c) Liaison	728

IV. TRENDS OF MEDICO-SOCIAL POLICY IN RURAL AREAS 729

I. INTRODUCTION

HISTORICAL RETROSPECT

The European Conference on Rural Hygiene of 1931.

The Conference met at Geneva on June 29th, 1931, as the outcome of a proposal made by the Spanish Government to the League Council, in September 1930, that a conference of representatives of European States should be convened for the purpose of a technical international study of rural hygiene, hygiene being regarded as one of the most important factors in the organisation of agricultural areas in Europe.

The three groups of experts of the Preparatory Committee had prepared reports on :

1. Guiding principles and suitable methods for ensuring effective medical assistance in rural districts.
2. The most effective methods of organising the health services in rural districts.
3. The most effective and economical methods of ensuring the sanitation of rural districts.

Twenty-three European nations sent delegations to the Conference, and eight nations outside Europe appointed observers. The International Labour Office and the International Institute of Agriculture at Rome co-operated, and the League of Red Cross Societies and the International Association of Medical Officers were represented.

At the request of the Conference, the Health Organisation of the League convened an urgent meeting of Directors of European Schools of Hygiene to consider how far those schools could undertake certain international studies recommended by the Conference.

The reports of the four committees, which were unanimously adopted, constitute the series of resolutions of the Conference, which closed on July 7th, 1931. The recommendations adopted formed

a brief but practical guide to efficient and economical health administration. They laid down a programme of studies to be carried out under the ægis of the Health Organisation ; and they urged the desirability of convening a new European conference in five years' time to examine the results achieved and to adapt those recommendations to current problems and to the progress of public health technique.

The European Conference on Rural Life of 1939.

Having been entrusted with the task of preparing for this second European Conference on Rural Hygiene, the Health Committee began, in 1931, a systematic study of factors affecting the health of the peasant population. These investigations, by clarifying the views outlined at the previous Conference, have shown that an amelioration of the standard of health in the countryside is inconceivable without a parallel improvement in the living conditions of the population. Obviously, health, economic, and social factors cannot be considered separately, and the concept of the standard of living must form the basis of any real progress in public health. The Health Committee accordingly concluded, in 1936, that the new conference ought to consider questions of rural hygiene as part of the more general problem of rural life as a whole, taking into account the factors of every description affecting the health of the rural population.

The Assembly approved this conclusion, and decided to convene a " European Conference on Rural Life " instead of a conference on rural hygiene.

The agenda comprises the following eight items : demographic conditions—land tenure systems—co-operatives—agricultural credit—education—medico-social policy—nutrition—rural planning.

The study of medico-social policy, which forms the subject of the present report, entails the examination of the " results of the recommendations of the European Rural Hygiene Conference of 1931 : health centres—collaboration and co-ordination of the action of the public health and relief authorities, of the medical practitioners, of insurance institutions, of mutual assistance associations, health co-operatives and benevolent societies, general study of certain diseases specially affecting rural populations and rural economy (including alcoholism) ". It will follow the plan of the 1931 recommendations—namely, historical—problems—methods.

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For the purposes of the present report, the term "medico-social policy" will be understood to cover all that concerns curative and preventive medicine, and the organisation and activities of the health services. Sanitation will not be dealt with here, because it is included in the work of the committee appointed to study the eighth item on the agenda of the 1939 Conference, entitled: "Rural planning (area planning, community planning, the rural house and outbuildings)"; nor will nutrition, which was not discussed in 1931, and is the seventh item on the new agenda.

We shall first deal in turn with each of the 1931 recommendations, and consider how curative and preventive medical assistance—that is to say, medical care—have been provided in rural districts, what methods have been found most effective for the organisation of health services in rural areas, and what investigations have been undertaken by institutes and schools of hygiene in connection with rural hygiene. We shall then see what tendencies have arisen since 1931. On the assumption that the rural population should enjoy the same advantages as the urban population, has it been found possible simply to extend to the countryside the medico-social protection afforded to urban areas? Or have the special methods recommended in 1931 been adopted and systematically applied in rural districts by the public authorities, and to what extent has it been possible to co-ordinate them with the measures in force in urban areas?

II. PROBLEMS

1. *In the largest sense, effective medical assistance may be considered as indicating a medical service organised in such a way as to place at the disposal of the population all the facilities of modern medicine in order to promote health and to detect and treat illnesses from their incipency.*¹

Some people might see a certain antinomy between treatment and prevention, but the evolutionary process which can be observed by

¹ In the present report, all the parts indented and in italics are textual reproductions of the recommendations of the 1931 Conference.

comparing different countries shows that there are four stages in the historical development of medicine.

To begin with, medical care is confined to cases of serious or very painful disease, or illness which prevents the breadwinner from providing for his family. This is the irreducible minimum of demand for medical care ; if the patient is very poor, the cost is borne by public assistance. It is not until later that the doctor is called in in less serious—or apparently less serious—cases to prevent complications, invalidity, whether partial or total, temporary or permanent, and death. This fraction of the demand is more elastic ; it usually comes only from the best educated and most affluent portion of the population. Later still, the preventive and social aspects come to the fore, the objective of medical care being to prevent the appearance and spread of disease within the family or group. That is the purpose of social medicine and social hygiene. Social insurance is designed to cover the whole demand, both the irreducible minimum and the elastic portion ; hence its constructive value in the sphere of health. At the final stage—that of the protection of public health—the aim is not merely to cure or prevent disease, but also to improve the health of the individual and the community.

To attack each series of problems separately on each of the fronts mentioned above would entail an excessive division of labour, and was recognised as a mistaken conception by the 1931 Conference, which asserted that the campaign against a disease which had broken out or which threatened the population should be carried on hand in hand and co-ordinated with the protection of public health. It has also been recognised that, for psychological as well as practical reasons, the Samaritan duty of looking after the sick must form the foundation of any complete system of curative and preventive medical assistance. •

The care of the sick—" medical assistance " in the proper sense of the term—so far as they are indigent, is in the hands of the district medical officer and the special services for free medical assistance and hospital treatment ; persons of modest means in rural districts are being looked after to an ever increasing extent by social insurance institutions. Public authorities are less inclined than in the past to spend excessive sums on the care of the sick at the expense of provision for the prevention of disease and the maintenance of health, whether in the form of medico-social protection or the improvement

of conditions generally. Detailed statistics to illustrate this are not available for Europe.

In countries where rural economy has retained its traditional form, where a health organisation has only recently been established and health equipment and personnel are limited, the problem of medical assistance¹ has in some cases been attacked chiefly from the preventive angle, by means of a campaign against infectious diseases and so-called social—that is to say, transmissible—diseases, which take a long time to cure and are costly to treat.

It has frequently been found that the public has no idea whatever of purely preventive medical assistance not concerned with the treatment of patients, and that the machinery and equipment of preventive medicine cannot produce their full effect unless direct contact is maintained with the services for combating diseases that have already made their appearance. Liaison between the towns and rural districts has therefore been strengthened, to enable the latter to benefit from the hospital institutions for treatment and diagnosis already established in urban areas.

“Medico-social protection” shows a steadily increasing tendency to go further than the immediate prevention of social diseases alone, and to concern itself directly with the health and well-being of the people or indirectly with their standard of living; its aim is to ensure an environment favourable to the development of the individual and the family and unfavourable to the appearance of all kinds of disease and to the transmission of infectious diseases. This series of complicated and interdependent measures covers both the patient and the healthy person, as well as the surroundings in which each lives.

The value of such a medico-social policy has been recognised in all countries by the public authorities, who find themselves obliged to take direct action in rural areas, more especially because, while manufactured products find a readier market there, owing to the downward trend of prices, the same cannot be said of medical care. Improved medical equipment has neither simplified nor lightened

¹ In this text and in the 1931 recommendations, the term “medical assistance” is used in the widest sense—*i.e.*, the placing at the disposal of the population of all the facilities of modern medicine. It does not simply mean assistance to “indigent” persons.

the doctor's task ; radiology and laboratory research have supplemented but not superseded his skill. Medical practitioners, whose number and qualifications are relatively high, have nearly all been trained in large towns, and have already tasted the higher standard of living that prevails there. For all these reasons, the cost of medical care is often beyond the peasant's means ; and the more so because the scattered nature of the rural population and the difficulty of communications make treatment more expensive still.

On the other hand, the spread of education and the decline of superstition have led to a steadily increasing demand for medico-social protection on the part of the people themselves.

It was at first thought that preventive medicine would " pay ", not only socially, but financially as well, and that, as it became more widespread, the services which provide medical assistance and care would have less work to do, thus enabling substantial economies to be made. But no such thing. Owing to the lack of care from which the peasants and poorer classes in all countries suffer, the development of the machinery of preventive medicine is accompanied by a parallel increase and improvement in the machinery of curative medicine, since the demand for medical care has not yet been satisfied. The number of medical practitioners is increasing ; this also applies to the number of beds in general, surgical, and " special " hospitals (for tuberculosis, mental diseases, etc.). The institutions providing treatment meet fundamental and inescapable needs which have by no means been fully met as yet, especially in country districts. In order that their development may not have a prejudicial effect on preventive medicine, they are being more and more used as the essential technical, or even administrative, basis of its organisation. The problem is how to organise preventive medicine so that it shall not play a subordinate rôle to curative medicine, and how to establish liaison between the existing urban institutions and patients in rural areas.

2. In order to furnish effective medical assistance to the rural population, the Conference is unanimous in the belief that 2,000 is the maximum number of persons who can be given proper medical attention by a duly qualified medical practitioner, on the understanding that, in proportion to the growth of the health services and the needs of the people, this number may be reduced to 1,000.

In rural districts the foregoing standard is achieved only in very exceptional cases and in countries where the multiplicity and excellence of communications make the remoteness of the practitioner most to be deplored.

The unequal distribution of practitioners—their excessive concentration in the towns—is such that, in certain countries such as Hungary, Latvia, and Roumania, legislation has been passed to provide the rural districts with a more adequate medical service.

In Belgium, where 87.4% of the communes (containing 38% of the population) have under 5,000 inhabitants, there is on an average one doctor to every 2,062 persons, as compared with 1,055 in the communes with over 5,000 inhabitants.

In Hungary, although there is now one doctor to every 2,000 persons in the rural districts, the problem has not yet been fully solved: in certain regions the population is very scattered, and communications are difficult, especially in winter. Nevertheless, there are now only fifty villages without a doctor.

In Roumania, it is estimated that no fewer than 5,000 or 6,000 more doctors are needed in the country districts, which have now only 1,500.

Switzerland, on the other hand, is well provided with doctors: except in the high mountains, there is one to every 1,900 inhabitants, and communications are excellent.

To sum up the question, we may conclude, therefore, that in sparsely populated rural areas where communications are defective, one doctor to 2,000 persons should be the absolute minimum.

3. It is desirable that the number and distribution of pharmacists and doctors who dispense their own drugs in rural districts should be such as to ensure that all medical prescriptions may be furnished rapidly to the rural population.

The 1931 Conference laid down no standards regarding the number of pharmacists, which is, indeed, difficult to determine. It depends on the number of medical practitioners, the density of the population, the adequacy of communications, whether it is customary for doctors to make up their own prescriptions, the extent to which patent medicines are employed, whether the number of pharmacists is limited by law, and, lastly, how far they sell various products which have only a remote connection with the healing art.

In some countries, such as France, certain pharmacies used to run travelling stores which supplied drugs direct to customers without a prescription. The drivers of these travelling stores were even led to giving medical consultations and dispense drugs on their own judgment. This objectionable practice of "hawking" has now been prohibited by law.

There are in France, and in various other countries, "médecins propharmaciens" (dispensing practitioners), who have the right to dispense drugs exclusively to their own patients. By enabling doctors to supplement their professional earnings, this arrangement offers them a certain inducement to settle in remote places, which is all the more desirable because the lack of medical care and the absence of an educated class are undoubtedly factors in the drift to the towns.

Stocks of drugs, especially therapeutic sera, are made available under certain conditions, either in health centres or in hospitals, as, for example, anti-rabies vaccine in Roumania, where the health services and hospitals have a supply for indigent patients not admitted to hospital.

4. Such medical assistance also requires a technically qualified auxiliary personnel comprising one or more nurses, or, provisionally, in the absence of qualified nurses, other persons possessing the minimum necessary technical training. However, it is essential that this auxiliary personnel abstain from all medical treatment, such treatment being only permissible under the direction of a qualified medical man.

The number of qualified auxiliary personnel is slowly but steadily increasing, although it is still inadequate, especially in Eastern Europe. The problem is all the more difficult to solve, because a large number of hospitals and of qualified instructresses are needed to give nurses theoretical and practical training.

Nurses.

There are practically no private bedside nurses in rural districts. In some countries, such as England, Denmark, and Sweden, home care is given by visiting or district nurses who are attached to voluntary organisations, like the English District Nurses' Association, or are employed by the local authorities or, in some cases, by a joint

body formed by the local authorities, social insurance institutions, and voluntary associations. These nurses work under the authority of medical practitioners and under the professional supervision of the medical officer of health. Being paid by the year and not by the case, they are not tempted to practise medicine illegally or to give treatment without definite instructions from the doctor. They are not concerned with preventive medicine, but the competent attention they are able to give at the right time under medical supervision has a beneficial effect on the course of diseases, especially in children.

In English rural districts, the duties of district nurse¹ and district midwife have been combined.

Visiting nurses, whom we shall call "family social workers", should, according to the views of the 1931 Conference, serve the same number of inhabitants as the rural doctor; we shall revert to them when we come to discuss health centres.

Midwives.

All countries which still possess uncertificated midwives are doing their utmost to replace them by certificated midwives, or, as a temporary measure, are establishing short theoretical and practical courses in obstetrics, special importance being attached to cleanliness and asepsis. These partly trained women are then placed under the supervision of the health services.

In Italy, Denmark, Sweden, and latterly England, there are district midwives employed by the commune or parish, who are kept under close supervision by the health authority, which investigates their competence and inspects their instruments and the detailed day-to-day confinement record they are required to keep for each birth. (This provides valuable statistical information regarding accidents of pregnancy.) An attempt is now being made in Italy to employ midwives as family social workers to co-operate with the pre-natal or infant consultation clinics.² Under medical supervision, midwives

¹ A bedside nurse attached to a public or private organisation.

² In the Meurthe-et-Moselle (France), private midwives are approved by the Office départemental d'hygiène, in agreement with their professional organisation; as regards maternal and infant welfare, they are placed under the supervision of a social worker holding a certificate in midwifery, and receive a bonus for every child they bring into the world who is found to be strong and healthy when it reaches a certain age.

render very valuable services, but it does not appear advisable that they should replace visiting nurses, even if they have made a special study of child welfare.

There is a growing tendency in Denmark and Sweden to urge all mothers, not only those who have been advised to do so by the medical or social service, to go to hospital for their confinement. The desirability of this recent innovation is still too controversial for us to recommend or discourage its systematic adoption.

5. It is recommended that, in the smallest rural settlement, the patient should be able to find a person capable of rendering first aid and of carrying out the doctor's orders,

This recommendation does not appear to have been fully carried out, especially in purely agricultural countries. Nevertheless, it is probable that the sense of isolation felt by some local authorities and the fear of being without first aid have led them to co-operate in the establishment of health centres or dispensaries. Stretcher-bearers, male and female Red Cross ambulance staff, and first-aid workers and stations are to be found in a growing number of villages, especially in districts where both general and health education are very widespread.

6. The rural population and rural doctors should be in a position to utilise the services of centres of diagnosis and, if necessary, of specialised treatment ; such centres should be suitably equipped and provided with a qualified staff : anti-tuberculosis and anti-venereal dispensaries, etc.

These services should maintain liaison with the patient's physician, who should be informed of the results of the examinations, or, if necessary, kept in touch with the treatment and its results.

The special clinics for tuberculosis, venereal disease, maternal and infant welfare, etc., or the primary or secondary health centres, are generally used as centres of diagnosis, and it is becoming more and more customary for them to convey to the patient's physician the results of examinations carried out either at his request or independently ; this often helps him to treat the case successfully, and obviates the risk of any friction between curative and preventive medicine and between towns and rural districts.

In countries such as Denmark and Sweden, where health centres are comparatively rare, the special equipment of the hospitals is used for purposes of diagnosis.

Hospital doctors and staff, especially if they are whole-time workers, endeavour to establish this kind of liaison, which is most likely to work satisfactorily if the hospital or centre has a special staff for the purpose. These almoners, hospital social workers, or medical secretaries, are to be found only in a few large city hospitals. Many examinations, some of which are very costly, still lead to no practical action, or are even repeated unnecessarily for lack of any systematic liaison.

When a delicate diagnosis has been made by the centre or institution concerned, should the hospital, health centre or dispensary also give treatment? The answer to this question depends on the local situation. If there is no doctor in charge of the case, it does not, of course, arise, and treatment is given on the spot. Where there is a sufficient number of doctors, treatment may be given when it is justified by prophylactic necessity, as in syphilis, trachoma and certain pneumothorax cases in tuberculosis, or when it is too specialised or too costly to be given elsewhere (deep X-ray treatment, Curie-therapy, mechanotherapy, etc.). If the administrative details are discussed beforehand with the medical organisations, many difficulties of principle and practice can be avoided.

In some cases, even when school medical examination reveals the existence of definite physiological defects, this discovery is not followed up by treatment, so that the examination is perfectly useless. School-children, not only those whose parents are indigent or in straitened circumstances, but also those belonging to fairly well-to-do families, are therefore often given treatment and especially dental care, because otherwise their parents would take no steps in the matter. It is in this connection that the social worker can render the greatest service by pointing out to parents the desirability of treatment; if necessary, she should keep on at them until they start it or follow it up.

7. Rural medical assistance also implies facilities for hospitalisation in appropriate suitably equipped institutions.

It is recommended that there should be such a hospital for a population of from twenty to thirty thousand people, a rational

organisation requiring about two beds per thousand of the population.

However, each such institution should have not less than some fifty beds.

Permanent means of communication (telegraph, telephone, etc.) and constantly available means of transport should be at the disposal of patients and doctors, to permit of rapid hospitalisation in urgent cases.

It is possibly in the sphere of hospital organisation that the greatest progress has been made, but much still remains to be done, especially in comparatively poor countries and districts.

While the views expressed in 1931 still hold good, there appears to be a tendency in Sweden and in certain French departments (Seine-et-Oise) to regard the hospital problem as a twofold one, entailing both a territorial and a functional division of labour for the purpose, first, of providing more specialised personnel and institutions for the population over a wider area, and, secondly, of co-ordinating the hospital system, not only internally, but also externally, with the health centres and the corresponding dispensaries. This enables patients needing hospital treatment to be rationally and economically sorted out, and the health centres can take regular advantage of the specialised personnel and costly equipment of the hospital centres or their outpatient departments.

The small rural hospitals, which are more or less autonomous, and the old small hospitals for infectious diseases, no longer used for that purpose, treat simple cases for which no special skill or equipment is required. In some cases, the technical resources of these small institutions are meagre or out of date, and they have therefore been converted into homes for chronic cases of tuberculosis or for old people, and occasionally into rest-homes. This is an economical solution which is highly satisfactory from the psychological standpoint, as it obviates the necessity for removing patients from the districts in which they live and which they are reluctant to leave.

Higher up in the scale, the cantonal hospital, thanks to improved communications, receives sick persons or complicated obstetrical cases requiring a simple surgical operation. The X-ray apparatus of such hospitals is used by the local health centre or dispensary.

Above them, there are bigger hospitals where surgical operations of all kinds are performed. They have several departments under

competent medical direction : medical, surgical, child welfare, tuberculosis, skin and venereal diseases, otorhinolaryngology and ophthalmology, obstetrics and gynaecology (invaluable for the early diagnosis of cancer in women), as well as laboratories, etc.

Lastly, there are regional establishments which employ the very powerful and expensive therapeutic equipment now considered indispensable, especially for the treatment of cancer ; their out-patient departments can also be used as " central consultation clinics " by the health centres.

The satisfactory linking-up of the hospital system, both internally as between the various grades of institutions described above, and externally with the corresponding health centres, enables the best possible use to be made of the services, as medical consultants or specialists, of the heads of the special departments of hospitals, and of their costly equipment, while at the same time it reduces the average period spent in hospital.

In certain poor countries, where the number of hospitals in rural districts is very small and private institutions are practically non-existent, the question of the treatment of paying patients and competition by the public hospitals with private nursing-homes does not arise ; no objection is raised to treatment in different " classes ". Some laws allow surgeons who are specialists in their own branch to receive fees direct from paying patients, while others prohibit them from doing so.

The specialisation of certain hospitals, and their administration in conjunction with sectors, established according to the division of labour and means of communication, appear to be difficult in countries where the majority of hospitals have been established by local " foundations ", the provisions of which are difficult to abrogate ; liaison with the health centres is thus more complicated. Agrarian expropriation and currency inflation are, however, tending to render this autonomy more and more precarious.

Other hospitals are still used for the benefit of the rural populations, although, in some cases, they have no direct administrative connection with them. If liaison is established, there are certain services which can be rendered under the best conditions by mental hospitals, sanatoria for tuberculosis patients, crèches and homes for foundlings or children under official guardianship. These institutions may be of valuable assistance in organising the campaign against mental

diseases in their own districts, as is the case in France—especially when they work in conjunction with the school medical inspection service—or by undertaking the X-ray examination of tuberculous cases or suspected cases, as in Denmark.

Children's homes are tending more and more to become centres for the medical and social care of deserted children who have been placed in families and who are thus kept under closer technical supervision, as in France and Roumania. These centres can do a great deal to fight infant mortality in their own districts, both by setting an example and by enlisting the services of the social workers of the competent health centres, or else co-operating directly in the medico-social protection of children boarded out by their own health visitors.

Although communications are improving rapidly, there are still districts where they are defective and where there is not even a telephone. In some cases, as in Sweden, communications may be interrupted in winter, and patients are then transported by air.

The Belgian Red Cross has solved the problem satisfactorily by running ambulances for the transport of sick and injured persons. A fee is charged if the patients can afford it ; if not, they are conveyed free. This transport of patients may be of great assistance in prophylaxis. For instance, in Denmark, they are conveyed to the diagnosis centre at the sanatorium free of charge ; and, in Switzerland, to and from the cancer centre for observation after they have undergone treatment there. In some countries, where expensive treatment is not allowed in outpatient departments, walking patients may be obliged to enter hospital unnecessarily ; such cases are becoming less frequent as the regulations for hospital outpatient departments are revised.

8. *Rural medical assistance should utilise the services of laboratories. Simple examinations and analyses may be carried out in the hospital laboratories. More complicated examinations and analyses (bacteriological, pathological, serological, etc.) should be carried out in large, specially equipped laboratories.*

Some countries show a tendency to concentrate laboratory examinations (except rapid analyses of urine or the examination of sputum for Koch's bacilli) in central institutions, the matter to be examined

being sent by post, in preference to having them carried out by a large number of local laboratories. The equipment required for the taking of samples is placed at the disposal of the medical practitioner, either beforehand or at his request, by the laboratories themselves or the hospitals, health centres, or dispensaries.

Certain countries, such as Czecho-Slovakia and Yugoslavia, are divided into regions, each with its regional laboratory or institute of hygiene, whose duty it is to carry out biological examinations and to analyse drinking-water. The examination of tissues taken from the living organism, for the detection of cancer, is usually carried out by the hospitals, their outpatient departments, or the cancer centres.

In countries such as Denmark, where there are no private laboratories, and where it is possible to compile anonymous case-records, the cross-checking that is thus practicable, thanks to the co-operation of the medical profession, is of great assistance in combating infectious diseases, particularly syphilis. The official laboratories are thus of considerable value, as they not only diagnose cases of infectious diseases but also assist in fighting epidemics, by means of the statistical data collected through them.

9. Rural medical assistance should also be able to utilise medical specialists. The specialists should keep in touch with the patient's doctor, informing him of the results of the examination and of the treatment and its results.

While the 1931 Conference rightly stressed the difficulty of providing a specialised medical service for rural populations, it should be noted that the excessive tendency on the part of doctors to specialise, either before or after graduation, interferes with the operation of an efficient medical service in rural districts, because specialists are reluctant to settle there, and, when they do so, they are necessarily compelled to practice general medicine. This is a paradoxical state of affairs, because these specialists do not possess the training required for the practice of the difficult branch known as general medicine, which is by far the most important in country districts.

Apart from certain special diseases and contagious affections to which the rural dispensaries devote particular attention, it is difficult to provide specialist treatment for peasants, except in rich countries with rapid communications, where there are specialists living in the

smaller towns. It is therefore usually considered necessary to organise a system of liaison between the health centres, dispensaries and medical practitioners on the one hand, and the hospital system on the other, in order to provide specialist medical treatment and equipment for the peasants as economically as possible.

In Hungary and Roumania, for instance, motorised dispensaries, and teams specialising in child welfare or tuberculosis, render the greatest service by paying periodical visits to isolated villages where there are no specialists or even no general practitioners.

In short, the public authorities have found that the value of specialist treatment depends on co-ordination with the medical profession and the health system as a whole.

10. Means of Realisation.

(a) Principles of Collaboration.—*The realisation of effective medical assistance in rural districts demands the collaboration of the public authorities—health and welfare (assistance)—of the medical profession, of health insurance institutions, of mutual benefit associations (sanitary, co-operative, etc.), of private agencies, etc.*

(b) The Public Authorities.—*The public authorities should ensure that the entire population benefits from an effective medical assistance. By means of a rational organisation of the health services, adequately staffed with specialists, they should attempt to develop the preventive tendencies of rural medical assistance.*

In the interest of effective medical assistance, it would also be desirable for the public authorities to seek to organise a rational and co-ordinated health programme on a territorial basis, taking account of local conditions.

The public authorities should stimulate, assist and co-ordinate the efforts of agencies and groups which attempt to realise effective medical assistance. They should seek to fill the gaps and avoid the duplications which may occur in the organisation of this assistance.

(c) Health Insurance.—*The Conference considers that, when health insurance applies to the entire body of agricultural labourers, it permits the realisation of effective medical assistance in rural districts under the best conditions.*

(d) Public Assistance.—*Nevertheless, where health insurance has not yet been established, rationally organised free medical assistance may intervene usefully in completing a system which partially satisfies the needs of rural populations.*

These recommendations were taken up, expanded, systematised and clarified by the "Conference of Experts to study the Best Methods of Safeguarding the Public Health during the Depression", in its "Appeal to Public Opinion and General Recommendations".¹

Though concise, these recommendations are very comprehensive, and still retain their full value, because the financial depression and the armament race have restricted the financial resources of the various countries just when the urban and rural populations, realising the importance of public health and medico-social protection, are urging the public authorities more and more to make a sustained effort to organise and improve those services.

Restrictions—the appeal states—should be effected only with great prudence and in accordance with clearly defined methods, not by a drastic reduction applying in the same proportion to all forms of social expenditure; and this applies particularly to rural areas, which are usually the least well-equipped and should be the last to suffer.

The important part played by sickness insurance was clearly brought out; we need not therefore go into the matter here, especially as it is engaging the attention of the International Labour Office. We would simply stress the desirability of co-ordinating the social insurance curative and preventive medical services with other institutions for medico-social protection, whether by means of a contribution to working expenses or by the establishment of institutions—whatever the form such collaboration takes.

The resources should be utilised to better advantage, so as not to hamper future reconstruction.

The effect of the economic depression on public health expenditure was examined by M. W. W. JAMESON, M. G. PITTALUGA, and M. A. STAMPAR in the second general report on certain European schools and institutes of hygiene (*Bull. Health Org.*, 1938, 7, 191). That report shows that, in the various countries, especially those with a rural economy, budgets had been cut down by from 10% to 25%; in industrial countries, public health expenditure had increased; while in rural countries, it usually showed a tendency to fall.

¹ Report on the Best Methods of Safeguarding the Public Health during the Depression. *Quart. Bull. Health Org.*, 1933, 2, 286, and references in document C.H.1139 [C.G. /C.E. /26(1), Geneva, December 1933].

The existence of a large number of different public and private services is a cause of waste and dispersal of effort. The establishment of a general and rationally planned organisation of medical services is therefore essential. In this connection, we would mention the striking example of Latvia, which has merged all its big private organisations for medico-social protection in a single polyvalent association with separate sections.

The management of hospitals and preventive institutions should, according to the recommendations of the 1933 Conference, meet the following requirements : it should provide for the rational distribution of establishments, should turn to account recent experience in building, equipping and managing hospitals, and should arrange for the centralisation of purchases, the calculation of running costs per day by uniform methods, and co-operation with other existing health organisations. These problems have not yet been solved, but are engaging the attention of the central services of Sweden and Denmark, for instance. The Institute of Hygiene in the latter country has published a very useful guide to nutrition for the use of hospitals. The central institutes of health statistics in Roumania and Yugoslavia keep medical and administrative statistics for each patient, which constitute a valuable source of medical, social and financial information.

Co-ordination and collaboration between all public and private services will help to protect public health. The following principles should be observed : there should be uniformity of views and methods as between the central services ; regional co-ordination committees and health centres, or offices performing the same functions, should be instituted ; a corps of polyvalent nurses (or family social workers) should be organised to carry out the co-ordinated measures in each locality ; and subsidies should be withheld from organisations which do not allow their work to be co-ordinated.

Co-operation with medical practitioners is essential, and should be well organised and controlled. The practitioner can co-operate directly with the various services of the health centre, especially in rural districts, as is the case in certain French departments, by helping in pre-natal clinics, infant consultation clinics, and school medical inspection, provided he is specially qualified in these branches and that the technical details of this collaboration are settled between the health organisation and the medical professional organisation.

In France, an attempt has been made to achieve systematic medico-social co-ordination in each department, either through the departmental social hygiene office, an official or semi-official body, or through the special committees set up in 1936. These committees comprise three different classes of members : (a) representatives of the public authorities or certain private bodies, the departments and communes, social insurance institutions, chambers of commerce, the Red Cross, medical associations, trade unions and employers' associations ; (b) experts ; (c) representatives of private organisations, appointed by a departmental union of voluntary organisations for medico-social protection desirous of obtaining grants from the authorities or co-operating with them.

The Executive Bureau of these " Health and Social Co-ordination Committees ", which is constituted on the same threefold basis, is presided over by the prefect ; the secretarial duties are performed by the departmental medical inspector of health.

A circular, dated August 26th, 1936, which has been confirmed and amplified by several later circulars issued by the Minister of Health, defines the functions of these co-ordination committees as follows :

- (1) To keep up to date a list of institutions for medico-social protection ;
- (2) To define the policy of preventive medicine and social assistance in the department ;
- (3) To investigate all requests for grants for the establishment, equipment, or running of any organisation.

There are local groups organised on the same lines and known as " Co-ordination Committees of the Health Centre ", the latter comprising all the various health and social assistance organisations in a given sector, whether they are housed in the same building or, as is still often the case, in separate premises. These local committees co-ordinate local activities, chiefly by promoting the establishment of a polyvalent social service at the health centre, so as to make sure that the same family will not be visited by several health nurses or social workers sent by different institutions. This type of organisation, which also plays a part in " medico-social planning " on the departmental scale, is making steady progress, and has fully borne out the value of the recommendations made by the European Conference on Rural Hygiene in 1931.

The policy of co-ordinating health activities in country districts varies according to whether the country is poor and wholly agricultural, agricultural but better off economically, semi-industrial, or wholly industrial. In this last case—in France, for instance—there is a large number of organisations, chiefly for child welfare, in rural districts. The committee's main task is not to initiate but to co-ordinate the various activities. These organisations for child welfare—a branch of social work usually undertaken by private agencies and local voluntary workers whose activities are under some sort of joint control—often form the starting-point of local co-ordination under the supervision of medical officers of health. They carry on their work, even in the smallest communes, through the “auxiliary primary health centres” set up by primary health centres.

The establishment of health centres covering all branches of medico-social protection is possible only when nothing whatever has been done in this sphere, or when, owing to the fact that the number of existing institutions is very small and the situation particularly favourable, it is decided to regroup them under the same roof, so that they may cover the ground more completely and be better organised.

In rural countries like those of Northern Europe, which are fairly wealthy, the number of private institutions engaged in medico-social work in rural areas is comparatively small. The protection of health may be based, as in Denmark and Latvia, on general social insurance: the simplest and most practical solution, now coming into favour, appears to be to establish polyvalent health centres, even if they are of a very simple kind, like the auxiliary primary health centre, consisting of two or three rooms or established in the district medical officer's consulting-rooms, as in Denmark.

In rural districts, medical attendance is given to poor persons by various means: in some cases, the public assistance authorities appoint their own doctors, while in others, the choice is left to the patient. In a number of countries, the district medical officer of health may also hold the appointment of poor law medical officer, in addition to treating better-off families, to whom he charges fees.

In England, the district medical officer receives a fixed yearly salary for attending poor persons in his district. He may also act as part-time medical officer of health, but full-time medical officers of health never attend the poor. In Central Europe, the

district medical officer nearly always acts as part-time medical officer of health ; in addition to attending the poor, he supervises sanitation, and is in charge of infectious diseases, forensic medicine, etc. In the Baltic and Scandinavian countries, the district medical officer may attend poor persons free of charge, and also the whole or a section of the rest of the population. In such a case, he is paid by persons who can afford it, according to a scale of fees based on the amount of taxes paid by them.

In other cases, attention is given direct by the doctor of the health centre, or (as in Yugoslavia) of the health co-operative society, who may or may not also discharge the duties of district medical officer. In sparsely populated countries whose economic development is yet sufficiently advanced to enable them to meet the cost of hospital treatment without difficulty, such as the Scandinavian countries, if it is not possible for the doctor to visit a patient confined to bed with a fairly serious affection as often as he should, the patient is admitted to a public hospital.

Poor persons are treated free of charge in the hospitals, but there is a growing tendency to adopt the system of " partially free medical assistance ", which enables persons not entirely without resources to contribute towards the cost of treatment or hospital care, a balance being struck, in the case of long and expensive treatment, between the patient's resources and its cost.

* * *

The organisation of public assistance and health, by providing practitioners with a " fixed " remuneration or a fee for their services, thus acts as a strong inducement to them to settle in rural areas ; whereas, in the opinion of some administrators, legislation establishing a *numerus clausus* in towns, or compelling certain practitioners to work for a time in the country, will not prove effective unless, at the same time, these practitioners are provided with accommodation, means of transport and a minimum income. The spread of social insurance in rural areas greatly encourages the settlement of doctors in country places and helps to keep them there.

III. PUBLIC HEALTH SERVICES

The Most Effective Methods of organising Health Services in Rural Districts.

A. GENERAL CONSIDERATIONS

1. *There are two principal forms of rural health organisation : the form in which the State administers the local services and the form in which the State has only supervisory functions, the local authorities being responsible for the local health administration.*

Both may give good results, and the form best suited to the rural districts of a given country depends on the manner in which the general administration of that country is organised.

When it is necessary to organise the rural health service, there is need for a State organisation which will assume control over local health work. As the country develops, its local administrative organism becoming sufficiently strong to carry out public health work, and the education of its people in hygiene being sufficient to cause them to support the local health service, there may be a gradual decentralisation in health matters until the responsibility can be assumed safely by the local authorities.

Even when such a decentralisation has taken place, the State should preserve its right to frame the health policy which it is the duty of the local authorities to carry out, as well as its right to supervise the work and remedy the deficiencies of the local health service.

In the countries which are most advanced economically—those which are either highly industrialised and those which have an industrialised agriculture—local autonomy is usually strongly developed, and the rural health organisation is in the hands of the municipalities, districts or counties (provinces, departments).

In other agricultural countries which are economically more backward, rural health is sometimes organised almost entirely by the State.

There are thus two tendencies. In industrial countries, a tendency towards decentralisation and devolution : the State does not direct the work, but merely plans and supervises very closely the activities

of the local services on a technical basis ; it exerts its influence chiefly in the form of financial inducements to which conditions are attached. In agricultural countries, where it is not so much a question of rationalising existing institutions, which are often inadequate, as of creating new ones, there is a tendency—probably temporary—towards centralisation. This is the case in Hungary and Roumania. In Hungary, under the old system, local health authorities were responsible for organising public health work. This system has now been superseded by a highly efficient Governmental system. In Roumania, the hospital system was originally controlled by local foundations, but after the agrarian reform the hospitals were taken over by the State, as the experiment of transferring them to local authorities proved a failure.

In Poland, a mixed system has been established by the creation of health and assistance centres with co-ordinating committees for each administrative grade.

In any case, where the health organisation is to a large extent centralised, efforts are made to pave the way for decentralisation by interesting the local population in the common task. Their interest is aroused, not only by means of propaganda and education, but also by the more and more active and extensive participation of the public in the running of the services provided for its benefit. In some cases, the local authorities contribute towards the cost of building and running a health centre, if only by providing a free site. In other cases, as in Poland, local committees, or, as in Hungary, the Green Cross, enable the public to serve its apprenticeship and constitute the first stage towards ultimate decentralisation.

Whether the system is highly centralised, as in Hungary, with a health scheme spread over several years and designed to cover the whole country by stages, or to a large extent decentralised, as in Denmark, we find that, in all countries, the central health services are endeavouring more and more to plan medico-social policy for some time ahead, and to provide for the gradual extension and co-ordination of health work, whether they direct the work themselves or merely promote and supervise it.

As finance is always a fundamental consideration, whether the public authorities establish health centres themselves or contribute towards the cost of local centres, Government departments are now taking steps to see that technical studies and financial studies proceed

pari passu. This is an innovation, and one which has a close bearing on progress in health matters.

2. *The public health officer fully responsible for the promotion of the health work in a rural district should give his whole time to his official duties; the practice of medicine,¹ in particular, is incompatible with the work of such an official. He should be a doctor trained in hygiene and preventive medicine, according to the recommendations of the Conferences of Directors of Schools of Hygiene at Paris and Dresden (document C.H./888). His compensation should be sufficient to assure him a comfortable living. He should enjoy security of tenure in office, subject to the proper discharge of his duties, and have the right to a reasonable pension when age or the completion of a fixed number of years of service makes it necessary for him to retire.*

In most countries, the tendency to employ full-time public health officers is becoming more and more marked. For instance, in France, the employment of full-time qualified public health officers, appointed by competitive examination, has recently been made compulsory in all the departments. The same tendency is encountered, though to a lesser extent, as regards doctors working in the "social medicine" services, such as those for tuberculosis, venereal disease, and maternal and infant welfare. While in the towns the part-time employment of qualified specialists is the usual practice, in rural districts it is becoming more and more the custom to engage public health officers who have been specially trained in social medicine to take charge of the anti-tuberculosis and anti-venereal services.

Since maternal and infant welfare (including school medical inspection) should be the most decentralised service and the one that comes closest to families, and since less technical equipment is required for the early detection of diseases of mothers and children than for other affections, such as tuberculosis, the tendency is to employ medical practitioners who, as in Meurthe-et-Moselle, for instance, have received a training for which a special certificate is given. This system, when suited to the circumstances, ensures better liaison

¹ This recommendation refers to the *private practice* of medicine. In some countries, where medical assistance is the responsibility of the public health service, work in the field of medical practice may be a duty of the medical officer of health (see Conference of 1931).

between medical practitioners and the health centre, provides the former with an income, and induces them to settle in rural districts. If the practitioner is the only one in the area, he runs no risk, by participating in the campaign for the protection of public health, of taking away patients from other doctors.

In sparsely populated countries, where communications are inadequate and the number of doctors practising in rural areas is very small, it has been found advisable for the primary health centre to employ the local practitioner, if he has received the necessary medico-social training. He may attend the poor, act as physician to the health centre (social medicine), discharge certain health duties under the supervision of the district medical officer (infectious diseases, minor sanitary operations, application of the health regulations, forensic medicine), and also possibly be able to supplement his income by attending paying patients, if there are any well-to-do peasants.

The system of making one appointment for varying types of work, either by a single or several authorities, is least unsatisfactory in cases where the doctor selected has received adequate training, when he is the only one practising in his area and when he receives his different salaries from one authority. It is essential that he should be under a single chief responsible for the administrative and technical direction of the work and for seeing that uniform methods are applied.

In larger districts, and where there are secondary health centres, the general tendency is to entrust the functions of head of the health centre or medical officer of health—sometimes of both, if the official in question has sufficient training—to a single full-time public health officer. In some countries, such as Denmark and Sweden, district medical officers have in theory the right to practise privately, but have renounced that right of their own accord owing to lack of time.

If the public services are to have the exclusive right to the services of public health officers, they must of course pay them an adequate salary; an increasing number of authorities now prefer to stipulate that the compulsory duties of a medical officer shall include various specific tasks for which he will receive an adequate all-over salary, rather than pay him separately at low rates for each of these tasks. Medical associations no longer oppose the full-time employment of

medical officers of health, and are raising less and less objection to their being treated as officials of dispensaries—that is to say, of the social hygiene services—when they are properly paid.

In short, there are two kinds of medical officer—full-time and part-time. The former may be entrusted with medico-social protection as a whole, or may discharge various separate but allied functions. Medical officers who also practise privately may be in charge of a service for which they receive a lump sum or a fee for each patient they attend, while in some cases they are paid for each service they perform, as, for instance, vaccination, supervision of infants, examination of school-children, and so on.

The tendency is more and more to appoint as whole-time public officials those doctors who are acting as executive officer under the public authorities—i.e., public health officers ; it is less usual in the case of those attached to dispensaries.

In any case, it is essential that the work should be conducted on uniform lines. It is usually under the technical direction of the head of the health service of the district, who, if possible, collaborates with the medical associations ; his medical colleagues who are engaged wholly or partly in combating social diseases in the various services endeavour to carry out the chief's instructions.

3. *The optimum size of a rural district¹ for which one full-time health officer may be responsible will vary with the density of the population, the means of communication, the prevailing diseases, and other local conditions. Subject to these variables, a population of from 20,000 to 100,000, or an average of 50,000, may be fixed, it being understood that one or more full-time assistant health officers will be needed for populations in excess of 50,000.*

The rural health district should preferably correspond with the administrative district in view of the difficulties which would otherwise result. As, in European countries, such administrative districts almost always have populations in excess of 50,000, they may be suitably staffed by the appointment of one full-time health officer with the proper number of assistants.

¹ In some countries, the law requires every commune to employ a doctor. This recommendation deals only with the *district*. The Budapest Conference decided that village doctors might be employed in primary health centres. There is no implication in this report that the practising physician should do no health work. Indeed, the Conference considered that the services of the practising physician should be utilised wherever possible.

In countries where the municipal or district authorities possess a large measure of local autonomy, medico-social work is usually based, for financial reasons, on the administrative division. The only possible drawback is that the basic unit—the rural commune (parish)—may be too small to afford a sufficiently comprehensive service. The laws often provide for the constitution of federations or unions of rural communes, so as to ensure the efficient working of certain services ; unfortunately, such unions are difficult to organise, on account of local differences of opinion. We may therefore still come across inadequate local organisations, sometimes even in rich countries, with doctors drawing several small fixed salaries, over whom it is difficult to exercise proper technical control.

In countries where the health organisation is highly centralised, the dividing-up of the local administration is less important, because these are usually comparatively poor agricultural countries in which the central authorities bear almost the whole of the cost. In such cases—as in Hungary or Poland—it is not possible for the organisation of public health work to cover the whole country at once ; it must be carried out gradually, in accordance with a pre-arranged plan.

The assistants of the departmental or county medical inspectors of health may be polyvalent if the district is sparsely populated and communications are difficult, the area in question being divided up between them ; or, if they are specialists, they may take charge of a certain part of that area, dividing it among them according to the branch of social medicine or dispensary work in which they specialise. It is therefore difficult to frame any fixed rules determining the population and area they should serve, unless the health centre is the pivot of action. We shall revert to this question later.

4. The Conference considers that the health authorities of the rural districts described above should be responsible for the protection and promotion of the public health in all its aspects. The district health officer, as executive officer of the health organisation, should be entrusted with the realisation of the entire programme, in order to ensure the economy and efficiency resulting from unity of direction.

In some countries, as the work becomes more technical and less a matter of routine simply enforcing the law, there is a tendency to

make the health authority responsible for medico-social protection. In more and more cases, a single county or departmental official—the medical inspector of health—is responsible for the whole of the work. He is assisted by committees who apply regulations based more or less closely on the “ model regulations ” issued by the competent Ministry and adapted by the committees to local needs. As this concentration of the responsibility for carrying out the regulations increases—even in cases where there is a large measure of local autonomy—the health officer in charge of a department or county acquires greater authority ; his appointment must either be approved by the Ministry, which may or may not contribute towards his salary, or else he is appointed, paid and dismissed by the Minister of Health. This official is therefore to a large extent beyond the reach of undesirable local influences, and the technical unity of medico-social protection is ensured without any discouragement of local initiative, the chief medium of public co-operation.

In countries with an old-established industrial economy, where a large number of commissions and committees have been formed, the health officer acts as secretary or chairman of the committees directly responsible for public health ; and it is usual for committees dealing with cognate questions to invite him to take part in their work.

The fact that local health officials are appointed or approved by the central authority gives them a certain amount of technical independence in countries where the prefectural system is in force, because the prefect represents authority and co-ordinates the work of the various local services. This necessity for granting extensive technical powers and authority to the departmental inspector of health is much greater in rural districts than in towns, where the various services are usually highly specialised and technically efficient, and keep in close touch with one another.

5. The minimum staff for such a rural health district should consist, in addition to the health officer, of one or more public health nurses, a sanitary inspector, and a clerk.

The nurse should have a diploma in generalised public health nursing from a recognised school of health nursing or its equivalent. The Conference considers that the programme of such nursing-schools should be studied by the competent commission of the League's Health Organisation.

The sanitary inspector should have received suitable training at a school or institute of hygiene. Under the direction of the health officer, he should be able to inspect foods investigate and abate nuisances and carry out the work of rural sanitation planned by the sanitary engineer.

Family Social Workers.

Since 1931, public opinion and the views of administrators and medical practitioners have made great strides. The utility of the specialist health nurse or the family social worker (polyvalent health visitor) is no longer disputed.

At one time, medical practitioners were afraid that family social workers would attempt to give medical advice and might thwart their efforts, especially as they were not under their direct orders. Experience has shown, however, that this is not the case, particularly when close contact is maintained between medical practitioners and public health officers.

A conference of experts held at Geneva on June 14th, 1938, on the subject of "Life and Health Indices for Rural Districts" (see document C.H.1331), defined the "family worker" as follows :

" ' Family social workers ' are persons attached to a medico-social service who have received an adequate training and visit homes for the purpose of tracking down, advising, educating and materially and morally assisting families.

" They are sometimes described as ' visitors ', ' visiting nurses ', ' health nurses ', or ' health assistants '. In practice, all of them work for the rehabilitation of the individual in the family life, and of the family in the community, by improving both health and economic and social conditions. It seems appropriate, therefore, to describe all such members of the medico-social services as ' social workers '.

" When these workers visit families by themselves (which is deemed preferable, except on certain occasions when they call in the assistance of ' specialist consultants '), they are known as ' family ' or ' polyvalent ' (general) social workers, while specialists are described as ' monovalent '."

The difference between the duties of the family social worker and those of the nurse has become more and more marked ; the former attends to the sick only in very exceptional cases, for the purpose of

rendering first aid or showing families how to look after sick persons themselves, especially children. Their work has proved to be all the more necessary because the dispensary doctor rarely visits families ; only the family worker can describe the environmental conditions to the dispensary doctor, and she alone can make sure, either by helping or by instructing the family, that the prophylactic rules laid down by the doctor are observed.

In countries where the density of the population renders social problems particularly acute, there is a tendency to employ " specialist social workers " even in rural areas. In many cases, these workers are actually secretaries dealing solely with legal and economic questions : working conditions, use of free time, economic and legal relations, etc. In most countries, however, both on economic grounds and for reasons of principle, it has been decided not to employ in rural districts a " social worker " in the strict sense of the term in addition to the family worker, who acts as polyvalent visiting nurse ; if social workers proper are employed by the secondary health centre, their duty is to co-operate with the polyvalent visiting nurse or family worker in the same way as the monovalent visiting health nurse specialising, for instance, in tuberculosis. In rural areas, therefore, especially where there is a health centre, the work of the visiting health nurse is really polyvalent ; she deals with prophylaxis, health and social education, hygiene and welfare. If she is occasionally called upon to attend the sick, it is only for demonstration purposes ; she does not do any nursing work herself, but puts families in touch with the appropriate institutions. The family worker therefore acts as a " liaison officer " between the family, the dispensary or health centre, and the various institutions that look after the peasants' welfare. She forms the basis of the system of health and social co-ordination in rural districts, of which the health centre is the concrete embodiment and symbol.

In small towns and rural districts, the municipalities often allot to family workers various duties connected with the different forms of public assistance, including enquiries otherwise entrusted to the police, thus enabling them to take part in " constructive assistance ". In rural districts, the health centre is therefore coming to play a more and more important part in social service in the proper sense of the term ; in the big towns, this constructive assistance work may be entrusted to " monovalent " social workers or " social secretaries ",

in which case co-ordination is all the more necessary because their functions are specialised and separate.¹

The rule that there should be one family worker to 6,000 or 8,000 persons, laid down in the recommendations of the 1931 Conference, though not the optimum, still holds good, constituting as it does a minimum which is rarely attained, especially in poor countries.

To enable workers to devote more time to visiting families in their homes, and to relieve them of sedentary work, the larger health centres, and particularly the secondary ones, often employ secretaries to assist the doctor.

In accordance with the Conference's recommendations, the training of visiting nurses has been studied by the Health Organisation. An exhaustive international enquiry was conducted in 1931 and 1932 by Miss H. Goff, a temporary official in the Health Section, who visited ten different countries for the purpose. At that time, out of a total of roughly 274,600 nurses in Europe, there were only 21,600 health visitors, of whom it was estimated that fewer than 1,200 had received really adequate specialised training. In fact, out of 1,350 schools for nurses, not more than 150 gave more or less comprehensive instruction in hygiene. The number of institutions exclusively engaged in the training of health visitors was very small, and the organisation of special practical courses, particularly in rural districts, quite inadequate.

Out of twenty-one European countries, the number of persons served by one health visitor was, in half the number, more than 15,000 (urban and rural districts together), and the proportion of health visitors to nurses as a whole was under 15%.

Since then, the training of health visitors has been intensified and improved, generally at the instigation of the division for nurses attached to the public health ministries. Admission to the schools

¹ In Meurthe-et-Moselle, the "specialised" workers co-operate with the "polyvalent" workers and undertake certain tasks such as enquiries connected with medical hygiene, neglected children and those in moral danger, and instruction in housewifery; they are called in when necessary by the family worker. This twofold task is carried on and co-ordinated under the supervision of the district "woman inspector of social workers". When it is organised and co-ordinated in this way, the social service constitutes a new and excellent means of cohesion, which is the more essential owing to the complexity of this service in a densely populated region provided with an ample system of communications, justifying the employment of different kinds of personnel.

has been made more difficult, the length of courses has been increased, and local training has been facilitated by health centres established in rural districts for demonstration purposes, which are frequently attached to institutes of hygiene. Instruction has become more autonomous : though still connected with the hospitals, the schools usually give different training from that intended for nurses.

Realising the value and the shortage of health visitors, the public authorities have endeavoured to facilitate the training of suitable girls, either by establishing schools or by making grants to these institutions or to promising but impecunious students (this system is employed where the students do not live in hospital all the time they are studying, as is frequently the case on the Continent). Different training is given for preventive and social health work, but, in view of the shortage of personnel, joint training may be necessary to enable students to combine these duties. Certain countries have found it essential to adjust recruitment for the various types of school to some extent to the openings for different classes of workers, by means of grants. But the main problem which remains to be solved in the case of both doctors and health visitors is not only how to turn out well-trained workers but how to induce them to settle in the country.

Sanitary Inspectors.

The sanitary inspector is one of the main pillars of the British edifice of health protection, and works hand in hand with the local authorities, dealing with local hygiene, especially " nuisances ", housing, the disposal of refuse, etc. We rarely come across this type of official on the Continent ; after the war there was a reaction, perhaps an excessive one, against the hygiene of air, water and soil, in favour of the improved organisation of so-called " social " hygiene, to which in some cases attention was exclusively paid. Various countries, even those which, like Hungary, had intended to provide sanitary experts for rural districts, at the present time show a preference for social workers, although their functions are altogether different. As, however, the reorganisation of health work on the basis of health centres is gradually extended until it covers the whole country, the appointment of an adequate number of sanitary inspectors will probably be provided for.

In France, although a sanitary technical institute for the training of sanitary engineers and experts has been in existence for fifteen years, the number who have been able to obtain posts in the health services is very small.

6. *Although, in many European countries, the rural district as defined above cannot alone afford to employ a sanitary engineer, the services of such an engineer should be available in all rural districts. Such engineers may be employed by the central health organisation, the State or the province. Their work should be that described by the Conference at Budapest.*

It is important that the programme and methods of training these engineers in all countries should be perfectly adapted to the work they are required to do. The Conference believes that the study of this subject should be undertaken by the Health Organisation of the League of Nations.

There does not seem to have been such rapid progress in this question¹ as in the training and employment of public health officers or qualified auxiliary personnel.

Various countries, which had old-established services and have reorganised them on modern lines, possess a corps of engineers who are employed in the roads and bridges, agricultural or public works services ; these officials deal with sanitation from the angle of their own special branch.

Other young agricultural countries, like Yugoslavia, have established straight away health services planned in accordance with the latest ideas on the subject. These services not only protect public health through their medico-social activities but are also modifying external conditions by the establishment of piped water-supply systems, systems for the disposal of refuse, land-reclamation systems, and the construction of wells, cisterns and shower-baths. Such work is often undertaken by the authorities themselves and directed by the sanitary engineers attached to the health services.

In Western Europe, on the other hand, the main problem is how to co-ordinate the services dealing directly or indirectly with health

¹ Which appears to fall mainly within the province of the committee dealing with rural reconstruction.

questions and also with questions of comfort and well-being. This co-ordination may be effected by the administrative services or by the health services, with or without the participation of joint committees.

7. *The programme of the health services in such a rural district.*

(a) *Branches of Work.*—*The programme of the rural health services should include measures for dealing with all the health problems which a survey of the district has revealed to be of real importance ; in particular, it should relate to :*

(1) *Infectious disease control (tuberculosis, venereal disease) ;*

(2) *The campaign against the so-called social diseases ;*

(3) *Maternal and infant welfare and school hygiene (including the supervision and protection of sickly children and sometimes the aged) ;*

(4) *Sanitation (including the supervision of small rural industries (brickyards, vegetable-fibre work, etc.) that may be dangerous to health) ;*

(5) *Hygiene of milk and foods ;*

(6) *Education in hygiene ;*

(7) *Sanitary supervision of medical institutions ;*

(8) *Where there is no legislation providing for the supervision of medical practice, the public health officer might be entrusted with the registration of medical personnel (the medical officer of health might be entrusted with the supervision of private nurses) ;*

(9) *Provision should also be made for first aid and for the transportation of the sick in urgent cases ;*

(10) *Laboratory facilities should be available, in accordance with the recommendations of the Budapest Conference.*

We have already seen, and shall see again later, how intricate the health services tend to become, and how all the activities directly connected with the protection of public health enumerated above are gradually assigned to them.

In certain rich and densely populated industrial countries, some of these activities have been organised one by one since the beginning of the century, in some cases with the co-operation of separate committees or various private organisations, as in England, Belgium, France and the Netherlands, where the adoption of official measures or health regulations is not required. This multiplication of activities has made it necessary to reorganise the work in accordance with a

comprehensive programme. The carrying-out of this programme, or at any rate the supervision of its execution, has been entrusted to the departmental or county medical officer of health.

Technical progress during the transitional stage of the work has increased the complexity of the services, since it has been necessary to introduce up-to-date methods for the diagnosis of the so-called "social diseases", such as X-rays, the examination of sputum, biopsies, hæmatology, etc. For syphilis, the blood and cerebrospinal fluid must be examined; in the case of infectious diseases, laboratory research has increased enormously, not only with regard to the treatment and isolation of diagnosed cases, but also from an epidemiological standpoint with regard to their environment and possible germ-carriers.

As a result of the fall in the birth rate in a large number of countries, a campaign to increase the number of births is being carried on in conjunction with maternal and infant welfare, with a view to obtaining quality as well as quantity. Medical and health action is accompanied by economic measures to help families to bring up several children; sums of money are distributed for this purpose to wage-earners by the public authorities or the "compensation funds", as in France. In order to assist large families, Sweden, for instance, is endeavouring to some extent to equalise consumption by supplying essential goods or services to families or children. It is thus possible, outside the public assistance system, to provide for the consumption of essential products and the supply of essential services in accordance with the laws of health. Such action sets an example and has an educative value. It may include the provision of skilled attention in childbirth, medical and dental care for children, social services, housing, the supply of extra food, especially in schools, the creation of pre-school establishments, and facilities for recreation. All these new social charges, which fall both on consumers (quotas, Customs duties, various countervailing duties) and on employers (various insurances, family allowances, etc.), make up what it has been agreed to call the "social wage".

The services for the medical protection of mothers and children, which have laid special stress on the importance of protecting expectant mothers, also need scientific equipment going beyond obstetrics and coming definitely within the framework of social diseases, especially for the detection of tuberculosis and syphilis and for combating

malnutrition. The introduction of scientific mass methods for the medical examination of school-children, particularly the mass performance of the tuberculin test, and sometimes the use of radioscopy and radiography, have made it necessary to reorganise the work. As the number of problems increases, each of them is attacked on several fronts simultaneously, thus adding to the complexity and making it necessary to consider the question as a whole.

The patient or prospective patient is then studied in relation to his family and social environment. This calls for unity of action and the application of a coherent programme, which should be as complete as possible. We shall see how the health centre, whether it has any physical existence or is merely represented by a co-ordinating body, makes uniform action possible.

This tendency to reorganise the services is to be seen in all countries. In the United Kingdom, it is represented by the medical officer of health and the committees of which he is a member ; in France, by the departmental health inspector, who acts as secretary of the health and social co-ordination committee ; in the Baltic countries, by the district medical officer and his colleagues ; and in Central Europe, by the regional institutes of hygiene.

This process is less clearly marked in regard to sanitation, and appears chiefly in minor sanitary operations. As regards foodstuffs, the public authorities no longer devote their attention exclusively to the prevention of fraud. The supervision of the sanitary conditions obtaining in hospitals is difficult in highly decentralised countries where the hospitals are controlled by practically autonomous administrative boards, but is more feasible in countries where hospitals are less independent and employ full-time physicians and surgeons.

The control of the qualifications of doctors and of medical practice, for which special boards or commissions are frequently responsible, is tending to spread with the establishment of social insurance and also, in certain countries, of medical associations. We shall revert later to first aid and laboratory examinations.

(b) Notifiable Diseases and Vital Statistics.—*The effective work of rural health services depends on the completeness of their information on the prevalence of infectious diseases and on the accuracy with which causes of death are certified.*

All doctors practising in rural health districts should be required by law to notify the health authorities immediately of

every case of an infectious disease¹ which they have examined. In special cases (absence of doctors), head of families, teachers and local officials should be required to notify suspected cases to the health authorities.

The attending physician should be required by law to fill in a standard certificate of the cause of death and to transmit that certificate to the local health authorities without delay.²

The health officer should utilise every means to keep in touch with the prevalence of infectious diseases in this district—routine epidemiological investigations of cases and contacts, charts and graphs, a diagnostic (consultation) service. The returns of causes of deaths should be studied regularly to the end that the general health programme may be suitably adapted to local needs.

From 1932 to 1936 inclusive, the list of the principal notifiable diseases was not increased to any considerable extent. The pestilential diseases (plague, cholera, yellow fever, typhus and smallpox) are compulsorily notifiable in European countries, all of which have acceded to the International Sanitary Convention of 1926. The position at the end of 1932 was as follows (it will be noted that nearly all European countries have made diphtheria and typhoid fever notifiable) : Whooping-cough (21), diphtheria (35), encephalitis lethargica (30), undulant fever (12), paratyphoid fevers (29), epidemic cerebrospinal meningitis (33), puerperal fever (28), recurrent fever (26), typhoid fever (34), leprosy (22), ophthalmia neonatorum (9), malaria (19), acute poliomyelitis (31), rabies (18), trachoma (17), chicken-pox (18).

Since then, Germany, in 1934, added whooping-cough, undulant fever, paratyphoid fever, leprosy, ophthalmia neonatorum, malaria, and rabies to her list. Poland, in 1934, struck off recurrent fever. Gibraltar added leprosy in 1934 and struck off recurrent fever in 1935. Switzerland added undulant fever in 1936.

In rural areas whose economy is still primitive, and where doctors are rare, a considerable proportion of the population still receives

¹ Diseases required by law to be notified. Compulsory notification might be extended to include the auxiliary health staff (nurses, midwife, sanitary inspector).

² Attention should be drawn to the system followed in Switzerland for notifying causes of death. (See document C.H.669.) This system, which protects professional secrecy, has been adopted in Western Flanders (Belgium) and in certain departments in France.

no medical attention. In such cases, it is useless to hope for accurate and complete statistics of notifiable diseases. Moreover, in certain countries which are more highly developed industrially, although doctors treat practically all contagious diseases except a few cases of what are called common infectious diseases of children, they may be somewhat reluctant to notify cases when the list of affections is too long ; sometimes, as in England, they are encouraged to do so by the grant of special fees.

French legislation has recently made it compulsory for the head of the family, as well as the doctor, to notify infectious diseases, and, as regards causes of death, the Swiss system of confidential notification has been made general, with the result that the number of deaths from unknown causes has decreased considerably.

Most health services, especially when they employ a full-time staff, make use of spot-maps and graphs, which are to be found in demonstration centres and in well-run health centres. The departmental health inspectors keep " health records " on which the essential vital and statistical data relating to mortality and morbidity are entered, commune by commune or canton by canton, together with those relating to sanitation and complaints of insanitary conditions.

(c) *Statistics on Social and Economic Conditions.—In addition to vital statistics, which permit the health authorities to appraise the results obtained and to adapt their programme to local needs, statistics relating to social and economic conditions (composition of the population, housing, hospitals and other medical institutions, etc.) collected by various agencies, in particular by health insurance institutions, should be utilised by such authorities.*

The health indices compiled as a result of FALK and STOUMAN's researches have enabled such enquiries to be carried out in Hungary and in Belgium (at Brussels and in the province of Luxemburg). Other investigations are in progress in various countries. This method has been systematically employed since 1937 by the Hungarian health services for administrative purposes, in order to ascertain each year what the various health organisations require and what they have done. Professor PITTALUGA succeeded in tracing isohygienic curves by means of a very brief list of similar indices.

In Czecho-Slovakia, Roumania and elsewhere, a large number of monographs have been compiled and numerous health and social

investigations undertaken in rural districts, usually at the instigation of the institutes of hygiene, or, in Roumania, as part of the normal work of the various health and social " teams " that visit the peasants during the vacation periods. These methods need to be further systematised and amplified, especially as regards health budgets ; the Health Organisation has not lost sight of the importance of this question, for which it has obtained the help of directors of institutes and schools of hygiene.

8. *In order to ensure the interest and enlist the support of the public, the Conference considers it advisable to set up advisory councils or consultative committees, composed of leaders in the community or of representatives of agencies¹ which carry on health work.*

The system of advisory councils or consultative committees has long been established in Western Europe, where local government is highly developed. These may be committees composed of representatives of the various communal, cantonal or departmental councils, or councils consisting partly of their representatives and partly of co-opted members, or special councils.

These committees may simply advise the health inspector or administrative health authority, or, in some cases, as we have seen in Sweden, in matters of sanitation, child welfare and alcoholism, they may possess administrative, or even to some extent judicial, powers in addition to their powers of supervision.

Care is taken not to grant too much autonomy or authority to these committees in places where local electoral influences may make themselves too strongly felt through the committees.

These committees, when they take their work seriously, are not only able to give useful advice to the health authorities regarding the local psychology and " atmosphere ", but also play a very active part in educating the public.

Certain committees may be made responsible for the collection of funds which are then distributed among the various associations, especially in connection with national " days " or " weeks " for tuberculosis, children, etc., on behalf of which they conduct useful propaganda as well.

¹ This recommendation does not apply to health insurance institutions, which are treated in Chapter II.

In other cases, a public institution may assume a semi-private form, so as to enable it to collect private funds more easily and to arouse public interest, as in the case of the polyvalent social service of the health centres in Hungary, known as the Green Cross.

Lastly, in some countries, such as Denmark, the communal nurse, who is responsible for nursing patients under medical supervision, is paid out of a joint fund constituted by the commune and social insurance institutions, or in some cases by a private organisation.

9. *In view of the wide variations in health programmes in the different countries and the considerable differences in local conditions, it is not possible at present to recommend a model budget for a rural health district, or to state what should be the per capita expenditure for health purposes. It is also impossible to decide on the percentages of the budgets of States, provinces, districts and communes which should be allocated to the health services.*

The Conference considers it advisable to secure further information on the cost of rural health services and, to this end, recommends that studies on a uniform plan should be carried out in rural districts under the auspices of the Health Organisation of the League of Nations.

The purpose of these studies should be to determine which effective form of rural health organisation is most economical and, in particular, the cost of the method described by the Budapest Conference in comparison with other methods in use.

The compilation of health indices includes the study of the total cost of the health services and the cost per head of population ; hygienists are taking more and more interest in this question, which, in their opinion, is of fundamental importance, and should form the basis of any sound medico-social policy.

A number of guiding principles for detailed investigations were laid down at the meeting of directors of institutes and schools of hygiene held at Geneva from November 22nd to 27th, 1937,¹ concerning enteric fever, the brucellosis and tuberculosis. The particulars given show how intricate the problem is.

1. *The Cost of Enteric Fever :*

(a) To the population itself (cost of medical care, drugs, hospital treatment, etc., loss of wages due to the patient's temporary incapacity and loss of wages of members of the family taking care of the patient ; capital loss represented by deaths, etc.) ; (b) to insurance funds ; (c) to public funds, both local and

¹ *Bull. Health Org., 1938, 7, No. 2.*

national (cost of hospital treatment, laboratory services, control of germ-carriers, etc.);

The cost of various measures against rural enteric fever :

Construction of piped water-supply systems and/or purification and distribution of water ; construction of protected wells ; protection of springs ; sanitary improvements to manure-pits, etc. ; construction of sanitary privies ; systematic removal of patients to hospital ; detection and control of chronic germ-carriers ; mass vaccination of the population ;

taking into account :

(a) The geographical type of the rural community ; concentrated or scattered population ; size of the villages ; accessibility and fitness for human consumption of the water-supply, etc. ; (b) the immediate outlay involved, amortisation and cost of upkeep on the one hand and the cost of continuing to apply the above measures on the other hand ; (c) their relative efficacy as demonstrated by practical experience (it would be useful to cite actual examples).

2. *The Cost of Tuberculosis :*

(a) To the population itself (cost of medical treatment, drugs, hospital treatment, etc. ; loss of wages due to the temporary incapacity of the patient and to his lowered efficiency on recovery ; capital loss represented by death, etc.) ; (b) to insurance funds ; (c) to public funds, both local and national (cost of treatment in hospital, treatment in sanatoria, preventoria, etc., including the amortisation of capital outlay on such institutions, and on dispensaries and district nursing services, etc.).

The cost of the various anti-tuberculosis measures :

Organisation of educative propaganda ; organisation of BCG. vaccination ; detection of cases by stationary and travelling clinics and their visiting nurses ; out-patient treatment by pneumothorax ; segregation of the most highly contagious cases in hospital (institutional treatment on the spot or at a distance ; hospitals, homes and special housing accommodation for the tuberculous) ; treatment of curable cases in sanatoria ; prophylactic treatment for cases of latent tuberculosis (preventoria) and subjects specially exposed to tuberculosis (boarding-out, holiday camps, open-air schools) ; social assistance to the tuberculous and their families (supplies in kind for treatment or convalescence in the home) ; financial aid and supply of food to patients and their families ; vocational readaptation for patients who have improved or recovered.

In calculating the cost of the various anti-tuberculosis measures, account should be taken of the immediate cost of constructing institutions, amortisation and running expenses.

Estimates should take account, as far as possible, of the actual cost of existing institutions in relation to the number of cases and the population served.

Where there are no such institutions, or where their number is inadequate, the probable cost of creating them or enlarging them to meet requirements should be estimated.

Estimates should cover the cost of institutions on simple lines, run with the maximum economy compatible with technical efficiency.

10. *Official funds for health work in rural districts are derived in varying proportions from the State, the province, the country, the district and the commune. While the State may have to provide the largest proportion when the rural health services are being organised, or in the case of poor districts, it is essential that the proportion contributed locally should gradually increase.*

These principles are gradually being adopted in all countries, if only for budgetary reasons ; but it is difficult to give any figures, because no special studies have been undertaken on the subject. It is highly desirable that these should be put in hand.

A proportion of the expenditure is transferred to the local authorities as soon as the local services are firmly established and have shown themselves efficient ; this new method of allocating the charges is usually applied with the greatest care, so as not to endanger those services when they are handed over to the local authorities.

It has also been realised that medical assistance should not be given altogether free of charge, but that the beneficiaries should contribute according to their means ; a similar question arises in connection with laboratory analyses and certain costly diagnostic examinations.

* * *

The other recommendations in this chapter relate to the various ways in which collaboration can be established between the different services (see point 11 in particular, and points 12, 13 and 14 of the 1931 resolutions), according to their technical nature and whether they are run by public institutions, private associations, or the various bodies dealing with rural welfare, from social insurance institutions to agricultural associations of all kinds, including rural educational centres.

We have already examined these various opinions when dealing with the question of co-ordination. It is usually recognised that the health officer can only co-ordinate purely health activities, but that the activities of the hygienist should be co-ordinated with those of

the services referred to above (social insurance institutions and organisations for raising the standard of living of the peasant population).¹

The experience of the American National Health Conference shows that the study of programmes covering both technical and financial questions provides objective data for effective collaboration. But attempts are rarely made to draw up a plan on these lines for a whole country, though the departmental health and social co-ordination committees may endeavour to do so on a local scale. It is to be hoped that a comparison of the results obtained by the various local co-ordination committees will enable useful conclusions to be drawn by the central authorities.

B. RURAL HEALTH CENTRES

1. Definition.—*The rural health centre may be defined as an institution for the promotion of the health and welfare of the people in a given area, which seeks to achieve its purpose by grouping under one roof or co-ordinating in some other manner, under the direction of the health officer, all the health work of that area, together with such welfare and relief organisations as may be related to the general public health work.*

In rural districts where such public health work has been organised for some time, it may be difficult to group all health activities under one roof or in the same organisation. Nevertheless, an attempt should be made to co-ordinate the work of existing agencies in the most effective way.

On the other hand, where a modern public health organisation is to be created in new territory,² the health centre, as defined above, is the best method of attaining the desired result.

In many countries of Europe, the European Rural Hygiene Conference of 1931 was followed by a strong movement in favour of the establishment of health centres.

¹ 11. *In order to avoid deficiencies and prevent duplications in the promotion of the health of the rural population, it is desirable that collaboration should be established between the public health services and social insurance institutions.**

* See in the annexes to Volume II (Minutes) the report submitted to the Conference by the International Labour Office: "Sickness Insurance as a Factor in Rural Hygiene, 1931".

² The term "new territory", as employed here, implies that an effective health service in the modern sense does not exist.

An exchange of views in the Health Organisation's Sub-Committee on Health Indices, which met at Geneva in June 1938, showed that the term "health centre" was sometimes applied to very different institutions—*e.g.*, mere medical consultation centres, the radiological departments of sanatoria, and monovalent dispensaries not under medical supervision and frequently with no service of visiting nurses. In some cases, the so-called health centre is nothing but a treatment centre; in others, it is merely an institution for the "preventive medical examination" of persons of all ages or of special categories of persons; and in still others, its purpose is the observation of the biological and physiological behaviour of the family unit in particular circumstances.

Even the premises may be entirely dissimilar—*e.g.*, the consulting-room at the private residence of a poor law medical officer, the corner of a hospital ward set aside for consultations, or the out-patient department of a big hospital.

The Sub-Committee therefore proposed (document C.H.1331(1)) that, for the purposes of "health indices", the following definitions should be strictly adhered to:

" The *Primary Health Centre* must :

" (1) Carry on at least two medico-social activities ;

" (2) Be placed under the direction of a doctor ;

" (3) Be provided with a 'family social worker'—*i.e.*, polyvalent—visiting families by herself in connection with the various medico-social activities of the centre ;

" (4) Assist, if local conditions permit, in co-ordinating all activities of the district for which it is responsible.

" The *Secondary Health Centre* must :

" Be a superior organ which must primarily co-ordinate all the activities of the district for which it is responsible, in collaboration with other organs for preventive medicine coming under public authorities, sickness insurance organisations or voluntary bodies.

" In addition to the minimum requirements in points 1 to 3 for the Primary Health Centre, the Secondary Health Centre must be so equipped as to supplement and reinforce the activities of the Primary Centre on the technical side; it must, for instance, provide, directly or indirectly, the various laboratory examination services afforded by an institute of hygiene, or by a medical organisation and its specialised diagnostic services."

These matters will be further discussed in considering the following recommendation :

2. *It is necessary at the outset to specify that rural health centres, considered as agencies particularly adapted to the promotion of public health in rural districts, constitute an integral part of the general health organisation. They are, in consequence, closely related to and dependent on all the elements which form that organisation—in particular, the State or provincial institutes of hygiene, which, in several countries, constitute the most fully developed centre on which all others may depend for technical guidance.*

This reform has, for example, been enthusiastically promoted by the institutes of hygiene in Hungary, Poland, Czecho-Slovakia and Yugoslavia.

In countries with no, or with only an imperfectly co-ordinated, organisation, the transition to the system recommended by the 1931 Conference may as a rule be brought about in one of two ways—starting from the higher authorities and working downwards or vice versa.

Starting from the Higher Authorities.

In the traditional type of county or departmental health organisation, the essential element of which is not the dispensary or health centre but the health authority proper, or in some instances the district medical officer, the health centre may be used to bring the medico-social staff and its equipment into touch with the people of the area.

In such cases, the entire area, with the exception of the towns, which are able to meet their own requirements or even to convert their health centres into secondary health centres, is systematically subdivided, so that the rural parts are entirely covered by an uninterrupted succession of adjoining districts each with its own health centre.

But this method cannot be applied unless it is possible to obtain sufficient numbers of responsible health officials conversant with medico-social policy and, more particularly, with the direction of the social services proper, a duty the difficulty of which is in direct ratio to the degree of polyvalence of the services.

District medical officers, district nurses, and district midwives cannot, it would seem, be successfully transformed by a stroke of the

pen into public health officers, family social workers and child-welfare nurses respectively. Whenever this has been attempted, both the medical officer and his assistants and the public have apparently found the old system of curative action easier than preventive action, with the result that the latter has been disregarded.

Starting from the Local Authorities.

When this method is adopted, as it has been in Hungary, the first process is the gradual laying of firm foundations. In urban areas it is relatively easy, with the assistance of a co-ordination committee, to combine and co-ordinate the various medico-social activities in a single health centre, but in the country there is very often nothing to build upon : everything has to be newly created, and that as cheaply as possible.

In such cases, the fullest advantage is taken of the existing administrative subdivisions and any efficient local institutions already in being, and any favourable circumstances are turned to account by the higher authorities to create health centres, generally primary or branch centres.

If it works satisfactorily, the system ultimately extends to the whole of the department, particularly if a general plan is drawn up at the outset.

An informed public can be induced to take the first steps itself, and to make certain sacrifices such as providing a suitable site at its own expense. Success will be more certain if a particularly well-informed or competent local practitioner—either official or independent—can be associated with the project ; otherwise, the appointment is offered to a well-trained doctor alive to social questions. A real health centre can then be set up, having all the characteristic qualities of a pioneer venture. The medical and social staff, conscious of being in the vanguard of a new and fruitful form of activity, will devote itself enthusiastically to securing the centre's success. Unspoiled by routine and undeterred by disappointment, it will accomplish something of permanent value.

But quality must not be sacrificed to quantity, and this will be the risk if the staff cannot be offered terms such as will ensure them a decent standard of living, the means of educating their children, and security in old age.

Once the public have been made health-conscious, not so much by deliberate propaganda as by the force of example, or, as in Roumania, by the work of "medico-social mobile units", it has been possible, as funds and qualified staff became available and public support grew, to co-ordinate existing institutions or to create entirely new health centres throughout rural areas and in the small townships they comprise. And all this has been done in a space of time which, viewed in retrospect, seems surprisingly short.

3. It is to be understood that the considerations which follow relate to average centres, and that, in addition to these, there may be a large number of different types, the development of any particular centre being necessarily conditioned by local exigencies.

In practice, the size of the different health centres, as has been seen, varies considerably. The standardisation attempted in certain countries—*e.g.*, Hungary and Poland—bears upon the components of the health centre rather than upon the centre as a whole. This matter will, however, be discussed below when the health centre is described.

4. There are two methods of classifying rural health centres ; they may be designated as small or primary centres and as larger or secondary centres, according to their varying organisation and development ; or they may be divided into village or communal, corresponding to primary, and district (arrondissement), corresponding to secondary, centres, according to the administrative subdivisions in which they work.

The Conference expressed its preference for the first of these classifications—that is, their subdivision into primary and secondary health centres.

There should also be branch health centres of the most simple type to enable the work of such primary centres to be carried into the smaller villages.

Such systematic grading of primary and secondary health centres is, however, but rarely met with in practice. The more difficult or complicated diagnoses are frequently performed, not in the secondary health centres, but in specialised hospital services.

I. THE PRIMARY HEALTH CENTRE

5.¹ *In the general public health armament of a given country, the primary health centre, with its branch centres, represents the terminal stage ; it is the smallest agency adapted to serve the public health needs of the smallest rural area.*

The working programme of this centre should be established on the basis of a preliminary survey concerning :

1. *The topographical conditions of the district—density of the population, distribution (dispersion) of homes, means of communication. This information will facilitate the selection of the sites, and the determination of the number of health centres and branch health centres required.*

2. *The health and epidemiological conditions among the people ; this information will be equally useful in establishing the centre's programme of work.*

II. THE SECONDARY HEALTH CENTRE

9.¹ *The secondary health centre is a more fully developed organisation than the primary centre, on account of its greater completeness of equipment, its larger personnel and the wider scope of its work.*

The secondary centre directs and co-ordinates the work of primary centres and, at the same time, ensures liaison between them and all other health and welfare agencies—in a word, with all agencies connected with the promotion of public health.

10.¹ *Programme.—In addition to its work as a primary centre (in its immediate neighbourhood) and to the prevention of those diseases which have been shown to be important problems by the preliminary survey already mentioned, the secondary centre should deal with the following :*

- (1) *The campaign against tuberculosis ;*
- (2) *The campaign against venereal diseases ;*
- (3) *Maternal welfare work ;*
- (4) *Infant welfare work (including the child of pre-school age), with special emphasis on the welfare of the child of school age (school polyclinics) ;*
- (5) *Health education : first, for the general population ; second, by means of special courses and field work for (a) doctors, (b) nurses, (c) midwives, (d) sanitary engineers and inspectors ;*

¹ The numerals refer to the recommendations of the 1931 Conference.

(6) *Sanitation ;*

(7) *Laboratory analyses, of a simple and routine character.*

The Conference was of the opinion that, in addition to this work, the centre might undertake the provision of first aid in urgent cases and ensure the prompt transport of sick and accident cases by supervising the proper organisation of this service.

The secondary health centres serve a population of from 20,000 to 100,000 (in general, about 50,000) inhabitants, according to the size of the town in which they are situated. They are usually set up in an administrative area, in which the chief locality may possess certain advantages—*e.g.*, specialists in pediatrics and social diseases, X-ray facilities, laboratories for routine examinations and a sanitary engineering service. As their staffs include a number of polyvalent health visitors, some of these may be specially trained as instructresses or consultants in child welfare matters, domestic science or social work proper, or to deal with any other problem peculiar to the district concerned—*e.g.*, tuberculosis, malaria, trachoma, etc.

The secondary health centre acts as a primary centre in the place in which it is set up and, in theory, as the secondary centre for all the primary centres which are situated in its area and are subordinate to it. But the extent to which this theoretical grading is applied in practice largely depends upon the relations between town and country—that is to say, in the main, upon communications. Such being the case, chief emphasis will here be laid upon the primary centre, which is the type most frequently met with, and, for the sake of simplicity, the dispensary will frequently be treated as the simplest special type of primary health centre.

The primary health centre, usually set up in the largest village or township in its area, which comprises a group of communes with a total population of from 5,000 to 20,000,¹ serves an area which does not coincide with any administrative subdivision and so has no financial resources of its own. The health centre usually holds consultations for mothers and children, general consultations for

¹ At the end of 1936, the primary health centres of the Green Cross organisation in Hungary served a total population of 1,067,000 inhabitants, 87.3% of whom were living in rural districts ; on an average, each centre thus served a population of 6,200. In two-thirds of the centres, maternal and child welfare work was in the hands of the Green Cross and, in the remaining third, of a private organisation—the Stefania Association.

sorting or for tuberculosis alone, and, fairly frequently, dental consultations. Where rural electrification has made sufficient progress, it will possess ultra-violet ray apparatus, particularly in the northern countries ; more rarely it will also have X-ray equipment, which, in electrified districts, is more often to be found in rural hospitals. The centres frequently employ one family welfare worker, but only in rare cases two.

Each primary centre may further cover its district with a network of very simple branch centres, each serving a single commune. These branch centres are periodically visited by the medical officer and health visitor of the main primary centre, to whose activities those of the branch centres are therefore not subordinate but parallel, whereas, theoretically at least, the primary centre is to some extent subordinate in technical, if not in administrative, matters to the secondary centre.

The 1931 Conference gave detailed consideration to the working of the primary and secondary health centres respectively.

- 6¹ and 10. *The minimum programme of the rural health centre* ; 7. *Medical treatment* ; 8 and 11. *Personnel (director, public health nurses, midwives, sanitary inspectors, laboratory technicians)* ; 12. *Co-ordination committee* ; 13. *Equipment* ; 14. *Relationship of the centre to other health agencies.*

These various points will be considered in the two following sections : (a) Functions ; (b) Premises and Equipment. No distinction will be made, other than incidentally, between the secondary centre and the primary centre, which is the commoner type ; and no further consideration will be given to personnel, which has already been dealt with and whose training has been fully treated in the general report of Professor JAMESON, Professor PITTALUGA and Professor STAMPAR, on certain schools and institutes of hygiene in Europe.

The 1931 Rural Hygiene Conference urged that the working programme of health centres should be established on the basis of a preliminary survey (5).

The increasingly frequent use of " health indices " should, in future, facilitate the organisation or extension of the activities of health centres on a rational basis.

¹ The numerals refer to the recommendations of the 1931 Conference.

(a) *Functions of the Health Centre.*

As a rule, the functions of the health centre are still determined empirically in the light of the programme followed in the entire area, the personal experience of the staff, and the medical and social staff, premises and means of transport available. Attention is concentrated on what is considered to be the most important problem.

The minimum programme varies according to the relative importance of the various health problems revealed by the preliminary survey. If, in the area concerned, any one health problem is of outstanding importance, it is naturally to it that the health centre first turns its attention (malaria, tuberculosis, trachoma, acute infectious diseases, etc.). In practice, the preliminary surveys are of relatively little value as a means establishing a common programme suitable for application by a large number of primary centres, each with no other staff than a doctor and family social worker. The usual course is gradually to build up and develop the system suggested by the experience of the first health centre set up in the area.

1. *Maternal and Child Welfare (including Infants and Children of Pre-school and School Age).* — Of the centre's various activities, it is generally the medico-social work in connection with maternal and child welfare that is most fully differentiated, either from technical considerations, or because it is most readily appreciated and understood by the public, or because it requires least in the way of costly equipment and is the most obviously productive of results.

In general, pre-natal examinations are carried out at the same time as infant consultations, except sometimes in areas where such examinations have been made compulsory by the social insurance authorities, who thus provide the health centre with an extensive *clientèle*.

In some places, the maternal and child welfare services are under the direct control, not of the health centre itself, but of a charitable organisation using the centre's premises, in which case the most satisfactory arrangement is that the organisation should also employ the centre's family social worker. The public health visitors should then be really polyvalent, or at least thoroughly competent in all maternal and child welfare matters, including those relating to children of pre-school and school age.

The results of infant consultation work are particularly satisfactory when followed up in the home by the activities of health visiting nurses or even of family social workers. Apart from the treatment for hereditary diseases given in the course of infant consultation work, the most effective action is assistance and advice given in the home itself. For this purpose, the family social worker, acting on the instructions of the medical officer of the health centre, first ascertains whether the mother possesses the necessary means and knowledge for carrying out the doctor's orders.

The healthy development of infants depends primarily upon the application to this special case of the general principles of domestic science—*i.e.*, tidiness, method, cleanliness, rational nutrition and personal hygiene. Instruction in these matters is even more essential when children are very young than when they are older, as by that time their families will have learnt by experience.

There is a tendency to discontinue the former practice of suspending infant consultations during the hottest months, when, indeed, they are most valuable. The drawbacks attendant upon the closing of the centre are to some extent obviated by the social worker's educational activities in the home, which go on throughout the year, except when the mothers work in the fields at harvest time and cannot therefore be visited.

For these various reasons, travelling *crèches* are sometimes sent into the fields, when the mothers working there are sufficiently numerous and, when this is impossible, the practice in Central Europe—*e.g.*, Poland and Roumania—is to have recourse to small summer day-nurseries. These are placed under the immediate supervision of the health centre's social worker and installed either in the centre itself or in adjacent houses. The children play in the yard under the eye of the social worker, who otherwise, as has been seen, has little to do at these times.

In the country as in the towns, the welfare of children of pre-school age is generally not as well provided for as that of infants, particularly when only a few children attend the kindergarten schools. In Hungary, such schools are under the direct control of the public health authorities.

As there is no very clear-cut difference between children at the age of 1 and children at the age of 2 or 3, a certain number of the latter are frequently dealt with in the course of infant consultation

work, but a very great deal still remains to be done for the welfare of children of pre-school age.

Marked progress is being made in the vaccination of children of this age, and the health centres, which succeed in vaccinating a high proportion of them against diphtheria, are increasingly numerous. Such vaccination is compulsory in France, Hungary, Roumania and various Swiss cantons.

School hygiene was one of the first health activities to which the public authorities, in particular the local authorities, turned their attention. In some countries, such as England, it is under the direct control of the school authorities ; very often, especially in rural districts, the health officer is placed for this purpose under the school authorities, and co-ordination is thus ensured.

Almost everywhere the pupils and buildings, if not the staff, are medically inspected, at least in summary fashion, by the district medical officer. Here, too, the health centre has considerable advantages. Through its family social worker and its own medical services, it can ensure, in the first place, that medical examinations are systematically carried out and, in the second place, that most defects are corrected and that specialised examinations are conducted, either by its own staff or on their indications. It has, moreover, particular facilities for securing admission to appropriate institutions.

At certain health and rural demonstration centres, school-children annually undergo tuberculin tests with a view to sorting and the detection and, if necessary, treatment of tuberculosis. At other centres, the children are sorted before being sent to holiday centres or before receiving milk or meals in school canteens. Certain health centres, even some very small ones, have an excellent dental organisation ; dental inspection followed by treatment is being systematically organised in the rural northern countries ; in Sweden, it is compulsory.

The health centre's family social worker does not confine herself to educational activities in the home, but very frequently continues such work in the schools, where, with the sympathetic co-operation of the teaching staff, she is able to give systematic instruction in hygiene and cleanliness.

2. *Tuberculosis*.—The anti-tuberculosis action of the health centre ranges, according to its size and to the training and equipment of its

medical officer, from mere sorting, detection of contacts or the treatment of symptoms (if this last is permitted in the absence of local practitioners) to complete diagnosis, artificial pneumothorax on the spot, or the direction of cases to institutions for appropriate treatment.

In most cases, the primary or branch health centre has two main activities : child welfare and general medical consultations with special reference to tuberculosis. Where differentiation between the primary health centre, secondary health centre and central dispensary is impossible, or is still incomplete, the tuberculosis patient generally remains under the care of the primary health centre, in which case it is not always possible to ensure very accurate diagnosis or to give the patient the benefits of modern thoracic surgery.

An economical and effective way of accommodating patients is to attach to the health centre one or two rooms where tuberculosis cases may remain as inpatients and receive pneumothorax therapy. Such a course may well be adopted for cases which cannot be placed in a sanatorium or for chronic patients, who must be kept apart from their families to prevent contagion, but whom it is impossible to send any distance from their homes. A method which has been tried in certain countries, such as Poland, is to add a special room to the family home for the exclusive use of the tuberculosis patient ; but in some areas this arrangement offended family feelings and had to be abandoned.

In many countries, the tuberculosis or, more usually, the child welfare service is rarely able to remove children from homes in which they are exposed to contagion for any length of time, unless they can be sent to relatives. Certain health centres therefore distribute BCG vaccine and observe the results. In this matter, as in the detection of " contacts " and sanitary improvements, the action of the family social worker is of the first importance.

3. *Venereal Diseases.*—In the northern countries, it is generally the district medical officer who is directly responsible for anti-venereal action and who treats venereal cases in his own surgery free of charge. Treatment is compulsory. Generally, syphilis is a subject of much greater concern to the authorities than gonorrhœa.

The advantage of the health centre in these matters is that it can carry on its anti-venereal action in close connection with its maternal

and child welfare work, cases being as a rule detected during pregnancy.

The problem is not so much that of ensuring treatment alone, but increasingly that of combining treatment with epidemiological action—that is to say, the detection of contacts and the constant observation of patients under treatment. The health centre, particularly in country districts, is well able to carry on such activities with proper discretion, as it is “polyvalent” and works through a non-specialised family worker, whom the public does not connect with any one disease.

4. *Epidemic Diseases.*—It is recognised that through its constant watchfulness the health centre is one of the most essential factors in the fight against contagious diseases.

One group, frequently of an eruptive character, chiefly attacks children (though diphtheria may also attack young adults and scarlet fever persons of all ages); the measures taken by the health centre to safeguard the health of children—that is, education, vaccination, detection, treatment, disinfection of excreta and timely isolation—obviously help to prevent the appearance and spread of these diseases and their pathological complications. Though here, and particularly in regard to the so-called “common” contagious diseases of childhood, disinfection of premises after the termination of the disease is of very little value, the educational action of the family worker in the home and in the school is of primary importance.

A second group of transmissible diseases—intestinal diseases (dysentery, typhoid infections), diseases propagated by insects (typhus), and certain diseases caused by an unknown virus such as trachoma—calls, above all, for unremitting efforts to eliminate dirt and poverty. In certain cases, it is true, the health centre may do something by means of vaccination (usually confined in practice to those immediately in touch with the patients); but the chief need is for constant action to ensure personal cleanliness and the cleanliness of premises by education and a minimum of sanitation. The value of the example set in the matter of cleanliness by the health centre's own sanitary installations—latrines, shower-baths and wells—cannot be overestimated.

The individual public health officer only appears in rural districts during epidemics, when he is accompanied by a “mobile unit” with

disinfecting apparatus, autoclaves, chemicals, and even transportable shower-baths, and sometimes has the material support of the gendarmerie ; a minimum of sanitation is thus secured, principally by the construction of latrines or W.C.'s. As soon as the epidemic has been wholly—sometimes only partly—stamped out, the mobile unit returns to its base and the peasants to their former habits, even destroying the sanitary installations set up for their benefit.

Much more effective and thorough than the action of the individual public health officer is that of the health centre, supported, when necessary, by epidemiologists from the institutes of public health, central laboratories, or equivalent services. This is because the action of the doctor, family social worker, and perhaps sanitary inspector, who compose the centre's staff, is carried on without intermission.

When its activities are carried on as they should be by a competent, sufficiently numerous and conscientious staff, the centre, not merely secures the application of the "sanitary regulations", but also works unceasingly for the improvement of local health conditions, both by domestic or general education and the supervision of sanitary arrangements. In this way, epidemics are as far as possible prevented ; and if isolated cases occur, the spread of the disease is checked. As regards the psychological factor, moreover, an educated public will co-operate much more readily in any rigorous measures that may be required if it feels that everything has first been done to prevent the outbreak.

Diseases connected with agricultural conditions may be caused by the state of the land and methods of cultivation. In certain countries, as in Roumania, the health centre in malaria-infected districts takes blood tests and is responsible for the supervision and treatment of malaria cases and the administration of prophylactic drugs to certain sections of the population in accordance with the methods recommended by the Malaria Commission. Through its social work in the homes of the people, it encourages the adoption of proper means of individual protection, though success here is very difficult to achieve if, as in some countries of Central and Eastern Europe, the family sleeps out-of-doors throughout the summer.

In certain cases where circumstances were relatively favourable, general reclamation measures have been successfully used to put an end to such conditions. These are all the more serious as, through

the weakening effect of the diseases, the peasants' output falls and their standard of living is lowered. This lowered standard of living leads in its turn to a lessened resistance to disease, and the standard of living again falls still further. By its daily action, the health centre helps the people to break this vicious circle. It facilitates the systematic detection of cases, and the detailed study of local epidemiological problems in the administrative centres enables malaria control to be placed on a rational basis.

Certain diseases, such as tuberculosis and undulant fever, are common to both man and animals. Tuberculosis in cattle can be eliminated only with the assistance and under the direction of the agricultural or veterinary services. Families are warned by the health centre to boil milk especially for the protection of their children, either at infant welfare consultations or more generally through domestic or general education.

Undulant fever makes its appearance more particularly in countries where *Brucella melitensis* is more frequent than *Brucella bovis*. It is really an occupational disease due to contact with cattle or sheep, particularly when in normal or premature labour. It calls for close co-operation between the health services and the veterinary and agricultural services. In the home, prophylaxis is carried out on the same lines as in the case of bovine tuberculosis ; here, particularly, however, the essential is scrupulous cleanliness in accordance with the principles of hygiene.

Rabies, another disease which is common to both man and animals, still causes considerable anxiety, particularly in certain rural areas where dogs are numerous and where the loss of valuable time consequent upon the lack of means of transport may prevent early treatment. Such a situation may best be met by the preparation of a vaccine capable of preservation for a considerable period of time and its distribution to a sufficient number of specially trained doctors throughout the country districts, so that treatment may be easily obtained at any point. This is the system in Czecho-Slovakia.

Certain infectious diseases, such as pneumonia, which may be very serious in cold countries, call for advanced laboratory facilities and an organisation whereby the "typification" of germs may be rapidly effected with a view to the use of the appropriate standardised sera. In Sweden, when distances are too great, the most modern means of transport, such as the aeroplane, are employed.

5. *Domestic Sanitation.* — In Hungary, Czecho-Slovakia and Yugoslavia, the institutes of hygiene have executive powers, which enable them to take direct action in the country districts in such matters as the construction of wells and latrines. Such action is taken in conjunction with the health centres, which are, as it were, their local agents. Though the staff of the health centre is not itself qualified to draw up plans for major sanitation works, it nevertheless gives its technical opinion in such matters on the basis of its knowledge of local conditions, and supervises the working of the installations once they are completed. Very often, for example, health centres in Central Europe have a public well or cistern and shower-baths, which are frequently copied by the peasants themselves.

The health officer in charge of the health centre, who may or may not be assisted by a sanitary inspector, sees to the application of the "sanitary regulations", which deal in the main with the salubrity of the external environment, for the normal duties of the health centre, unlike those of the social hygiene dispensary, usually include the administrative supervision of the locality.

That "domestic sanitation"—by which is understood the sanitation both of the dwelling-house and its outbuildings (wells, latrines and W.C.'s, solid and liquid manure, sheds, to some extent dairies, and nuisances)—must on no account be separated from medico-social protection was emphasised by the 1931 Conference; here, too, experience shows that the health centre, if properly integrated in the general system for the protection of public health, is capable of rational and effective action, particularly if its chief medical officer is a full-time official.

When empowered to deal with major sanitation questions, the health centre usually acts through a sanitary inspector, who for technical purposes is under the control of the sanitary engineering service of the regional or central institute of hygiene or other similar central services. More usually the chief medical officer of the health centre, aided by the family social worker, who frequently visits homes in the area, has to use his powers of persuasion to obtain the best possible environmental sanitation. The family social worker acts, not as a member of the sanitary police or a sanitary inspector—though she may require the latter's assistance—but as a teacher of domestic science.

Through its "polyvalent" social service, the health centre is able to avail itself of every opportunity of getting into touch with the individual families; contact once established, instead of concentrating on the incidentals which were the original cause of the visit to the family concerned, it attacks the whole problem, dealing, that is to say, with education and the general improvement of sanitation in the environment, the latter being considered, not only from the standpoint of the family and community in general, but also with reference to housing and mode of life.

Thus understood, not only does domestic science deal with the family budget, which is very small in certain rural areas whose inhabitants rarely handle actual cash; not only does it include cookery and the rational use of existing local resources or the improvement of such resources; not only does it teach weaving, embroidery, sewing and needlework; not only does it emphasise the importance of child welfare, which in reality is merely one special application of the rules set out above; but it also inculcates principles of orderliness and method, of which cleanliness is only one special case. Certain French and Greek health centres, for instance, have specialised teachers of domestic science on their own staff.

6. *Education and Propaganda.* — The dispensary differs from the mere clinic through its educational purpose, through the fact that its activities are confined to one branch of preventive medicine and through the domiciliary work of its specialised visiting nurses in the patient's home.

The educational influence of the general visiting nurse or family social worker attached to the health centre is much stronger, as the centre subdivides its total area—which would require several specialised nurses from each type of dispensary—into smaller districts, each of which can then be placed under the care of a single family social worker. The latter thus loses less time in travelling—a vital consideration in country areas—and can use a visit to a given place to deal with a number of different cases; she is better known to the families in her district and, through the constant use of the same methods, her influence is more surely established. Her educational influence, which is the outcome of her general personal influence, is thus greatly enhanced.

A similar educational influence is exercised by the health centre though its baths and showers, its latrines or W. C.'s, its well, its well-kept premises, the educational posters in its waiting-room and the lectures of its chief medical officer and his staff.

In practice, numerical insufficiency of the social staff means that the district for which each family social worker is responsible is too extensive and that the number of families under her care is too great for her to be able to give personal attention to all those who should have recourse to her. Though, by the force of their example, the successfully readapted families exert a salutary influence over the others, it is none-the-less necessary that this influence should be carried still further afield by systematic propaganda. This is even more necessary in areas where there is no social service and where the deficiency must be made good by other means, or public opinion prepared for the establishment of such a service.

The propaganda is conducted either by specialists or by specialised health officers from the regional or central health institutes, or, better still, by the health officer of the health centre and his assistants employing the usual modern methods, which, however, must always be carefully adapted to rural audiences. An interesting type of educational propaganda organisation set up by a health centre is the system of "health co-operatives" in Yugoslavia. In addition to the lectures which they give in a special room at the health centre of the "health zadougra", their medical officers systematically inspect all the houses in their area once or twice a year and discuss individual problems with the residents on practical lines.

Does the elaborately organised, spectacular type of propaganda, with its striking slogans, produce a real and lasting effect on peasant populations, except when it is informed by true missionary zeal? The educational work of the "mobile health units" in Roumania has been found to be of permanent worth, because it is in direct touch with the daily life and toil of the peasants and has often led to the establishment of permanent institutions such as a health centre.

As has been shown by the work of the conferences of directors of public institutes and schools of hygiene, the rural health centre is of vital importance as a demonstration centre and school of practical training, where doctors, family social workers, health visitors, midwives and sanitary inspectors can familiarise themselves with the conditions in which they will have to work; such periods of practical

training are frequently compulsory for all aspirants to posts in the health services, who are thus able to acquaint themselves with administrative practice and also to observe peasant conditions scientifically when preparing monographs or compiling "health indices". Such research may be of great scientific value, as may be seen from the publications of the health institutes.

7. *Laboratory Analyses of a Simple Routine Character.*—Such examinations—even the simplest of them—are gaining in importance through the development of pre-natal consultations and the increasingly systematic detection of tuberculosis, both of which are matters of constant concern to the health centres.

The full chemical examination of urine is in less frequent demand than formerly, and mere testing for albumen and sugar is done in the primary and branch health centres. The direct examination of sputum or homogenisation for tuberculosis may in case of necessity be carried out in the secondary or primary health centres. Methods of packing have so far improved and the rapidity of postal communications is such that it is almost always thought preferable to send certain samples to other laboratories—*e.g.*, samples of sputum, of blood for the Wassermann test or blood counting, swabbings for diphtheria and gonorrhœa, or fœces for diarrhœa, typhoid and dysentery. Examinations are carried out in the central laboratories or in certain hospitals, as has been seen to be the case in Czecho-Slovakia, or in the routine analytical laboratories of the institutes of hygiene.

This procedure, when properly organised, as it is in the serological institutes or institutes of hygiene in Denmark and Hungary, keeps the health authorities fully informed of the most recent development regarding the appearance or progress of epidemics, while the practitioner or health officer can be sure that the examination is carried out under proper supervision.

8. *First Aid, Transport of Sick and Injured Persons.*—In some countries, the organisation of first aid and the transport of sick and injured persons devolves primarily upon the Red Cross organisation and its local branches; the activities of the health centres in these matters are as a rule limited.

If the rural health centre tends to become a first-aid station or a minor treatment centre, the family social worker may be enabled to

move about as she should. Yet one of the most effective arguments in stimulating local efforts for the construction of a health centre—gift of site, contributions in kind or in cash towards building expenses—is that the health nurse and some member of the medical staff will be in residence and that the people of the area can thus be sure that they will not be left to themselves ; on humanitarian grounds, the health centres are ready to assist in urgent cases, but in these only, unless officially classed as treatment centres.

For the transport of patients, they use the motor-car of the medical officer or family social worker, if they have one. Sometimes, as in Hungary and Poland, a few beds are placed in an annex of the health centre for use in urgent cases.

The health centres and their staff, in conjunction with the Red Cross, have rendered invaluable services in cases of natural calamity or war. The premises of health centres are sometimes equipped to receive civilian gas cases and also as first-aid stations. The social service can help in evacuating and finding shelter for civilian refugees, and holiday camps may provide valuable accommodation for school-children evacuated from the big centres.

During the reconstruction period, the part played by the health centres in the medico-social field was of such importance that the rural medico-social service in France owes its origin very largely to the reconstruction of the devastated areas.

(b) *Buildings and Equipment.*

The health centre and dispensaries are usually set up in the heart of the community. They are sometimes surrounded by a model orchard and vegetable garden.

The erection of big and costly buildings is usually avoided, though in certain cases the rural administration centres are planned on a more ambitious scale. The work of these latter institutions is, indeed, such that their premises require more careful planning and they need more and larger rooms for the accommodation of pupils and for the purposes of the largely practical instruction which they provide ; the necessary simplifications are then introduced into the plans for the smaller subsidiary centres whose activities are of a more routine character.

Provided they can obtain qualified staff in sufficient numbers, the authorities usually tend to increase the number of centres rather than to concentrate on the lavish equipment of a few model institutions.

The architecture of the centres is primarily functional in character, the designs being prepared by the technical architectural and engineering services in consultation with the staff of the centres themselves. In Hungary, it has been found desirable to standardise the design of the fittings, furniture and rooms, and the State Institute of Hygiene provides model plans of health centres or dispensaries.¹

These plans are not too rigidly adhered to, certain variations being necessitated by the purpose to which the buildings are put and by the use of local materials, whenever this is possible. As the work of the larger health centres is naturally more complex, they require more rooms, and the disposition of these is a further complication. The difficulty of finding exactly suitable sites in the towns prevents complete standardisation and thus makes for greater variety in design.

In the case of small dispensaries with the simplest technical equipment, the authorities may prefer to avoid the expense of specially constructed premises. A very economical arrangement is to set up quite simply equipped health centres provisionally in a room in the village hall, or even to instal them permanently in an ordinary dwelling-house rented or bought for the purpose. Such prudent courses may be particularly advisable in view of the rapid progress of communications and technique and the possibility that, in the relatively near future, medico-social problems may develop in unexpected directions.

In designing the larger health centres comprising X-ray equipment, laboratories and a wide variety of activities, the technical services have recognised that working arrangements and facilities for the movements of staff and patients must be studied with the greatest care, as the savings on a building designed with excessive regard

¹ The technical service of the Budapest Institute of Hygiene begins by designing the minimum standard fittings, which include desks, examination tables, cupboards, filing cabinets, seats, etc., with a view to their being made in the village itself. Once the fittings have been designed, consideration is given to the space to be allowed for movement, and in this way the area and optimum dimensions of the various rooms are calculated. It is thus possible to build up the complete plan of a standard primary or branch primary dispensary.

for economy might be exceeded by the cost of maintaining too numerous a staff. Faulty design has sometimes had the effect of greatly increasing annual charges over a period of many years, and this is especially regrettable, as it is sometimes easier to obtain large sums for building than relatively small sums for the annual upkeep of an institution.

The simplest primary or branch primary health centres usually consist of a rectangular building. The waiting-room is situated in the centre, facing the main entrance ; this room is also used for weighing infants brought for examination. On one side of the waiting-room is the consulting-room, which is used by the physician for the examination of patients and which, in the doctor's absence, is the family social worker's office. On the other side of the waiting-room are shower-baths, which are available to school-children without charge and to adults on payment of a fee.

In addition, the primary health centre frequently comprises, particularly in the sparsely populated rural areas, living-quarters for the family social worker and perhaps an apartment for the medical officer ; the family social worker's kitchen and vegetable garden may be used to give housekeeping demonstrations to peasant women.

Health centres of a somewhat more advanced type also possess dental equipment and an ultra-violet ray lamp. In the more highly developed primary health centres and the secondary health centres, there is a certain amount of specialisation ; they include, for example, a special consulting-room for the examination of infants and expectant mothers and another room for general consultations—*i.e.*, sorting of cases or treatment where appropriate.

The unnecessary multiplication of consulting-rooms and separate rooms for the health centres' different activities is avoided (particularly as it is generally admitted that it is not here that contagion is usually spread), as the building and maintenance of little used premises is obviously a source of unnecessary expenditure.¹

When there is a separate tuberculosis department, particularly if electricity is available in the village so that it is possible to instal X-ray apparatus and thus to carry out complete examinations and,

¹ Special premises not requiring any particular equipment cost roughly 50 to 100 Swiss francs a square metre. The cost per visit per patient of premises 30 square metres in size, when the consulting-room is only used twice a month, can thus be realised.

if necessary, administer pneumothorax treatment, it is usual to divide the premises of the health centre into two main wings, the first for tuberculosis and venereal diseases and the second for other activities, including child welfare. There may then be two separate waiting-rooms for patients.¹

The general practice is to make furniture simple but at the same time comfortable and sufficient for all purposes ; the benches are made with backs to them, and the undressing cubicles in recent buildings communicate directly with the consulting-room. If the staff of the health centre is engaged in special research requiring fairly expensive apparatus, this is lent to the centre but not added to its permanent equipment.

The sanitary installations are simple, inexpensive, and of the type most suited for use by the inhabitants of the area, and are usually kept in a state of such perfect cleanliness as to serve as an object-lesson in practical hygiene ; this applies to the latrines, W.C.'s, shower-baths and wells.

(c) *Liaison.*

14. Relationship of the Centre to Other Health Agencies.

—Certain of the agencies with which the primary health centre should be in relationship (secondary health centres, specialised dispensaries, institutes of hygiene) also form integral parts of the general health organisation of the country. In such cases, the proper relationship already exists. With others (establishments for treatment and prevention, hospitals, sanatoria, preventoria, social insurance institutions), relationships should be established which will permit the centre to obtain their help either directly or through the secondary centres.

¹ When the site permits, the buildings in which these secondary health centres are housed are not usually rectangular but square. A social worker's or secretary's office (preferably without a pigeon-hole window) near the entrance may be used as an enquiry office ; then comes a waiting-room, which may or may not be partitioned off, with the different medical services on either side—tuberculosis on one side and infant welfare on the other. The premises are so arranged that the social workers, secretary-nurses and the central filing cabinet are accommodated between the patients and the medical staff. Each family record file contains, in addition to the results of the social enquiry regarding the home and each member of the family, the different medical record cards with up-to-date particulars of the various examinations, diagnoses, treatments, forms of social care and advice carried out or provided by the health centre or bodies working in conjunction with it.

Periodic conferences at regular intervals for the staff of the medico-social service have been found to be most desirable, particularly in the country, as, by facilitating personal contacts, they are a means of overcoming some of the difficulties of maintaining contact between the various institutions and of relieving the staff's feeling of isolation, while affording opportunities for mutual instruction. In addition, certain countries organise less frequent conferences which are held several times a year at the headquarters of the departmental or county administration.

The co-ordinating committees already referred to organise co-operation between the various services or institutions on a more formal basis. It has been found that, if staff conferences are to be of real value, they must be held at regular intervals and must be properly prepared in advance.

IV. TRENDS OF MEDICO-SOCIAL POLICY IN RURAL AREAS

1. The European Conference on Rural Health in 1931, after affirming that the sick country-dweller must be cared for and the healthy country-dweller protected no less than the town-dweller, showed how such medico-social protection might be provided in practice. The public authorities in all countries are striving increasingly to make the benefits of medical science and sanitation available to country-dwellers. Making due allowance for national conditions, they have created, reorganised or extended numerous institutions for medico-social protection.

2. The 1931 Conference laid down guiding principles and appropriate methods for providing country-dwellers with medical attention, and indicated the most effective methods of organising public health services in rural areas. Sufficient time has now elapsed for it to be seen that the use of these methods, though differing sometimes from those employed in the towns, has been justified, and has been willingly accepted, if not actually demanded, by the rural populations.

3. In country districts, the non-elastic portion of the demand for medical care represents the most urgent need. As the economic level is usually lower than that obtaining in the towns, this portion

of the demand consists of diseases which cause such pain or other physiological troubles as to make work completely impossible. In regard to pathological conditions in which these characteristics are less marked, the demand is unfortunately more elastic, though such conditions may be contagious and constitute a direct danger to the community or may be symptoms of the early stages of diseases capable of leading to temporary or permanent, partial or total invalidity, or even premature death.

4. The public assistance services are instrumental in meeting the non-elastic portion of the indigent person's demand ; otherwise, they would be quite unable to afford treatment ; the public health services are increasingly active in meeting the more elastic portion of the demand of an ever-growing section of the population through organised action against contagious and social diseases ; the sick insurance organisation which totally disregards these distinctions aims at meeting all needs, whatever their elasticity. In practice, the three systems may be combined in various ways with the personal resources of patients to ensure the fullest treatment for the individual and the defence of the health of the entire rural population.

5. Medico-social protection is effective if the public authorities, instead of contenting themselves with a more or less stereotyped solution for each separate health problem according to the disease, age or category of the persons to be protected, apply a comprehensive policy aiming at the co-ordination of public and private activities as regards, not only the improvement of local health conditions, curative and preventive medicine, but also social work and health insurance and the welfare of the peasant.

6. The public authorities, while improving their local public health services, whose duty it is to stimulate, adapt, direct and co-ordinate the application of the medico-social measures recommended, are at the same time improving their national health system—for example, by perfecting their hospital system and regrouping dispensaries in the form of health centres or creating such centres. The staff is also claiming their attention, as it has been found that, as the result of the shortage of doctors in country districts, the gaps in their medico-social training and the lack of trained auxiliary workers, the results are not commensurate with the very considerable sums laid out.

7. The experience gained during these seven years of progress has convinced all those concerned with medico-social protection of the imperative need for improving the peasant's education. The peasant must be the instrument of his own betterment and join a great movement to attack his various problems in all their aspects—direct or indirect protection against disease and general rural well-being alike.

8. At the same time, public authorities have undertaken the co-ordination of activities on a national scale. They have endeavoured to ensure unity of action and the maximum efficiency through the establishment of central departments whose task it is to work out and facilitate the execution of technical and financial programmes applicable to the whole country and covering a period of years.

9. It is frequently observed that, while there is a gradual trend towards local autonomy, the central services are increasing their technical control with a view to improving the efficiency of the health services and of the medical and social work of the health centres and dispensaries, and to ensuring that liaison between technical bodies in town and country which, on both technical and financial grounds, is held to be indispensable.

REPORT OF THE HOUSING COMMISSION ON ITS MEETINGS HELD FROM JUNE 26TH TO JULY 1TH, 1939

The Housing Commission¹ and several of its expert groups¹ met at Geneva, from June 26th to July 1st, in order to examine the programme of its activities and to discuss questions relating to country and city hygiene.

¹ The following attended the meetings :

Housing Commission :

- Dr. G. P. CROWDEN, D.Sc., M.R.C.P., Department of Industrial Physiology, London School of Hygiene and Tropical Medicine, London ;
Dr. J. Axel HÖJER, Directeur général de l'Administration médicale de Suède, Stockholm ;
M. H. VAN DER KAA, Inspecteur en chef de l'Hygiène publique, The Hague ;
Professor B. NOWAKOWSKI, Professeur d'Hygiène à l'Université Stefana Batorego, Wilno (Antokol) ;
Professor J. PARISOT (*Chairman*), Président du Comité d'Hygiène, Professeur d'Hygiène et de Médecine sociale, Nancy ;
Professor C. E. A. WINSLOW, Professor of Public Health, Yale University, New Haven (Connecticut).

Expert Groups :

- Professor Frederick J. ADAMS, Associate Professor of City Planning, School of Architecture, Massachusetts Institute of Technology, Cambridge (Massachusetts) ;
Professor S. D. ADSHEAD, M.A., M.Arch., F.R.I.B.A., Town Planning Institute, London ;
M. H. J. N. H. KESSENER, Directeur de l'Institut gouvernemental pour l'épuration des eaux résiduaires, The Hague ;
M. E. KOHN-ABREST, Directeur du laboratoire de toxicologie de la Préfecture de Police, Paris ;
M. André MENABREA, Secrétaire général de la Société française des urbanistes, Paris ;
M. Anders O. MOLIN, Civil Engineer, Stockholm ;
Sir William SAVAGE, M.D., B.Sc., Taunton (Somerset) ;

A. REPORT ON THE WORK OF THE COMMISSION

I. PROGRAMME OF WORK OF THE COMMISSION

1. In its first report on the hygiene of housing,¹ the Commission recorded its decision to study the following problems :

- (a) Hygiene of the environmental conditions in dwellings (temperature, purity, humidity, movement of the air and temperature of the surroundings) ;
- (b) Noise and housing ;
- (c) Insolation ;
- (d) Natural and artificial lighting ;
- (e) Density of the population, " zoning " and open spaces (gardens, parks, playgrounds, etc.) ;
- (f) Smoke abatement and air pollution ;
- (g) Methods of water-supply ; sewage, waste and garbage disposal ;
- (h) Administrative and legislative aspects of housing hygiene ;
- (i) Definition of healthy urban and rural dwellings, as well as healthy cities and rural areas (regional types of urban and rural dwellings and of urban and rural planning).

M. L. S. P. SCHEFFER, Ingénieur en chef de la Section d'urbanisme du Département des Travaux Publics de la ville d'Amsterdam, Amsterdam ;

M. François SENTENAC, Inspecteur général des Ponts et Chaussées, chef du Service des Eaux et assainissement de la ville de Paris, Professeur à l'Institut d'urbanisme de Paris, Paris ;

M. Alexander B. SZNIOLIS, Chief of the Water Division of the State Institute of Hygiene, Warsaw.

The International Labour Office was represented by :

M. Carl Major WRIGHT, Member of the Economic Section.

Technical Secretary :

Dr. O. OLSEN, Health Section, League of Nations' Secretariat.

¹ Bull. Health Org., 1937, 6, 505-550.

II. WORK ACCOMPLISHED

2. At its first meeting in June 1937, the Commission began to study questions relating to the environmental conditions of housing determining bodily heat exchanges (temperature, purity, humidity and movement of air, and temperature of the surroundings) and also the problem of noise in relation to housing.¹

At its meeting in June 1938, a group of experts, representing the various national committees which are co-operating with the Commission, considered the problem of insolation and natural and artificial lighting in relation to housing and town-planning.²

3. The chief object of the work done in these various fields was to define physiological requirements in relation to the various factors influencing the life of individuals inside the dwelling, to investigate the value of the various methods employed for measuring these factors and, lastly, to study the architectural and technical methods best suited to meet physiological needs.

4. At its first two sessions, the Commission accordingly studied the most important factors in relation to the hygiene of housing. It reviewed our scientific knowledge and technical equipment in this field, particularly in regard to space, the quality of the air (purity, temperature, humidity and movement), insolation, lighting, noise.

5. From the point of view of the structure, planning and equipment of houses, the Commission's recommendations deal more especially with the constructions of walls, partitions, floors, ceilings, and roofs, in relation to the transmission of heat and noise, the space required per person inside the dwelling, fenestration, the orientation of buildings in relation to sunlight, the space between buildings, heating, ventilation, air-cooling and conditioning, artificial lighting.

6. Other questions of great importance in connection with the hygiene of the dwelling itself, such as water-supply and the disposal of sewage and refuse have been examined at the meeting held from

¹ *Bull. Health Org.*, 1937, 6, 505-550.

² *Ibid.*, 1938, 7, 581-608.

June 27th to July 1st, 1939.¹ The report of this meeting on " Town and Country Hygiene " is reproduced below.

7. This first part of the Commission's work therefore relates to questions of hygiene connected with the actual conditions obtaining inside houses, which affect the lives of individuals and families.

. In the course of its work on insolation and lighting, the Commission defined the factors which should be taken into account in determining the space between buildings and the orientation of buildings so as to provide for the desirable amount of solar radiation and light inside the building. It also indicated the principles which might be followed in studying the orientation of streets and formulated certain desiderata with regard to the planning of open spaces, playing-fields and swimming-pools in relation to solar radiation.

This brought the Commission to the second part of its work, which includes the study of those factors of human environment outside the home which determine the living conditions of the community.

8. The report on rural housing and planning drawn up as the outcome of a meeting of experts, representing the various national committees, held in December 1938,² which is to be regarded as a special contribution of the Housing Commission to the forthcoming Conference on Rural Life, deals mainly with rural environment.

Adhering closely to its programme of work, the Commission, at its meeting held from June 27th to July 1st, 1939, dealt with the study—in relation to hygiene—of methods of planning space, methods of smoke abatement and of combating dust and toxic gases, methods of water-supply and the disposal of sewage and refuse (see report on Town and Country Hygiene, page 744).

9. In accordance with the principles followed in carrying out the first part of its work, the Commission considered on this occasion the effect upon the human organism of the vital factors in the environment outside the home ; it investigated the value of the various methods employed for measuring such factors, and studied the methods of planning and sanitary technique best suited to meet the physiological needs of individuals and communities.

¹ Certain important problems such as those connected with dampness of dwellings and vermin have not yet been dealt with by the Commission. These problems will be discussed at a later meeting.

² *Bull. Health Org.*, 1939, 8, 87-142.

10. During the first triennial period of its work (1937-1939), the Commission has thus dealt with the problems enumerated under paragraphs (a) to (g) of its programme of work (see paragraph 1).

III. FUTURE WORK

11. As regards its future work, the Commission, at its first meeting, stressed the importance of undertaking special studies on housing hygiene in tropical regions. Other international conferences, such as the Intergovernmental Conference of Far-Eastern Countries on Rural Hygiene, held at Bandoeng in 1937, also emphasised the great importance of this question.

In view of the fact that considerable progress has recently been made in the investigations carried out in various tropical areas, the Commission considers it advisable to draw up, at a later meeting, a report on the problem of housing hygiene and the hygiene of towns and rural areas in the tropics. This meeting might be held in 1940.

12. The Commission is of the opinion that the work so far accomplished should enable it to carry out its work systematically, and in particular to study point (i)—that is to say, the “definition of healthy urban and rural dwellings, as well as healthy cities and rural areas (regional types of urban and rural dwellings and of urban and rural planning)”.

A meeting to study these questions might be contemplated for 1941.

13. In this connection, the necessity for taking into account customs and climatic conditions when defining the rules and standards relating to the hygiene of housing and the hygiene of towns and rural areas should be borne in mind.

Moreover, due account should be taken of demographic conditions and, in particular, of the size of families and of age distribution. Careful planning is needed to adjust new housing to the increasing mean age of the population and to the changing distribution of that population according to family size.

It should also be remembered that standards are required, not only for new construction, but also for the reconditioning of houses, both urban and rural.

In accordance with the principles followed by the Commission, account should finally be taken, in preparing plans for dwellings and housing, of economic conditions, and more especially the cost of construction, rents and the cost of installation in relation to the income of the various population groups and budgets of the towns and communes of the regions in question.

It would therefore seem desirable, that, in preparing the 1941 meeting, each national committee should define the rules and standards in question and prepare model plans for urban and rural houses and dwellings, and for towns and rural areas, having regard to the special conditions obtaining in the various parts of their country.

14. As regards the basic elements for these investigations already furnished by the Commission in the course of its work, it should be noted that certain of the standards, rules or recommendations formulated by it were regarded as provisional.

At the 1941 meeting, it should therefore be possible also to review from the international standpoint the whole of the work already accomplished.

15. The Commission requests its technical secretariat to supply the national committees in due course with a draft scheme based on the findings reached by the Commission in its reports, to enable the work referred to in paragraph 13 to be carried out on a uniform basis.

16. The Commission's attention has been drawn to the following suggestion made to the 1938 Assembly during its examination of the housing question (document A.59.1938.III): ". . . that national surveys should be made of existing housing conditions and needs in relation to a national minimum standard of housing for cities, towns and country".

17. It is accordingly desirable that the definitions formulated by the national committees and by the Commission should also serve for surveys of this kind.

The Commission considers therefore that one of its future tasks would be to determine the methodology of these surveys, having

regard to the definitions adopted and the various methods of measurement examined in the course of its work.

18. Lastly, in 1942, the Commission might take up the study of point (h) of its agenda concerning questions of organisation, administration and legislation in relation to the hygiene of housing and the hygiene of towns and rural areas.

19. Concurrently with the study of new problems of the hygiene of housing, it is desirable that advances in scientific and technical knowledge on matters already considered by the Housing Commission should be reviewed and subjected to detailed consideration by groups of experts from time to time. In particular, some mechanism to ensure continuity of study and appraisal appears to be desirable in regard to questions on which international agreement has not yet been possible owing to lack of knowledge. It is hardly necessary to point out that housing is a problem which cannot be solved for all time ; it will continue to present new features.

20. The provisional programme of the Commission's meetings for the next three years might therefore be summarised as follows :

- 1940* : Hygiene of housing and hygiene of towns and rural areas in tropical regions.
- 1941* : Definition of healthy urban and rural dwellings, as well as healthy cities and rural areas.
Regional types of dwellings and urban and rural planning.
Methods of conducting planning and housing surveys.
- 1942* : Questions of organisation, administration and legislation in relation to the hygiene of housing and the hygiene of towns and rural areas.

IV. NATIONAL HOUSING COMMITTEES

21. At its first meeting, the Commission recommended that national housing committees should be set up in all countries. In response to the appeal made to health administrations, a new committee has been set up in Mexico. In other countries—Bengal,

Chile, Costa Rica, Greece, Haiti and Tunisia—the question is still under consideration.

At the present time, the national committees of the following countries are co-operating with the Commission : the United States of America, the United Kingdom, France, Mexico, the Netherlands, Poland, Sweden.

22. In this connection, the Commission points out once more¹ that national housing committees offer the best possible organs for ensuring extensive and rational co-operation in the fields of planning and housing, both in the international and the national spheres. It reiterates its recommendation that, in the interests of community health, such committees should be set up in all countries and that they should be represented in the International Housing Commission of the Health Organisation of the League of Nations.

The Commission strongly recommends that every possible effort should be made by the Secretariat, as well as by members of the Health Committee and of the Housing Commission, to draw the attention of Governments and of competent authorities and individuals to the need for ensuring that reliable information in regard to advances in knowledge and practice in respect of housing should be made readily available in this way.

It considers that it would be particularly valuable for this purpose if the personal visits of the Technical Secretary of the Commission, which have greatly contributed to the organisation and development of its activities in the past, could be extended to countries which have not yet set up national housing committees.

* * *

The following are statements made by the various representatives present regarding the activities of their national committees :²

23. The *British Committee*, under the chairmanship of Professor Sir Wilson JAMESON, has continued its work of providing a recognised, though unofficial, platform for the exchange of views between the medical officer of health, the scientist, the town-planning

¹ See report, *Bull. Health Org.*, 1937, 6, 505-550.

² As regards the constitution, organisation and activities of the Mexican Committee, which has recently been created, see document C.H./Com. Hab./99.

authority, the architect and the various branches of the building and engineering industries which are necessarily concerned with housing. Special consideration was given to the subject of daylight amenity for dwellings by a sub-committee prior to the meeting of experts convened by the Housing Commission at Geneva in June 1938.

By the circulation of memoranda and personal contacts with individual workers, the Committee's central organisation at the London School of Hygiene and Tropical Medicine has kept abreast of advances in knowledge and practice. From time to time, information in the form of special reports or reprints of scientific papers has been sent by the Committee to the Housing Commission of the Health Organisation of the League of Nations at Geneva for the use of other national committees, and similarly the reports received from the Housing Commission dealing with work in other countries have been circulated to members of the British Committee, while the previous reports of the Commission on ventilation, noise, and natural and artificial lighting have been used for teaching purposes in the post-graduate course provided for medical men and women studying for the University of London diploma in public health.

24. The *French Housing Committee* has been engaged on two different sets of tasks since the despatch of its previous report on organisation, working and activities¹ and the publication of the volume in which the reports of its various sub-committees were brought together.²

On the one hand, it has collaborated with the Housing Commission of the League of Nations by preparing a number of reports on questions now under study by the latter.

On the other hand, it has proceeded with and completed the large-scale enquiry into the condition of rural housing in France initiated in 1936 in accordance with the guiding principles recommended by the Health Organisation of the League. That enquiry, conducted by M. Vignerot, Chief Engineer for Rural Public Works at the Ministry of Agriculture, with the assistance of the departmental health inspectors, the rural public works engineers and a

¹ *Bull. Health Org.*, 1937, 6, 505-550.

² République française, Ministère de la Santé publique : *L'Habitation en France*, Paris, Imprimerie nationale, 1937.

large number of qualified investigators, has resulted in the collection of a considerable mass of information which has now been brought together in two volumes containing numerous plans and photographs; useful information on the health situation and the vital statistics of rural areas has also been added. These two volumes represent a valuable contribution of interest both to the Housing Commission of the Health Organisation and to the forthcoming Conference on Rural Life convened by the League of Nations.

25. The main task of the *National Housing Committee of the Netherlands* is to co-ordinate the activities of different bodies and institutions dealing with the study of housing hygiene and to encourage necessary research.

The Netherlands Centre for Research on Applied Natural Sciences, which created the Committee, provided, for instance, funds for the Committee on Air Conditioning in Buildings for the employment of a skilled engineer who devoted his full time to the work of that Committee.

The Committee dealing with the abatement of noise in dwellings reported favourable results as regards new constructions of partition walls and floors in tenement houses in Amsterdam. The insulating capacity of these floors and walls amounted to 62 decibels, or 4 decibels more than that of walls and floors of ordinary construction, whereas the difference in price was not prohibitive. Definitive progress has therefore been made by the Committee in its endeavours towards achieving increased comfort conditions in dwellings.

26. The *Polish Housing Committee* started its work mainly in order to co-operate with the Housing Commission of the League of Nations Health Organisation.

This work is based on the principle of co-operation of representatives from all professional groups interested in the housing problem. The Polish Committee, under the chairmanship of Dr. W. CHODZKO, former Minister of Public Health, unites thirty members: nine medical men, seventeen engineers, and others representing the social, economic and administrative viewpoint.

One of the objects of the activities of the Committee was to prepare the reports for the different meetings of the Housing Commission of the League of Nations and to make the official reports issued by that Commission widely known. It has also stimulated research

work within the limits set by the small funds which were at its disposal. The chief object is the fostering of the idea of continuous co-operation of the different professional groups concerned, which is of primary importance if a sound solution of the problem of healthful housing is to be found.

The Polish Committee has therefore decided to constitute itself as a *permanent* Housing Committee. It is hoped that it will function in the near future as an Advisory Council of a National Housing Research Institute. Since for financial reasons it is impossible to create a new institute, it has been envisaged to create a functional unit of the different existing laboratories working on special problems of the housing problem and which, if working in accordance with a common plan, could solve many problems in relation to planning and housing.

27. The main work of the *Swedish Housing Committee* consists in co-operating with the International Commission of the Health Organisation of the League of Nations.

The Committee is composed of representatives of the various bodies and associations engaged in activities in relation to housing in the country — for instance, the Social Board, the Medical Board, the Bureau for building grants, for co-operative building, etc. These activities having been particularly intense during recent years, it is deemed desirable that the Committee should be given official attributions.

28. The *Committee on the Hygiene of Housing of the American Public Health Association* was set up in 1936 to serve as the organ for the United States of the Housing Commission of the League.

In beginning the work of the Committee, it seemed desirable, first of all, to formulate the specific basic health needs which housing should subserve; and, in so doing, it was felt important to maintain a broad view of health, including emotional—as well as the more elementary physical—“wholeness”. The report, first published in 1938, formulates thirty basic principles of healthful housing, with specific requirements and suggested methods of attainment for each. The principles and specific requirements are believed to be fundamental minima required for the promotion of physical, mental, and social health, essential in low-rent as well as high-cost housing, on the farm as well as in the city dwelling. Under methods

of attainment are suggested the more important means by which these requirements can be met, without considering in all cases alternative means of attaining the same ends. A second revised edition of these basic principles has just been issued (May 1939).

From the outset, the Committee had planned a series of staff investigations into conditions of heating, ventilation, lighting and noise which obtain in occupied housing projects and other dwellings, in order to check on the adequacy of accepted practice and to establish a base-line for needed improvements. Summer and winter investigations of this type have been under way for over a year in New York City, New Haven, and (in co-operation with the Tennessee Valley Authority) at Norris, Tenn. The basic procedures and apparatus used are those agreed upon by the League of Nations' Housing Commission. These studies are believed to be the first ever made in the United States which accurately reveal the basic conditions of physical environment which prevail in the home.

Soon after publication of the report on "basic principles of healthful housing", the Committee was asked by public health and housing groups in several cities to re-express these principles in terms of existing slums and blighted areas, in order that there might be made available both a yardstick for the appraisal of these areas, in terms of healthful adequacy, and a guide to the programmes of demolition or rehabilitation which are required of local authorities by the U.S. Housing Act. The Committee is therefore developing a housing survey technique which will classify and rate substandard urban housing in terms of the relatively fixed shortcomings of site and structure, on the one hand, and the relatively controllable conditions of occupancy and upkeep, on the other hand.

In response to requests from health officials in several localities, a study of local sanitary and housing ordinances will shortly be undertaken, with a view to encouraging the modernisation of those housing provisions which relate to public health. Also on the Committee's agenda for the coming months is a study of overcrowding regulations and of desirable room-occupancy standards.

B. TOWN AND COUNTRY HYGIENE

Earlier reports of the Housing Commission have dealt with the hygiene of man's environment inside the dwelling. Following out its programme of work, the Commission has since embarked on the study of the hygiene of the outdoor environment in town and country.

The present report comprises the following chapters :

- I. THE HYGIENE OF THE PLANNING OF SPACE.
- II. THE ABATEMENT OF SMOKE, DUST AND TOXIC GASES.
- III. WATER-SUPPLY.
- IV. SEWAGE TREATMENT.
- V. THE COLLECTION AND TREATMENT OF DOMESTIC REFUSE.

As regards the various aspects of rural housing and planning, the reader should refer to the report¹ of the group of experts appointed to study these questions.

I. THE HYGIENE OF THE PLANNING OF SPACE²

GENERAL CONSIDERATIONS

1. The institution of special bodies to study problems of planning is evidence of the great importance which the authorities in many countries attach to these problems, believing that their solution is likely to contribute to the well-being of the people, by providing a rational basis for the development of their individual and collective life. How the said problems should be solved depends on demographic and climatic conditions, the nature of the soil, the natural resources of the area considered and many other factors. The

¹ See *Bull. Health Org.*, 1939, 8, 87-142.

² Professor F. J. ADAMS, Cambridge (Mass.), acted as Chairman during the discussions on the e questions.

measures planned and adopted in this respect in the various countries are designed to cover, some the whole range of factors governing the life of the people, others more especially its economic and social or its physical aspects (planning of space).

2. The planning of space is generally acknowledged to be an indispensable part of public policy in all countries. Its object is to ensure, both on the national and on a regional plane in town and country alike, the rational use of the land for agriculture, forestry, industry, commerce, recreation and housing. From the standpoint of health, the planning of space should afford both the individual and the community the best conditions of work, housing, communications and transport, recreation and rest.

HYGIENIC CRITERIA

3. In determining the hygienic conditions which should serve as criteria in drawing up plans for houses and dwellings, the Commission took account of the influence exerted by the various factors, not only upon the occurrence of disease and the standard of health, but also upon the comfort and the physical and mental fitness of the individual.¹

4. Similar hygienic criteria should also be brought to bear in establishing urban and rural development plans. Thus, from the standpoint of health, zoning serves an important purpose, inasmuch as it ensures the rational distribution and growth, according to function, of the various parts of whole areas or of urban districts (see paragraph 2) by separating, among other things, the residential from the industrial districts and thus providing the populations, more especially the town-dwellers, with a sufficiency of space, sunshine, light and fresh air of adequate quality, and protecting them from dust, smoke and noise.²

In the planning of residential districts, the trend should be to bring the classes together rather than to segregate them.

¹ See *Bull. Health Org.*, "The Hygiene of Housing", 1937, 6, 505-550, and "Natural and Artificial Lighting in relation to Housing and Town Planning", 1938, 7, 581-608.

² As regards the physiological needs of man in respect of air, insolation, lighting and noise, see the reports quoted above.

5. In order to meet all physiological, psychological and practical requirements, certain standards are in use in various countries, which concern in particular the density of buildings (or of their inhabitants) in relation to area, the minimum size of building lots, the proportion of the lot covered by the building, the distance between houses, the height of buildings and width of streets, and the space to be reserved for recreational purposes (in particular, parks, green areas, playing-fields and sports-grounds, public gardens, allotments, etc.). Experience has shown that the slum has been the inevitable consequence of the unrestricted crowding of population.

6. Architects and town-planners have at their disposal methods of measurement for determining the distance between buildings, the height of buildings, the width of streets and courtyards, and the orientation of houses which, if carefully followed, ensure provision of the requisite insolation and natural lighting both within and without the dwellings. Such methods, which take account of differences in latitude, altitude, and climatic conditions, should form a basis for regulations governing the maximum height of buildings in relation to their distance apart.

7. In its report on insolation and lighting, the Commission has already discussed these questions in their bearing upon town-planning. It has defined the rules to be followed in this connection in order to provide the desirable insolation and natural lighting for the inhabitants.

It noted, in particular, that in view of the beneficial effects of sunlight on health, the hygienist is justified in asking that, as far as possible, a certain amount of insolation should be available for every room ; it also took the view that the optimum daylight in a room will be obtained when as large an area as possible of the room receives direct light from the sky.

STANDARDS OF DENSITY

8. The standards of maximum density applied in various countries vary considerably according to the density of the population and its character—agricultural or industrial—in the various areas considered.

In England, for instance, it is considered desirable to limit the maximum density to twelve houses per acre. This standard is regarded as satisfying all requirements in respect of insolation and lighting, whilst taking account of psychological needs. It should be mentioned that this standard enables a small garden of about 300 square yards to be attached to each house, thus providing the inhabitants with certain amenities and opportunities for occupation and recreation. In rural districts, the desirable standard is eight houses per acre.¹

In the United States of America, the "President's Conference on Home-building and Home Ownership" has recommended that in single-family districts the density should not exceed eight families per acre, and gave its opinion that six families per acre is more desirable. Recent experience in the United States indicates that, in the case of properly designed groups of row or terrace houses, a density of fifteen families per acre is not excessive.²

9. Concerning the density of population in urban districts in which blocks of flats predominate, reference may be made, by way of example, to the standards advocated by the Amsterdam City Public Works Department, which permits in its plan for future development a maximum density of 85 to 110 families per hectare in urban areas and 55 to 70 families in suburban areas. In urban districts in England, it has been found desirable to change the basis for calculating densities from houses to people, and a maximum density of 100 persons per acre has been recommended by the Ministry of Health.

It is considered highly desirable that restrictions on population density, similar to the examples given in the preceding paragraph, should be universally adopted wherever the danger of overcrowding exists—and particularly in the large cities.

¹ In English examples cited, the "acre" includes local roads but not public open spaces other than small playgrounds in the centres of blocks.

² These figures are based on the "gross" acre or hectare, which would include sites for schools, churches and other community buildings as well as roads and local open spaces.

BUILDING COVERAGE AND SIZE OF PLOTS

10. Other standards are in use in various countries regarding the minimum size of building-plots and the area to be built upon within each plot. Thus, in England, for instance, the minimum size of plot recommended is 250 square yards given a density of twelve houses per acre, 400 square yards given a density of eight houses per acre, and 500 square yards given a density of six houses per acre. In the United States, provision is being made in an increasing number of zoning ordinances for restrictions on the size of plots in residential areas. Such restrictions may vary from a minimum area of 4,000 square feet per plot in urban areas to a minimum of 40,000 square feet or more in exclusive residential communities outside the suburban fringe.

11. In the United States, a number of authorities have recommended that, in residential districts, buildings should not be allowed to cover more than 40% of the area of the plots, and 25% is considered much more desirable. It is usual for American zoning ordinances to include restrictions on the coverage of buildings in different districts of a city. The corresponding English standards vary according to the height of the buildings and the purposes for which they are intended : they range from 25% to 33 $\frac{1}{3}$ % for dwelling-houses and blocks of flats, and from 33 $\frac{1}{3}$ % to 50% for other residential buildings.

SPACES FOR RECREATION

12. Considerable attention has been given in many countries to the open spaces set aside for recreational purposes, and certain countries have proposed that the whole of these spaces should be planned on a national scale, in order that present and future generations may enjoy full opportunities for open-air recreation.

After careful study, standards have been set up in these countries which determine the area per inhabitant to be set aside for parks, public gardens, workers' gardens, sports-grounds, playing-fields of various kinds and bathing-beaches.

13. In some countries, the standards have been raised considerably in the course of the past few years. Whereas in England, for instance, the standard for open spaces advocated by certain authorities a short time ago was 5 acres per thousand inhabitants, the National Playing-fields Association and other bodies are now recommending 7 acres per thousand inhabitants, whilst in the United States, the standard of 10 acres per thousand inhabitants is more generally accepted. The Regional Planning Committee for Greater London proposes that, in addition to 7 acres per thousand inhabitants to be set aside as sports-grounds and playing-fields, a further 10% of the area should be reserved for parks, etc. It is interesting to note that the practice followed at Letchworth Garden City, for instance, is well above this standard, 14.5 acres per thousand inhabitants being available in the form of sports-grounds and playing-fields.

The above standard is probably ideal rather than practical—at least for large cities—and in London at the present time there is probably not more than 1 acre of space devoted to active recreation for each 1,000 inhabitants. A more realistic minimum standard would probably be 4 acres per 1,000 persons.

14. In the United States, recent studies have been made of standards for recreational facilities and of procedures for their application to communities and regions. Standards for outdoor recreation areas in new housing developments have been the object of careful study by a committee appointed by the National Recreation Congress held in October 1938. This Committee has since published a report¹ which provides a sound basis for estimating local neighbourhood needs.

As has been stated by the Committee on the Hygiene of Housing :²
“ The attainment of the purposes indicated requires consideration of the reciprocal relations between internal space for social use and external provision for recreation. There should be adequate floor area within the dwelling, and outside space suitable for organised

¹ *Play Spaces in New Neighbourhoods*, National Recreation Association, New York City, 1939.

² *Basic Principles of Healthful Housing* (second edition), Committee on the Hygiene of Housing, American Public Health Association, May 1939, pages 16-17.

recreation, meeting the needs for different groups and sexes and located so as to serve their convenience with the greatest possible economy in construction and maintenance.

“ . . . For city-dwellers it has been suggested that the recreation area should include a playground within such distance as to be practically accessible, and an athletic field within half a mile of each home for the use of adolescents. It is desirable to provide play spaces for very young children (separate from those of adolescents) within each block or large group of dwellings, so as to facilitate parental supervision and minimise traffic hazards.”

15. In preparing its development plan for Amsterdam up to the year 2000, the Amsterdam City Public Works Department decided, on the basis of a minute analysis of the population and its play habits, the character of the sites available and the conditions of soil and climate, to adopt standards of 4.5 square metres per inhabitant for neighbourhood parks, 4 to 5 square metres for playing-fields, 1.3 square metres for children's playgrounds, 5 square metres for workers' gardens, etc.

16. Similar standards have been set up in various countries for the different age-groups of children and for the schools.

17. In many countries, the question of providing allotment gardens on the outskirts of towns has been given careful attention, both because of the health aspects and because such gardens assist in providing families of low income with fresh vegetables.

This movement has been developed in some countries on a larger scale, such as by the establishment of subsistence homesteads in the United States and what are known as “ small-holdings ” and land settlement schemes in England. The area allotted to each family, which might range from 1 to 5 acres, is limited by the size that can be worked by one man. In Germany, homestead settlements have been developed on a large scale. It is held there that the size of a building lot in such settlements should not be less than 400 square metres ; in Poland, the figure laid down is from 300 to 600 square metres ; whilst at Stockholm, the average size of a worker's garden is 325 square metres.

GENERAL RULES

18. It is impossible to generalise these various standards, which have to take account of local conditions and especially—as regards, for instance, the kind of games and sports to be provided for—of the age-group composition of the population and national customs.

As the examples cited show, it is essential that all the factors concerned shall be carefully analysed before such standards are set up. In view of the universal use of standards based on the percentage of area which should be reserved for open space or on the number of acres, square metres, etc., which should be provided for a specified number of persons, it should be emphasised *that such standards are useless* unless consideration is given to the characteristics of the population to be served and to the physical conditions obtaining on the site. Standards which are satisfactory when applied on a city-wide basis are often quite inadequate when applied to a neighbourhood or residential section within the town.

It is also important that the preservation of attractive views and of areas of natural beauty or historic interest should be given consideration in the selection of sites for recreation.

Certain types of unbuilt-upon areas, such as cemeteries, which are sometimes found in densely occupied sections of large cities, are valuable, because they serve as open spaces and as places of meditation and rest.

19. In this connection, emphasis should be laid on the desirability of locating the open spaces in sufficient proximity to the inhabitants for whose benefit they are intended.

Planning for recreation is obviously a problem in city or neighbourhood planning, and the optimum size and effective radius of indoor and outdoor recreational facilities will greatly influence the determination of neighbourhood boundaries.¹

¹ *Basic Principles of Healthful Housing*, page 17.

ECONOMIC ASPECTS

20. In several countries careful consideration has been given to the possibility of applying these various standards in practice, with due regard to variations in the physical characteristics of the land and the distribution and density of the population. In applying these standards, consideration should be given to the cost of land, means of communication, drainage, sewerage, electric power, etc., and plans for future development should be prepared in such a way that the maximum amenities should be provided at the lowest possible cost.

21. In this connection it may be mentioned that numerous municipalities in many different countries have acquired vast areas of property in connection with well-considered land policies ; this has enabled them to lay out public free spaces with a minimum outlay so far as the cost of the ground is concerned.

22. Schemes of outstanding interest have already been carried out in many countries in the form of garden cities, satellite towns, suburban settlements, green wedges, green belts, natural reserves, national parks, bathing-beaches and other free spaces set aside for recreational purposes. If the lead given by such schemes is followed, populations can be assured of outdoor environmental conditions satisfying modern standards of hygiene in respect both of their physiological need of air, sun and light and of their psychological requirements, thereby counteracting the prejudicial influence which the monotony of city life is bound to exert on the outlook of succeeding generations.

PASSIVE AIR DEFENCE IN RELATION TO PLANNING

23. It is an unfortunate circumstance that in regional planning and in providing for the extension of towns, consideration must be given to the dangers of aerial bombardment.

So far as the general effect on planning is concerned, it is fortuitous that the tendency of such consideration is to cause dispersion and,

unlike the congested condition obtaining in the old walled town, calls for the provision of open space and wide and easy means of communication and, where possible, the separation and duplication of public services.

II. ATMOSPHERIC POLLUTION BY SMOKE, TOXIC GASES AND DUST¹

1. The expansion of industry, the use of coal and the development of road traffic have resulted in a pollution of the air—especially that of cities and industrial districts—which has many dangers and drawbacks, both economic and hygienic. Thus in England it has been estimated that the total cost to the country caused by the smoke nuisance amounts to at least £80,000,000 a year.

The problems of atmospheric pollution are highly complex, but they have been carefully studied at specialised laboratories, observation stations and institutes and schools of hygiene, as well as by national bodies created *ad hoc* in various countries.

In the following pages, we shall deal separately with smoke, toxic gases and dust, although, in many cases, all three are produced simultaneously by the same source, and collectively cause a harmful degree of pollution in the atmosphere of residential areas.

In any comprehensive scheme of planning or zoning (*vide* Chapter 1 of the report), the possibility of atmospheric pollution should be borne in mind when determining residential and industrial areas; moreover, in some cases, the direction of the prevailing wind may be a factor of considerable importance influencing the final decision.

Dusty industries should not be located in the immediate vicinity of large aggregations of houses.

SMOKE

2. The smoke which taints the atmosphere of our cities is, in most cases, a product of the combustion of coal; the amount is

¹ Chairman : M. E. KOHN-ABREST, Paris.

frequently so considerable that the waste of unconsumed matter involved is of great economic importance ; the atmospheric changes entailed are, moreover, injurious to the health and to the physical and mental fitness of the population.

In its report on insolation and lighting, the Commission has already noted that the resulting loss of light and radiation amounts to from 10% to 30% in certain towns ; it adds, however, that the effects produced require further study, which should have special reference to the various wave-lengths emitted by solar radiation and the diffuse radiation of the sky.

3. In addition to this, it is held that smoke may lead to increased formation of fog and so cause a further considerable reduction in the number of hours of sunshine. Thus, the number of hours of sunshine in the city of London during the months of December and January is only fifteen, whereas at Kew, in the outer suburbs, it is seventy-one.

METHODS OF MEASURING SMOKE AND STANDARDS

4. Many methods have been devised for determining the amount of smoke in the atmosphere. Among those which are based on the principle of air filtration, we may mention, by way of example, Owen's automatic air-filter recorder.

5. Other methods use the colour or density of the smoke as an index of pollution. Among these, the Ringelmann scale is the simplest. This method, which consists in estimating the density of smoke by means of white cards bearing a criss-cross pattern of black lines of different thickness, is used in many countries ; it is applicable only to black smoke.

6. Standards based on the Ringelmann scale exist in numerous countries ; many American cities, for instance, prohibit the discharge of smoke of a density above value No. 3 of the scale. In England, it is required that the best practicable means be adopted to prevent a smoke nuisance, and with this end in view certain maximum times for the emission of smoke from factory chimneys have been adopted in some districts. Thus, in one district, it is permissible for chimneys to emit smoke for periods ranging from two to six minutes per hour, depending on the size of the plant.

7. The incomplete combustion of fuel of various kinds leads to the production of smoke, and methods for testing the degree of combustion have been devised. Thus, the measurement of the air-pressure reduction and of the carbon dioxide content of the flue gases may serve as an index of the degree of combustion. Several instruments have been devised for this purpose, which are based on chemical or physical processes, and these enable combustion to be kept under constant supervision by means of automatic registration.

METHODS OF SMOKE ABATEMENT

8. In defining the measures taken to deal with the pollution of air by smoke, account must be taken of the fact that domestic fires can contribute in no inconsiderable degree to this pollution. An improvement in this respect can be effected by the use of soot interceptors and of grates ensuring the best possible conditions of combustion, by the substitution of smokeless coal, coke and heavy-grade oils, gas and electricity for smoke-producing coal or by the abandonment of individual in favour of collective heating, as already installed in various countries for blocks of buildings, for groups of dwellings and even whole cities.

9. So far as consumption of fuel in industry is concerned, the design of furnaces, height of chimney flue, choice of the fuel best suited to the conditions, adequate draught and skilled stoking are among the factors which ensure the best possible combustion and thus contribute in a large measure to the prevention of air pollution, thereby safeguarding the interests both of manufacturers and of the community.

10. Reference should also be made to the many smoke-consuming grates which have been designed during the past few decades, especially those with an automatic feed (mechanical shovels, revolving grates, overfeed travelling grate stokers, underfeed automatic stokers, etc.).

11. Finally, we may mention various forms of smoke-consuming apparatus designed to improve combustion in the grate (air-feed apparatus, operating by natural draught, by steam jets, by fans

(air-heating) and by either steam jets, or fans ; apparatus supplying both liquid fuel and another combustion-promoting agent (steam and air)).

TOXIC GASES

12. The toxic gases which pollute the atmosphere are produced for the most part by the combustion of coal, by various industrial processes, and by internal combustion engines.

13. To prevent the injury to health that may be caused by the toxic or malodorous gases discharged in the course of various industrial processes is one of the main purposes of industrial hygiene. This is a subject which comes within the purview of the International Labour Office, and reference should be made to the numerous publications which have been issued on these questions by that Organisation.

These publications also describe the methods of analysis for the determination of the various toxic gases and the means to be employed to protect both the workers and the vicinity of factories. (The use of hermetically closed apparatus, removal of gas by suction, condensation in water or suitable liquids, chemical neutralisation, saturation, pyrogenous transformation, etc., or a combination of these various methods.)

SULPHUR DIOXIDE AND SULPHUR TRIOXIDE

14. Among the gases released by the combustion of coal (which may be particularly rich in sulphur), sulphur dioxide and sulphur trioxide (SO_2 and SO_3) have been the subject of numerous investigations.

These have shown that the sulphur trioxide content of the air is usually negligible compared with its sulphur dioxide content, and that the destructive action of these gases on vegetation and on buildings is usually slight ; though a noticeable effect is produced when it persists over a number of years. It is possible that, in special meteorological circumstances (fog, for instance), sulphur trioxide may be formed in appreciable quantities.

15. Standards have been laid down in certain countries in regard to the maximum allowable acidity of flue gas. These are (in terms of sulphur dioxide), for instance, 5 grammes per cubic metre in Germany, and 6 grammes in Italy.

16. Up to the present, no economical method has been devised to prevent the pollution of the atmosphere by these gases, except dilution with a large volume of air and use of fuel with a low sulphur content, although in some cases the washing of flue gases has proved effective.

CARBON MONOXIDE

17. Among the other toxic gases which may be present in the atmosphere, carbon monoxide may be mentioned. The air of numerous towns has been extensively tested in regard to its content of carbon monoxide produced from the exhaust of motor vehicles. When the findings are viewed as a whole, it is found that the content in question varies considerably according to traffic density, but that, in city streets, it does not exceed 0.2 per thousand.

Although the values thus recorded give no cause to fear acute intoxication by carbon monoxide, its presence together with malodorous and irritating fumes from the exhausts of motor vehicles must be regarded as deleterious from the standpoint of health.

18. It appears from investigations undertaken in certain towns that the degree of carbon monoxide saturation of the hæmoglobin found in persons who have spent many hours in places where the motor traffic is very dense (policemen on point duty) amounts, in certain cases, to 20%-30%. In such cases, the possibility of ill effects cannot therefore be dismissed.

19. High percentages of carbon monoxide have been observed in certain road tunnels and in garages, and special measures should be taken under such conditions to limit and control the concentration of the gas in the interests of health.

The public should be more generally aware of the serious risk of carbon monoxide poisoning occasioned by allowing motor-car engines to run in a garage with closed doors. Many fatalities from this cause have been recorded.

20. In order to make possible the comparison of data collected in various countries, it is necessary that some international agreement should be reached with respect to the method or methods which may be employed for the measurement of the concentration of carbon monoxide in the air.

DUST

21. The dusts contained in the surrounding air are of very varied origin. Those produced by factories, by the combustion of coal in the form of fly ash, the wear and tear of road surfaces and motor vehicles, as well as refuse of various kinds (especially sweepings), contribute in large measure to the pollution of the atmosphere.

22. As regards the dust produced in the course of industrial processes, reference should be made to the remarks contained in paragraph 13 of this chapter.

23. Among the measures to be adopted for the protection of workers and of the vicinity of factories, a description of which will be found in the publications of the International Labour Office, mention may be made of the use of closed apparatus, the collecting and exhausting of dust by mechanically operated ventilators, the removal into collectors of various kinds, dust-chambers, cyclone separators, water separators—with floats or water-jet devices, or felt filters, electrostatic precipitation, etc.

THE EFFECTS OF DUST ON HEALTH

24. Industrial hygiene has also supplied valuable information regarding the effect produced on the organism by the inhalation of dust in large quantities, as observed in the form of lung affections (pneumoconioses).

We know very little, however, of the influence exerted by the slight amount of dust commonly found in the air under ordinary environmental conditions. The information given on this subject is usually limited to the statement that this amount of dust may cause irritation of the naso-pharyngeal and tracheo-bronchial mucous membrane, which may, in turn, facilitate infection.

25. The pollen and other like ingredients contained in dust may also induce allergic conditions (hay fever, asthma, etc.).

26. It is generally agreed that our knowledge of the part played by dust as a vehicle of pathogenic organisms is somewhat meagre. Most of the research from which it has been derived has indeed been carried out by a bacteriological technique dating back many years.

27. The current doctrine evolved on the basis of this research is that pathogenic organisms of various kinds may survive occasionally in dust, but that the great majority die fairly quickly as a result of desiccation, insolation and other influences.

28. It is highly desirable that this research work should be taken up afresh with the help of the new methods recently devised for the determination of the bacterial content of the air (in dust or droplets), in order, among other things, to throw light upon the epidemiology of infectious disease of naso-pharyngeal origin. Judging by the experimental work already undertaken in this field, more particularly in the United States, it seems likely that the further prosecution of this work would also open up new possibilities of prevention.

METHODS OF MEASUREMENT AND STANDARDS

29. The number of methods devised for the purpose of detecting and analysing atmospheric dust is considerable. They have been described in recent publications, and there is hence no need to dwell upon their details here. Among widely used devices, we may mention the "settlement dust counter", the "automatic air-filter recorder" already mentioned above, the jet dust-measuring apparatus and funnel-gauge, all of them designed by Owens, the Greenburg-Smith impinger and the thermal precipitator of Green and Watson, the konimeter of Kotze, as well as the measurement of dust on slides.

30. Certain methods have also been suggested for the sampling of gases in flues. Among these, there are some which use tubes through which the grit is sucked, and then blown into filters by ventilating fans. Simple devices have also been recently described in the form of small cyclones, which are suspended in flues and give

a semi-automatic quantitative determination of the fly-ash content of gas and smoke (TER LINDEN).

31. In some countries, standards have been set up in regard to the maximum allowable dust content of flue gases discharged into the outside air.

Here, as in the case of the other standards mentioned in this chapter, much still remains to be done.

METHODS OF DUST ABATEMENT

32. Since dust settles within a radius which is proportional to the height from which it falls, the height of chimney flues is an important factor in its dissipation. It is held by some authorities that the height of the chimney should be two and a-half times that of the boiler-house or factory building if down draughts taking dust and fumes to ground level in the vicinity are to be avoided.

Again, in order to prevent the pollution of air by the dust issuing from chimneys, dust intercepting devices, either static or dynamic, dry, damp or electric, have also been designed (see paragraph 23 of this chapter).

33. To these devices for the prevention of air pollution there should be added the measures applied in the construction, surfacing, upkeep and cleansing and watering of roads and streets, as well as all other means of promoting environmental cleanliness in town and country (see also Chapter V).

34. In conclusion, it may be said that, despite all the efforts made to prevent the pollution of the atmosphere by smoke, toxic gases or dust, the reports published by the authorities of certain countries show that much still remains to be done. From the standpoint of modern hygiene, which regards pure and fresh air as an indispensable pre-requisite for the physical and mental fitness of the population, it is desirable that these efforts should be still further developed, both in the sphere of research and on the practical plane, and that all available educational, propaganda and legislative resources should be utilised to the full in view of the influence of the atmospheric environment on health.

III. WATER-SUPPLY¹

GENERAL IMPORTANCE OF WATER

1. In view of the manifold purposes for which it is used in nutrition, individual and collective hygiene, agriculture, pisciculture, industry, navigation, recreation and fire fighting, water is one of the most valuable of natural resources, and one of the basic elements of all civilisation.

2. Recognising its unique importance, many countries have contemplated a comprehensive planning of their water resources on a national scale, and have set up central bodies with a network of peripheral institutions to study the problems connected with these resources and their utilisation.

3. From the standpoint of hygiene, water is of importance as one of the essential factors of nutrition, and the obvious basis of individual and collective cleanliness ; it also affords the population many recreational possibilities. On the other hand, as a vehicle for pathogenic germs, it may constitute a source of grave danger to public health.

4. For these various purposes, water should therefore possess qualities which satisfy all the requirements of hygiene. In many regions, however, the increasing density of population, the growth of towns and the expansion of industry have led to the contamination of the subsoil water, streams and rivers, lakes and ponds. The measures applied to supply the public with pure water have therefore had to be supplemented by suitable arrangements for the disposal and purification of the wastes produced by urban centres and industrial undertakings.

METHODS OF SUPPLY OF WATER

5. On the administrative side, there is a decided need for water requirements to be considered on a broad basis. On the one hand,

¹ Chairman : Sir William SAVAGE, Taunton (Somerset).

the subject should receive consideration nationally as regards available water sources and their distribution and utilisation ; and, on the other, the authorities responsible for the provision of the water and its control should have sufficient financial resources to be able to plan water schemes for large areas and to be able to carry them out.

At the same time, there is need, especially in some countries, to educate the people to appreciate the supreme value of pure and adequate water and to demand its provision. In rural districts, large-area schemes which spread the water charges are valuable means to facilitate a demand for water.

6. The wide experience acquired during the past few decades in the field of public health engineering makes it possible to define with tolerable accuracy the methods to be followed in order to supply the public with water satisfying all the requirements of hygiene. These methods involve the careful choice of the water to be distributed, the construction on sound lines of the impounding and collecting system and of the treating and distributing plant, the protection of the water against contamination from the source to the point of consumption, and strict and permanent supervision and control of the water and of the whole water-supply system.

7. All these measures require close co-operation between the hygienist, the geologist, the engineer, and continuous collaboration between the water-supply service and the public health administration, as well as specialised training for the analytical laboratory and water-supply service staff, in order to fit them thoroughly for the work they have to perform. In many countries, the class of specially trained public health engineers has rendered invaluable service in these branches of work.

8. With so many agencies concerned, it is necessary to define with precision the responsibility of each official and to make it clear who is ultimately responsible for maintaining the requisite standard of purity.

9. Frequent supervision by competent sanitary experts is required of the catchment area of every water-supply. Special care is required when the water is derived from strata which are liable to be fissured and where, in consequence, contaminated material may travel long distances without natural purification.

10. Many public health services have laid down standards to be applied in the construction of cisterns and wells and collecting basins and have drawn up regulations to protect the drinking-water from contamination from various sources. Standards have also been established in several countries in regard to the materials to be used for the construction of piped water-supply systems.

11. In rather a different category as measures of protection against water-borne diseases may be included steps to maintain the general cleanliness of a country, especially that of the areas and places from which the water is drawn, whether it be obtained from underground sources, or from large reservoirs, or is impounded behind dams or otherwise derived from surface water.

The methodical sterilisation or destruction of the excreta of persons suffering from infectious intestinal diseases, systematic action against germ-carriers, and the removal and adequate treatment of liquid sewage and solid refuse in town and country are of great importance in this connection.

12. It is indispensable that the drinking-water supply system should be sufficiently separated from any sewage disposal system. Defects of construction and lay-out giving rise to intercommunication between the water-supply system and sources of water of a lower standard of purity, or even the sewerage system, have frequently caused epidemics and should be absolutely avoided.

13. All repair or other work carried out in connection with water-supplies requires skilled supervision in relation to the risks of possible contamination and the personnel engaged in such work also needs careful supervision.

PURIFICATION OF WATER-SUPPLIES

14. Local conditions may provide a supply of water which is pure in its natural state and very little liable to any risks of harmful pollution. In other areas, only water contaminated or liable to contamination is available. In a third group, the water available is of high purity but is liable to contamination, possibly only periodically, from sources not readily removable. A pure uncontaminated supply is the hygienist's aim, taken wherever possible from a

naturally pure source, but, in every case where there is known pollution or liability to pollution, some method of treatment of the water is necessary before distribution to make it pure and bacteriologically safe.

15. Modern technical science provides for this purpose, economic and effective methods in the form of storage and settling processes, slow or rapid filters (with or without coagulant) and the use of chemical agents such as chlorine gas, hypochlorites, ozone, etc.

16. These methods need stringent supervision and technical control, including the control of filtration, repeated bacteriological analyses, and constant watchfulness in regard to the efficient operation of the process.

17. The use of water-disinfection methods, which modern technical science has brought to a high level of perfection, is recommended in all cases where there is any doubt as to the safety of the supply.

18. Where methods using chlorine are applied, routine chemical analysis and the permanent recording of the results by automatic or other means are essential, in order that a constant check may be kept on the efficiency of the chlorination.

19. The disadvantage attaching to the method of chlorination imperfectly applied that a disagreeable flavour is sometimes imparted to the treated water can be avoided by the use of chloramine or other agencies or by correct dosage.

20. There are also numerous processes for treating water in order to correct the colour, remove unpleasant tastes and smells, neutralise acidity, take away the hardness, eliminate the iron and manganese and the sodium and magnesium chlorides, or demineralise it altogether.

21. One or more of these processes may often be required to make the water fit for human consumption or other practical and technical uses. Their application will mainly depend on their cost and ease of application as compared with the gain in palatability or in usefulness for the technical and industrial purposes for which water is intended.

STANDARDS OF QUANTITY

22. The consumption of water depends upon many different factors such as climate, customs, the level of civilisation, the requirements of industry and of public services, and the cost involved. Wide differences are therefore found to occur in this respect between various countries, between various parts of the same country and between the various districts of the same town. Recent developments, many of which have special reference to housing requirements, have materially increased the consumption of water. Amongst these may be enumerated the installation of baths in newly constructed houses, the provision of a water-carriage system for excretal disposal with flushing cisterns (capacity usually 2 gallons) for each water-closet, the installation of water-taps in the houses themselves instead of water being obtained only from stand-pipes placed in the streets, the more extensive use of piped water for fire control with provision of fire hydrants, and the increased usage of water for general purposes due to a higher standard of cleanliness.

23. Figures of daily *per caput* consumption vary greatly in different towns and in villages, and no definite standards of requirements can be laid down. Broadly, however, it may be stated that provision should be made as a minimum for 270 litres (60 gallons) per head per day in large cities, scaling down to 120 litres (26.6 gallons) for village supplies. These figures do not allow for any material wastage from leaks but refer to amounts available for actual use.

24. In view of the various purposes for which water is required—*i.e.*, domestic uses, agriculture, trade industries and the public services—these must be regarded as minimum figures, and it is desirable that water should be available in abundance, or at all events in adequate quantities.

25. Increased modern needs for water both per head and to supply an expanding population are causing, in a number of areas, difficulties as regards supply. In this connection, measures to conserve water and to prevent waste merit consideration. Restriction of water for household purposes is undesirable on hygienic

grounds, but appropriate measures should be taken to avoid wastage. In England, it is considered desirable to sell water for industrial and agricultural purposes on a basis of the amount used, controlled by meter. In France and the United States, it is held to be sound policy to extend this plan to cover domestic use. Public water-supplies should have taps of the stop-tap type and measures against leakage should be enforced. In some countries, stress is laid upon the use of shower-baths instead of ordinary soak baths, as these use much less water. More use might be made of rain-water for general flushing purposes.

26. The use of rain-water for drinking purposes is occasionally unavoidable for individual houses in some places, where it is the only available source of supply. Provided the rainfall is adequate and sufficiently spaced to yield enough water with reasonable storage, such a source is not objectionable. Necessary conditions are that the storage should be adequate (1,000 gallons for an average household), that the tank must be of material which is impervious and not acted upon by the water, that the stored water should be protected from contamination and, if possible, that a device should be installed to reject the first water falling on the collecting area.

METHODS FOR THE CONTROL OF THE PURITY OF WATER-SUPPLIES

27. So far as the purity standards of drinking-water are concerned, it is essential that it should be entirely free from pathogenic organisms, free, except in traces, from poisonous substances (lead, arsenic, fluorine) ; it should also be colourless, odourless, tasteless and free from turbidity, and its temperature should, if possible, be low, whilst its content of certain chemical substances, especially lime, iron, manganese and other salts, should not exceed certain limits.

28. While it is generally acknowledged that we do not, so far, possess a reliable test for the presence in water of the bacteria of typhoid fever or other pathogenic germs, laboratory methods (chemical, biological, physical and especially bacteriological) can nevertheless provide valuable evidence of the degree of pollution of water by human and animal excreta.

29. For purposes of analysis, laboratories have numerous methods which have reached a high level of perfection. Certain standard methods have been recommended in various countries by the health authorities or by other bodies such as the American Public Health Association.

30. Under methods of control must be included reliable and careful supervision of the sources of supply and the whole water system by a reliable expert. This supervision is required, not only at the initiation of the supply, but must be continuous. In this way, many actual or possible sources of pollution can be recognised and removed. It is also of the greatest importance in connection with the interpretation of unfavourable bacteriological examinations, the significance of which can often be assessed by a detailed study of the sources of supply and the possibilities of some local contamination. Efficient topographical control must be placed in the first line of protection.

BACTERIOLOGICAL INDICES AND STANDARDS

31. Indications have been supplied by certain public health authorities for guidance in the interpretation of the results obtained by the application of the various methods of analysis. While various procedures, such as agar plate counts at different temperatures, the determination of streptococci and other special organisms, have their utility, general experience indicates that the *B. coli* (using the term rather widely) estimation is by far the best index of undesirable bacterial contamination.

The correct utilisation of this estimation is a matter of considerable complexity and, in particular, is markedly affected by the type of water under examination. The implications of these and other tests are fully discussed on the publications indicated below.¹ For the purposes of this report, it may be pointed out that bacteriological

¹ See *U.S.A. Treasury Department Standards for Drinking-water supplied to the Public by Common Carriers (1925)*; *Standard Methods for the Examination of Water and Sewage* (American Public Health Association, New York, 1936); *The Bacteriological Examination of Water-supplies*, H.M. Stationery Office, London, 1939. These reports enumerate definite standards as regards *B. coli*, and should be consulted.

examinations are of the utmost value in controlling and safeguarding the purity of individual supplies, but considerable experience is necessary for their interpretation, and they reach their greatest value when elucidated in the light of the known topographical and geological features of the particular supply under consideration.

They are of equal value for controlling the efficiency of chlorination and other methods of water purification.

CHEMICAL PROPERTIES AND INDICES

32. While the more sensitive bacteriological methods have largely replaced chemical examinations as a test for purity, the latter are still required for certain purposes. When a new supply is under consideration, a chemical examination is essential to determine general palatability and quality, the presence of undue organic matter, the hardness, if mineral constituents with undesirable properties are present in objectionable amounts, the actual presence of harmful minerals such as lead, zinc or arsenic, and whether the water has any corroding action upon lead or other materials with which it is likely to be brought into contact. In addition, chemical analysis is of special value to detect remote ground-water pollution which may subsequently become immediate. In special cases, chemical analyses may be required to investigate some abnormal taste or smell which has developed. Such analyses may also be required in connection with purification processes, such as an estimation of the amount of organic matter in relation to chlorination.

33. In practice, a distinction needs to be drawn between constituents, such as chemical salts giving a high degree of hardness, which are undesirable, and others, such as the presence of lead, zinc, etc., which must be rigidly controlled and maximum limits prescribed.

WATER OF SWIMMING-BATHS AND BATHING-BEACHES

34. Control, both by supervision and by laboratory methods, is required to test the quality of the water in swimming-baths and to some extent for bathing-beaches.

35. In recent years, great improvements have been made in the construction and design of swimming-baths. Standards have been laid down by certain authorities as regards both the quantity and the quality of water to be used.¹

36. To guard against the dissemination of infectious diseases, regular testing of the water by chemical and bacteriological analyses is essential. In order to attain the necessary degree of security in this respect, effective methods of circulation, together with aeration, filtration, precipitation, alcalinisation and, especially, disinfection by chlorine, ozone and other agencies, have been developed and recommended for general use.

GENERAL

37. Several decades of unremitting work in the field of public health have led to considerable progress in various directions. In many countries, the infectious intestinal diseases which were formerly widespread among the population and caused much fatal sickness have now practically disappeared, thanks, more especially, to the introduction of supply systems capable of furnishing pure drinking-water.

38. An increased realisation of the value of water has resulted in its much more extended use. Running hot and cold water in dwelling-houses connected with a bath or shower-bath and with appliances permitting of the rational use of hot water for domestic and laundry purposes has thus become one of the customary amenities of urban and even of rural life in many countries.

39. At the same time, there are still many districts in which modern scientific and technical knowledge has not yet been turned to practical account. The improvement of the water-supply of

¹ The standards of the American Public Health Association, which have been adopted in other countries, require that the total number of persons using a swimming-pool during a given period should not exceed twenty per thousand gallons of pure water delivered into the pool during that same period.

The establishment of such standards will obviously depend upon the state of cleanliness and educational level of the populations concerned, the facilities available to them for cleaning themselves before using the pool and other factors of a similar character.

populations will therefore continue to occupy a foremost place in the public health policy of many countries, and merits most detailed and careful consideration.

IV. SEWAGE TREATMENT¹

DANGERS CAUSED BY EXCRETA AND OTHER LIQUID SEWAGE

1. Human and animal excreta may constitute a danger to public health, inasmuch as they are liable to transmit infectious diseases, whether these be caused by bacteria, by protozoa, or by worms. The risk of transmission of some of these diseases can be still further increased by the breeding in large numbers of flies and other insects.

2. The contamination of the subsoil and surface water by excreta and other liquid sewage constitutes another very serious danger of transmission. The risk of contamination in these various ways depends upon the frequency of particular contagious diseases in the area considered.

Great harm has been done to streams, rivers and other surface waters in various parts of the world as a result of industrial development and the concentration of population. This has led to the tainting of sources of drinking-water, the pollution of spaces reserved for bathing, injury to fisheries, and the contamination of the water used for domestic, agricultural and industrial purposes.

GENERAL PRINCIPLES TO BE APPLIED IN GUARDING AGAINST THE VARIOUS DISADVANTAGES AND DANGERS

3. Thanks to the scientific research carried out by the specialised laboratories of various countries, under the auspices of the organisations concerned with such problems, great progress has been

¹ Chairman : M. H. J. N. H. KESSENER (The Hague).

made since the middle of last century in removing the dangers of sewage and the objectionable characteristics resulting therefrom in town and country. The methods of treatment and removal of objectionable matter which are applied for this purpose must be suited to the particular conditions encountered, which may range from the most primitive—those of the isolated dwellings in the primæval forest—to those of highly industrialised and crowded areas in which full treatment of the sewage is applied.

4. The mechanism of the best methods of treatment so far known is based in the main on two fundamental principles—*i.e.*, that of processes leading up to the filtration, fermentation or decomposition of the organic matter in the soil, and that of the processes which operate in the self-purification of rivers and other surface waters.

GENERAL HYGIENIC RULES

5. Most public health authorities have issued guiding instructions and have laid down standards for the removal and treatment of excreta or other liquid sewage which are adapted—so far as both individual and collective processes are concerned—to the special conditions encountered.

The hygienic principles which are enunciated in this connection are designed more especially to prevent the contamination of the surface of the soil, the pollution of sources of drinking-water and the breeding of flies and other insects, and the occurrence of smells and other nuisances.

6. Since the choice of standard processes for a given region depends largely upon the geological configuration of the soil, close co-operation between the hygienist, the planner, the sanitary engineer and the geologist is essential. This is equally necessary for the application of rules of hygiene to the various installations, especially those designed to protect sources of water.

7. For the purpose of testing the efficiency of the various processes from the standpoint of hygiene, in regard more especially to surface and ground water pollution, laboratories have at their disposal the whole range of methods which have already been mentioned, and which may be used to determine the degree of water

pollution by human excreta. Some of these methods have been developed for the special purpose of following the treatment of sewage through its successive phases, and to this we shall revert in due course.

INDIVIDUAL METHODS

8. In the rural areas of the tropics, primitive pit latrines are used. Among these, the so-called bored-hole Java type is becoming more and more common.

9. Elsewhere, in the agricultural districts, certain types of latrine, especially pit latrines of cheap and simple design, have been recommended by the health authorities. In yet other regions, peat and earth closets have proved serviceable.

10. In many tropical regions and, for the matter of that, in others as well, methods of treating excreta have been evolved, after careful research, which bring "composting" processes into play (*e.g.*, the so-called "Indore" method). Such systems operate by means of aerobic and anaerobic decomposition, and consist in mixing human excreta with the soil simultaneously with other domestic and agricultural waste. These methods have the advantage of furnishing a product which is rich in humus and can be utilised for agriculture, provided they effect a sufficient reduction of the number of pathogenic bacteria as well as of ankylostoma eggs.

11. In many countries, the public health services have undertaken, through their sanitary engineers, to organise and watch over the construction of these sanitary installations and to supervise their operation.

Such supervision, exercised by competent officers, is essential when the plant is one which has to be emptied and requires periodical inspection, such, for instance, as septic tanks and chemical action tanks.

12. In the case of isolated dwellings having sufficient water, settling tanks, with or without sludge digestion chambers, with several compartments have been recommended in combination with bacterial contact beds or with a system of subsoil irrigation.

Such systems also require competent supervision, exercised by the health authorities if possible, and extending both to their construction and to their operation.

COLLECTIVE METHODS

13. Very great progress has been made in the past thirty years in the development of collective processes for the treatment of sewage and industrial effluents.

14. Many towns on the sea coast or on the shores of large estuaries, rivers or lakes discharge their sewage, untreated, directly into the water. This method involves a danger for health, in case sewage is discharged in the vicinity of bathing-beaches, shellfish beds, etc. Purification should be applied with chlorination, or measures should be taken to prevent the entrance of sewage into the zones concerned, allowance being made in this connection for the effect of winds and currents.

15. Elsewhere, it has been found possible to increase the self-purifying capacity of the rivers and streams used to carry away sewage by erecting dams and laying out reservoirs and artificial fish-ponds. In order to avoid the progressive accumulation of periodically discharged sludge in the lower reaches of the stream, it is desirable that the sewage should be settled first.

16. Direct discharge into the soil is the oldest of the methods at present in use for the treatment of sewage. This method is carried out either by some form of intermittent filtration or by surface irrigation, involving the distribution of the sewage over the fields by trenches or by sprays, or else by subsoil irrigation. Vegetables grown on this soil should be cooked before use.

This system has the advantage of turning to account the fertilising value of sewer effluents for purposes of agricultural production and of helping to maintain the ground-water level.

17. Many purification processes have been devised to enable sewer effluents to be discharged into rivers and streams and other surface waters without causing pollution. The measures to be applied depend on the capacity of the rivers into which the sewage will be discharged.

The first stage in the treatment of sewage consists in the elimination of large solids by screens, and of grit and suspended matter by settling tanks. These measures are also necessary as a pre-treatment where complete purification is required.

The removal of suspended matter through sedimentation was assisted, during the second half of the last century, by the addition of chemicals.

Whereas the use of chemical treatment has since then become less frequent in most countries, it has spread extensively again in the past decade among the sewage treatment plants of the United States. Such a method may have its advantages in some well defined cases, especially when the sewage contains certain industrial effluents.

18. After the sewage has passed through grit chambers, screens and settling tanks, it may have to be freed from colloidal and dissolved organic matter. For this purpose, recourse is had, in many places and especially in Great Britain, to the artificial methods of biological oxidation which imitate the oxidation processes occurring in sewage discharged direct into the soil.

Two main types of artificial filters are utilised in this connection : the contact beds, which are nowadays used in a few places only, and trickling or percolating filters with or without artificial draught or with recirculation of a part of the effluent.

19. The activated sludge method, which is twenty or twenty-five years old, is nowadays widely used in sewage treatment plants in many parts of the world. In this process, the sewage is stirred and aerated through previous mixing with aerated (" activated ") sludges. Several methods are in use for the aeration and stirring of the mixture of sewage and activated sludge. By such processes, particularly well-purified terminal effluents can be obtained.

The sludge of all kinds obtained in the sewage plants requires special treatment. The methods advocated for the purpose are of very different kinds. They are based upon the fermentation or digestion of the sludge, on its desiccation in pools and basins, or by centrifugation, filtration and heating, or on its modification by the action of chemical substances.

The products thus obtained are either discharged into the sea, or burned, or used as agricultural fertilisers. Certain methods,

especially those which involve mixing with solid, domestic or agricultural refuse, are designed to increase the proportion of humus in such products, thereby improving their fertilising properties and making them suitable for use in agriculture.

20. Much progress has been made in the treatment of industrial effluents. Here, it is especially important to avoid or reduce the loss of valuable raw material and to recover that which is carried off with the waste waters. Consideration of these complex questions calls for a thorough knowledge of the manufacturing processes concerned, and frequently requires the installation, by factories themselves, of specialised laboratories, which are also called upon to supervise the efficient operation of such methods of treatment as may ultimately be found necessary.

21. As regards the methods to be employed, such industrial effluents can frequently be treated by mixing them with the ordinary sewage and subjecting them to processes of purification by sedimentation, or to chemical or biological treatment, or a combination of several such methods.

In view of the detrimental effect of certain industrial effluents on the self-purification process, it frequently becomes necessary to treat them separately and subject them to elaborate forms of treatment, if they are to be discharged into rivers and streams without causing pollution.

22. A large variety of methods of purification and combinations of processes are in use in the various countries of the world. The extent to which they are severally employed in different countries varies considerably according to historical development and special conditions.

23. The method of sewage treatment which is likely to prove most effective in a given district can only be ascertained after due consideration of all local conditions and requirements and of the comparative cost of the various systems with respect to lay-out of plant and upkeep.

The climatic conditions, temperature, height above sea level, and rainfall, and the composition of the sewage as determined by the prevailing diet of the population and other local habits, as well as the local industries, are factors of which special account must be taken.

STANDARDS OF PURITY FOR SEWAGE

24. Certain standards have been set up defining the degree of purification to be attained by sewage when it has to be treated before discharge.

The rate of dilution of the sewage effluent in the water which carries it away has frequently been taken for the purpose ; the practice of taking this value as an index of the treatment required is, however, falling more and more into disuse at the present time, it being essential to take account of other more important factors, such, for instance, as the pollution to which the carrying water has been previously exposed.

25. The decomposition of organic matter in the process of self-purification of streams depends largely upon the content of dissolved oxygen in the water and of re-aeration ; the greater the quantity of organic matter, the greater will be the oxygen demand for its complete oxidation.

The oxygen content, as well as the biochemical oxygen demand, of the water are hence valuable criteria of the degree of pollution and of the necessary purification.

26. Such standards¹ are applied in various countries ; thus, the Royal Commission on Sewage Disposal, of Great Britain, is of

¹ German authors, for instance, define the oxygen demand of water of different degrees of purity as follows (determined as above) :

	Per litre Milligrammes
Very pure stream	Less than 1
Pure stream	1 to 2
Practically pure stream	2 to 2.5
Stream of average purity	2.5 to 3.7
Stream of doubtful purity	3.7 to 5
Impure stream	5 to 10

For comparative purposes, we give hereunder approximate figures showing the relative efficiency of the various methods of treatment in terms of the resulting reduction of oxygen demand :

	Reduction of oxygen demand %
Screen	5 to 10
Settling tank	33 to 40
Chemical treatment	60 to 75
Percolating filters	60 to 90
Activated sludge	85 to 95

opinion that the oxygen demand of sewage-polluted water should not exceed 2 milligrammes per litre (determined on a five-day basis at 18° C.). Similar standards are advocated in the United States of America.

27. Formulæ have also been devised and used, especially in the United States of America and Germany, to calculate the degree of purification which is required in order to maintain the oxygen content of streams at the requisite level. Such formulæ take account of the many factors involved, in particular the volume of sewage and the volume of the carrying stream, the depth, width and speed of flow of the latter, the biochemical and replacement oxygen demand, and the quantity of matter in suspension.

It is no less essential to allow for the important influence exerted on this process by temperature.

It is of course always important that the reduction in oxidisable organic matter effected by sewage treatment should be controlled by determination of oxygen demand, and by other appropriate chemical and physical observations.¹

28. Up to the present, no standards have been established specifying the maximum permissible content, in rivers and streams, of such poisonous impurities as may be contained, for instance, in industrial wastes. It is highly desirable that such standards should be instituted, especially in regard to the use of such water for domestic use, bathing, pisciculture and agriculture.

FLY CONTROL AND THE PREVENTION OF SMELLS

29. To turn to a matter which is of special interest to hygienists—namely, the prevention of smells and of the breeding of flies and other insects in sewage plants—this can be completely achieved by suitable choice of process design and supervision.

30. The growing tendency to pass the effluent through the various phases of treatment whilst it is still fresh helps very greatly to keep down smells. When, despite all such precautions, evil smells

¹ Instructions on this subject have been issued by the Conseil supérieur d'hygiène de France.

cannot be avoided, chemical treatment, with chlorine for instance or artificial ventilation, is frequently recommended.

EFFECTS ON PATHOGENIC ORGANISMS

31. Although, according to the evidence of the studies carried out on the subject, pathogenic organisms, such, for instance, as those of the typhoid group, may be assumed to be destroyed in the course of the self-purification of streams, research work conducted on the basis of a perfected technique has shown that such organisms may be present in sewage, even after it has been treated.

32. The cultivation of produce intended for human consumption should be regulated.

33. It would appear very desirable that research work should be continued in this field by modern bacteriological and parasitological methods, in order to ascertain exactly what happens to pathogenic organisms during the various phases of sewage treatment.

34. Under certain conditions, as, for instance, in case of epidemics or where bathing-beaches or shellfish beds, etc., have to be protected, the disinfection of sewage effluents may be indispensable. For this purpose, chlorine treatment is widely used, especially in the United States, being applied to sewage more especially when it has already undergone partial or complete treatment.

35. In many countries, special laboratories have been installed for the routine examination of stream water from the chemical, bacteriological, botanical and zoological standpoints. The work of such laboratories, which enables a systematic check to be kept on the efficiency of purification methods, may be regarded as forming an essential part of the campaign against stream pollution.

36. Despite the considerable progress already made in the discharge and removal of excreta and liquid sewage, much yet remains to be done.

Even among those countries which have reached an advanced stage of civilisation and possess large numbers of urban and rural houses which attain to the desirable standard of one water-closet per dwelling, there still remain some in which the rural houses of whole districts are entirely without privies.

37. As a result of the joint organisations set up by communes industry and agriculture to combat stream pollution, considerable improvements have been made, in this respect also, in certain countries. The creation of national research institutes for the special purpose of studying these problems has contributed greatly to the establishment of the scientific principles on which practical action can be based.

38. The extension of this movement to other countries and the co-ordination of the various activities concerned would appear to be desirable if wholly satisfactory solutions are to be found for these problems, which are not only of national but may be even of international importance when anti-pollution measures have to be applied to rivers which pass through the territories of several countries.

39. It is desirable that communities should be obliged to draw up sewage disposal plans, and to study these plans in conjunction with those of neighbouring communities. Such joint studies should, if necessary, be extended to cover the whole catchment area of a river or coast-line.

V. COLLECTION AND DISPOSAL OF REFUSE¹

GENERAL AND HYGIENIC CONSIDERATIONS

1. The question of the collection and treatment of solid wastes is a highly complex one from the administrative, hygienic, technical and economic standpoints. Although for the various purposes concerned very many processes have been devised and applied, none, so far, appears to have proved wholly satisfactory from all these different points of view.

2. From the standpoint of hygiene, the solid wastes of the towns and of the country, especially the domestic refuse, may be highly objectionable, for they are liable to be malodorous and unsightly and to breed flies and rats as well as other rodents and insects.

¹ Chairman : Professor C.-E. A. WINSLOW, New Haven.

They may also endanger the public health by disseminating infectious diseases either directly, or indirectly, through insect and rodent vectors, or by dust.

METHODS OF COLLECTION

3. In the collection of refuse, the first thing is to avoid smells, dust and other nuisances. This can be achieved to a large extent by a regular system of collection at intervals which may vary according to climatic conditions, and by the use of standardised and well-closed metallic refuse bins, which can be easily cleaned and deodorised and can be discharged into the transport vehicle without raising a cloud of dust. It is desirable that collections be made at such times of day as to minimise inconvenience to passers-by.

4. A large number of refuse bins and collecting vehicles of various types have been put on the market. Of the latter, some have been brought to a high level of perfection, so that they can be loaded and unloaded in a rational way without noise or dust and, being well designed and efficiently closed, they are neither unsightly nor evil smelling. Tight closing of vessels and vehicles is important for the control of dust, and those designed for the carriage of garbage should be of impermeable materials, in order to minimise odours.

5. In order to prevent the occurrence of the nuisance entailed by storing refuse inside dwelling-houses and emptying it into dustbins which are placed outside, removal systems have been planned which are based upon the use of dry or wet discharge conduits. In the latter case, special precautions should be taken for the removal of the water used to facilitate the transport of the solid wastes.

6. The use of dry conduits in the form of various systems of refuse chutes, which are already widely used in many countries, has certain disadvantages, owing to the fouling of the inner surface of the chutes and the smells which they give off. These disadvantages are difficult to avoid, in spite of the improvement of their design and regular cleansing and even disinfection. The opening into such chutes should not be from the interior of the dwelling but from a hallway or preferably from a terrace or balcony or other

point in the open air ; and the chutes should be ventilated by a duct opening above the roof.

7. Much interest has been aroused by various systems of wet discharge which are based upon the principle of direct evacuation into the sewers and provide for the removal of the refuse with a water flush operated from the kitchen itself, as worked out in France and already introduced into other countries. It is to be noted that this system may create awkward problems in regard to the purification of the sewage into which such discharges are made.

8. These systems, which require the laying of special pipes inside the house and—where appropriate—of pneumatic conveyance conduits, have been greatly simplified of late in the United States by the installation, in the kitchen itself, of an automatic grinder, which makes it possible to discharge the refuse—then reduced to a fine pulp—direct into the ordinary sewer.

METHOD OF TREATMENT

9. Household refuse includes essentially three different kinds of wastes :

Ashes (residue of burned or partially burned fuel) ;

Rubbish (including such materials as paper, wood, tin cans and bottles, etc.) ;

Garbage (kitchen and table refuse).

The first two are relatively inoffensive and contain much readily combustible material. The last—garbage—presents far more serious problems on account of its high water content and putrescibility.

These three kinds of wastes are sometimes collected together, while in many American cities garbage, ashes and rubbish are collected independently. The method of disposal is naturally influenced by the particular kind of refuse concerned.

Difficulties in the treatment of refuse may be materially reduced if householders dispose of their own wastes to a considerable extent by combustion in domestic stoves of a suitable type. Trade garbage, particularly from slaughter-houses and fish-shops, may often be wisely excluded from public collections. The public authorities

should in all cases formulate regulations indicating the precise nature of the wastes which will be accepted for public collection, particularly with regard to wastes of commercial and industrial origin, in view of the difficulty in treating such wastes.

10. The simplest and most primitive method of disposing of household refuse—*i.e.*, dumping on land—is generally condemned by hygienists, owing to its serious drawbacks, and in particular the fact that refuse dumps breed rats and flies and give off nauseous smells and are unsightly.

11. The discharge of refuse into the sea is also liable to cause trouble, owing to the consequent pollution of the shore ; more and more this practice is being dropped, on hygienic grounds.

12. These primitive methods are tending to be replaced by so-called “ controlled tipping ”, which has been developed in England on a rational basis in the course of the past ten years and has also been introduced into other countries.

This method consists in the systematic spreading of layers of refuse which must not exceed a certain depth, covered by a sufficient quantity of earth.

As a result of the fermentation processes which take place inside the layers, the organic matter is rapidly disintegrated without giving off any bad smell. The contamination of water-bearing strata can be avoided by suitably choosing and, if necessary, draining the spot at which the refuse is discharged.

The method of controlled tipping has been used with great success in the levelling-up of hollows, the improvement of land and its utilisation for agriculture and the laying-out of parks and playing-fields.

13. Many other methods have been devised with the object of using refuse for agricultural purposes. Its fertilising value, which depends upon the content of organic matter, can be improved when it is subjected to fermentation processes, of which the method of controlled tipping constitutes one example.

The burying of fresh refuse on an individual farm and its immediate covering with sufficient earth may be a satisfactory procedure.

In the United States, the tipping process (called “ sanitary fill ”) is commonly used for the disposal of garbage separated from ashes and combustible wastes.

14. Another process for the disposal of refuse is incineration, which may be very successful if the caloric properties of the refuse are sufficiently great (cinder, fragments of coal, coke, etc.). Since these properties vary considerably from country to country, the process is not applicable everywhere.

Since the construction of community incineration plants involves a heavy initial outlay and fairly considerable maintenance charges, attempts have been made to use the caloric energy available in refuse to generate electric power, gas, steam, etc. Other by-products are bricks and other building materials made of clinker.

From a hygienic standpoint, the main problem for consideration in the laying-out of incineration plants is that of the smoke and dust given off by the burning refuse. It is essential to use forced draught for high-temperature combustion and to provide special chambers for the settling-out of flue dusts, unless the plant is located at a point remote from residential areas.

Local incineration plants have been used with success in the United States and some European countries for blocks of flats and even for individual dwellings, but precautions must be taken to design and operate such plants so as to avoid atmospheric pollution with dust or fumes.

15. Ashes, separated from garbage and rubbish, may be used for filling in waste-lands if offensive conditions due to smouldering fires and the blowing about of dust be avoided.

16. Rubbish can readily be burned, and in some large cities it has been found profitable to sort the wastes and conserve the paper, metal, etc., for industrial uses. In certain cases, before treatment proper has started, the refuse is sifted with a view to the recovery of materials of commercial value. It has, however, often been found that the cost of installing and operating a plant of this kind is not always offset by the proceeds of the sale of the recovered materials.

17. In view of the fact that hand sifting is both hygienically undesirable and inefficient, a whole series of mechanical separation processes (screens, moving bands, mechanical separators, sifting under water, separation by crushing) have been devised. It is even more obvious that the picking over of individual household

waste from receptacles in the streets is undesirable and should be prevented as far as possible.

18. In the course of certain processes, the garbage is dried and ground up or pulverised. The terminal product is then used as a fertiliser, either directly or after previous fermentation.

The composting processes, which have been known for a long time, have recently been further elaborated, especially in the tropics, on the lines of utilising mixtures of refuse and of human and animal faeces. They constitute the simplest and most rational methods of treatment that can be applied in rural areas.

19. In the same connection, reference should also be made to the fermentation processes in concrete cells which were developed in Italy, but have also been introduced into other countries where climatic conditions are different.

20. In the United States, feeding of garbage to hogs has been found a highly economical method of disposal ; but this procedure has led to serious dissemination of trichinosis, human as well as porcine. It should not be employed unless the garbage to be fed to the hogs is first sterilised.

21. Another process for garbage treatment is reduction, which consists in the extraction of fats and fertilising materials by use of steam or chemical solvents. This procedure has not proved generally profitable in recent years.

22. A recently devised method of garbage disposal is to mix the collected refuse with the city sewage and subject it to the treatment which is applied to the latter.

Such methods are followed in certain towns of the United States of America, which have ground up together the whole of the collected garbage and have discharged the resulting mass into the sewage without experiencing any difficulty as regards the operation of the usual methods of sewage treatment.

In paragraph 8 of this chapter, we have already mentioned a new phase of this development, which consists in the discharge of ground-up refuse direct from the dwelling into the ordinary sewer.

GENERAL CONCLUSIONS OF CHAPTER V

23. Local authorities have at their disposal a large number of methods of dealing both with the collection and the treatment of domestic refuse. The choice of method must depend upon a careful analysis of all factors, more especially the composition of the refuse, initial construction costs, available transportation facilities, the possibility of selling by-products, the price and abundance and fertilising value of other competing manures, and other economic and financial factors. The provision of a sanitary and inoffensive method of disposal should of course be always a primary consideration.

24. Among the various processes listed above, tipping, incineration or biological fermentation in special chambers may perhaps be expected to prove most generally satisfactory, providing always that design is adequate and continuously controlled.

25. The achievements of the past few years point the way to fresh solutions of the problems under review. If scientific research is directed along the lines thus indicated, further progress may be expected both from the point of view of finance and hygiene.

26. It should be noted that, even in rural areas, community collection of household wastes and collective disposal by tipping, incineration or biological fermentation may be practical and highly desirable. Such possible measures are discussed in the report on Rural Housing and Planning.¹

* * *

It will be noted that this report of the Housing Commission of the Health Organisation of the League of Nations deals with a number of closely, in fact necessarily, related subjects, all of which have been under consideration and discussion at one meeting of the Commission.

The planning of residential areas, the provision of an adequate and safe water-supply for the use of residents in their homes, the

¹ *Bull. Health Org.*, 1939, 8, 87-142.

adoption of measures calculated to preserve the natural amenity of sunlight and fresh air by controlling and limiting atmospheric pollution, the treatment of sewage, and finally the arrangements made for the collection and disposal of household refuse are hygienic measures none of which can be overlooked when attempting to deal comprehensively with the housing of the people in the light of present knowledge and past experience.

In the various chapters, we have considered, as far as possible, the principles and standards of hygiene which are applied in the various branches surveyed, the methods of measurement which are used and the processes which are able to satisfy the requirements of the standards defined. As contemplated in the Housing Commission's programme of work, questions relating to organisation, administration and legislation will be treated at a later phase of its proceedings.

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ENQUIRY ON THE ASSAY OF
GAS-GANGRENE ANTITOXIN (PERFRINGENS)

carried out under the auspices of the Department of Biological Standards
of the State Serum Institute, Copenhagen.

I

COMPARATIVE TITRATIONS
OF GAS-GANGRENE ANTITOXINS (PERFRINGENS)

By

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and A. SORDELLI (Buenos Aires).

Until some years ago, the toxin of *Cl. perfringens* Type A was considered an antigenic entity. GLENNY, BARR, LLEWELLYN JONES, DALLING & ROSS (1933) established the parallelism of the lethal, necrotic and hæmolytic properties of this toxin, which was called α to distinguish it from the toxins of type B, C and D.

In 1936, R. PRIGGE found that the hæmolytic property was different from the lethal and suggested designation α for the hæmolytic and ζ for the lethal. This author claimed that toxins containing very little hæmolysin in relation to their content of lethal toxin and toxins relatively rich in hæmolysin give divergent results in comparative titrations of various perfringens antitoxins. These divergences do not, however, amount to more than 30%.

PRIGGE draws attention to the need for working with pure strains of *Cl. perfringens* in the production of toxin and emphasises that all such strains should be derived from one organism isolated by micromanipulation.

Since 1936, Professor WEINBERG has published papers giving evidence that even the lethal factor of perfringens toxins is not an entity. With various toxins produced from the same strain, he finds considerable discrepancies in the titres assigned to various sera by the mouse assay. His conclusion is that all workers should use the same toxin and antitoxin for the assay of anti-perfringens sera.

Confronted with these problems, Dr. Th. MADSEN suggested, in January 1938, that comparative titrations with different toxins and sera should be undertaken in different laboratories. The Department of Biological Standards of the Copenhagen Institute outlined a plan providing for the comparative titration of different perfringens antitoxins against various toxins. Miss M. LLEWELLYN SMITH, Hampstead, and Professor A. SORDELLI, Buenos Aires, agreed to collaborate in the execution of this plan.

THE PLAN OF INVESTIGATION

The purpose of the investigation was to examine the following questions :

1. Do the perfringens antitoxins show the same activity when assayed against different toxins ?
2. Does the hæmolysin content influence the assay on animals ?
3. Do intravenous assays on mice give results corresponding to those obtained intracutaneously in guinea-pigs ?
4. Is there any relation between the activity of a perfringens antitoxin determined *in vitro* (hæmolysis) and *in vivo* ?

THE MATERIALS USED IN THE INVESTIGATION

Toxins.

The work had to be carried out with toxins prepared from a pure strain. The strain used at Copenhagen for the production of toxin was therefore sent to Professor ZEISSLER, Altona, who was kind enough to examine it. He found that it remained pure and homogeneous in repeated subcultures. A toxin produced by this strain could accordingly be used for the investigation.

The other two toxins were made available by the kindness of Professor PRIGGE, who had been asked to supply the Copenhagen Institute with a toxin rich in hæmolysin and a toxin poor in hæmolysin. He produced these toxins by his method of fractional precipitation which he has described.¹

The three toxins used in the investigation were :

1. *Toxin B.35*, produced in Copenhagen ($\frac{\text{m.l.d.}}{\text{m.h.d.}}$ ratio = about 1.0).
2. *Toxin Prg.484*, produced in Frankfort ($\frac{\text{m.l.d.}}{\text{m.h.d.}}$ ratio = about 0.04).
3. *Toxin Prg.590*, produced in Frankfort ($\frac{\text{m.l.d.}}{\text{m.h.d.}}$ ratio = about 20.0).

Sera.

The activity of three commercial sera was to be compared with that of the international standard issued to the participating workers in the usual glycerol solution containing 20 A.U. per c.c. Three commercial sera produced at the Copenhagen Institute were selected. They were numbered V, VI, and VII, and their activity was first determined *in vivo* with toxin B.35, and, by the hæmolytic

¹ *Z. f. Immunitätsforsch.*, 1937, 91.

test, with toxin Prg.377. The potencies, as determined by these two methods, were :

Serum	A.U. <i>in vivo</i> (Toxin B.35)	A.U. <i>in vitro</i> (Toxin Prg.377)
V	200	200
VI	115	450
VII	300	640

These three sera were considered suitable for the purpose, as the ratio of the anti-hæmolysin to the anti-toxin content appeared different in the three sera.

METHODS PROPOSED FOR THE ASSAY

1. *Intravenously in Mice.*

Weight of the mice, 16-20 gr. For the final determination, 6 mice per dose should be employed. At least 3 doses of serum differing by 10% should be tested against a constant test dose of toxin.

The test dose of toxin was left for the investigator to choose, but it was suggested that it should contain at least 25 m.l.d., so that the accuracy of the tests performed at the different institutes could be assumed to be equal. Mixtures of serum and toxin were to be allowed to combine 1 hour at room temperature, and the animal was to be observed for 3 days. If the sera were to be tested on different days, a series with a standard serum was to be run simultaneously, so that the resistance of each lot of animals was controlled.

2. *Intracutaneously in Guinea-pigs.*

Mixtures of serum and toxin were to be injected in a volume of 0.1 c.c. Serum doses differing by 10% were to be tested against a constant test dose of toxin. Each animal was to be injected with a control series of the standard serum. The test dose was left for the investigators to choose, but it was decided that it should contain at least 25 m.n.d. The reactions of the guinea-pigs were to be read 24 hours after the injection and the result recorded by the size of the necrosis (largest and smallest diameter given in mm.).

3. *Hæmolytic with 5% Sheep Erythrocytes.*

Combining time, 1 hour at room temperature. The reading of the reaction was to take place after hæmolysis for 2 hours at 37° C. and again after standing overnight at room temperature. For strict comparison, the degree of hæmolysis was to be recorded as 0, 25, 50, 50-100%.

RESULTS AND COMMENTS

The three participants gave full details of their experiments, so that a strict comparison of the results was possible.

In each case, a certain end-point was defined and the doses of toxin and toxin-antitoxin giving this end-point were compared, so that a uniform computation of the result was secured.

A. **The Properties of the Test-toxins.**

A toxin is defined by the minimum indicating dose and the dose neutralised by the unit of antitoxin. As perfringens toxin has more than one biological action, the minimum reacting dose and the test dose of each property must be considered.

1. LETHAL EFFECT IN MICE

The dose causing the death of 50% of the animals within 3 days was chosen as end-point of the reaction. For the computation of the dose from each experiment, the method of Behrens has been used as proposed by Miss M. LLEWELLYN SMITH.

Table 1 presents the minimum lethal dose of the three toxins and the amount of toxin neutralised by the amount of standard serum chosen in each laboratory as the level of titration.

Table 1.
CONSTANTS OF THREE TOXINS, MICE I.V.

Laboratory	Toxin B.35		Number of A.U. neutralising the test dose	Amount of toxin neutralised by 1 A.U. (calculated)	Number of m.l.d.	
	M.l.d.	Test dose used			In the test dose used	Per A.U. (calculated)
	Mgrm.	Mgrm.	A.U.	Mgrm.		
A	0.20	5.0	0.429	11.65	25	58
C	0.18	6.0	0.56	10.70	33	59
H	0.183	2.12	0.20	10.60	c. 12	58
		5.2	0.50	10.40	27	57
	Toxin Prg.484					
	Mgrm.	Mgrm.				
A	0.195	5.0	0.474	10.55	26	54
C	0.18	5.5	0.553	9.95	30	55
		5.2	0.532	9.80	29	54
H	0.179	2.12	0.20	10.60	12	59
		5.0	0.513	9.75	28	55
		4.7	0.459	10.2	25	57
	Toxin Prg.590					
	Mgrm.	Mgrm.				
A	0.38	10.0	0.366	27.3	26	72
C	0.44	16.0	0.60	26.7	36	61
H	0.182	5.8	0.195	29.7	32	163

M.l.d.

Toxins B.35 and Prg.484.—The results from the three laboratories show a very high degree of agreement, the divergence being less than 10%. For Prg.590, the Hampstead result is only half that found in the other two laboratories.

Test Dose.

In order to compare the results obtained by the different workers, the amount of toxin neutralised by 1 A.U. was calculated assuming the law of multiple proportions to be valid. These values are given in the fourth column of Table 1. For all three toxins, the results from the three laboratories agree closely and diverge less than 10%; this applies also to the results of toxin Prg.590, although the minimum lethal dose determination showed wide variations. The determination of the reaction between toxin and antitoxin thus shows good concordance in all laboratories.

The participants were asked to choose a test dose containing more than 25 lethal doses, and this seems to have secured a good basis for comparison of the results of the mouse titrations.

2. INTRACUTANEOUS TITRATIONS IN GUINEA-PIGS

The choice of the end-point in this assay is beset with far greater uncertainty than in the mouse experiments. In this connection, reference may be made to Miss M. LEWELLYN SMITH's remarks in the report of the Hampstead Institute, which describe the difficulties encountered in some laboratories :

“ First, only a small margin exists between a dose which is too small to give a measurable reaction and that which causes a reaction inconveniently large.

“ Secondly, there is a large variation in sensitivity between different guinea-pigs.

“ Thirdly, the skin of any one guinea-pig is by no means uniformly sensitive, so that the same mixture injected into different skin-sites produces reactions of very different sizes.

“ Fourthly, perfringens toxin contains a diffusing factor which increases the permeability of the skin.¹ Different samples of toxin contain different proportions of this spreading factor, and antitoxin samples contain different amounts of anti-diffusing substances. Probably because of this, some, but not all, samples of toxin-antitoxin mixtures diffuse rapidly after intracutaneous injection, so that œdema and necrosis occur, not at the site of injection, but in a more ventral position, and may mask the reactions due to other injections.

“ A combination of these phenomena makes comparative assays of perfringens antitoxins by the intracutaneous method a very difficult, if not impossible, task.

“ In addition, it appears that the dermo-necrotic substances in toxin B.35 and Prg.484 are qualitatively different. B.35 produces necrotic reactions which are yellow in colour, develop somewhat slowly (maximum 24-48 hours) and are not wholly inhibited even by large doses of any of the antitoxins examined.

¹ McCLEAN, *J. Path. Bact.*, 1936, **42**, 477.

“ Prg.484 produces reactions which are purplish in colour, develop rather more quickly than those caused by B.35 (maximum within 24 hours), and are inhibited in a clear-cut manner by antitoxin.

“ The variations in results when this toxin is used for the intracutaneous assay of antitoxins are, however, almost as great as when toxin B.35 is used. Possibly this is attributable to a greater proportion of diffusing factor in Prg.484. Even when comparable dilutions of the sera being compared are injected into comparable sites on opposite flanks of the same animal, and even when the same series of mixtures is given to several animals, the results are difficult to interpret.”

Protocols from Hampstead show the difficulties which may be encountered and which make the choice of the end-point very difficult.

PROTOCOL OF INTRACUTANEOUS ASSAY IN GUINEA-PIG

Lab. H.

Guinea-pig No. 15.

Mgrm.	Toxin B.35	Standard serum A.U.	Diameter necrosis (mm.) after 48 hours	Dose giving 5 × 5 mm. necrosis
1.25	0.083	17 × 5	
”	0.091	2 × 2	
”	0.100	2 × 2	0.087 A.U.
”	0.110	2 × 2	
”	0.121	2 × 2	

Guinea-pig No. 24.

Mgrm.	Toxin Prg.484	Standard serum A.U.	Diameter necrosis (mm.) after 48 hours	Dose giving 5 × 5 mm. necrosis
1.35	0.083	Very large, confluent	
”	0.091	” ” ”	
”	0.100	15 × 5	0.105 A.U.
”	0.110	Trace	
”	0.121	0	

In the above example of the assay with toxin Prg.484, the choice of the end-point should be very easy, although some workers might choose a trace of reaction and reckon the dose giving the end-point reaction as 0.11 A.U., while others would select a more definite reaction, and choose the end-point at 0.10 A.U. The interpretation of the protocol showing the titration with toxin B.35 is more difficult. Since the reactions showed no increase in size when the

dose of antitoxin was varied from 0.121 to 0.091 A.U., the assumption seems justified that the necrosis of 2×2 mm. was caused by non-specific factors which were not neutralised by the antitoxin. It would therefore be reasonable to place the end-point, not at the first trace of reaction, but at the appearance of a necrosis just larger than these non-specific necroses.

After careful examination of all the detailed protocols from the three laboratories, it became evident that necrosis of 5×5 mm. or more might be regarded as specific—*i.e.*, caused by free perfringens toxin. In consequence, the end-point in titrations was placed at 5×5 mm. necrosis or (roughly speaking) 25 sq. mm.

Table 2.
CONSTANTS OF THREE TOXINS, GUINEA-PIGS I.C.

Laboratory	Toxin B.35		Number of A.U. neutralising the test dose	Amount of toxin neutralised by 1 A.U. (calculated)	Number of m.n.d.	
	M.n.d.	Test dose used			In the test dose used	Per A.U. (calculated)
	Mgrm.	Mgrm.	A.U.	Mgrm.		
A	0.023	0.625	0.045	13.9	27	600
C	0.068	1.20	0.09	13.3	18	196
H	0.059	2.25	0.20	11.3	38	192
		2.50	0.20	12.5		212
		1.25	0.091	13.7	21	232
		1.20	0.095			
			0.105	12.3	20	208
			0.095			
			0.10			
	Toxin Prg.484					
	Mgrm.	Mgrm.				
A	0.023	0.625	0.042	14.9	27	650
C	0.024	1.10	0.085	12.9	46	540
H	0.05	2.0	0.20	10.0	40	200
		2.3	0.20	11.5	46	230
		2.4	0.22	10.9	48	248
		1.2	0.091	13.2	24	264
		1.35	0.10		27	
			0.11	13.2		264
			0.10			
			0.10			
	Toxin Prg.590					
	Mgrm.	Mgrm.				
A	0.042	1.10	0.031	35.5	26	840
C	0.20	3.5	0.112	31.2	18	156
H	0.24	6.0	0.20	30.0	25	125

Reconsideration of the two reproduced protocols in the light of this decision led to the conclusion that the end-point dose in the assay with toxin B.35 would be between 0.091 and 0.083 (0.087 A.U.), and that in the assay with toxin Prg.484, it would be 0.105 A.U.

M.n.d.

The above table gives the figures found in each laboratory when taking this reaction as the end-point. The variations displayed by the m.n.d. findings are, as might be expected from the above considerations, very large for all three toxins, although they remain within the limits of 50% to 200% of the mean value.

Test Dose.

The test dose used, or, rather, the level of testing, was very different in the three laboratories. In order to compare the results, the dose of toxin neutralised by 1 A.U. was calculated in each instance on the assumption that, for any given toxin to antitoxin ratio, the degree of neutralisation is the same at all dose levels. These figures are given in column 4 of Table 2. It will be seen that the findings show better agreement than those relating to minimum necrotic doses. Nevertheless, the divergences are greater than is the case with the figures obtained in the intravenous assays on mice; at the same time, a close examination shows that they bear a systematic relation to the level of testing, this being such that a smaller amount of toxin requires proportionately more antitoxin for neutralisation than a larger one. Hence, the law of multiple proportions is not quite valid, but, as will be shown later, another law can be found. It can be stated, moreover, that the findings of the three laboratories in respect of the doses of toxin and antitoxin with which neutralisation is obtained conform to this law with a standard deviation of about 10%. This justifies the selection of the end-point as 5 × 5 mm. necrosis, and indicates that the intracutaneous titration of perfringens antitoxin is not "an impossible task".

3. HEMOLYTIC TITRATIONS

The instructions for the test laid down that sheep-cells should be used and that the tubes should be placed in the incubator for

2 hours and then be left to stand overnight at room temperature. The final reading was to be recorded as the degree of hæmolysis in the supernatant fluid. A totally hæmolysed sample and 1 : 2 and 1 : 4 dilutions of this were to be used for comparison, so that the degree of hæmolysis could be stated as 0, < 25%, 25%, 25-50%, etc.

The final reading was to be made after the tubes had stood overnight at room temperature, but, in addition, the laboratories C and H recorded readings after 2 hours at 37°C. This has given extra information as to the properties of the toxins. The end-point chosen was 0-25% hæmolysis. The three toxins examined display differing hæmolytic properties and it will hence be convenient to treat the results of each toxin separately (see Table 3).

Table 3.

CONSTANTS OF THE THREE TOXINS, HÆMOLYTIC

Laboratory	M.h.d.		Test dose used	Against		Against 1 A.U. calculated	M.h.d. neutralised by 1 A.U.
	2 hours at 37°C.	Over-night		2 hours at 37°C. A.U.	Over-night A.U.		
	Mgrm.	Mgrm.	Toxin B.35 Mgrm.			Mgrm.	
A		0.026	0.725		0.063	11.5	443
C	0.063	0.063	2.5	0.16	0.25		
H	0.063	0.045	2.3	0.16	0.20	11.1	176
				0.21	0.25		
				0.21	0.23	10.0	223
	0.125	0.045		0.21	0.23		
				0.20	0.24		
			Toxin Prg.484 Mgrm.				
A		0.018	0.595		0.063	9.45	525
C	2.5	1.25	40.00	< 0.5	1.2	33.3	26
H	0.31	0.16	8.3	< 0.38	0.63	13.2	83
	0.23	0.16					
			Toxin Prg.590 Mgrm.				
A		0.035	1.25		0.11	11.4	325
					0.50	10.0	310
C	0.032	0.032	5.0	0.32	0.36	13.9	433
H	0.063	0.063	1.6	0.21	0.23	7.0	223
	0.023	0.013		0.23	0.25	6.4	

*Toxin B.35.**M.h.d.*

The reading after 2 hours and overnight showed very little difference, although laboratory H in one case found a decrease from 0.125 mgrm. to 0.045 mgrm. The figures from the three laboratories are in as good agreement as could be expected, the range being 0.026 mgrm. to 0.063 mgrm.

Test Dose.

The neutral point shifts about 10-20% towards the excess antitoxin side during the interval between the reading after 2 hours at 37°C. and the final reading after 18 hours at room temperature.

The equivalent mixture of toxin and antitoxin determined from the final reading is in good concordance in the different laboratories, and the calculated amount of toxin neutralised by 1 A.U. is of the same order as found by the mouse and guinea-pig test (see also Table 4).

*Toxin Prg.484.**M.h.d.*

A most marked deviation was found between the minimum hæmolytic doses determined in the three laboratories. Indeed, the toxin seemed to be 100 times more active in Buenos Aires than in Copenhagen. It may be added that the minimum hæmolytic dose found in Frankfort was 5.0 mgrm., making an even wider variation. Another peculiar phenomenon of the toxin was found in the neutralisation experiments. In the C and H laboratories, it was found that no hæmolysis occurred after 2 hours at 37°C., but that hæmolysis took place during the period at room temperature. As remarked in the report from Hampstead, this effect cannot be compared with the "hot-cold" lysis of staphylococcus β hæmolysin. As it was not very evident with toxin alone, the effect is more probably due to dissociation of the toxin-antitoxin complex in a low temperature.

Test Dose.

The test dose selected varied considerably in the three laboratories on account of the large differences found in the minimum hæmolytic doses. The test doses 0.595 mgrm. used in laboratory A contained 525 m.h.d., while the test dose of 40 mgrm. used in Copenhagen contained only 26 m.h.d. The equivalent mixtures of toxin and antitoxin found in each laboratory were not proportional, but contrary to the circumstances found in the intracutaneous tests it seemed that higher doses of toxin required relatively larger doses of antitoxin for neutralisation. This may be due to a tendency of the toxin-antitoxin complex to dissociate on dilution.

The next protocol shows the dissociation phenomenon of toxin Prg.484 in neutralisation experiments.

Laboratory C.

Toxin Prg.484 Mgrm.	Standard serum A.U.	Reading after	
		2 hours at 37°C.	18 hours at R.T. %
40	1.6	0	0
40	1.2	0	< 25
40	1.0	0	25
40	0.8	0	25
40	0.63	0	25
40	0.50	0	25-50

Toxin Prg.590.

M.h.d.

The variations between the findings of the laboratories are of the same order as for toxin B.35. No remarkable difference was found between the first and second readings, either in experiments with toxin alone or in toxin-antitoxin experiments.

Test Dose.

The variation of the relation between equivalent toxin and anti-toxin mixtures is greater than in the experiment with B.35, and there is a tendency for higher doses to require relatively more antitoxin.

The following synopsis illustrates the difference in the hæmolytic properties of the toxins.

		Toxin B.35	Toxin Prg.484	Toxin Prg.590	
M.h.d...	{	Variation in sensitivity of cells found in different laboratories	(+)	+++	0
		Increase in lysis between first and last readings	(+)	+	0
L.h.....	{	Increase in lysis between first and last readings	+	+++	(+)
		More toxin requi- { more antitoxin res relatively .. { less antitoxin	(+)	—	—
			++	+	

A comparison of the biological properties of the three toxins is shown in Table 4.

Table 4.
CONSTANTS OF THREE TOXINS (SYNOPSIS)

Toxin	Method								Ratio $\frac{LN}{L+}$	Ratio $\frac{LH}{L+}$
	Mice i.v.		Guinea-pigs i.c.		Hæmolytic.					
	M.I.d.	L+	M.n.d.	LN.	M.h.d.		LH.			
					2 hours	Over- night	2 hours	Over- night		
B.35 ...	0.187	10.84	0.05	12.83	0.08	0.043	12.48	10.4	1.18	0.96
Prg. 484	0.185	10.14	0.032	12.27	2.5	0.018	> 80.0	9.45	1.21	0.93
					0.25	1.25		33.3		3.28
							> 21.8	13.2		1.30
Prg. 590	0.33	27.9	0.024 0.22	32.23	0.037	0.032	9.80	9.28	1.17	0.33

1. All toxins are lethal to mice and give necrosis in the guinea-pig's skin.

2. The relative amounts of lethal and necrotic substance in the three toxins is equal, LN/L+ being about 1.20. Evidence is given later that these substances seem identical.

3. The hæmolytic properties appear different. Prg.590 contains relatively more hæmolysin than lethal substance, LH/L+ being 0.33. B.35 has about the same content, the ratio of hæmolytic to lethal antigen being 0.96. Prg.484 was in one laboratory (C) found to be a very feeble hæmolysin, while in another (A), it was found to be of the same hæmolytic activity as toxin B.35.

To summarise : All toxins are lethal and necrotic, Prg.590 being " rich " in hæmolysin, B.35 a medium hæmolysin and Prg.484 a poor or medium hæmolysin.

B. Titrations of the Three Sera against the International Standard Serum.

The investigators—in accordance with the plan of work—have compared the activity of varying doses of serum against a constant dose of toxin containing 25 minimum indicating doses or more. A series of the standard serum was run simultaneously with the serum to be assayed, so that the resistance of each lot of mice, or the skin of the guinea-pig, or sample of cells was controlled.

The calculation of the titres given in the following tables was made from the dose of antitoxin giving the chosen end-point in the series of serum to be assayed and in the series of standard serum. If the actual end-point defined did not occur with the doses injected, the dose giving this end-point was calculated by interpolation between the doses causing less and more reaction than the end-point reaction.

The following tables (5 to 7) show the test dose used in each titration and the equivalent amounts of serum in c.c. or of standard serum in A.U.

The titre in A.U. per c.c. was calculated by dividing the equivalent amount of standard serum by the equivalent amount of serum under test.

1. THE ERROR OF TITRATION WITH A SINGLE TOXIN

From each group of determinations, the standard deviations of the results from all laboratories were calculated from the logarithms of the titres, and the percentage standard deviation calculated therefrom. These statistics are indicated below. The means in each case are given in Tables 5 to 7. By combining the deviations obtained for a single toxin and again combining these figures, we can obtain an estimate of the accuracy of the three methods employed.

Table 5.

TITRATIONS MICE I.V.

Toxin	Lab.	Test dose	Dose giving 50% death within three days				Titre A.U. per c.c.			
			Standard	V c.c.	VI c.c.	VII c.c.	V	VI	VII	
B.35 ...	A	Mgrm. 5.0	A.U. 0.429	0.00180	0.0035	0.00128	238	123	335	
		C 6.0	0.54	0.0027	0.0048		200	113		
	H	5.2	0.60	0.0028	0.0047		214	128		
			0.54			0.00193			280	
			0.475	0.0024	0.0042	0.00165	198	116	288	
			0.505	0.0025	0.0042	0.00210	202	120	240	
			0.505		0.0044	0.00206		115	245	
								210	119	275
				m geometric mean			7.9 %	4.7 %	14.4 %	
				σ standard deviation						
			σm standard deviation of mean			3.5 %	1.9 %	6.2 %		
Prg.484.	A	5.0	0.474	0.0025	0.0038	0.00146	190	125	325	
		C 5.5	0.57		0.0045			127		
	H	4.7	0.54			0.00157			344	
			0.53	0.0025			212			
			0.459	0.0023	0.0035	—	199	131		
			5.0	0.51	0.00265	0.0041	0.00141	192	124	362
							m	199	127	344
							σ	4.3 %	2.4 %	5.5 %
				σm	2.1 %	1.4 %	3.1 %			
Prg.590.	A	10.0	0.366	0.0020	0.00273	0.00107	183	134	354	
	C	16.0	0.60	0.0030	0.0044	0.00184	200	136	326	
	H	5.8		0.195	0.00107	0.00148	0.000615	182	132	318
							m	188	134	333
							σ	5.4 %	1.6 %	5.7 %
					σm	3.0 %	0.9 %	3.3 %		

Table 6.

GUINEA-PIGS I.C.

Toxin	Lab.	Test dose	Dose giving 5 × 5 mm. necrosis				Titre A.U. per c.c.		
			Standard A.U.	V c.c.	VI c.c.	VII c.c.	V	VI	VII
B.35 ...	A C H	Mgrm.							
		0.625	0.045	0.000165	0.000332	0.000149	273	132	302
		1.20	0.09	0.00043	0.00075	0.00033	209	120	273
		2.5	0.20	0.00011			182		
			0.20	0.000105			190		
		1.2	0.095	0.00045	0.00087		211	109	
		1.25	0.087	0.000476	0.00079		183	110	
			0.095	0.000476	0.00082	0.000385	200	116	247
		1.20	0.105			0.00035			300
			0.10			0.000405			247
				m	205	117	273		
				σ	14.9 %	8.1 %	10.4 %		
				σm	7.1 %	3.5 %	4.5 %		
Prg.484.	A C H	0.625	0.0425	0.00025	0.000332	0.000149	170	131	285
		1.10	0.085	0.00045	0.00071	0.000285	189	120	298
		2.4	0.21	0.00115			183		
			0.23	0.0012			192		
		1.2	0.095	0.00050			190		
		1.35	0.10	0.00058	0.00087	0.00032	172	115	
			0.105	0.00058			181		
			0.115		0.001005			115	
			0.10		0.00087	0.000385		115	
			0.091			0.00033			260
	0.095			0.00033			276		
				m	182	119	281		
				σ	5.0 %	5.8 %	5.2 %		
				σm	1.9 %	2.5 %	2.3 %		
Prg.590.	A	1.1	0.033	0.000135		0.000099	244		334
			0.031	0.000165	0.000249		188	125	
			0.031		0.000260			119	
			0.30			0.000084			357
			0.12	0.000525					
	C H	3.5	0.105		0.00084	0.000385	229	125	273
			0.20	0.00105	0.00163		190	123	
			0.195	0.00105		0.000625	186		312
			0.21		0.00168	0.00067		125	314
						m	206	123	317
				σ	13.5 %	2.1 %	10.5 %		
				σm	6.1 %	0.9 %	4.6 %		

Method	Percentage standard deviation			All toxins	
	Toxin B.35	Toxin Prg.484	Toxin Prg.590	Standard deviation	Limits of error (P = 0.99)
	%	%	%	%	%
Mice i.v.	9.5	4.2	4.6	7.2	83.5-120
Guinea-pigs i.c.	12.0	5.3	10.1	9.4	79.5-126
Hæmolytic ..	7.9	12.2	15.4	12.6	73.0-136

The estimates of the limits of error of the three methods can only be regarded as very rough. There is evidence that, for example, toxin B.35 gives less accurate results in the mouse and guinea-pig methods than toxin Prg.484. This supports the immediate impression of the investigators and may be due to a larger content of non-specific substances in toxin B.35.

As a whole, the standard deviations are greater than those found in titrations of other types of antitoxin—*e.g.*, tetanus (limits of error of titration with one toxin 87-117%)¹ or staphylococcus α antitoxin (limits of error for hæmolytic assay 86-114% ; for mice i.v. 92-108%).²

This may be explained by the fact that perfringens toxins ordinarily contain few indicating doses per test dose in comparison with, for example, tetanus toxin, which may contain up to 2,000 m.l.d. per test dose L + /5.

2. THE DEVIATION OF THE RESULTS OBTAINED WITH DIFFERENT TOXINS

Having found the range of deviations between the results obtained with the single toxins, we are able to judge whether the results obtained with different toxins can be regarded as significantly different.

First, the results of each method are computed separately. The mean result of titrations with all toxins is calculated, and the deviations of the means obtained with each toxin are squared, multiplied

¹ Bull. Health Org., 1938, 7, 728.

² British Pharmacopœia Commission. Reports of Subcommittees 10, Aug. 1936, pages 15-16.

in each case by the number of titrations performed with the toxin concerned—and the products are summed. The square root of this sum divided by the square root of 2 (the number of toxins minus 1) is the weighted estimate of the deviations of the titrations obtained with various toxins. This figure should be compared with the standard deviations for titrations with a single toxin by means of the z-test of R. A. FISHER to judge whether the deviations obtained with the three toxins are significantly larger than that allowed by the error of the test.

A. *Mouse Test.*

		Serum V Toxin B.35	Serum VI Toxin Prg. 484	Serum VII Toxin Prg. 590
Standard deviation of means obtained with three toxins. }	Log.	0.0467	0.0545	0.1074
	%	11.4	13.4	28.1
Standard deviation for assays with one toxin }	Log.	0.0305	0.0305	0.0305
	%	7.2	7.2	7.2
Deviations with several toxins .. }		Not significant	Not significant	Significant

From this it is evident that the results obtained with various toxins deviate somewhat more than those obtained with single toxins for serum VII sufficiently to render the results with the three toxins significantly different.

The error of the mouse assay of perfringens sera with several toxins therefore consists of :

1. The error of assay with a single toxin.
2. Deviations due to (non-specific) variations in toxin.

The correct indication of the limits of error of the test must therefore include this variation of the toxins. Our result gives the following estimate.

Titration with Several Toxins. Mice i.v.

Standard deviation log.	0.0422
Percentage	10.2
Limits of error (P = 0.99)	78-128.5%

It has been emphasised by R. PRIGGE that a varying ratio of hæmolysin to lethal toxin will increase the deviation of the mouse

tests when several toxins are used. Our results—as presented in Table 5—give no support to this view. Toxins Prg.484 and Prg.590, which have quite different proportions of hæmolysin, give results by the mouse method which are closer to each other than to those obtained by toxin B.35, the hæmolysin ratio of which lies between that of the two other toxins.

B. *Intracutaneous Assays.*

The test for significance of deviations among the mean results obtained with the three toxins has been repeated in the same manner as for the mouse assay.

		Serum V Toxin B.35	Serum VI Toxin Prg.484	Serum VII Toxin Prg.590
Standard deviation of means obtained with three toxins. } Log.		0.0774	0.0252	0.0767
	%	19.5	5.9	19.3
Standard deviation for assays with one toxin } Log.		0.0390	0.0390	0.0390
	%	9.4	9.4	9.4
Deviations of means }		Not significant	Not significant	Not significant

The deviations between the means are greater than those determined with one toxin, though these differences are not significant. The error of the intracutaneous test estimated by the combination of results is as follows :

Titration with Several Toxins. Guinea-pigs i.c.

Standard deviation log	0.0436
Percentage	10.5
Limits of error (P = 0.99)	77-129.5%

C. *The Hæmolytic Assays.*

The analysis of the biological constants of the three toxins led to the suspicion that the hæmolysin fractions of the three toxins differed quantitatively *inter se* in their biological effects. The titration of the three sera against the standard serum gives information whether these differences are due to hæmolysins of different antigenicity.

Table 7.
HÆMOLYTIC ASSAYS

Toxin	Lab.	Test dose	Dose giving 0-25% hæmolysis after 2 hours at 37°C. + 18 hours at R.T.				Titre A.U. per c.c.		
			Standard A.U.	V c.c.	VI c.c.	VII c.c.	V	VI	VII
B.35	A	0.725	0.063	0.00028	0.00048	0.000208	225	131	303
	C	2.5	0.25	0.0011			227		
			0.20		0.0018	0.00071		111	352
	H	2.3	0.242		0.0019	0.00080		128	302
			0.231	0.00109			213		
			0.256	0.00127			202		
					mean	216	123	318	
					σ	5.5 %	9.4 %	9.3 %	
Prg.484	A	0.595	0.063	0.00032	0.00039	0.000163	199	161	386
	C	40.00	1.2	0.005	0.0105	0.0033	240	114	368
	H	8.3	0.63	0.0029	0.0049	0.00164	218	138	378
						mean	218	136	377
						σ	9.8 %	18.9 %	2.4 %
Prg.590	A	1.25	0.12	0.000468	0.000208	0.000125	266	577	959
	C	5.0	0.36	0.0016		0.00047	225	800	766
			0.50		0.00063				
	H	1.6	0.231	0.00089	0.00032	0.000216	258	728	1070
			0.253	0.00095	0.00032	0.000216	265	796	1170
						mean	253	720	978
					σ	8.3 %	16.5 %	20.1 %	

Table 7 shows that the means of the results obtained with toxins Prg.484 and B.35 are quite close, while those derived from experiments with toxin Prg.590 deviate considerably from the former ; for sera VI and VII, the titre is 3 to 4 times that obtained by the first two toxins.

The test for significance of deviation between the results with toxins B.35 and Prg.484 showed that there is no significant deviation in the results obtained with these toxins. As mentioned before, the behaviour of the toxins is different, toxin Prg.484 showing a late hæmolysis at room temperature in neutralisation experiments.

The antigen in the two toxins is thus probably the same, but the " avidity " or ability to combine with antitoxin is different.

The hæmolytic assay with toxin Prg.590, however, gave divergent results, the significance of which for sera VI and VII needs no statistical testing.

The mean titre of serum V has a somewhat higher value than that obtained with the other toxins, although not significantly different.

There is no doubt that the hæmolysin in this toxin must be regarded as a different antigen from those of toxins B.35 and Prg.484.

As stated above, a preliminary test of the three sera with a hæmolytic toxin (Prg.377) gave the following results :

Titre determined with Toxin Prg.377

Serum V	200
Serum VI	450
Serum VII	640

The values are fairly close to those found with toxin Prg.590, thus supporting the assumption of the existence of two hæmolysins of different antigenicity.

C. The Multiplicity of the Toxins in Perfringens Filtrates.

In the investigation, three biological properties of the perfringens filtrate were examined—its lethal effect on mice, its skin necrotising effect on guinea-pigs and its hæmolytic effect on sheep cells. For the sake of simplicity, a “lethal factor”, a “necrotisin” and a “hæmolytic” factor have been mentioned, but this does not mean that different biological effects may not be caused by one toxic entity, or that the same effect may not be caused by different partial toxins.

The results obtained in assaying the three sera intracutaneously in guinea-pigs and intravenously in mice were concordant, and the assumption that the same entity causes the two different effects is quite reasonable.

The standard deviations of mouse and guinea-pig results taken together are as follows :

STANDARD DEVIATIONS

Mouse and Guinea-pig Results together.

Toxin	Serum V	Serum VI	Serum VII	All sera	
	%	%	%		
B.35	12.3	6.2	11.8		
Prg.484	6.5	5.4	12.2		
Prg.590	11.7	4.7	8.9		
All toxins	10.9	6.1	13.1	Standard deviation 10.4 %	Limits of error 77.5-129 %

The differences obtained by the two methods do not, accordingly, exceed the limits of error estimated for the guinea-pig method (77-129.5%).

If the lethal and necrotic effects are caused by different substances, the ratio of the one to the other in the three toxins must be by chance exactly the same.

Another method of computation, however, would more directly give evidence that the substances are identical.

If the logarithms of the doses of serum and toxin giving the end-point—the equivalent toxin and antitoxin mixtures—are plotted against each other for each toxin and serum, the values obtained by mouse assays as well as by guinea-pig assays fit the same straight line (see diagram on following page).

The experiments were performed with a sufficiently wide range of doses to confirm this for all toxins and sera. The fact that the doses of antitoxin and toxin found to be equivalent by the two different methods conform to the same law strongly suggests the identity of the lethal and necrotic factor in the three toxins concerned.

The law of the equivalent mixtures of antitoxin and toxin is given by the equation

$$\begin{aligned} \log S &= \alpha \log Tx + K \\ \text{or} \quad S &= K' \cdot Tx^\alpha \end{aligned}$$

This law is not identical with Ehrlich's law of multiple proportions, which assumes the exponent $\alpha = 1.00$. In this case, α varies from 1.075 to 1.165. Statistical analyses show that : (1) there is no significant change in the value of α when different sera or toxins are used ; (2) the mean of all values of α (1.125) is significantly different from 1.00.

The equation can therefore be written as :

$$S = K' \cdot Tx^{1.125}$$

The standard deviation of all 107 observations concerning this law has been determined as :

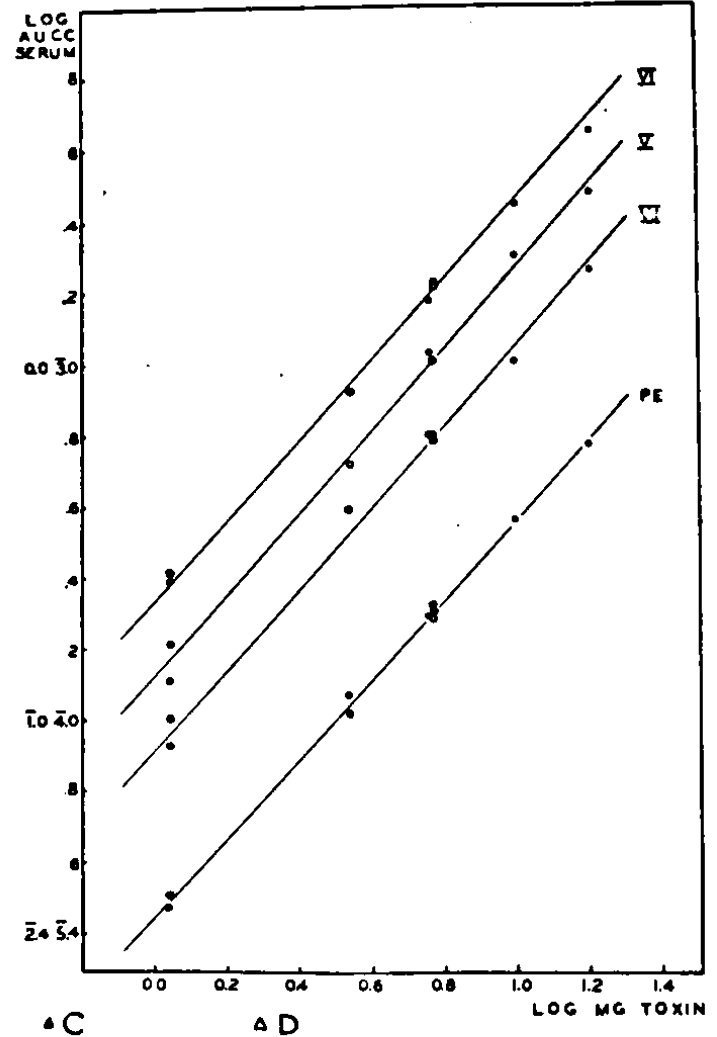
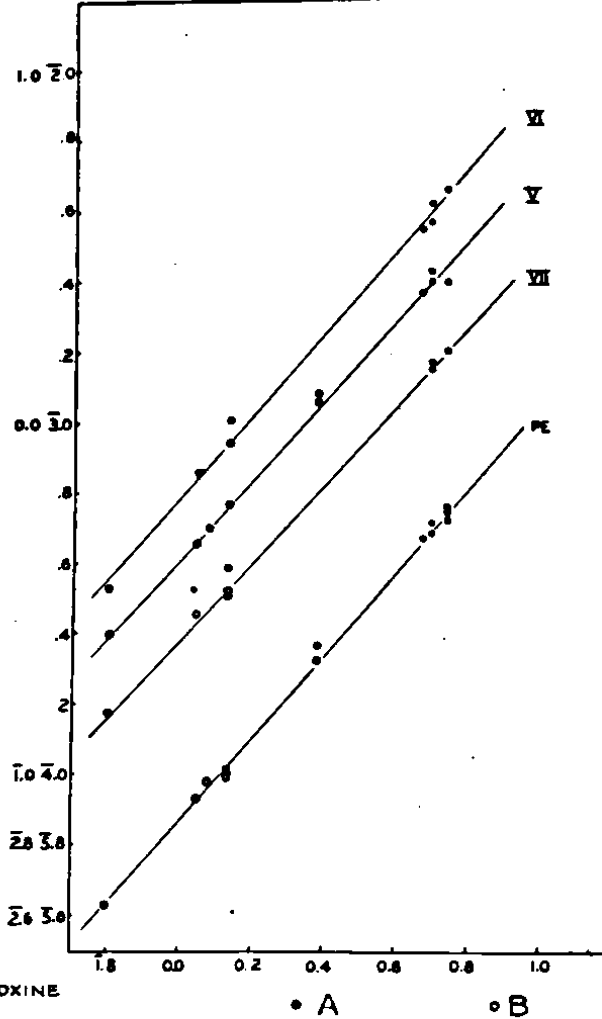
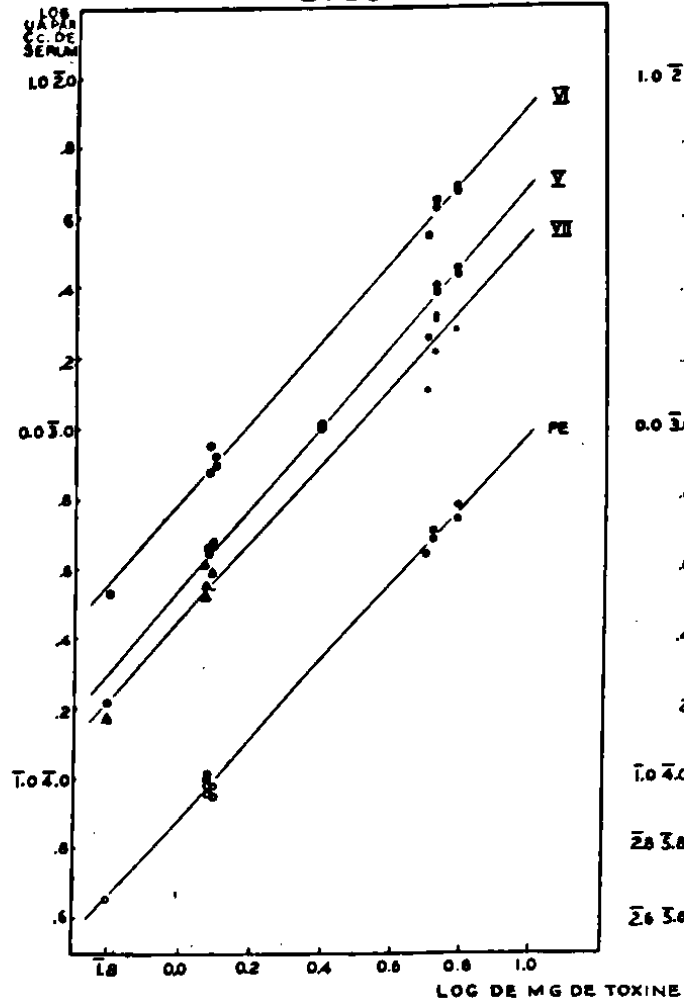
$$\begin{aligned} &0.0438 \text{ (log.)} \\ &\text{or } 10.6\% \end{aligned}$$

EQUIVALENT MIXTURES OF PERFRINGENS TOXIN AND ANTITOXIN

TOXINE - TOXIN
P.R.G. 484

P.R.G. 590

B. 35



- A. I.v. in mice. Antitoxin V. 50% mortality on the 3rd day.
- B. I.c. in guinea-pigs. Antitoxin V. 5 × 5 mm. necrosis.
- C. I.v. in mice. Antitoxin VII. 50% mortality on the 3rd day.
- D. I.c. in guinea-pigs. Antitoxin VII. 5 × 5 mm. necrosis.

The limits of error in the determination of the end-point (the equivalent mixtures of toxin and antitoxin) are accordingly :

73.5—136%

for mouse and guinea-pig test together.

THE EQUIVALENT CURVES OF THE HÆMOLYSINS

The equivalent mixtures of toxin and antitoxin determined by the hæmolytic method have been plotted against each other.

The curves are more irregular than those provided from titrations in mice and guinea-pigs.

The few observations do not allow of any conclusions. None of the slopes of the curves differ significantly from 1.00 or 1.125 or from each other.

CONCLUSIONS

In the toxins examined, we were able to distinguish different antigens.

(1) A partial toxin causing the death of mice and necrosis of the skin of guinea-pigs. This substance is almost certainly the same as Prigge's ζ toxin.

(2) A hæmolysin in toxin Prg.590 different in antigenicity from

(3) Another hæmolysin (B.35 and Prg.484).

It may be debated whether the hæmolysin of B.55 is identical with the ζ toxin. In favour of this view is the fact that the ratio $LH/L +$ was about 1.0 and that the sera had the same relative potency when assayed by the hæmolytic and the *in vivo* tests. Opposed to this view is the observation of PRIGGE that lethal toxins may be isolated from hæmolysin by fractional salting out, and the experiments of Sarah STEWARD and Marion CLAMPIT,¹ who were able to isolate the lethal from the hæmolytic toxins by filtration through graduated membranes.

¹ Bull. Health Org., 1938, 7, 802.

But the fact that both Prg.484 and B.35 give the same titre to the three sera and that these values are identical with those found by the *in vivo* test leads one to the conclusion that the ζ toxin is hæmolytic, although only to a small degree. The constitution of the two toxins can be interpreted as :

Prg.484 is an almost pure ζ toxin. B.35 is largely composed of ζ toxin ; it contains also the hæmolytic factor of Prg.590, but in insufficient quantity to affect the results of hæmolytic tests.

An additional experiment performed in Copenhagen gives further evidence in favour of the last hypothesis : the sera VI and VII were tested hæmolytically with a mixture of 3 parts of Prg.484 to 1 part of Prg.590. The result presented in Table 8 was that, according to the readings after 2 hours at 37° C., the titres of the two sera agreed with those found with Prg.590 in previous experiments ; read after 18 hours at room temperature, the titre agreed with that obtained with Prg.484 or in the *in vivo* test.

We have thus artificially made a toxin of the nature of B.35 : more hæmolytic than Prg.484, but giving the same titre as Prg.484 under certain conditions.¹

The ζ toxin should thus be characterised as being :

- (1) Lethal for mice ;
- (2) Necrotic for guinea-pigs' skin ;
- (3) Weakly hæmolytic for sheep cells.

The hæmolytic factor of Prg.590, probably the α -lysin of PRIGGE, may be lethal too, but it could not be shown in the results of the mouse tests.

¹ As additional evidence of the complexity of toxin B.35, a test was performed by Miss LLEWELLYN SMITH, in May 1939, on a serum of a low $\frac{\text{anti-hæmolysin}}{\text{anti-}\zeta}$ content. Tested by the hæmolytic method, this serum (G.G.C.3089, Burroughs Wellcome) was found to have

With toxin Prg.484	460	A.U. per c.c.
• • Prg.590	60	• •
• • B. 35	290	• •

Thus the complexity of B.35 can be detected by a serum which contains a considerably lower ratio of anti-hæmolysin (Prigge's α) to ζ antibody than the standard of reference.

Table 8.

EVALUATION OF SERA VI AND VII WITH A MIXTURE OF TOXINS PRG.484 AND PRG.590

Toxin 3 c.c. Prg.484 (1 c.c. = 100 mgm.) + 1 c.c. Prg.590 (1 c.c. = 100 mgm.)	Standard serum (0.2 + 3.8) 1 c.c. = 1 A.U.	Reading after		First reading	Second reading	
		2 hours at 37°C.	18 hours at R.T.			
0.10 c.c. in each tube = 30 mgm. Prg.484 + 10 mgm. Prg.590	A. U.					
	0.10	50-100	100			
	0.16	25-50	50-100			
	0.25	< 12	12			
	0.32	0	< 12			
	0.50	0	0			
	0.63	0	0			
	0.80	0	0			
	Serum VI c.c.					
	0.0002	50	100			
	0.00032	25	50-100			
	0.00040	< 12	50-100	0.0004 c.c. = 0.25 A.U.	0.0032 c.c. = 0.32 A.U.	
	0.00050	0	25			
	0.00063	0	12-25			
	0.0032	0	< 12	1 c.c. = 625 A.U.	1 c.c. = 100 A.U.	
	0.0040	0	0			
	0.0050	0	0			
	0.0064	0	0			
	0.0080	0	0			
	0.010	0	0			
	Serum VII c.c.					
	0.00016	50-100	100			
	0.00025	25-50	50-100	0.00032 c.c. = 0.25 A.U.	0.00125 c.c. = 0.32 A.U.	
	0.00032	< 12	25-50			
	0.00040	0	12-25			
	0.0010	0	< 12	1 c.c. = 800 A.U.	1 c.c. = 256 A.U.	
	0.00125	0	< 12			
	0.0016	0	0			
	0.0020	0	0			
	0.0025	0	0			

The conclusion is that the mouse and guinea-pig test permits titrations of perfringens antitoxin with a standard error of 10%. But the observations of WEINBERG and GUILLAUMIE contradict this finding. In using the mouse test, these authors are able to determine the potency of a given serum as 200 A.U. with one toxin and as 575 A.U. with another.

The only reasonable explanation is that WEINBERG's toxins contain a lethal factor different in antigenicity from the ζ factor.

We do not incline to the view that a standard toxin should be placed at the disposal of all workers before further experiments have made it possible to define quantitatively and qualitatively all the partial antigens found in perfringens filtrate.

If a standard toxin is to be used, its properties must be so well defined that it is possible to reproduce it when necessary.

SUMMARY

1. Three institutes have titrated three different perfringens antitoxins against the international perfringens standard antitoxin by means of the three different toxins.

2. The comparison was performed intravenously in mice, intracutaneously in guinea-pigs and *in vitro* against sheep erythrocytes.

3. The minimum hæmolytic, lethal and necrotic doses varied considerably in the different laboratories, while the equivalent doses of toxin and antitoxin agreed with a standard deviation of 10%.

4. In the serum assays, performed intracutaneously in guinea-pigs and intravenously in mice with the three toxins, the potency readings agreed with a standard deviation of 10%.

5. The hæmolytic test showed that one of the three toxins had an antigen different from that of the other two. For the two toxins with the lowest hæmolysin content the hæmolytic test gave the same serum titres as the *in vivo* test. For the most highly hæmolytic toxin, the divergent titres produced indicated the presence in the toxin of a hæmolysin (α -lysin), different in antigenicity from the lethal and necrotic factor (ζ toxin).

6. The existence of two different antigens in perfringens toxin has thus been confirmed, but the literature gives evidence that lethal factors other than that present in the three toxins in question (ζ toxin) seem to exist.

II

COMPARISON OF TEST TOXINS FROM
VARIOUS INSTITUTES

By Johs. IPSEN, Copenhagen.

In the previous report, it was concluded that it was possible—using the mouse intravenous test or the guinea-pig intracutaneous test and assaying against perfringens toxins of apparently different composition—to obtain estimates of the potency of various perfringens antitoxins which agreed within the limits of 78-129%.

The hæmolytic test, however, gave different results with some toxins. The conclusion was that only one essential lethal factor was active in the three toxins and that this factor was identical with the necrotoxin and with one of the hæmolytic toxins, while the other hæmolytic toxin appeared antigenically different.

The investigation did not therefore confirm the findings of WEINBERG and GUILLAUMIE, who observed deviations in titre with various toxins going well beyond the limits of 78-129%. These authors only used the mouse test.

The most reasonable explanation was that the three toxins used in our experiments did not contain all the possible components of the perfringens toxin, and that WEINBERG's toxin might contain another lethal factor that was wholly absent or else present in only very small amounts in the toxins previously examined, which were produced in Frankfort and Copenhagen.

We therefore held it necessary to undertake some additional experiments with toxins and sera from the Pasteur Institute of Paris.

Professor WEINBERG very kindly placed at our disposal a toxin E₂₇ with a high content of hæmolysin and the two sera, Nos. 415 and 135, mentioned in his recent paper.¹ These reagents were used together with other toxins and sera, some of which had been tested in the previous investigation.

¹ *Bull. Health Org.*, 1938, 7, 818.

*Materials used.**Toxins :*

E ₂₇ from the Pasteur Institute	$\frac{\text{m.l.d.}}{\text{m.h.d.}} = 200$
Prg.590 from Frankfort	" = 10
B. 35 from Copenhagen	" = 4
PENX 18 from Beckenham ¹	" = 0.05

Sera :

Serum VII from the Copenhagen Institute	} from the Pasteur Institute
Serum 415	
Serum 135	
Serum 425 Vienna	

(Serum 425 was sent to us by Dr. E. SCHMID, Staatliches Serotherapeutisches Institut, Vienna. It had been bought from the Pasteur Institute with an indicated potency of 400 A.U. per c.c. The Vienna Institute found the titre to be 50 A.U. per c.c. The history of this serum illustrates the practical importance of the question dealt with here.)

METHODS USED FOR TITRATION

The sera were tested intravenously in mice, intracutaneously in guinea-pigs and by the hæmolytic method upon sheep-erythrocytes. The details of the technique were the same as described in the previous paper, but, owing to the small amounts of the various toxins available, it was necessary to test with a more widely spaced range of serum doses and to economise the number of mice per dose.

The deviations found are, however, of such a magnitude that they cannot be ascribed to the lesser accuracy of the technique.

¹ The Copenhagen Institute is greatly indebted to Mr. A. T. GLENNY, of the Wellcome Physiological Research Laboratories, Beckenham, for the generous supply of this toxin.

SYNOPSIS OF RESULTS

Titre of the Four Sera in International Units per c.c.

Toxin	Method	Test dose	Serum			
			VII	Vienna (425)	415	135
		Mgr.				
PENX 18	Hæmolytic	LH : 9.5	300	64	46	64
	I.v. Mouse	L+ : 6.0	250	80	36	50
	I.c. Guinea-pig	LN : 7.0	300	66	40	61
Prg.590	Hæmolytic	LH : 12.5	980	250	940	20
	I.v. Mouse	L+ : 30.0	333	63	25	40
	I.c. Guinea-pig	LN : 33.0	317	50	—	—
B.35	Hæmolytic 1st reading ...	LH : (12.5)	(>940)	(250)	(320)	(25)
	" 2nd reading ...	LH : 10.4	375	100	80	50
	I.v. Mouse	L+ : 10.6	275	63	36	60
	I.c. Guinea-pig	LN : 12.0	273	63	35	55
E.27	Hæmolytic	LH : 0.30	1,000	360	1,100	23
	I.v. Mouse	L+ : 2.00	720	400	500	280
	I.c. Guinea-pig	LN : 10.00	275	60	83	105

RESULTS

The above table contains a synopsis of the results expressed in antitoxin units per c.c. In the third column, the dose of toxin neutralised by 1 A.U. is indicated.

In cases where the determination of the test dose took place at levels other than 1 A.U., the dose was calculated by assuming simple proportionality between doses of toxin and antitoxin combining.

I. *Titrations with Toxin PENX 18.*

This toxin has high lethal and necrotising power, but is only feebly hæmolytic, the hæmolytic activity being more evident after the second reading (18 hours at 37° C.). The intracutaneous reactions were very clear-cut.

The test doses obtained by the three methods (LH, L+ and LN) are of the same order of magnitude, which suggests that the three biological reactions are caused by the same toxin. This hypothesis is supported by the fact that the potency estimates of the sera were the same with all three toxins.

II. *Titrations with Toxin Prg.590.*

The mouse and skin test shows that the same amount of toxin is neutralised by 1 A.U., but only one-third of this amount is neutralised by 1 A.U. in the tests on sheep cells. The 1st and 2nd readings of the hæmolysis gave the same result. Very little of the toxin was left, and only a few tests could hence be made with mice and guinea-pigs.

The mouse and guinea-pig tests gave the same result, a result equal to that recorded for toxin B.35. The hæmolytic test confirms the results obtained with toxin Prg.590 in the previous investigations, the hæmolytic titre of the sera being quite different from the *in vivo* titre, a fact which indicates that this toxin contains another antigen possessing hæmolytic activity.

III. *Titrations with Toxin B.35.*

This toxin is a little less hæmolytic than Prg.590. There was some difference in the hæmolytic test according to whether 1st and 2nd reading was chosen. By the mouse and guinea-pig methods, the potencies of the four sera were the same as when the former two toxins were used.

In the hæmolytic test, however, a peculiar phenomenon appears. With some of the sera, the 1st and 2nd readings showed a wide divergence—wider than that recorded for the standard serum. Serum 135, however, gave identical end-points at both readings. In the case of sera VII, Vienna (425) and 135, the interesting point is that the potency estimated from the first reading approaches the titre found by the hæmolytic test with Prg.590, while the second reading tallies with the results of the *in vivo* test with B.35 and Prg.590 and all tests with PENX 18.

This may be explained by the presence of both antigens in the toxin. The hæmolysin that is identical with the necrotoxin and lethal factor (ζ), predominates, however, but is slower to react than the purely hæmolytic factor (α), the latter producing the results obtained at the first reading.

IV. *Titrations with Toxin E.27.*

While the three toxins mentioned above, originating from Beckenham, Frankfort and Copenhagen, gave the same results in the animal test and differed only in the hæmolytic assays, this toxin

from the Pasteur Institute gave quite different results by all tests. The nature of toxin E.27 is shown by the numerical values of the test doses. The low LH indicates a potent hæmolyisin. The L+ is only a fifth of the LN, which is evidence of the presence, in this material, of a lethal factor other than the necrotoxin.

The titres obtained by the mouse assay confirm this assumption ; these values being quite different from those obtained by the skin or by the hæmolytic tests and quite different from results yielded by the three toxins discussed above.

The hæmolytic test gives the same result as that recorded for toxin Prg.590, which indicates the presence of the same hæmolyisin in the two test toxins.

The results of the guinea-pig tests were somewhat difficult to interpret, as the necrotic areas were small and did not increase markedly with decreasing doses of antitoxin.

The titres come close, however, to those obtained by the three toxins previously discussed, although there is some doubt whether the values of sera 415 and 135 are within the limits of error of the test.

DISCUSSION

The above-mentioned experiments afford evidence that at least three antigens may exist in perfringens toxins, and that the corresponding antitoxins are present in varying amounts in all the sera examined.

The 1st Factor.

This factor is probably the ζ toxin of PRIGGE. It is :

- (1) Necrotic to guinea-pigs' skin ;
- (2) Lethal to mice ;
- (3) Feebly hæmolytic. Neutralisation experiments show increase in hæmolysis after standing overnight at room temperature.

The 2nd Factor.

Probably identical with α -lysin of PRIGGE. Its predominant feature is its hæmolytic activity for sheep cells. There is little or no change in hæmolysis after standing at room temperature.

It is not known whether it has any lethal or necrotising activity.

The 3rd Factor may be called X.

It is lethal to mice. No evidence is available to show that it is hæmolytic, but it may possibly have necrositing properties (*cf.* skin test for S.415 and 135 with toxin E.27).

The composition of the four toxins may be represented thus :

Toxin	Origin	Factor		
		ζ	α	X
PENX 18	Beckenham	++	0	0
B.35	Copenhagen	++	(+)	0
Prg.590	Frankfort	+	++	0
E.27	Paris	+	+++	++

And the antibodies of the sera may be given as :

Serum	Origin	Anti- ζ	Anti- α	Anti-X
VII	Copenhagen	292	990	720
Vienna	Paris	65	305	400
415	Paris	43	970	500
135	Paris	62	22	280
PE ¹ Standard	Hampstead	(20)	(20)	(20)

The anti- ζ titre is calculated as the geometric mean of the results obtained :

I.c. with all toxins ;

I.v. with all toxins except E.27 ;

Hæmolysis with toxins PENX 18 and B.35 (2nd reading).

The anti- α titre is calculated from the hæmolytic titre obtained with Prg.590 and E.27.

The anti-X titre is the titre found by intravenous tests with toxin E. 27. It is possible that the anti-X titre indicated is not the "true" titre but rather a composite value made up of the "anti-X factor" and the anti- ζ factor. A striking fact which emerges from the study of WEINBERG's and GUILLAUMIE's findings is that their results cannot be separated into two groups, one representing the ζ titre and the other the X titre. They display an unsystematic dispersion

¹ The content of the three antitoxins in the standard is taken as 20 A.U.

which suggests that the test toxins contain both lethal factors and give results which depend upon the relative content of the antibodies in the serum.

The fact that there was no evidence of the presence of the X-factor in the toxins produced at Beckenham, Frankfort and Copenhagen may suggest that the X antigen is an aberration of *Cl. perfringens* only found in the strain at the laboratory of Professor WEINBERG. But the presence of abundant quantities of antibody against the X-factor in serum VII produced in Copenhagen and the international standard serum produced in England would seem to contradict this view.

The presence of the α -hæmolytic factor in the toxins would appear not to affect the standardisation and administrative control of perfringens sera, provided only *in vivo* tests are used. The X-factor, however, gives rise to peculiar difficulties. It is not possible to conclude from a single mouse test whether or not the test toxin contains the X-factor, and it seems that two toxins containing various amounts of X-toxin in relation to ζ -toxin will give quite different results.

The standardisation of perfringens sera by the mouse test can be effected independently of the test toxin, if toxins containing only ζ and α toxins are used, but toxins containing X-factor will make a standardisation by means of a standard serum impossible.

It must now be considered whether the X-factor is a commonly occurring phenomenon of which account must be taken in the production of therapeutic sera, or whether it is associated only with certain strains of *Cl. perfringens*, in which latter case standardisation against ζ toxin, as performed hitherto in most countries, is sufficient for the control and production of anti-perfringens sera.

An international enquiry into the occurrence of the X-factor in various toxins might be advisable.

SUMMARY

1. Three perfringens toxins originating from Beckenham, Frankfort and Copenhagen yielded the same titres for four anti-perfringens sera tested intravenously in mice and intracutaneously in guinea-pigs.

2. A toxin prepared by Professor WEINBERG yielded widely divergent titres for these sera when tested by the intravenous mouse method.

3. In hæmolytic assays of the sera, the titres fell into two groups, the one corresponding to those of the test mentioned under 1, the second differing from both the latter and from those of the intravenous mouse test with Weinberg's toxin.

4. Anti-perfringens sera will show the same relative potency when ζ toxins are used as test toxins in the intravenous mouse test. Further investigation of the nature of the toxins produced by Professor WEINBERG is necessary.

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III

**THE ANTIGENIC CONSTITUTION OF PERFRINGENS
TOXINS PRODUCED WITH VARIOUS STRAINS
AND MEDIA**

By

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The comparison of perfringens test toxins from various institutes (see preceding paper) has shown that a toxin produced at the Pasteur Institute clearly differed in its antigenic properties from test toxins of three other institutes, the difference being most evident in the mouse assay.

It was therefore necessary to determine whether this discrepancy could be explained by variation in the strains of *Cl. perfringens* used for the production of toxins and whether the composition of the media played any rôle in the quality of the toxin.

We decided to limit this enquiry to the examination of two strains and two different media—namely, those used in routine production at the Pasteur Institute, Paris, and at the State Serum Institute, Copenhagen.

This preliminary investigation gave results which induced the examination of other strains and media. As is shown below, the exact analysis of the antigens of perfringens toxin is elaborate and requires a large number of experimental animals (in these experiments, we used about 3,000 mice).

MATERIAL EMPLOYED

“*Souche Lechien*”.—According to Professor WEINBERG, this strain has been used for twenty-three years at the Pasteur Institute for the production of perfringens toxin. It was isolated by

WEINBERG in 1916 from a fatal case of gas gangrene. Professor WEINBERG very kindly supplied us with a subculture of this strain. His authority guarantees that it is a typical *Cl. perfringens*, type A, strain and, moreover, it was sent to Professor J. ZEISSLER, in Altona, who examined it and confirmed its purity.

Strain S.S. has been used for some years at the Copenhagen Institute for routine production. It originates from the "Sächsisches Serumwerk" and is a pure strain of *Cl. perfringens*, type A.

Antitoxins.—The perfringens antitoxins described in the preceding report were assayed; we also examined two interesting antitoxins produced at the Wellcome Physiological Research Laboratories, Beckenham. Our attention was drawn to them by Mr. A. T. GLENNY, who sent us an ample supply. Their unusual antitoxin content is shown in the following table:

Antitoxin	Origin	A.U. per c.c.	
		Anti- ζ toxin	Anti- α lysin
International Standard	Beckenham	20	(20)
"Vienna" (415)	Pasteur Institute	65	400
135	"	70	23
415	"	43	1,000
VII	Copenhagen	290	990
"Welchii" (R.5603)	Beckenham	280	0.15
"Welchii" (R.5432)	"	0.35	120

Media.—WALBUM and REYMANN's medium, as described in the *Jl. of Path. & Bact.*, 1933, 36, 469.

Bouillon V.f. (Viande-foie), described by WEINBERG and GOY (*C. R. Soc. Biol.*, 1924, 91, 148 and 1140).

We used the modification indicated in a recent paper by WEINBERG and GUILLAUMIE¹ in which pig's stomach ("*panse de porc*") is substituted by commercial pepsin for the digestion. During a visit to Professor WEINBERG's laboratory, one of us (R. D.) copied the formula at present used at the Pasteur Institute. For the peptic digestion, WEINBERG indicated 30-40 gm. of dry pepsin (titre 500). We prepared the media in the following manner:

V.f.(1).—The pepsin used was a Parke Davis preparation of titre 3,000, 5 gm. of which were added to an infusion of

¹ *Rev. d'Imm.*, 1939, 5, 5.

6 kg. of beef and 1½ kg. of ox liver. After 24 hours, the preparation was not entirely digested and formed a pulpy emulsion which it was difficult to filter. The V.f.(1) is taken to contain less peptone than ordinarily.

V.f.(2).—The amount of pepsin was increased to 10 gm. of the same preparation. This time the broth was more fluid and filtered easily.

The difference between the two preparations gave rise to variations in the quality of the toxins produced.

The main difference between WALBUM and REYMANN'S medium and the two V.f. preparations can be illustrated as follows :

Origin of peptone	Walbum & Reymann Commercial (Riedel)	Weinberg V.f. Peptic digestion of broth
Pieces of meat on bottom	+	0
Basal broth	Beef	Beef + liver

PREPARATION OF THE TOXINS

The media were inoculated with a few c.c. of a preliminary culture grown in the same medium. After 20 hours at 36°-37°C., the broth was passed through a Seitz filter and saturated with ammonium sulphate.

In some cases, we saturated only to ½ or ⅓, the proportion of 700 gm. to 1 litre being taken as full saturation.

The precipitate was collected on filter paper and dried *in vacuo*.

BIOLOGICAL ANALYSIS OF THE TOXINS

As in previous experiments, the direct and indirect toxicity of each toxin was determined by the following methods : intravenous in mice, intracutaneous in guinea-pigs and hæmolytic on sheep erythrocytes.

The result of this analysis is summarised in Table 1. The following abbreviations are used :

M.l.d. = the least dose which causes the death within 48 hours of some, but not all, of a group of mice injected intravenously.

Table 1.
ORIGIN AND CONSTANTS OF TOXINS EXAMINED

No.	Strain	Medium	Degree of saturation with ammonium sulphate	Lethal action		Hæmolytic action		Necrotic action LN Mgrm.	Ratio			Antigen-formula
				M.l.d. Mgrm.	L + Mgrm.	M.h.d. Mgrm.	LH Mgrm.		M.l.d. m.h.d.	L + m.l.d.	LN L +	
K.3 ...	S.S.	V.f.(1)	1/1	0.63	25	1.25	32	32	0.50	40	1.25	ζ
K.5 ...	"	"	1/1	0.16	6.4	5	8	6.4	0.03	40	1	ζ
K.7 ...	"	Walbum & Reymann	1/1	0.12	6.4	1.25	10	8	0.10	53	1.25	ζ
W.3 ...	Lechien	V.f.(1)	1/1	1.25	16	1.25	50	64	1	13	4	ζ η
W.5 ...	"	"	1/1	1.25	20	5	63	70	0.25	16	3.5	ζ η
W.5a ..	"	"	3/4	1.25	15	1.25	50	63	1	12	4.2	ζ η
W.5b ..	"	"	1/2	1.25	12.5	1.25	50	63	1	10	5	ζ η
W.7 ...	"	Walbum & Reymann	3/4	0.20	8	0.04	12.5	10	5	40	1.25	ζ(α)
W.1 ...	"	"	1/1	0.16	8	0.05	6.4	12.5	3.2	50	1.5	ζ α
K.1 ...	S.S.	"	1/1	0.16	11.5	0.016	8	16	10	72	1.4	ζ α
W.12 ..	Lechien	"	1/1	0.32	5	0.004	6.5	7	80	16	1.4	ζ α
W.13 ..	"	"	1/1	0.63	14	0.006	12.5	25	100	22	1.8	(ζ)α
K.10 ..	S.S.	V.f.(2)	1/1	0.50	25	0.005	4	80	100	50	3.2	(ζ)α
K.9 ...	"	"	1/1	1	18	0.005	6.4	100	200	18	5.5	(ζ)α
W.9 ..	Lechien	"	1/1	0.63	12.5	0.005	2.5	80	125	20	6.4	(ζ)α
W.11 ..	"	"	1/1	5	50	0.01	10	500	500	10	10	(ζ)α
W.10 ..	"	"	1/1	4	80	0.02	15	>400	200	20	>5	η α

We used only 2-3 mice per group and tested with doses differing one from another by 100%—*e.g.*, 0.64—0.32—0.16—0.08 mgrm.

$L + /1$ = the least dose of toxin which, mixed with 1 unit of antitoxin, causes the death of some, but not all, of a group of mice in 2 days. As a rule, we determined the dose of toxin against half an antitoxin unit ($L + /2$) and calculated the $L + /1$ value.

M.h.d. = the least dose of toxin causing a trace of hæmolysis of sheep erythrocytes (0.5 c.c. of a 5% suspension to 2 c.c. of the toxin dilution). Reading after 2 hours at 37°C. and 18 hours at room temperature.

LH/1 = the least dose of toxin causing the above hæmolytic reaction when mixed with 1 unit of antitoxin. Determined as $LH/2 \times 2$.

LN = the dose of toxin which, after mixture with 1 unit of antitoxin, causes a clear-cut yellow necrosis of about 5×5 mm. on the skin of a depilated guinea-pig. For the determination of this dose, the same mixtures of toxin-antitoxin were used as for the determination of $L + /2$ in mice. Injecting 0.1 c.c. of this mixture intracutaneously, we determined the dose of toxin causing the skin reaction when mixed with $1/10$ A.U. ($LN/10$). The LN was then taken as $LN/10 \times 10$.

As some of the toxins are very unstable in solution, they were in each case dissolved just before use.

SIGNIFICANCE OF THE ANALYSIS OF CONSTITUENTS

The examination of the constituents and biological effects of each toxin aimed at estimating the relative amounts of the various partial toxins contained in perfringens filtrate.

The ratio $\frac{\text{m.l.d.}}{\text{m.h.d.}}$ proposed by PRIGGE has been used to express the "hæmolysin" content of the toxin. It would, however, be correct to state that it indicates the ratio ζ/a , as ζ toxin also has some hæmolytic action. Pure ζ toxins are supposed to have a ratio below 1 or equal to 1.

A ratio > 1 will indicate the presence of α toxin. It cannot be expected that the ratio between α -containing toxin and pure ζ toxin can be narrowly defined, as a large error is involved in the determination of both m.l.d. and m.h.d. This arose during our enquiry, when the m.h.d. of toxin Prg.484 was determined as 0.018 mgrm. in Buenos Aires and 1.25 mgrm. in Copenhagen, while the m.l.d. was found to be almost equal in both institutes.

The ratio $\frac{LN}{L+}$ is about 1-1.25 for ζ toxins. If lethal factors other than ζ toxin are present, the ratio will increase. *Toxins with ratio > 1.8 are not suitable for the assay of ζ antitoxin by the mouse test.*

The ratio $\frac{L+}{m.l.d.}$ can also be used to indicate whether lethal toxins other than ζ toxin are present. Whereas for ζ toxins this ratio ranges between 40 and 70, other lethal factors will lower the ratio to values < 30 . The error in the determination of m.l.d. and the possible change of toxin to toxoid will, however, affect the ratio and limit its value.

As regards the ratio $\frac{LN}{LH}$, the hæmolytic and intracutaneous test doses will appear almost equal for ζ toxins. *If this ratio is > 1.25 , it shows that the amount of α toxin present is such that the hæmolytic titre of an antitoxin will be determined by its anti- α content.* If the ratios $\frac{m.l.d.}{m.h.d.}$ and $\frac{LN}{LH}$ are both considered, the α content of a toxin can readily be estimated.

RESULTS OF TITRATION OF PERFRINGENS ANTITOXIN WITH TOXINS OF DIFFERENT ANTIGEN FORMULA

By establishing the ratio of their constituents, we have been able to classify our 17 toxins according to the antigens they contain and to indicate the classes to which they belong by means of an "antigen formula" (see last column of Table 1).

After this analysis, the toxins were used for comparing the activity of various antitoxins to that of the International Standard

Table 2.
TITRATION OF PERFRINGENS ANTITOXINS WITH TOXINS OF VARIOUS CLASSES

Toxin	Antigen formula	Intravenous in mice					Titre	Hæmolytic			
		Antitoxin						Vienna	135	415	Titre
		R. 5603	VII	Vienna	135	415					
K.3 ...	ζ	280	240	50	70	50	= anti-ζ	75	100	50	= anti-ζ
K.5 ...	ζ	—	300	60	63	45		60	60	50	
K.7 ...	ζ	280	—	60	63	45		75	80	50	
W.7 ...	ζ(a)	280	—	60	63	40	= anti-ζ	130	30	63	Between anti-ζ and anti-a
W.1 ...	ζa	280	—	67	80	63		417	25	1,135	
K.1 ...	ζa	280	—	43	63	50		430	20	1,000	
W.12 ..	ζa	255	—	45	80	40	—	16	—		
W.13 ..	(ζ)a	120	—	60	55	50	Between anti-ζ and anti-a	375	18	1,000	= anti-a
K.10 ..	(ζ)a	32	800	240	40	320		—	—	—	
K.9 ...	(ζ)a	<140	600	—	—	—		—	—	—	
W.9 ...	(ζ)a	40	—	180	<40	320	= anti-ζ	428	25	1,110	= anti-ζ
W.11 ..	(ζ)a	—	—	—	<40	100		375	22	1,050	
W.3 ...	ζη	440	—	75	160	80	Between anti-ζ and anti-η	50	55	40	= anti-ζ
W.5 ...	ζη	340	—	70	80	90		—	—	—	
W.5b ..	ζη	350	—	70	120	120		—	—	—	
W.10 ..	ηa	—	—	—	100	250	Between anti-η and anti-a	428	22	1,050	= anti-a

antitoxin. The intravenous test on mice and the hæmolytic test were used. A fixed test dose was added to a series of antitoxin dilutions, differing by 25% one from another. As a rule, 10-20 lethal doses were contained in the test dose corresponding to $L + /2$, but for the toxins of type ζ, η and $(\zeta), \alpha$, 10-20 lethal doses corresponded to $L +$.

These assays showed that the potencies attributed to the antitoxins by each of our toxins varied, and that the titres found could be grouped according to the antigen-formula of the toxins as deduced from the analysis of the antigens (Table 2). We shall deal with each of these groups separately.

I. Toxins of Formula ζ .

$$\text{Criteria : } \frac{LN}{L+} 1-1.5. \quad \frac{m.l.d.}{m.h.d.} < 1. \quad \frac{LN}{LH} 0.8-1.$$

The necrotic, hæmolytic and lethal properties of these toxins are due to the same antigen. Toxins K.3, K.5 and K.7 belong to this group.

As far as the titration of antitoxins is concerned, its characteristic is that *the mouse test and the hæmolytic test give the same results*; as stated before, the same would be true of the intracutaneous assay.

II. Toxins of Formula ζ, α .

These were divided into three groups :

1. $\zeta, (\alpha)$ Toxins.

Criteria.—The same as ζ toxin, except that $\frac{m.l.d.}{m.h.d.} > 1$.

Toxin W.7 has this characteristic : in mouse assay, it yielded the same titres as the ζ toxin ; but in the hæmolytic assay, the titres were between the anti- ζ and anti- α titres. This was the only difference between this and the following group.

2. ζ, α Toxin.

$$\text{Criteria : } \frac{LN}{L+} 1-1.5. \quad \frac{LN}{LH} > 1. \quad \frac{m.l.d.}{m.h.d.} > 1 < 100.$$

To this group belong toxins W.1, K.1 and W.12. In the mouse test, they gave the same antitoxic titres as ζ toxins, while all the hæmolytic tests yielded the anti- α titre. The α content of the toxin accordingly had no lethal effect on the mouse organism.

3. (ζ), α Toxins.

$$\text{Criteria : } \frac{LN}{L+} > 1.5. \quad \frac{LN}{LH} > 1. \quad \frac{\text{m.l.d.}}{\text{m.h.d.}} \geq 100.$$

This group, which includes toxins W.13, K.10, K.9 and W.11, is of special interest, as these toxins are strongly hæmolytic. The α toxin is present in so high a proportion that it influences the mouse assay. The hæmolytic test with these toxins reveals the anti- α content of the antitoxins, but the mouse-assay titre is between the anti- ζ and anti- α titres. For example, R.5603, which has a very low content of anti- α , appears weaker than might be expected from its anti- ζ content, while serum 415, on the contrary, appears stronger than in the tests with ζ toxins on account of its high content of anti- α .

No evidence was found in the experiments described in the preceding papers to support PRIGGE's view that highly hæmolytic toxins influence the mouse assay. This is now explained by the fact that none of the toxins examined had a $\frac{\text{m.l.d.}}{\text{m.h.d.}}$ ratio exceeding 20.

We must now conclude that the α toxin is lethal, but only in large quantity.

The symptoms of intoxication and especially the speed at which these symptoms appear gives evidence of the presence in our toxins of a new lethal factor. Within a few minutes of intravenous injection with toxin-antitoxin mixtures containing only a small excess of free toxin, the animals rushed about and fell on their backs with protruding eyes. Most of them died within a quarter of an hour.

In titration with ζ toxin, death occurs less abruptly and at times varying between $\frac{1}{2}$ to 18 hours.

Instability of α Toxin in Mouse Experiments.—An experiment was made to show that the lethal fraction of α toxin is very unstable

Table 3.
INSTABILITY OF α TOXIN. (5), α TOXIN K.9

Dose per mouse		Number of mice per dose	Combining time for toxin-antitoxin mixture											
			¼ hour			1 hour			3 hours			¼ hour after the toxin had been kept in solution for 2½ hours		
Surviving			Surviving			Surviving			Surviving					
Toxin	A.U.		¼ hour	3 hours	18 hours	¼ hour	3 hours	18 hours	¼ hour	3 hours	18 hours	¼ hour	3 hours	18 hours
			after injection			after injection			after injection			after injection		
10 mgrm.	0.70	2	1	1	0	2	2	2	2	2	2	2	2	2
	0.50	2	2	2	2	2	2	2	2	2	2	2	2	2
	0.35	2	1	0	—	1	1	1	2	2	1	2	2	2
	0.25	2	1	1	1	2	1	0	2	2	0	2	2	2
	0.18	2	0	—	—	1	1	1	1	1	0	1	1	1
	0.125	2	1	0	0	0	—	—	1	0	—	0	—	—
	0.09	2	0	—	—	0	—	—	0	—	—	1	0	—

M.h.d. immediately after dissolving 0.005 mgrm.
 M.h.d. 3 hours after dissolving 0.01 mgrm.

even at 20°C., whilst M. LLEWELLYN SMITH has given evidence of the instability of its hæmolytic action.¹

Mixtures of a given dose of toxin K.9 dissolved just before the experiment and of various amounts of the International Standard antitoxin were prepared and kept at room temperature (20°C.) for $\frac{1}{2}$ hour, 1 hour and 3 hours after mixing ; groups of mice were then injected with these mixtures. Table 3 shows that the toxicity of the mixtures decreased in the course of the three hours. In order to prove that this decrease was not due to a progressive neutralisation by the antitoxin, we let the solution of toxin stand for 2 $\frac{1}{2}$ hours and then prepared mixtures with the same doses of antitoxin as before, allowing them to combine for $\frac{1}{2}$ hour before injection. The degree of toxicity was then found to be the same as that of the mixtures which had combined for 3 hours.

Finally, we determined the m.h.d. of the toxin immediately after being dissolved and after the 3 hours at 20°C. The hæmolytic action decreased by about 50%.

Three conclusions connected with the lethal action of α toxin can be drawn from Table 3 : its instability in solution, the suddenness of its action and the lack of parallelism between mortality rate and dosage of toxin. These explain the difficulty encountered in obtaining in repeated assays with the same toxin of constitution (ζ), α an identical titre for a given antitoxin. With toxin K.9 we titrated three antitoxins, the combining time being 4-6 hours at room temperature. The titres found were identical with the anti- ζ content. During this interval, the α toxin diminished to such an extent that its lethal action was no longer noticeable.

Table 4.

ABSORPTION OF THE α FACTOR IN (ζ) α TOXIN WITH ANTITOXIN R.5432

Toxin	Antitoxin	Titre		Mean titre from assays with pure toxins	
		Before α absorption	After α absorption	ζ	α
W.9	Vienna	180	60	65	400
"	415	320	40	43	1,000
"	135	< 40	63	70	23
"	R.5603	40	280	280	0.15
W.13	"	120			

¹ Private communication.

Removal of the α Factor from (ζ), α Toxins.—We titrated various antitoxins with toxins W.9 and W.13 from which the α fraction had been absorbed with antitoxin R.5432 (120 anti- α units and 0.35 anti- ζ unit). The titre was now found to be identical with the anti- ζ content (Table 4).

It is peculiar to (ζ), α toxins that toxin-antitoxin mixtures which are lethal to mice cause no necrosis or only a faint hæmorrhagic skin reaction. The removal of the α content will, however, eliminate this discrepancy between the end-points of mouse assay and skin test (Table 5).

Table 5.

Toxin K.9	International Standard	Antitoxin R.5432	Surviving mice out of 3 injected	Reaction on skin of guinea-pig
Mgrm. 12.5	A.U. 0.70	—	3	0
"	0.50	—	1	0
"	0.35	—	0	0
"	0.25	—	0	Slight hæmorrhagia.
"	0.18	—	0	" "
"	0.125	—	0	Moderate hæmorrhagia (4 mm.).
"	0.09	—	0	Necrosis (5 × 5 mm.).
"	0.70	2 anti- α units	3	0
"	0.50	"	3	0
"	0.35	"	3	0
"	0.25	"	3	0
"	0.18	"	3	0
"	0.125	"	3	Trace of necrosis.
"	0.09	"	0	Necrosis (8 × 12 mm.).

These experiments show faint dermal action of the α toxin which causes hæmorrhagia but no necrosis. The reaction is too indistinct to serve as a basis for the titration of α antitoxin.

Experiments with ζ -absorbed (ζ), α toxin showed that 1 m.l.d. of α toxin corresponds to 1,000-2,000 m.h.d.

A test dose usually consists of 10-20 lethal doses of toxin. If the ratio $\frac{\text{m.l.d.}}{\text{m.h.d.}}$ of a ζ , α toxin is > 100 , a test dose will accordingly contain a lethal quantity of α toxin. As this amounts only to 1-2 lethal doses, it is understandable that the neutralisation experiments will give very irregular results.

III. ζ, η Toxin.

Criteria : $\frac{LN}{L+}$ 1.8. $\frac{m.l.d.}{m.h.d.}$ 1. $\frac{LN}{LH}$ 1-1.25.

The lethal and necrotic actions of the toxins in this group differ to the same extent as those of the (ζ), α toxins ; but the toxins themselves differ from the (ζ), α toxins in that they contain no other hæmolysin than ζ.

Our experiments lead us to the conclusion that these toxins contain a new factor, the action of which is lethal but neither necrotic nor hæmolytic. We have designated it by the letter η.

Its presence was evident only in toxins W.3, W.5, W.5a and W.5b made by cultivating the Lechien strain in the medium V.f.(1), which contains little peptone.

The toxins W.5a and W.5b were prepared from the same filtrate as W.5, but were precipitated with ammonium sulphate at a lower degree of saturation.

The fact that the ratio $\frac{LN}{L+}$ increases with the degree of saturation may lead to the assumption that the η fraction is salted out at a lower salt concentration than the ζ toxin.

PRIGGE found a similar difference between α and ζ toxins, α being salted out at a lower concentration than ζ.

Table 6.
TITRATION WITH ζ ABSORBED ζ, η TOXINS

Toxin	Antitoxin	Before absorption	After absorption	Previously known titres	
				ζ	α
W.3	Vienna	75	225	65	400
W.5b	"	70	220		
W.3	135	160	320	70	23
W.5b	"	120	320		
W.3	415	80	250	43	1,000
W.5b	"	120	220		
W.3	R.5603	440	350	280	0.15
W.3	R.5432	<10	60	0.35	120

The titration of antitoxin with ζ, η toxin gave widely differing titres for some antitoxins in the mouse assay, while the hæmolytic

assay revealed only the anti- ζ content of the antitoxins (Table 2). For this result to be interpreted, it is necessary to know the titre of the antitoxins when determined with a pure η toxin (Table 6.) This was obtained by absorbing the ζ fraction with the International Standard antitoxin, which obviously contains less anti- η than anti- ζ .

Table 6 shows that η is an antigen which differs from ζ and from α , and that all the antitoxins examined contained appreciable amounts of antibody against it.

IV. η , α Toxin.

Toxin W.10 is a hæmolytic toxin with very weak lethal action (m.l.d. = 5 mgrm.) ; it was not ascertained whether it was pure α or whether it contained traces of η or ζ . As we could find no necrotic action, we supposed that no ζ was present, and as antitoxin 135 appeared stronger in the mouse assay than its anti- α content but weaker than its anti- η content, we suggested for toxin W.10 the antigen formula η , α .

We had no means of demonstrating directly the presence of the η factor in α -containing toxins, as all our antitoxins with high anti- α content also had a large anti- η content ; the α factor could therefore not be absorbed without removing η .

ANTIGEN FORMULA OF OTHER TOXINS

In order to make it possible to compare the results of the former investigations with those given in this report, the toxins mentioned in the previous paper can be classified according to their antigen formula, as follows :

Toxin	Origin	Antigen formula
PENX 19	Beckenham	ζ
Prg.484	Frankfort	ζ
B.35	Copenhagen	$\zeta(\alpha)$
Prg.377	Frankfort	ζ
Prg.590	Frankfort	ζ
E.27	Paris	(ζ), η , α

Toxin B.35 has the same hæmolytic activity as W.7, giving a hæmolytic titre between anti- ζ and anti- α .

Toxin E.27 gave a hæmolytic titre corresponding to anti- α . The mouse results could be explained by the presence of α in lethal doses ($\frac{\text{m.l.d.}}{\text{m.h.d.}} = 200$), were it not for serum 135, which in the mouse assay appeared more potent than its anti- ζ and anti- α content and about equal in potency to its anti- η content. The (ζ) content was evident from the necrotic property of toxin E.27.

The "X-factor"—as we provisionally called the lethal factor of toxin E.27, which differs from the ζ factor—is accordingly not an entity, but the sum of the lethal effect of η and α partial toxins. The expression X-factor should therefore be abandoned.

INFLUENCE OF STRAIN AND MEDIUM UPON THE CONSTITUTION OF TOXINS

STEWART and CLAMPIT¹ have demonstrated the rôle of certain peptones in the production of "hæmolysin"—i.e., α toxin—in perfringens filtrates. Table 2 shows that the highly hæmolytic toxins are all produced on the medium V.f.(2), which contains a considerable amount of peptone after peptic digestion.

On the other hand, the toxins obtained with the V.f.(1) medium in which the peptic digestion was not complete showed a low hæmolytic content.

The hæmolytic content was moderate or low when WALBUM and REYMANN's medium was used, particularly when inoculated with the S.S. strain.

The French strain "Lechien" showed a greater tendency to produce hæmolysin than the S.S. strain, but from our results it is hardly possible to differentiate between the rôle played by the medium and that played by the strain.

The η toxin was only produced by the Lechien strain and in medium V.f.(1). It is possible that the η factor does exist in other toxins in smaller quantities, but that its effect is concealed by that of the α lysin.

¹ *Bull. Health Org.*, 1938, 7, 802.

HOW MANY TOXINS ARE CONTAINED IN PERFRINGENS FILTRATES ?

The existence of multiple toxins in perfringens filtrates is by no means a new finding. According to a statement in WEINBERG, NATIVELLE and PRÉVOT's volume entitled " Les microbes anaérobies " (1937), the existence of at least six toxins (three hæmotoxins and three non-hæmolytic toxins) in these filtrates has been proved.

It is, however, a fact that one antigen often has several biological effects, and it would be illogical to give to each of these effects the name of a toxin.

The proposal by GLENNY and his collaborators to classify the toxins according to their antigenicity is far more logical, although in some cases not an easy matter.

In the perfringens filtrates, we have been able to demonstrate the existence of only three toxins with the following biological effects :

Toxins	Hæmolysis of sheep cells	Lethality to mice	Dermal reaction
ζ	+	+ +	Necrosis
α	+ + +	(+)	(Hæmorrhagia)
η	0	+	0

We are now able to answer the four questions put at the beginning of the enquiry (see page 798).

1. Do the perfringens antitoxins show the same activity when assayed against different toxins ?

Yes, if the toxins contain one and the same predominant antigen.

2. Does the hæmolysin content influence the assay on animals ?

Yes, when the ratio $\frac{\text{m.l.d.}}{\text{m.h.d.}}$ exceeds 100.

3. Do intravenous assays on mice give results corresponding to those obtained intracutaneously in guinea-pigs ?

Yes, when pure ζ or ζ, α toxins are used.

4. Is there any relation between the activity of a perfringens antitoxin determined *in vitro* (hæmolysis) and *in vivo* ?

Yes, but only if pure ζ toxins are used in both tests.

IV

**THE PREPARATION OF TEST TOXINS SUITABLE
FOR THE ASSAY OF GAS-GANGRENE ANTITOXINS
(PERFRINGENS)**

By

Johs. IPSEN (Copenhagen).

In October 1938, Professor M. WEINBERG made a statement before the Permanent Commission on Biological Standardisation concerning the results of his assays of perfringens antitoxins with various test toxins produced in his laboratory. After discussing the problem,¹ the Commission reached the following conclusions :

“ Taking into consideration the interesting observations brought forward by Professor WEINBERG, the Commission is of opinion that the Biological Standards Department, Copenhagen, should be requested to prepare a convenient amount of a perfringens toxin, which could be distributed to interested laboratories for the purpose of carrying out further investigations into problems relating to the determination of the potency of perfringens antitoxins.”

Prior to our Department being able to meet the request of the Commission, it was necessary to finish the comparative work on perfringens toxins already in hand at various institutes, and to carry out further experiments to increase our knowledge of the divergent nature of certain toxins.

The results of these investigations are presented in the foregoing papers, and have contributed to the solution of the problem to such an extent that we can now form an opinion as to the nature of the test toxins to be used.

¹ *Bull. Health Org.*, 1938, 7, 695-697.

The recommendation of the Commission makes no mention of the quality of the test toxins, but Professor WEINBERG, both in his papers and during the discussion, made certain proposals. The following is quoted from the conclusions of WEINBERG and GUILLAUMIE :¹

“ . . . the *standard toxin* made up of all antigens secreted by *Cl. perfringens A*. . . . may be represented either by the toxin of a single strain of *Cl. perfringens A* abundantly secreting all the antigens of this species, or by the mixture of the toxins produced by different strains”

Our knowledge of the antigenic constitution of various perfringens toxins has, however, led to another conclusion. We have been able to demonstrate that all the three separate antigens secreted by strains of *Cl. perfringens* are lethal to mice when present in sufficient amounts. The potency attributed to an antitoxin assayed with a test toxin containing all these toxic fractions in sufficient amounts will depend upon which of the corresponding antitoxins is present in the smallest relative quantity.

The drawback of using a test toxin with more than one lethal factor can be illustrated by the following analogy.

Suppose a “polyvalent” gas-gangrene antitoxin were to be tested with a complex toxin made up of the toxins of perfringens, vibriion septique and œdematiens in equal amounts. If the antitoxin contained 400 anti-perfringens, 1,000 anti-œdematiens and 20 anti-vibriion septique units, the result of the assay would be 20 “units”.

If the toxin of vibriion septique were left out of the mixture, the serum would yield a titre of 400 “units”.

Tests carried out with polyvalent toxins will not supply information on all the properties of the antitoxin assayed.

The three partial antibodies of perfringens antitoxins must be tested *separately* as follows :

1. *Anti-ζ*.—Intravenously in mice or intracutaneously in guinea-pigs with a toxin containing pure ζ or ζ and a little α.
2. *Anti-α*.—Hæmolysis test with a strong α toxin (LH < LN).
3. *Anti-η*.²—Intravenously in mice with a ζ, η toxin from which ζ has been absorbed.

¹ *Bull. Health Org.*, 1938, 7, 826.

² See above, page 845.

TO WHICH PARTIAL ANTITOXIN
DOES THE INTERNATIONAL UNIT OF PERFRINGENS
STANDARD ANTITOXIN REFER ?

The international unit was defined in 1931 as 0.266 mgrm. of the dry stable preparation of perfringens antitoxin kept in Copenhagen. The same preparation is also kept at Hampstead, from where it originated. Dilutions containing 20 of the units thus defined are prepared periodically in Copenhagen and Hampstead, and distributed respectively as the International and the British standards for perfringens antitoxin.

National standards are issued officially in other countries (*e.g.*, the United States of America, Germany and the Union of Soviet Socialist Republics). They are obtained from dry preparations of different perfringens antitoxins, but the value of the unit is identical with that of the International and British standards. This identity is based upon comparative titrations in mice.

Until R. PRIGGE proved in 1936 that the German, American and British standards showed a divergence of about 20% when hæmolytic toxins were used in the mouse assay, no evidence had been published that the unit of the national standards was not identical with that of the international.

From the findings of M. WEINBERG which are confirmed in the foregoing reports, we must now deduce that the concordance of the units of the various national standards can be achieved only if the adjustment is made with pure ζ toxins or with ζ toxins containing only a small amount of α .

Consequently, we must conclude that *the present international unit is a unit for ζ -antitoxin.*

If the standardisation of antitoxins in international units is to be carried out on a uniform basis, it is essential to use toxins containing almost exclusively ζ -toxin. The possibility of producing such toxins is outlined below.

Another question arises —namely, how can the other two partial antitoxins be expressed in international units ? The α content can be estimated by means of a strong hæmolytic toxin *in vitro* and

1/20 c.c. of the dilution of the International Standard antitoxin can be used provisionally as α unit, as in the above papers. But it must be emphasised that the various national standards — except the British, which is made from the same material as the International—cannot be used for this purpose until their α content has been defined.

For example, the German perfringens standard antitoxin contains 50 ζ units per c.c., as we have been able to confirm in our experiments. Its relative α content is, however, lower than that of the International Standard, as appears from Table 1. It contains about 18 α units and 50 ζ units, whereas a content of 20 ζ and 20 α is attributed to the International Standard.

Table 1.

COMPARATIVE TITRATION OF THE GERMAN AND INTERNATIONAL STANDARD PERFRINGENS ANTITOXINS WITH TOXIN W.9 (α TOXIN)

Toxin	International 1 : 20		German 1 : 50	
	c.c.	% Hæmolysis	c.c.	% Hæmolysis
1 mgrm.	0.61	0	1.80	0
	0.55	0	1.60	0
	0.50	0	1.40	0
	0.45	0-25	1.25	0-25
	0.40	25-50	1.10	50
	0.36	50	1.00	50-100
	0.32	50-100	0.90	100
	0.28	100	0.81	100

$$\text{Result : 1 c.c. of German Standard} = \frac{0.45 \times 50}{1.25} = 18 \alpha \text{ units.}$$

On this basis, the German standard may very well be used as a standard for the α antitoxin, if it is admitted that 1/18 c.c. of the currently issued dilution is equal to 1 provisional α unit.

Similarly, the national standards can be adapted for use as η standards if the η content of the International Standard is taken as 20 units.

IS IT NECESSARY TO STANDARDISE ALL PARTIAL PERFRINGENS ANTITOXINS ?

Our knowledge of the therapeutic and prophylactic value of perfringens antitoxins in man is still very limited and little information is available concerning its effect on experimental infections in animals. To be of value, any contribution to this question should give full information as to the composition of the antitoxin.

Some investigators may claim that only ζ -toxin is really of importance, because of its common occurrence and its strong biological effect. If so, it is indispensable to ascertain that the potency indicated really corresponds to ζ units and not to a mixture of the ζ , α and η contents.

It may perhaps not be necessary to indicate the potency of all the partial perfringens antitoxins, but it is indispensable to state clearly to which partial antitoxin the titre refers.

PREPARATION OF A ζ -TEST TOXIN

These considerations led us to decide, as a first step towards meeting the request of the Commission, to prepare a large stock of almost pure ζ toxin.

We have demonstrated (IPSEN & DAVOLI) that the use of our routine S.S. strain and of the medium and technique described by REYMANN & WALBUM yielded ζ toxins, the α content of which was so small that it did not influence the assay in mice.

This process was used for the production of 10 batches of perfringens toxins (IX-XX). Each filtrate was saturated with ammonium sulphate, the precipitate collected and redissolved in distilled water, centrifuged and the supernatant fluid reprecipitated by saturation with ammonium sulphate. For each batch, the following values were determined : m.h.d., m.l.d., L+ /2, LN /10, and LH /2. (For definitions, see pages 835 and 837.)

Three antitoxins known to have different relative contents of anti- ζ , anti- α and anti- η factors were then assayed intravenously

in mice against the International Standard antitoxin. The results of these determinations are given in Table 2.

Table 2.

ANALYSIS OF 10 BATCHES OF PERFRINGENS TOXIN PREPARED WITH S.S. STRAIN AND WALBUM AND REYMANN'S MEDIUM

Toxin	Constants of toxins						Titres in A.U. per c.c. of antitoxin		
	L + /2	LN/10	LH.2	M.l.d.	M.h.d.	M.l.d. M.h.d.	Welchii (K.5603)	415	135
	Mgrm.	Mgrm.	Mgrm.	Mgrm.	Mgrm.				
IX ¹ ...	7	1.8	7.2	0.32	0.32	1	280	44	73
X	1.6	0.4	2	0.08	0.04	2	318	45	80
XI	1.8	0.5	4	0.08	0.005	16	308	44	70
XII ...	2	0.5	3.2	0.08	0.08	1	280	49	70
XIII ...	5.5	1.25	4.4	0.32	0.04	8	280	35	56
XV ...	1.5	0.4	2.5	0.08	0.04	2	255	40	70
XVI ...	0.8	0.2	0.63	0.04	0.005	8	255	45	70
XVII ...	0.8	0.2	0.63	0.04	0.01	4	280	40	63
XVIII ...	0.4	0.1	0.5	0.02	0.008	2.5	350	45	80
XX ...	0.25	0.08	0.4	0.01	0.008	1.25	280	45	70

¹ Toxin IX was obtained from a medium which contained 10% normal horse serum, besides the reagents indicated by WALBUM and REYMANN. The presence of this horse serum unduly increased the unspecific content of the precipitated toxin and was subsequently omitted. The evident increase in the strength of the toxin per mgrm. weight is probably due to an improvement in our technique of reprecipitating the toxin.

All 10 toxins showed the characteristics of a toxin suitable for titration of perfringens ζ antitoxin—namely :

- (1) The test dose L + /2 contained 20-30 m.l.d. ;
- (2) The test dose L + /2 was not greater than 3-4 times the test dose LN/10 ;
- (3) The ratio $\frac{\text{m.l.d.}}{\text{m.h.d.}}$ did not exceed 20.

The titres of the three antitoxins determined with each of the 10 batches of toxin were concordant, the standard deviation of distribution of these titres being 10.5%.

This value corresponds exactly to that found by titration carried out at three institutes¹ with toxins of the same character as above.

¹ See IPSEN, LLEWELLYN SMITH and SORDELLI, this volume, page 818.

The standard deviation of these results—*i.e.*, 10.2%—is given in Report I.

The 10 batches of toxin were pooled, mixed carefully and grained in a ball mill. The substance was distributed in ampoules, which were placed in an exsiccator till constant weight was obtained and then sealed.

This toxin preparation is designated P.1.

The test dose against $\frac{1}{2}$ an international antitoxin unit determined intravenously on mice (L+ /2) was 2.5 mgrm.

Comparative assay of the German standard antitoxin carried out with this toxin gave the result : 1 = 50 A.U., corresponding to the indicated values.

CONCLUSION

For the assay of perfringens antitoxins by the mouse intravenous method and by the hæmolytic method, toxins with only one predominant factor must be used. The existing International Standard for perfringens antitoxin contains antibodies against the three hitherto described partial toxins, and can be used as a standard for each of them. Most of the existing national standards are established with reference to the ζ antibody and have very probably a relative content of α and η antibodies different from that of the International Standard.

A perfringens toxin (P.1) suitable for estimating the ζ antibody content in perfringens antitoxins is prepared in Copenhagen, and will be placed at the disposal of institutes wishing to compare its qualities with their existing test toxins or with toxins to be analysed before use.

A PROPOSED INTERNATIONAL STANDARD FOR GAS-GANGRENE ANTITOXIN (SORDELLI)

By

Ida A. BENGSTON (Washington) and
Johs. IPSEN (Copenhagen).

At a meeting held in October 1938, the serologist members of the Permanent Commission on Biological Standardisation considered a proposal for the establishment of an International Standard for gas-gangrene antitoxin (Sordelli) and the results obtained by the Copenhagen Institute in assaying the dried antitoxin prepared by the National Institute of Health, Washington.¹

The following conclusion was reached :

“ The Commission decides to adopt as the International Standard for gas-gangrene antitoxin (Sordelli) the dried serum prepared by the National Institute of Health at Washington, the unit of activity to be defined only when comparative assays have been carried out.

“ Provisionally, this unit might, however, be regarded as equivalent to 0.06668 milligramme of this dried serum.

“ Before the final adoption, samples of different Sordelli antitoxins should be assayed against the proposed standard by means of two or more toxins, and using the mice intravenous method proposed in Annex 3*b*.

“ Various institutes should be invited to take part in these comparative assays, the results of which should show, first, whether the unit is of the same magnitude as those of the antitoxins corresponding to the other organisms of the gas-gangrene group and, secondly, whether the assay is affected by the toxin used. ”

Acting upon this decision, the Department of Biological Standards, Copenhagen, in conjunction with the National Institute of Health, Washington, framed a plan of investigation, and asked two other

¹ *Bull. Health Org.*, 1938, 7, 698.

experts who had special experience in the production and assay of Sordelli antitoxin to participate in this research work. These experts were :

Professor A. SORDELLI, Instituto de Bacteriología, Buenos Aires ;

Dr. A. DEMNITZ, Institut für experimentelle Therapie, " Emil von Behring ", Marburg, a.d.L.

PLAN OF INVESTIGATION

The four participants were supplied with the following reagents :

A. *Antitoxins.*

1. A glycerol solution of the dry Washington standard of such strength that *1 c.c. contained 20 provisional units (P.U.)*, a provisional unit being defined as above—namely, 0.06668 mgrm. of the dried antitoxin.

2. A dilution of a dry antitoxin supplied by Professor WEINBERG. The antitoxin was produced in 1931 at the Pasteur Institute, Paris, and has since been kept in a dry condition. The dilution in saline was such that *1 c.c. contained 100 mgrm. of the dried antitoxin*. The preparation was designated W.31.

3. An antitoxin supplied by the Marburg Institute and designated B.12.

B. *Toxins.*

1. A dried toxin prepared at Washington (for details see Sarah E. STEWART and Ida A. BENGSTON, " Studies on the Standardisation of Gas-gangrene Antitoxin (Sordelli) ", *Public Health Reports*, 1939, 54, 1435).

2. A dried toxin prepared by G. C. REYMANN at Copenhagen with strain 1317 supplied by Professor Ivan C. HALL, Denver, Col. This toxin was designated SO₂.

In Copenhagen, the minimum lethal dose for mice (intravenous) was found to be about 0.002 mgrm. for both toxins.

Method to be used.

After preliminary experiments,¹ the following method was found to be the most convenient and was recommended to the investi-

¹ *Bull. Health Org.*, 1938, 7, 807.

gators. Amounts of antitoxin differing one from another by 10% should be mixed with a fixed dose of test toxin. This test dose should be determined against a defined fraction of the provisional unit.

It was left to the investigator to decide which level of titration he would use, but it was recommended not to determine the test dose against less than 1/10 provisional unit.

As the test toxin has proved very unstable in dilution, the solution should be prepared on the same day as the assays are carried out. Six mice should be injected intravenously with each mixture of toxin-antitoxin and observed for 4 days.

The reading of the 4th day should be taken as final. The investigators should record the mortality rate for each day.

In testing the unknown antitoxins, a control series with the standard antitoxin should be made, using the same batch of mice.

Purpose of the Investigation.

The potency of antitoxins B.12 and W.31 should be determined in terms of the provisional standard with both toxins; in addition, the investigators should, as far as possible, include other toxins or antitoxins in their titrations.

As the Commission raised the question of the order of magnitude of the provisional unit in comparison with the units for the other four gas-gangrene antitoxins, the reports of the investigators should indicate the potency of a number of batches of antitoxin produced at their institute.

The assays were all performed during the summer of 1939, and the results were sent to the Department of Biological Standards, Copenhagen, where the following records were worked out :

SUMMARY OF RESULTS
OF EXPERIMENTS CARRIED OUT ACCORDING TO PLAN OF INVESTIGATION

Laboratory	Toxin SO ₂			American toxin		
	Test dose	Serum	Serum	Test dose	Serum	Serum
	L+5	B.12	W.31	L+5	B.12	W.31
	Mgrm.	P.U.	P.U.	Mgrm.	P.U.	P.U.
Buenos Aires	0.33	1,435	330	0.35	1,600	360
Copenhagen	0.38	1,440	338	0.40	1,600	333
Marburg	0.41	1,600	338	0.44	1,575	300
Washington	0.34	1,558	281	0.38	1,636	295

ADDITIONAL EXPERIMENTS

Laboratory	Toxin SO ₄		American toxin		Argentine toxin received in 1928		
	Serum 468	Serum 471	Serum 468	Serum 471	Test dose L+5	Serum B.12	Serum W.31
	P.U.	P.U.	P.U.	P.U.	Mgrm.	P.U.	P.U.
Copenhagen	1,140	1,555	—	—	0.50	1,470 1,410 1,450	393 343 400
Marburg ...	1,400	1,680	1,400	1,600	—	—	—

SUMMARY OF ANALYSIS OF VARIANCE OF RESULTS

	Degrees of freedom	Standard deviation	Limits of error (P = 0.99)
Determination of test dose	20	11.5%	70%-142%
Evaluation of sera with the same toxin ..	18	8.7%	80.5%-124%
Evaluation of sera with three toxins	24	9.1%	80%-125%

DISCUSSION OF RESULTS

From the above synopsis of the values obtained by the investigators, it appears that very satisfactory agreement between the results of the four institutes was obtained.

In order to compare the variance among the results with the variance known for other antitoxins tested in a similar way, we made an elementary statistical analysis of the variance, according to the principles advocated by R. A. FISHER. We used the same procedure as in the computation of the results of the enquiry on the assay of tetanus¹ and perfringens² antitoxins. It will be seen that the standard deviation of determinations of the test dose of toxin in various laboratories was 11.5%. This percentage is about the same as that found for the titration of perfringens antitoxin, but about double that found for tetanus antitoxin. This difference is, however, compensated when the same standard antitoxin is used for comparison simultaneously with the assay of an unknown antitoxin, so that investigators are able to determine the

¹ Bull. Health Org., 1938, 7, 713.

² See above, page 797.

titre of an antitoxin with a standard error of 8.7% when using a defined toxin. The last line in the summary of the statistical results, however, indicates that the error of the titration is not significantly increased when various toxins are employed.

In this connection, we should call attention to the results obtained in the assay of tetanus antitoxin, for which the same standard deviation was found to be respectively 5.5% and 14.3%, thus indicating the dependence of the result of titration on the test toxin used.

We can accordingly summarise as follows the results of the experiments carried out with toxins from Buenos Aires, Copenhagen and Washington, and with antitoxins from Paris, Marburg and Washington : *The evaluation of Sordelli antitoxin can be made with satisfactory accuracy and the result is independent of the toxins used.*

ORDER OF MAGNITUDE OF THE UNIT

The potency of various horse sera containing Sordelli antitoxin was calculated in terms of the provisional unit :

Origin	Provisional units
U.S.A. (various factories)	{ 800
	{ 800
	{ 1,450
	{ 1,700
Germany (" Behringwerke ")	{ 1,400
	{ 1,600
	{ 1,700
	{ 2,000
Denmark (State Serum Institute) (preliminary immunisation)	{ 400
	{ 450

The number of provisional units per c.c. in these products is larger than the number of international units usually found in perfringens and histolyticus antitoxins ; for vibriion septique and œdematiens, it is not unusual for the number of international units per c.c. to be similar to the number of provisional units mentioned above.

However, to secure a larger measure of equivalence in the designation of the potency of gas-gangrene antitoxins, it may be advisable

to propose a unit larger than the provisional unit. The Washington and Copenhagen institutes have therefore agreed in recommending that *0.1334 mgrm. of the dry stable Washington preparation be defined as the international unit for gas-gangrene antitoxin (Sordelli)*. Accordingly,

1 international unit = 2 provisional units.

The stock of this dry standard antitoxin will be kept in Copenhagen and Washington and a dilution containing 20 international units per c.c. will be sent periodically to the institutes interested in this preparation.

**ANALYSIS OF THE ASSAYS CARRIED
OUT IN VARIOUS LABORATORIES ON THE
CONTRIBUTIONS OFFERED TOWARDS THE
INTERNATIONAL STANDARD PREPARATION
OF THE GONADOTROPHIC SUBSTANCE
OF URINE OF PREGNANCY**

By

C. W. EMMENS

(National Institute for Medical Research, Hampstead, London).

INTRODUCTION

The third International Conference on the Standardisation of Hormones, meeting at Geneva in August 1938 under the auspices of the Health Organisation of the League of Nations, recommended the establishment of an international standard preparation of the gonadotrophic substance from human pregnancy urine. The preparations which had been offered as contributions to the standard were in the form of dry powder, consisting either of undiluted urine extract or of such extract diluted with various amounts of lactose and sodium chloride. Samples of these preparations, labelled PU.1, 2, 3, 4, 5, 8 and 10, had been circulated to a number of laboratories in different countries, in order that their potency and suitability for inclusion in the final standard preparation could be determined on a wide basis. The Conference decided, from the data then available, to prepare the standard preparation by mixing all the contributions except PU.4, which was found by several investigators to give atypical results. Of the remainder, PU.2, 3 and 5 were to be

diluted to the activity of PU.1, before mixing, by the addition of lactose, and the whole mixture then diluted again with an equal amount of lactose. These recommendations were closely followed in the actual preparation of the standard, and full details can be obtained from the memorandum (M.40, Department of Biological Standards) which accompanies each ampoule of the standard.

It was further decided by the Conference that the international unit should be defined, subject to confirmation after practical tests by members of the Conference, as the specific gonadotrophic activity of 0.1 mg. of the standard so prepared, and that it should be used for recording the activities of all preparations of human pregnancy urine, but only of such. Details of the recommendations are contained in the report of the third International Conference on the Standardisation of Hormones.¹

The present report contains an analysis of the co-operative assays carried out on the original contributions, and is a completed version of the document MM.5 prepared for the meeting of the Conference in 1938. In addition, as agreed by the Conference, a summary is included of the results obtained by members of the Conference who took part in the confirmatory tests, together with descriptions of the methods of biological comparison used.

SOURCES OF INFORMATION

Table 1 shows the persons or laboratories providing reports on the activity of some or all of the contributions. Five of these are not included in the calculations: four, because they were received after the completion of the report; and one other, because its author did not assay PU.5, the preparation adopted in the preliminary trials as a provisional standard of activity. The reference number for each source of information is used in discussing and tabulating the results.

¹ *Bull. Health Org.*, 1938, 7, 887.

Table 1.

LIST OF PERSONS OR LABORATORIES SUPPLYING ASSAY RESULTS

Ref. No.	Assayed by
1.	DR. F. E. D'AMOUR, Denver, Colorado, U.S.A.
2.	AYERST, MCKENNA and HARRISON, Montreal.
3.	BAYER PRODUCTS LTD., London (I.G. Farbenindustrie, Elberfeld).
4.	BRITISH DRUG HOUSES, LTD., London.
5.	BOOTS PURE DRUG CO., Nottingham.
6.	Professor J. H. BURN, Oxford.
7.	Professor J. B. COLLIP, Montreal.
8.	Professor G. W. CORNER, Rochester, N.Y., U.S.A.
9.	Professor F. A. E. CREW, Edinburgh.
10.	Professor E. A. DOISY, St. Louis, U.S.A.
11.	DR. M. H. FRIEDMAN, Pennsylvania, U.S.A.
12.	Professor J. H. GADDUM, London.
13.	Professor E. GEIGER, Budapest.
14.	DR. C. HAMBURGER, Copenhagen.
15.	Professor S. E. DE JONGH, Leyden.
16.	Professor E. LAQUEUR, Amsterdam.
17.	DR. A. LOESER, Freiburg.
18.	LØVENS KEMISKE FABRIK, Copenhagen.
19.	DR. R. MORICARD, Paris.
20.	DR. W. O. NELSON, Michigan, U.S.A.
21.	NATIONAL INSTITUTE FOR MEDICAL RESEARCH, London.
22.	N. V. ORGANON, Oss (Netherlands).
23.	DR. O. RIDDLE, Cold Spring Harbor, U.S.A.
24.	SCHERING LTD., London (Schering-Kahlbaum, Berlin).
25.	Professor P. E. SMITH, New York, U.S.A.
26.	SQUIBB & SONS, New Brunswick, U.S.A.
27.	Professor E. WITSCHL, Iowa, U.S.A.
28.	DR. H. R. CATCHPOLE, New Haven, Conn., U.S.A.
29.	Professor H. H. COLE, Davis, Calif., U.S.A.
30.	DEPARTMENT OF PUBLIC HEALTH, Cape Town, Union of South Africa.
31.	Professor E. C. DODDS, London.
32.	DR. T. MARTINS, São Paulo, Brazil.

METHODS OF COMPARISON

The great majority of the assays have been carried out by subcutaneous injection into immature female rats. Three were carried out on immature male rats (1, 12 and 20), three on immature mice (4, 18 and 19), two on rabbits (8 and 11) and one on ring-doves (23). Activity has been estimated by the different investigators by observation of the following different kinds of change : (1) the resulting increase in ovarian weight, or (2) uterine weight ; (3) the proportional incidence of vaginal cornification, or (4) of vaginal opening ; (5) the formation of corpora lutea, or (6) changes in the histology

of the ovary, vagina and uterus in female rats and mice ; (7) the increase in weight of the seminal vesicles or the combined weight of the seminal vesicles and prostate gland in male rats ; (8) the increase in the weight of the testes of the ring-dove, or (9) the production of ovulation on intravenous injection into female rabbits. Full references are given in the tables.

COMPARISON OF PREPARATIONS AS RECEIVED

Tables 2 to 6 give the results of the assays by the different methods, those in Table 6 being a heterogeneous collection of methods, used with insufficient frequency for an estimate of the accuracy of any one of them to be made.

Not all preparations have been tested by each laboratory. Since PU.5 is by all tests the most active, and has also been assayed by all but one laboratory, it has been adopted in this report as a standard of reference by which to assess the comparative activity of the others. Activity has been expressed in terms of the number of mg. of each preparation necessary to equal the activity of 1 mg. of PU.5, a procedure which avoids an index of less than unity, and which facilitates tabulation and computation.

In each table, the geometric mean of the estimates is given for each preparation, all computations having been carried out logarithmically, together with the variance of the logarithms of the estimates in that table. The use of the geometric mean is to be preferred to that of the arithmetic mean in work of this type, where larger deviations can and do occur in a positive than in a negative direction.

In many instances, several comparisons are available from the data given in a single report. Such multiple comparisons have been included in the tables whenever possible, even if the author considered one particular method to be superior. Report 14, for instance, yielded four sets of data, based on ovarian weight, uterine weight, corpus luteum formation and vaginal smears in the rat. These groups of tests from one source have also been used to form estimates of the inter- and intra-laboratory variation occurring in the determination of potency (see below). The accuracy of individual estimates clearly varies greatly, when any one test method is considered, depending on the number of animals used and the

particular technique and dosage employed, but no attempt has been made to weight individual estimates in the determination of the means for each table, as sufficient information to do so is in most cases lacking. It seems from the data available that some of the discrepancy in results is due, not to random deviations from an imaginary true mean, but to differences in true relative potency when the same preparation is assayed, by similar but not identical methods, and on different stocks of animals. However, in view of the further probability, discussed below, that not all of the contributions distributed were homogeneous at the time samples were removed, it is impossible to arrive at definite conclusions.

The weighted geometric mean for each PU. preparation, and the number of estimates upon which it is based, are given in the first three columns of Table 7. These means have been calculated by weighting the mean value obtained for each preparation by each test method, inversely according to the estimated variance of that mean. Owing to the fact that estimates for all samples are not available from all sources, the tables are asymmetrical, but fortunately not to such a degree as to invalidate the use of variances for complete tables (test methods) in determining the weights to be assigned. It has been found that both test methods and different PU. samples vary among themselves in the accuracy of the estimates obtained, but, in view of the large differences between methods, the relative contribution of each sample to different tables is sufficiently uniform to allow a reasonably accurate estimate of the variance,

Table 2.

THE NUMBER OF MG. OF EACH PU. PREPARATION REQUIRED TO EQUAL 1 MG. OF PU.5 WHEN TESTED BY INCREASE IN OVARIAN WEIGHT							
Ref.	Animal	PU.1	PU.2	PU.3	PU.4	PU.8	PU.10
6	Rat	—	3.0	9.0	60	17	60
9	„	3.3	2.8	5.0	30	10	20
12	„	21.0	3.0	9.0	38	—	—
14	„	8.0	3.0	12.0	36	8	21
20	„	—	3.7	8.3	83	33	—
21	„	6.7	2.5	6.7	10	10	20
25	„	13.0	2.7	5.9	35	9	—
Geometric mean .		8.65	2.94	7.69	35.5	12.6	26.6
Logarithmic variance		0.10650	0.00317	0.01650	0.08267	0.05440	0.05567

Table 3.

THE NUMBER OF MG. OF EACH PU. PREPARATION
REQUIRED TO EQUAL 1 MG. OF PU.5 WHEN TESTED BY THE VAGINAL
CORNIFICATION TECHNIQUE

Ref.	Animal	PU.1	PU.2	PU.3	PU.4	PU.8	PU.10
2	Rat	9.8	2.8	7.7	39	20	12
3	"	—	2.3	6.3	25	—	35
5	"	7.9	3.0	8.6	47	20	19
7	"	11.0	2.5	7.9	34	16	40
9	"	6.7	4.0	7.7	80	9	18
12	"	—	3.0	9.0	78	—	—
13	"	9.3	4.0	10.0	(>20)	13	23
14	"	7.6	3.3	10.0	35	—	32
15	"	—	3.0	9.0	36	—	—
16	"	13.0	3.0	9.0	30	—	27
17	"	—	3.0	7.3	8	—	—
22	"	—	3.3	13.0	46	—	—
24	"	23.0	3.0	9.0	10	11	14
Geometric mean .		10.24	3.06	8.68	32.4	14.2	22.7
Logarithmic variance		0.02843	0.00458	0.00583	0.09118	0.02020	0.03238

Table 4.

THE NUMBER OF MG. OF EACH PU. PREPARATION
REQUIRED TO EQUAL 1 MG. OF PU.5 WHEN TESTED BY INCREASE
IN UTERINE WEIGHT

Ref.	Animal	PU.1	PU.2	PU.3	PU.4	PU.8	PU.10
3	Rat	—	3.2	14.9	108	—	28
9	"	10.	3.3	8.0	80	8.0	14
10	"	—	5.1	12.1	38	18.0	—
12	"	21	3.5	10.0	44	—	—
14	"	6.1	3.0	9.0	30	8.4	25
18	Mouse	—	1.0	1.5	3	8.0	—
22	Rat	—	2.6	10.0	54	—	—
Geometric mean .		10.86	2.84	7.91	35.4	9.92	21.4
Logarithmic variance		0.07300	0.04833	0.10917	0.25800	0.02967	0.02600

Table 5.

THE NUMBER OF MG. OF EACH PU. PREPARATION
REQUIRED TO EQUAL 1 MG. OF PU.5 WHEN TESTED BY
THE FORMATION OF CORPORA LUTEA

Ref.	Animal	PU.1	PU.2	PU.3	PU.4	PU.8	PU.10
3	Rat	—	5.3	6.7	20	—	37
4	Mouse	6.0	3.0	—	62	8.0	28
14	Rat	8.0	3.0	9.0	28	—	30
16	„	4.5	3.0	13.0	35	—	—
18	Mouse	6.3	2.0	7.0	13	9.5	22
19	Rat	—	1.7	10.0	33	3.3	—
19	Mouse	—	6.4	9.6	80	8.0	—
20	Rat	—	4.7	12.8	83	33.0	—
25	„	12.7	5.1	14.0	—	7.6	—
26	„	17.3	6.6	16.2	102	—	34
Geometric mean .		8.18	3.71	10.48	41.3	8.92	29.7
Logarithmic variance		0.04800	0.04300	0.01775	0.09438	0.10340	0.00775

Table 6.

THE NUMBER OF MG. OF EACH PU. PREPARATION REQUIRED
TO EQUAL 1 MG. OF PU.5 WHEN TESTED BY VARIOUS OTHER METHODS

Method	Ref.	Animal	PU.1	PU.2	PU.3	PU.4	PU.8	PU.10
Vaginal opening ..	10 ..	Rat	—	1.5	12.0	42	20	—
	19 ..	„	—	3.3	—	33	3.3	—
	25 ..	„	—	2.0	7.0	(> 92)	5	—
Histology of ovary, uterus and vagina .	27 ..	„	—	5.6	14.0	63	—	—
Prostate and seminal vesicle weight	12 ..	„	19.0	3.0	8.0	15	15	30
	20 ..	„	—	4.4	20.0	80	32	—
Weight of seminal vesicles	1 ..	„	5.2	2.2	6.2	20	15	25
Increase in testis weight	23 ..	Ring-dove	3.0	5.0	4.0	138	27	—
Ovulation	8 ..	Rabbit	1.6	1.2	1.1	4.2	3.4	5.5
	11 ..	„	—	—	5.2	25	18	—
Geometric mean			4.67	2.77	6.68	31.5	11.6	16.0
Logarithmic variance			0.21300	0.05513	0.13475	0.20000	0.14500	0.16400

relative to that of the others, to be calculated directly for each method. The weights assigned to the methods listed in Tables 2 to 6 respectively were 2.955, 4.441, 1.346, 2.673 and 1.000, Table 6 having the greatest variance, as would be expected from its heterogeneity. Each mean was then further weighted according to the number of estimates contributing to it.

COMPARISON IN TERMS
OF ACTUAL URINE EXTRACT PRESENT

Several of the preparations contained diluents, the activity of the original undiluted extract differing widely from that of the preparation as tested. The number of mg. of the undiluted extracts required to equal the activity of 1 mg. of PU.5 (which was not diluted) is also given in Table 7, together with the percentage of diluents in the samples as circulated. The limits of error within which 99% of the estimates fall ($\pm 2.576 \sigma$) and the corresponding limits of error for the mean values assigned to samples are appended in Table 7, and were calculated directly from the distribution of the whole of the estimates for each preparation. These limits are greater than those that would be found had all the assays been carried out by some of the individual test methods, since each assay by the vaginal smear technique, for instance, has given on the average more than three times the information of an assay by the uterine weight method. Moreover, the exclusion, in particular, of the information conveyed by Table 6, where the results of miscellaneous methods are collected, would

Table 7.

WEIGHTED GEOMETRIC MEANS FOR THE NUMBER OF MG. OF EACH PU. PREPARATION REQUIRED TO EQUAL 1 MG. OF PU.5, ALL TESTS COMBINED, AND THE CORRESPONDING VALUES FOR THE UNDILUTED EXTRACTS FROM WHICH THE PREPARATIONS WERE COMPOUNDED.

PU. No.	Number of estimates	Weighted mean (mg. \equiv 1 mg. PU.5)	% diluent	Number of mg. of actual urine extract \equiv 1 mg. of PU.5	Limits of error (P = 0.99) %	Limits of error of individual tests (P = 0.99) %
1	26	9.080	99.1	0.08172	72.0-139.0	18.7-535.2
2	46	3.125	0	3.125	86.2-116.0	36.6-273.2
3	45	8.598	99.4	0.05159	82.0-122.0	26.3-379.9
4	44	34.67	95.5	1.560	72.6-137.7	12.0-833.7
8	31	11.91	90.25	1.161	74.6-134.2	19.5-513.6
10	24	24.04	98.75	0.3005	78.2-127.8	29.2-342.6

actually result in a decreased error of estimation of the means. For the purpose of the Conference, however, a highly accurate estimation of the potency of the contributions was less important than the knowledge that, when tested by a variety of methods, the relative potencies remained approximately constant, and that the estimates upon which the compounding of the standard depends had a wide inductive basis. Owing to the fact that small samples of each preparation were circulated, not all at the same time, to those taking part in these co-operative assays, it was not possible, in many cases, to establish dose response curves or to make simultaneous comparisons of all extracts. This has doubtless lowered the accuracy with which comparisons have been made.

THE RELATIVE ACCURACY WITH WHICH THE PU. PREPARATIONS HAVE BEEN ASSAYABLE

The limits of error for the individual estimates of the potency of each PU. preparation, given in Table 7, have already served to indicate that the substances in question are not assayable with equal accuracy. These limits were determined from the data given in Table 8, in which the variances of the preparations are compared, using combined data from all tests. The ratio of the variance of estimates for each preparation to that of each of the others—the “variance ratio”—shows that several of the preparations exhibit a significantly greater variance than others. The significance was determined by reference to FISHER and YATES' (1938) tables for the variance ratio. The variance for PU.4 is thus significantly greater than those for PU.2, 3 and 10 ($P > 0.99$); and that for PU.2 significantly smaller than all but that for PU.10. The ratio of the variance of estimates of the potency of PU.3 to that for PU.2 is 1.77 ($P = 0.95$), and may be accepted as statistically significant. PU.1, 4 and 8 were therefore subject to greater errors of assay, while PU.2 and 10 were subject to smaller errors of assay, than the rest. The figures indicate that PU.2 has actually been assayable with over four times the accuracy obtainable with PU.4, the variance for PU.2 being less than $\frac{1}{4}$ of that for PU.4. Owing to the general distribution of the various PU. preparations among the different test methods, these estimates have been little affected by the degree of accuracy

Table 8.

VARIANCE RATIOS FOR PU. PREPARATIONS, ALL TESTS COMBINED

PU. No.	4	1	8	3	10	2
Mean square.....	0.12788	0.08000	0.07610	0.05068	0.04309	0.02871
Degrees of freedom	43	25	30	44	23	45
PU. with greater variance	4	1.60	1.68	2.52 ^b	2.97 ^b	4.45 ^a
	1		1.05	1.59	1.86	2.79 ^b
	8			1.50	1.77	2.65 ^b
	3				1.18	1.77 ^a
	10					1.50

* $P > 0.999$ ^b $P > 0.990$ • $P > 0.950$

which a given test method is found to have. Table 9 shows the actual distribution, using grouped data, of the separate estimates for each PU. preparation. In the case of PU.2, 3 and 10, there is no

Table 9.

DISTRIBUTION OF THE LOGARITHMS OF ESTIMATES OF THE NUMBER OF MG. OF EACH PU. PREPARATION REQUIRED TO EQUAL 1 MG. OF PU.5

Log. potency	PU.1	PU.2	PU.3	PU.4	PU.8	PU.10
2.1				1		
2.0				2		
1.9				6		
1.8				2		
1.7				3		1
1.6				4		1
1.5				11	3	4
1.4				4	1	5
1.3	3		1	4	3	7
1.2	2		1		4	2
1.1	3		6	2	3	2
1.0	2		8	2	3	1
0.9	4		13	1	9	
0.8	4	2	8		1	
0.7	4	4	4			1
0.6	1	5	2	1	1	
0.5	1	7			3	
0.4	1	18		1		
0.3		6				
0.2	1	1				
0.1		1	1			
0.0		2	1			

reason to suspect a departure from the normal type of distribution, but that of PU.4 is shown by tests using the statistics g_1 and g_2 (FISHER, 1938) to be definitely abnormal. The doubtful examples PU.1 and 8 have not been investigated statistically. The use of a standard error in these cases gives therefore only an approximate indication of the accuracy of the mean estimates.

THE RELATIVE ACCURACY OF DIFFERENT TEST METHODS

Table 10 gives data relating to the accuracy of test methods, variances for each method being calculated in a similar manner to that for each PU. preparation in Table 8. The differences between the accuracy of test methods turn out to be of the same order as those between the accuracy of assay of different preparations, but are not due to a preponderance of assays of any one PU. preparation having been made by any particular method. *The variance ratios show that each assay by the vaginal cornification technique has contributed, on the average, over four times the information given by one of the miscellaneous assays listed in Table 6, and more than three times the information given by an assay based on uterine weight, the latter being not significantly more accurate than the miscellaneous assays. The assays using ovarian weight as a criterion are not significantly less accurate than those by the vaginal cornification technique, and are estimated to have given between two and three times the amount of information per test, as compared with either the uterine weight or the*

Table 10.

VARIANCE RATIOS FOR THE DIFFERENT METHODS,
ALL PU. ASSAYS COMBINED

Method	Miscellaneous methods (Table 6)	Uterine weight (Table 4)	Corpus luteum formation (Table 5)	Ovarian weight (Table 2)	Vaginal cornification (Table 3)	
Mean square	0.12490	0.09277	0.04709	0.04226	0.02812	
Degrees of freedom	42	30	44	35	60	
Method with greater variance :	{ Table 6 { Table 4 { Table 5 { Table 2		1.35	2.65 ^b	2.96 ^b	4.44 ^a
				1.97 ^c	2.20 ^c	3.30 ^a
					1.11	1.67 ^c
						1.50

^a $P > 0.999$ ^b $P > 0.990$ ^c $P > 0.950$

miscellaneous assays. Assay by corpus luteum formation falls centrally, giving significantly more information per test than the uterine weight ($P > 0.99$) and miscellaneous assays ($P > 0.95$), significantly less information than a vaginal cornification assay ($P > 0.95$) and apparently less than an assay by ovarian weight, although the difference is not statistically significant.

The accuracy of which any given assay or assay method is capable is naturally dependent upon the number of animals used in the test, the skill of the assayer, etc. The results under discussion have been obtained from assays of all types, using a great variety of techniques and a wide range of numbers of animals per group and of total number used, but these numbers have been distributed in an apparently random manner throughout the tests, with the exception that the miscellaneous test methods in Table 6 include some assays on rather few animals, as in the use of rabbit ovulation. The lower accuracy of assay of these miscellaneous tests, considered as a whole, has probably been thus accentuated. In the other tests, there has been no detectable bias of this kind; many of the tests using different criteria of response, but coming from the same source, have, in fact, been carried out on identical or similar groups of animals.

THE RELATIVE POTENCIES OF PU. PREPARATIONS BY DIFFERENT TEST METHODS

Turning again to Tables 2 to 6, it is clear that there is no significant difference in the relations between the potencies of the PU. preparations, as determined by the different test methods. The only detectable bias is again due to the tests in Table 6, which tend to give rather lower values than the rest, but this is not significant in any one test, and is mainly due to one entry (8) in that table. In Table 11, the variances between and within the different test methods are compared separately for each preparation, according to the algebraic identity:

$$\Sigma (y - \bar{y})^2 = \Sigma \{ n_p (\bar{y}_p - \bar{y})^2 \} + \Sigma \Sigma (y - \bar{y}_p)^2,$$

where any particular method is designated by the suffix p , the number of observations by that method by n_p , and their mean value by \bar{y}_p ; \bar{y} being the general mean for all methods (after FISHER, 1938). The left-hand side of the equation is the sum of the squares of the deviations of all values from their general mean, which may

Table 11.

INTER- AND INTRA-METHOD VARIANCES AND VARIANCE RATIOS
OF ESTIMATES OF THE POTENCY OF EACH PU. PREPARATION

PU. No.	Type of variance	Degrees of freedom	Mean square	Variance ratio	P
1	Between methods	4	0.0872	0.90	< 0.95
	Within	21	0.0787		
2	Between	4	0.0240	1.22	< 0.95
	Within	41	0.0292		
3	Between	4	0.0469	1.09	< 0.95
	Within	40	0.0511		
4	Between	4	0.0168	8.26	> 0.95
	Within	39	0.1391		
8	Between	4	0.0375	2.19	< 0.95
	Within	26	0.0820		
10	Between	4	0.0364	1.22	< 0.95
	Within	19	0.0445		

be broken up into the two parts on the right-hand side. The first term on the right-hand side represents the sum of the squares of the deviations of the means from the general mean, each multiplied by the number of values from which each mean is determined; this, divided by one less than the total number of methods, gives the variance between methods. The second term represents the sum of the squares of the deviations of each observation from the mean of the method to which it belongs; this, divided by $\sum (n_p - 1)$, gives the variance within methods.

In the case of PU.1, 2, 3 and 10, the variance within methods is approximately equal to that between methods, although it is the greater for all but PU.1. With PU.8 it is twice as great, and with PU.4 it is eight times as great as the variance between methods, only the last being statistically significant, with $P > 0.95$. This means that, with PU.4, the means for each method are significantly closer together than is to be expected from the degree of variation exhibited by the individual estimates, and that they tend to be so in the other cases. The explanation of this tendency is seen when those estimates by different test methods which were made by the same person or laboratory, using the same or similar animals, are examined (see below). These are the tests the key numbers of which occur in two

or more of the Tables 2 to 6, and represent 118 of the 216 estimates dealt with.

There is therefore complete lack of evidence that the nature of the test-object has influenced the determinations of relative activity, a result which confirms the belief that only one active substance is concerned.

VARIANCE BETWEEN AND WITHIN LABORATORIES

Those estimates referred to above, which were made from data collected by the same person or laboratory with the same stock of animals, are analysed in Table 12, which is similar in plan to Table 11, with the general mean square ($\Sigma (y - \bar{y})^2$) added in each case, for comparison with the corresponding general mean squares for the PU. preparations given in Table 8. The general variances in this sample tend to be smaller than in the complete data, although in no single case is the difference significant. This follows from the fact that we have sorted out those estimates which contribute an intra-laboratory correlation to the estimate of the variance. Thus, since the intra-laboratory variance turns out to be less than inter-laboratory variance in most cases, we have selected a more homogeneous sample of estimates.

Proceeding as before, we calculate the variance within estimates from the same source, and between their means and the general mean, separately for each preparation. In all cases, the variance between laboratories is greater than that within them, and significantly so for all but PU.2. The variance within laboratories is remarkably low, not exceeding 0.0347 (that for PU.4). In general, it is smaller than, but of the order of, the general mean square ($\Sigma (y - \bar{y})^2$) of PU. 2. There is a tendency for all of the assays in some tests to be higher or lower than the average, but this must usually be due to the fact that the assay of PU.5, used as the standard of reference, has, in that particular set of tests, given abnormally low or high results, as the case may be. This has no effect on intra-test correlations, nor can any particular significance be attached to it. With the exception of that for PU.2, the greater part of the variance of all estimates from their means turns out to be due to inter-laboratory differences, which is rather to be expected in view of the probable

Table 12.

INTER- AND INTRA-LABORATORY VARIANCES AND VARIANCE RATIOS OF ESTIMATES OF THE POTENCY OF THOSE PU. PREPARATIONS WHICH WERE ASSAYED BY MORE THAN ONE METHOD BY THE SAME LABORATORY

PU. No.	General mean square	Degrees of freedom	Type of variance	Degrees of freedom	Mean square	Variance ratio	P
1 ...	0.06000	12	{ Between laboratories ..	4	0.12125	4.13	> 0.950
			{ Within ..	8	0.02937		
2 ...	0.02626	27	{ Between ..	10	0.03000	1.25	< 0.950
			{ Within ..	17	0.02406		
3 ...	0.03912	25	{ Between ..	9	0.06344	2.53	ca. 0.950
			{ Within ..	16	0.02504		
4 ...	0.09921	24	{ Between ..	9	0.20677	5.96	> 0.990
			{ Within ..	15	0.03469		
8 ...	0.08607	15	{ Between ..	6	0.19133	39.78	> 0.999
			{ Within ..	9	0.00481		
10 ...	0.01889	9	{ Between ..	2	0.06450	10.93	> 0.990
			{ Within ..	7	0.00590		

differences between stocks of animals. However, the fact that the estimates for PU.2 do not show this phenomenon, and that the others show it in varying degree, points strongly to the conclusion that there is not necessarily a much greater variation, in estimates based on a mixture of the same and different test methods in different laboratories, than in those based on different test methods in the same laboratory. It is noteworthy, in this connection, that PU.2 is the only other undiluted extract which is being compared with the undiluted PU.5. The assayers concerned have, with the same methods and the same stocks of animals, been able to determine the potency of PU.2 relative to PU.5 with considerably greater accuracy than in some of the other cases, notably that of PU.4; but there seems no reason why their technique should yield less reliable results with some extracts than others, unless they did not receive identical samples in the first place. The intra-laboratory variances confirm the suspicion that estimates for PU.4 were not significantly more variable than those for PU.2, within any one laboratory, but that the differences found are due to increased variability between estimates coming from different laboratories. PU.8 and 10 show significantly depressed intra-laboratory variances relative to the

rest, but the samples in these cases are small (sets of assays from 7 and 3 sources respectively).

There is thus a considerable amount of evidence that those PU. preparations which were diluted with inert material were not diluted in a homogeneous manner at the time when the samples were taken. As an example, although the inter- and intra-laboratory variances for estimates of the potency of PU.2 are not significantly different, the inter-laboratory variance for PU.4 is nearly six times the intra-laboratory variance. This discrepancy is most easily accounted for as being due to differences between the samples of PU.4 which were circulated ; differences which must, on this hypothesis, have been large. It was difficult to believe that such was the case, although no other explanation is obvious, but the manufacturers of PU.4 are inclined to agree that the contribution may have been heterogeneous. PU.4 was not included in the standard, but it seems likely that some at least of the other contributions, as received, were affected by a similar defect of homogeneity, though to a smaller extent. To eliminate such inequalities, very great care was taken to ensure a thorough and accurate mixing of the final standard preparation, and the compression of the mixture into tablets, before any separation of physically different constituents could occur, should guarantee the permanent equivalence of all samples of the completed standard preparation, as now adopted and issued for international use.

VARYING AMOUNTS OF A PU. PREPARATION NEEDED FOR ASSAY BY DIFFERENT TEST METHODS

The amount of PU.5 needed to give the required response, in assaying its potency by different test methods, has been found to be very variable. However, there is no correlation between the amount of PU.5 needed and the potencies determined for the different preparations in terms of PU.5. In the ovarian weight tests, and those using the formation of corpora lutea as a criterion of activity, the effective amount of PU.5, or the amount needed to give a desired increase in weight (usually to double the ovarian weight), or to give 50% of ovaries with corpora lutea, has varied from about 3 to 50 μ g. The variation is far less dependent upon the particular level of

response used than upon the injection technique, 6 to 8 injections over a short period of time (2 to 3 days) needing the lowest amount of active substance. The vaginal smear tests show considerably less variation, all of the doses required to produce 50% of cornified smears falling between 1 and 3.5 μg . Tests by uterine weight have required between about 2 and 10 μg ., and are again relatively smaller in range than the ovarian tests. In general, the production of positive vaginal smears and of a measurable increase in uterine weight occur on much the same dosage, the latter usually needing a somewhat higher amount, but measurable changes in the ovary occur usually at a considerably higher dose level. The miscellaneous tests on Table 6 have naturally a very large range of effective doses.

THE CHOICE OF A TEST METHOD

The production of vaginal cornification in the rat is the method of testing PU. preparations which the data show to be, not only the most accurate, approached in this respect only by tests employing ovarian weight as a criterion of response, but the one which has the most predictable requirements in the way of dosage when technique is varied, and which is the most labour-saving and inexpensive. It also has the advantage that the animals need not be killed after the test, and may be used for other purposes later. On the other hand, if they are killed, the added test of uterine weight is usually available as a check to the findings by vaginal cornification. There is, however, one important drawback to the test, in that its accuracy depends on the absence of oestrogenic material from the preparation tested, which must be controlled by a parallel test on ovariectomised animals. Tests by ovarian weight or corpus luteum formation are independent of the presence of small amounts of oestrogenic material and, in view of their reasonably high accuracy, may be preferred for this reason.

The action of PU. preparations in hypophysectomised rats shows that they do not contain follicle stimulating substance (*cf.* SELYE, COLLIP and THOMSON, 1933, *Endocrinol.*, **17**, 494 ; LEONARD and SMITH, 1934, *Amer. J. Physiol.*, **108**, 22), and it should be emphasised that, with other types of gonadotrophic extracts, the relative accuracy of the methods may not be the same. Urine of pregnancy

preparations, containing luteinising substance, must, it seems, produce their effects in immature intact rats and mice partly in a secondary manner, presumably by stimulation of the animal's own pituitary gland. None of the test methods employed can therefore confidently be regarded as involving solely the observation of a direct gonadotrophic effect, uncomplicated by the action of the animal's own pituitary gland.

SUMMARY

1. The contributions offered towards the international standard preparation for the gonadotrophic substance of urine of pregnancy have been assayed in a large number of different laboratories, by a variety of test methods. These assays have furnished material upon which to base a survey of the differences between the contributions, of their suitability for inclusion in the standard and of the comparative values of different test methods.

2. The test method does not influence the determination of relative activity, a result which supports the view that there is only one gonadotrophic luteinising substance in pregnancy urine. The highly improbable alternative would be to suppose that, if more than one active substance were present, the proportions of such substances were constant in all of the PU. preparations tested.

3. Different preparations were, however, assayable with significantly different degrees of accuracy, and the fact that PU.2, the only other preparation besides PU.5 that had not been diluted with inert material, was the most accurately assayable led to the suspicion that the other preparations may not have been homogeneously mixed. This view was confirmed by the finding that the variance between estimates from different laboratories was significantly greater than that between estimates by different test methods, from the same laboratory, for all preparations but PU.2.

4. Different test methods also show significantly different degrees of accuracy. The methods employing vaginal cornification and ovarian weight respectively were the most accurate of those for which adequate data were available. Uterine weight was the least accurate criterion.

5. The vaginal cornification technique is therefore recommended as a test method, provided that the absence of oestrogenic material from preparations is verified by control tests.

* * *

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Appendix.**METHODS OF BIOLOGICAL ASSAY OF GONADOTROPHIC EXTRACTS OF HUMAN URINE OF PREGNANCY USED BY MEMBERS OF THE THIRD INTERNATIONAL CONFERENCE ON THE STANDARDISATION OF HORMONES, AND PRELIMINARY RESULTS OBTAINED BY THEM WITH THE STANDARD MATERIAL***Professor S. Aschheim's Method.*

Groups of about 20 immature female rats are used, of average body weight 35 g., range 28-46 g., 21-28 days old. The total dose per animal of the preparation to be tested is dissolved in a volume of 0.5-1.5 c.c. of distilled water and given by 5 equal subcutaneous injections over a period of 48 hours. Vaginal smears are taken on the 3rd, 4th and 5th day after the first injection, the animals being killed for sectioning of the uterus on the 5th day. The criterion of response is the production of vaginal cornification, the uterine reaction also being noted.

By this method, Professor ASCHHEIM found that 33.3 mg. of the standard (0.33 I.U.) produces 70% of cornified smears, equalling 1 rat unit. The uteri of animals with negative smears were all small, most of those with positive smears being enlarged.

Professor J. B. Collip's Method.

Groups of 10 immature female 21-day-old hooded rats are used, of average body weight 38-42 g., range 35-75 g. The total dose per animal of the preparation to be tested is dissolved in 1.5 c.c. of 10% aqueous alcohol, and given by 3 equal subcutaneous injections, once on each of 3 days. Vaginal smears are taken at 72, 96 and 120 hours after the first injection, and the animals are killed at 120 hours. The criterion of response is the production of squamous vaginal smears.

Professor H. M. Evans' Method.

Preliminary groups of 3 immature female Long-Evans strain 21-day-old rats are used, of average body weight 47 g., range 40-55 g. The total dose per animal of the preparation to be tested is dissolved in 3 c.c. of water, pH 7.5, and given, in different groups, by both subcutaneous and intraperitoneal injections, one per day on each of 3 days. Final groups of 10 rats per group are injected subcutaneously under the same conditions. The animals are killed 96 hours after the first injection. The criteria of response are the production of vaginal opening, ovarian weight and follicular growth and uterine weight and development. Some further tests were done with the standard using 25-28-day-old hypophysectomised rats, and 3 daily subcutaneous or intraperitoneal injections, followed by autopsy at 72 hours from the first injection. The post-operative interval was 8-10 days. The criterion of response is repair of the characteristic nuclear pattern of the ovarian interstitial cells (deficiency cells).

By subcutaneous injection, 1 L.U. of the standard produced oestrous distention of the uterus in 70%, and 2.5 L.U. produced corpora lutea and also vaginal opening in 70% of the test animals. The standard was less effective when given intraperitoneally. The minimum effective dose for repair of the ovarian interstitial tissue in hypophysectomised rats was between 2.5 and 5 L.U. subcutaneously, or 1-2.5 L.U. intraperitoneally. With these doses, there was no follicular development, the vaginae were closed and the uteri small.

Dr. C. Hamburger's Method.

(a) Groups of 20-40 immature female rats are used of average body weight ca. 37 g., range 30-45 g., 26-28 days old. The total dose per animal of the preparation to be tested is dissolved in 1 c.c. of 0.9% aqueous sodium chloride solution and given by 5 equal subcutaneous injections over a period of 48 hours. The animals are killed on the 5th day, 90-97 hours after the first injection, vaginal smears are taken and the ovaries and uteri are weighed fresh. The criteria of response are uterine weight, ovarian weight and luteinisation, and the production of cornified vaginal smears.

(b) Immature 21-day-old mice are used, with a similar technique, for estimation of the percentage of luteinisation only.

(c) Groups of 20 virgin rabbits of body weight 1,800-2,000 g., 16 weeks old, are also used. A single intravenous injection of the preparation to be tested is given in 1-8 c.c. of 0.9% aqueous sodium chloride solution, and the animals are killed 40-48 hours later. Hæmorrhagic follicles, rupture points and cystic follicles with partial bleeding are recorded as positive reactions. The following table gives a comparison of various animal units in terms of the standard.

Unit	I.U.
Rat, 50 mg. uterus	0.3
Rat, 50% vaginal cornification	0.4
Rat, 50% luteinisation	1.1
Mouse, 50% luteinisation	2.5
Rabbit, 50% positive reactions	5.0

The dose response curves for the action of the standard on rats were compared with those for the separate contributions, and found to be similar in shape. The curve with rabbits was compared with those for two other chorionic gonadotrophins, and also found to be similar to them.

Professor E. Laquéur's Method.

Groups of 5, preferably of 10, immature female hooded rats are used of a body weight 25-35 g., 21-28 days old. The total dose of the preparation to be tested is dissolved in either 0.6 or 0.8 c.c. of water, containing 0.3% tricresol. Subcutaneous injections are given of 0.1 c.c. each. If the total dose is dissolved in 0.6 c.c., 6 injections are given within 48 hours. If the total dose is dissolved in 0.8 c.c., 8 injections are given over a period of 84 hours, as a rule beginning in the evening of the first and ending in the morning of the fifth day. The latter type of experiment is preferred, since especially the occurrence of corpora lutea is more regularly observed after this type of treatment. Therefore we recommend this as a standard procedure. Vaginal smears are taken on the 3rd, 4th and 5th day, the animals are killed on the 8th day after the first injection, and the ovaries and uterus are weighed fresh; the corpus luteum count is taken at 10-fold magnification in crushed preparations.

The primary criterion of response is the disappearance of leucocytes from the vaginal smears, other criteria being the weight and corpus luteum count of the ovaries and more than 50% increase of the uterine weight.

About 0.6 I.U. of the standard produced more than 50% of positive smears, and this dose also gave corpora lutea in a few animals. Luteinisation occurs at 2 to 8 times the minimal œstrogenic dose; the results with these other dose levels were variable.

Ovarian weight was not significantly changed by 12 I.U. The seasonal sensitivity of the rats was controlled by parallel experiments with known preparations. Comparison is admitted between the smallest doses which yield

more than 50% positive responses. The arbitrarily chosen dose intervals largely determine the accuracy of the assay rather than the comparative intensity of response. Only simultaneous treatments were used and are to be used in future for comparison.

Dr. R. Moricard's Method.

(a) Groups of 10 immature female hooded rats are used, of average body weight 28-30 g., 25-30 days old. The total dose per animal of the preparation to be tested is dissolved in 2 c.c. of distilled water at pH. 8 and given by 4 subcutaneous injections over a period of 72 hours. Vaginal smears are taken at the opening of the vagina and on each day subsequently, and the animals are killed 120 hours after the first injection. The criteria of response are the production of vaginal cornification, vaginal opening, follicular ripening, ovarian luteinisation, and increase of the weight of the uterus and of one ovary.

(b) Infantile female mice, 6-8 g., 18-20 days old, are also used in a similar manner.

0.75 I.U. was found to equal one rat cornification unit, which is the minimum dose that produces pure cornification at the 120th hour in more than half of the animals.

Dr. O. Riddle's Method.

Groups of 2-4 young male ring-doves are used, of body weight 130-160 g., 10-14 weeks old. The total dose per animal of the preparation to be tested is dissolved in 1 c.c. of distilled water and given by 4 equal intramuscular injections over a period of 96 hours. The animals are killed 96 hours from the first injection. The criterion of response is the increase in testis weight over that of uninjected controls.

Professor P. E. Smith's Method.

Groups of 5 or 6 immature female rats are used, of average body weight 50-60 g., range 45-70 g., 22-23 days old. The total dose per animal of the preparation to be tested is dissolved in 1.2 c.c. of distilled water and given by 6 equal subcutaneous injections, 2 per day, over a period of 72 hours. The animals are killed 96 hours from the first injection, and the ovaries and uteri weighed fresh. The criteria of response are the production of corpora lutea; the ovarian and uterine weights, the incidence of vaginal opening also being recorded.

One corpus luteum rat unit was found to be slightly less than 2 I.U. of the standard, this dosage also producing between 2 and 3 times the control ovarian weight. Vaginal opening occurred with 4. I.U.

Method used at the National Institute for Medical Research.

Groups of 10 immature female rats weighing 40-50 g. are injected subcutaneously once daily for 5 days. The substance under test is injected daily in a volume of 1 c.c. of distilled water at pH 7 (approximately). Twenty-four hours after the last injection, the rats are killed with chloroform, weighed and the reproductive organs dissected. The ovaries are decapsulated and cut free from the Fallopian tubes; the uterus is cleanly dissected of all fat, and both organs are fixed in Bouin's fluid overnight. The following day, the ovaries and the uterus are removed to 70% alcohol and after 2-4 hours they are weighed on a torsion balance. The criterion of response is the average weight of the ovaries.

By this method, 1 unit is the activity of 1 mg. of a "laboratory standard" preparation, and is equal to the amount required to cause a 4-fold increase in ovarian weight. One such unit was found to equal 12-15 I.U.

**MEMORANDUM ON THE INTERNATIONAL
STANDARD FOR THE GONADOTROPHIC
SUBSTANCE OF HUMAN URINE OF PREGNANCY
(CHORIONIC GONADOTROPHIN)**

Established by

The Department of Biological Standards,
National Institute for Medical Research,
(Hampstead, London, N.W.3).

INTRODUCTION

During 1937 and 1938, an enquiry was made among interested workers as to the practicability and desirability of establishing an international standard for the gonadotrophic substance of human urine of pregnancy. It was recalled that preparations of this substance were standardised in a great variety of ways and that there was no method of equating the various types of units, defined in terms of animal reactions, used by different workers and manufacturing organisations. The survey showed that there was complete unanimity as to the desirability of establishing a standard, and the offers of material received from various quarters made it evident that there would be no practical difficulty in constituting a standard preparation in adequate quantity to serve world requirements.

At the third Conference on the Standardisation of Hormones, held in Geneva in August 1938, under the auspices of the Permanent Commission on Biological Standardisation, the results of the preliminary survey were considered, and it was unanimously decided to arrange for the establishment of an international standard for the gonadotrophic substance of human urine of pregnancy.

The Conference had before it the results of a co-operative examination of the various contributions offered towards the proposed standard, and they were able to formulate details of the manner in which the contributions should be mixed. They also defined a unit of activity in terms of the proposed mixture, subject to confirmation after specimens of the mixture had been assayed by members of the Conference.

The contributions were subsequently mixed as arranged and a specimen approved by each member of the Conference. The standard was established, and the unit brought into current use, on April 1st, 1939.

PREPARATION AND FORM OF ISSUE
OF THE INTERNATIONAL STANDARD

Contributions from six sources were used in preparing the standard, substantial amounts of material approved by the Conference having been generously provided by each of the following :

- Boots Pure Drug Co., Ltd., Nottingham, England.
- I.G. Farbenindustrie Aktiengesellschaft, Elberfeld, Germany.
- Løvens Kemiske Fabrik, Copenhagen, Denmark.
- N. V. Organon, Oss, Netherlands.
- Parke, Davis & Co., Detroit, Mich., U.S.A.
- E. R. Squibb & Sons, New Brunswick, U.S.A.

Several of these preparations were already largely diluted with lactose and, as a first step in the mixing of the contributions, those preparations not already so treated were diluted to an activity equal to that of the most active diluted preparation by the addition of an appropriate amount of lactose. The whole of the contributions were then carefully mixed and further diluted with an equal amount of lactose. At this stage, a bulk of material amounting to about 800 grm. was obtained. The material was then dried by exposure to P, O, *in vacuo* and made into tablets of approximately 10 mgrm. without the addition of further excipient. A test weighing of tablets showed that 86% were within $\pm 5\%$ of the 10 mgrm. aimed at.

The tablets were then packed in lots of 25 in small amber tubes, which were plugged with cotton wool and placed in ampoules. The ampoules were evacuated, filled with pure, dry nitrogen and sealed. A cork to fit the inside amber tube was also enclosed in each ampoule. This method of double packing was devised to ensure the exclusion of oxygen from the finally sealed ampoule, as laid down in the report of the Conference, and, at the same time, to provide a suitable container for the tablets after the ampoule had been opened and discarded. The finished ampoules were transferred to the cold room and are maintained constantly at a temperature of -2°C . 2,854 of these ampoules, each containing twenty-five 10-mgrm. tablets, were prepared. The standard is kept by the Department of Biological Standards, National Institute for Medical Research, London, N.W.3.

The whole of the mixing, compressing and packing of the standard was generously carried out by Burroughs Wellcome and Company, as a contribution toward the work.

DEFINITION OF THE UNIT

The definition of the unit adopted by the third Conference is as follows :

“ The specific gonadotrophic activity of 0.1 mgrm. (= 100 gamma) of the standard preparation shall be the international unit for recording

the activities of all gonadotrophic preparations of human urine of pregnancy, *but only of such.*"

The unit so defined is an amount of activity very similar to that required, under the conditions used by many workers, to cause cornification of the vaginal epithelium of the immature rat.

SUGGESTIONS FOR USE

After the ampoule has been opened, the inner tube should be removed, freed from cotton wool and closed with the cork provided. One or more tablets, each of which contains *about* 100 units, should be removed as required. The tablets are as constant in size as is practicably possible, but it is essential that they should be weighed before use, so that a solution can be made of an exactly known strength, on the basis of 10 units for each milligramme of ascertained weight. The tablets dissolve very readily in water or saline.

After the ampoule has been opened, the amber tube containing the tablets of the standard preparation should be kept in a small desiccator containing P_2O_5 .

USE OF STANDARD IN BIOLOGICAL ASSAY

The following recommendations for use of the standard are taken from the report of the Conference :¹

" The only tests for the comparative determination of gonadotrophic activity, in units as above defined, on which the Conference has evidence to justify recommendation, depend on :

" (a) The observation of a direct or indirect gonadotrophic effect, shown by morphological changes in the gonads ;

" (b) The observation of secondary changes in the accessory reproductive organs, in animals not deprived of their gonads. When this type of test is used, the absence of substances directly causing such changes in the accessory reproductive organs should be assured by control tests on animals deprived of their gonads. "

¹ *Bull. Health Org.*, 1938, 7, 889.

**ANALYSIS OF THE ASSAYS CARRIED
OUT IN VARIOUS LABORATORIES ON
THE SEPARATE CONTRIBUTIONS OFFERED
TOWARDS THE INTERNATIONAL STANDARD
PREPARATION FOR THE GONADOTROPHIC
SUBSTANCE OF PREGNANT MARES' SERUM**

By

C. W. EMMENS

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INTRODUCTION

The establishment of an international standard preparation for the gonadotrophic substance of the serum of pregnant mares was recommended by the third Conference on the Standardisation of Hormones (Geneva, August 1938).¹ It was agreed that specimens of the several contributions offered towards the standard should be circulated among experts, including members of the Conference, so that the suitability of the contributions for inclusion in the standard might be determined.

The extracts were in the form of dry powder, consisting either of undiluted serum extract or of such extract diluted with lactose. Samples of these preparations, labelled MS.1, 4, 5, 6 and 7 + 2 were circulated to a number of laboratories in different countries, as in the case of the contributions offered towards the international standard preparation of the gonadotrophic substance of urine of pregnancy (chorionic gonadotrophin).

¹ *Bull. Health Org.*, 1938, VII, 7, 887.

This report embodies an analysis of the co-operative assays carried out on the original contributions and, as agreed by the Conference, a summary is also included of the methods used by members of the Conference who tested the original contributions. The use made of the information so obtained has been described in the memorandum published above.

SOURCES OF INFORMATION

Table 1 gives the persons or laboratories providing reports on the activity of some or all of the contributions. One report is not included in the calculations, because its author assayed MS.1 only. The reference numbers in Table 1 are used for convenience in later tables.

METHODS OF COMPARISON

All but four of the assays have been carried out by subcutaneous injection to immature female rats. One was carried out with immature female rats and mice (13), one on immature mice (19), one on male rats (1) and one on rabbits (10). The activity of the preparations has been estimated by different investigators by observing the following kinds of change : (1) increase in ovarian weight ; (2) occurrence of vaginal cornification alone or (3) together with the ovarian and uterine changes ; (4) formation of *corpora lutea* ; (5) changes in uterine weight together with the incidence of vaginal cornification in female rats or mice ; (6) increase in weight of the seminal vesicles of male rats, and (7) production of ovulation on intravenous injection to female rabbits. Full references are given in the tables.

COMPARISON OF THE PREPARATIONS AS RECEIVED

Table 2 gives the results of assays carried out by observing changes in ovarian weight, of which 13 series were available. Table 3 gives the remaining assays, which form a miscellaneous collection, none of the methods described therein having been used with sufficient frequency for estimates of their respective accuracies to be made.

As in the analysis of the PU (pregnancy urine) contributions, not all of the preparations were tested by each laboratory, but the gaps in the tables are few. The Conference recommended that MS.1 be used as a temporary standard of comparison. This was convenient, as it had been assayed by all persons concerned. It was easier in this case to express the activities of the other samples directly as their potency in terms of that of MS.1, first, because many assayers had already done so and, secondly, because many indices of less than unity are avoided. The method differs in form from that used in the corresponding analysis of the PU contributions, in which activity was expressed as the reciprocal of potency, but the change has, of course, no effect on the results of the analysis, since computation is carried out logarithmically.

The geometric mean of the estimates for each preparation is given in each table, together with the variance of the logarithms of the estimates concerned. The use of a geometric mean and logarithmic variance counteracts the tendency, shown by the crude data, to deviate more in a positive than in a negative direction, so that the logarithms of the estimates of potency tend to be more normally distributed than the estimates themselves.

In only two instances has more than one comparison of the activities of the preparations been available from the data of a single laboratory. In general, assayers have limited their criteria of response more than they did when assaying the PU preparations or, in a few instances, have pooled their data to give a single mean determination. It has not, therefore, been possible to compare inter- and intra-laboratory variation in the estimates of potency, but there is fortunately no reason to suspect heterogeneity of the original MS samples as distributed. Had there been any reason to suspect this, the use of estimates of the variation occurring in the potencies as determined within individual laboratories, when compared with that occurring between laboratories, would have formed a valuable criterion, as it did in the case of the PU contributions.

No attempt has been made to weight observations according to the established or suspected degree of accuracy of the individual assays, as, in most cases, sufficient data are lacking. However, in the final determination of the potencies, given in Table 4, the means from Tables 2 and 3 were weighted in each case inversely according

to the variance of the table as a whole and directly according to the number of estimates of each MS sample. The variance for complete tables (test methods) has been used in determining the weights to be assigned, as this gives the best estimate of the value of the information in a table. The few gaps in the tables have been ignored, since their effect on the estimate of the variance to be adopted would be negligible. The weights assigned to Tables 2 and 3 were 3591 and 1652 respectively.

COMPARISON IN TERMS OF ACTUAL SERUM EXTRACT PRESENT

All of the preparations, except MS.4, were diluted with lactose before circulation. The potency of each undiluted extract is given in Table 4, together with the percentage of diluent in the sample as circulated. Table 4 also lists the limits of error within which 99% of the estimates fall ($\pm 2.576 \sigma$) and the corresponding limits of error for the mean values assigned to the samples. It will be seen that the limits of error of individual estimates differ little among themselves and are of the same order as those found for the PU samples in the preceding analysis. The potencies of the original undiluted extracts did not differ widely, varying between 0.76 and 3.2 times that of undiluted MS.1, although the varying degrees of dilution to which they were subjected caused a greater variation in the potencies of the circulated preparations. It must be emphasised that the wide limits of error found for the individual tests may reflect not so much the inaccuracies of any given assay as the actual variations in potency which may result from the use of different test methods and different stocks of animals, etc.

THE RELATIVE ACCURACY WITH WHICH THE MS PREPARATIONS HAVE BEEN ASSAYABLE

When investigating PU preparations, it was found that different PU samples were not assayable with equal accuracy, and we were able to decide that much of the rather surprising variation encountered could be attributed to incompletely homogeneous dilution of the samples. In the case of the MS preparations, there is little ground for a similar suspicion. When the ratio of the variance of

estimates for each preparation to that of the others is calculated, it is seen to reach a significant level only in the case of MS.5, estimates of the potency of which are significantly more variable ($P > 0.95$, but < 0.99) than those of MS.7 + 2. As the significance attained is not high, we may safely assume that no great dissimilarity existed between the accuracies with which the various MS preparations were able to be assayed. It is worth noting, however, that a few statistically significant differences ($P > 0.95$) occur between the variances of the MS samples within Tables 2 and 3, but always with a relatively low degree of significance ($P < 0.99$). These differences are, moreover, not in the same direction in each table, for, whereas MS.4 and 6 show a higher variance in Table 2 than MS.5 and 7 + 2, MS.7 + 2 shows a higher variance than the others, which do not differ significantly from each other, in Table 3. In these calculations, tables for the "variance ratio", published by FISHER and YATES (1938), have been consulted.

The distribution of the logarithms of the separate estimates for each MS preparation is shown in Table 6, in which the means have been shifted to correspond with each other at approximately 1.0. There seems no reason to suspect any marked deviation from normality, and it has not been thought worth while to test the distributions statistically, as the numbers are small, and a significant result could only be anticipated if the data were added together as in the last column and tested *en masse*.

THE RELATIVE ACCURACY OF DIFFERENT TEST METHODS

Only tests using an increase in ovarian weight as a criterion of response have been used in sufficient numbers to be considered separately from the others. The weights assigned to the means of Tables 2 and 3 were inversely proportional to the logarithmic variances for these tables, which were 0.02784 and 0.06055 respectively. These variances differ significantly ($P > 0.99$), and each assay by ovarian weight has contributed, on the average, over twice the information given by one of the miscellaneous assays in Table 3. When PU samples were tested, an assay by ovarian weight was found to give between 2 and 3 times the information given by miscellaneous assays, agreeing in this respect with the present finding. However, assays by techniques using vaginal

cornification and *corpus luteum* formation as criteria are included in Table 3 of the present paper, and may have lowered its variance, as their accuracy was found to be higher than that of the miscellaneous tests when considering PU preparations.

THE RELATIVE POTENCIES OF MS PREPARATIONS BY DIFFERENT TEST METHODS

We have only one comparison for each MS sample, that between its potency as determined by techniques using an increase in ovarian weight and the potency given by the other assays combined. *In no case do these mean potencies differ significantly, and it is again clear that there is no significant difference between the potencies of the MS preparations as determined by an ovarian weight method or by a collection of other methods.* A similar and more fully substantiated result was arrived at when dealing with the PU preparations, and it was argued that this fact confirms the belief that only one active substance is involved. *However, as MS preparations are known to exert both a follicle-stimulating and a luteinising activity, we must, in this instance, conclude that, if there be two active principles concerned, these were present in the original contributions in an approximately constant ratio.* This conclusion is in keeping with the fact that the various preparations produced qualitatively similar changes in the ovaries of hypophysectomised rats.¹

In this connection, it is clear that if varying amounts of follicle-stimulating and luteinising hormones were present in different contributions, methods using the formation of *corpora lutea* as criteria should in particular give different relative potencies from those using vaginal cornification, but this is not seen in the few examples available.

VARYING AMOUNTS OF AN MS PREPARATION NEEDED FOR ASSAY BY DIFFERENT TEST METHODS

The amount of MS.1 needed to give the specific response required by different test methods may serve as a guide to the relative

¹ These experiments will be the subject of an independent publication by Dr. ROWLANDS and his collaborators.

requirements of these tests. There is no correlation between the amount of MS.1 needed and its potency relative to that of the other MS. preparations. In the ovarian weight tests, an average ovarian weight of 50 mgrm. was given by between about 2 and 8 mgrm. of MS.1. These tests showed, therefore, less variation in the way of requirements than when PU preparations were assayed. Luteinisation occurred at a considerably lower level of dosage, around 0.25 mgrm. in the few tests available, and 50% positive vaginal smears were also given at about this level, the actual range being 0.13-0.38 mgrm. in different tests.

There are insufficient data upon which to recommend any particular test method for its convenience or accuracy. Methods using vaginal cornification do not appear to have the relatively high accuracy seen with PU preparations, but this is not certain, as so few assays are available.

SUMMARY

(1) An analysis is made of the large number of assays carried out in different laboratories by a variety of test methods on the contributions offered towards the international standard preparation for the gonadotrophic substance of pregnant mares' serum. All contributions were found acceptable and were included in the standard preparation.

(2) As far as the data show, the test method does not influence the determination of relative activity, but only assays using an increase in ovarian weight in rats have been performed in sufficient numbers to be considered separately from the rest. It is concluded that, if two active principles (F.S.H. and L.H.) occur in these extracts, they must be present in approximately constant proportions

(3) There is little to indicate that different preparations were assayable with different degrees of accuracy, and those preparations which were mixed with lactose before circulation were probably so mixed as to give a fully homogeneous product.

(4) The tests using ovarian weight as a criterion of response were more accurate than the miscellaneous tests using other criteria

considered together, but no further information as to the accuracy of various test-methods is available.

REFERENCE

FISHER, R. A., and YATES, F. (1938) : Statistical Tables for Biological, Agricultural and Medical Research, London.

* * *

Table 1.

LIST OF INVESTIGATORS OR LABORATORIES SUPPLYING ASSAY RESULTS

Reference No.	Assayed by :
1.	D'Amour, Dr. F. E., Denver, Colorado, U.S.A.
2.	Ayerst, McKenna & Harrison, Montreal, Canada.
3.	British Drug Houses Ltd., London.
4.	Boots Pure Drug Co., Nottingham.
5.	Burn, Professor J. H., Oxford.
6.	Catchpole, Dr. H. R., New Haven, Conn., U.S.A.
7.	Cole, Professor H. H., Davis, Cal., U.S.A.
8.	Collip, Professor J. B., Montreal, Canada.
9.	Dodds, Professor E. C., London.
10.	Friedman, Dr. M. H., Beltsville, Md., U.S.A.
11.	Gaddum, Professor J. H., London.
12.	Glaxo Laboratories, Greenford, Middlesex.
13.	Hamburger, Dr. C., Copenhagen.
14.	Hill, Professor R. T., Bloomington, Ind., U.S.A.
15.	De Jongh, Professor S. E., Leiden.
16.	Laqueur, Professor E., Amsterdam.
17.	Løvens Kemiske Fabrik, Copenhagen.
18.	Martins, Dr. Thales, São Paulo, Brazil.
19.	Moricard, Dr. R., Paris.
20.	National Institute for Medical Research, London.
21.	N.V. Organon, Oss, Netherlands.
22.	Schering Ltd., London (Schering Kahlbaum, Berlin).
23.	Upjohn Co., Michigan, U.S.A.

Table 2.

THE POTENCY OF EACH MS PREPARATION COMPARED WITH THAT OF MS.1 WHEN TESTED BY INCREASE IN OVARIAN WEIGHT

Reference No.	Animal	MS.4	MS.5	MS.6	MS.7 + 2
2	Rat	41	1.4	3.3	1.1
5	"	—	2.0	6.6	1.0
8	"	—	1.1	1.7	1.3
9	"	29	1.3	4.7	0.83
11	"	75	1.8	5.0	1.2
12	"	40	2.0	—	2.0
13	Rat and mouse	32	1.6	3.3	0.90
14	Rat	136	1.3	5.7	—
17	"	32	1.6	3.0	0.80
20	"	23	1.0	3.2	0.80
21	"	40	1.4	3.3	0.77
22	"	26	1.0	1.2	0.91
23	"	37	1.5	4.2	1.0
Geometric mean		40.1	1.43	3.43	1.02
Logarithmic variance		0.04960	0.01020	0.04441	0.01334

Table 3.

THE POTENCY OF EACH MS PREPARATION COMPARED WITH THAT OF MS.1 WHEN TESTED BY VARIOUS OTHER METHODS

Method	Reference No.	Animal	MS.4	MS.5	MS.6	MS.7 + 2
Vaginal cornification .	3	Rat	23	0.72	1.3	0.25
	4	"	130	1.6	3.5	0.27
	15	"	20	2.2	1.5	1.1
	21	"	50	1.7	4.4	0.89
Vaginal cornification plus ovarian and uterine reactions ..	16	"	50	3.3	2.0	3.3
<i>Corpus luteum</i> formation	6	"	30	1.6	4.0	1.2
	7	"	28	—	—	—
	15	"	36	2.5	1.7	1.1
Uterine weight and vaginal opening ..	19	Mouse	25	0.75	1.5	1.0
Weight of seminal vesicles	1	Rat	45	1.8	2.0	2.2
Ovulation	10	Rabbit	55	1.2	3.9	0.65
Geometric mean			38.6	1.57	2.33	0.915
Logarithmic variance			0.05330	0.04471	0.04184	0.12270

Table 4.

WEIGHTED GEOMETRIC MEANS FOR THE POTENCY OF EACH MS PREPARATION COMPARED WITH THAT OF MS.1, ALL TESTS COMBINED, AND THE CORRESPONDING VALUES FOR THE UNDILUTED EXTRACTS FROM WHICH THE PREPARATIONS WERE COMPOUNDED.

MS No.	Number of estimates	Weighted mean (MS.1 = 1)	% Diluent	Potency of original extract (MS.1 undiluted = 1)	Limits of error ($P = 0.99$) %	Limits of error of individual tests ($P = 0.99$) %
1	(23)	1.000	98.1	1.000	—	—
4	22	39.63	0	0.7565	75.6-132.3	26.9-372.1
5	23	1 467	97.0	0.9294	82.5-121.3	39.6-252.3
6	22	3.130	96.5	1.699	75.4-132.7	26.5-377.4
7 + 2 ...	22	0,9926	99.4	3.243	73.2-136.6	23.2-430.7

Table 5.

VARIANCE RATIOS FOR MS PREPARATIONS, ALL TESTS COMBINED

MS No.	7 + 2	6	4	5
Mean square	0.06060	0.05014	0.04908	0.02434
Degrees of freedom	21	21	21	22
MS with greater variance	$\left\{ \begin{array}{l} 7 + 2 \\ 6 \\ 4 \end{array} \right.$	1.24	1.23 1.02	2.49* 2.06 2.02

* $P > 0.95, < 0.99$.

Table 6.

DISTRIBUTION OF THE LOGARITHMS OF THE ESTIMATES OF THE POTENCY OF EACH MS PREPARATION, SO ADJUSTED THAT THE MEANS FALL AT APPROXIMATELY 1.0

Adjusted log. potency	MS.4	MS.5	MS.6	MS.7 + 2	Total
1.5	2			1	3
1.4					
1.3	1	1	2	2	6
1.2		1	2		3
1.1	4	5	4	4	17
1.0	5	6	6	8	25
0.9	4	5	0	4	13
0.8	5	3	2	1	11
0.7	1	2	4		7
0.6			2		2
0.5				1	1
0.4				2	2

Appendix.**METHODS OF BIOLOGICAL ASSAY OF EXTRACTS
OF THE SERUM OF PREGNANT MARES
USED BY MEMBERS OF THE THIRD CONFERENCE
ON THE STANDARDISATION OF HORMONES**

Method used by :

Professor J. B. Collip.

Groups of 10 immature female rats are used, and the test method is the same as in the assay of chorionic gonadotrophin, except that the rats are killed 96 hours after the first injection. The criteria of response are the production of squamous vaginal smears and of an increase in ovarian weight.

Dr. C. Hamburger.

Groups of 10-20 immature rats or mice are used, the technique of injecting, etc., being the same as that described for the assay of chorionic gonadotrophin. The primary criterion of response is the increase in ovarian weight ; the uterine weight is also recorded.

Professor E. Laqueur.

Groups of 5 or 10 immature female hooded rats are used, by a technique similar to that described for the assay of chorionic gonadotrophin. Eight injections are given in the course of 4 days, and the animals are killed on the 8th day after the first injection. The criteria of response are the production of vaginal cornification, the increase in ovarian and uterine weight, and the production of corpora lutea.

Dr. R. Moricard.

Groups of 10 immature female rats or mice are used, by the same technique as that described for the assay of chorionic gonadotrophin. The criteria of response are the production of vaginal cornification, vaginal opening, follicular ripening, luteinisation, and the increase of the weight of the uterus and of one ovary. Assays are primarily based, however, on the production of vaginal cornification.

The National Institute for Medical Research.

Groups of 10 intact immature female rats, or female rats 10 days after hypophysectomy at 40-50 g., are used in the same manner as described for the assay of chorionic gonadotrophin. The criteria of response are the average increase in ovarian weight and the detailed histology of the ovaries.

**MEMORANDUM ON THE INTERNATIONAL
STANDARD FOR THE GONADOTROPHIC SUBSTANCE
OF PREGNANT MARES' SERUM**

Established by

the Department of Biological Standards,
National Institute for Medical Research,
Hampstead, London, N.W.3.

INTRODUCTION

During 1937 and 1938, an enquiry was made among interested workers as to the practicability and desirability of establishing an international standard for gonadotrophic preparations of the serum of pregnant mares. It was recalled that these preparations were being used increasingly and that several different methods of standardisation, and several units defined in terms of different animal reactions, were being evolved. It seemed desirable that steps should be taken to provide an international standard preparation, in terms of which the potency of other preparations should be assayed and expressed in a uniform notation. The survey showed that there was almost complete unanimity as to the desirability of establishing such a standard, and a further enquiry suggested that there would be no great difficulty in obtaining adequate quantities of suitable material.

At the third Conference on the Standardisation of Hormones, held in Geneva in August 1938 under the auspices of the Permanent Commission on Biological Standardisation, the results of the preliminary survey were considered, and it was unanimously decided to arrange for the establishment of an international standard for gonadotrophic preparations from the serum of pregnant mares.

The Conference agreed that specimens of the several contributions offered towards the material required for the standard should be distributed among experts, including members of the Conference, so that their suitability for inclusion could be considered. It was further agreed that members of the Conference should decide by correspondence as to the method of mixing the various contributions approved, and as to the dimensions of the international unit to be defined in terms of the completed standard preparation.

PREPARATION AND FORM OF ISSUE OF THE INTERNATIONAL STANDARD

Five substantial contributions were received and a number of comparative assays were carried out by workers in various countries. There was general agreement that all the material offered was suitable for incorporation in the standard. The contributors, whose generous helpfulness is here acknowledged, were :

Boots Pure Drug Company, Nottingham, England.
Cutter Laboratories, Cal., U.S.A.
Løvens Kemiske Fabrik, Copenhagen, Denmark.
Laboratories du Dr. Roussel, Paris.
Upjohn & Company, Kalamazoo, U.S.A.

Consideration of the relative activities of these contributions, as determined by the co-operative assays, made it easy to formulate proposals as to mixing them, and as to the definition of the international unit to be defined in terms of the approved mixture. These proposals were circulated to all members of the Conference and were unanimously approved.

Four of the five contributions were already largely diluted with lactose, two of these, as well as the undiluted one, being considerably more active per milligramme than the remaining two. As a first step, the three more active preparations were diluted, or further diluted, with lactose, so as to make all the preparations about equally active per milligramme, as thus finally diluted.

The whole of the contributions were then carefully mixed and granulated, giving a total of 625 gm., containing 98% of diluent. The material was then dried by exposure to P_2O_5 *in vacuo*, and from this mixture 23,400 tablets, each of approximately 25 mgrm., were obtained, there being, as usual, a small amount of machine waste. A test weighing of tablets showed that 85% were within 2%, and a further 13% within 5%, of the 25 mgrm. aimed at.

The tablets were then packed in lots of ten in small tubes of amber glass which were plugged with cotton wool and placed in ampoules. The ampoules were evacuated, filled with pure, dry nitrogen and sealed. A cork to fit the inside amber tube was also enclosed in each ampoule. This method of double packing was devised to ensure the exclusion of oxygen from the finally sealed ampoule, as laid down in the report of the Conference, and, at the same time, to provide a suitable container for the tablets after the ampoule had been opened and discarded. The finished ampoules were transferred to the cold-room and are maintained constantly at a temperature of $-2^{\circ}C$. 2,311 of these ampoules, each containing ten 25-mgrm. tablets, were prepared. The standard is kept by the Department of Biological Standards, National Institute for Medical Research, London, N.W.3.

The whole of the procedures involved in the mixing, compressing and packing of the material was generously carried out by Burroughs Wellcome and Company, who also designed and provided the glassware used, as a contribution toward the production of the international standard.

DEFINITION OF THE UNIT¹

The definition of the unit, on the lines agreed to by the members of the third Conference, is as follows :

The specific gonadotrophic activity of 0.25 milligramme (= 250 gamma) of the standard preparation shall be the international unit for recording the activities of all gonadotrophic preparations of the serum of pregnant mares, *but only of such*.

SUGGESTIONS FOR USE

After the ampoule has been opened, the inner tube should be removed, freed from the two cotton-wool plugs and closed with the cork provided. One or more tablets, each of which contains *about* 100 units, should be removed as required. The tablets are as constant in size as is practicably possible, but it is essential that they should be weighed before use, so that a solution can be made of an exactly known strength, on the basis of four units for each milligramme of ascertained weight. The tablets dissolve very readily in water or saline.

After the ampoule has been opened, the amber tube containing the tablets of the standard preparation should be kept in a small desiccator containing P_2O_5 .

USE OF THE STANDARD IN BIOLOGICAL ASSAY

The following recommendations for use of the standard are taken from the report of the Conference².

" The only tests for the comparative determination of gonadotrophic activity, in units as above defined, on which the Conference have evidence to justify recommendation, depend on :

" (a) The observation of a direct or indirect gonadotrophic effect, shown by morphological changes in the gonads ; or

" (b) The observation of secondary changes in the accessory reproductive organs, in animals not deprived of their gonads. When this type of test is used, the absence of substances directly causing such changes in the accessory reproductive organs should be assured, by control tests on animals deprived of their gonads. "

¹ The Conference recommended that the final mixture should be such that the amount of activity contained in 0.1 milligramme (= 100 gamma) would be suitable as representing 1 unit. It was found, however, that the most convenient method of mixing the constituents yielded a somewhat weaker preparation than that earlier contemplated, so that the specified gonadotrophic activity of 0.25 milligramme (= 250 gamma) was agreed to be suitable for adoption as 1 international unit.

² *Bull. Health Org.*, 1938, 7, 895.

**ANALYSIS OF THE ASSAYS CARRIED
OUT IN VARIOUS LABORATORIES ON THE
SEPARATE CONTRIBUTIONS OFFERED
TOWARDS THE INTERNATIONAL STANDARD
PREPARATION OF THE LACTOGENIC
(CROP-GLAND STIMULATING) SUBSTANCE
OF THE ANTERIOR PITUITARY GLAND**

By

C. W. EMMENS

(National Institute for Medical Research, Hampstead, London, N.W.3.)

INTRODUCTION

At the third Conference on the Standardisation of Hormones, held in Geneva in August 1938, under the auspices of the Permanent Commission on Biological Standardisation¹, it was decided to establish an international standard for the lactogenic (crop-gland stimulating) substance of the anterior pituitary gland. It was agreed that the contributions, labelled LP.5, 7, 9, 10, 11, 15, 16 and 19, which were in the form of dry, undiluted powder, should be circulated among experts for assay in relation to LP.1, which was already assayed in Riddle units.

This report contains an analysis of the co-operative assays carried out on the original contributions, together with a summary of the methods used by members of the Conference who took part in the tests.

¹ *Bull. Health Org.*, 1938, **7**, 887.

The use of these results in preparing the standard and defining the unit is described in the memorandum which follows this report.

SOURCES OF INFORMATION

The persons or laboratories providing reports on the activity of some or all of the samples are shown in Table 1. Three of these reports were omitted from the calculations—one because LP.1 was not assayed, and the other two because only LP.1 was assayed. The reference number for each source of information is used in discussing and tabulating the results.

METHODS OF COMPARISON

Pigeons or doves of various types were used by all assayers, mixed batches of males and females generally being employed. The substances were given systemically by intramuscular or subcutaneous injection in all but two instances (1 and 9), when the local, intradermal method of administration was used. The criterion of response was an increase in the weight of the crop sacs or dissected crop glands, or the appearance of stimulation on visual examination of the crop glands when compared with uninjected controls. This latter method is, in particular, employed when an intradermal method of administration has been used.

The tests have therefore been of a limited nature, consisting of observations of growth produced in the crop gland of the pigeon or dove, since this is the only test recognised by the Conference as giving sufficiently quantitative results for the comparative assay of preparations.

COMPARISON OF PREPARATIONS

The results of the assays are given in Table 2. They are few in number and offer little scope for useful analysis. Activity has been expressed directly as potency in terms of LP.1, in accordance with the recommendation of the Conference, adopted by the majority of assayers.

The figures given by the two testers using the intradermal technique have been omitted from the calculations of the mean and variance of each preparation and are appended at the bottom of the table. A glance shows that they give a quantitatively different result from the rest, and it would have been interesting to obtain further estimates by this method, in order to establish with reasonable certainty whether such tests should be excluded from the recommendations for methods of assaying LP. preparations. In the single instance in which one preparation—LP.5—has been assayed by both the investigators using the intradermal test, they agree in finding its potency relative to that of LP.1 to be about a tenth of that found by the assayers using the systemic method. The figures for the other LP. samples are in all cases low, but not at any consistent level relative to the general findings, and it is clear that, in view of the relatively small degree of variation shown by the other estimates, these particular intradermal tests do not belong to the same population of assays.

The geometric mean and the logarithmic variance have been used in comparing the preparations, for reasons already described when dealing with gonadotrophins. The potencies of the different LP. samples have not a very wide range, and, in most cases, are not distinguishable with any certainty from that of LP.1. The variances differ rather more among themselves; that for LP.9, due mainly to a single estimate, however (3), is significantly greater than that for LP.5 ($P > 0.95$) and LP.10 ($P > 0.99$). The variance for LP.10 is furthermore significantly lower ($P > 0.95$) than that for LP.7, 11 and 19. The other preparations do not differ among themselves in regard to variance, and, if we take a grouped estimate of the variance for all preparations—0.02678—we have a figure which shows with fair accuracy the degree of confidence which may be placed in any particular assay. Using this figure, it appears that 99% of such assays should give an estimate which falls between 38% and 264% of the true value. This is the same order of precision as was found for the most accurately assayable gonadotrophins, and distinctly higher than for many of them.

RESPONSE TO THE INTERNATIONAL STANDARD PREPARATION

Details of the response to the standard preparation, when assayed by the method used at this Institute, are given in Table 3. Only 5 birds were used per group, but the results are in good agreement with the expectation of members of the Conference—that the potency of the standard differs little from that of LP.1. It is worth noting in connection with these assays that a simultaneous comparison of test preparations seems essential, as the response to LP.1 has been found to vary considerably from time to time, a total dose of 0.6 mgrm. having given a response of from 2.41 to 3.39 grm. and a total dose of 1.5 mgrm. a response of from 3.39 to 5.94 grm., when the crop-gland weight is adjusted to correspond with that which would be possessed by birds with a standard body-weight of 300 grm.

SUMMARY

(1) The contributions offered towards the international standard preparation for the lactogenic (crop-gland stimulating) substance of the anterior pituitary gland have been assayed in a number of different laboratories. These assays established the suitability of all contributions for inclusion in the standard.

(2) There does not appear to be any great difference between the accuracy with which the various contributions were assayable when a systemic method of administration was used. Results of a few tests using the local, intradermal method of administration were available, and these gave a lower estimate of potency, relative to that of LP.1, in all cases.

Table 1.

LIST OF INVESTIGATORS OR LABORATORIES SUPPLYING ASSAY RESULTS

Reference No.	Assayed by :
1	Allen, Professor E., New Haven, Conn., U.S.A.
2	Armour Laboratories, Chicago, Ill., U.S.A.
3	British Drug Houses Ltd., London.
4	Burn, Professor J. H., Oxford.
5	Collip, Professor J. B., Montreal, Canada.
6	Folley, Dr. S. J., Reading.
7	Geiger, Professor E., Budapest.
8	Hamburger, Dr. C., Copenhagen.
9	Long, Professor C. N. H., New Haven, Conn., U.S.A.
10	Lyons, Dr. W. R., Berkeley, Cal., U.S.A.
11	National Institute for Medical Research, London.
12	N.V. Organon, Oss, Netherlands.
13	Riddle, Dr. O., Cold Spring Harbor, U.S.A.
14	Roussel Laboratories, London.
15	Turner, Dr. C. W., Columbia, Mo., U.S.A.

Table 2.

THE POTENCY OF EACH LP. PREPARATION COMPARED WITH THAT OF LP.1 BY ITS ACTION ON THE PIGEON CROP SAC

By Intramuscular or Subcutaneous Injection.

Reference No.	LP.5	LP.7	LP.9	LP.10	LP.11	LP.15	LP.16	LP.19
2	1.0	0.40	1.0	—	—	—	—	—
3	0.96	0.56	4.9	0.66	0.45	0.43	2.0	2.5
4	0.81	0.75	0.98	0.96	1.5	1.1	2.0	1.5
6	0.77	—	—	—	—	—	—	—
7	0.71	—	—	—	—	—	—	—
8	1.5	0.80	1.0	1.0	1.6	1.1	1.3	2.0
11	0.67	0.75	1.0	1.0	0.85	0.70	0.85	1.0
12	1.0	0.75	0.75	0.91	0.94	0.73	1.6	2.5
13	0.68	0.55	0.70	0.80	0.91	0.66	0.96	0.85
15	1.0	—	—	—	—	—	—	—
Geometric mean	0.884	0.635	1.141	0.879	0.961	0.679	1.376	1.586
Logarithmic variance	0.01156	0.03003	0.09860	0.00509	0.03969	0.02335	0.02517	0.04046

By Local, Intradermal Injection.

Reference No.	LP.5	LP.7	LP.9	LP.10	LP.11	LP.15	LP.16	LP.19
1	0.089	0.036	0.057	—	—	—	—	—
9	0.075	—	—	0.2	0.2	0.2	1.1	1.0

Table 3.

ASSAY OF INTERNATIONAL STANDARD OF PROLACTIN IN COMPARISON WITH LP.1
(All Assays were carried out simultaneously.)

Substance	Total amount injected	Number of I.U.	Number of pigeons	Body-weight	Weight of crop gland	Weight of crop gland 300 grm. body-weight
	Mgrm.			Grm.	Grm.	Grm.
Standard preparation	0.15	1.5	5	340	1.09	0.96
	0.30	3.0	5	294	1.29	1.32
	0.45	4.5	5	334	2.03	1.83
	0.60	6.0	5	422	2.63	1.86
	0.90	9.0	5	350	2.99	2.52
LP.1	0.60	—	5	328	3.30	3.03

Appendix.

METHODS OF BIOLOGICAL ASSAY OF LACTOGENIC EXTRACTS USED BY MEMBERS OF THE THIRD CONFERENCE ON THE STANDARDISATION OF HORMONES

Method used by :

Professor J. B. Collip.

Groups of 2 or 3 young or adult male or female pigeons of *ca.* 250-350 g. body-weight are used. The total dose per bird of the preparation to be tested is dissolved in 4 c.c. of 10% alcohol and given as 4 equal subcutaneous injections, one on each of 4 consecutive days. Successive groups of pigeons receive the same substance in doses which increase in geometrical progression. The birds are killed on the 5th day, and the response assessed by the weight increase, and appearance of stimulation, of the crop glands.

Dr. C. Hamburger.

Groups of 3-8 mixed male and female pigeons are used, 6-7 weeks old and of an average body-weight of about 300 g., with a range, in 71 birds, of 237-390 g. The total dose per bird of the preparation to be tested is dissolved in 1-4 c.c. of distilled water, made slightly alkaline with a few drops of a 10% solution of sodium hydroxide, and neutralised afterwards with a 10% solution of acetic acid, care being taken that the solution remains clear.

Each bird receives 4 equal injections into the pectoral muscles, one on each of 4 consecutive days, and is killed 24 hours after the last injection. The crop-sacs are taken out at autopsy, washed and freed from fat, and the whole crop-sac is weighed, since it has been found very difficult to determine the extent of the stimulated area. The criterion of response is the increase in the weight of crop-sacs over those of untreated controls.

Dr. O. Riddle.

Groups of 10 mixed male and female white Carneau pigeons are used, 48-66 days after hatching, the average body-weight being 420-520 g. The total dose per bird of the preparation to be tested is dissolved in 0.8 c.c. of distilled water at pH8.0, and given by 4 equal intramuscular injections over a period of 96 hours, at the end of which the birds are killed.

The criterion of response is the increase in weight of crop-sacs, and the activity of the sample is determined by reference to a standard table, with a correction factor for the particular race of pigeon used.

The National Institute for Medical Research.

Groups of 10 pigeons, male or female, with a range of body-weight of from 250-450 g., are used. One daily subcutaneous injection is given on each of 6 consecutive days and the birds are killed 24 hours after the last injection.

The crop-sacs are removed, washed thoroughly in saline, and the stimulated areas dissected and fixed in Bouin's fluid overnight. They are transferred to 70% alcohol and weighed after removal of the surface fluid by blotting-paper.

The criterion of the response is the actual weight of the crop-sacs calculated for a pigeon weighing 300 g., and the activity of an extract is expressed in units by reference to a dose response curve.

**MEMORANDUM ON THE INTERNATIONAL
STANDARD FOR THE LACTOGENIC
(CROP-GLAND STIMULATING) SUBSTANCE OF THE
ANTERIOR LOBE OF THE PITUITARY GLAND
(PROLACTIN, GALACTIN, MAMMOTROPHIN)**

Established by

the Department of Biological Standards,
National Institute for Medical Research,
Hampstead, London, N.W.3.

INTRODUCTION

During 1937 and 1938, an enquiry was made among interested workers as to the practicability and desirability of establishing an international standard for the substance commonly known as the lactogenic, or crop-gland stimulating, hormone of the anterior pituitary lobe. It was recalled that preparations of this substance were standardised in a variety of ways and that a number of definitions of unit amounts were in existence. The survey showed that there was virtual unanimity as to the desirability of establishing a standard and, in view of the fact that a unit defined by Dr. Riddle in terms of an amount of a dry preparation kept in his laboratory was already widely used, it seemed likely that there would be little trouble in establishing an international unit, also defined in terms of an amount of a standard preparation. A preliminary enquiry among manufacturing organisations suggested that it would be possible to obtain enough material to constitute a suitable standard in adequate quantity.

At the third Conference on the Standardisation of Hormones, held in Geneva in August 1938, under the auspices of the Permanent Commission on Biological Standardisation, the results of the preliminary survey were considered, and it was unanimously decided to arrange for the establishment of an international standard for the lactogenic (crop-gland stimulating) substance.

The Conference agreed that preparations offered towards the standard should be circulated among experts to be examined for their suitability as constituents of the standard. It was agreed that no contribution should be accepted if it was found to contain less than about 5 Riddle units of the specific activity per

milligramme when tested in comparison with Dr. Riddle's own contribution, which was already available and assayed in such Riddle units.

The Conference further agreed that the international unit should be so defined as to conform as closely as possible to the existing Riddle unit. The standard was accordingly established as indicated and brought into current use on November 1st, 1939.

PREPARATION AND FORM OF ISSUE OF THE INTERNATIONAL STANDARD

Contributions from nine sources were offered towards the standard, and all of these were found, by each of the co-operating experts, to contain more than the stipulated 5 Riddle units per milligramme. These contributors, whose generous helpfulness is here acknowledged, were :

Allen and Hanbury Ltd., London.
 Ayerst, McKenna and Harrison Ltd., Montreal.
 Armour and Company, Chicago, Ill., U.S.A.
 The Glaxo Laboratories Ltd., London.
 Etablissements Byla, Paris.
 N.V. Organon, Oss, Netherlands.
 National Institute for Medical Research, London.
 Parke, Davis and Company, Detroit, Mich., U.S.A.
 Dr. O. Riddle and Dr. Bates.

None of these preparations was diluted and, in accordance with the procedure laid down by the Conference, no diluent was added during the course of the mixing operations. Except for the removal of the specimens which were circulated for co-operative examination, the contributions were mixed as received, and a total of 107 gm. of material was obtained. The mixture was dried by exposure to P_2O_5 *in vacuo*.

It had already been ascertained that this material could be made into tablets directly without the use of excipient, after a process of granulation which was found not to interfere with the biological activity. It was decided therefore that the standard, for ease of manipulation, should be dispensed in the form of tablets, as had been done with the two gonadotrophin standards.

The definition of the unit given below suggested that tablets of 10 mgrm. would be of convenient size and that 10 such tablets per ampoule would be a convenient packing. 95.2 gm. of such tablets was obtained and a test weighing showed that 78% of the tablets were within 2% of the 10 mgrm. aimed at. The tablets were then packed in lots of 10 in small tubes of amber glass which were plugged with cotton-wool and placed in ampoules. The ampoules were evacuated, filled with pure dry nitrogen, and sealed. A cork to fit the inside amber tube was also enclosed in each ampoule. This method of double packing was devised to ensure the exclusion of oxygen from the finally sealed ampoule, as laid down in the report of the Conference, and, at the same time, to provide a suitable container for the tablets after the ampoule had been opened and discarded. The finished ampoules were transferred to the cold room and are

maintained constantly at a temperature of -2°C . 932 of these ampoules, each containing ten 10-mgrm. tablets, were prepared. The standard is kept by the Department of Biological Standards, National Institute for Medical Research, London, N.W.3.

The whole of the procedures involved in the mixing, compressing and packing of the material was generously carried out by Burroughs Wellcome and Company, who also designed and provided the glassware used, as a contribution toward the production of the international standard.

At the time of the third Conference, it seemed likely that only rather small amounts of material might be forthcoming towards this standard, and the Standards Department of the National Institute for Medical Research was asked to consider the practicability of issuing a portion of the standard in diluted form for use in the intradermal test. The supply of material, however, has exceeded expectations, and it has not been considered necessary to issue the standard in more than one form.

DEFINITION OF UNIT

The results of the co-operative assays gave an average for the whole material of about 11 Riddle units per milligramme, but examination of the data showed that the figure could not be of precise significance and was unlikely to be distinguishable from 10 Riddle units per milligramme. Dr. Riddle's own determinations indicated that the mixture contains slightly less than 10 units per milligramme. It was decided therefore, in keeping with the report of the Conference and to simplify calculation, to define the International unit as :

The specific activity contained in 0.1 milligramme (= 100 gamma) of the standard preparation,

and to recommend the use of this unit for recording the activity of all crop-gland stimulating preparations.

SUGGESTIONS FOR USE

After the ampoule has been opened, the inner tube should be removed, freed from the two cotton-wool plugs and closed with the cork provided. One or more tablets, each of which contains *about* 100 units, should be removed as required. The tablets are as constant in size as is practicably possible, but it is essential that they should be weighed before use, so that a solution can be made of an exactly known strength, on the basis of 10 units for each milligramme of ascertained weight. The tablets dissolve very readily in water or saline.

After the ampoule has been opened, the amber tube containing the tablets of the standard preparation should be kept in a small desiccator containing P_2O_5 .

USE OF THE STANDARD IN BIOLOGICAL ASSAY

The following citation, relative to the use of the standard in biological assay, is taken from a report of the Conference¹ :

“ The Conference cannot, on the information before it, recognise any test as giving sufficiently quantitative results for the comparative assay of preparations in relation to this standard, except those which depend on the measurement or observation of growth produced in the crop gland of the pigeon or dove, whether as the result of systemic or of local administration.”

¹ *Bull. Health Org.*, 1938, 7, 893.