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QUARTERLY BULLETIN
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THE BEST METHODS OF TREATING
MANURE-HEAPS
TO PREVENT THE HATCHING OF FLIES

by

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INTRODUCTION.

This question, which the European Conference on Rural Hygiene convened in 1931 by the League of Nations Health Organisation, requested schools of hygiene to study, was specially deserving of the attention of the Nancy Institute of Hygiene.

The campaign against flies, and therefore against one of the main sources of their multiplication—dung—cannot, indeed, be a matter of indifference to those who are concerned with the sanitation of rural districts and with the improvement of the hygienic and living conditions of the rural population. This question is of peculiar interest in our part of the country.

The traveller whose itinerary takes him into Lorraine, and especially the motorist who passes through the villages in the

Departments of Meurthe-et-Moselle, Moselle, Meuse and Vosges, is astonished to see, in the great majority of them, that his road is sign-posted by manure-heaps in front of the houses, bearing witness by their size to the quantity of live-stock belonging to each owner. This is a feature of our villages which produces an unfavourable impression upon the visitor, especially as in other parts the manure-heaps are generally concealed in the farmyards behind the houses.

Does this mean that, in the last-named circumstances, the villages are healthier ? That depends entirely on the method of protecting the manure-heaps. Their presence in front of the houses, at the edge of the public road, striking though it is, and plainly though it demonstrates a complete disregard of cleanliness, is really insanitary only because of the way in which the manure is kept.

What is the reason for this arrangement, which is peculiar to our countryside ? It derives not only from immemorial custom, but also, and more especially, from the actual structure of the old villages of Lorraine, in which the houses are very close together and the farm buildings stand on long, narrow strips of land and generally adjoin one another, so that gaps are few and far between. Usually, where there is no farmyard, or no lane leading to it, it becomes necessary either to carry the dung from the byre straight out of the village, or to deposit it either in front of the houses on ground belonging to the owners, or on the edge of the highway. This practice has serious drawbacks from the standpoint of sanitation. As there are often no platforms or cemented pits, the manure being piled actually on the ground, liquid manure trickles on to the highway or into the gutter. Things are still worse when it rains, because stagnant and foul puddles are produced ; and all these factors ultimately contribute to insanitary conditions by infecting the subsoil and underground waters, the streets and the atmosphere. We should also point out that these manure-heaps, close to the houses and very often close to the wells, may have a very bad effect on the health of the people.

It was essential to give a brief outline of the position, from this point of view, of the communes in the Department of Meurthe-et-Moselle, thus affording a general idea of the ground covered by our researches. A glance at figures 1 to 4 will supplement the rapid description given above.

We need not refer to all the efforts that have been made to remove these drawbacks and to overcome deeply rooted habits, but it may be well to mention some of the more recent attempts, especially since 1914.

During the war, many of the villages in our department were the scenes of fighting and destruction, and others were occupied by the armies. In the latter, all the manure-heaps disappeared during the war period ; this improvement was doubtless greatly helped by the presence of the military authorities, the labour they had at



Figure 1. — MOIVRONS.

their command, the strict orders they issued, and even more by the evacuation of a large part of the population and the considerable decline in the number of live-stock.

When peace returned, people soon went back to their old ways, and villages resumed their former appearance. The departmental authorities then endeavoured to make a change both in villages that had not suffered and in those which had been destroyed in the war and were being rebuilt. The Prefect sent out two successive circulars to the mayors of communes, on February 15th, 1922, and August 1st, 1923, followed by an order concerning the disposal of manure, dated December 31st, 1923. These circulars and order laid down very full regulations for the disposal of manure, giving

4 THE BEST METHODS OF TREATING MANURE-HEAPS

details of the methods of sanitation and protection to be employed, and concluding as follows :

"All manure-heaps, which must no longer be formed close to the public highway, must be completely removed, and their sites levelled and cleaned before June 1st, 1924. Where exceptions are allowed, the improvements (construction of cemented pit and drain-off tank) must be completed before November 1st, 1924.

"Where this is admittedly impossible, an extension of time may, at the request of the persons concerned and on the advice of the mayor, be granted by the Prefect in the area of the departmental capital, and by the sub-prefects in other areas, but such extension may in no case run beyond November 1st, 1925."

Notwithstanding this detailed, documented and imperative order, no appreciable change has taken place in the great majority of our rural communes. A few mayors have succeeded in securing the removal of manure-heaps from the edge of the public road, the peasants carrying the manure daily to their fields at a distance from the villages. In a number of villages which had been almost completely destroyed, and in which, consequently, a real re-distribution of properties had been feasible, the farms have been provided with yards containing cemented pits and drain-off tanks ; but, for the most part, our villages still present the insanitary aspects and reveal the errors which we have described above.

As the purely administrative action so far taken has proved ineffectual, we felt that our work should be directed towards a practical and local aim. After all, it is the business of a regional institute of hygiene to endeavour to direct the action to be taken and to collect the information on which it can be based.

I. MANURE-HEAPS AND THE INSALUBRITY OF RURAL DISTRICTS IN THE DEPARTMENT OF MEURTHE-ET-MOSELLE.

There can be no doubt that, in our rural districts, the position of manure-heaps and the way in which they are kept is in most cases one of the principal sources of insalubrity. We think it necessary, however, to supplement our foregoing observations with a few facts and figures.

The very special location of manure-heaps in our department tends to pollute the air, particularly in nearby dwellings, and to promote the breeding of flies. Furthermore, the manner in which the dung

is stacked is a very important factor in the infection of streets, of the subsoil, of the subsoil water and thereby of the wells, which still to a considerable extent supply the drinking-water of the population.

It would be difficult, if not impossible, to prepare accurate statistics of the total number of stacks of manure in each commune, differentiating manure stacked on a cemented pit with a drain-off tank for liquid manure and dung not so stacked. As a result, however, of co-operation between the Institute of Hygiene and



Figure 2. — SOMMERVILLER.

the Director of the agricultural services of the department, we have been able to obtain sufficiently reliable figures for all farms possessing not less than one hectare of ploughland. These statistics have not only been prepared for the whole department, but have been classified by "arrondissements", by "cantons" and by "communes".

A few figures taken from these general statistics will give a general view of the situation :

| | |
|---|--------|
| Total number of farms of from 1 hectare to 500 hectares and over in the whole of the department | 21,374 |
| Number of these farms possessing a cemented manure pit with a drain-off tank for liquid manure | 3,799 |

The proportion of properly laid out manure-heaps is, therefore, for the whole of the department 17.7 per cent.

This proportion varies in each of the three "arrondissements" : Nancy, 15.4 per cent ; Lunéville, 27.6 per cent ; Briey, 14.2 per cent.

It will be seen, therefore, that protection of the subsoil against infection by manure-heaps and liquid manure is still very slight, since in about 83 per cent of the cases it is entirely lacking.

In reality, however, the situation is even much more serious, because there are many other manure-heaps besides those in the farms referred to above. Many owners of small live-stock and less extensive lands also have their stack of manure, which, even if it be small, is nevertheless a potential source of infection owing to the absence of any protection. We have thus been able, in the course of thorough enquiries conducted in a very appreciable number of communes, to see, for instance, in one commune 150 small stacks of manure and only three large stacks with a cemented pit ; in other communes, the proportion of protected stacks was 5, 3, 1 and even 0 per cent.

It has been noted that manure-heaps without cemented pit or drain-off tank are stacked only a few metres away from wells which provide drinking-water for the houses. By way of example, we give a few results of the numerous analyses made by the Institute of Hygiene of water taken from wells situated near manure-heaps (see table, page 7).

It should be noted that the analyses shown were selected from among those made in a period of drought when the degree of infiltration was very slight—when, in other words, liquid manure and liquids in general penetrated less into the subsoil, pollution being thus reduced to a minimum. The danger of manure-heaps from the point of view of the health of the inhabitants is therefore, in this respect, proved beyond all doubt.

Admittedly, the danger has been decreased by the great extension (above all, since 1920) throughout our Department of piped water supplies. According to a paper by one of our students on the problem of potable water in Meurthe-et-Moselle, about 50 per cent of the communes now have a piped water supply (total number of communes in the department, 600).

The extension of piped water supplies is therefore one indirect method of combating the infection of well water. But the fact is

that, in spite of such a water supply, some inhabitants continue to use the water from their wells. As an instance of this, we have given in the table below the analysis of water from a well at Cercueil (a well contaminated by a manure-heap nearby) which

RESULTS OF THE BACTERIOLOGICAL ANALYSIS
OF WATER FROM WELLS SITUATED NEAR MANURE-HEAPS.

(Villages of Lorraine)

| Locality | Date | Observations | B. coli per litre | Colonies to the c.cm. | Conclusion |
|------------------|------------|---|-------------------|-----------------------|------------|
| Crion | 25.VIII.32 | Drought Manure-heaps 15 metres distant | Over 1,000 | 108,292 | Bad |
| Drouville | 22.VIII.32 | Drought Manure-heap 5 metres distant | Over 1,000 | 202,232 | Bad |
| Buissoncourt ... | 22.VIII.32 | Drought Manure-heap 5 metres distant | Over 1,000 | 327,269 | Bad |
| St. Firmin | 23.VIII.32 | Drought Manure-heap 10 metres distant | 500 | 300,585 | Bad |
| Morville | 5.IX.32 | Drought Manure-heap 10 metres distant | Over 1,000 | 412,000 | Bad |
| Diarville | 23.VIII.32 | Haut Bout Manure-heap 12 metres distant | Over 1,000 | 730,000 | Bad |
| | | Neuf Pont | Over 1,000 | 100,262 | Bad |
| | | Dr. M's well No manure- heap | 0 | 580 | Potable |
| Cercueil | 9.IX.33 | Drought Manure-heap 6 metres distant | 100 | 10,412 | Bad |
| Sommerviller ... | 6.IX.32 | Piped water supply Numerous manure-heaps | 10 | 328 | Potable |

the inhabitants drink in spite of the fact that a supply of potable water has been laid on for the use of the village. It should be noted that one of the consumers of this water has contracted undulating fever, that the manure-heap neighbouring on his well had received the scourings of a sheepfold infected with the same disease, and that, as no other case of contamination could be found, it is quite possible that this may be the origin of his illness.

II. STUDIES ON FLIES.

1. RESEARCH INTO THE AMOUNT OF THE EXTERNAL BACTERIAL FLORA CARRIED BY FLIES, CONSIDERED BOTH QUANTITATIVELY AND IN RELATION TO THE PLACE FROM WHICH THE FLIES ARE OBTAINED.

Long before the era of bacteriology, many authors, proceeding from observed facts, incriminated the fly as the vector of certain pathogenic germs ; later, after the discovery of microbes, this hypothesis became a confirmed fact, and it was shown, not only that flies could harbour numerous germs on the surface of their body, but that such germs were to be found in their excreta, in the products of regurgitation and in the larvæ of infected flies.

Many species, pathogenic or not, have been identified, and our purpose has been, not to determine, after many others, the nature of this extremely varied bacterial flora, but simply, in a very general way, to bring out the fact that the number of microbes carried on the surface of a fly's body amounts to several tens of millions, and, in particular, that the amount of this bacterial flora depends upon the place from which the flies are obtained.

It appeared to us essential, however, to test this bacterial flora for one germ whose presence carries with it the suggestion of extensive pollution—namely, *B. coli*.

Despite the simplicity of our technique, we regarded it as wholly adequate, for it gave us results that were both sufficient and comparable *inter se*.

Our primary object being the spread of popular knowledge on the subject, we have brought together the most striking evidence which, whilst confirming known facts, can be used for propaganda in favour of an anti-fly campaign. Furthermore, as fly-breeding

is specially promoted by the existence of manure-heaps, every well-planned campaign against flies should be accompanied by measures designed, not to bring about the disappearance of manure-heaps, but to make them inaccessible to these insects and—killing two birds with one stone—to protect the atmosphere and the subsoil from the pollution which they involve. In addition to the part which is played by manure-heaps as “reservoirs of virus”, experience

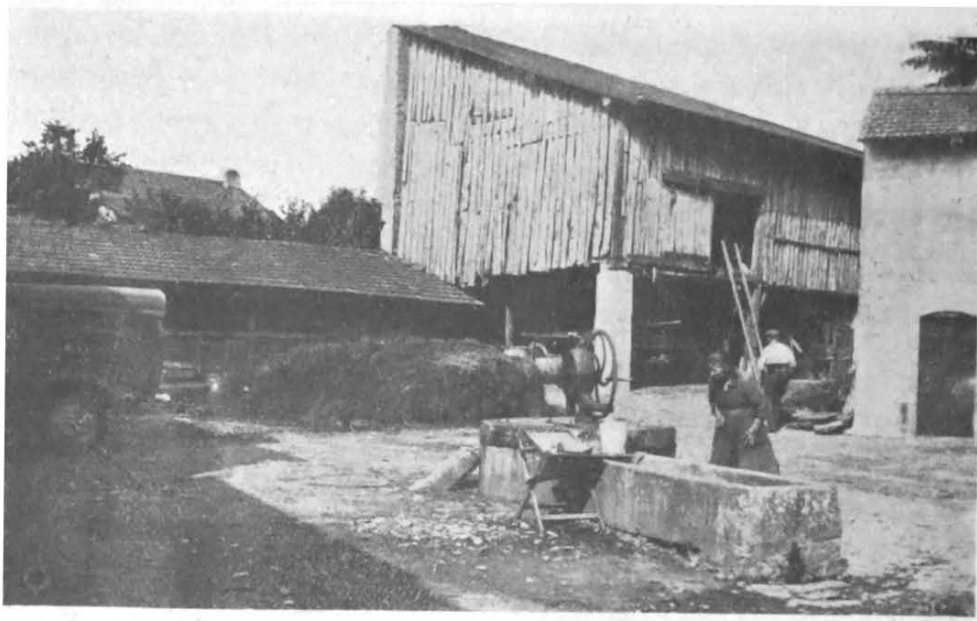


Figure 3. — DIARVILLE.

showed that flies caught in proximity thereto and in nearby houses were much more heavily infected than others caught, for instance, in town flats. Now, in our area, where manure-heaps are particularly numerous, the peasant houses are swarming with flies and an anti-fly campaign is, more than anywhere else, closely bound up with hygienic measures concerning manure-heaps.

We have already seen the difficulties which are encountered by public departments and health services in their endeavours to sanitise rural communes ; the documentary evidence which we have brought together appeared to us to afford a valuable and practicable means of educating the peasant. By this means he can be made to understand more fully the dangers of local customs and will be willing to apply measures of which no regulations, however imperative in character, could have shown him the advantage.

Our research work has been carried out on flies caught in immediate proximity to manure-heaps, on flies from village houses, on flies from town flats, and finally on flies caught in mid-forest.

Bacterial Count (Plate I).

The flies are caught by hand (the hands having previously been thoroughly washed with soap) and placed in sterile bottles of about 20 c.cm. Each bottle contains ten flies. In each bottle 10 c.cm. of sterile physiological saline are added—*i.e.*, 1 c.cm. per fly. The flies are kept in the solution for thirty minutes and frequently shaken up so that the bacteria carried may be so far as possible completely washed off. Then, with a sterile pipette yielding twenty drops per c.cm., one drop of the liquid is withdrawn and diluted to 1 : 1,000. This is seeded on to gelatine or agar, and the colonies are counted at the end of three days where gelatine is concerned, and after forty-eight hours in the incubator at 37° C. in the case of agar.

In order to determine the number of colonies corresponding to one fly, the figure given by the count should be multiplied by 1,000 and then by 20, seeing that we are dealing with a 1 : 1,000 dilution and have seeded one drop, or one-twentieth of a c.cm. It is understood, of course, that the figures found are only approximate, for, even though the flies should be washed for several hours, it would be impossible to detach the external bacterial flora completely.

Special Test for B. coli.

Ten tubes of peptone broth carbolised to 1.25 per thousand are prepared.

In the 1st tube, 20 drops of the liquid used for washing are delivered.

| | | | | | | |
|----------|------|--------------------|---|---|---|-------------------|
| — 2nd | — 10 | — | — | — | — | |
| — 3rd | — 5 | — | — | — | — | |
| — 4th | — 4 | — | — | — | — | |
| — 5th | — 2 | — | — | — | — | |
| — 6th | — 1 | — | — | — | — | |
| — 7th | — 1 | — | — | — | — | |
| — 8th | — 1 | — | — | — | — | diluted to 1 in 2 |
| — 9th | — 1 | — | — | — | — | — 1—5 |
| The 10th | — | serves as control. | | | | — 1—10 |

These tubes are then placed in the incubator for five days at 38° C., and the presence of *B. Coli* is determined by testing the cultures

for indol production, according to the method used for water analysis.

A positive reaction in the :

| | | | | | | | | |
|----------|-------|------|-------|----|-----|----------------|-----|------|
| 1st tube | means | that | there | is | 1 | <i>B. coli</i> | per | fly. |
| 2nd | — | — | — | — | 2 | — | — | — |
| 3rd | — | — | — | — | 4 | — | — | — |
| 4th | — | — | — | — | 5 | — | — | — |
| 5th | — | — | — | — | 10 | — | — | — |
| 6th | — | — | — | — | 20 | — | — | — |
| 7th | — | — | — | — | 40 | — | — | — |
| 8th | — | — | — | — | 100 | — | — | — |
| 9th | — | — | — | — | 200 | — | — | — |



Figure 4. — LEYR.

Results and Conclusions.

What strikes one at first sight in the following table is the very large number of living germs that a fly can carry. These figures, as we have noted, are only approximate, for it is obvious that a more minute and accurate technique would make it possible to get closer to the exact facts of the case. None the less, we may state that all flies without distinction of origin are regular reservoirs of microbes, of which they can carry a number ranging from 60,000 to 25,863,000. Next, if we compare these figures *inter se*, we find that they relate essentially to two categories of flies : (1) those that are liable to infection at any time by contact with unprotected or ill-protected manure-heaps—*i.e.*, the flies that swarm in our

villages ; (2) those which, on the contrary, come into contact with filth only by accident, as, for example, the flies found in clean town dwellings. As to flies caught in the woods, it is obvious, *a priori*, that their bacterial flora will be comparatively poor, and that hypothesis is borne out by experience.

SUMMARY TABLE.

I. Flies caught in Immediate Proximity to Manure-heaps on Walls or Tilling Implements not exposed to the Sun.

| Species | Place | Date | Colonies | B. coli | Plate I | |
|------------------------|------------------|-------------|---------------|---------------|---------|---------------|
| <i>Musca domestica</i> | Sommerviller ... | 22.VIII.32 | 24,580,000 | More than 200 | Fig. 1 | |
| | Haraucourt | 22.VIII.32 | 25,863,900 | More than 200 | | |
| | Buissoncourt ... | 22.VIII.32 | 20,080,000 | More than 200 | | |
| | Diarville | 23.VIII.32 | 26,160,000 | More than 200 | | |
| | Drouville | 23.VIII.32 | 10,960,000 | More than 200 | Fig. 2 | |
| | | 28.VIII.32 | 18,293,000 | More than 200 | | |
| | | Crion | 25.VIII.32 | 13,860,000 | | More than 200 |
| | | Leyr | 5.IX.32 | 15,280,000 | | More than 200 |
| Cercueil | 2.VIII.33 | 21,292,000 | More than 200 | | | |

II. Flies caught on Grazing Cows.

| | | | | | |
|------------------------|-----------------|-----------|------------|---------------|--------|
| <i>Musca domestica</i> | Saulxures | 2.VIII.33 | 11,007,000 | More than 200 | Fig. 6 |
|------------------------|-----------------|-----------|------------|---------------|--------|

III. Flies from Village Houses.

| | | | | | |
|------------------------|----------------|------------|------------|---------------|--------|
| <i>Musca domestica</i> | Einville | 25.VIII.32 | 12,122,000 | More than 100 | Fig. 3 |
| | Leyr | 5.IX.32 | 15,271,000 | More than 100 | |
| | Fresnes | 7.X.32 | 9,760,000 | More than 200 | |

IV. Flies from Town Flats.

| | | | | | |
|------------------------|-------------|------------|-----------|----|--------|
| <i>Musca domestica</i> | Nancy | 20.VIII.32 | 4,080,000 | 10 | Fig. 4 |
| | | 1.IX.32 | 3,052,000 | 7 | |
| | | 13.IX.32 | 992,000 | 5 | |
| | | 4.XII.32 | 623,210 | 0 | |

V. Flies caught in Forests.

| | | | | | | |
|------------------------|-------------------|-----------------|------------|---------|------------------|---|
| <i>Musca domestica</i> | Sainte-Libaire .. | 4.IX.32 | 125,000 | 0 | Fig. 7 Fig. 8 | |
| | | 2.X.32 | 602,000 | 1 | | |
| <i>Tabanus bromius</i> | Malzéville | 4.VII.33 | 229,000 | 0 | | |
| | | Fresnes | 10.VIII.33 | 120,000 | | 0 |
| | | Gérardmer | 28.VII.33 | 60,000 | | 0 |

Whereas the presence of *B. coli*—and, indeed, its presence in large numbers (upwards of 200 per fly)—has always been demonstrated in flies caught in villages where manure-heaps lie about, this

bacillus is, on the contrary, rare or entirely absent in the second category of flies.

From these experimental data derived from researches that we have carried out in villages where the sanitary conditions are bad and, in particular, where there are numerous manure-heaps, it appears that the bacterial flora of the "village" fly is numerically very much greater than that of the "urban" fly, and, in view of this difference, which appears likewise in the *B. coli* count, the flora of the pathogenic species of the first-named category must be much more abundant than that of the second.

This dung-heap fly should then be constantly starting epidemic foci all round ; generally speaking, however, the course of summer epidemics started and kept going by flies is not as severe as the potential infective power of the fly might lead one to expect. The fly—as WOLLMAN has pointed out—possesses the faculty of "autosterilisation", and, if it did not continually find around it fresh sources of infection, in a few days its rôle as a vector of disease would be considerably reduced. This autosterilisation is carried out, on the one hand, by mechanical means, "the fly spending its life in cleaning itself" (WOLLMAN), and, on the other, by the microbicidal action of the sun's rays. We have verified experimentally this second factor which intervenes in the autosterilisation of flies, and we now propose to deal with it.

2. INFLUENCE OF THE SUN'S RAYS ON THE EXTERNAL BACTERIAL FLORA OF FLIES.

Our intention was not to study the sterilising action of the sun's rays on certain species of the external bacterial flora of flies, but to demonstrate in a general manner the fact that the sun could by itself diminish, often to a very considerable extent, the amount of such flora. Employing the technique which we have already described, we reached results which point conclusively to such natural sterilisation.

We used flies caught in town flats and flies caught in villages near manure-heaps ; a batch of twenty flies caught simultaneously in the same place was divided between two sterilised bottles—*i.e.*, ten flies per bottle. The flies in the first bottle, which were to serve as controls, were washed for thirty minutes with sterile

physiological saline, and gelatine plates were seeded with one drop of the washing liquid diluted, as needed, in varying proportions, to permit of the easier counting of the colonies. The flies in the second bottle were treated in the same way, but *after having been exposed to the sun's full rays* for two hours (the temperature varying from 30° to 40° C. during the experiments).

The gelatine plates thus seeded were kept at a temperature of about 20° C., and after seventy-two hours the colonies were counted.

The following are two examples of the results obtained (see Plate II) :

(a) *Flies from Town Flats.*

Whereas the bacterial flora per fly at the moment of capture numbered 2,540,000 colonies, after two hours' exposure to the sun the figures fell to 160,000, thus demonstrating in no uncertain manner the sterilising action of the sun's rays.

(b) *Flies caught in the Neighbourhood of Manure-heaps.*

The same conclusions were arrived at, but with an even more pronounced difference, since, of the 32,560,000 germs that the fly was carrying when caught, there remained, after the sun test, only 6,720,000—*i.e.*, destruction of 25,840,000.

It would appear from our experiments that the bactericidal action of the sun's rays may be extremely powerful. It varies presumably with the seasons, and we would point out that our experiments are valid only for the actual period at which they were carried out—*i.e.*, in July and August, the months during which the light is most intense.

Accordingly, since the fly, apart from the mechanical means at its disposal, is naturally subjected in certain conditions to the sterilising action of the sun, it is understandable that it should rid itself of the greater part of the germs that it is carrying and that its infective power should thereby be considerably reduced.

The fly will prove the deadlier enemy when it has access to manure-heaps or filth capable of infecting it continually and when its habitat is devoid of direct light, as in the case of unhealthy urban and rural dwellings or slum dwellings.

These facts must be borne in mind when, for example, we come to determine the rôle of the fly in the spread of certain infectious

diseases ; in preventive measures, due account must be taken of this "autosterilisation", as noted by WOLLMAN.

3. INFECTIVE CAPACITY OF FLIES AND POLLUTION OF LIQUID AND SOLID FOODSTUFFS.

We have been at pains to show by figures and illustrations—always with the purely general object of spreading information on the subject—that flies feeding on our foodstuffs contaminate them very rapidly and in many cases very extensively.

In a first series of experiments we endeavoured to determine the number of germs deposited by a fly on a solid culture medium, in relation to length of contact. As the greater number of our foodstuffs contain all the elements necessary for the growth of microbes, the danger of consuming contaminated foodstuffs uncooked will be realised.

A fly, caught with aseptic hands, is kept captive in contact with an ordinary agar plate. By its movements to and fro, which can be stimulated and guided by slanting the plate at different angles, it seeds the medium. After from one to ten minutes, the fly is removed, the plate is placed in the incubator and the results are read twenty-four hours later.

With *Musca domestica* from a town flat, we obtained, after ten minutes' contact, a culture in which the colonies were so numerous as to be impossible to count. We then progressively reduced the length of the contact and found that after one minute's contact of the fly in question (*Musca domestica*) a culture was obtained in which it was easy to count the colonies.

We quote in illustration the results as shown in Plate No. III.

(1) Contact of *Musca domestica* for ten minutes with an ordinary agar plate gives in twenty-four hours a culture with too many colonies to count.

(2) With one minute's contact, ninety-three colonies were counted after twenty-four hours.

(3) The same experiment with *Calliphora vomitoria* gave 1,790 colonies.

Using flies from villages with manure-heaps, we arrived at much more striking results. Allowing one minute's contact, we found,

after twenty-four hours in the incubator, a number of colonies varying between 1,500 and 4,000.

While the fly can get rid of its bacterial flora by mechanical means or through the sterilising action of the sun, there is a third, much more dangerous, possibility—namely, that of dropping some of the germs on our foodstuffs. The majority of these germs, no doubt, are of a harmless non-pathogenic kind ; but, to quote one instance only, it is common knowledge that the manure-heaps of farms in the country are made the repository, not only of the sweepings of the sheds, styes and stables, but also of the excreta of healthy and sick persons or animals. Always on the lookout for fresh fecal matter, the fly will, if the excreta is that of, say, a typhoid patient, certainly pick up a number of Eberth bacilli and, in view of its habit of continually flying in and out of dwelling-houses, it will leave these bacilli, alive and ready to spread their infection, on such foodstuffs as may be lying about.

The campaign against flies, in practice, is governed by these considerations. If, by judicious education, the countryman could be brought to realise the danger to which he exposes himself by all-too-frequent neglect to protect his foodstuffs, certain epidemics, such as choleric diarrhoea of infants, would not assume the seriousness which is frequently found.

But, of all foodstuffs, there is one which flies more particularly affect, and which is all too frequently treated with a minimum of care, and that is *milk*.

The researches which we have made in regard to the pollution of milk show clearly that a fly, by simple contact, is capable of transforming sterilised milk into a real microbial culture, as rich as it is dangerous.

In a flask containing 500 c.cm. of milk, sterilised in the autoclave (thirty minutes at 115° C.), and bacteriologically tested for sterility, a fly is placed on the surface of the milk. It is left in contact for thirty minutes, and the flask is then left to stand at the ordinary temperature for twenty-four hours. A drop of this milk seeded on to gelatine produces total liquefaction of the latter within twenty-four hours. In order to secure isolated colonies, the milk must be diluted in proportions rising to as much as 1 in 1,000,000. In this way, we were able to estimate at 10,220,000,000 the number of germs polluting 1 c.cm. of the milk used for the test (Plate No. IV).

As, further, the possible presence of *Bacillus coli* in this milk would confirm the fact of serious and dangerous pollution, we looked for this germ by means of seeding Besson bouillon with an admixture of lactose. When contaminated by *Calliphora vomitoria* for thirty minutes, this milk contained (after twenty-four hours) more than 100 *B. coli* per litre.

Repeating this experiment by taking samples, not after twenty-four hours, but after two and six hours at ordinary temperatures, we found with *Calliphora vomitoria* 1,572,000 germs per c.cm. and 25 *Bacilli coli* per litre after two hours, and, with *Musca domestica*, 1,822,000 germs per c.cm. and 10 *Bacilli coli* per litre after six hours. The flies with which the experiments were made were taken from a town flat. Village flies would have given even more striking results (Plate No. V).

These experiments are, in our view, sufficient to show that milk, which is an excellent culture medium, may become a dangerous foodstuff if it is not treated with due regard to cleanliness and scrupulously protected against flies. Our researches show that :

- (1) Contact of a few minutes only with a fly is sufficient to seed the milk ;
- (2) This seeding is rapidly followed by a very considerable microbial development, which increases the longer the milk is left ;
- (3) In this abundant and polymorphic bacterial flora, the frequent presence of *Bacillus coli*, in itself a dangerous germ, is further an indication of possible contamination by other germs of fecal origin (typhoid, dysentery, cholera strains, etc.) ;
- (4) These findings are all important from a practical point of view, owing to the fact that the contamination which we induced experimentally is capable of taking place naturally, having regard to certain current practices of everyday life.

Is it not an everyday experience to see milk consumed several hours after it has been boiled, having in the meanwhile been kept in receptacles without lids, so that protection from contamination by flies is in no way ensured ? For the adult, the dangers of drinking such milk may be comparatively small, but this is not the case with children and, in particular, with infants. In the country, especially, such causes of infection, in conjunction with other causes

and dietary errors, may undoubtedly help to bring about those cases of gastro-enteritis and summer diarrhoea which are important factors of infantile morbidity and mortality.

These few facts go to show once more the need for an anti-fly campaign and for action in connection with the various factors which facilitate the breeding of flies and their infective activities (manure-heaps, ill-protected latrines, filth, etc.) ; but it is quite clear that, in the organisation of this campaign, the public authorities will only have the support of the village populations in so far as the full need for the campaign has been brought home to the latter.

III. RESEARCHES INTO THE MOST SUITABLE METHODS OF PREVENTING INFECTION OF THE SOIL AND THE BREEDING OF FLIES OWING TO THE PRESENCE OF MANURE-HEAPS.

The foregoing evidence shows the necessity of adopting measures calculated to remedy a situation prejudicial to public health. Such measures must, however, be preceded by researches with a view to determining what methods are most suitable and how those methods shall be adapted logically both to the requirements of the situation and to the conditions of the country : preliminary survey of the field of action, the habits and methods adopted locally by peasants, the "lay-out of the villages"—*i.e.*, the particular arrangement of the dwellings, barns, cowsheds, pigsties, etc.

A summary of the measures hitherto taken in our region shows :

(1) In a comparatively unimportant number of communes the total suppression of manure-heaps, the manure being carried out into the fields outside the village as and when available : a radical method, but one which it is impossible to make general ;

(2) The existence of a very small number (less than 15 per cent) of cemented pits and drain-off tanks ;

(3) In the large majority of cases a total absence of arrangements with a view to the protection of the soil or atmosphere or the destruction of flies.

After considering, on the one hand, the documentation on available methods, the studies carried out by other schools and institutes of hygiene—in particular, the researches conducted under Professor THOMSEN's direction, and Dr. VON SCHUCKMANN's programme of experiments—and, on the other hand, the results of our investigations which bring out certain indications peculiar to our region, we decided to abandon the idea of employing chemical methods and to concentrate on experiments into physical processes complying with the following desiderata :

- (1) A process which would protect the soil and the subsoil from pollution by manure, which would be effective in the suppression of flies (*i.e.*, destroy eggs, larvæ, pupæ in the manure) and which would prevent flies from laying eggs on the surface ;
- (2) A process which would not injure the "agricultural" qualities of the manure ;
- (3) A process which would admit of practical application—*i.e.*, easy to employ and not too expensive.

Our experiment was based on the principle of the biothermic method described by ROUBAUD in several papers and also employed by SCHUCKMANN. We modified their technique, however, in order to obtain an *installation* answering to the desiderata set forth above. We borrowed, on the one hand, from the "manure-heap" technique described in agricultural treatises—by the agronomist ARNOUT, in particular, for promoting fermentation of the manure—and from BECCARI's zymothermic chamber process for the destruction and conversion into mould of household rubbish.

Where ROUBAUD's biothermic method is used—for the destruction of fly eggs and larvæ in the manure by means of the heat produced by decomposition, a method endorsed by SCHUCKMANN—a temperature of 60° C. can often be obtained, as we have proved, but the temperature may remain lower at various points and even at the centre of the heap, varying according to the kinds of manure—*i.e.*, horse, cow or pig—and according to their respective proportions in the common heap.¹

¹ Cf., on the temperature of the various kinds of manure, Professor THOMSEN's report, document C.H.1115.

Figure 5. — CLOSED CELL FOR KEEPING MANURE.

1. Loading of the cell (front view).



2. Back view and liquid-manure pump.

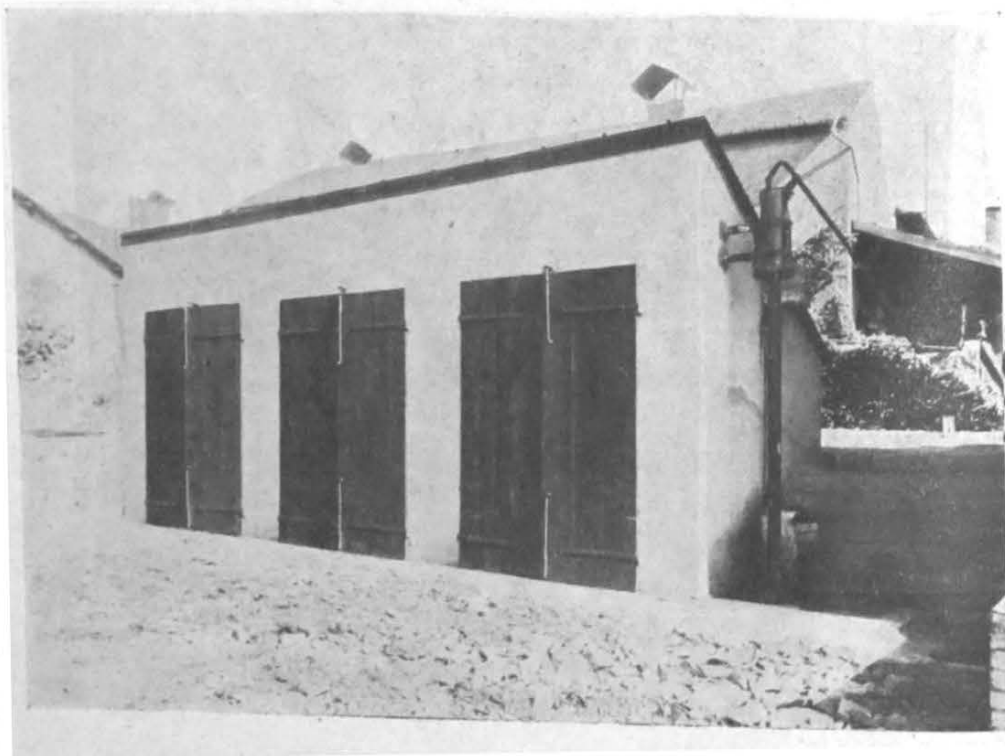
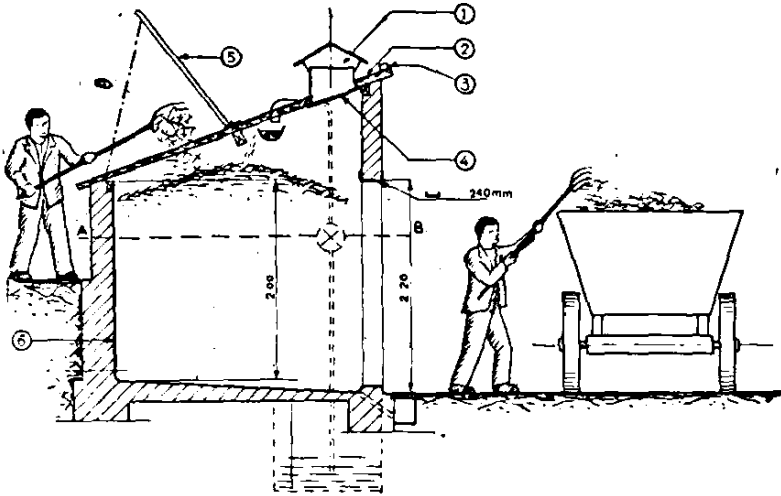
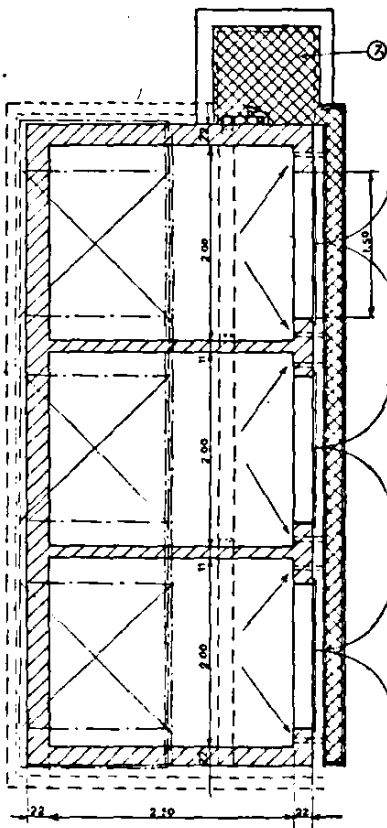


Figure 6. — CELL FOR THE TREATMENT OF MANURE.



1. Ventilation shaft.
2. Roofing-felt lining.
3. Joist 4 cm.
4. Wire gauze 1 mm.
5. Trap-door.
6. Water-tight cement coating.
7. Liquid manure pit, 1 cubic metre.



CHARACTERISTICS.

| | |
|-----------------------------------|--|
| Output : 10 cubic metres per week | } 5 cubic metres in chambers. 5 cubic metres in heap. |
| Capacity of each cell | |
| Duration of treatment | 1 month. |

PROGRAMME OF THE EXPERIMENT.

| | |
|------------|--|
| Cell No. 1 | } Filling 1st to 15th. Emptying 1st to 15th of following month. |
| Cell No. 2 | |
| Cell No. 3 | } Filling 1st to 15th. Emptying 1st to 15th of following month. |
| | |

That is a first indication pointing to the desirability of obtaining by means of fermentation a higher general temperature, especially since, as THOMSEN has noted and as we ourselves have observed, larvæ (probably under the influence of heat) tend to come to the surface of the manure-heap.

On the other hand, while fermentation under certain conditions is capable, by producing a sufficient rise in temperature, of killing eggs and larvæ, the manure, when exposed without protection to the open air, is a regular place of attraction for flies, which collect in swarms on its surface, become infected and also lay their eggs there.

This gives a second indication, pointing to the necessity of covering the manure-heap.

These indications, together with another derived from local conditions (the absence of means for protecting the soil or underground water deposits from pollution), were taken as a guide in the experiments carried out in the summer of 1933 with the collaboration of the "Société des Hauts Fourneaux de Pont-à-Mousson", which is engaged, *inter alia*, in sanitation work.

One of the company's farms (at Ludres) was used as an experimental centre. Only the principal points will be summarised, as figures Nos. 5-7 give data which are sufficiently conclusive.

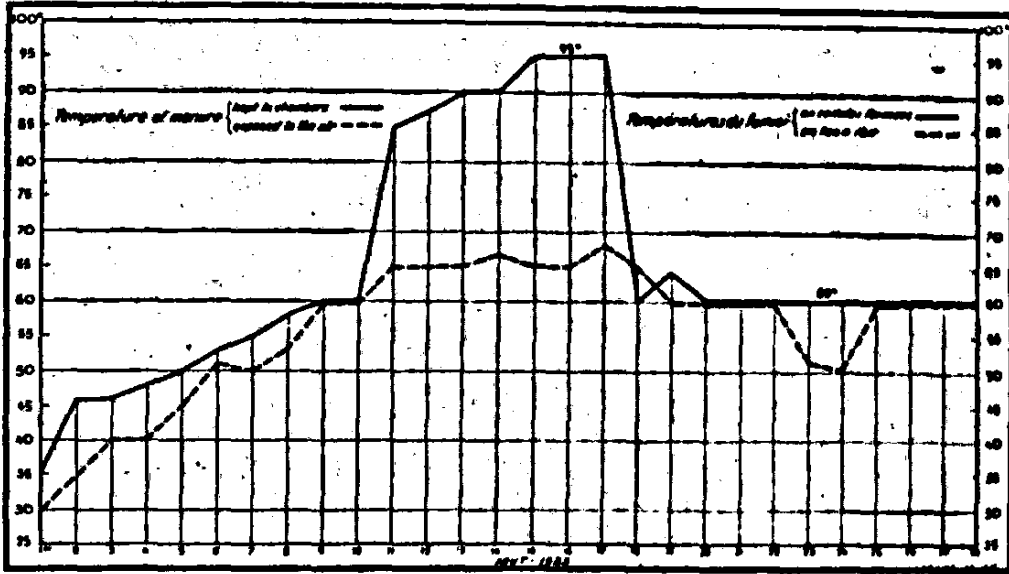
1. Construction of three watertight chambers (ventilation shaft covered with wire gauze to prevent the flies from getting in), with a trap-door for filling and a door for emptying, sloping floor and channel conveying the liquid to a cemented tank with pump, connected with the three chambers by a pipe to permit of "watering" the manure (sluices permitting of the watering of the contents of one chamber without the other two). Capacity of each chamber, 10 cubic metres.

2. Manure-heap, stacked in the usual way, to which was added daily a further quantity of exactly the same composition as was stored in the chambers. This heap was used as a control for all research purposes (temperature, analyses, etc.).

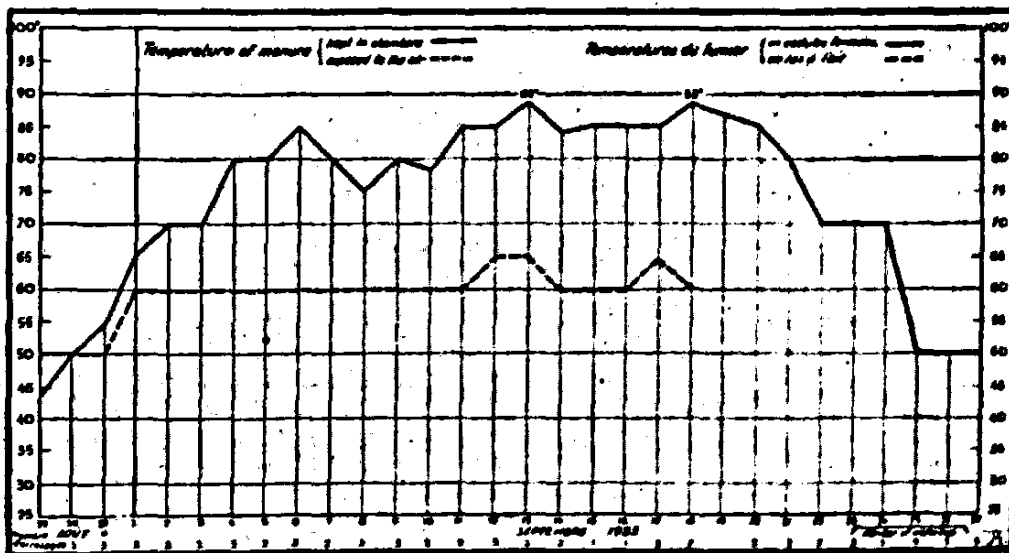
The manure (cow and horse) was divided up between the two installations, the composition and proportions being identical for both.

Figure 7. — EXPERIMENTS IN THE FERMENTATION OF MANURE.

1. One "watering" per day (August 1933).



2. Several "waterings" per day (September 1933).



The temperature was taken each day in the manure stored in the chambers and in the control heap.

Results.—The design of the chambers ensures in itself the complete protection of the soil, subsoil and atmosphere and the collection of liquid manure, whilst at the same time protecting the manure from flies, thus preventing them from becoming infected and from laying eggs.

The temperature curves for the manure in the chambers and the control heap are sufficiently conclusive to require no comment ; special emphasis may, however, be laid on the difference in the heat recorded (30° to 40° C. at peak figures). The temperature curve for the manure in the chambers varied according to the number of daily waterings (once a day in the case of curve 1, several times in that of curve 2), but reached a maximum far in excess of the temperature necessary to kill eggs and larvæ. This destructive action was demonstrated in practice by the entire absence of larvæ and flies in the cells when the latter were emptied.

It might have been asked whether such a temperature would not have an unfavourable influence on the chemical composition and hence on the agricultural value of the manure. Analyses, carried out by the Nancy Agronomic Station, of the manure of the chambers and control manure showed that the latter was actually not so rich as the former, while maturation proceeded much faster in the chambers. For example, the nitrogen content was as follows :

| | Per cent |
|-----------------------------------|----------|
| Manure exposed to the air | 0.418 |
| Manure kept in the chambers | 0.513 |

Conclusions.—These experiments, which were very conclusive from an experimental standpoint, proved satisfactory both as regards the protection of the atmosphere and soil and the suppression of flies.

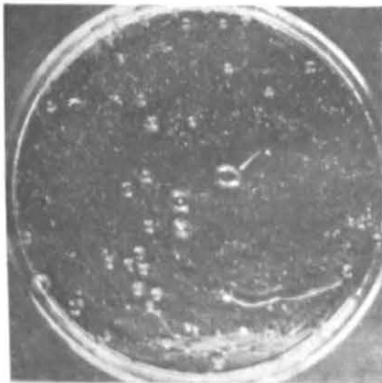
Although, on being tested, the working of this installation proved satisfactory for the farmer who employed it, its practical employment has to be considered from the standpoint both of its adaptation to the requirements and size of the various agricultural enterprises and of its construction in standardised material at a reasonable cost price within the financial reach of everyone. That point is at present being investigated by the technical services of the "Société des Hauts Fourneaux de Pont-à-Mousson".

Plate I.

THE BACTERIAL FLORA OF FLIES, CONSIDERED QUANTITATIVELY.

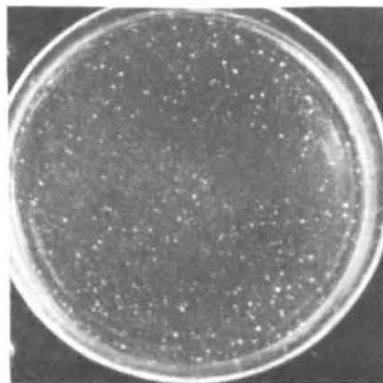
Figure 1—*Gelatine culture* ; figures 2 to 8—*Gelose cultures*. (Dilution 1 : 1,000.)

Musca domestica
(neighbourhood of manure-heaps).
1



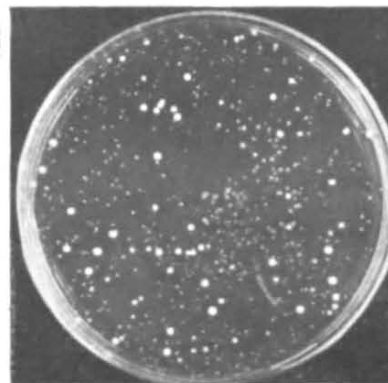
Over 20,000,000 germs per fly.

Musca domestica
(neighbourhood of manure-heaps).
2



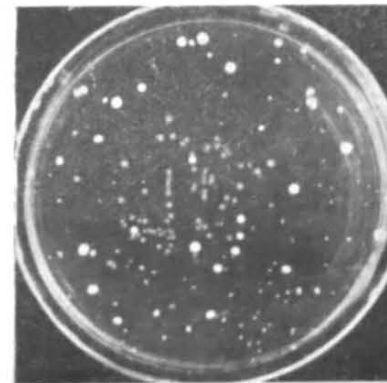
Over 15,000,000 germs per fly.

Musca domestica
(village flat).
3



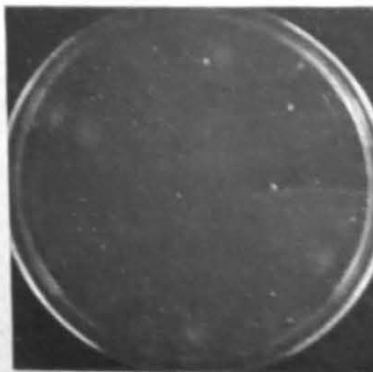
12,122,000 germs per fly.

Musca domestica
(town flat).
4



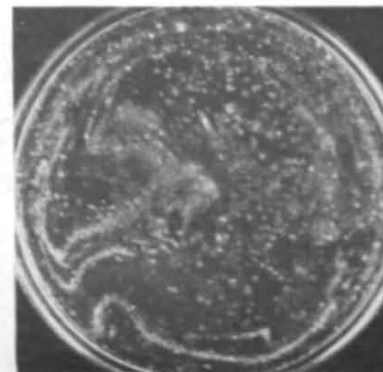
4,080,000 germs per fly.

Musca domestica
(laboratory).
5



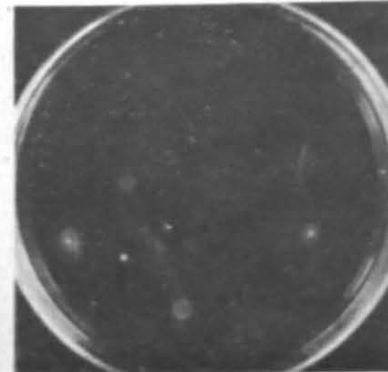
3,052,000 germs per fly.

Musca domestica
(on grazing cows).
6



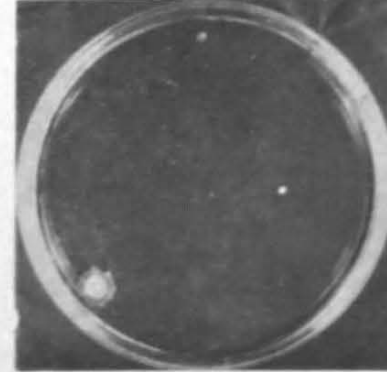
11,007,000 germs per fly.

Tabanus bromius
(in forest).
7



120,000 germs per gadfly.

Tabanus bromius
(in forest of fir-trees).
8



60,000 germs per gadfly.

Plate II.

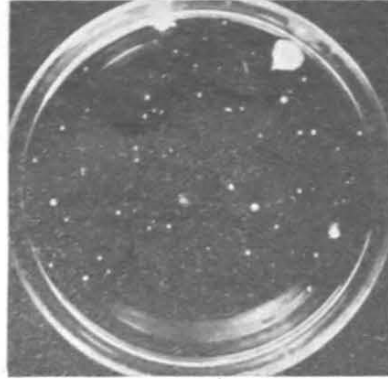
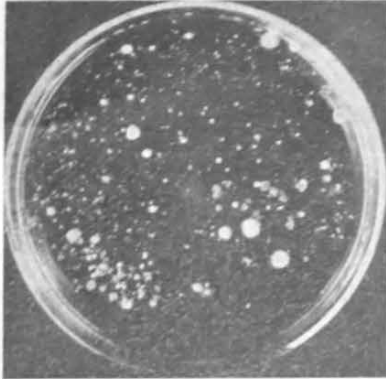
**STERILISING ACTION OF THE SUN'S RAYS ON THE BACTERIAL FLORA OF FLIES (*Musca Domestica*).
72-hour' gelatine cultures.**

A. Flies from Flats.

I. Not exposed to the sun's rays.

Dilution 1 : 100.

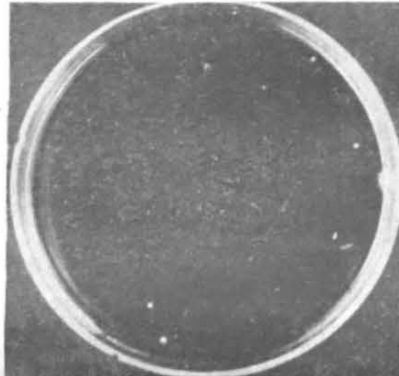
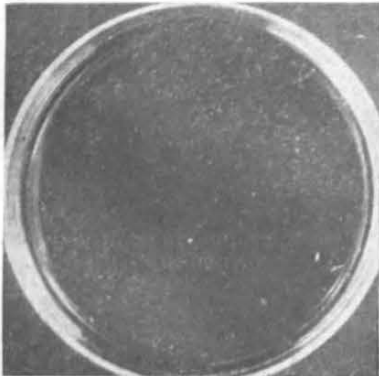
Dilution 1 : 1,000.



Results

| | | Number of colonies per fly |
|---------------------------|--------------|----------------------------------|
| Not exposed to the sun | flat | 2,540,000 |
| | manure | 32,560,000 |
| Exposed to the sun | flat | 160,000 |
| | manure | 6,720,000 |

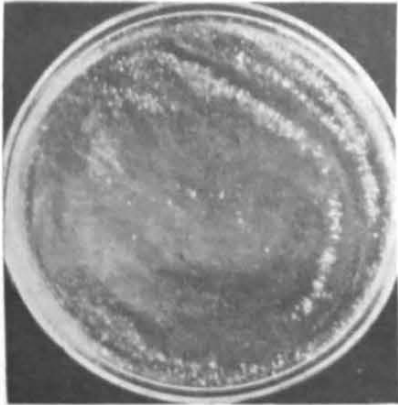
**II. Exposed during two hours to the sun's rays ;
temperature, 34° C.**



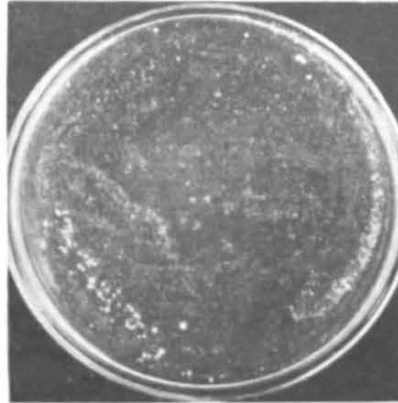
B. Flies captured in the Neighbourhood of Manure-Heaps.

I. Not exposed to the sun's rays.

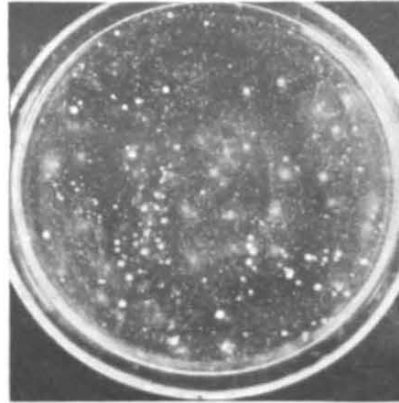
Dilution 1 : 10



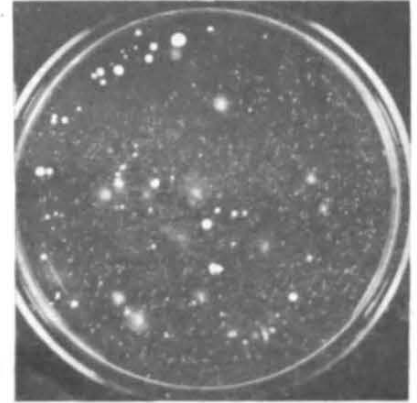
Dilution 1 : 100



Dilution 1 : 1,000



Dilution 1 : 10,000



II. Exposed during two hours to the sun's rays.

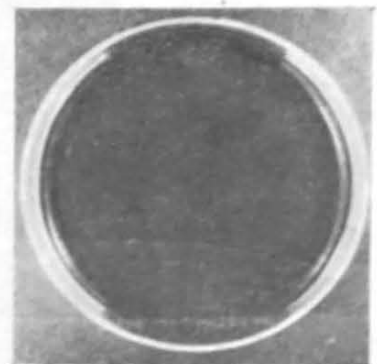
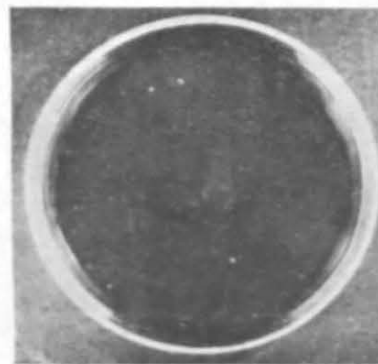
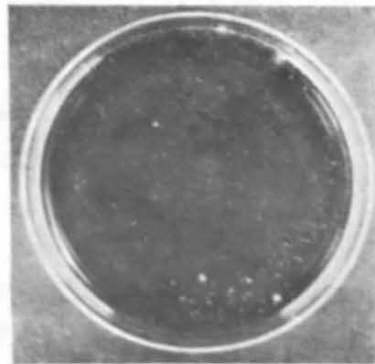
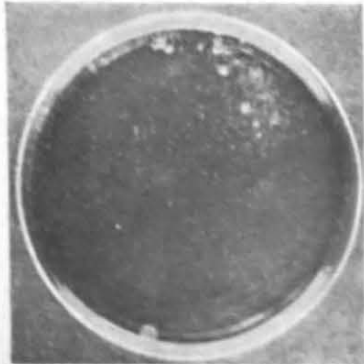
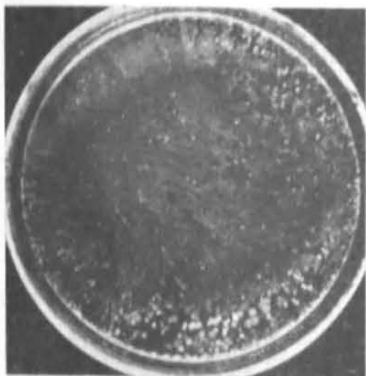


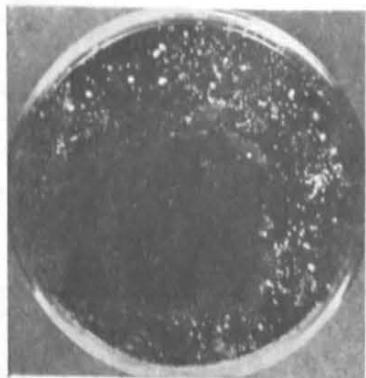
Plate III.

INFECTIVE CAPACITY OF FLIES.

Direct Seeding on Ordinary Agar Plates.



Culture obtained with 10 minutes' contact (*Musca domestica*) ... n colonies



Culture obtained with one minute's contact (*Calliphora vomitoria*) 1,790 colonies



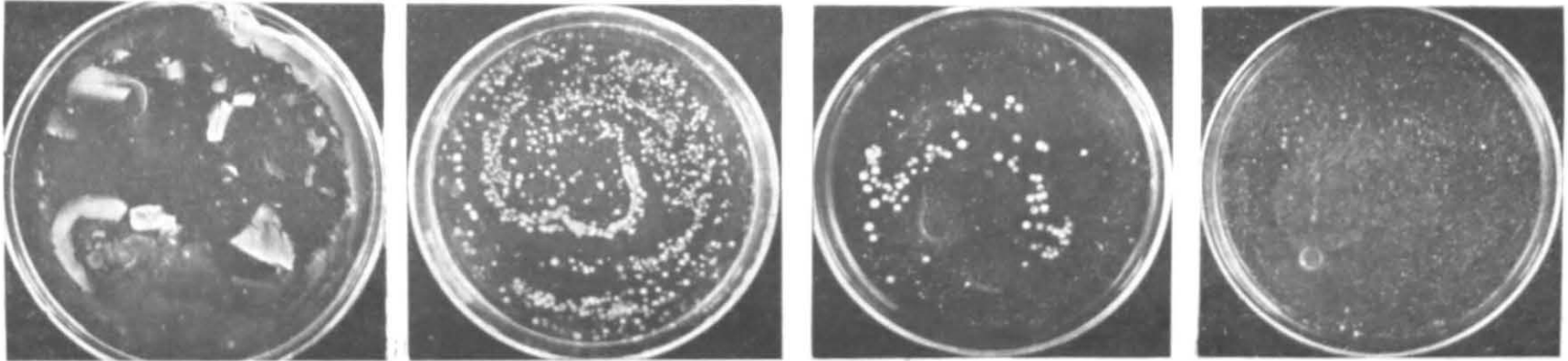
Culture obtained with one minute's contact (*Musca domestica*)..... 93 colonies

Plate IV.

A big blue fly, *Calliphora vomitoria*, is put in contact for 30 minutes with 500 c.cm. of sterilised milk.
The flask is then left to stand at the ordinary temperature for twenty-four hours.

One drop of this milk in a 1:100 dilution produces total liquefaction of the gelatine within twenty-four hours.

Twenty-four hours' culture on agar T seeded with one drop in the proportion of

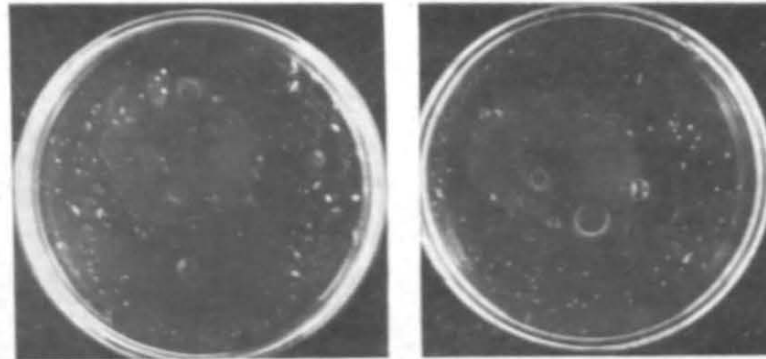


1 : 100

1 : 1,000

1 : 10,000

Twenty-four hours' culture on agar T seeded with one drop in the proportion of



1 : 1,000,000

1 : 1,000,000
(10,220,000,000 germs per c.cm.)

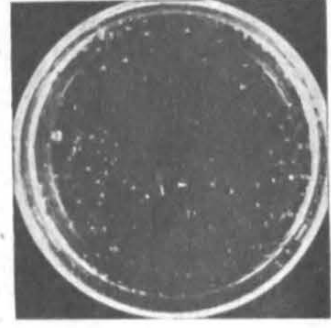
Plate

TWENTY-FOUR-HOUR CULTURES ON ORDINARY AGAR OBTAINED BY SEEDING

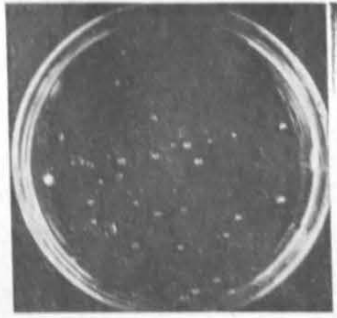
After 2 hours with *Calliphora vomitoria*
1,572,000 germs per c.cm.



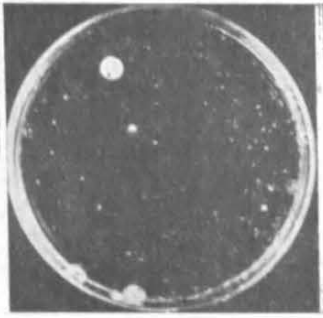
Dilution 1 : 10



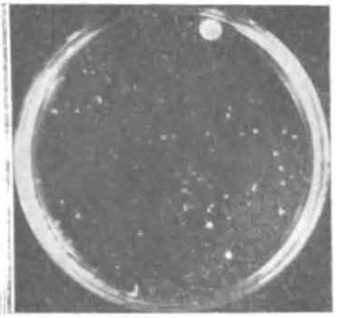
Dilution 1 : 100



Dilution 1 : 1,000



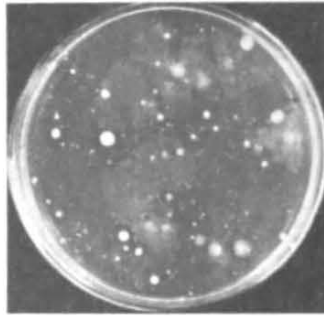
Dilution 1 : 10,000



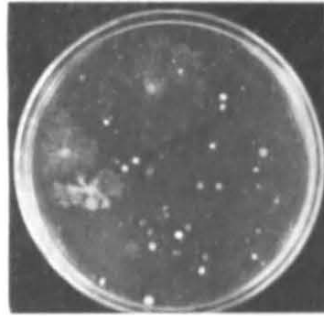
Dilution 1 : 100,000

DROP OF POLLUTED MILK DILUTED IN VARYING PROPORTIONS.

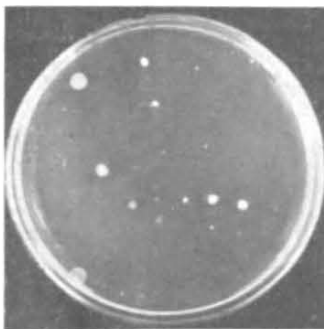
After 6 hours with *Musca domestica*
1,822,000 germs per c.cm.



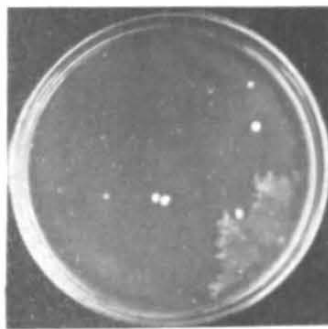
Dilution 1 : 10



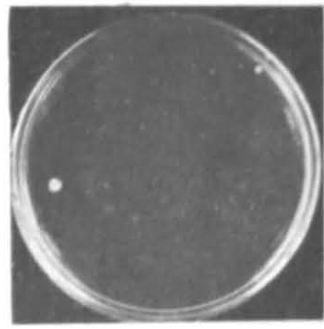
Dilution 1 : 100



Dilution 1 : 1,000



Dilution 1 : 10,000



Dilution 1 : 100,000

HEALTH AND THE ECONOMIC DEPRESSION IN THE UNITED STATES OF AMERICA

I. Illness in Families of Wage-earners in Five Surveyed Cities in the Early Part of 1933

By

H. S. CUMMING, Surgeon-General,
United States Public Health Service.

What has been the effect of the depression on health ? This question has been asked with increasing frequency each year since 1930, but there has been no means of giving an adequate answer. Social workers, visiting nurses, free clinics, and charity hospitals, the "case loads" of which have tremendously increased, all have felt that a grave national crisis existed. On the other hand, physicians who have seen their private practice dwindle, or directors of hospitals who have contemplated their empty private rooms could have no reason to believe, on the basis of such evidence, that sickness had increased.

Actually, none of these groups can know how many illnesses that in more prosperous times would have had a physician's care now flourish entirely unchecked by medical aid ; or how many people who formerly would have been treated as private patients, now go to free clinics for treatment. Without a systematic record, it is impossible even for persons engaged in treating the sick to tell from their own experience whether or not there has been more sickness during the depression than during the years of prosperity.

The death rate, the usual barometer of ill-health, has shown a surprisingly large decrease during the years of the depression in spite of the undoubted hardship of unemployment and consequent loss of income for many. Some sanitarians have expressed the opinion that excesses of eating and drinking, as well as the nervous

tension incident to a modern life of prosperity, have been reduced, and, for this reason, health has really improved during the depression. However true this may be for families whose incomes remain well above the "health and decency" level, it obviously has no application to the families of that 10 to 30 per cent of wage-earning population whose breadwinners have been forced into the ranks of the unemployed. Among many of these families, the weekly income from all sources averaged as low as a dollar *per capita* in 1932, as data to be considered later will show. An actual increase in the death rate among these unemployed and their families could have taken place, but has been entirely masked by the downward trend of the death rate among the more prosperous members of the population.

At best, mortality rates are poor indices of health. The purpose of the present investigation was to obtain at first hand an unbiased record of all types of illness among wage-earning families which had suffered from the depression in varying degrees of severity. This information was obtained by a canvass of households in the poorer districts of industrial communities severely affected by unemployment.

METHOD AND SCOPE OF THE INVESTIGATION.

Records obtained by house-to-house canvass of some 12,000 families in ten cities included, in addition to such items as age, sex and race of the members of the household, (*a*) illness and medical care for a three-month period in 1933 and (*b*) an income and employment record for the four years 1929 to 1932. A study of diet and housing was made among a small group of families in each city, and school-children in enumerated families were examined in two of the cities.

The present report relates to sickness in five of the canvassed cities—Birmingham (Ala.), Detroit (Mich.), Greenville (S. C.), Pittsburgh (Pa.) and Syracuse (N. Y.). The other surveyed cities were Baltimore (Md.), Brooklyn (N. Y.), Cleveland (Ohio), Morgantown (W. Va.) and New York City. The Greenville survey covered a series of cotton-mill villages, and the Morgantown area a group of coal-mining towns. The other eight places are large industrial cities.

Districts in the poorer sections of the cities were selected for survey, as it was in such sections that the maximum effect of deprivation might be expected. Slum areas, however, were avoided.

Even in these poor districts, there were some families which were still in reasonably comfortable circumstances ; that is, they had adequate food, clothing and shelter. These "comfortable" families, living side by side with the unemployed, serve as a control group whose illness record can be compared with that of families which have been in a state of comparative poverty for one or more years. In the selected districts, every family was included unless the information was refused, and refusals were exceedingly rare.

Local supervisors who were already trained in the collection and tabulation of this kind of data were sent to each city after an intensive training in the meaning of the items on this schedule and the method of recording the data. A general supervisor visited all but two of the communities to start the work. Uniform instructions for collecting the data were used in all cities.

Enumerators were hired locally. It was possible to secure very capable men and women for the work, due partly to prevailing economic conditions. After preliminary training with the schedule, enumerators were taken by the local supervisor to interview several families before making any visits alone. Enumerators were instructed and encouraged to be thorough rather than rapid in their work.

About 6,000 white families were canvassed in the five cities included in this report. Of these schedules, about 4,600 were sufficiently complete to compute exact incomes for each year from 1929 to 1932. There were 20,283 individuals included in these families.

ECONOMIC HISTORY OF FAMILIES (Table 1 and Figure 1).

Income was defined to include all receipts from any source—salary, royalties, interest, pension, savings, borrowed funds, gifts, public and private relief, whether in cash or in food tickets of a known value. Family income *per capita* was used as the basis of classifying the households, because it was felt that this represented economic status better than the total family income, which takes no account of size of family.

Table 1.

DISTRIBUTION OF THE SURVEYED POPULATION ACCORDING TO ANNUAL FAMILY INCOME "PER CAPITA" FOR THE YEARS 1929 TO 1932, BIRMINGHAM, DETROIT GREENVILLE, PITTSBURGH AND SYRACUSE.

| Annual family income per capita | 1929 | | 1930 | | 1931 | | 1932 | |
|---------------------------------|-------------------|------------|-------------------|------------|-------------------|------------|-------------------|------------|
| | Number of persons | Percentage | Number of persons | Percentage | Number of persons | Percentage | Number of persons | Percentage |
| "Poor" | | | | | | | | |
| Under \$50 ... | 220 | 1.1 | 607 | 3.0 | 1,212 | 6.0 | 2,027 | 10.0 |
| \$50—99 ... | 879 | 4.3 | 2,097 | 10.3 | 3,308 | 16.3 | 4,842 | 23.9 |
| \$100—149 ... | 1,592 | 7.9 | 2,283 | 11.3 | 2,904 | 14.3 | 3,555 | 17.5 |
| "Moderate" | | | | | | | | |
| \$150—199 ... | 1,909 | 9.4 | 2,431 | 12.0 | 2,833 | 14.0 | 2,629 | 13.0 |
| \$200—249 ... | 2,006 | 9.9 | 2,032 | 10.0 | 2,048 | 10.1 | 1,940 | 9.6 |
| \$250—299 ... | 1,883 | 9.3 | 1,871 | 9.2 | 1,571 | 7.7 | 1,337 | 6.6 |
| \$300—349 ... | 2,111 | 10.4 | 1,823 | 9.0 | 1,459 | 7.2 | 1,056 | 5.2 |
| \$350—424 ... | 2,174 | 10.7 | 1,884 | 9.3 | 1,378 | 6.8 | 960 | 4.7 |
| "Comfortable" | | | | | | | | |
| \$425—499 ... | 1,811 | 8.9 | 1,250 | 6.1 | 986 | 4.9 | 665 | 3.3 |
| \$500—749 ... | 3,388 | 16.7 | 2,507 | 12.4 | 1,736 | 8.5 | 857 | 4.2 |
| \$750 and over. | 2,310 | 11.4 | 1,498 | 7.4 | 848 | 4.2 | 415 | 2.0 |
| Total | 20,283 | 100.0 | 20,283 | 100.0 | 20,283 | 100.0 | 20,283 | 100.0 |

Figure 1.

PERCENTAGE DISTRIBUTION OF THE SURVEYED POPULATION ACCORDING TO ANNUAL FAMILY INCOME PER CAPITA FOR EACH OF THE YEARS 1929-1932. THE POPULATION INCLUDES 20,283 INDIVIDUALS IN ABOUT 4,600 FAMILIES IN BIRMINGHAM, DETROIT, GREENVILLE, PITTSBURGH, AND SYRACUSE.

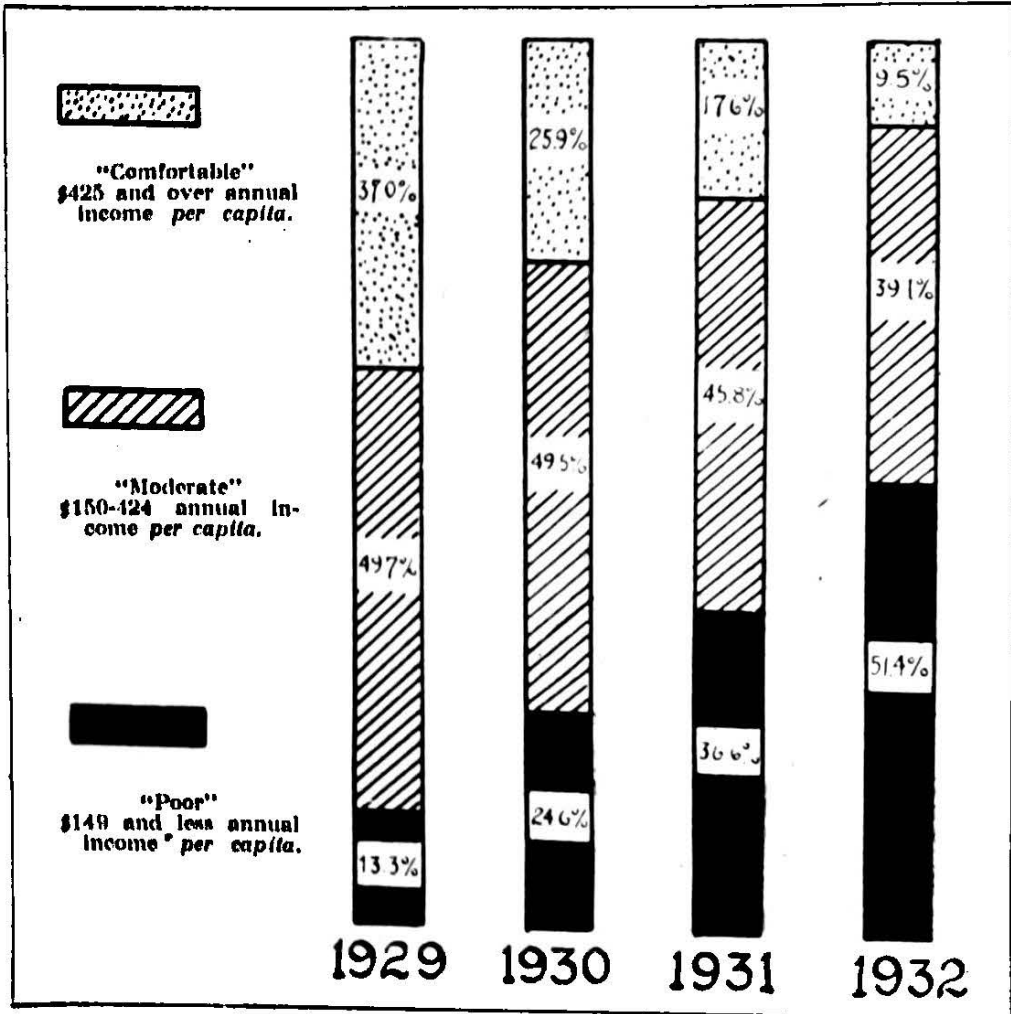


Table 1 and Figure 1 show the population grouped according to annual *per capita* income for the years 1929 to 1932. For convenience in discussion, the individual income classes have been combined into three groups and designated as follows :

- (1) *Poor* : \$149 or less *per capita* per year ;
- (2) *Moderate* : \$150 to \$424 *per capita* per year ;
- (3) *Comfortable* : \$425 and over *per capita* per year.

These names have no significance other than as convenient labels indicating a rising scale of *per capita* income.

It will be seen that the "poor" group, which made up only 13 per cent of the total in 1929, constituted 51 per cent in 1932, while the "comfortable" group dropped from 57 per cent of the total in 1929 to 10 per cent in 1932.

The change from one income class to another is better illustrated by tracing the income history of the groups of individuals in 1929 through each year to 1932. Only about one-fourth of the families comfortably situated in 1929 retained that status in 1932, and nearly an equal number had become poor. Over half of those in moderate circumstances in 1929 had fallen into the "poor" category by 1932. Nine out of ten persons classified as "poor" in 1929 remained in that state throughout the period.

ILLNESS AND 1932 INCOME (Table 2 and Figure 2).

In Table 2, the incidence of illness is shown for four groups of the surveyed population classified according to annual *per capita* income in 1932. The rates are for the three-month period of the survey—that is, three months early in 1933. Illnesses are classified as having (1) onset within the survey period and (2) onset prior to the survey period. Each of these groups is shown as (a) all cases, (b) disabling cases, consisting of those causing inability to carry on their usual activities, and (c) cases in which the patient was

Table 2.—ILLNESS AND 1932 INCOME.

Incidence of illness as related to 1932 family income per capita in canvassed white families in Birmingham, Detroit, Greenville, Pittsburgh and Syracuse. The Group comprised about 4,600 families, including 20,283 individuals.

| Annual family income per capita in 1932 | Illness rate per 1,000 persons for three-month survey period ¹ | | | | | | Population observed |
|---|---|-----------|-----|-----------------------|-----------|-----|---------------------|
| | Onset within period | | | Onset prior to period | | | |
| | Total | Disabling | Bed | Total | Disabling | Bed | |
| Under \$150 . | 167 | 112 | 103 | 88 | 50 | 35 | 10,424 |
| \$150—\$249 . | 157 | 107 | 96 | 88 | 47 | 34 | 4,569 |
| \$250—\$424 . | 139 | 85 | 76 | 83 | 46 | 35 | 3,353 |
| \$425 and over | 138 | 84 | 69 | 96 | 51 | 37 | 1,937 |

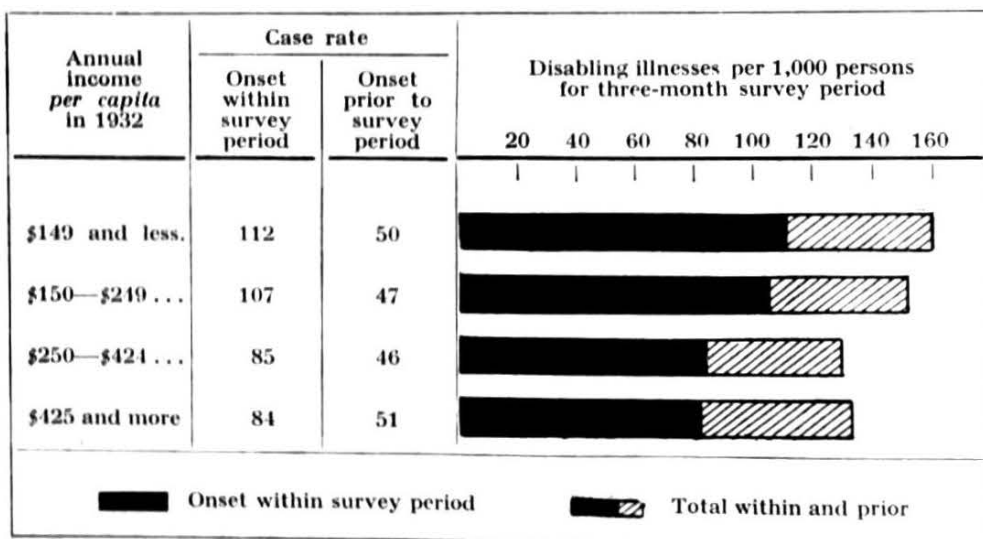
¹ The survey period refers to the three-month period prior to the enumerator's visit. The canvass in each city required from three to four weeks. The dates of the canvass were slightly different in each city, but were between March 20th, 1933, and May 15th, 1933, for all five cities.

confined to bed for one or more days. All bed cases are included in the disabling class.

The sickness rate is lower for the higher income groups, when illnesses with onset within the survey period are considered. Illnesses with onset prior to the survey period, largely chronic cases, show no relation to income (Figure 2).

Figure 2.

DISABLING ILLNESS DURING A THREE-MONTH PERIOD IN THE EARLY SPRING OF 1933 IN WAGE-EARNING FAMILIES CLASSIFIED ACCORDING TO INCOME *per capita* IN 1932, IN BIRMINGHAM, DETROIT, GREENVILLE, PITTSBURGH, AND SYRACUSE.



The disabling cases probably constitute a better measure of real sickness in the various groups than total illnesses because the former are more accurately and completely reported. A case sufficiently severe to interfere with work or other usual activities or to confine the patient to his bed within the three-month period is very likely to be remembered and reported to the enumerator, while other minor ailments may be forgotten. For illnesses within the survey period, the disabling case rate among the lower income group (\$149 or less) is 33 per cent higher, and the bed case rate 49 per cent higher, than among the group having an annual family *per capita* income of \$425 and over. The poor in the surveyed group are obviously subject to more illness than their more fortunate neighbours in relatively comfortable circumstances.

ILLNESS AND INCOME CHANGE (Table 3 and Figure 3).

In this analysis, the individuals were divided into six categories according to economic status in 1929 and 1932 as follows :

I. Individuals experiencing lowered family income *per capita* between 1929 and 1932 were classified as :

- (a) Comfortable in 1929 and poor in 1932 ;
- (b) Moderate in 1929 and poor in 1932 ;
- (c) Comfortable in 1929 and moderate in 1932.

II. Individuals who had not experienced lowered family income between 1929 and 1932 were classified as :

- (a) Comfortable in 1929 and 1932 ;
- (b) Moderate in 1929 and 1932 ;
- (c) Poor in 1929 and 1932.

Table 3.—ILLNESS AND CHANGE IN INCOME.

Incidence of Illness among Families classified according to Change in the Annual Per Capita Income from 1929 to 1932, Birmingham, Detroit, Greenville, Pittsburgh and Syracuse.

| Depression history ¹ | | Case rate per 1,000 persons for three-month survey period ² | | | | | | Population observed |
|--|-------------|--|------------|-----|-----------------------|------------|-----|---------------------|
| 1929 | 1932 | Onset within period | | | Onset prior to period | | | |
| | | Total | Dis-abling | Bed | Total | Dis-abling | Bed | |
| I. Families with diminished income, 1929-1932. | | | | | | | | |
| Comfortable | Poor | 204 | 135 | 118 | 102 | 57 | 42 | 1,772 |
| Moderate | Poor | 161 | 110 | 101 | 79 | 45 | 32 | 6,209 |
| Comfortable | Moderate | 147 | 96 | 83 | 85 | 45 | 34 | 3,919 |
| II. Families with no material change in income, 1929-1932. | | | | | | | | |
| Comfortable | Comfortable | 142 | 87 | 71 | 97 | 51 | 36 | 1,818 |
| Moderate | Moderate | 151 | 99 | 91 | 87 | 47 | 35 | 3,761 |
| Poor | Poor | 155 | 103 | 95 | 102 | 56 | 40 | 2,413 |

¹ Comfortable = \$425 and over *per capita* per year.

Moderate = \$150-\$424 *per capita* per year.

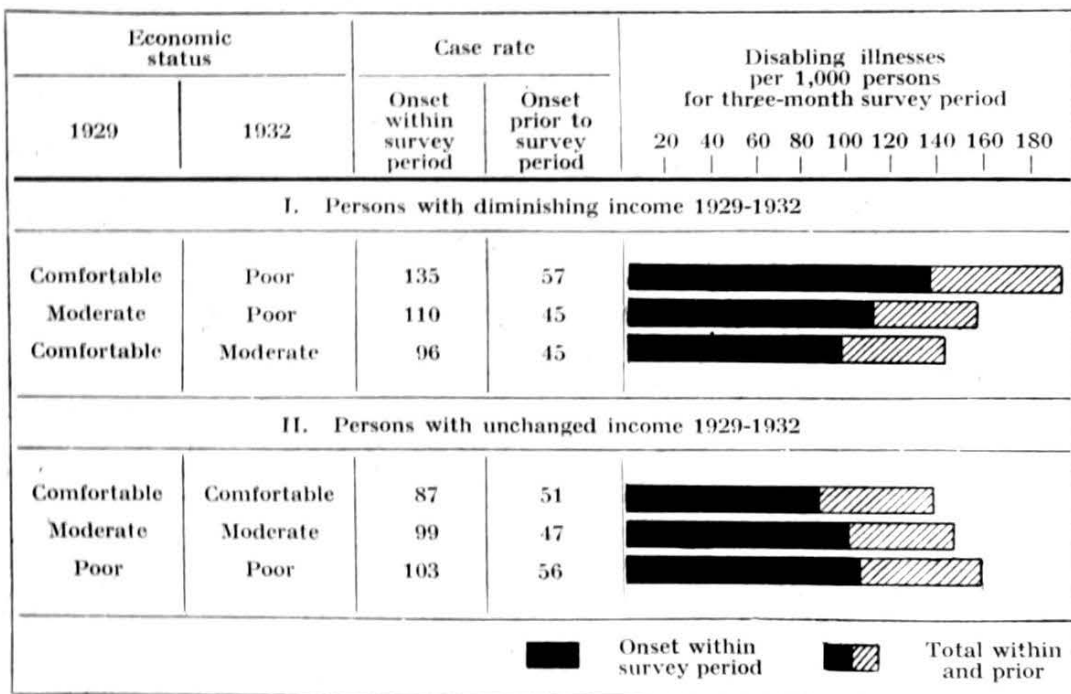
Poor = \$149 or less *per capita* per year.

² See footnote to Table 2.

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Figure 3.

DISABLING ILLNESS DURING A THREE-MONTH PERIOD IN THE EARLY SPRING OF 1933 IN WAGE-EARNING FAMILIES CLASSIFIED ACCORDING TO CHANGE IN ECONOMIC STATUS 1929-1932, IN BIRMINGHAM, DETROIT, GREENVILLE, PITTSBURGH AND SYRACUSE.



Comfortable = \$425 and over per capita per year.
 Moderate = \$150-424 per capita per year.
 Poor = \$149 or less per capita per year.

Rates for the different income change classes are shown in Table 3 and Figure 3. Those individuals who suffered the greatest reductions in income between 1929 to 1932 have the highest sickness rates. The "comfortable" group of 1929 which had fallen to the "poor" group by 1932 had a disabling sickness rate that was 55 per cent above the "comfortable" of 1929 which remained in the same "comfortable" class in 1932.

Those families which had been poor throughout the four-year period had a slightly higher rate than those which had been in the "moderate" class the whole time, and these "moderate" families in turn had a higher rate than those which had been "comfortable" throughout the period. However, those which were poor throughout the period reported considerably less sickness than the more recently "poor" which had been comfortable in 1929.

The same trends are observed for total illnesses with onset within the survey period, and even the addition of the cases with onset

prior to survey period (largely chronic) does not obscure the fact that a relatively large drop in economic status appears to be associated with a high illness rate.¹

UNEMPLOYMENT AND ILLNESS (Table 4 and Figure 4).

The surveyed families were classified according to the extent of unemployment during 1932 as follows :

- (a) Families with no employed workers ;
- (b) Families with one or more part-time workers but no full-time workers ; and
- (c) Families with one or more full-time workers with or without additional part-time workers.

Table 4.—ILLNESS AND UNEMPLOYMENT.

Incidence of Illness among Families classified according to the Number of Employed Workers during 1932, Birmingham, Detroit, Pittsburgh.

| Employed workers in the family | Case rate per 1,000 persons for three-month survey period ¹ | | | | | | Popula- tion observed |
|--|---|-----------|-----|-----------------------|-----------|-----|-----------------------------|
| | Onset within period | | | Onset prior to period | | | |
| | Total | Disabling | Bed | Total | Disabling | Bed | |
| No employed workers. | 160 | 122 | 114 | 91 | 55 | 40 | 1,402 |
| Part-time workers (1 or more ; no full- time) | 157 | 98 | 89 | 70 | 40 | 30 | 4,561 |
| Full-time workers (1 or more with or without additional part-time workers). | 127 | 88 | 77 | 72 | 42 | 32 | 5,367 |

¹ See footnote to Table 2.

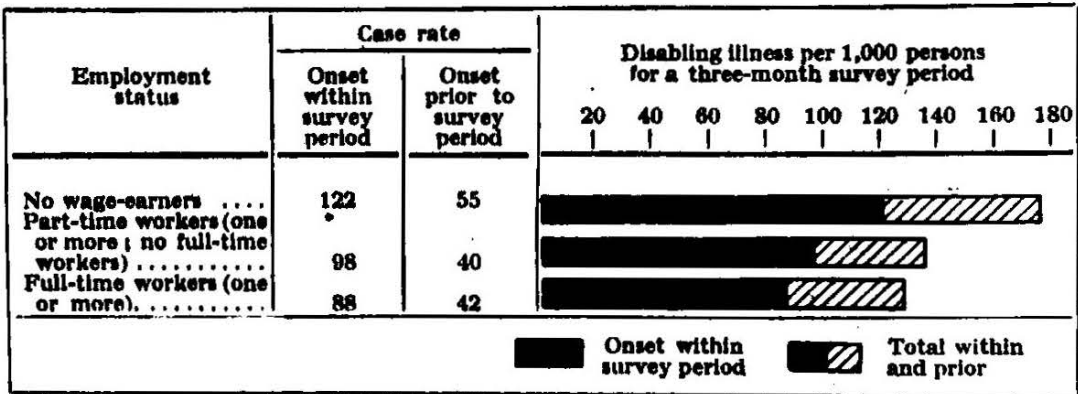
This tabulation is available for only three cities at present. The illness rate is highest in families having no employed workers and

¹ About 1,000 school-children in the surveyed families of two cities were given careful physical examinations. The physician did not know the income status of the child's family at the time the examination was made. In agreement with the results on sickness, a higher percentage of children from low *per capita* income families were judged as of poor nutrition than of children from families with higher incomes. Furthermore, when the nutrition of children in families suffering the greatest drop in income during the depression was compared with that of children in families not so seriously affected, it was found that the percentage with poor nutrition in the former group was considerably higher than in the latter. Children in families without social relief were found to have a higher percentage of poor nutrition than in similar families aided by relief.

lowest in the households having full-time workers. This result was to be expected in the light of the relation between income and sickness that is shown in Figure 2.

Figure 4.

DISABLING ILLNESS DURING A THREE-MONTH PERIOD IN THE EARLY SPRING OF 1933 IN FAMILIES CLASSIFIED ACCORDING TO THE EMPLOYMENT OF WAGE-EARNING MEMBERS, IN BIRMINGHAM, DETROIT AND PITTSBURGH.



AGE AND CAUSE OF ILLNESS.

A few tabulations have been made of sickness among persons of specific ages, but a detailed analysis must await the completion of the tabulations for all the cities. Although there are some inconsistencies, the differences between the various income classes that have been described show up in the majority of the age classes. The largest differences occur in the adult ages.

In these studies, respiratory illness, as usual, constitutes a large part of all the sickness, and, among children, the infectious and communicable diseases occur frequently. Minor respiratory attacks tend to occur more frequently in the lower income groups, but the communicable diseases show no differences between the various income classes that cannot be attributed to chance. Illnesses, other than respiratory, infectious, and communicable diseases, tend, like the respiratory, to occur more frequently in the lower income groups.

With regard to the significance of the findings, it is impossible at the present time to draw conclusions as to their broad implications. No estimate of the number or percentage of the entire wage-earning population that has suffered increased illness can be made from these surveyed urban sample populations.

II. Nutrition of School-children.

Communication by H. S. CUMMING, Surgeon-General, on Two Investigations made by the Office of Child Hygiene Investigations of the Public Health Service of the United States of America.

1. GROWTH OF SCHOOL-CHILDREN.

The material on which this study is based consists of weighings made during May 1933 on all white school-children in the first six grades in Hagerstown, compared with data collected in Hagerstown during 1921-1927. Analysis of these data in sex and age specific distributions and comparisons of the statistical constants derived show the following :

1. For 6-, 7-, 8- and 9-year-old boys and 6- and 9-year-old girls, the average weight is slightly less in 1933 than in 1921-1927. However, the average weight of children in the present and previous period presents no consistent or statistically significant differences. *Therefore*, the average weight of children in Hagerstown, Maryland (a typical small urban community), has remained fairly constant since 1921.

2. The variability of body weight (measured by standard deviations) is not, for boys, consistently different for the two periods. For girls, body weight is slightly more variable in 1933 than in 1921-1927, particularly in the 7-, 8- and 9-year-old groups. *Therefore*, there is a suggestion that the past few years of economic depression tend to be associated with an increase in variability in body weight for girls.

Table 1.—WEIGHT OF ELEMENTARY SCHOOL-CHILDREN, HAGERSTOWN.**A. May 1933.**

| Age nearest January 1st, 1933 (years). | 6 | 7 | 8 | 9 | 10 | 11 |
|---|--------------|-------|-------|-------|-------|-------|
| | Boys | | | | | |
| Number | 121 | 200 | 240 | 231 | 234 | 219 |
| Mean weight (pounds). | 46.23 | 49.73 | 55.65 | 60.66 | 67.98 | 74.05 |
| Standard deviation (pounds) | 5.29 | 5.70 | 7.58 | 7.96 | 10.78 | 10.90 |
| | Girls | | | | | |
| Number | 114 | 205 | 241 | 236 | 233 | 240 |
| Mean weight (pounds). | 44.91 | 49.19 | 54.39 | 58.38 | 66.20 | 74.80 |
| Standard deviation (pounds) | 5.95 | 7.17 | 9.76 | 10.74 | 11.30 | 15.21 |

B. May 1921—May 1927.

| Age nearest January 1st of school year (years). | 6 | 7 | 8 | 9 | 10 | 11 |
|--|--------------|-------|-------|-------|-------|-------|
| | Boys | | | | | |
| Number | 238 | 596 | 839 | 987 | 992 | 868 |
| Mean weight (pounds). | 46.83 | 50.63 | 55.97 | 61.57 | 67.22 | 73.91 |
| Standard deviation (pounds) | 5.32 | 6.44 | 7.38 | 8.71 | 10.53 | 12.36 |
| | Girls | | | | | |
| Number | 237 | 573 | 811 | 921 | 925 | 798 |
| Mean weight (pounds). | 45.78 | 49.11 | 54.18 | 59.50 | 66.07 | 74.10 |
| Standard deviation (pounds) | 5.34 | 6.25 | 7.51 | 9.25 | 11.50 | 14.29 |

3. During the period 1921-1927, there is a systematic and regular increase with advancing age in the percentage of children 12 per cent or more under weight. In 1933, there is a general lack of such systematic increase with increasing age. In 1933, there are relatively more younger boys and relatively fewer older boys under weight than in 1921-1927. Similar differences are noted for girls, except that, for the younger girls, the differences are more marked and are negligible for the older ones.

In the totals of 1,245 boys and 1,269 girls weighed in 1933, there are four fewer boys and forty-one more girls who are 12 per cent or more below average weight than would be expected had the same

proportions been under weight as were found in the 1921-1927 period. *Therefore*, there is substantially no change in the weight of boys and a slight increase in the number of under-weight girls during the past few years of the economic depression.

4. The mean weight of children from these groups of families was considered : (a) families of the unemployed ; (b) families of the part-time employed ; (c) families of the regularly employed.

Analysis of the weight of these children shows approximately the same differences as are generally found between children from different socio-economic classes. *Therefore*, there has been no widening nor obliteration of class differences in average weight of children during the period of depression.

Table 2.—MEAN WEIGHT OF SCHOOL-CHILDREN GROUPED ACCORDING TO THREE CLASSIFICATIONS OF PARENTS' EMPLOYMENT, HAGERSTOWN, MAY 1933.

| Age nearest January 1st, 1933 (years). | 6 | 7 | 8 | 9 | 10 | 11 |
|---|------------|-------|-------|-------|-------|-------|
| | Both sexes | | | | | |
| Children, neither of whose parents was employed more than two days per week : | | | | | | |
| Number | 26 | 65 | 92 | 89 | 84 | 64 |
| Mean weight (pounds) | 43.41 | 48.05 | 54.05 | 57.66 | 63.85 | 73.44 |
| Children, one of whose parents was employ- ed more than two days but less than four days per week : | | | | | | |
| Number | 24 | 33 | 46 | 43 | 52 | 57 |
| Mean weight (pounds) | 45.38 | 48.09 | 52.14 | 58.55 | 64.76 | 70.03 |
| Children, one of whose parents was employ- ed more than four days per week : | | | | | | |
| Number | 185 | 307 | 343 | 335 | 331 | 338 |
| Mean weight (pounds) | 45.92 | 49.90 | 55.67 | 60.12 | 68.28 | 75.38 |

2. NUTRITIONAL STATUS OF SCHOOL-CHILDREN.

This study was undertaken as a part of a broader study of the health of the unemployed and their families. In two areas, Pittsburgh and New York City, the school-children whose names appeared on the roster of the families interviewed in the general sickness survey were given a careful physical examination, including measurements of height and weight ; and hemoglobin estimations and red blood cell counts were made.

The statistical analysis of the data based on the records of examinations of 406 school-children in Pittsburgh and 508 school-children in New York City indicates the following :

1. In Pittsburgh, 31 per cent of the children from families with *per capita* annual income of less than \$250 are estimated by the physician to have "good nutrition", while 15 per cent are classified under "poor nutrition". Forty-seven per cent of the children among the families with a *per capita* income of \$250 or more are rated as having "good nutrition" and 4 per cent as "poor".

In New York, 21 per cent of the children among families with a *per capita* income of \$250 per annum or less were rated as having "good nutrition" and 36.5 per cent, "poor nutrition". Thirty-three per cent of the children among the families with a *per capita* income of \$250 a year and over fall in the "good nutrition" group and 30 per cent in the "poor nutrition" group.

Table 3.—NUTRITION OF A GROUP OF PITTSBURGH AND NEW YORK CITY CHILDREN CLASSIFIED ACCORDING TO THE ANNUAL *Per Capita* INCOME OF THE FAMILY IN 1932.

| Annual <i>per capita</i> income | Pittsburgh | | | New York City | | |
|------------------------------------|-----------------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| | "Poor" nutrition | "Fair" nutrition | "Good" nutrition | "Poor" nutrition | "Fair" nutrition | "Good" nutrition |
| Under \$250 | 14.7 | 54.4 | 30.9 | 36.5 | 42.3 | 21.2 |
| \$250 and over | 4.2 | 48.6 | 47.2 | 30.2 | 36.9 | 32.9 |
| Annual <i>per capita</i> income | Total number of children examined | | | | | |
| | Pittsburgh | | | New York City | | |
| Under \$250 | 333 | | | 359 | | |
| \$250 and over | 72 | | | 149 | | |

2. Considering the nutritional status of children in relation to the *per capita* income of families during the four-year period 1929-1932, data indicate that those whose family *per capita* income remained unchanged show a higher percentage of good nutrition than those who dropped from a high level in 1929 to a lower level in 1932. The number of children considered is relatively small, but the differences in percentages seem consistent enough to suggest a change in nutritional status. (In the study of illness in relation to economic status, there was also found to be a definite increase of incidence among the group of children in the families where there had been a change of *per capita* income from a high level in 1929 to a lower one in 1932.)

Table 4.—PROPORTION OF PITTSBURGH CHILDREN ADJUDGED AS HAVING "POOR", "FAIR" AND "GOOD" NUTRITION IN FAMILIES CLASSIFIED ACCORDING TO THE *Per Capita* INCOME, 1929-1932.

| | Percentage of children | | | Total number of children examined |
|--|------------------------|------------------|------------------|-----------------------------------|
| | "Poor" nutrition | "Fair" nutrition | "Good" nutrition | |
| I. Change in economic status. | | | | |
| Above \$300 <i>per capita</i> in 1929 but dropped below \$200 in 1932.... | 16.3 | 55.1 | 28.6 | 49 |
| \$200-\$300 <i>per capita</i> in 1929 but dropped below \$200 in 1932.... | 14.3 | 64.8 | 20.9 | 91 |
| Above \$300 <i>per capita</i> in 1929 but dropped to \$200-\$300 in 1932.. | 2.3 | 54.5 | 43.2 | 44 |
| II. No material change in economic status. | | | | |
| Under \$200 <i>per capita</i> all four years | 12.1 | 53.5 | 34.3 | 99 |
| \$200-\$300 <i>per capita</i> all four years | 18.2 | 48.5 | 33.3 | 33 |
| Above \$300 <i>per capita</i> all four years | 4.7 | 41.9 | 53.5 | 43 |

3. There is no significant correlation of the hemoglobin index of children to the annual *per capita* income of the family in 1932.

Table 5.—HEMOGLOBIN INDEX OF A GROUP OF PITTSBURGH CHILDREN CLASSIFIED ACCORDING TO THE ANNUAL *Per Capita* INCOME OF THE FAMILY IN 1932.

| Annual <i>per capita</i> income | Percentage with hemoglobin under 75 ¹ | | | Average hemoglobin index | | | Total children examined | | |
|------------------------------------|---|------|-------|-----------------------------|------|-------|----------------------------|------|-------|
| | Both sexes | Boys | Girls | Both sexes | Boys | Girls | Both sexes | Boys | Girls |
| Under \$100 | 32.1 | 32.8 | 31.4 | 75.7 | 75.4 | 76.0 | 162 | 76 | 86 |
| \$100-\$250 | 18.1 | 16.4 | 19.1 | 77.6 | 77.4 | 77.7 | 172 | 67 | 105 |
| \$250 and over | 15.9 | 17.2 | 15.0 | 78.3 | 78.3 | 78.4 | 69 | 29 | 40 |

¹ An index of less than 75 is usually considered as indicating malnutrition.

CONCLUSIONS.

The data obtained in these two studies indicate :

- (1) A slight increase in the number of under-weight girls and a slight variability in the body weight for girls may be associated with the past few years of economic depression (Hagerstown) ;
- (2) There has been no widening nor obliteration of socio-economic class differences in average weight of children during the depression years (Hagerstown) ;
- (3) An apparent increase in the percentage of malnutrition in the group of children of families whose *per capita* income changed from a high to a lower level during 1929-1932 as compared to those children of families whose income remained unchanged during the four years (Pittsburgh and New York City).

THE HEALTH ORGANISATION AND THE NARCOTICS PROBLEM (1921-1933)

By

I. WASSERBERG, M.D.,

Member of the Health Section of the League of Nations Secretariat.

Opium has always played an important part in international relations. On several occasions, until well into the nineteenth century, it was the cause of international conflicts, whereas to-day it has become a focus of international co-operation, the organisation of which is centred in Geneva and is being carried each year to a still higher pitch of efficiency.

The ultimate aim of such co-operation, which had its inception at the Hague International Opium Conference of 1912, is determined by the nature of opium itself. Opium is, indeed, a very peculiar substance ; with highly valuable analgesic properties it combines others the effects of which lead to disease, vice and crime. The ultimate object of the work to be done in this field must therefore be to devise ways and means of preserving and developing the first category of properties, with all their practical possibilities for the well-being of suffering humanity, while at the same time restricting and eliminating the second category.

Such being the case, and as, under Article 23 of the Covenant, supervision of the application of the international Conventions regarding opium and other narcotic drugs was transferred to the League of Nations, a complicated mechanism has gradually been built up in the course of the last twelve years, the various components of which fit together like the cogs in the works of a watch. During these twelve years, the Health Organisation, which in matters relating to opium is merely one of the minor cogs, has co-operated

in the common task with others of much greater magnitude. Certain of its more valuable contributions are very briefly summarised in the following pages.

DETERMINATION OF OPIUM AND COCAINE CONSUMPTION.

The Advisory Opium Committee, which is responsible for seeing that the provisions of the Hague Convention are observed by the contracting parties, clearly realised from the very outset of its activities that its efforts were bound to remain fruitless as long as medical requirements in narcotic substances were an unknown quantity. It was, above all, patently impossible to decide whether the manufacture of morphine, cocaine, etc., corresponded "to medical and legitimate purposes" (as required by Article 9 of the Hague Convention), unless the latter could be at least approximately ascertained. Furthermore, the limitation of the production of opium, which would have to be dealt with in a somewhat more remote future, was naturally dependent upon the same condition. The consumption of narcotic substances for medical purposes was, however, in point of fact, an unknown quantity. When, therefore, in June 1921, the Council of the League called upon the Health Committee "to undertake an enquiry . . . to determine approximately the average requirements of the drugs specified in Chapter III of the Convention for medical and other legitimate purposes in different countries", the Committee found itself in the difficult position of being required to carry out a highly responsible task without possessing the slightest data on the point and at a time, moreover, when no suitable method of solving the problem was known.

"LEGITIMATE" CONSUMPTION.

Before dealing with the essential problem, moreover, a certain preliminary question had to be solved : What was to be understood by consumption which, though not medical, was legitimate ? The expression is to be found in the Hague Convention, Article 9 of which refers to "medical and legitimate purposes".

On this point, the Health Committee took the view that "other legitimate purposes" could only apply to veterinary and purely scientific requirements. As a body of medical experts, the Committee held that any other interpretation was quite inadmissible ; in particular, it refused to regard any form of consumption as legitimate in the medical sense of the term—*i.e.*, as medically justified—merely because it was permitted by the laws of any given country and was therefore legal within the territory of that country.

In consequence of this expression of opinion, the Geneva Convention of 1925, Article 5 of which corresponds to Article 9 of the Hague Convention, substituted the expression "medical and scientific purposes" for "medical and legitimate purposes". Similarly, the Geneva Convention of 1931 also speaks of "medical and scientific purposes" (Article 4, paragraph 1).

METHODS OF DETERMINING CONSUMPTION.

The next question was that of method. In this connection, there were several possibilities, each of which had its own advantages and disadvantages.

Trade Statistics Method.

The simplest course appeared to be to take trade statistics as a basis of calculation ; the total represented by manufacture, imports and exports, due regard being had to the stocks in hand at the beginning and end of a stated period, appeared to afford a satisfactory index to consumption in a stated territory. The quantity revealed by this method, however, is not that of medical consumption alone, but total consumption. Were there some other means of determining medical consumption, the trade statistics method would have the advantage of making it possible to ascertain the figures for illegitimate consumption, and, *vice versa*, if the latter were known the former could also be calculated. In itself, however, this method does not permit of the solution of the problem of medical consumption.

Direct Method.

The second method, which we will call the direct method, aims at recording consumption at the stage in which the substances

concerned pass into the hands of the consumer. If it succeeds in recording all the quantities supplied to consumers on doctors' prescriptions by duly authorised persons (public and hospital pharmacists, doctors and dentists, veterinary surgeons, etc.), it affords the most efficient and perhaps even the ideal method ; because, in the first place, it records purely medical consumption ; while, in the second place, the record being taken so close to the point at which the drugs pass into the hands of the consumer, possibilities of error are reduced almost to a minimum. On the other hand, the direct method has the disadvantage of being extremely complicated technically, and requiring the expenditure of considerable administrative effort, as a result of which it is only applicable in the smaller countries where pharmacists are not too numerous. As far as is known, indeed, this method is only applied in Switzerland, Denmark, and perhaps Austria.

Morbidity Method.

The third method, which, though proposed, could not be recommended, is based upon morbidity. As a preliminary, it requires the calculation of the average consumption of the various narcotic substances per sickness-day in representative hospitals in the territory under consideration. In order to calculate the total consumption of a given country, it would therefore clearly be necessary to know the number of sickness-days in respect of the whole population. As, however, no country possesses morbidity statistics of this kind, the method is practically valueless.

Sickness Insurance Method.

The fourth and last method to be considered by the Health Committee is perhaps the most promising from a practical standpoint. A number of the biggest possible sickness insurance organisations are selected from among those which are responsible for providing medical attention, not merely for the heads of families, but also for all the members of these families. Provided such a group of insured persons, which consists of individuals of different ages and both sexes, is sufficiently numerous, it can be taken as representative of the whole population of the territory concerned, and its consumption of narcotic substances can also be regarded

as representative of the consumption of the entire population. If, then, the average consumption of the group over a stated period is multiplied by the total population, the result will represent the consumption of the territory concerned over the period under consideration.

This method has two evident advantages :

1. As compared with the numerous attempts to deduce national consumption from hospital consumption, it has the advantage of being based upon a group of insured persons which, like the total population of the country, is of a mixed character and consists of both healthy persons and sick, whereas all the inmates of a hospital or clinic are sick and therefore not typical of the population as a whole. Such being the case, the consumption of the insurance group can be regarded as representative of the country, whereas hospital consumption cannot.

2. The consumption of the sickness insurance organisation is unquestionably of a purely medical character, and is relatively easy to ascertain. Such consumption is of two kinds :

- (a) Drugs supplied to insured persons on medical prescriptions ;

- (b) Drugs consumed by insured persons as patients in hospitals.

The first of these quantities can be easily ascertained, as, generally speaking, medical prescriptions are preserved by insurance organisations for a number of years, and the larger organisations, moreover, generally employ their own pharmacists.

The second quantity can be arrived at through multiplication of the average consumption per sickness-day in representative hospitals of the area concerned by the number of days spent by insured persons in hospital. The latter figure is well known to all insurance organisations, as it is the fund which pays for all time spent in hospital.

If, now, the sum of both quantities is divided by the number of members belonging to the insurance fund, the result is the average consumption of such members, which, as has already been explained above, can be taken as representative of the average consumption of the entire population.

Conclusions.

Which, then, of the four methods was the Health Committee to recommend to the various countries for application ? Preference was given to no single one of them. The Committee considered that conditions in the various countries differed too widely for it to be possible to expect that a single method could be equally suitable for all, and therefore came to the conclusion that, in the last instance, the individual Governments were themselves in the best position to decide which method would enable them to ascertain national consumption of narcotic drugs with the greatest accuracy. The Health Committee confined itself to making the above suggestions and pointing out in general terms that, wherever possible, several methods should be employed for purposes of verification.

ATTEMPTS AT THE QUANTITATIVE DETERMINATION OF CONSUMPTION.

The pioneer attempts to determine consumption quantitatively were made in certain relatively small non-manufacturing countries, which, in consequence, were obliged to rely exclusively upon imports—viz., Denmark, Sweden, Belgium, Australia and New Zealand and also in Switzerland, where it was hoped that the direct method could be successfully applied. For various reasons, however, which it is unnecessary to analyse here, the results of this first attempt were highly unsatisfactory.

First Attempt, 1923.

It was during 1922 that the figures supplied by sixteen European¹ and a few extra-European countries in reply to a questionnaire were found to be sufficiently accurate to permit of the first attempt to determine consumption statistically. This experiment, like those which succeeded it, dealt with the more important opiates quantitatively, and more especially, therefore, with medicinal opium and pantopon, morphine, diacetylmorphine and also, wherever possible, with codeine and cocaine. Codeine, the consumption of which has been steadily increasing in recent years, presents particular

¹ Albania, Austria, Belgium, United Kingdom, Bulgaria, Czechoslovakia, Denmark, Estonia, Finland, Germany, Hungary, Italy, Luxemburg, Poland, Roumania, Sweden.

difficulties, as it does not fall within the scope either of the Hague or the Geneva 1925 Convention, with the result that statistics are very difficult to obtain. For the purposes of all calculations, the various opiates were reduced to a common denominator—the quantity of raw opium required for their manufacture—and raw opium was always assumed to contain 10 per cent morphine.

A preliminary estimate, which was not prepared by the Health Committee and was made at a time when only part of the data was available, gave 600 mg. of raw opium as the annual per head consumption of all opiates in highly civilised countries. This figure, however, was regarded as too high by the Health Committee (January 1924), which reduced it to 450 mg., with a note to the effect that the latter figure represented a maximum, and in any case only applied to countries in which the public health organisation was of outstanding efficiency. Any attempt to use this figure as a basis for the determination of world consumption was, therefore, to be avoided ; for the available reports clearly proved that, in countries the technical development of which was in a more or less backward state and which, indeed, represent the bulk of the world's population, consumption falls far short of 450 mg.

Additional investigations, more particularly rectifications in the conversion of morphine and codeine salts into bases, demonstrated that, leaving out codeine, the per head consumption in the above-mentioned sixteen European States, with a total population of rather more than 250 millions, does not exceed 285 mg. The difference, $450 - 285 = 165$, therefore represents the per head consumption of codeine.

The total of 450 mg. raw opium is distributed amongst the various opiates as follows :

| | Mg. of raw opium | Percentage |
|------------------------|---|---|
| Medicinal opium | 113 | 25 |
| Morphine | 155 | 34.4 |
| Diacetylmorphine | 17 | 3.7 |
| Codeine | 165 | 37 |
| | <hr style="width: 100px; margin: 0 auto;"/> 450 | <hr style="width: 100px; margin: 0 auto;"/> 100 |

At the same time, the per head consumption of cocaine was computed at 7 mg. on the basis of the same data.

To-day, after an interval of ten years, it is not without interest to compare the above figures for the year 1923 with the following

official figures for the United States of North America for the year 1931. The per head consumption of all opiates of the total population of the United States, which is estimated at 124,511,800, amounted, in 1931, to 450.28 mg. (including codeine and other opiates not falling within the scope of the Hague Convention). The corresponding consumption of cocaine was 6.84 mg.¹

Second Attempt, 1929.

The second attempt to ascertain world requirements in narcotic drugs was made in 1929 in connection with the preliminary work for the Conference for the Limitation of the Manufacture of Narcotic Drugs, which was to meet two years later. The prospects of success were now much brighter than in the case of the first attempt in 1923, for, in the meantime and as a result of the application of the 1925 Opium Convention, many important factors in the problem had become incomparably better known. Here it will suffice to point out that, since 1925, the League of Nations Secretariat had been in possession of statistical data which, even when they did not reproduce the facts with absolute fidelity, nevertheless afforded—as far as they went—a more or less reliable picture of the position in regard to manufacture, international trade and even smuggling. They also made it possible to form a good idea of consumption, as, under Article 22, paragraph (d), of the Geneva Convention, the contracting parties undertake to supply the League of Nations with accurate annual reports regarding the consumption of narcotic substances.

The reports were, however, incomplete. In the autumn of 1929, the competent services were in possession of consumption figures for a group of countries in all five continents, with an aggregate population of approximately 600 millions, in respect of medicinal opium, morphine, diacetylmorphine and cocaine for each of the four years 1925 to 1928. Figures for codeine consumption were supplied only by certain of these countries, with an aggregate population of approximately 200 millions.

The Health Section was now faced with the task of determining approximate world requirements on the basis of these data.

¹ United States Treasury Department, "Traffic in Opium and Other Dangerous Drugs for the Year ended December 31st, 1931", Washington, D.C., page 73.

In view of the considerable variations in the figures supplied, it was clear from the outset that the calculation could not be based simply upon the average consumption of the whole 600 millions. In regard to morphine, for example, the average figure over the four-year period varied between 0.72 mg. and 585 mg. of raw opium per head ; in regard to cocaine, between 0.01 mg. and 10.25 mg. Some other method had therefore to be found, those ultimately applied being as follows :

(1) Countries the consumption of which was known were divided into a number of categories on the basis of total consumption and a separate average consumption was computed in respect of each category.

(2) Countries where consumption was unknown were incorporated in the various categories in accordance with certain specified characteristics—geographical position, climate, general situation in regard to public health, technical development in sanitary matters, mortality, number of doctors, hospitals, etc.—which they had in common with countries where consumption was known.

(3) The total population of each category was then multiplied by the average consumption of that category.

(4) The sum of all the products obtained under (3) represents total consumption.

The figures for world requirements arrived at in the manner described above are as follows :¹

| | Tons ² |
|------------------------|-------------------|
| Medicinal opium | 94.6 |
| Morphine | 9.74 |
| Diacetylmorphine | 0.79 |
| Codeine | 9.74 |
| Cocaine | 6.05 |

Naturally, this attempt resulted in nothing more than a first approximate estimate intended to serve as a quite general provisional guide to the future Conference. The numerous hypotheses that had to be formulated, the reliability of which could not be exactly assessed, left room for considerable doubt as to how far the

¹ These figures are erroneously placed somewhat higher in the Proceedings of the Conference for the Limitation of the Manufacture of Narcotic Drugs (*cf.* documents O.C.1112, page 36, and C.509.M.214.1931.XI, pages 123 and 124).

² Of the substance indicated.

estimate corresponded to the facts or how far it fell short of them. The uncertainty became all the more pronounced when the estimated figures were compared with the figures for manufacture, which at that time were only partially known, and when the extent to which they differed was duly realised. Fears were expressed that the estimated figures had in all probability been fixed too low.

DETERMINATION OF CONSUMPTION ON THE BASIS OF TRADE STATISTICS BY THE OPIUM SECTION.

It was therefore a fortunate circumstance which, at the beginning of 1931, made it possible for the Opium Section of the Secretariat to propose a new estimate of consumption on the basis of much more reliable data. For the year 1929 had marked a veritable turning-point in the international treatment of narcotic substances.

The effects of the 1925 Geneva Opium Convention first began to make themselves felt in 1929, and statistical information for the two years 1929 and 1930 also made it possible to deal with the problem of consumption in a much more practical manner than had previously been possible.

On this occasion, the estimates were based on consumption statistics in the case of manufacturing countries ; whereas, in the case of consuming countries, which form the vast majority, it was trade statistics which were taken as a basis. The quantities of morphine, diacetylmorphine and cocaine imported into such countries from manufacturing countries was taken as representing maximum consumption, due regard being had to re-exports and to quantities seized in the course of illicit traffic and destroyed.

Thus determined, the consumption of morphine and cocaine for the years 1929 and 1930 was as follows :

| | Morphine | Cocaine |
|------------|-------------------|---------|
| | Tons ¹ | |
| 1929 | 9.5 | 5.7 |
| 1930 | 8.5 | 5.2 |

Comparison of these figures with those of 9.74 tons of morphine and 6.05 tons of cocaine previously arrived at in respect of the

¹ Of the substances indicated.

period 1925 to 1928 points to the conclusion that the hypotheses on which the first estimate was based have stood the test of experience and were therefore quite legitimate.

At first sight, comparison of the two figures seemed to point to a serious discrepancy in regard to diacetylmorphine. For each of the two years 1929 and 1930, maximum world consumption amounted to approximately 2,000 kg., whereas the average annual consumption for the period 1925 to 1928 was computed at 790 kg.

Closer analysis of the figures for 1929 and 1930 show, however, that, out of the total 2,000 kg., Japan alone consumed some 1,380 kg. Japan's consumption of diacetylmorphine was, however, unknown at the time of the first estimate, and it could scarcely have been supposed that it exceeded the consumption of the rest of the world by more than 200 per cent. If, however, Japan's share of the 2,000 kg. is left out of account, a figure of 620 kg. remains for the consumption of the rest of the world, and the discrepancy originally detected between the results of the two estimates appears much less marked.

"NEW" DERIVATIVES.

Article 14 of the Hague Convention, paragraphs (a), (b) and (c), enumerates all substances which come under the Convention. Paragraph (d) provides for the future. In future, "all new derivatives of morphine, of cocaine, or of their respective salts, and every other alkaloid of opium which may be shown by scientific research, generally recognised, to be liable to similar abuse and productive of like ill-effects" are to be brought under the Convention in the same manner as the substances enumerated under (a), (b) and (c).

New substances, within the meaning of the Convention, are those which were still unknown at the time when the Convention was concluded in 1912. But the Convention makes no mention of any criterion on which authoritative decision could be based as to whether a newly invented derivative of morphine was likely to produce addiction or not. Every individual Government is entitled to regard the scientific opinion held in its country as decisive; and, so long as all the Governments are not agreed, there is no generally recognised scientific opinion. Moreover, how could any Government

take the initiative, except on the occasion of some future international conference, which may not be convened for years ?

It was such considerations as these which caused the second Assembly and the Council of October 1921 to request the Advisory Committee on Opium to enquire whether there were not other habit-forming substances than those mentioned in the Hague Convention which would justify the convening of a new international opium conference.

Shortly afterwards, the French Government submitted a list of such substances, and a joint commission, consisting of members of the Advisory Committee on Opium and the Health Committee, made a careful examination of the entire list. Although some of the substances were found to be habit-forming, it was impossible, for the above-mentioned reasons, to take any steps to make the substances subject to control.

APPLICATION OF ARTICLE 10 OF THE GENEVA CONVENTION OF 1925.

The difficulty of bringing new habit-forming substances within the scope of the Convention was only overcome in the Geneva Convention of 1925, Article 10 of which created the necessary machinery for the purpose. Under this article, the Health Committee is entitled to recommend the contracting parties, through the Council of the League, to apply the necessary measures of control to any habit-forming substance which does not come under the Geneva Convention. If the Governments accept the Health Committee's recommendation, the substance in question immediately comes under the Convention, without the necessity of waiting for the decision of a new international conference.

Although this article does not make the Health Committee's recommendation binding on the States, there has hitherto been no case of such recommendation not being adopted. It is true that the procedure under Article 10 is somewhat complicated, since, out of consideration for some States which do not belong to the League of Nations, the Health Committee is obliged in each case to obtain the opinion of the Permanent Committee of the Office international d'Hygiène publique ; in practice, however, it has been possible to reduce the difficulties and delays in this connection to a minimum.

OBLIGATION TO REPORT NEW DERIVATIVES.

With reference to Article 10, the following important fact should be mentioned. Only a substance proved to be habit-forming can be brought under the Convention. In some cases, however, years may elapse before cases of addiction caused by a certain substance become known. An equally long time may elapse until the existence of a new substance which may possibly be habit-forming becomes generally known. The Health Committee therefore proposed in 1922 that the Governments should be requested to bring all new derivatives of opium and cocaine periodically to the knowledge of the Secretariat of the League of Nations. This recommendation on the part of the Health Committee was, however, never complied with, and the Health Committee's numerous proposals since 1925 with a view to applying Article 10 to new habit-forming substances have been made on its own initiative.

Only the latest Opium Convention—that of 1931—reverted to the Health Committee's original idea. According to Article 11 of that Convention, the contracting parties are compelled to notify the Secretariat of the League of Nations of the manufacture of any new derivative of the phenanthrene alkaloids of opium, and the Secretariat must pass on the notification to all contracting parties and to the Health Committee. The latter is then immediately in a position to set on foot the procedure provided for in Article 10 of the Geneva Convention of 1925.

CONVERTIBILITY OF INOFFENSIVE INTO HABIT-FORMING SUBSTANCES.

Article 11 of the 1931 Convention represents a further and very important step forward. The Health Committee has frequently had occasion to refer to the inadequacy of Article 10 of the 1925 Convention, since it applied exclusively to substances capable of producing addiction, while leaving entirely out of consideration substances which, though not habit-forming, may be converted into such substances.

In view of the close chemical relationship of all the substances in question, the possibility of such conversion can, in theory, never be excluded, and conversion has often enough been effected in

practice. The best-known example is that of codeine and thebaine. These substances, though not themselves habit-forming, may be converted respectively into heroin and eucodal, which are habit-forming. Nevertheless, Article 10 of the 1925 Convention offered no possibility of applying measures of control to these substances. Here again, the 1931 Convention provides a remedy: a number of non-habit forming substances, which are convertible into habit-forming substances such as thebaine, benzylmorphine, codeine, dionine¹ and others, were made subject to control, and the possibility was created of bringing such substances under control in future at the suggestion of the Health Committee.

**LIST OF SUBSTANCES TO WHICH ARTICLE 10 OF THE OPIUM
CONVENTION OF 1925 HAS BEEN APPLIED.**

- | | | |
|--|---|---|
| <ol style="list-style-type: none"> 1. Dihydrooxycodine 2. Dihydrocodeinone 3. Dihydromorphinone 4. Acetyldihydrocodeinone 5. Dihydromorphine | } | <p>Their esters, their salts and the salts of their esters.</p> |
| <ol style="list-style-type: none"> 6. Morphine N-oxide, the morphine-N-oxide derivatives and the other pentavalent nitrogen morphine derivatives. 7. Morphine esters and their salts. 8. Thebaine and its salts. 9. Ethers of morphine and their salts, except methylmorphine and its salts and ethylmorphine and its salts. 10. Preparations containing any of the substances enumerated under 1 to 9. | | |

GROUPS OF SUBSTANCES.

On examining this list, it will immediately be observed that, in addition to individual alkaloids mentioned by name, it includes entire groups of alkaloids, such as morphine esters, morphine-N-oxide derivatives, etc. A hard struggle was necessary in order to make not only *individual substances* but *groups of substances* subject to supervision. Legal and what appeared to be expert arguments

¹ The measures of control for codeine, dionine and their salts are not the same as for the other substances.

were brought forward to prove that only individual alkaloids should be made subject to supervision. It was stated that control should only apply to substances which had been found to produce addiction ; on the other hand, groups sometimes included substances the effect of which was still entirely unknown, or had at any rate not been established by experience. Moreover, groups included substances which, in many cases, did not yet exist and could merely be considered as theoretical possibilities.

The Health Committee, on the other hand, took the view that in many cases the campaign against the abuse of habit-forming substances was hopeless, and even senseless, unless entire groups of substances were brought under the Convention. The first case which arose concerning a group is highly instructive in this respect. It referred to benzoylmorphine—*i.e.*, an ester of morphine. When the Health Committee, in connection with this substance, took the initiative of proposing the application of Article 10 of the 1925 Convention to the entire group of morphine esters, it was aware of the following facts :

- (1) That benzoylmorphine was not used for therapeutic purposes ;
- (2) That no cases were known of addiction caused by benzoylmorphine ;
- (3) That it had been proved that the desire for morphine could be satisfied by benzoylmorphine ; and,
- (4) That morphine could be very easily recovered from the ester.

This last quality was the main reason why the Health Committee wished to make the entire group of esters subject to control. The ease with which morphine can be recovered is based on the chemical constitution of esters as such, and any morphine ester may be used as raw material for obtaining pure morphine.

While these somewhat prolonged debates were going on, another morphine ester, propionylmorphine, appeared on the Egyptian market. As soon as the procedure set on foot by the Health Committee under Article 10 became known, the firms manufacturing benzoylmorphine for non-medical purposes immediately stopped its manufacture and began to produce another morphine ester, with which they hoped to do as good business in legitimate trade as they

had previously done with benzoylmorphine. When it is considered that there are over 100,000 possible esters of morphine,¹ it is evident that the campaign against abuses would be hopeless unless the entire group of morphine esters could be brought under the Convention at one time, instead of each morphine ester being made subject to control as it appeared on the market. The Health Committee's view finally prevailed, and, at the time of the 1931 Conference, the principle had already been universally accepted.

PREPARATIONS.

The supervision provided for in all three Conventions applies, not only to pure alkaloids, but also to the preparations containing them.² The Hague Convention and the Geneva Convention of 1925, however, found it advisable—in order not to prejudice the legitimate interests of the consumers and pharmacists—to fix limits of tolerance for preparations, so that those containing less than the percentage of alkaloids fixed in the Convention should be exempt from any supervision.

LIMITS OF TOLERANCE.

The Health Committee, when called upon to deal with preparations, found that this point raised a certain difficulty. In the first place, it considered that the limits of tolerance had been somewhat arbitrarily fixed. In the second place, it was not evident how these limits of tolerance, which were expressed in percentages, could offer any guarantee against possible abuse if any desired quantity of alkaloids could be withdrawn from control by the admixture of a sufficiently large quantity of any other substance. Thirdly, the Health Committee always considered that, if a habit-forming alkaloid came under the Convention on account of its dangerous character, all preparations in which it formed an ingredient should

¹ See Hermann EMOE: "Ether Salts and Ethers of Morphine used as Narcotics" in *Deutsche medizinische Wochenschrift*, No. 52, 1931.

² A "preparation", within the meaning of the Convention, is any mixture of various substances in any proportion, as distinct from a chemical compound, which is a combination of elements based on chemical affinities in proportions determined by natural laws.

logically be placed under control. It was not obvious why an alkaloid should be less dangerous as an ingredient in a preparation than the pure alkaloid.¹

Once the Health Committee had been placed in a position to subject new habit-forming alkaloids to control in application of Article 10 of the 1925 Convention, it followed these principles and never made any distinction between pure alkaloids and preparations containing alkaloids and never recommended a limit of tolerance for preparations.

SOLUTIONS.

The Health Committee considered that the possibility of abuse was especially great in the case of ordinary solutions in which chemically inert substances, liquid or solid, were mixed with the alkaloid. The Health Committee frequently drew the attention of the Advisory Committee on Opium to this defect in the Geneva Convention of 1925, until Article 13 (b) of the 1931 Convention finally supplied the necessary remedy in the case of solutions of morphine and cocaine.²

Consequently, according to the provisions in force, all preparations containing habit-forming alkaloid are subject to control, with the exception of the three following groups : (1) preparations of morphine containing 0.2 per cent or less of morphine ; (2) preparations of cocaine containing 0.1 per cent or less of cocaine ; and (3) preparations containing extract or tincture of Indian hemp. These three groups of preparations will have to be dealt with in future.

PREPARATIONS OF INDIAN HEMP.

The group of preparations of Indian hemp will call for a decision of the Health Committee in the near future, since it represents a particularly serious gap in the 1925 Convention. Under Article 4(f)

¹ Apart, naturally, from the cases provided for in Article 8 of the 1925 Convention. See below.

² The article reads :

“The High Contracting Parties shall treat solutions or dilutions of morphine or cocaine or their salts in an inert substance, liquid or solid, which contain 0.2 per cent or less of morphine or 0.1 per cent or less of cocaine, in the same way as preparations containing more than these percentages.”

of that Convention, galenical preparations—*i.e.*, extract and tincture of Indian hemp—are subject to control as habit-forming substances ; on the other hand, preparations containing extract or tincture of Indian hemp are exempt from control. The degree of tolerance for these preparations is 100 per cent—that is to say, preparations containing less than 100 per cent of extract or tincture are free, even if they contain as much as 99.99 per cent of extract or tincture. The control applies only to 100 per cent extract and 100 per cent tincture. In view of this paradoxical position, the Egyptian Government proposed that the Health Committee should, in application of Article 10 of the Geneva Convention of 1925, bring a number of Indian-hemp preparations under the provisions of the Convention.

APPLICATION OF ARTICLE 8 OF THE GENEVA CONVENTION OF 1925.

The Geneva Convention of 1925, Article 8, lays down the procedure by which the Health Committee may in certain cases declare preparations containing habit-forming alkaloids and falling under the Convention to be exempt from control. The Health Committee is entitled to take this step in the case of preparations fulfilling the following two conditions :

- (1) That they do not give rise to the drug habit on account of the substances with which the alkaloid is compounded, and,
- (2) That the substances mixed with the alkaloid in practice preclude its recovery.

Since the 1925 Convention came into force, eighteen Governments¹ have recommended the Health Committee to apply Article 8 to about 290 different preparations. Of these preparations, after careful consideration and consultation with the Permanent Committee of the Office international d'Hygiène publique, only fifty-one were found to fulfil the conditions of Article 8 of the 1925 Convention and were declared exempt from control.

¹ Argentine, Austria, United Kingdom, British India, Bulgaria, Estonia, France, Germany, Hungary, Latvia, Netherlands, Poland, Roumania, Siam, Union of South Africa, Sudan, Sweden and Switzerland.

DIACETYLMORPHINE (HEROIN).

Since 1923, the problem of diacetylmorphine has, on several occasions, engaged the attention of the Health Committee. The Hague Convention of 1912 made diacetylmorphine, its salts and preparations containing more than 0.1 per cent of diacetylmorphine subject to control. The Health Committee, which considered in general that there might be objections to limits of tolerance for preparations, regarded them as particularly unsuitable in the case of diacetylmorphine, the most powerful of all known narcotic substances. Moreover, in view of the opinion widely held by pharmacologists and doctors that diacetylmorphine can be entirely dispensed with for therapeutic purposes, the Health Committee considered that the question of stopping the manufacture of diacetylmorphine altogether was worthy of careful consideration. When, in the course of time, more exact statistical reports became available and it was shown that the medical consumption of diacetylmorphine was comparatively small and that a quantity many times in excess of this amount was used for the illegitimate requirements of the criminal classes of all countries, the Health Committee raised the question whether the social evils of diacetylmorphine did not so far exceed its therapeutic value as to make the stoppage of manufacture advisable.

The Health Committee's unfavourable view of diacetylmorphine was still further confirmed in 1924, when the manufacture and therapeutic use of diacetylmorphine were forbidden in the United States of America without any adverse effects on the state of health of the country being observable, and, in particular, when, in the course of time, new narcotic substances appeared on the market which had the same therapeutic effect as diacetylmorphine but were, at the same time, if not entirely harmless, at any rate much less dangerous than diacetylmorphine. The 1931 Conference was not in a position to adopt the Health Committee's proposal, although the Advisory Committee of Experts shared the Health Committee's view. As a result of the Health Committee's warnings, however, the two Geneva Conferences of 1925 and 1931 succeeded in effecting a considerable improvement in the existing provisions.

The 1925 Convention abolished the limit of tolerance for the preparations of diacetylmorphine, so that preparations containing

less than 0.1 per cent of diacetylmorphine have since that time been subject to control.

In view of the special danger of this substance, the 1931 Convention provided for special measures of control ; diacetylmorphine, its salts and preparations, may now only be imported by Governments, while the distribution in the country to wholesalers and retailers is under special State supervision.

COCAINE.

The Health Committee's attention was first drawn to the cocaine question by the French Government's suggestions referred to above. Among many other substances which were therein brought to the attention of the League of Nations as requiring supervision were synthetic cocaine, a series of synthetic substitutes for cocaine (holocaine, eucaine, novocaine, tropacocaine) and certain derivatives of ecgonine. Ecgonine itself was not in the list.

Synthetic cocaine was declared to be identical with natural cocaine, whereupon the Geneva Convention of 1925 removed from the Hague definition of cocaine the reference to its being the principal alkaloid of the leaves of *Erythroxylon coca*, and merely defined cocaine by its chemical formula.¹

The four derivatives of ecgonine mentioned by the French Government were also declared to require supervision, whereupon the Geneva Conference of 1925 extended the scope of this decision and thus made not only the mother substance, ecgonine, but all its derivatives, subject to control.

¹ It may here be said that, some years later, the Health Committee had to answer a similar question regarding synthetic morphine. On that occasion, it appeared to one Government that the problem of producing synthetic morphine had been solved and the claim was made that synthetic morphine was exempt from control, since, in accordance with Article 1 of the Geneva Convention of 1925, the term "morphine" must be understood to mean the principal alkaloid of opium (chemical formula : $C_{17}H_{19}NO_2$). The Health Committee thereupon merely decided that each substance whose chemical constitution corresponds to the above formula is the principal alkaloid of opium, and that, consequently, the question of its origin is of no importance. Further, the artificial alkaloid is to be distinguished from the natural alkaloid, not by the fact that the first is synthetic and the second not synthetic, but because the synthesis of the artificial product is brought about by the chemist in the factory and the synthesis of the natural substance is accomplished by the cell of the plant.

Lastly, the Health Committee took this opportunity of making to the Governments the following recommendations which, in its view, would tend to limit the improper use of cocaine :

(1) Synthetic cocaine substitutes should, wherever therapeutically admissible, be used in place of cocaine. Although up to that date (1923) cocaine was indispensable in laryngology and ophthalmology, its use as a local anæsthetic in dentistry seemed to be less indispensable ;

(2) Cocaine should never be entrusted for use to a patient, but should always be administered by the doctor himself ;

(3) Specialities containing cocaine should, in principle, only be retailed on a doctor's prescription ;

(4) To prevent the illicit traffic and to facilitate control, cocaine should, apart from the specialities containing cocaine, only be retailed in the form of solutions.

CERTAIN SPECIAL PROBLEMS.

The Health Committee also undertook a series of special investigations, of which the following three may be mentioned :

ANTI-OPIUM PILLS.

In the last few years, the smoking of so-called anti-opium pills has become very popular in the Far East. The pills are smoked in the same way as prepared opium, and, according to the advertisement, are said to be quite harmless and to lead quickly and painlessly to freedom from opium addiction. The pills appear in many forms, and all are manufactured in the Far East. The first chemical analyses (made in the Hong-Kong Government laboratory) showed that, besides caffeine, quinine or strychnine, the pills also contain diacetylmorphine in varying quantities. As, however, no diacetylmorphine could be traced in the smoke, the popularity of the pills remained a problem, for the solution of which the assistance of the Health Committee was asked by the Opium Advisory Committee.

The investigations were found to be difficult and at first (1926) gave a negative result. Only after the elaboration of a special

microchemical method did it become possible (1923) to obtain crystals of diacetylmorphine direct from the smoke. The investigations are proceeding in order to render possible a quantitative determination of the diacetylmorphine content.

STANDARDISATION OF A METHOD OF ASCERTAINING THE MORPHINE CONTENT OF RAW OPIUM.

One of the most important requirements for a successful supervision of the manufacture of narcotics is a reliable method of ascertaining the morphine content in raw opium. It is well known that the morphine content of opium varies between about 8 and 20 per cent, and different analytical methods often show variations in morphine content of from 2 to 3 per cent in the same test. The analytical methods provided for raw opium in national pharmacopœiæ also differ widely ; but raw opium delivered to factories is never analysed by these methods. In practice, Governments were content with the analysis supplied to the purchaser of raw opium by a London analytical laboratory of world-wide repute and enjoying the confidence of Governments.

The Geneva Convention for limiting the Manufacture and regulating the Distribution of Narcotic Drugs, 1931, however, makes Governments directly responsible for the accuracy of analyses ; Article 17(a) provides that methods used for determining the preparation of morphine shall be prescribed by the Governments and the analysis carried out under conditions considered satisfactory by Governments.

For this reason, in 1930, the United Kingdom Government suggested that the Health Committee might be entrusted with the working-out of a uniform method of determining the morphine content of raw opium giving the most accurate results possible. A committee of chemical and pharmaceutical experts from Austria, Denmark, England, France, Germany, Japan, the Netherlands, Switzerland and the United States of North America, after two years' laboratory researches, has worked out the desired method, which fulfils all practical requirements. It has also been adopted in the most recently published pharmacopœiæ of 1933—*i.e.*, in those of Denmark and Switzerland.

A similar task—*i.e.*, the working-out of a method of determining the cocaine content in coca leaves--was, on the proposal of the Japanese Government, entrusted to the same Committee, and is now well on its way to a satisfactory solution.

METHODS OF TREATING ADDICTS.

On the proposal of the Conference on the Suppression of Opium-smoking (Bangkok, 1931) and of the Opium Advisory Committee, the Council of the League of Nations referred the question of the treatment of addicts to the Health Committee for investigation.

After experts, clinicians and medical officers from ten European and extra-European countries had expressed their opinion on the matter in valuable reports, the Health Committee (November 1933) decided, in the first place, to prepare, in collaboration with the Opium Advisory Committee, a detailed programme of study of the opium-smoking problem and the treatment of addicts, and, in accordance with the recommendation of the Bangkok Conference, to transmit this to Far-Eastern Governments.

THE ART OF HEALING 'AND THE SALE OF REMEDIES IN FRANCE'

By

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I. HISTORICAL RETROSPECT.

The medical and surgical art has been regulated in France for a very long time past. As early as 1311, an edict of Philippe le Bel forbade the practice of surgery to anyone who had not passed an examination before the sworn master-surgeons.

Side by side with doctors of medicine and surgeons, there existed barbers, bone-setters and itinerant surgeons who were regarded as belonging to an inferior order. In 1332, the number of doctors practising illicitly in Paris exceeded that of the approved and licensed practitioners. Briquet, Henry III's jester, told his royal master that the profession most commonly exercised among his subjects was that of doctor, meaning that anyone could at a moment's notice reveal himself as a skilful therapist. Things have not changed since Briquet. Civilised as we claim to be, we are still surprisingly credulous in regard to "mystery medicine".

On August 18th, 1792, the Revolution abolished corporations and guilds. The Faculty of Medicine and the College of Surgeons therefore disappeared and the practice of the medical and surgical professions became free.

Three years later, under pressure of circumstances, the *École de Santé* was founded. The laws of 19th Ventôse and of 21st Germinal of the Year XI (1803) once again regulated the practice of medicine and pharmacy, in which no one might engage "without being examined and passed in the prescribed form". Moreover, any person

¹ We are largely indebted to Professor APPLETON and M. SELAMA for the information on medical jurisprudence and to Professor PERREAU as regards pharmaceutical law and jurisprudence.

wishing to practise medicine or pharmacy was required to have his diploma registered at the prefecture and with the registrar of the court. In order to meet the requirements of the rural populations who were insufficiently provided with doctors, the law of 19th Ventôse of the Year XI (March 10th, 1803) created a lower grade—that of *officier de santé*. *Officiers de santé* were passed by the judges of the *départements* until 1838 and afterwards by the Schools and Faculties of Medicine. They were only entitled to practise in the *département* they had selected, and they were not allowed to perform major surgical or obstetrical operations. The *officier de santé*, although severely criticised in 1811 by Dupuytren, nevertheless did good work in the country districts, to some extent making up for the shortage of doctors.

The standard of studies was gradually raised throughout the nineteenth century, until the increase in the number of doctors made it possible to abolish the grade of *officier de santé* (Law of November 30th, 1892). In 1866, there were 11,254 doctors of medicine and 5,568 *officiers de santé*. In 1926, the number of doctors was 23,992 and that of *officiers de santé* was only 217, so that the latter will very soon become extinct.

II. CONDITIONS GOVERNING THE PRACTICE OF MEDICINE.

The practice of medicine in France is subject to strict regulations. It is governed by the Law of November 30th, 1892.

No one may practise medicine in France unless he is provided with a diploma of doctor of medicine delivered by the French Government after examinations undergone before a higher medical institution of the State. There is only one category of doctors—those who have obtained the diploma of doctor of medicine at a French Faculty. The former grade of doctor of surgery has been abolished. The *internes* at the French hospitals and hospices who have passed examinations and can show sixteen “inscriptions”, and medical students who have completed their studies and can show twenty “inscriptions”, may practise medicine during an epidemic or act as substitutes for medical practitioners. This authorisation, which is limited to three months but may be renewed for

the same period, is delivered by the prefect of the *département* in which the student is to practise. Any person wishing to engage in the practice of medicine or allied activities (doctor of medicine, dental surgeon, or certified midwife) is obliged, as soon as he sets up his practice and before performing any act of his profession, to have his title registered free of charge at the prefecture or sub-prefecture and with the registrar of the civil court of his district, and to have it endorsed at the town hall of his place of domicile.

Any change of domicile to another *département* necessitates a fresh registration of the title within the same time-limit.

Failure to comply with the obligation to have a diploma registered within the time-limit and subject to the conditions mentioned above is punishable by a fine of 25 to 100 francs.

In order that these provisions may not remain a dead letter, a judicial and administrative supervision of the position of doctors has been organised under the law. Every year prefects and judicial authorities have lists drawn up in each *département* giving the names and surnames of physicians, dental surgeons, and certified midwives, their residence, and the date and origin of their diplomas, these lists being posted up during the month of January in all the communes of the *département*.

Previous to the Law of 1892, doctors in possession of foreign diplomas were allowed to practise medicine in France subject to a simple Government authorisation. To-day, they must be in possession of the State diploma of doctor of medicine delivered by a French Faculty (there is also a university diploma which does not entitle the holder to practise medicine).

III. ILLEGAL PRACTICE OF MEDICINE.

According to the Law of November 30th, 1892 (Article 16), the following are regarded as illegally practising medicine :

- (1) Any person who, not possessing a diploma of doctor of medicine, *officier de santé*, dental surgeon or certified midwife, or who fails to comply with the conditions laid down in Articles

6, 29 and 32 of the present law,¹ habitually takes part in or directs, otherwise than occasionally, the treatment of diseases or surgical cases or practises dentistry or midwifery, except in cases of proved emergency ;

(2) Any certified midwife who, although holding a regular diploma, exceeds in the exercise of her profession the limits of her functions as defined in Article 4 of the present law ;²

(3) Any person who, although possessing a proper title, exceeds the limits of his or her statutory functions ; in particular, by assisting the persons mentioned in the foregoing paragraphs, in order to enable them to evade the provisions of the present law.

(4) The provisions of paragraph (1) of the present article do not apply to medical students acting as doctors' assistants or detailed by a doctor to attend to his patients, nor to nurses, nor to persons who, without assuming the title of dental surgeon, extract teeth in accidental circumstances.

The illegal practice of medicine is an offence, and therefore makes the guilty party liable to punishment.

IV. CHARACTERISTICS AND CONSTITUENTS OF THE OFFENCE.

A. GENERAL CONSTITUENTS OF THE OFFENCE.

1. *Voluntary Nature of the Act.*

Like any other offence, the illegal practice of medicine must be a voluntary act.

¹ Article 6 relates to the replacement of doctors by *internes* or students in the capacity of *locum tenens* ; Article 29 relates to health officers and Article 32 to dentists.

² In virtue of Article 4, certified midwives are forbidden to employ instruments. In cases of difficult delivery they must call in a doctor or *officier de santé*. They are also forbidden to prescribe medicaments, except in the case provided for in the Decree of June 23rd, 1873 (sale of ergotised rye), and in the decrees which may be promulgated under the same conditions after consultation with the Academy of Medicine.

Hence the following circumstances preclude guilt : physical or moral coercion, insanity, lack of discernment in a person under 18 years of age, somnambulism not voluntarily induced.

2. *Intent to commit an Offence.*

Intent to commit a breach of the law is not indispensable. There have been numerous judgments to this effect.

B. ILLEGAL PRACTICE BY UNQUALIFIED PERSONS.

The practice of medicine is only an offence for persons without qualification if the following two constituents are present :

1. *Treatment.*

In order to be illicit, the action of the unqualified person must consist "in taking part" (according to the actual term used by the law) "in the treatment of diseases or surgical affections and in dentistry or midwifery". By treatment is meant handling a disease with a view to curing it or to reducing its dangers or alleviating the sufferings which it causes or attenuating or dispelling the consequences it may involve. It may be concluded that the fact of establishing a diagnosis, even by scientific means, does not suffice to constitute the offence of illegal practice of medicine. On the other hand, the methods of cure employed are immaterial *unless their inefficacy is absolute*. Setting out from this idea, legal practice does not limit the definition of treatment to actual manipulations. It declares mere advice of a medical nature to be punishable, with the exception of that given by friends or relations. Consultations of all kinds are also punishable, together with the use of magnetism and treatment of different kinds by means of massage, electrotherapy, hydrotherapy, radiotherapy, mecanotherapy, actinotherapy, etc.

A person is also guilty of illegal practice of medicine if, without having a diploma of doctor of medicine, he prescribes and sells a medicinal preparation to a number of persons whom he has attracted by posters and advertisements in the newspapers.

By "surgical affections or diseases" is meant all kinds of organic lesions or functional disturbances, even if they are mere indispositions.

Dentistry.

Dentistry consists in the treatment of dental affections and the diseases connected therewith. Manufacturers of dental appliances who are considered as mere "mechanics" are not regarded as practising dentistry in the legal sense of the term, and consequently need not be provided with a dental surgeon's diploma. If, however, such manufacture is combined with the taking of casts or the setting of artificial teeth or other appliances, the administration of anaesthetics or the application of dental dressings, these various acts must be regarded as constituting acts of illegal practice.

Practice of Midwifery.

By midwifery is meant "all activities connected with bringing a child into the world, from the first pains until the conclusion". In principle, therefore, quite apart from the exceptions indicated below, the fact of assisting this labour at any moment of its duration, otherwise than by giving purely domestic assistance such as would be given by a nurse, would constitute the illegal practice of midwifery. The courts have discretion to appreciate the circumstances of each case.

2. *The Factor of Habit or Continued Treatment.*

The illegal practice of medicine is not a single offence but an habitual offence.

It is the outcome of the repetition of acts which, considered separately, are not sufficiently serious to merit punishment but which become punishable when repeated. This is a question of pure fact, to be freely and finally appreciated by the judge on its own merits. But, while it is necessary, in principle, that the accused should be found guilty of at least two successive acts of practising medicine, *it is immaterial whether such acts relate to the same person or to different persons.*

An isolated act of practising medicine not being an offence, no offence is committed by a chemist who modifies a single prescription or a person who in accidental circumstances extracts a tooth.

a priest who practises a Cæsarian operation in order to baptise a child, etc. The same applies as regards the administration of anæsthetics to extract a tooth, when the incriminated acts can only be regarded as accessory to the extraction ; not being habitual, these acts cannot come under the application of the law.

As regards proof, the practice of the court is that the accused must prove that the acts with which he is charged are not habitual acts but acts independent one of another.

C. ILLEGAL PRACTICE BY PERSONS HOLDING DIPLOMAS.

The possession of a qualification is not in itself sufficient to preclude the possibility of an offence (see above, Article 16 of No. 3 of the Law of 1892).

1. *Offence common to Doctors, Dentists and Certified Midwives.*

Generally speaking, whenever the holder of a diploma diverts it from its legal purpose to cover the actions of other persons prohibited by the law, he renders himself liable to the application of the provision mentioned above.

This applies to doctors of medicine who consent to assist persons without a diploma or who act as the auxiliaries of empiricists or who associate with persons illegally practising medicine in order to cover the acts of such persons with their name and diploma, without participating in the treatment which they give to their patients.

Assistance given to unqualified practitioners being mentioned by the law only as an example, the judges can, if occasion arises, punish any other illicit use of a diploma.

2. *Dentists and Certified Midwives overstepping the Limits of their Statutory Functions.*

Dentists and midwives have strictly limited functions, which they cannot exceed without committing the offence of illegally practising medicine.

(a) *Dentists.*

A dentist who oversteps the limits of his functions, as determined by his diploma, by encroaching on the general functions of medicine

or pharmacy renders himself liable to the application of Article 16 mentioned above. Since the law has not defined the profession of dentist, the scope of dentistry is open to discussion.

In principle, reference has to be made to the curriculum fixed by the Decree of January 11th, 1909, to which the Law of November 30th, 1892, alludes (Article 2). This curriculum includes affections of the teeth, the different professional dental operations (filing, filling, extraction) and the insertion of the different pieces of dental prosthesis.

It should be noted that dentists licensed before January 1st, 1892, are not entitled to administer anæsthetics without the assistance of a doctor of medicine or of an *officier de santé*. Any breach of this prohibition constitutes the offence of illegal practice of dentistry with false assumption of title.

(b) *Midwives.*

Like dentists, certified midwives have limited medical functions which they may not exceed (see above).

V. EXCEPTIONS TO THE OFFENCE OF ILLEGAL PRACTICE OF MEDICINE.

1. FREE ATTENDANCE.

Does absence of remuneration exempt from the charge of illegal practice of medicine? The Law of 1892 makes no distinction between the illegal practice of medicine for gain or with charitable intent. Absence of remuneration does not exempt from the application of the prohibition laid down by law. If the offender has been actuated by feelings of charity or generosity, he can only plead extenuating circumstances.

2. GENERAL KNOWLEDGE.

For illegal practice of medicine to exist, the medical attention given must require special knowledge; ordinary physical treatment based only on general knowledge does not come under the application of the law. Thus, the treatment which is habitually given in

the family—the dressing of trifling wounds, massages, and the administration of family medicines in current use—cannot constitute an offence under the law.

3. PROVED EMERGENCY.

The provisions of the law on the illegal practice of medicine are not applicable to cases of proved emergency.

Urgency is a question of fact that the courts will have to decide in each case. But urgency is an excuse only if it is proved—that is, generally speaking, when it is impossible to await the doctor's arrival without serious danger to the patient. It is for the accused to adduce proof. His good faith is taken into consideration.

Cases of urgency are assimilated to *force majeure*.

4. PERSONS NOT IN POSSESSION OF A DIPLOMA BUT AUTHORISED TO PRACTISE.

These include, under the terms of the Law of 1892 :

(1) Medical students acting as assistants to a doctor or placed by the latter in charge of his patients, and nurses.

(2) Medical *internes* and students authorised to practise during an epidemic or as *locum tenens* (Article 6).

In the case of nurses or assistants of any kind, it is essential that they should confine themselves to carrying out the orders of the doctor under whose supervision they are placed.

5. MANUFACTURE AND SALE OF MEDICAL ACCESSORIES.

This is entirely unrestricted, even when accompanied by the explanations necessary for the use of such accessories. A manufacturer is guilty of the offence of illegal practice of medicine only if he questions his customer and examines him directly, or if he takes measurements or casts in order to manufacture on his own authority appliances or artificial parts.

Such acts must be performed in the presence of the doctor or dentist, or under their direction.

VI. PROSECUTIONS, JURISDICTION AND PUNISHMENT.

A. PROSECUTIONS.

1. *Their Nature.*

Prosecutions are conducted under the ordinary law of the land. Like any other offence, the illegal practice of medicine gives rise to a public action (right of the community to inflict punishment) and to a civil action (right to obtain reparation for damage caused by the illicit act).

In principle, the community alone is entitled to bring a criminal or public action through the Director of Public Prosecutions (*Ministère public*); such action is only directed against the principals or accessories.

Any injured party may bring a civil action; this may be brought, not merely against the author of the damage, but against his heirs and the persons responsible for him at law.

2. *Persons who may prosecute.*

Under Article 17 of the Law of November 30th, 1892, the following may prosecute:

(a) *The Director of Public Prosecutions.* He may bring only a public action; he may decide to act on his own initiative without waiting for the injured party to lodge a complaint. On the other hand, if a complaint is lodged, he is not necessarily bound at law to institute a public action.

(b) *Medical practitioners, dental surgeons and certified midwives.* These may, when injured, institute proceedings on the ground of illegal practice. Under Article 17 mentioned above, they may lay an information in person before the proper judicial authorities with a view to the institution of a public prosecution, provided they conform with Article 182 of the Code on Preliminary Procedure in Criminal Matters. (*Code d'instruction criminelle.*) They may also institute proceedings as *partie civile*—i.e., bring a civil action

personal—when criminal proceedings have been instituted by the Director of Public Prosecutions. The only condition limiting their action is that they must prove that they have suffered material or moral damage, however difficult it may be for the judge to assess such damage.

The same individual may not be sentenced twice for the same offence, but every injured party entitled to bring an action personal for compensation for damage suffered may bring such an action, and may be accorded satisfaction notwithstanding the fact that the offender has already been sentenced for the same offence, but in respect of other medical practitioners.

(c) *Associations and unions (syndicats) of medical practitioners, dental surgeons and certified midwives.* These possess the right to institute proceedings under Article 17 of the Law of 1892, provided they, too, furnish proof of material or moral damage suffered. In the case of associations, the damage must have been done to their members and not merely to the general interests of the profession. This condition does not apply to the institution of proceedings by unions (*syndicats*).

B. JURISDICTION.

The parties concerned may bring their action before either the civil or "correctional" courts.

The proper correctional court is that of the locality in which the offence was committed or of the locality in which the accused may be discovered.

The proper civil courts are :

(1) The local magistrates (*juges de paix*)—up to 1,000 francs without appeal and up to 3,000 francs subject to appeal to the *département* courts of first instance ;

(2) The district courts—if the claim exceeds 3,000 francs, an appeal lies to the Court of Appeal.

C. LIMITATION.

The right to bring a public or civil action on the ground of illegal practice of medicine lapses by limitation three years from the date on which the alleged offence was committed.

D. SENTENCES.

1. The sentences provided are :

(a) *Practice of medicine proper* : a fine of from 100 to 500 francs and, if the offence be repeated, a fine from 500 to 1,000 francs and a term of imprisonment varying from six days to six months, or one of these sentences only (Article 18) ;

(b) *Dental surgery* : a fine of from 50 to 100 francs and, if the offence be repeated, a fine of from 100 to 500 francs (Article 18) ;

(c) *Midwifery* : a fine of from 50 to 100 francs and, if the offence be repeated, a fine of from 100 to 500 francs and a term of imprisonment varying from six days to one month, or one of these sentences only (Article 18).

As regards the aggravation of the offence by false pretence to title, see *infra*.

2. *Sentences are not consecutive.* The offence of the illegal practice of medicine is subject to the principle that the sentences shall not be consecutive. Consequently, a person committing this offence as well as another offence, whether it be a crime or misdemeanour, either at the same time or subsequently, but who has not been sentenced for the first offence at the time when the second was committed, may only be sentenced to the heavier punishment of the two if the proceedings taken against him for the two offences are simultaneous or, if the proceedings are not simultaneous, the lesser sentence runs concurrently with the greater.

3. *Deferred sentence (sursis).* Execution of sentence pronounced for the offence of the illegal practice of medicine may be deferred by decision of the court, provided the offender has not previously been sentenced for crime or misdemeanour under the ordinary law of the land.

4. *Extenuating circumstances.* The court may admit such circumstances and consequently reduce the sentence below the minimum specified by the law (Article 27).

5. *Accessories.* Any person who instigates, prepares or facilitates the commission of the offence of the illegal practice of

medicine is deemed to be an accessory under the terms of Article 60 of the Penal Code.

A case in point would be that of a pharmacist who delivered medicines on the prescription of a person whom he knew to be unqualified, or that of a qualified dental surgeon—director of a dental institute—who allowed an unqualified person to carry out dental operations therein.

6. *Additional punishment.* In addition to the main sentence mentioned above, the Law of 1892 provides for additional punishment, the object of which is to eliminate from the profession persons who have been guilty of unprofessional conduct.

Article 25 of this law, as supplemented by the Law of July 13th, 1929, lays down :

“Courts and tribunals may, in addition to the main sentence, temporarily or definitely preclude from the exercise of their profession any medical practitioner, *officier de santé*, dental surgeon or certified midwife sentenced :

“(1) To punishment involving loss of liberty and loss of civil rights (*peine afflictive et infamante*) ;

“(2) To a correctional punishment inflicted for the crimes of forgery, theft or swindling, or for crimes or misdemeanours specified in Articles 316, 317, 331, 334 and 335 of the Penal Code ;

“(3) To a correctional punishment inflicted by a court of assize for acts qualified as crimes by law and by Article 2, paragraph 2, of the Law of July 12th, 1916, for having aided another to use narcotics either with or without remuneration. In no case may political crimes or misdemeanours involve the temporary or total loss of the right to practise the professions referred to in this article.”

Medical students are referred to in paragraph 6 of Article 25, which is worded as follows :

“Students of either sex working for the degree of doctor of medicine, medical officer of health, dental surgeon or certified midwife who have been sentenced to any one of the punishments specified in paragraphs 1, 2 and 3 of the present article [the punishments set out above] may be prohibited from

frequenting higher educational establishments. The punishment of exclusion shall be pronounced under the conditions laid down on February 27th, 1880 (by the *Conseil académique*, an appeal lying to the *Conseil Supérieur de l'Instruction publique*). In no case may political crimes or misdemeanours involve exclusion from medical training establishments."

VII. FALSE PRETENCE TO TITLE.

A. FALSE PRETENCE ACCOMPANIED BY ILLEGAL PRACTICE.

This misdemeanour is specially mentioned in, and punished under, Article 19, paragraph 1, of the Law of November 30th, 1892. It concerns the use by a person illegally practising medicine of the title of doctor of medicine, *officier de santé*, dental surgeon or certified midwife.

(a) *Constitution of the offence.* In the first case, the person must have engaged in illegal practice ; consequently, *officiers de santé* or students assuming the title of doctor would not be held guilty of this particular misdemeanour. Nor would dental surgeons nor certified midwives employing it be guilty of an offence so long as they confine their activities to their particular branch.

There must, moreover, have been use of title and absence of right. The title is held to be employed when the full and entire expression *docteur en médecine* has been used. The employment of the single words *docteur*, *médecin* or *chirurgien* would not suffice to constitute the misdemeanour of false pretence to title. Absence of right occurs in the case of a person possessing a foreign degree who practises any branch of medicine without stating, either before or after his degree, that that degree was acquired abroad (Article 20).

It makes very little difference whether the title of doctor of medicine has been used in prescriptions or certificates, or on name-plates or visiting-cards or in announcements or advertisements.

(b) *Sentences.* The sentences provided are as follows (Article 19):

False pretence to the title of doctor or officier de santé : fine from 1,000 to 2,000 francs ; if the offence be repeated, fine from 2,000 to 3,000 francs, and a term of imprisonment varying

from ten months to one year, or one of these two sentences only.

False pretence to the title of dental surgeon : fine from 100 to 500 francs ; if the offence be repeated, fine from 500 to 1,000 francs and a term of imprisonment varying from six days to one month, or one of these sentences only.

False pretence to the title of certified midwife : fine from 100 to 500 francs ; if the offence be repeated, fine from 500 to 1,000 francs and a term of imprisonment varying from one to two months, or one of these sentences only.

B. FALSE PRETENCE TO THE TITLE OF DOCTOR IN THE LICIT PRACTICE OF MEDICINE.

Such false pretence is only a misdemeanour if accompanied by the actual practice of medicine in any of its branches (medicine proper, dentistry, or midwifery).

1. Constitution of the Offence.

Two conditions are necessary :

(a) *Employment of the title* "docteur en médecine". As for false pretence to the title with illegal practice, the whole term *docteur en médecine* must have been employed.

Since the law makes no provision for false pretence to the title of dental surgeon or certified midwife, neither act constitutes a punishable offence.

(b) *Omission to indicate foreign origin*. Any person, whether of French or other nationality, who engages in the art of healing without stating the foreign origin of his title of doctor is punishable at law. But persons licitly practising in France—in particular, *officiers de santé*—who assume a title of doctor which they have obtained neither abroad nor in France are not liable to any punishment.

2. Sentences.

The offender is liable to a fine of from 100 to 200 francs in all cases (Article 20). The sentence is not increased if the offence is repeated.

Paragraph 1 of Article 259 of the Penal Code, which punishes the illegal wearing of a uniform or decoration, is thus supplemented by the Law of March 26th, 1924 :

“Any person who employs a title belonging to a profession regulated by law, without having fulfilled the conditions which would entitle him to employ it, shall be sentenced similarly (a term of imprisonment varying from six months to two years).”

It is generally agreed that this new text protects, *inter alia*, medical degrees. Nevertheless, it is very difficult to make it concord with Articles 19 and 20 of the Law of 1892.

It should be noted, perhaps, that the above-mentioned law of 1924 applies to the protection of all medical degrees in every branch of medicine, and that its terms apply in all probability only to official scientific degrees—doctor of medicine, dental surgeon, *officier de santé*, and certified midwife, to the exclusion of their shorter forms or abbreviations (doctor, dentist, midwife, etc.).

This at least is how the courts generally interpret the Laws of 19th Ventôse, Year XI, and November 30th, 1892. Finally, false pretence is in itself an offence, apart from all practice of the profession.

The punishment provided is a term of imprisonment varying from six months to two years.

VIII. APPLICATION OF THE LAW.

LENIENCY OF JUDGES.

In spite of the fact that costs are added to fines, the sentences provided by law are light and the law itself is too often rendered inoperative by the incredible leniency of the magistrates to quacks. In France, there is no special official organisation for combating the illegal practice of medicine. Following on the congress on illegal practice held in 1906, an *Office central pour la répression de l'exercice illégal de la médecine* was established. This office is affiliated to the Association of French Medical Unions, which supports it both morally and financially. Moreover, whenever

proceedings are taken against a quack as a result of a complaint, the regional medical union generally institutes proceedings as *partie civile*.

The number of sentences pronounced annually is fairly small, and the punishment inflicted is very light. Doctors hesitate to bring proceedings against charlatans for fear of providing the latter with a first-rate advertisement. Moreover, as we have seen, the sentences provided are inadequate, and the following examples will show that magistrates are often far too lenient towards accused.

In this connection, the recent history of a celebrated "healer", Germaine de Rouen, is most illustrative as a typical example of mass delusion. This woman was able to imagine incredible things and risk absurd demonstrations of certain scientific ideas, without ever losing her grip on a public eager for hollow mysteries and extravagant fables.

Germaine Beguin's first cures date from 1913. In 1921, she appears at Trouville as "Madame Germaine", to become later at Caen "*la petite dame de Lourdes*". In 1925, she is back at Rouen on the high tide of success. Then a first public demonstration is organised at the Club du Faubourg, introducing the healer to Paris. From that moment the "*petite dame de Lourdes*" disappears and we meet "Germaine de Rouen". She frequently changes her residence, but not in order to escape justice. She has never been sentenced, because, both in Normandy and at Lyons, the complaints against her were disallowed.

Vichy, through its mayor, accords her an almost official reception. Finally, after an impassioned struggle with the faculty of Nancy, in which ardent partisans reveal themselves in the course of violent episodes and after ironical appearances before the magistrates, Germaine attains her apotheosis in the north. Lille in 1928 and Roubaix in 1929 have no halls large enough to shelter her "miracles" and the hundreds of sick persons seeking her "miraculous" cures which she brings about by the mere laying on of hands, or even—in some cases—without direct contact.

At Nancy, near the house to which Coué attracted the sufferers of Europe, Germaine de Rouen leased, in 1927, a villa soon to be a common topic of the Press in Madrid, Belgrade and Mexico City. Her prestige increased to such an extent that the faculty of medicine became anxious and finally took up a definite position against her.

Professors SPILLMAN and PARISOT, writing in the *Revue d'hygiène et de prophylaxie sociales*, conclude that "the baneful action of healers must be stopped in the interests of the community and the protection of public health".

After many sudden changes of fortune, the official representatives of the law, in spite of two previous disallowals of complaint, drew up a new complaint, and on May 11th, 1928, indicted Germaine de Rouen for swindling and the illegal practice of medicine. Against the judgment given on November 3rd, 1928, under which she was sentenced to one year's imprisonment and a fine of 1,000 francs, Germaine de Rouen appealed at law. She also appealed to public opinion and organised a public demonstration at Lille. In order to protect the Conservatoire against the onslaughts of the crowd, which even dragged the sick on their crutches with it, the Chairman was obliged to announce that a second meeting would be organised in a larger hall. Germaine de Rouen obtained a triumphal success and worked numerous cures. After two new demonstrations at Roubaix, at which sick persons previously cured came to express their gratitude, the miracle-worker announced the creation of the *Institut de l'Étoile du Nord* with the aid of funds placed at her disposal by rich local industrialists.

On February 21st, 1929, the Nancy court of appeal dropped the charge of swindling and only maintained the charge of the illegal practice of medicine. The sentence was reduced to a mere fine of 500 francs, and Germaine de Rouen escaped prison and loss of civil rights (*la peine dégradante*).

Another example: In 1930, in one of the most peaceful and delightful localities in the Ile-de-France, there lived a doctor and a healer. The healer had invented a remedy for tuberculosis of remarkable efficacy—namely, pills made of cigarette paper soaked in chlorine water. The doctor, indignant at this fraud and its possible consequences, but sceptical of receiving any help from the law, wrote a book in which he bitterly stigmatised what he called "a healer's crime". The healer brought an action against the doctor for libel, and *won his case*. True, the judgment finds the charlatan nominally guilty, but admits that it is, so to speak, constrained and obliged to do so by the undoubted existence of the offence. But the judgment is prefaced by an apology and pronounces a veritable panegyric of the offender, for whom it provides a most flattering advertisement.

One last example : In the following judgment the healer was not merely acquitted but was accorded damages with interest. The latter, indeed, were assessed at 1 franc, in compensation for moral damage, but the implication is as clear as if the healer had been accorded the 3,000 francs he claimed.

Judgment of the Court of Aix (July 6th, 1931).

Whereas R., suing B., bonesetter, at A., for the payment of 25,000 francs damages with interest, he alleging that his young child, treated by B. as suffering from a luxation of the arm, whereas in fact it is alleged that this limb was fractured, so that Dr. P., of M., was obliged to operate surgically ;

And whereas both the parties admit that it was on September 4th, 1929, the very day of the accident to the left arm of the little girl R., that the latter was brought by her mother to B. for diagnosis and treatment, and that the child was brought to him for a second and last visit on September 7th, and that it was only on October 30th following—namely, seven weeks later—that the child was examined by Dr. P., as the certificate signed by the latter on May 24th, 1930, shows, he carrying out a surgical operation on November 5th, for which he submitted a bill for fees and clinic charges amounting to 5,000 francs ;

And that in August 1930, R. addressed a complaint to the Procurator of the Republic, alleging illegal practice of medicine, this complaint having been filed without further action, a petition for the institution of proceedings was submitted on January 15th, 1931, to the President of the court ;

Whereas the action thus instituted has not brought out any facts justifying its admissibility ;

Because, in fact, more than five weeks elapsed between the last visit to B. and the doctor's examination, and no facts have been brought forward to enable the court to ascertain what may have happened in this relatively long period, it is not possible to state that the fracture of the arm attested to by Dr. P.'s certificate existed when the child was brought to B. or consequently that B. was guilty of negligence in failing to diagnose a fracture.

Supposing it to be exact that B. recommended that the bandage set by himself should be left in place for nineteen days, and that then M. and Mme. R. noted, on taking the bandage off, that, as it seemed to them, the arm was stiff at the elbow and had become thinner, and that the child was in great pain, *they ought, it would seem, either to have taken her back to the bonesetter or have caused her to be examined by a local doctor, whereas they took no steps at all until October 30th, five weeks later . . .* and whereas B. has brought a counter-claim for 3,000 francs damages and interest in compensation of the material damage caused to him and 1 franc for the moral damage ;

Whereas there can be no doubt that the action brought causes him moral damage and has been of a nature adversely to affect his reputation and to impugn his honour . . .

The court decides and proclaims that R. has not proved any fault involving the responsibility of B., and consequently disallows his claim ; the court sentences R. to pay B. the sum of 1 franc damages and interest for the moral damage caused.

IX. CRITICISMS AND PROPOSALS FOR REFORM.

There continues to be a steady reaction against the illegal practice of medicine. Medical unions and guilds of dental surgeons bring before the courts all those who exploit human credulity and dabble in medicine without possessing proper qualifications.

Is this reaction effective ? Dr. BOUDIN, an experienced lawyer, does not think so. In a small locality, possibly, the bonesetter may go in fear of prosecution ; but in a large town unqualified practitioners, who are legion, are little concerned at the thought that they may be summoned before the court. The sentences pronounced are absolutely useless—a fine of 25 francs, for instance—while patient after patient is passing through the charlatan's consulting-room, and the charlatan himself is earning several hundred thousand francs a year !

✓ Sentences should be heavier, and in dental cases the authorities should have power to confiscate the unqualified practitioner's apparatus.

Then there is the publicity accorded to the name of the unqualified practitioner. How many quacks have been set up in their trade, or have acquired considerable notoriety, as a result of a prosecution ? The real victims keep quiet, so as not to have to confess their credulity in public, but there are always plenty of convinced or paid adepts ready to step into the witness-box and extol the charlatan's virtues. In the course of the proceedings even magistrates have come forward to praise the accused and recount the many merits of the unqualified man of medicine.

Consequently, the charlatan obtains a free advertisement in the Press. Cases are quoted of extraordinary cures effected after qualified practitioners had abandoned hope. Many people as a result denounce the vengeful spirit of the doctors, who, because they have a degree, seek to prevent the possessors of certain powers or

courageous pioneers from relieving suffering humanity. The masses have always had a love for the supernatural. Certain leading journals are past-masters in the art of praising quacks, and, if adequately remunerated, they will prominently feature the merits of a popular "scientist", victimised by the jealousy of the recognised medical profession.

If the Procurator of the Republic is requested to take up one of these cases, the complainant will have to pay in several thousand francs in advance in order to have himself recognised as *partie civile*, and that without any certainty of securing a conviction. The efficacy of such prosecutions is doubtful. An unqualified practitioner once wrote to Dr. BOUDIN :

"I cannot sufficiently thank the Seine Medical Union for having brought me before the court on a charge of illegal practice. The number of my patients has greatly increased since that date."

Dr. IGERT believes that, whereas ordinary charlatans can sometimes be effectively dealt with by the law, mystic healers "*either gain fresh prestige through their conviction by the courts, or an official testimonial in the form of an acquittal*".

PROPOSED LAWS.

(a) Following on a report submitted by M. QUEYRAT and M. PFEIFFER (July 20th, 1927), the *Commission de Prophylaxie des Maladies vénériennes* adopted the following draft law, which has not yet been passed by Parliament :

Article 1.—Any person who, by any means of publicity whatsoever, either directly or indirectly, proposes or indicates any treatment, remedy or other means intended to prevent, treat, alleviate, attenuate or cure venereal disease shall be sentenced to a term of imprisonment varying from one month to two years and to a fine of from 5,000 to 25,000 francs, or to one of these sentences only.

Article 2.—Any person who offers on the public highway or in public places any medicaments or apparatus for the treatment of venereal disease shall be sentenced to the same punishment.

Article 3.—The present law shall not apply to the following :

(1) Announcements, advertisements or other information inserted in medical or pharmaceutical papers or publications, whether periodical or

not, unless such papers or publications are sent free of charge to persons not practising as doctors of medicine, pharmacists, dental surgeons or certified midwives ;

(2) Information regarding arrangements for treatment or consultations posted at the entrances of hospitals, dispensaries or associations recognised as being of public utility or pursuing disinterested aims, and at the residences of doctors ;

(3) Methods of publicity utilised by the public authorities or associations recognised as being of public utility.

Article 4.—Objects used for the commission of the offence shall be confiscated and the court shall, in its sentence, order their destruction.

Article 5.—Sentences may be increased twofold if the offence has been committed against minors.

Article 6.—Article 463 of the Penal Code shall be applicable to the offences specified in this law, but only in so far as concerns imprisonment.

Article 7.—Any person convicted under the present law who, within five years from the date on which the said conviction takes effect, commits a further offence coming under the provisions of the present law shall thus be deemed punishable with heavier sentence owing to second offence (*état de récidive légale*). In such case sentence of imprisonment must be pronounced.

It has been proposed that this law should also be made to apply to tuberculosis and cancer.

(b) Draft submitted to the "Concours médical" by Dr. BOUDIS.

Law of November 30th, 1892.

Proposed text.

Article 4.

Certified midwives may not use instruments. In case of difficult delivery, they shall call in a doctor of medicine or an *officier de santé*.

Certified midwives may not engage in any gynæcological or pediatric practice. Their services must be confined to attending to normal delivery and its physiological sequelæ. In cases of difficult delivery, they shall call in a doctor of medicine or an *officier de santé*. They shall be authorised to use various instruments to be specified in a decree promulgated after consultation with the Academy of Medicine.

No change.

They may not prescribe medicaments except in the cases provided by the Decree of June 23rd, 1873,

and by other decrees which may be issued under the same conditions after consultation with the Academy of Medicine.

Certified midwives may vaccinate and revaccinate against smallpox.

No change.

Article 5.

Medical practitioners, dental surgeons and certified midwives who have obtained their degrees or certificates abroad, whatever their nationality may be, may not practise in France unless they have obtained therein the diploma of doctor of medicine, dental surgeon or certified midwife, and conform to the conditions laid down in the preceding articles.

No change.

Exemption from prescribed periods of study and examinations may be granted by the Minister in conformity with rules laid down by the *Conseil supérieur d'instruction publique*. In no case may dispensations granted in the matter of obtaining a doctor's degree be accorded in respect of more than three subjects.

No change.

An exception shall be allowed in the case of medical practitioners, surgeons, dentists and certified midwives living near the frontier who, as the result of diplomatic agreements guaranteeing reciprocal treatment to French medical practitioners, surgeons, dentists and certified midwives, may practise in the adjacent French communes specified by name in the said diplomatic agreements. No person may engage in medicine, dentistry or obstetrics in virtue of the preceding paragraph unless he has previously caused his title to be registered at the prefecture of the French *département* in which he proposes to practise.

The sentences imposed for offences against the above provisions shall be those laid down in Article 18 of the present law.

Article 6.

Internes in French hospitals and hospices appointed by competitive examination and in possession of sixteen *inscriptions* and students of medicine who have terminated the prescribed period of study and are consequently in possession of twenty *inscriptions* may be authorised to practise medicine during an epidemic or as substitutes for doctors of medicine or *officiers de santé*.

No change.

The provisions of the above paragraph shall not apply to *internes* in French hospitals and hospices, or to students of medicine who are merely candidates for a university degree of doctor. In no case may authorisation to practise medicine or act as substitute for a doctor of medicine or *officier de santé* be granted them.

Such authorisation issued by the prefect of the *département* may not cover a period of more than three months. It may be renewed under the same conditions.

Such authorisation issued by the prefect of the *département* may not cover a period of more than three months. It may only be renewed twice under the same conditions.

The provisions of the present article shall apply to students of dental surgery who have completed their prescribed period of study, so that they may act as substitutes for dental surgeons or dentists to whom the provisions of Article 32 of the present law apply.

Nevertheless, in the case of students of medicine still subject to the former system, which laid down a maximum of sixteen *inscriptions*, such authorisation may still be granted to them, as previously, when they are in possession of their sixteen *inscriptions* or at least twelve

No change.

Inscriptions if they are *internes* in French hospitals or hospices.

Students who have completely interrupted their studies for two years cannot be authorised to act as substitutes.

Article 9.

Doctors of medicine, dental surgeons, unqualified midwives and certified midwives are bound, as soon as they have set up their practice and before performing any act in the exercise of their profession, to cause their title to be registered free of charge at the prefecture, sub-prefecture or registrar's office of the civil court of their *arrondissement* and to have their title endorsed at the town hall (*mairie*) of the place of their domicile.

Doctors of medicine, dental surgeons and certified midwives are bound, as soon as they have set up their practice and before performing any act in the exercise of their profession, themselves to take steps to cause their title to be registered free of charge at the prefecture, sub-prefecture or registrar's office of the civil court of their *arrondissement* and to cause it to be endorsed at the town hall (*mairie*) of the place in which they are domiciled, and at the other town halls (*mairies*) of their various places of professional residence.

This condition must be complied with by every doctor of medicine, dental surgeon or certified midwife who acts as substitute for a colleague for more than one month.

No change.

In the case of persons who have not previously practised . . .

In the case of transfer of domicile to another *département*, the title must be registered within the same period.

No change ; but add : Every change of domicile or of professional residence must be notified by the holder of the diploma in person to the *mairie* of the place in which he or she last practised and in which he or she proposes to practise.

No change.

Persons who have not been in practice for two years . . .

Pseudonyms may not be used . . .

No change.

Article 10.

Every year in the various *départements*, the prefects and judicial authorities shall draw up separate lists showing the names and surnames, the

Every year in the various *départements*, the prefects, mayors and judicial authorities shall draw up separate lists showing the names and

residence, and the date and origin of the diplomas of medical practitioners, dental surgeons and certified midwives, covered by the present law.

These lists shall be posted up . .

surnames, the domicile and professional residence, the origin with its serial number of issue by the faculty, the date, place and registration number of the diplomas of medical practitioners, dental surgeons and certified midwives, covered by the present law.

No change; but add a last paragraph : The Faculties of Medicine shall transmit each month to the Ministry of Labour, Health and Social Welfare the names of students who have obtained the State diploma of doctor of medicine, dental surgeon, or certified midwife, and the serial number of each diploma.

Article 13.

As from the date of application of the present law, medical practitioners, dental surgeons and certified midwives shall be entitled to form themselves into unions (*associations syndicales*) under the conditions laid down in the Law of March 21st, 1884, to defend their professional interests against all persons other than the State, the *départements* and the communes.

This article is abrogated under the provisions of Article 9 of the Law of March 12th, 1920 (Article 2, Chapter 1 of Book III of the Labour Code), under which all the liberal professions are allowed freely to form themselves into unions (*syndicats*).

New Article.

Any person practising medicine, dentistry or midwifery must state, after his name and without any abbreviations, the nature and origin of the diploma which confers upon him the right to practise, when he makes any mention of this diploma in any way, otherwise than in his signature.

All notepaper or prescription paper used by him in the practice of his profession must show, immediately after the details specified in the previous paragraph, the name of the prefecture or of the sub-prefecture at which the diploma has been registered,

In conformity with Article 9 of the present law, and the serial number of this registration.

Army surgeons (*médecins militaires*), practising within the limits of their functions, may mention their rank and unit instead of the said registration.

No certificate issued in conformity with a law or regulation shall be valid unless it indicates the above-mentioned details.

No prescription for poisonous products may be made up by a pharmacist unless it complies with the above conditions.

When any person, legally entitled to practise medicine, dentistry or midwifery in France, also possesses a foreign diploma which he or she desires to mention, he or she must register this title under the conditions laid down in Article 9 of the present law with the permission of the Dean of the Faculty of Medicine of the university area in which the said practitioner practises.

In every case a complete statement of the French title, printed in bolder lettering, must precede the foreign title, the origin and nature of which must be given in full without abbreviations.

Any infraction of this article shall be punished with a fine of from 200 to 500 francs.

Article 16.

The following shall be deemed to be practising medicine illegally :

1. Any person who, not possessing a French State diploma of doctor of medicine, *officier de santé*, dental surgeon or certified midwife, or who fails to comply with the conditions laid down in Articles 6, 29 and 32 of the

The following shall be deemed to be practising medicine illegally :

1. Any person who, not possessing a French State diploma of doctor of medicine, *officier de santé*, dental surgeon or certified midwife, or having failed to comply with the conditions laid down in Articles 6, 29 and

present law, habitually takes part in or directs, otherwise than occasionally, the treatment of disease or surgical cases, or practises dentistry or midwifery, except in proved cases of emergency.

2. Any certified midwife who, in the exercise of her profession, exceeds the limits of her functions as defined in Article 4 of the present law.

3. Any person who, though possessing proper title, exceeds the functions assigned to him or her by law ; in particular, by assisting the persons mentioned in the foregoing paragraphs in order to enable them to evade the provisions of the present law.

4. The provisions of paragraph 1 of the present article shall not apply to medical students acting as doctor's assistants or detailed by a doctor to attend to his patients, nor to nurses, nor to persons who, without assuming the title of dental surgeon, extract teeth in accidental circumstances.

32 of the present law, participates or endeavours to participate, except in proved cases of emergency, in the diagnosis or treatment of disease or surgical cases, or in the practice of dentistry or midwifery, either directly, or orally, or by correspondence, or through the Press by means of posters, prospectuses or other means of publicity.

The above description applies to any act or advice, in whatever form it may be done or given, tending to alleviate, heal or prevent an actual or supposed condition of indisposition or disease.

No change.

No change.

4. The provisions of paragraph 1 of the present article shall not apply to medical students acting as assistants to a doctor under the effective direction of the latter, or whom the latter details to attend his patients, nor to male or female nurses or nurses holding a diploma under the Decree of June 27th, 1922, and who merely carry out the orders of the responsible physician.

Article 18.

Any person who illegally practises medicine shall be sentenced to a fine of from 100 to 500 francs, and, if the offence is repeated, to a fine of from 500 to 1,000 francs and to a term of imprisonment varying from six days

Any person who illegally practises medicine, dentistry or midwifery shall be sentenced to a fine of from 1,000 to 3,000 francs and to a term of imprisonment varying from fifteen days to three months. The text of the

to six months, or to one of these two sentences only.

Any person illegally practising dentistry shall be sentenced to a fine of from 50 to 100 francs, and, if the offence be repeated, to a fine of from 100 to 500 francs.

Any person who illegally practises midwifery shall be sentenced to a fine of from 50 to 100 francs, and, if the offence be repeated, to a fine of from 100 to 500 francs, and to a term of imprisonment of from six days to one month, or to one of these sentences only.

judgment shall be posted up on the door of the offender's domicile and shall be published in three local newspapers.

If the offence be repeated, the fine shall be from 3,000 to 5,000 francs, and the term of imprisonment shall vary from three months to six months. The judgment shall be posted up on the door of the offender's residence and shall be published in five local newspapers.

In the case of every conviction imposed under this article, the professional apparatus used shall be confiscated and shall escheat to the State.

Article 19.

The illegal practice of medicine or dentistry, with false pretence to the title of doctor of medicine or *officier de santé*, shall be punished with a fine of from 1,000 to 3,000 francs, and, if the offence be repeated, with a fine of from 2,000 to 3,000 francs and a term of imprisonment varying from six months to one year, or one of these two sentences only.

False pretence to the title of dentist shall be punished with a fine of from 100 to 500 francs, and, if the offence be repeated, with a term of imprisonment varying from six days to one month, or with one of these two sentences only.

False pretence to the title of certified midwife shall be punished with a fine of from 100 to 500 francs and, if the offence be repeated, with a fine of from 500 to 1,000 francs and a term of imprisonment varying from one month to two months, or with one of these sentences only.

Any person who, whether practising medicine, dentistry or midwifery or not, assumes, without being entitled thereto, the title of doctor, *officier de santé*, dental surgeon, dentist or certified midwife, shall be deemed guilty of false pretence to the title of doctor of medicine, doctor, *officier de santé*, dental surgeon or certified midwife.

Such false pretence shall, under the provisions of the Law of March 26th, 1924, be punished with the sentence specified in Article 259 of the Penal Code.

In the case of the illegal practice of medicine, dentistry or midwifery, accompanied by false pretence to any of the above titles, the sentences provided under Article 259 of the Penal Code shall be added to those provided under Article 18 of the present law.

Article 20.

Any person engaging in the practice of medicine who places before or after his name the title of doctor of medicine without indicating that the degree is of foreign origin shall be deemed to have falsely assumed the French title of doctor of medicine.

The offence shall be punished with a fine of from 100 to 200 francs.

Any person engaging in the practice of medicine or dentistry who assumes the title of doctor or dental surgeon with or without abbreviations and without indicating immediately after this title in French the name of the foreign faculty which granted the diploma shall be deemed to have falsely assumed the French title of doctor of medicine or dental surgeon.

He shall be sentenced to the punishment specified in Article 259 of the Penal Code, irrespective, if he be also guilty of the illegal practice of medicine, dentistry or midwifery, of the sentences defined in Article 18 of the present law.

X. THE FACTS : TYPES OF HEALERS.

Although an enquiry has been undertaken into this subject by the International Professional Association of Medical Practitioners, the information at our disposal is very incomplete and indefinite.

Quacks working under their own or somebody else's name are very numerous, whereas, on the other hand, healers with mystical tendencies are rare.

There are a large number of masseurs, shepherds and "old wives" practising medicine illegally. There are also a large number of so-called hydrotherapists and electrotherapists, a very large number of mesmerists, a fair number of priests (homeopaths) and nuns who give advice, a still greater number of pharmacists who exploit public confidence in imaginary ecclesiastics whose infallible formulæ they claim to possess, and a very large number of pharmacists who supply both advice and medicaments without consulting the doctor. Again, there are a great number of persons who advertise marvellous cures in the chief daily papers, which make large profits out of this form of publicity and for this reason are inclined to favour the illegal practice of medicine.

A large number of publications have dealt with quackery. Among the most important we would mention *Au pays des miracles*, by Marcel REJA (1930), and *Le problème des guérisseurs*, by P. IGERT (1931).

Marcel REJA, on the basis of the studies undertaken by Levi BRÜHL, points out that those who believe in miraculous cures and have faith in healers are neither mad nor mentally deficient, but are persons who, in reasoning, accept preconceived ideas and follow a mystical or prelogical method as opposed to the experimental method. Such a reversion to primitive processes of thought among civilised people is much more frequent than is commonly believed.

Moreover, the healer often acts in good faith and in some cases has the fervour of an apostle who is convinced of the reality of the gift which he believes himself to possess and of the supernatural powers which he considers to have been bestowed upon him. It is necessary to distinguish him from the quack who is a swindler. People flock to healers on account of the uncertainty displayed by medical men in their diagnosis and because of their contradictory statements, their caution and, in many cases, the powerlessness of their art to cure the patient.

In addition to this, there is the great attraction which the mysterious and the marvellous have and will always have over the human mind.

Marcel REJA divides healers or performers of miraculous cures into mystics, empiricists, mesmerists, doctors and visionaries.

The mystical class embraces everything connected with religion and, as he has a very intimate knowledge of Berry in particular, Reja enumerates the saints of that province who possess healing powers, each of whom has his own speciality—St. Christopher and St. Barbara, who preserve people from sudden death ; St. Adrien and St. Roch, who cure plague ; St. Anthony, who cures shingles and infectious diseases ; St. Hubert, who cures rabies, etc. Dr. J. NOIR noted the same facts in the Ardennes in 1905 (*De quelques préjugés, superstitions, sanctuaires et pèlerinages à attributions curatives dans la région des Ardennes*).

Alongside pilgrimages providing the occasion for miracles, such as that of St. James of Compostella in the past and nowadays

those of Lourdes and St. Theresa of Lisieux, Marcel REJA places the work of *theurgists*, such as Paul Sédit, who cured the sick by advising them to discover the sin which was the cause of their illness and repent of it.

There are a large number of mystical sects whose chief object is to cure the sick. Two are deserving of special mention on account of the extraordinary success they have obtained—Christian Science and the “Antoiniste” creed.

Christian Science was founded in 1865 by Mrs. Mary Baker Eddy, of Boston, who was suddenly cured of a paralysis from which she had suffered for several years when reading the beginning of Chapter IX of the Gospel of St. Matthew. Mrs. Eddy wrote “Science and Health”, in which she asserted that disease was due to a belief in disease and that faith alone was needed to cure it. This curative mysticism met with enormous success in the United States. It has a fairly large number of followers in the districts around Lyons and Paris.

The “*Antoiniste*” *creed*, which was founded some thirty years ago, spread fairly rapidly in Belgium and the north-east of France. A church has been built by its followers at Paris in the thirteenth *arrondissement*. Its founder, Père Antoine, was formerly a Belgian metal worker who cured himself of a disease stated to be incurable simply by means of his faith in God. The “Antoiniste” *creed* is a very simple one : the deacons and deaconesses, who act as priests, all earn their living by following some occupation ; the worshippers simply meet in deep silence and listen to the word of God, which is read in French by the officiating priest. There is only one remedy, faith in God, and disease is treated by exhortation and prayer.

The religious ceremonies of certain mystics are more complicated, but they nevertheless attract a credulous clientèle : one mystical healer in the Vaugirard district of Paris distributes “cosmic fluids” in all good faith.

The *barreurs* and *souffleurs* to be found in Berry and in the Ardennes cure wounds, burns and ulcers : they are also mystics who are convinced of their supernatural powers. This also applies to the *marcoult*, a popular mystic healer who, in order to possess the

gift, must be the seventh son of a family, no daughter coming between.

Some rare specimens of *sorcerers*, both men and women, are still to be found in France in the mountainous regions (Dordogne).

The *empiricists* resemble the mystics, but belief in the family traditions handed down to them and the secrets they consider that they possess are often supplemented by fraud. *Raccrocheurs d'estomac*, "stomach fixers", and healers by simples, urine quacks, who are descendants of the old urine gazers, may be included in this group, as may also the visionary herbalist priest who, when he was prosecuted by the medical syndicate, studied and obtained a herbalist's certificate. The practice of healing by simples is sometimes handed down from father to son, and, in Berry, the Lapurge constituted a veritable dynasty.

Mesmerists claim to possess scientific knowledge. They add massage to mesmerism and have brought their methods up to date by converting the fluid into "waves".

Some are not lacking in either skill or originality. For instance, there is the Hindoo mesmerist near the Champs Elysées who attracts large crowds and practises "pranotherapy". The "prana" is the vibratory force which, when converted by the brain, becomes the nervous fluid. The Hindoo mesmerist gives "prana" to the organs. He undoubtedly effects cures, and, with the help of suggestion and pathos, he induces his customers to part willingly with the 100 francs which he charges each time.

We shall not do more than mention *mediums*, as, if we were to deal with them more fully, we should have to go into metapsychics, with the phenomena of cryptæsthesia or clairvoyance, telekinesis, levitation, ectoplasm or materialisation. In the world of mediums, it is obvious that a large number of frauds are committed and metapsychics are disappointing.

We should like to say something about the *Coué* method. Coué refused to prescribe any treatment for sick persons, whom he recommended to follow the advice of their doctor. He simply endeavoured to revive their spirits and to restore their lost self-confidence. Emile Coué was born at Troyes in 1857 and died at Nancy in 1926. He practised pharmacy for thirty years and realised in the course

of his work that, except in a comparatively small number of cases, medicaments usually acted by suggestion. A profound psychologist, a past master of the art of suggestion, which he regarded as a therapeutic agent of a high order, Coué, who was an excellent and compassionate man, resolved to place his great experience and sincere convictions at the service of persons suffering from incurable diseases.

The *country of miracles* explored by Marcel REJA will always exist, since superstition and the attraction of the marvellous, added to human stupidity and the hope of a cure against all hope, are rooted in the minds of us all, even those of us who are most civilised and reasonable. "The cunning of the delinquent and the complicity of his client", Marcel REJA concludes, "are forces with which we have to reckon. To see the healer making fun of the doctor is like seeing Punch belabouring the policeman—and what could be a more gratifying spectacle?"

Dr. IGERT regards as a *healer* "any person who engages in curative practices under the inspiration of mystical feeling—religious or otherwise".

The social significance of healers corresponds to the collective mysticism that reveals the survival of primitive mentality which is combated by the progress of rationalism. The "gift of healing" is, after all, a special social function, an occult power which stirs up the latent mysticism of the crowd against scientific rationalism.

The healer is influenced by, and gratifies the myth-loving tendencies of, the crowd. Like primitive man, and the savage, the child of modern civilisation is a prey to mystical beliefs, which are counteracted by a rational and scientific education. The healer has the power to arouse these mystical beliefs which lie dormant, and sometimes awaken, in a community.

Dr. IGERT divides mystical healers into the sentimental and intellectually weak type (such as Germaine of Rouen) and the intelligent type (such as Béziat). They are all undoubtedly sincere and believe in their own powers. Béziat, the healer of Avignon, drew to his farm less than ten years ago all the incurables in the south of France and even from neighbouring countries. A man of good faith, who was obviously sincere, self-taught and a certified herbalist, he was the first to be amazed by his success, which he did

not attempt to explain but spoke of with unaffected pride. After having for a long time effected cures free of charge, he began to issue tickets which had to be paid for and distributed pamphlets extolling the virtues of his "Vitalogène", thus displaying his commercial ability. He was advised to ask a doctor to use his undisputed influence. "Don't make any mistake", he replied, "the public love what is marvellous and unexpected, and once they thought that I was covered by a doctor I should no longer have the same prestige and my clients would drop off." This reply reminds Dr. NOIR of the story of the fountain of St. Hilary, near Matagne-la-Petite, in the neighbourhood of Givet, in the Ardennes. Persons with suppurating wounds, chronic eczema, varicose ulcers flocked to this fountain to bathe in it. Some who were suffering from internal diseases drank this polluted water without repugnance. A number of recoveries occurred. A new priest then came to Matagne; disgusted by this spectacle, he had the bath separated from the drinking-water. Unfortunately, however, the faithful abandoned the spring which they now considered to be ineffective. "He has spoilt our spring", the peasants said, looking askance at their priest. In such cases, as in the case of the healers, mysticism has nothing to do with reason.

Credulity is a general weakness, and it is not necessarily the common people who are the most prone to it. Society folk, the educated classes, poets, artists, sailors and all those whose ardent imagination delights in fiction are often amazingly credulous. This also applies to the army officers and magistrates, who make up a large proportion of the healers' clientèle.

The great and powerful—even kings—are not exempt from this failing. On the contrary, they "have frequently been used as bait by quacks and tricksters" writes A. CHEREAU. St. Louis took with him on his expedition overseas a quack woman "physician", whom he loaded with honours, and the influence of a Lyons healer at the Russian Court before the advent of Rasputin is well known.

The most distinguished minds which have been trained to the strictest scientific discipline sometimes display profound scepticism in regard to medicine. S. DE MADARIAGA writes: "Good doctors are not those who are most scientific. There is even a danger that, because they are *scientific*, they may be the worst."

XI. SALE OF REMEDIES IN GENERAL.

The Law of 21st Germinal, Year XI (March 11th, 1803), still governs the practice of pharmacy. Under this law :

“No one may practise as a pharmacist or prepare, sell or supply any medicament unless he possesses the requisite qualifications.”

This is a general and absolute rule which applies both to compound medicaments, pharmaceutical specialities and drugs prepared in advance, and to simple medicaments ; it is not necessary that the drugs should actually be supplied by their medicinal weight.

Pharmacists may only supply medicinal preparations or compound drugs against the prescription and signature of a medical practitioner.

They may not sell any secret remedy.

They may not carry on in the same premises or offices any other trade than that in drugs and medicinal preparations.

Grocers or druggists are not allowed to sell any pharmaceutical compound or preparation.

No person may sell native medicinal plants or parts of plants or practise as a herbalist unless he has passed, at a school of pharmacy or before a medical jury, an examination designed to discover whether he has an accurate knowledge of medicinal plants.

The possession of a pharmacist's certificate issued by the State is therefore compulsory for the practice of pharmacy. The pharmacist is required to register his certificate under the same conditions as a doctor of medicine.

In communes which do not possess a pharmacy, doctors and veterinary surgeons are allowed to supply the medicaments which they prescribe, but may not keep a public pharmacy.

XII. FROM SECRET REMEDIES TO REGISTERED SPECIALITIES.

Under the old regime in France, patents conferring a monopoly of sale were granted by the King to inventors of new remedies, on

the advice of the Royal Society of Medicine established by Letters Patent of August 1778, and in conformity with a Decree of the Council of May 5th, 1781. Under cover of the disorders of the Revolution, many abuses crept in. Certain individuals falsely claimed that they had already obtained patents, others maintaining that, with the total abolition of privileges, the former system of patents had given place to entire liberty for every individual to sell any medicament that he might invent. Never were more fantastic remedies in vogue and never did they produce such ravages.

The Law of 21st Germinal, Year XI (1803), in order to put a stop to this danger, prohibited even the advertisement of secret remedies and forbade pharmacists in particular to sell them to the public (Articles 32 and 36). The Decree of 25th Prairial, Year XIII, confirmed and extended this prohibition, forbidding the advertisement and sale of remedies not approved by the public authorities, whether before or after the promulgation of that law, thus settling, in the most drastic sense, the discussions concerning its application to remedies already in use on the promulgation of the Law of Year XI. Lastly, the Decree of August 18th, 1810, cancelled all previous authorisations, thus putting an end to the insolvable controversies that had arisen regarding alleged authorisations of very old date, and decided that, in future, remedies recognised as being of general utility should, after specific examination, be bought by the Government. This Decree was supplemented by that of December 26th, 1810, and by the Order of December 20th, 1820.

It was impossible thenceforth, without a special medical prescription, to depart from the Codex. This rigorous measure put an end to all the dangerous quack medicines or trivial, old-wives' remedies which prevented proper medicines from being used when called for.

But in course of time useful inventions reappeared ; and, as the Codex was only recast at long intervals, many years passed before those inventions could be freely used, the Government refraining, for budgetary reasons, from purchasing new pharmaceutical inventions. In order to enable such inventions to be put into use without undue delay, the Decree of May 5th, 1850, made it permissible to sell, in any pharmacy, remedies approved by the Academy of Medicine and published in its *Bulletin*, which had become, as it were, a permanent supplement to the Codex.

The slowness and solemnity of this procedure of approval, by discouraging the majority of inventors, prevented it from producing the far-reaching results anticipated. Moreover, the transformations undergone by pharmacy during the nineteenth century, and which occurred simultaneously, and for the same reasons in other branches of trade and industry, revealed the shortcomings of our legislation in the matter. Medicaments prepared in each individual case by small local laboratories were replaced more and more by products manufactured wholesale, on industrial lines, in big works which specialised in one or several products, whence the name of "specialities". Many of these "specialities", after having been tested throughout a number of years, proved of the greatest utility to the public, to doctors and to pharmacists, by reducing prices, helping to determine the choice of medicines and perfecting processes of preparation. It may be added that about 1850, chiefly under the influence of the Montpellier School, the pharmacy substituted for the former unpleasant medicines more agreeable remedies in which the introduction of syrups and scents was not allowed to interfere with the effects of the active constituents.

The judicial tribunals and administrative authorities took it upon themselves, towards the middle of last century, to extend, by means of a more liberal interpretation of the law, the range of medicaments that might be sold and offered for sale. Further, the public authorities exhibited great tolerance in regard to known useful specialities by refraining from taking proceedings on the grounds that they were secret remedies and even by encouraging their manufacture, while legal practice guaranteed those responsible for their preparation the protection of the Law of June 23rd, 1857, concerning trade-marks, irrespective of whether they did or did not constitute secret remedies.

The growth of the Press and of posters led to a considerable increase in the advertisement of specialities ; accordingly, in 1871, the Government, in agreement with the Academy of Medicine, contemplated departing entirely in the case of specialities from the principle laid down in the Year XI with regard to secret remedies ; instead of prohibiting their advertisement by making it punishable, the State proposed, on the contrary, to utilise that very publicity and to levy a tax on specialities which formed the subject of advertisement. The idea has since been taken up on several occasions, more particularly in the draft budget for 1907, and finally resulted

in the provisions of the Finance Laws of December 30th, 1916 (Article 16), and of December 31st, 1917 (Article 29), imposing a tax on specialities.

Thenceforth specialities ceased to be prohibited articles and became taxable material. Thus the free sale of specialities was sanctioned, subject only to observance of the Law of August 1st, 1905, concerning fraud in the sale of medicaments.

Preventive supervision gave place to repressive action in case of fraud. That is a logical and normal result of a more general evolution of trade and industry, the products of which, originally manufactured in accordance with rules laid down in advance (as was the case under our former guilds of arts and crafts), were later manufactured freely, subject only to good faith in the matter of sale to the public.

XIII. DEFINITION AND REGULATION OF SECRET REMEDIES AND PHARMACEUTICAL SPECIALITIES.

A. DEFINITION OF SECRET REMEDIES.

In the absence of any explicit legal definition, it is possible, by reference to the texts of the Year XI (Articles 32 and 36), the Year XIII, and the years 1810 and 1850, to apply that description to any remedy the formula of which has not been inserted in the Codex, acquired by the Government, or published in the *Bulletin* of the Academy of Medicine.

No form of publicity by other means (books, pamphlets, newspapers, reviews, leaflets, etc.), even going back to a distant date, could be deemed to take the place of these official methods of publicity.

Even patents—that is, in the days when they were granted, and in these days, within the limits still permissible under the Law of July 5th, 1844 (Article 3)—could not be held to alter the fact of such medicaments being of the nature of secret remedies.

This designation would appear to apply, not only to products, combinations of products and mixtures constituting pharmaceutical preparations or compounds properly so called, but also to chemical products obtained by laboratory processes foreign to the pharmaceutical art (for example, heroin or urotropine). Here again, the

foreign origin of the product is not held to alter the fact of its being a secret remedy.

Lastly, the fact of all the elements of the product being found in the Codex would make no difference, if they did not appear in it associated in the same way as in the remedy in question or if the latter were prepared in a manner foreign to the Codex and capable of altering the curative properties of the product.

This, however, is the utmost limit of the severity displayed in legal practice. Thus a medicament inscribed in the Codex will not, when made unrecognisable simply for purposes of advertisement under a fancy name, be thereby converted into a secret remedy (for example : "Quet's Syrup", which is the sarsaparilla syrup of the Codex).

Minor changes in the form of the medicament do not convert it into a secret remedy : digitalis pastilles may replace the syrup of the Codex. Furthermore, changes in the composition of an officinal remedy by the addition or the substitution of an adjuvant, excipient or vehicle are never objected to ; we may give as an example Pergame iodised oil, in which the oil serves as a vehicle for the iodine.

Lastly, modifications in the process of manufacture which do not impair the curative qualities of the medicament do not convert the latter into a secret remedy. This was decided, for example, in the case of "Labélonye Syrup", obtained by the alcoholic extraction of digitalis, instead of infusion in water, in order to remove the bitter taste and disagreeable smell.

The person responsible for judging the facts is called upon to determine authoritatively the therapeutic effect of the modifications made.

It may be added that, in the opinion of the Codex Commission, the insertion of a formula in any edition of that work, when that formula has not been modified since insertion but has simply been omitted in subsequent editions, is sufficient to deprive the medicament of any "secret" quality (Law of January 11th, 1892, Table A, No. 315, this medicament appearing in *one* official pharmacopœia).

Further, under the terms of numerous decrees, a *statement of all the components, on the label attached to a remedy*, is sufficient to preclude the latter from being regarded as a secret remedy (LATERRADE, *Code des Pharmaciens*, Nos. 167 and 170). Legal practice in this

matter is confirmed by the Decree of December 14th, 1916, and the Finance Law of December 30th of that year.

B. ABOLITION OF THE PROHIBITION OF THE SALE OF SPECIALITIES AS SECRET REMEDIES.

The Decree of September 14th, 1916, refers to pharmaceutical specialities (Articles 25 and 43). In that connection, the report, which serves as preamble to the regulations, reads as follows :

“The third (new provision) refers to medicaments prepared in advance and described currently as *specialities*. The sale of such of these specialities as include poisonous substances has necessarily been made subject to the formalities laid down for the sale of officinal and magistral preparations of equivalent toxicity. Article 25 of the decree simply confirms this assimilation. Without destroying the trade in specialities, it was essential not to leave it as a loophole by means of which it would have been easy to evade the stipulations of the present decree.”

This clause fulfils a double purpose : it brings toxic specialities under the same rules as other medicaments containing poisonous substances and it avoids imposing upon their sale any exceptional measures of restriction. While anxious to prevent specialities from affording a means of evading the regulations applicable to poisonous substances, the authors of the decree, realising the advantages of specialities from the standpoint of doctors, pharmaceutical chemists and patients, desired to make the sale of those specialities subject to the same conditions as other toxic medicaments.

Provided that they fulfil the conditions laid down for the sale of all poisonous medicaments, the sale by pharmaceutical chemists of specialities containing toxic substances will thus be perfectly legal and will not be exposed to any restriction on the grounds that they are secret remedies. The authors are agreed on this point, and the solution is so natural that it does not appear ever to have been questioned in the courts.

In the circumstances, it was paradoxical that, in principle, the trade in specialities should have been lawful when the latter contained toxic substances, but should, on the other hand, have been

strictly prohibited, by reference to secret remedies, when the specialities contained no toxic element. It was equally paradoxical that sale should have been lawful when a speciality contained the minimum toxic dose necessary, under the terms of the stipulation laid down in Article 29 of the decree, to bring trade in that substance within the scope of the meticulous precautions thus newly provided, but that it should cease to be lawful when, that dose not being reached, the product was held to be less dangerous.

One can only explain such a settlement of the question on the part of the Government by the intention, in the case of specialities not containing any poisonous elements, to remove the prohibitions relating to secret remedies by means of a legislative provision which was shortly to be enacted—namely, the Finance Law of December 30th, 1916 (Article 16).

C. PRESENT REGULATIONS CONCERNING SPECIALITIES.

The authors conclude that the specialities referred to in the Law of December 30th, 1916 (Article 16), are no longer secret remedies and that their sale is lawful.

It now remains to be considered what medicaments shall be regarded as specialities and hence as authorised medicaments. The law contains no general definition and simply deals in succession with four hypotheses (Article 16, paragraphs 6 and 7) :

Products to which the manufacturer or seller gives a special name (what is obviously meant is a characteristic name which may serve as a trade-mark) ;

Those in regard to which he claims priority of invention or exclusive ownership ;

Those whose superiority he affirms by means of advertisements, prospectuses or labels ;

Those which pharmacists prepare themselves for direct delivery to their clients, without publicity, with a statement of the component substances, and sold exclusively retail.

In all these various cases, the usual dangers of secret remedies are met by the threat of further penalties—namely, those applicable under the Law of August 1st, 1905 (Articles 1 and 3), to fraud in the sale of medicaments. Indeed, in the last of the four above-

mentioned cases, the composition of the remedy being attested by the seller himself, it would be easy to detect any fraud. In the first three cases, the products sold as constituting a certain speciality are clearly defined by their name, by the exclusive claims of the seller or manufacturer or by the measures of publicity employed in regard to them, so that it will always be possible at once to discover frauds by a comparison with the samples taken in conformity with the decrees of January 22nd, 1919, and July 4th, 1921, from the products offered to the public as being of the same character. In a word, thanks to advertisement, the regular composition of specialities becomes as constant as that of the products included in the Codex, and judicial practice now tends to treat them as the latter.

The Academy of Medicine is in favour of this interpretation of the Law of December 30th, 1916. The practice of the judicial courts, which have had very few such cases before them, still appears to be uncertain, and the Court of Cassation has not yet had to give judgment in such a case.

The former prohibition of secret remedies has not, however, been rescinded and is still fully valid as regards medicaments which do not come within any one of the foregoing categories of specialities. The prohibition still applies to the advertisement and sale of medicaments of which the formula is *a priori* unknown, not being divulged in detail by the seller and not being recognisable by the external indication accompanying the product when sold. These are the only really dangerous cases. The same applies to anonymous remedies of which the nature is not revealed and which are sold clandestinely by persons who, not claiming to be either their inventors or their exclusive owners, decline responsibility for their effects.

D. LEGAL PROTECTION OF SPECIALITIES.

The transformation of the manufacture of pharmaceutical specialities into an important industry called for legal measures of protection on the mode of those applicable to big industry in general.

On the other hand, the urgent necessity, in the interests of public health, of taking as prompt and as full advantage as possible of

new pharmaceutical products made it essential not to extend to pharmacy, without some measure of caution or limitation, the monopoly procedure admitted in ordinary trade.

These two conflicting factors resulted in the adoption of a modified system applicable to pharmaceutical specialities.

The law remaining practically silent in the matter, legal practice, under the pressure of the changes in pharmacy which occurred in the nineteenth century, worked out, by a series of judgments, a system of protection that had become indispensable in the light of analogies derived from the whole body of industrial legislation.

1. *Patents.*

French law, which protects only industrial inventions, does not permit of extending the same guarantees to theories and methods of which the industrial application is not stated (Law of July 5th, 1844).

On the other hand, in the interests of public health, fearing the dangers which may result from the popular prejudice in favour of patented inventions, the law precludes any person from obtaining, by means of a patent, a monopoly over pharmaceutical compositions or remedies of any kind (Law of July 5th, 1844, Article 3, paragraph 2). The first principle implies, therefore, that the inventor of a scientific method which admits of immediate therapeutical application (for example, a system of mecanotherapy or medical gymnastics) possesses no exclusive rights over that system and has, moreover, no legal means of preventing its exploitation by another.

The second principle implies that the Government is entitled to refuse a patent for a pharmaceutical compound, even if the latter can be applied to industrial uses and even if the inventor has mentioned that fact in his application, unless exact details of such industrial uses are given in the application.

The Council of State has even decided that the Minister of Commerce shall refuse to issue the patent when the applicant does not mention the pharmaceutical nature of his product in his application for the patent.

Lastly, in order to ensure to the inventors of useful remedies fair remuneration for their labours, while protecting the public from

unjustified expectations, the law confers on the Government the right to purchase the formula of their inventions from the authors of new medicaments, after examination by a special Commission appointed by the Ministry of the Interior, with the approval of the Council of State (Decree of August 18th, 1810, Article 7).

2. *Trade-marks.*

For the last half century at least, legal practice has prohibited the false assumption of trade-marks affixed to medical products and constituted and registered in conformity with the Law of June 23rd, 1857.

The mark, being the subject of a law distinct from that which governs the thing to which it is affixed, must be protected, even if affixed to illicit objects. That is why it must be safeguarded, even when affixed to secret remedies.

Industrial trade-marks consist either of the lines of an original drawing or of names independent of any picture (Law of June 23rd, 1857).

In the case of a trade-mark deposited at the Registry of the Commercial Tribunal, the law punishes any use or fraudulent imitation of it by another party, even if the mark is not affixed to a product, when such imitation is calculated to confer an advantage by reason of the reputation of the author of the trade-mark.

3. *Criminal Law.*

Any person who affixes or causes to appear on an industrial product, by any means whatsoever, the manufacturer's name or the name of a place of manufacture other than the true ones is liable to the penalties laid down in Article 423 of the Criminal Code (Law of July 28th, 1824, amended by the Law of August 1st, 1905, Article 15). On more than one occasion the judges have decided that this law would apply, if necessary, to medicinal substances.

Further, deception or attempted deception as to the origin of any product, when, according to use and custom, such origin is the principal inducement to the purchase of the object, is punished with particular severity under the Law of August 1st, 1905 (Article 1).

4. *Civil Law.*

The mere false assumption of the patronymic of a person, of the denomination of a product or of the title of a commercial concern is at all events punishable by the bringing of a civil action with a view to the prohibition of such acts in the future and the granting of damages for the past.

5. *Protection of Secrets of Manufacture.*

The divulging to competitors by managers, clerks or workers of the manufacturing secrets of establishments to which they are or have been attached is punishable under Article 418 of the Penal Code. No doubt the establishments in which pharmaceutical products are manufactured benefit, like others, from this legal protection against competition.

6. *Literary Property.*

The inventor of any curative means possesses the exclusive literary property in the writings that he may devote to it. This right is his absolutely, whatever the nature and purpose of those writings and whatever the process employed by the counterfeiter (Law of July 19th, 1793).

7. *Unfair Competition.*

Like any other tradesman, a pharmaceutical chemist has the right to attract clients by any means of advertisement, subject to the sole condition that he shall not wittingly appropriate to himself the merits of another person and shall not wittingly deceive the public as to his own.

Redress for non-observance of this double condition would lie in a civil action, brought by any competitor to whom such non-observation might have caused injury, with a view to the cessation in future of prohibited acts of unfair competition and compensation for the past.

E. PRESCRIPTION OF SPECIALITIES IN SOCIAL MEDICINE.

The legislation with regard to free medical assistance, the treatment of war pensioners, industrial accidents and social insurance leaves to the medical practitioner attending the case *full freedom to prescribe as he thinks fit*.

For the purposes of social insurance, as in ordinary medicine, there is complete liberty as to magistral prescriptions. As regards free medical assistance and war pensioners, on the other hand, certain restrictions have been introduced (prohibition of certain vehicles, such as wines and spirits ; quantitative limitations on the use of certain medicaments).

The law provides for a commission responsible for drawing up a list of the pharmaceutical specialities which may be used in the treatment of members of sickness insurance funds. That list has not yet been published, but, in any case, it would place no real restrictions upon the doctors' rights in the matter of prescriptions. As the composition of specialities is shown on the label, the practitioner can always copy the formula on to his own prescription, or—a still simpler method—he can prescribe “syrup according to X's formula” whenever he wishes a patient to take X's syrup. As a general rule, the margin of profit on specialities is sufficient to induce the pharmacist to supply the speciality rather than himself to make up the preparation according to the doctor's prescription. Sickness insurance funds, however, remunerate the pharmacist according to fixed rates, as if he had himself made up the doctor's prescription.

Similarly, in the case of prisoners of war, a doctor wishing to prescribe hemostyl or pancrinol has to prescribe hematopoietic serum or potable extract of liver. As regards these medicaments, freedom of prescription is restricted by a departmental commission whose decisions vary slightly from one *département* to another. In the Dordogne, the doctor is not allowed to prescribe more than twelve ampoules of hematopoietic serum or extract of liver per quarter. The list of specialities which doctors are expressly authorised to prescribe to prisoners of war is strictly limited. The same applies to persons receiving free medical assistance. In that case, the work is in the hands of a departmental or sometimes (in the

larger towns) municipal service. The list therefore varies from *département* to *département* and sometimes from town to town, but here, too, it is extremely limited.

XIV. INSPECTION AND SUPERVISION.

Under the Law of Year XI, as amended by the Law of June 25th, 1908, there is an inspection at least once each year of pharmacists' shops, stocks of medicaments in the possession of doctors and veterinary surgeons, druggists', herbalists' and grocers' shops, barbers' shops, perfumeries, depots of artificial mineral waters and, generally speaking, of all places where medicaments or other medicinal products are exhibited or offered for sale, the purpose being to ensure the application of the laws and regulations in force regarding the practice of pharmacy and the elimination of fraud in matters relating to medicaments and, more especially, to test the quality of such products and trace the manufacture and sale, without legal authority, of medical preparations or compounds (there are special provisions with regard to serums and vaccines, together with poisonous substances, more especially narcotic drugs).

Such inspection is carried out under the authority of the Minister for Agriculture. The inspectors are appointed by the Prefect in accordance with proposals laid before him by the Dean of the Faculty or the Director of the local School of Pharmacy.

When going their rounds, inspectors may, if they so desire, be assisted by police commissioners or, where that is impossible, by the mayors or deputy mayors. They may, moreover, require the afore-said officers of the judicial police to take samples of goods in pharmacists' shops or in the stocks of medicaments kept by doctors and veterinary surgeons (Decree of August 6th, 1908).

As regards establishments other than those mentioned above, work in connection with the tracing of frauds and the adulteration of medicaments may be entrusted to assistant inspectors appointed and commissioned by the Prefects (Decree of August 6th, 1908). The appointment of assistant inspectors does not in any way restrict the right of inspectors to visit such establishments whenever they think fit.

The premises which are liable to be visited by inspectors in the case of persons subject to this measure are "dispensing-rooms, laboratories and all places appertaining thereto, shops, workshops, commercial vehicles, together with warehouses and railway stations of departure and arrival" (Decree of August 6th, 1908).

In the course of his visits, the inspector draws up a report recording any infringements which he may have found. Furthermore, in order to satisfy himself of the quality of products and expose fraud, he takes samples. The procedure to be followed in regard to the taking of such samples and their analysis is laid down in the Decree of August 6th, 1908, and in Articles 10 to 16 of the Decree of January 22nd, 1919 (taking the place of Articles 5 to 10 of the Decree of July 31st, 1906).

Where, however, there is flagrant non-observance of the Codex or adulteration, the inspector seizes the product objected to, the whole of it—whatever the quantity—being placed under official seal.

XV. SANCTIONS OF THE LAW.

In former times, the corporations were themselves responsible for the supervision of their members' activities and also for the defence of their rights. Therefore, when the colleges of pharmacy and apothecaries' corporations disappeared, society was left completely unprotected, as experience proved during the Revolution.

The revival under the Empire of a Public Prosecutor's Department with wide powers for proceeding against offences of all kinds was only a slight palliative, as the responsible officials were overwhelmed by the enormity of their task. As a result, the nineteenth century saw the halcyon days of the quack pharmacist—qualified or unqualified—until the interests concerned, combining once again to form associations and subsequently syndicates, gradually took over the internal supervision and external defence of the profession of pharmacist.

A. DEFICIENCIES OF THE LAW OF 21ST GERMINAL, YEAR XI.

After requiring pharmacists to comply in the matter of pharmaceutical preparations and compositions with the Codex and medical

prescriptions, the Law of 21st Germinal, Year XI (Article 32), specified no punishment in the case of infringement. Hence innumerable abuses. The law soon proved defective in other respects also. More especially it lays down no punishment for the infringement of the provisions prohibiting the opening of chemists' shops by unqualified persons (Article 25), those prohibiting grocers and druggists from selling plain drugs by "medicinal weight" (Article 33), those prohibiting pharmacists from engaging in any other trade (Article 32), and those prohibiting the sale of medicaments by "commercial weight" by persons other than grocers (Articles 33 and 36). No punishment having been provided for all these offences, the law was rendered completely inoperative.

An attempt was made to introduce a broad interpretation of Article 36 of the Law of year XI, which would have attached penalties to all these prohibitions in the absence of any other specific penalty. The Supreme Court itself appeared to accept this interpretation in 1836 and 1839.

Both legal writers and courts of law, however, to an increasing extent endeavoured to discover the necessary additional rules in the Declaration of April 25th, 1777 (see Annexes).

Generally speaking, it was held, from 1845 onwards, that the Declaration of 1777 was still in force in regard to all points which had not been specifically regulated by the Law of year XI and which were not in contradiction with other more recent legislation.

The Declaration of 1777 had been drawn up exclusively for the purposes of the Paris College of Pharmacy and had not formerly force of law outside the area constituting the college's sphere of activities. In both legal theory and practice, it was held that, even apart from the references to previous legislation in Articles 29 and 30, the Law of Germinal, by reproducing certain of the provisions of the Declaration, incorporated that enactment in such a way as to render it applicable wherever its own provisions were in force, irrespective of the limits of the college's former sphere of activity and even in colonies acquired since the end of the old regime.

Since the establishment of the foregoing legal practice, the Law of June 25th, 1908, which amended Articles 29 and 30 of the Law of Germinal, has removed its references to previous legislation ; as, however, there is no indication that it was intended to do away with the former sanctions, the latter are still deemed to be in force.

There is a well-known principle in criminal matters that all texts must be strictly interpreted without the possibility of their extension by analogy to new cases. The necessity of putting down abuses, however, sometimes obliges judges to depart from this principle, and it should be observed that it is less respected in the matter of pharmacy legislation than in any other branch of law. For instance, the Law of 21st Germinal, Year XI (Article 36), prohibits the *advertisement* of secret remedies but does not expressly mention *sale*. Logic, however, makes it impossible to permit the latter while forbidding the former. Arguing *a fortiori* from the prohibition of advertisements, legal practice therefore visits the sale of secret remedies with the same penalties.

Article 33 of the same law forbids grocers or druggists from "selling" any pharmaceutical compound or preparation ; of mere "offering for sale" there is no mention. Does that mean that it is not reprehensible ? Since 1805, legal practice has assimilated offering for sale to actual sale. It has even gone further and, instead of confining itself to treating goods kept in the shops in which their owners actually effect sales as goods offered for sale, it has applied the same principle to goods in store, or kept in outhouses of all kinds or back premises, to which the customer has no access. The same measures were adopted in regard to secret remedies as soon as it was recognised that sale was prohibited.

The archaic wording of the laws enacted prior to the Revolution has given rise to difficulties. Thus in the Declaration of 1777, for example, the fines are stated in *livres*. Legal practice has since substituted francs. In certain cases, it is the absence of any provisions in the laws regarding pharmacy or the prevention of fraud which causes inconvenience. Such is the case in regard to the scope of the right to seize and destroy adulterated or badly prepared medicaments. In accordance with legal practice, seizure cannot be ordered on the ground of the sale of secret remedies.

B. NATURE OF THE INFRINGEMENT.

On the one hand, the situation is governed by police regulations, which give the infringements committed the character of contraventions ; on the other hand, they are punishable by "correctional" penalties which, to some extent, assimilate them to delicts proper.

They have therefore been included in the category of the so-called "delict-contraventions . . . governed by rules drawn to some extent from those applicable to both these categories . . . and it would be more accurate to describe them as *unintentional delicts*".

As *contraventions*, infringements are punished irrespective of the intentions of those committing them and without any reference to bad faith on their part. *Thus, the accused person incurs the penalty even when acting in complete good faith.*

Moreover, the fact that all these offences are punishable by "correctional" penalties results in their being treated as delicts in the strict sense of the term. Hence a number of deductions as regards jurisdiction, limitation, consecutive sentence and variations of sentence into which we need not go at present, and which are analogous to those described in connection with the illegal practice of medicine.

C. PROHIBITION OF SECRET REMEDIES.

This entails both criminal and civil penalties.

1. *Criminal Penalties.*

(a) *Definition of the Offence.*

Two distinct offences are punishable : advertisement and sale.

Advertisement of Secret Remedies.—This is prohibited under Article 36 of the Law of 21st Germinal, Year XI, and is punishable under the Law of 29th Pluviôse, Year XIII, which lays down the penalty. For the purpose of these laws, advertisement is deemed to mean any kind of publicity through the medium of posters, the Press, books, booklets, leaflets, prospectuses or otherwise. This would therefore include a newspaper article, an advertisement in a medical journal, the insertion in a periodical of a letter inviting readers not to confuse such and such a remedy with another sold by some other person.

Supplying Secret Remedies.—This prohibition ensues from the linking of Article 32 (under which it is forbidden in the case of pharmacists) and 36 (which prohibits advertisements relating thereto by any person whatsoever) with the Law of 21st Germinal, Year XI ;

Article 1 of the Decree of 25th Prairial, Year XIII, and the preambles to the decrees of August 18th, 1810, and May 3rd, 1850.

As no distinction is made by the law, *this prohibition applies equally to their distribution and sale.*

The mere fact that any person other than a dealer—*e.g.*, a doctor or midwife—is in possession of such drugs would not make such person liable to punishment unless the prosecution could prove that there had been actual sale. As stated above, however, the same rule does not apply to dealers.

Whether the charge be one of advertisement or supply, as the latter constitutes a contravention it is immaterial whether the accused person claims to have acted in good faith or even solely with a view to doing a service to someone else. As the law lays down no special conditions, the accused would be liable to punishment even if the medicament were not actually injurious to health.

(b) *Sentences Imposable.*

In the first place there is a fine of 25 to 600 francs established by the Law of 29th Pluviôse, Year XIII, and, in the case of second offence, imprisonment of from three to ten days.

Where the remedy giving rise to the charge contains toxic substances it may be confiscated in the cases enumerated in the Law of July 12th, 1916 (Article 4), and, if the accused is also charged with fraud, the medicament may be confiscated in pursuance of the Law of August 1st, 1905 (Article 6).

(c) *Complicity and Alternative Charges.*

The courts have, without exception, held that, being liable to "correctional" penalties, infringements of the pharmacy regulations give rise to proceedings for complicity against any person having aided and abetted the delinquent in his offence.

Other offences may be committed concurrently with the supply of secret remedies. When the punishable acts are the same in the various cases, only one charge will be proceeded with. When the punishable acts are distinct, even though parallel and connected, they may all give rise to proceedings under separate charges, subject to the judge's option to inflict one sentence only—the heaviest—in pursuance of Article 365 of the Code d'instruction criminelle ;

an instance in point is when the advertisement of a secret remedy is accompanied by the delict of falsely claiming that the remedy is approved by the Academy of Medicine, or misrepresentation as to the nature of the goods, or swindling.

2. *Civil Redress.*

These are of three kinds : the obligation to compensate competitors ; that to compensate purchasers where necessary ; and the absence of rights of any kind on the part of the person selling the remedy.

(a) *Obligation to compensate Persons whose Profits are reduced through the Sale of the Secret Remedies.*—Even before 1916, it had been decided that pharmacists are entitled to claim compensation from persons selling secret remedies.

As the slightest prejudice occasioned by a delict gives cause for action or compensation, pharmacists would be entitled to complain even of the mere advertisement of secret remedies without being obliged to prove actual sale, as such advertisement might in itself be responsible for their losing customers.

(b) *Obligation to compensate Customers to whom the Sale of a Secret Remedy has done Harm.*—The courts are severe on this point. They hold more especially that, in consenting to sell a secret remedy to a sick person, the seller commits a medical error under which he becomes responsible for any unfortunate results of his act, including the death of the sick person as a result of the substitution, in error, of a highly dangerous toxic substance for the medicament ordered.

(c) *Absence of Rights of any Kind on the Part of the Person selling a Secret Remedy.*—As such sale constitutes a delict, it cannot confer upon the seller any rights whatsoever. He cannot therefore proceed against persons selling secret remedies invented by him, for unfair competition.

Any contract for the exploitation of such remedies would be null and void.

Similarly, the seller would not be able to proceed against purchasers for non-payment.

3. *Position of Pharmacists.*

They would be punishable in the same way as persons possessing no diploma, though, on this point, Article 32 of the Law of 21st Germinal, Year XI, is far from explicit.

As the mere fact of being in possession of such remedies with a view to their sale can be assimilated to the act of sale itself, pharmacists may not prepare in advance any medicaments other than those in the Codex, without incurring the penalties applicable to persons supplying secret remedies, subject to the above-mentioned exception in the case of specialities.

Doctors engaging in pharmacy, either in places where there is no pharmacist's shop, or when they are themselves qualified pharmacists, would not be able to justify the existence of secret remedies on their premises by the fact that they would be entitled to prescribe these remedies in their medical capacity, since a prescription can only be issued at the moment it is required in each individual case.

Furthermore, a pharmacist may only supply a remedy not in the Codex under a detailed medical prescription, specifying its composition. He could not, therefore, accept a prescription on which nothing more than the name and quantity of the remedy were specified. Legal writers agree that a detailed prescription would no longer be necessary in the case of specialities which have since been duly recognised. If, however, such specialities were to contain a toxic substance, the prescription would have to comply with all the conditions laid down in the Decree of September 14th, 1916 (Article 20).

Annexes.

I. THE PRACTICE OF MEDICINE.

Law of April 21st, 1933 (made applicable to Algeria by decree of November 3rd, 1933).

Article 1.—No one may practise medicine in France unless :

- (1) He has the French State diploma of doctor of medicine ;
- (2) He is a French citizen or subject or a national of countries placed under the protectorate of France. Foreign

countries, where doctors of French nationality are authorised to practise medicine may, however, approach the French Government with a view to the conclusion of agreements under which these doctors may be dispensed from French nationality in certain cases. A parity must, however, be established between the number of doctors coming from countries with which agreements have been concluded to practise medicine in France and the number of French doctors practising medicine in those countries.

The same provisions shall apply to dental surgeons.

II. THE PRACTICE OF PHARMACY.

(a) *Declaration by the King on April 25th, 1777.*

Article 7.—We forbid chandlers and all other persons from manufacturing, selling or retailing any salts, compositions or preparations for human consumption in the form of medicaments, or to make any mixture of simple drugs for administration in the form of medicine, on pain of a fine of 500 livres, or a heavier fine if need be.

Article 8.—Secular or regular communities, even hospitals and mendicant religious orders, may not possess a pharmacy except for their private and interior use ; we forbid them to sell or retail any simple or compound drugs, on pain of a fine of 500 livres.

(b) *Law of 21st Germinal, Year XI (April 11th, 1803).*

Article 32.—Pharmacists may not deliver or retail any medicinal preparations or compound drugs, save according to a prescription made therefor by doctors of medicine or surgery or by *officiers de santé* under their signature. They may not sell any secret remedy . . .

Article 33.—Chandlers and druggists may not sell any pharmaceutical compound or preparation on pain of a fine of 500 francs. They may continue to carry on wholesale trade in simple drugs, but may not retail drugs by medicinal weight.

Article 36.—All retailing by medicinal weight, all distribution of drugs and medicinal preparations in playhouses or booths, in public places, fairs and markets, all advertisements and printed posters

indicating secret remedies, under whatever name they are presented, shall be strictly prohibited. Persons guilty of this offence shall be prosecuted under correctional police proceedings and shall be punished in accordance with Article 83 of the Code of Offences and Penalties.

(c) *Law of July 12th, 1916, concerning the Importation, Trade in, being in Possession of and Use of Poisonous Substances.*

Sole Article.—The Law of July 19th, 1845, on poisonous substances is modified and supplemented as follows :

Ad Article 1.—Infringements of the public administrative regulations regarding the sale, purchase and use of poisonous substances shall be punished with a fine of from 100 to 3,000 francs and with a term of imprisonment varying from six days to two months, or with one of these sentences only.

Ad Article 2 (modified).—Any person who contravenes the provisions of these regulations regarding narcotic drugs shall be punished with a term of imprisonment varying from three months to two years and with a fine of from 1,000 to 10,000 francs, or with one of these sentences only.

MALARIA CONTROL IN TURKEY

by

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THE CAUSES OF MALARIA.

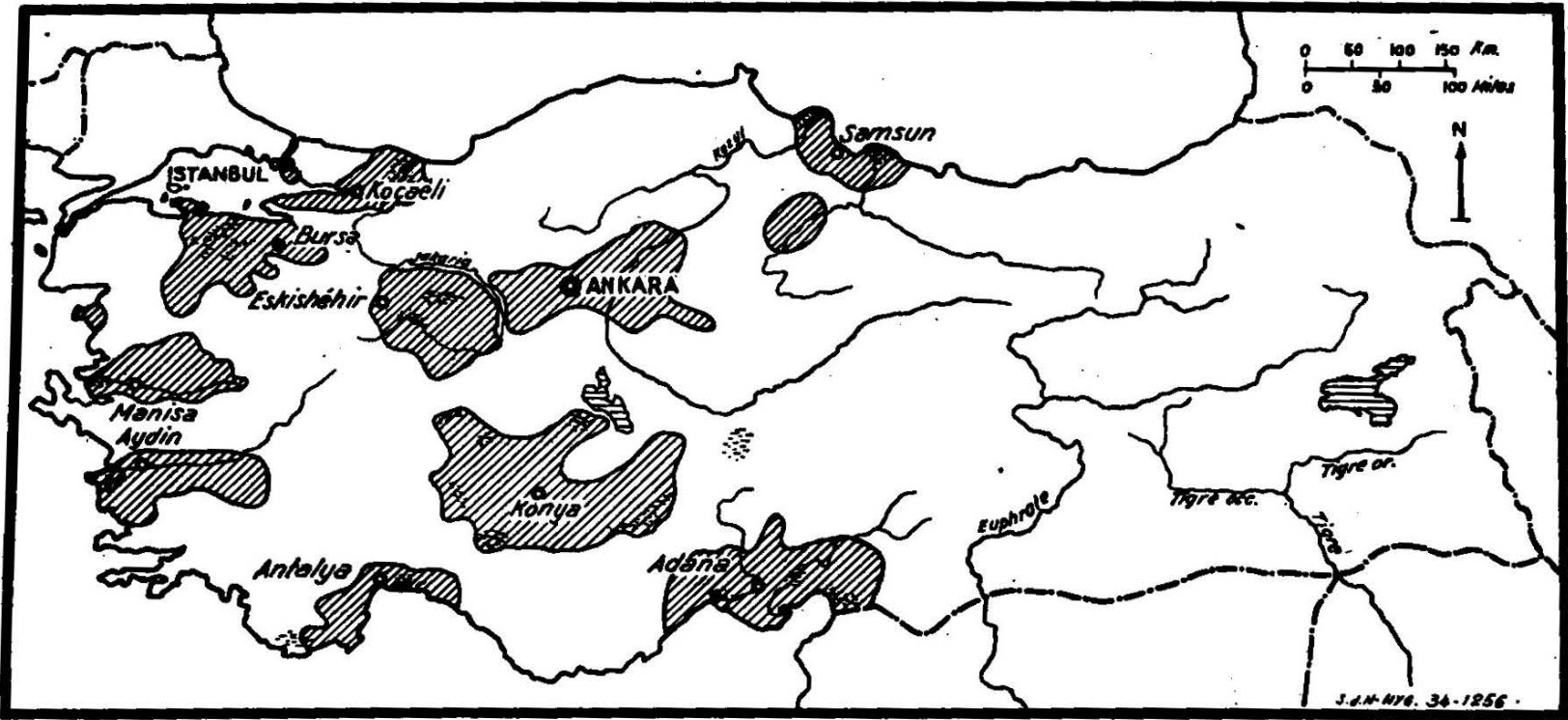
Anatolia may be divided up into two entirely distinct regions : the coastal plains and the central plateau.

Apart from the western massif, most of the mountain ranges run parallel to the coast. Between them and the sea are plains, sometimes a hundred kilometres wide, the slope of which diminishes as they approach the sea. In some places in the north and south, the mountains fall straight into the sea ; but between the western ranges, the waters have carved out numerous steep-flanked valleys. The coastal regions—those in which agriculture prospers most but where malaria is most prevalent—are traversed by many watercourses rising as torrents in the mountains, but gradually growing more sluggish as they straggle across the plains.

The high plateaux are also scored by meandering streams. Near the coast, their flow is stayed both by their own silt and by dunes formed by the sea.

To the north, the Yeşil Irmak, the Kizil Irmak and the Sakarya, which flow into the Black Sea, on the west the Gediz, the Greater and the Lesser Menderes, which flow into the Ægean, and in the south the Seyhan, the Jeyhan, the Göksou and the Tarsus, which flow into the Mediterranean, form, on the high plateaux, in the coastal plains and at their mouths, vast sheets of stagnant water which are favourable breeding-grounds for the mosquito. Spring

TURKEY — ANTI-MALARIA CAMPAIGN AREAS.



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floods cover large areas, and the pools formed in low-lying land when the waters recede are the homes of many generations of anopheles.

In addition to the larger rivers along the coast, many brooks and streams form countless residual pools. For instance, the mouths of the brooks in the Istanbul region and in Thrace, the fringes of the Lesser and the Greater Çekmece, the land inundated by the Tunca, the Ergüne and the Miriç, and the Inos region near the mouth of the Miriç, suffer from malarial epidemics every year.

The average height of the Anatolian plateaux is about 1,000 metres, and those parts of Anatolia which lie 200 metres or less above sea-level do not form more than 5 per cent of the total area of Anatolia. Central Anatolia is traversed by the Kizil Irmak, which, after describing a vast curve, descends into the coastal plains, where it spreads out into extensive marshes before entering the Black Sea.

The Konya plateau, of an average height of 1,000 metres, possesses some ten small lakes. Numerous streams rise in this region and disappear again after many meanderings and the formation of stagnant pools, which, with the shallow and reed-covered lakes, are all breeding-grounds for the anopheles.

Rain also plays an important part in the persistence of malaria. The rainfall is heaviest along the coast and in the interior, in the north in the provinces of Trabzon and Risé, and in the south in the provinces of Antalya and Dörtyol. It attains an average of 1,000 millimetres in the provinces of Trabzon and Risé, and 800 to 900 millimetres in the provinces of Antalya and Dörtyol. It is 700 millimetres at Istanbul and in Thrace, and 600 millimetres in the Adana region. Farther inland, towards the centre of the peninsula, the rainfall decreases to between 250 and 400 millimetres. During the rainy season, in the spring and in summer, the formation of sheets of stagnant water is a very important factor in the recrudescence of endemic malaria.

In addition to the natural formations of stagnant pools by rivers, lakes and rain-water, there are reservoirs dug out for farming purposes : irrigation canals, wide-mouthed wells sunk in the tobacco fields and vegetable gardens, fountain basins and pools formed near wells and springs or in old clay-pits—all factors which help to give malaria a character of permanent endemicity.

There are also vast differences in the temperature between the coastal belt and the interior. In the Mediterranean coastal plains, the maximum is 42.5° Centigrade in summer and the average for the year is about 19°; in the north, the annual average is 14.5° at Trabzon, 14.2° at Samsun and 13.8° at Istanbul; in the west, in the Smyrna region, it reaches 17.4°.

The temperature is distinctly lower on the high plateaux, where the annual average varies between 8° and 12°—11.7° at Konya, 11.9° at Ankara, 8.8° at Sivas and 4.6° at Kars. In the interior of Anatolia, the difference in temperature between night and day sometimes reaches 30° to 35°.

The incidence of malaria is very heavy in the coastal region, which has a high average temperature, many pools of stagnant water and an abundant rainfall; here, also, agricultural labourers are constantly moving from place to place wherever labour is required. In the interior, on the other hand, certain places show a slight or average incidence of malaria, this depending upon the configuration of the country (lakes, marshes, reed-beds, rice-fields, etc.).

THE CAMPAIGN AGAINST MALARIA.

Legislative Measures.

For centuries past, malaria has been endemic in several provinces of Turkey; each year, previous to the systematic organisation of the anti-malaria campaign, a considerable number of adults and children in the plains, where farming and commercial activities are intensive, were obliged to cease work owing to malaria. One of the first aims of the Government of the Republic was therefore to create an organisation which would be able to supply medicaments to even the remotest villages. Law No. 839, of May 13th, 1926, laid down the technical and administrative bases of the campaign against malaria.

The main features of this law may be summarised as follows :

- (a) In all regions declared to be malarial by the Ministry of Health and Social Assistance, special organs shall be created for the campaign against malaria; post-graduate courses shall

be organised to ensure the proper training of doctors and health officers who may be called upon to work in the various institutes, laboratories, hospitals and dispensaries of these organs ;

(b) All Government services shall be bound to co-operate in the campaign against malaria in such places and at such times as the Ministry shall specify ;

(c) In regions declared to be malarial, the Ministry of Health and Social Assistance shall distribute free of charge quinine or other febrifuges to poor peasants or to taxpayers who are called upon to provide labour in lieu of the road tax, and to all indigent persons in towns and villages ;

(d) In the regions declared to be malarial, public or private undertakings and farmers shall be bound to distribute to their employees quinine or other febrifuges free of charge and in accordance with scientific methods. They shall likewise be bound to take all such measures for the prevention of malaria as may be necessary to protect their staff ;

(e) No stagnant water which may serve as a breeding-ground for mosquitoes shall be allowed to remain within dwellings or in vineyards or gardens, within the precincts of towns and villages, or within a distance from such localities as the anti-malaria campaign shall specify ;

(f) Within two years from the coming into force of the law on the campaign against malaria, towns and villages possessing a municipal organisation shall submit to the Ministry of Health and Social Assistance plans for the removal of waste water and stagnant water ;

(g) The local population shall drain off all stagnant water within the campaign areas wherever this can be done by "minor improvement works"—i.e., works which do not necessitate more than five days' labour a year. This work, which shall be divided between the inhabitants by the body of elders in the villages and by the municipal authorities in the towns, may be furnished either in the form of labour or in the form of a cash payment ;

(h) The departmental authorities shall be responsible for the draining of marshes too extensive to be dealt with by "minor improvement works" ;

(i) The villages situated within a radius of three kilometres from a large centre of infection which it would be too difficult an undertaking to render healthy may be evacuated to the nearest healthy region.

(j) Any person infringing the law relating to the anti-malaria campaign or failing to carry out the obligations it imposes, or seeking to hinder anti-malaria campaign officers when inspecting dwellings, or repeatedly neglecting to conform with the health instructions issued by the anti-malaria campaign organs are liable to punishment ;

(k) When an owner omits to drain off stagnant water likely to form a breeding-ground for anopheles, the necessary work shall be carried out by the State at the expense of the party concerned.

At the end of each malaria season, bonuses in money or in kind are granted to doctors, health agents or officers who have obtained particularly good results by their activity in the campaign ; bonuses are also granted as a reward for anti-malaria propaganda and land improvement works, undertaken by schoolmasters, village elders or private individuals.

Under Law No. 826, of April 26th, 1926, medical practitioners who have obtained their diploma since 1927 and all civil and military medical officers attached to the State, departmental or municipal administrations are bound to undergo a three months' training course in the anti-malaria institutions to which they are assigned by the Ministry of Health and Social Assistance. For this purpose, a malaria institute was created at Adana in 1928, in which theoretical and practical courses for civil and military medical officers are given each year on hæmatology, parasitology, entomology, epidemiology and the clinical aspects of malaria and methods of carrying out land reclamation and improvement works. These courses also include study tours in the antimalaria campaign areas.

Law No. 827, of April 26th, 1926, provides for the purchase by the Government of certain quantities of quinine known as State quinine, to be sold at a low price to the inhabitants of malarial regions. This quinine, issued in the form of rose-coloured pills, is sold through the agricultural banks. Moreover, for the

requirements of the anti-malaria campaign organs, the State issues free of charge to malarial patients green quinine pills, the sale of which is strictly forbidden.

The rules for the application of the Law on the Anti-Malaria Campaign came into force on February 16th, 1927.

Anti-Malaria Organisation.

In 1924, the Government of the Republic instructed a Malaria Commission, presided over by Dr. Refik Bey, Minister of Health and Social Assistance, to draw up a technical and administrative basic plan for the creation of an anti-malaria service ; this Commission's first act was to conduct a preliminary enquiry into the incidence of malaria in Turkey.

As soon as the most heavily infected areas had been mapped out, three anti-malaria missions, under the direct orders of the Ministry of Health and Social Assistance, were set up at the beginning of 1925 at Ankara, Aydin (basin of the Lesser and the Greater Menderes) and Adana (basins of the Seyhan and Jeyhan, between the Taurus range and the Mediterranean).

In 1926, two new areas were opened at Bursa and Konya ; in 1928, areas were established at Samsun (mouths of the Kizil Irmak and the Yeşil Irmak), at Koçaeli at the mouth of the Sakarya, and finally, in 1929, the areas of Istanbul, Eskisehir (basins of the Sakarya and the Porsok), Antalya, on the Mediterranean sea-coast, and Manisa. At present there are, in Turkey, eleven anti-malaria campaign areas, including twenty-four departments with 228 towns, 3,356 villages and a total population of 3,659,864 (25 per cent of the population of the Republic and 24.9 per cent of its area) ; this network is extended and supplemented as a greater number of specialised doctors and health agents becomes available for this work.

Each area is under the direction of a qualified malariologist, with the rank of President. A motor-car is placed at his disposal and a central laboratory with one or two heads of laboratory, who make blood tests and conduct anopheles research.

The eleven areas are divided into sixty-four sectors, directed by medical officers, and into 255 sub-sectors in charge of health agents ; as each sub-sector includes from ten to twelve villages, health agents of the rural districts make their rounds on a horse or mule.

Each sector possesses its policlinic : most of them also possess a small laboratory. There is a hospital with twenty beds for malaria patients at Adana, and dispensaries with from five to ten beds in the centres of a number of sectors. Lastly, in certain areas, workmen skilled in drainage, land improvement, paraffin-spraying, etc., have been placed at the disposal of the medical officers of sectors.

All the inhabitants of localities within the campaign areas are examined twice annually, in the spring and in the autumn, by the doctors of the campaign missions. The results of these inspections are entered in a register, in which, against the name of each individual, the following information is given : date of examination, general health of individual, previous malarial history, presence or absence of enlarged spleen, results of blood tests. The various degrees of splenomegaly are indicated by the following signs :

- (+) = spleen extending not more than two fingers' breadth beyond the false ribs ;
- (++) = spleen reaching the middle of the distance separating the tenth false rib from the umbilicus ;
- (+++) = spleen reaching the umbilicus ;
- (++++) = spleen extending beyond the umbilicus.

The registers are prepared in such a way as to allow of the entry of the results of four successive inspections for each person—*i.e.*, inspections covering a period of two years. The doctors must themselves carry out the general examination, the patient being in a recumbent position.

Curative Treatment.

All acute or chronic cases of malaria and relapses discovered during the half-yearly inspections or in the dispensaries are classified and treated. Patients requiring treatment are entered in the registers for the distribution of quinine under the same serial number as in the register of general examinations—a system which allows all the necessary information to be obtained rapidly. The quinine distribution registers are made up for a twelve-months period, daily entries being made concerning the curative and

preventive treatment applied (doses in cgrm. of quinine). Curative treatment is given according to Nocht's method : 10 cgrm. of hydrochloride of quinine per year of age up to 10 years and 1 grm. of quinine per diem on an average above 10 years of age (in serious cases, this dose may be increased). Children under 3 years of age are given 10 cgrm. pills of euquinine. Formerly, quinine tannate made up in chocolate tablets was used for children of from 3 to 10 years of age, but this system had to be abandoned, owing to difficulties of transport and preservation in a warm climate ; these tablets will be replaced by sugar-plums.

In acute cases or relapses with fever, the treatment is as follows : administration of quinine for seven days (initial treatment) ; two days' rest ; then administration of quinine for three consecutive days, followed by four days' rest, over a period of four weeks (follow-up treatment).

In chronic cases with enlarged spleen and general weakness but without fever attacks, the treatment referred to above as "follow-up" treatment is immediately applied.

Every malaria patient undergoing treatment receives a card indicating the method of treatment applied. Advice to the patient as to how to take care of himself is given on the back of each card. The quantity of quinine to be taken is entered both on the personal card and in the distribution register, opposite the date on which the patient should take his quinine.

Health agents visit the villages systematically and distribute to the persons entered on their register the amount of quinine necessary for one week. If, in the course of treatment, a patient suffers from a severe attack, the treatment is recommenced ; this is also the case when hæmatozoa are found in the blood of a patient who has completed his treatment.

Two quinine distribution registers are kept for each village : one by the village headman (*muhtar*) and the other by the health agent.

Carriers of the tropical form receive a "follow-up" treatment which is repeated twice or thrice annually, according to requirements.

Serious cases accompanied by vomiting and diarrhœa are given intramuscular or intravenous injections of 0.5 cgrm. quinine hydrochloride plus 0.25 cgrm. uretane, in 10 to 20 c.c., or sometimes more, of physiological saline. Patients who, on completing their quinine

treatment, still show signs of anæmia and weakness, are given a tonic in the form of pills containing each :

| | | |
|-----------------------------|-------|-------|
| Quinine hydrochloride | 0.1 | cgrm. |
| Sodium arseniate | 0.002 | cgrm. |
| Iron peroxalate | 0.05 | cgrm. |

two pills per day for the first week, three pills during the second week, and a rest of five days. This treatment may be continued for two or three months.

Preventive Treatment.

Quinine is distributed for preventive purposes to the malaria-free inhabitants in the campaign areas and is administered according to Ziemann's method—*i.e.*, every four days. This treatment is continued during the whole of the malaria season. Up to the age of ten, 10 cgrm. is administered per year of age ; for persons over 10 the dose is 1 grm. per day. All persons undergoing preventive treatment receive a treatment card, and the quantities of quinine administered free of charge are entered both on these cards and in the quinine distribution register. Preventive treatment is given only to persons who can be kept under close supervision, such as schoolchildren, soldiers, policemen, gendarmes, workmen engaged in road making or repairing, officials, railwaymen, etc. The quinine is distributed either by the agents of the anti-malaria missions or direct by the undertakings or establishments concerned.

Blood-Tests.

Blood specimens, which are taken once a year in the spring, are examined by the thick-drop method at the central laboratory of the area concerned. Each slide is wrapped in a sheet of paper which gives the name, age, address, the serial number under which the patient is entered on the examination register, his general condition and the state of the spleen. After they have been examined, the slides are returned to the campaign sectors, together with the wrapper on which the species of hæmatozoon found have been entered. This information is recorded in the test and case register and in the quinine distribution register. The laboratories also keep their own register in which they enter the results of their analyses. The object of these general blood tests is to establish, once a year, the parasite index of the villages.

CAMPAIGN AGAINST MOSQUITOES.

The central laboratories of the campaign areas are required to identify the species of mosquitoes to be found in their sector, to keep a register specifying the place where they are caught and the date, and to make a collection of the various mosquitoes and anopheles in the sector.

In 1926, the Ministry of Public Health and Social Assistance requested Professor MARTINI, of the Hamburg Institute of Tropical Diseases, to undertake a study tour in the various Turkish provinces and campaign areas for the purpose of identifying the different species of anopheles and mosquitoes. These investigations have since been continued by the presidents of the campaign areas who accompanied him on this tour. Fellowships have been granted by the Ministry of Public Health and the Health Organisation of the League to enable a certain number of presidents of the campaign areas, heads of laboratories and medical officers of the campaign sectors to follow the courses of the International Schools of Malariology at Hamburg, Paris and Rome.

LIST OF MOSQUITOES IDENTIFIED IN TURKEY.

| <i>Species.</i> | <i>Where caught</i> |
|--|--|
| <i>Anopheles maculipennis</i> Meigen. | In all the campaign zones. |
| • <i>elutus</i> Edwards | Ankara, Konya, Aydin, Adana, Samsun, Bolvandin. |
| • <i>bifurcalus</i> Meigen. | Toros, Ankara, Aydin, Osmaniye, Tekirdag. |
| • <i>algeriensis</i> Theobald | Aydin, Kusadasi, Adapazar, Kutahya, Ezine, Afyon-Karahisar, Dillskelesi, Adana. |
| • <i>nigripes</i> Staeger | Izmit, Aydin, Toros. |
| • <i>hyrcanus</i> Pallas | Samsun, Terme, Izmir, Izmit, Aydin, Adana. |
| • <i>superpictus</i> Grassi | Ankara, Afyon-Karahisar, Adana, Konya, Eskisehir, Samsun, Iznik, Bursa, Aydin, Mersin, Tekirdag. |
| <i>Uranotaenia unguiculata</i> Edwards | Adana, Aydin, Ankara, Izmit. |
| <i>Mansonia richiardii</i> Ficalbi | Afyon-Karahisar. |
| <i>Theobaldia longiaerolata</i> Macquart | Adana, Konya, Urfa, Samsun, Istanbul, Izmit, Ankara, Aydin. |

| <i>Species</i> | <i>Where caught</i> |
|--|--|
| <i>Theobaldia annulata</i> Schrank | Afyon-Karahisar, Adana, Bolu, Aydin, Bursa, Ankara, Izmit. |
| • <i>morsitans</i> Theobald | Adana, Aydin, Istanbul, Izmit. |
| • <i>jumipennis</i> Stephens | Adana, Izmit. |
| <i>Orthopodomyia pulchripalpis</i> Rondani | Izmit. |
| <i>Edes caspicus</i> Pallas | Ankara, Afyon, Bolu, Tekirdag, Sam- sun, Izmit, Aydin, Adana. |
| • <i>mariae</i> Sergent | Mersin. |
| • <i>zammittii</i> Theobald | Kusadasi. |
| • <i>pulchrilarsis</i> Rondani | Izmit, Aydin. |
| • <i>excrucians</i> Walker | Ankara. |
| • <i>lutescens</i> Fabricius | Kutahya, Afyon, Ankara. |
| • <i>diversus</i> Theobald | Izmit, Aydin. |
| • <i>lepidonotus</i> Edwards ¹ | Ankara, Izmit, Yalova, Aydin. |
| • <i>refski</i> Medjid ² | Ankara. |
| • <i>subtrichurus</i> Martini | Izmit, Aydin. |
| • <i>nigrocanus</i> Martini | Afyon. |
| • <i>salinus</i> Ficalbi | Aydin, Izmit, Kusadasi. |
| • <i>ornatus</i> Meigen | Aydin, Izmit, Adana. |
| • <i>echinus</i> Edwards | Izmit, Aydin, Adana. |
| • <i>vexans</i> Meigen | Adana, Ankara, Bolu, Bursa, Dinar. |
| • <i>cinereus</i> Meigen | Adapazar. |
| • <i>ægypti</i> Linnæus | Samsun, Istanbul, Adapazar, Izmit, Adana, Fethiye. |
| <i>Culex modestus</i> Ficalbi | Izmit. |
| • <i>pusillus</i> Macquart | Tarsus. |
| • <i>hortensis</i> Ficalbi | Konya, Ankara, Afyon, Adana, Aydin. |
| • <i>apicalis</i> Adams | Bursa, Izmit, Aydin. |
| • <i>martinii</i> Medjid ³ | Mersin. |
| • <i>deserticola</i> Kirkpatrick | Adana. |
| • <i>mimelicus</i> Noé | Samsun, Adana, Ankara, Aydin. |
| • <i>tritæniorrhynchus</i> Giles | Adana, Aydin. |
| • <i>theileri</i> Theobald | Ankara, Izmit, Adana, Aydin, Bursa. |
| • <i>torrientium</i> Martini | Adapazar. |
| • <i>talicinctus</i> Edwards | Izmit, Aydin, Adana. |
| • <i>perexigus</i> Theobald | Aydin, Adana. |
| • <i>pipiens</i> Linnæus | In all parts of Turkey. |

¹ Larva discovered by Dr. Medjid in 1927. Bibliography : Report of the Second Turkish National Medical Congress. *Archiv für Schiffs- und Tropenhygiene*, 1928, Bd. 32, S. 306.

² Discovered for the first time at Ankara. Bibliography : Report of the Second Turkish National Medical Congress. *Archiv für Schiffs- und Tropenhygiene*, 1928, Bd. 32, S. 310.

³ Discovered in 1929 at Mersin. Bibliography : Third Turkish National Medical Congress.

Malaria-carrying Anopheles.

Up to the present, the following seven species have been identified in the campaign areas :

1. *A. maculipennis*.—Although this is met with in every area, it does not always act as a carrier ; it is rarely found south of the Taurus, but abounds in the Eskişehir district and the Sakarya and Porsuk valleys; however, it is *A. elutus* which is most commonly found in dwellings and epidemic foci. Although the stomach contents of the *maculipennis* caught in the Eskişehir district have not been subjected to the precipitin test, and the eggs of these anopheles have not been studied with a view to identifying their varieties in accordance with Falleroni's list of types, the external appearance of these insects enables them to be classed as zoophiles.

In all the other areas, *A. maculipennis* is the principal carrier.

2. *A. elutus*.—Like *A. maculipennis*, this species is very common in every area and is the chief carrier in the Adana district. On examination, the sporozoite index was found to be 2.5 per cent (Ekrem Tok).

3. *A. bifurcatus*.—This is found in all the campaign areas, although in smaller numbers than the previous species. During the winter, it remains in the larval stage, assuming the adult form in the first warm days of spring. Although it is usually considered to play an important part at that season in transmitting malaria, it appears to be less dangerous in this respect in Turkey than elsewhere.

4. *A. algeriensis*.—This has been identified in the Aydin, Bursa, Koçaeli and Adana areas ; it is found in the adult form from the month of May onwards and all through the summer. In Turkey, it possesses all the characteristics of the "wild" anopheles and therefore only plays a minor rôle.

5. *A. nigripes*.—Dr. Medjid's investigations have shown that the larvæ of this species are found in hollows in trees ; it has been identified in the Ankara, Aydin and Koçaeli areas and in the Taurus, and plays a very small part in the transmission of malaria.

6. *A. hyrcanus*.—This is found in very large numbers in the rice-fields in the Ankara, Aydin, Bursa, Koçaeli, Adana and Samsun areas; it is a "wild" anophele and hence of little importance as a carrier.

7. *A. superpictus*.—This is found in very large numbers in all the campaign areas, especially during the summer and autumn; it ranks next in importance as a carrier to the *A. maculipennis* and the *A. elutus*.

Destruction of Larvæ.

The Ministry of Public Health attaches great importance to the destruction of malaria-carrying mosquitoes and to the draining-off of stagnant water forming a favourable breeding-ground for these mosquitoes. The removal of such water has been made compulsory wherever this is practicable, and the officials of the Anti-Malaria Service are required to see that the law is carried out. Where it is not possible to drain off the water, recourse is had to larvicides; the one most commonly used is Paris green mixed with road-dust, ashes or very fine earth in the proportion of 2 per cent. This mixture is spread on the surface of the water by means of sprays, or even by hand, from 5 to 10 grammes being used per square metre. This method always produces excellent results, provided account is taken of the biological characteristics of the larvæ and of the climatic conditions. Paris green has been used in certain areas since 1927 and its employment has now become general.

Mazout is also employed as a larvicide, but, as it is more costly, its use is confined to the large towns. Lastly, the following culiciphage fishes have been introduced:

1. *Cyprinodon fasciatus* Valenciennes.
2. *Hemigrammacapoeta culiciphaga* Pellegrin.
3. *Cyprinodon cipris* Heckel.
4. *Phoxinellus Kervillei* Pellegrin.
5. *Nemachilus argyrogramma* Heckel.

Destruction of Imagoes.

The law on the prevention of malaria requires all doors and windows of public establishments, factories, barracks and schools

situated in the campaign areas to be screened. It is the duty of the medical officers of the Anti-Malaria Service to see that this law is carried out and that buildings are properly screened.

During the months of January, February and March, as soon as the anti-larval campaign has ended, efforts are made to destroy adult anopheles hibernating in dark corners of dwellings and stables. A solution of 25 grm. of black soap in 1,000 c.c. of formalin is used as a spray, after all openings in the rooms have been stopped up. After a certain time, the walls and ceilings are swept and the insects collected.

At Istanbul and Ankara, a special campaign has been inaugurated for the destruction of adult mosquitoes.

At Ankara, the anti-larval campaign has been pursued so energetically that all breeding-places of mosquitoes may be said to have been cleaned up. Since 1925, a very large number of marshes have been drained and strict and constant supervision is exercised by a special organisation over all accumulations of water which are likely to serve as breeding-places for anopheles larvæ. Moreover, a permanent team of officials of the Anti-Malaria Service disinfects all passenger or goods coaches by spraying as soon as they arrive at Ankara. The anopheles and *culex* thus collected are sent for examination to the Central Laboratory of the Anti-Malaria Service.

At Istanbul also, special teams are employed to destroy the larvæ in winter and to deal with imagoes in summer.

IMPROVEMENT WORKS.

Whereas minor improvement works are carried out by communities in accordance with the plans of the hydraulic engineers attached to the anti-malaria campaign missions and under the supervision of these engineers, major works, such as the improvement of the banks of rivers and lakes, the draining of huge marshes or the building of dykes against floods, are undertaken by the Ministry of Public Works, which has been very active and successful in this field. For instance, since 1925, more than 32,000 hectares of marshland have been drained and 340,000 metres of canals have been dug.

Wherever spring rain-water has collected and is likely to become a breeding-place for anopheles, these pools are either treated with larvicide or drained by means of motor-pumps which discharge the water on to permeable soil. Each campaign area possesses a mobile motor-pump with 150 to 200 metres of piping, capable of pumping 40 to 50 cubic metres per hour.

PROPAGANDA.

The Ministry of Health believes that its campaign against malaria will only be crowned with final success when the most backward elements of the population have been convinced of the campaign's usefulness and converted to new methods by carefully conducted propaganda. Consequently, all possible means are employed to disseminate knowledge of the danger of malaria and the methods by which it may be combated. The medical officers of the campaign missions give numerous lectures to the public and the school-children, while propaganda of every kind is carried on by means of posters, the cinema, the Press and the distribution of pamphlets.

STATISTICS.

The *health agents* prepare each week and forward to the medical officer of their sector a table showing the number of malaria patients in their sector, the quantities of quinine and other medicaments distributed during their visits, the number of patients who have completed their treatment or have left the sector before its completion, the number of deaths, the quantities and the localities in which paris green has been employed, and the nature of minor improvement works carried out during the week.

The *medical officers of sectors* transmit to the presidents of campaign areas a weekly account of the statistical tables communicated to them by their health agents.

The *presidents of the campaign areas* prepare fortnightly a statistical table of the data supplied to them by the medical officers of sectors, which they transmit to the Ministry of Health, with the meteorological bulletin of the last fortnight and a statement of the

number of patients treated either at the malaria hospital or in the dispensaries.

Twice annually, after the general spring and autumn inspections, campaign sectors and areas also prepare tables showing the number of persons examined during the six months ; the number of cases of enlarged spleen noted and its degree in the age-groups 0-10 years, 11-20 years and over 20 years ; the spleen rate of each of these age-groups ; the number of blood tests made ; the nature of the hæmatozoa identified ; the parasitical index of each age-group and the proportion of splenomegaly among carriers.

At the end of each year, the presidents of the campaign areas send to the Ministry of Health a detailed report, illustrated by maps, photographs and graphs, on the work of their mission.

We have grouped in a table (pages 146 and 147) the essential data gleaned from the statistics prepared by the anti-malaria campaign missions from 1929 to 1932.

ENDEMIC INDEXES.

In order to ascertain the incidence of endemic malaria in a given area and to discover cases of malaria, it may be sufficient in the early stages of the enquiry to examine the spleen, as a simple and rapid method of diagnosis. In a country, however, in which the campaign against malaria is being conducted over a vast territory among millions of individuals, the spleen rate alone does not give results by which the endemic situation in one year may be compared with that in another. It only provides an adequate basis of comparison in a definitely delimited region in which the population remains relatively stable.

As, in Turkey, the campaign areas are being extended each year, and the number of inhabitants is increasing proportionately, the spleen rate for a given year cannot be compared with that for the previous year. It might, at first sight, be thought that, unless a new epidemic occurred, the spleen rate ought to decrease after twelve months' anti-malaria treatment ; but, as a matter of fact, it has been noted that sometimes the index has increased rather than diminished. In the Ankara area, for instance, the spleen rate for the spring pre-epidemic period, which was 17.3 in 1926,

rose to 18.1 in 1927 and 21.4 in 1928. It then fell to 13.5 in 1929, 16.3 in 1930 and 14.1 in 1931. In this case, the figure for the spleen rate does not connote an actual increase of malaria incidence, but is due to the fact that the anti-malaria campaign was extended to new groups of inhabitants. When interpreting the fluctuations of the spleen rate for a given area, it should also be remembered that this index is not only augmented each year by the adjunction to the campaign area of new malarial communities, but also that regions rendered healthy by the anti-malaria campaign are no longer included in the campaign area.

The anti-malaria campaign service attaches capital importance to the sterilisation of virus reservoirs. It therefore employs large quantities of quinine for the treatment of malaria patients. Taking into account the action of this medicament on splenomegaly, it is obvious that the number of hypertrophied spleens among a population systematically treated with quinine is no criterion for the determination of the endemic index. The criterion adopted is therefore the parasitic index, several hundreds of thousands of blood tests being made for this purpose annually.

The simultaneous determination of the splenic and parasitical index in a given region makes it possible, not only to estimate the endemicity at any given moment and to compare it with the endemicity in previous years, but also to judge the intensity and duration of epidemics.

While the search for hæmatozoa in the blood of malaria patients is a delicate operation and not always successful, splenomegaly is a lasting and sometimes permanent symptom in the endemic zones. Consequently, the splenic index is normally higher than the parasitic index. A parasitic index higher than the splenic index therefore indicates a recrudescence of the epidemic. If this ratio remains constant for a number of months, it may be concluded that there is a persistent epidemic.

In areas where a serious malarial epidemic is prevalent, the spleen rate, after decreasing for a number of years, attains an almost constant level with very slight variations. As the effects of systematic and continuous treatment have a very marked effect on the health and social and economic situation of the locality in which the campaign is being conducted, the persistence of the splenic index has led the anti-malarial services to seek out second-and third-

degree splenomegaly indices. At the beginning of the campaign in a given area, when the distribution of the various degrees of splenomegaly (+, ++, +++, +++) is being studied, it is seen that the results of the campaign are reflected each year by an appreciable decrease in splenomegaly of the +++ and ++++ degrees, of which a very small number of sclerosed cases remain stationary and unamenable to treatment. Thus, in the Adana area, where malaria endemicity was characterised by a spleen rate of 71 per cent at the beginning of the campaign (1925), it was noted at the end of twelve-months' systematic treatment that this index had fallen to 21.4 per cent in the spring pre-epidemic period, and to 21.1 per cent in the autumn post-epidemic period. Subsequently, the spleen rate fell to 15 per cent, a level at which it has now become almost constant.

The following table shows the percentages of distribution of cases of splenomegaly observed in the Adana area in 1926 and 1928 :

| Splenomegaly | 1926 | | 1928 | |
|--------------|--------|--------|--------|--------|
| | Spring | Autumn | Spring | Autumn |
| ++++ | 2.5 | 2.9 | 1.8 | 1.0 |
| +++ | 7.4 | 8.9 | 7.5 | 5.3 |
| ++ | 20.0 | 23.3 | 28.3 | 23.6 |
| + | 69.9 | 64.6 | 62.2 | 70.0 |

The fact that, after a few years' treatment, most of the cases of splenomegaly are classified in category +, and that categories +++, ++, and even ++, show a marked decline, is a sure sign of the improvement in the endemic position.

In the Aydin zone, the distribution of cases of splenomegaly from 1925 to 1929 was as follows :

| Periods of tests | + | ++ | +++ | ++++ |
|-------------------|-------|------|-------|------|
| Autumn 1925 | 36.2 | 38.8 | 19.1 | 16.1 |
| Spring 1926 | 44.1 | 35.2 | 15.4 | 5.05 |
| Autumn 1926 | 49.5 | 33.2 | 13.09 | 4.1 |
| Spring 1927 | 55.7 | 27.8 | 11.3 | 5.01 |
| Autumn 1927 | 60.01 | 26.6 | 10.1 | 3.1 |
| Spring 1929 | 63.3 | 26.1 | 8.4 | 2.0 |

A study has also been made of the distribution of the various categories of splenomegaly among carriers of parasites. In the Ankara area, in 1931, 2,281 carriers of hæmatozoa were found out

of 45,582 blood tests. The distribution of cases of splenomegaly among carriers of *P. vivax* was as follows :

| | Percentage |
|------------|------------|
| ++++ | 0.7 |
| +++ | 6.8 |
| ++ | 14.6 |
| + | 18.9 |

Of these, 59 per cent had normal spleens.

The carriers of *P. falciparum* were as follows :

| | Percentage |
|------------|------------|
| ++++ | 1.6 |
| +++ | 8.4 |
| ++ | 14.1 |
| + | 16.2 |

Of these, 59.7 per cent had normal spleens.

Lastly, among the carriers of *P. malariae*, the figures were as follows :

| | Percentage |
|------------|------------|
| ++++ | 1.8 |
| +++ | 6.9 |
| ++ | 13.4 |
| + | 20.8 |

Of these, 56.9 per cent had normal spleens.

FORMS OF MALARIA.

The spring epidemics are caused by the tertian form in almost all the areas. For instance, since the establishment of the Ankara area, the spring tests in that area have always shown the predominance of this form. The autumn tests, on the other hand, always show a higher proportion of *P. falciparum* than the spring tests ; according to the locality and the season, sometimes the tertian form predominates and sometimes the tropical form.

The general tests of 1926, 1929, 1930 and 1931 showed a preponderance of *P. vivax*, while the tests in 1927 and 1928 showed a predominance of the tropical form. The quartan form is encountered in all areas, but the rate is not high. This form is more frequently found in the blood tests carried out in the autumn and winter than in those of spring and summer.

In the Aydin area, except in the general tests in the spring of 1926 and 1928, the tertian form always proved to be less frequent than the tropical form. The rate of the quartan form is always low.

The tertian form predominates in the Adana area. In 1931, however, during the epidemic following upon the great spring floods, *P. falciparum* proved to be more frequent than *P. vivax*; the quartan form is infrequent in this area.

In the Bursa area, the tertian form is most frequently encountered in spring and autumn; in 1931, exceptionally, the tropical form was the most frequent. The quartan form is still rarer than in the other areas; it was found only once in 1926, 1930 and 1931, and the rate was 0.4 per cent in the autumn of 1927, 0.2 per cent in the spring of 1928, 1.3 per cent in the autumn of 1928, 0.2 per cent in the spring of 1929 and 0.1 per cent in the autumn of 1929.

In the Konya area, the tertian form predominates in the spring and autumn epidemics, while the tropical form always ranks second and is more frequent in autumn and winter than in the spring.

In the Samsun area, the tertian and tropical forms predominated alternately in the spring and autumn of 1928. At the beginning of summer in 1929 and in the spring and autumn of 1930, the tropical form was the most frequent.

In the Eskisehir area, the tertian form predominates in spring and the tropical form in summer and autumn.

In the Manisa area, the tropical form was the most frequent in the spring, at the end of the summer of 1929 and during the whole of 1930; in 1931, on the other hand, the tertian form predominated.

In the Antalya area, the tertian form predominates in spring, summer and winter, while the tropical form is of secondary importance. As in the other areas, the quartan form is rare.

The table on page 150, which summarises the observations made on 542,838 individuals in 1931, shows that, after a few years of the anti-malaria campaign, spleens of the categories + + + and + + + + are becoming very rare among the carriers of the three types of parasites. Moreover, *P. vivax*, to which the authors agree in attributing most of the cases of splenomegaly, does not appear to have caused a higher proportion than the other types of hæmatozoa.

SUBJECTS TO WHICH THE MALARIA COMMISSION DESIRES TO DRAW THE ATTENTION OF MALARIOLOGISTS.

The MALARIA COMMISSION, when it published its Third General Report, which appeared in the June 1933 issue of the Quarterly Bulletin of the Health Organisation, was fully aware of the fact that the subject was far from exhausted, for, in spite of the progress achieved, many points still remain dark and require further research. Everywhere studies on malaria are being pursued, and the Commission felt it might serve a useful purpose by drawing up a list of the problems whose solution appeared most urgent and whose study might usefully be undertaken by malariologists in various countries. These subjects are as follows :

1. CLINICAL AND THERAPEUTICAL RESEARCH WORK.

Determination in hyperendemic and endemic regions of the age groups most seriously affected by the disease and consequently requiring most attention in the matter of treatment. Investigations should cover in the first place the indigenous population and then be extended to immigrants.

Determination of the minimum dose of quinine sufficient for the treatment of the disease in hyperendemic and endemic areas where the natives have attained a certain degree of immunity.

Ascertainment of the dosage (by age groups) of plasmoquine sufficient to prevent the gametocytes from infecting the anopheles and the intervals (per week) at which it should be administered.

Determination of the extent, if any, to which the therapeutical action of quinine is increased by the administration of plasmoquine (combined medication).

A beginning should be made with laboratory research on cases of induced infection before proceeding to apply this method in the field.

Continuation of clinical tests with both types of "totaquina" in accordance with the method laid down by the Commission.

Experiments in malaria-control by means of medicaments alone without the application of anti-anophelene measures.

Blackwater fever ; investigation of the relations between quinine and blackwater fever by means of experiments on animals (malaria in monkeys).

2. HOUSING AND MALARIA.

Biology and geographical distribution of the different varieties of *A. maculipennis*.

Study of the following species of tropical anopheles from the point of view of a possible differentiation of races :

(a) *A. hyrcanus* and its several varieties (though widely disseminated, this strain is not as a rule very dangerous, though it may become so in certain countries, and especially Sumatra).

(b) *A. bifurcatus* (unimportant in Europe but dangerous in Palestine).

(c) *A. ludlowi* var. *sundaicus* (dangerous everywhere, though there is a great difference between its breeding-places on the coast of Java and in the interior of Sumatra).

(d) *A. gambiae* (dangerous everywhere, though its breeding-places differ in the Union of South Africa and in Tropical Africa).

Causes of the very great variations met with in the distribution of malaria in certain tropical regions—such as the phenomenon of immune areas in the immediate vicinity of hyperendemic areas—and in particular the possibility of a relation existing between this phenomenon and the nutritional deviation of the anopheles.

Investigation of the factors which make certain rice-growing areas highly subject to malaria while others remain immune.

Study of African anopheles and the connection between the various species of anopheles and malaria in Africa.

3. MALARIA IN DELTAS.

Initiation or pursuit of research on the varieties of *A. maculipennis* found in European deltas in connection with malarial foci (Danube, Ebro, Rhine, Rhone, Po).

Investigation of the influence of agriculture on the domesticity of anopheles and on malarial endemicity.

Study of live-stock in connection with local anophelism and the disease.

Historical study with special reference to malaria of variations in the topographical and demographical characteristics of deltas.

Investigation of the degree of susceptibility to malarial infection of inhabitants of deltaic areas.

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THE RECLAMATION
OF THE PONTINE MARSHES

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The *Agro Pontino* is a vast plain in Central Italy, in the form of a quadrilateral, on the Tyrrhenian slope, extending from the massif of the Alban Hills to Monte Circeo, and from the Monti Lepini and the Monti Ausoni to the seashore.

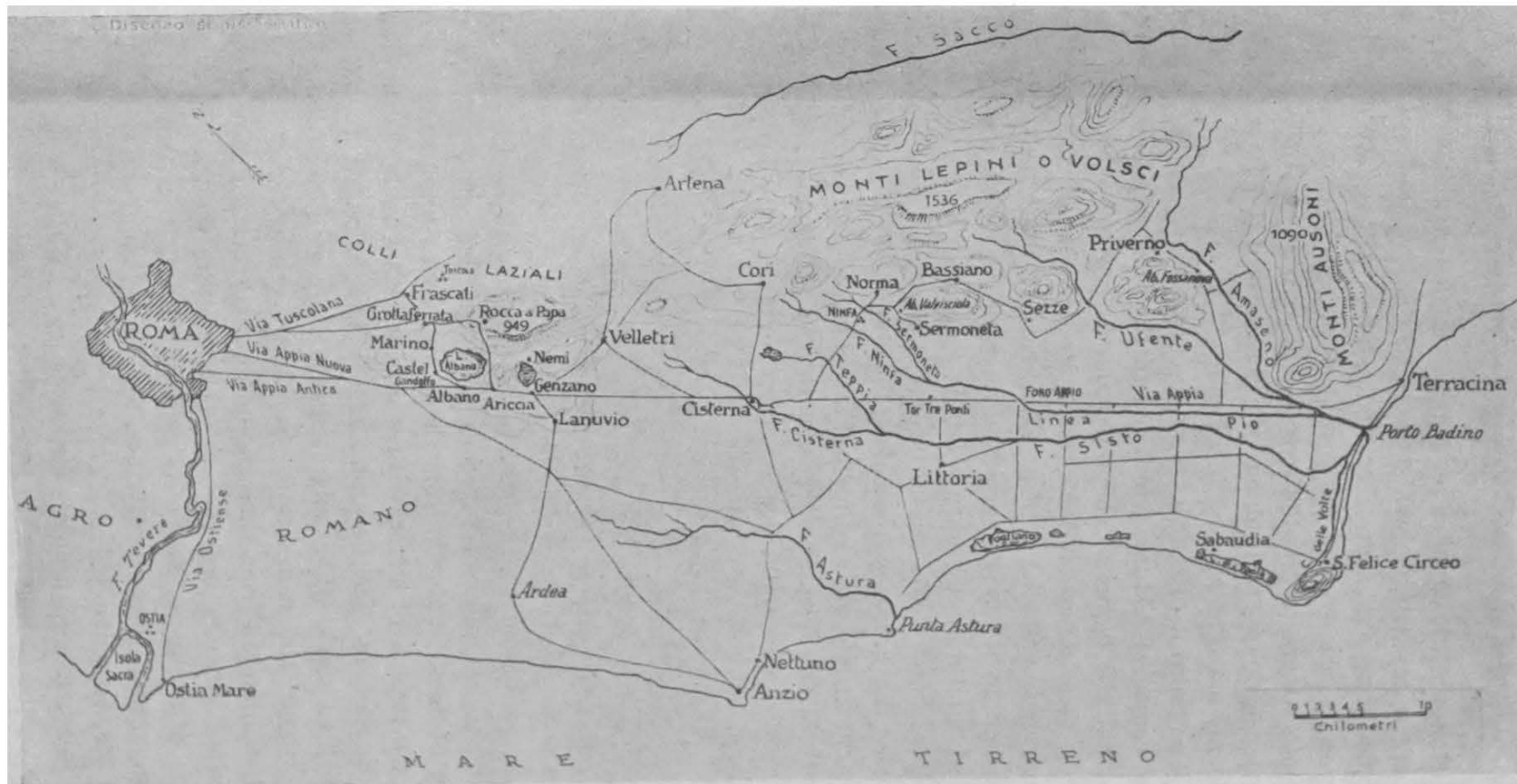
It varies in width from 30 to 8 kilometres, and its length, which exceeds 50 kilometres, is approximately that of the Via Appia, which forms its major axis (see map on page 159).

The area of the catchment-basin is calculated at 130,261 hectares, this including, in addition to the plain, the whole district bounded by the watershed of the Alban Hills to the north, by the crest of the hills of Lariano, and by the Monti Lepini, which, on the other side, feed the river Sacco. The area under reclamation has been fixed by recent legislation at roughly 80,000 hectares, or about 70 per cent of the entire area of the catchment-basin. An

enormous tract of land is thus being systematically dealt with, the collection and drainage of rain-water, the system of cultivation and alternation of crops, and the siting of houses being artificially regulated. The mission of French and Italian hydraulic engineers appointed by Napoleon I, which, under the direction of de Prony, made a study of the hydraulic system of the Agro Pontino in 1810, formulated the hypothesis that the great plain received, not merely the rain-water from the basin already mentioned, but also waters from the Sacco valley, which crossed the barrier of the Monti Lepini by means of subterranean siphons. The hypothesis proved to be unfounded, for the hydraulic improvements worked out and put into practice by Italian engineers during the last ten years were based on the assumption that only the waters of the natural catchment-basin need be collected and regulated, and they have been completely successful. There is only one distant source of water, and that is perfectly well known—from the river Amaseno, which flows down from the mountains around Frosinone to the plain of Terracina. It appears that below the bed of the river there runs a subterranean stream which indirectly influences hydraulic conditions at the surface.

The drainage of the surface waters of the Agro encounters numerous difficulties. In the first place, there is the insufficiency of the gradient immediately following a sharp declivity from 40 to 30 metres at the base of the Monti Lepini down to 5 to 1 metres, so that any loop or obstacle in the bed or along the banks of the natural watercourses can very easily produce stagnant waters and floods. The rain-waters also form swamps on the arable land, owing to the clayey nature of the soil and the nearness to the surface of the impermeable stratum, in consequence of which, through the greater part of the year, there is not sufficient dry land for growing crops, while the sheets of water provide excellent conditions for the growth of reeds and for the larvæ of mosquitoes. The position is further aggravated by the existence of a barrier following the axis of the territory, below and parallel to the Via Appia, attaining an altitude of 20 metres above sea-level. This is believed to represent the remains of an ancient coastal ridge of the quaternary era, which was formed in the gulf between the Alban Hills and the mountains of Terracina, and behind which, it is supposed, a natural process of silting gradually raised the

MAP OF THE PONTINE MARSHES.



bottom until it equalled and then exceeded sea-level in the higher part, near Cisterna, while it is still below sea-level over some 15,000 hectares near Terracina. Below the quaternary barrier again is the coastal ridge of the present epoch, running from Punta Astura to Monte Circeo. The part nearest the sea is still under swamps and under the lagoons of Fogliano, Caprolace, Monaci and Paola.

The natural difficulties were aggravated by gradual changes in the course of history, which led to the abandonment of the land, so that the banks of the watercourses ceased to be kept up, the fields were deserted, the ditches for draining off rain-water were neglected, and the whole plain turned into one huge swamp swarming with many species of mosquitoes, which there found an ideal habitat, and broken by tall woods, low scrub, bushes, reeds, and wide stretches of natural pasture-land. The situation was made even worse by unsuccessful attempts at correcting the water-system : the courses of certain rivers were changed, and they were diverted to unsuitable beds, with the result that floods became more frequent and wider areas were under water during the rainy season.



A memory of ancient prosperity hovers over this area, but it is not possible to draw the line between fact and legend.

The tribes of the Volsci are first met with in Livy in about 530 B.C. Tarquinius Superbus, the last King of Rome, took the city of Suessa Pometia from them, and levied upon them a tribute of 400 talents of silver, with which he began to build the Temple of Jupiter on the Capitol. The Volsci belonged to the Osco-Sabellian stock, which migrated into Italy over the Alpine passes. At about the same time—the sixth century B.C.—the Oscan tribes migrated from their mountain settlements in the Apennines to the Campania, and took the Greek city of Cumæ. In the early wars with Rome, the Volsci were allied with the Arunci, a group of mountain tribes who lived on the Monti Lepini and were followed by the Ausonian tribes. These latter gave to Italy one of her earliest names—Ausonia, which was used by the Greek navigators who visited this area early in the first millennium B.C. Tarquinius

Superbus also took from the Volsci Ardea, which was the home of the Rutuli, and sent Roman colonists to Signia and to Circæum, on the mountain of the same name; which is evidence that, from the sixth century B.C. the whole of the Pontine region was crossed by roads and cultivated. The origin of the name is highly controversial; the two most common views are that it is derived from *pontus*, the sea, or that the Latin name *Ager Pomptinus* has the same origin as the city of Pometia, and means a land rich in apples

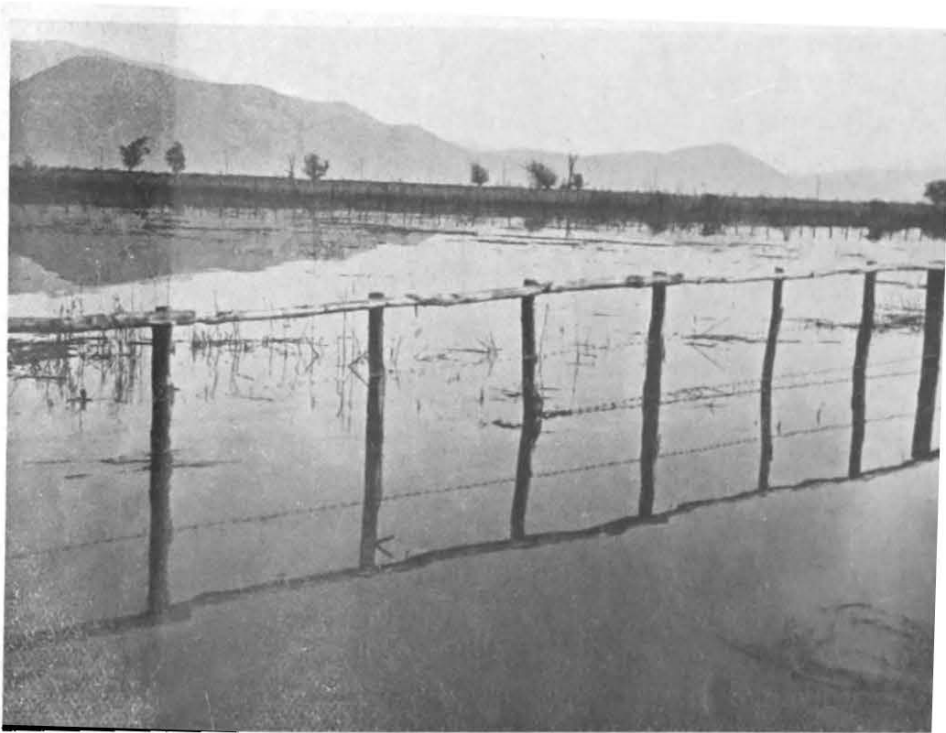


Fig. 1. — FLOODED PASTURE LAND NEAR TERRACINA.

(*poma*) and other fruit-trees. In the subsequent wars, which lasted two hundred years, mention is also made of the following other Volscian cities: Antium (the most powerful of all), Cora, Velitrae, Norba, Cenone, Ecetra, Artena, and Setia. Some of these Anzio, Cori, Norma, Artena, Sezze, are still in existence, and are situated either on the coast or on the hills which bound the plain. The site of others is disputed, as in the case of Suessa Pometia, which, according to Livy, could be reached in a night's march from Rome. This indication would seem to invalidate the theory that the city in question was in the heart of the area which

subsequently became marsh. Indeed, the reclamation works in the *Agro* have revealed no trace of any city, and it is therefore to be supposed that the land, though under intensive cultivation—so much so that the Romans had recourse to Pontine grain in periods of scarcity—was uninhabited except in the mountains and on the healthier borders. The only traces of drainage works are found on the quaternary dyke and on the coastal range, and no exact date can be assigned to them; they consist of a cut through to the trench known as Gorgo Lecino, at Foce Verde, apparently to take the waters of the north-western drainage channel to the sea near Antium; and a cut known as the Rio Martino, about halfway down, leading to the Lago dei Monaci.

In 347 B.C., three Roman armies invaded the *Agro Pontino* from different directions, one marching on Antium, one on Ecetra, and one on Anxur, in the extreme south of the region; this last-named city was captured, and subsequently took the name of Tarracina. It was, says Livy, *urbs prona in palude*, and from the imperfectly guarded marshes the soldiers entered the walls. Probably at that time the area that was more or less constantly under water was limited to the extreme south-east of the *Agro Pontino*, around the mouths of the Ufens and the Amasenus; and the level of the open plain is still so far below the sea that pumps have to be employed. The part nearer the Latian hills, however, was kept free of water by the careful upkeep of the channels. With the conquest of Anxur and the sending-out of military colonists to all the Volscian cities, control of the territory passed into the hands of the Romans, who also possessed themselves of the oldest road from Rome to Aricia over the Latian hills, and from Aricia along the foot of the Monti Lepini to Tarracina. The paving of this road with flints was begun by Appius Claudius Cæcus, who was Censor in 313 B.C. and took the work as far as halfway to Tarracina, to a point which was called Forum Appii in his honour, and is called Foro Appio to this day. His name was also given to the road, which was prolonged a century later by the Consul Cethegus, as far as Capua, and was of strategic value in the wars with the Samnites and Campanians.

Julius Cæsar had some idea of diverting the Tiber from its course in order to increase the amount of available building-land around Rome, and to raise the level of certain low-lying areas in the *Ager*

Pomptinus. According to Dio Cassius, he even succeeded in obtaining a decision from the Senate to that effect, but his projects were cut short by his death. It is, however, hardly to be imagined that he had any idea of reclaiming the land, and in any case the swampy area cannot have been very dangerous, seeing that a few years earlier the millionaire Lucullus had built an aqueduct to carry ferruginous water (now known as the Bagnara Aqueduct), and had a country house on the slopes of the *Circæum*, where some traces



Fig. 2. — TYPICAL FARM BUILDING AT THE FOOT OF THE MOUNTAIN.

of it still remain and are popularly believed to be part of the Palace of Circe. In the Lake of Paola he had fitted up his famous eel-breeding station, the tanks of which have been found in a very good state of preservation, although they have been centuries under water. Mention should also be made of the well-known passage in which Horace describes his journey from Rome to Capua. The first stop was at Aricia ; the second at Forum Appii, where he arrived towards evening, and, while others continued on the Via Appia, he embarked on a barge which was drawn through a network of inland canals by mules walking on the bank ; and,

annoyed by the croaking of the frogs and the buzzing of the mosquitoes, he arrived towards dawn at the spring of Feronia, three miles from Tarracina. Such was the condition of the *Agro* in the Augustine age.

Antium was Nero's favourite residence, and he toyed with the idea of a navigable canal from the Tiber near Ostia to the *Ager Pomptinus*, with an extension to Baiæ, the great naval port of the Empire. Domitian had a private villa near Aricia, and was closely acquainted with the region at the foot of the Monti Lepini, where works were projected to prevent the lower-lying parts of the Via Appia from remaining under water for months at a time in winter. These works were begun under his successor, Nerva, and completed under Trajan ; the bridge over the river Sisto at the place called Tripontium (later Tor Tre Ponti) is still intact and used for its proper purpose ; it bears the name of the great Emperor. Subsequently, the *Ager Pomptinus*, like the *Ager Romanus*, suffered to an increasing degree from the effects of a grave social development against which the Roman Empire put forth its utmost efforts in vain—the decline in the birth-rate. The great families died out, and with them their inherited tradition and mentality. The labourers were no longer local peasants, but slaves under the direction of freedmen ; and later these also began to die out, and foreigners had to be enrolled in mercenary armies to defend the country. Rural districts were more and more deserted, and rational agriculture was supplanted by semi-wild conditions ; where the waters were not regulated, swamps and malaria prevailed. At the fall of the Western Empire, the population of Italy was calculated at less than six millions.

Attempts were made to counter these developments, to lift the deadly pall that was spreading over so large a part of the most fertile land, from which the most advanced cultivators in the world had drawn wealth for so many centuries. In the case of the *Ager Pomptinus*, the Gothic king Theodoric, being anxious to restore the Via Appia, which was indispensable as a line of communication with Campania and Southern Italy, made the Roman patrician Cæcina responsible for its upkeep and for reclaiming the marsh at his own expense, in return for which he was to retain the ownership of the reclaimed land. Cæcina carried out the works and obtained some results, which lasted during his lifetime ; but all

efforts were abandoned when the Goths were defeated by the Byzantine troops on the slopes of Vesuvius and had to leave Italy a bare half-century after their invasion. As witness of these efforts there remained the Temple of Jupiter on the mountain which dominates Terracina and the Via Appia ; it was designed as a fortress, and still bears the name of "Theodoric's Castle". The Popes attempted to stimulate reclamation work about the eleventh century by means of *domus cultæ*—monasteries of labouring monks,



Fig. 3. — CHARCOAL-BURNERS IN FRONT OF THEIR HOUSES.

around which were grouped the buildings essential for a peasant village. Hence arose the Abbey of Valvisciolo, on the edge of the marsh, on the slopes of the Monti Lepini near Sermoneta ; the Abbey of Triponzio, in the heart of the marsh, not far from the ancient Setia (now Sezze) ; and the Abbey of Fossanova, in the southernmost part of the marsh, near the place now known as Priverno, to which St. Thomas Aquinas retired to die of anasarca, apparently due to chronic malaria.

At the beginning of the sixteenth century, Pope Leo X conceived the idea of reclaiming the marsh at his own expense, using for the

purpose the immense capital of the Medici family, and he entrusted the task to his brother Giuliano. The work was started in the neighbourhood of Terracina, a short outlet canal being dug to lead off into the sea the waters surrounding the settlement ; this, known as the Canale Portatore, still exists, and runs into the sea not far from the town, at the place called Badino.

Towards the end of the same century, Pope Sixtus V caused works to be carried out with the object of protecting from the waters at all events the higher part of the plain, below Sermoneta, and the depression along the base of the Monti Lepini. The bed of an ancient watercourse, which crossed the plain from north-east to south-west, from Ninfa to Terracina (reaching the sea between Terracina and the Circeo), was excavated and corrected. In particular, the left bank was raised, and the river was given the name of Fiume Sisto, which it still bears. It is of fundamental importance to the hydraulic system of the region.

After investigations and attempts by other Popes, the works were resumed in 1777, on the initiative of Pius VI. A new longitudinal canal known as the "Linea Pio" was dug, parallel and adjacent to the Via Appia, from Foro Appio to the Canale Portatore, which discharged its waters into the sea. To right and left a new hydraulic system was created, in the form of a series of minor canals parallel to the Linea to collect the rain-water, and cross-canals at intervals of one Roman mile, known for that reason as "mile ditches" (*fosse miliare*), to lead these waters into the Linea. The Via Appia was thus made permanently high and dry, and was restored ; large tracts of land were uncovered, but they lay so low that their condition depended entirely on the level of the Linea, which in turn depended on the tides and the upkeep of the canal. In addition, the torrents that came down from the mountains of Norma and Sermoneta—the Cisterna, the Teppia, the Ninfa, and the Sermoneta brook—were also to be led into the same canal. As, however, the new canal very easily silted up; they were diverted into the Sisto, but the bed of the latter was not deepened in its lower reaches, so that floods and stagnant water became more frequent and prolonged even in that part of the *Agro* which had formerly been dry. In the southern part, a new bed was dug for the river Ufente, but part of the water continued to follow the old bed.

In February 1787, Goethe, travelling by coach from Rome to Naples, looked down from the heights of Velletri on the Pontine marshes, and saw them traversed by passing clouds discharging showers of rain, alternating with bursts of sunshine. The vast plain appeared deserted ; the only signs of life were a few huts made of marsh reeds and stubble, from which tenuous threads of smoke rose into the sky. The next day he passed along the road from Cisterna to Terracina, stopping only for a moment at the

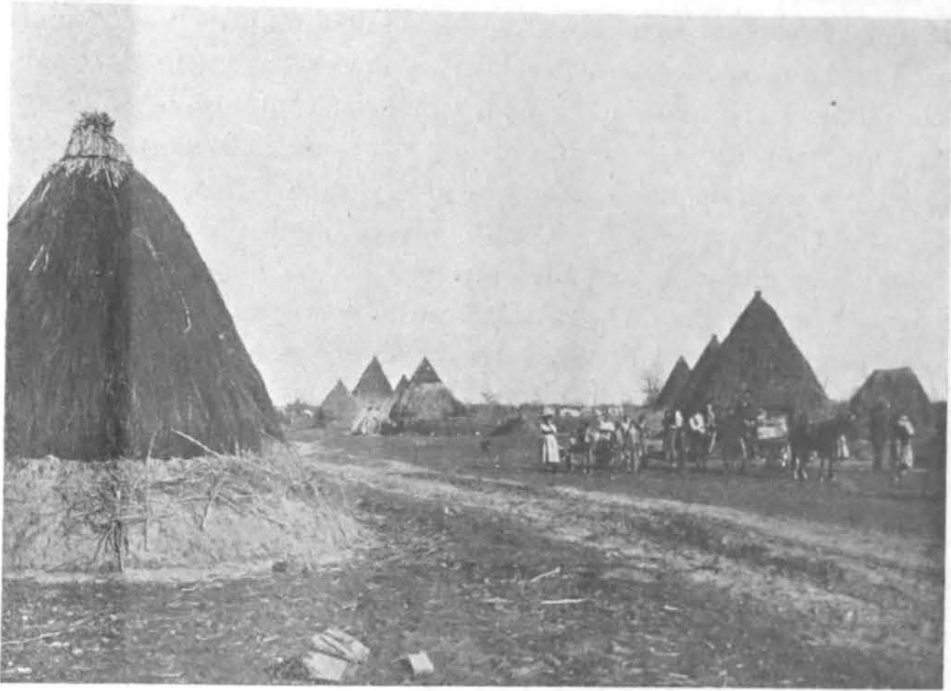


Fig. 4. — VILLAGE OF REED-HUTS (*lestre*).

Sezze posting-station to change horses. A bluish vapour hung over the countryside, and was interpreted by the passengers as a tangible proof of the legend of its deadliness ; they endeavoured not to sleep, and to keep the windows closed, to prevent the mephitic air from penetrating into the coach. The only living creature was a white horse, which Goethe's travelling-companion, Tischbein, hurriedly drew. The poet looked over the countryside and saw it covered with bright flowers, heralding the early Campanian spring, whereas he had left behind him in Rome the cold of winter ; and in the neighbourhood of Terracina, as the outline of Monte Circeo gradually became clearer, Indian fig-trees, intermingled

with pomegranates and olives, grew more and more frequent—the emblem of an exceedingly fertile land ready to burst forth into exuberant life as soon as the touch of a lucky hand should have liberated it from the terrible disease. He found good reason for hope in the reclamation works that Pius VI had initiated.

* * *

After the studies carried out at the instance of Napoleon I, in 1810, by a commission consisting of Fossombroni, de Prony, and a number of experienced agriculturists, it was not until 1817 that Pope Pius VII initiated the policy of legal compulsion, ordering that an association of landowners of the *Agro Pontino* should be formed to continue and extend the work begun by his predecessor. The association was not actually formed, however, until many years later—in 1862—and then received no financial aid from the Papal Government. When the latter was succeeded by the Italian Government, the efforts were intensified and speeded up under the pressure of statesmen and scientists, especially after the discovery and proof, with the help of distinguished Italians, of the life-cycle of the malaria parasite within and without the human organism, which made it possible to elucidate the epidemiology of the disease, to ascertain the reason for its persistence in the endemic state among the populations of certain areas and for its epidemic outbreaks, and to lay down rules for the execution of the works. It may be well to mention at this point, as a background for the subsequent work, that, during the first ten years of the twentieth century, Italy delimited, with the help of doctors and engineers, all the “zones of endemic malaria” in her territory, made an accurate survey thereof with considerable legislative consequences, established the State factory for the preparation of reliable quinine, and provided every facility for its distribution to the inhabitants of the malarial zones, thus bringing about an enormous reduction in the malaria death rate.

At that time, however, the fundamental principle that the hydraulic system must be indissolubly linked with rational cultivation and with the protection of the peasants' health was not yet grasped. Hydraulic, agrarian and human “bonification” are three parts of one whole, which, by a recent Italian enactment

(1928), has been called *bonifica integrale*. The principle thus enunciated in the law had had but one pioneer, in the person of a great physician Guido BACCELLI, who in 1910 obtained sanction for a scheme of bonification of the area surrounding Rome, which provided not only for the systematic regulation of the surface waters, but also for the erection of peasants' houses, the building of roads, and the organisation of adequate health services. It was he who taught that "the only way to reclaim malarial land is to

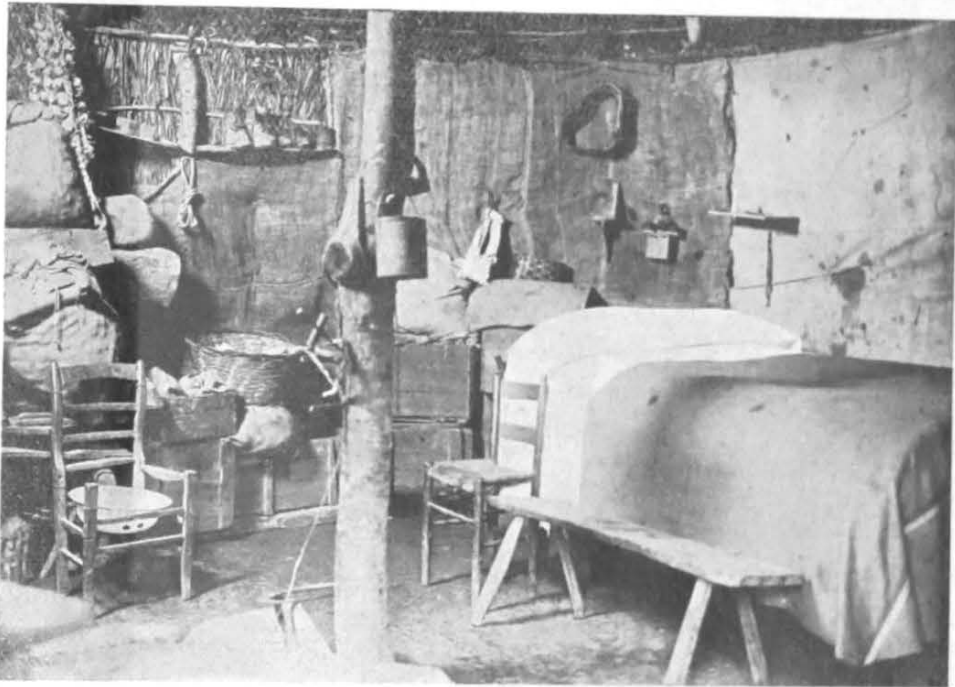


Fig. 5. — INTERIOR OF SHEPHERD'S COT.

settle the peasants on it, and the best weapons against malaria are the ploughshare and the spade". He gained little support, however, outside the medical profession, and the works which he projected in the area surrounding Rome dragged on for years, because sufficient funds were not forthcoming.

Almost down to 1930, conditions in the *Agro Pontino* remained very similar to those that Goethe had seen. The only settled population was on the slopes of the Monti Lepini. They went down to cultivate the nearest tracts of land as far as the Via Appia; but their crops were poor, owing to winter floods. They lived in round huts of marsh reeds, and malaria was so widespread that 80 per

cent of the population of Sermoneta suffered from enlarged spleen, and nearly 50 per cent of the young men of Sermoneta, Sezze and Terracina were rejected for the army on account of chronic malaria, infantilism, etc. The tract of land from the Via Appia to the coast ridge between Punta Astura and Monte Circeo was uncultivated ; part of it was natural pasture, ranged by herds of horses or buffaloes, part was low scrub, and in the neighbourhood of Circeo were the forests of San Donato and Terracina ; a very large part was under water in winter and covered with reeds in summer. There were shepherds who stayed there from October to May, living in huts grouped in tiny hamlets, lost to the civilised world, to which the name of "lestre" was given. Figs. 1 to 5 give a rough idea of these conditions ; the photographs date from 1924. In June, the marsh was deserted ; shepherds and charcoal-burners fled to the mountains, where they often fell ill of malaria which they had contracted in the warm months of spring ; and the few inhabitants of the neighbouring villages who ventured upon the Via Appia took good care not to stay there after dark, because it was known that the marsh fever took so firm a grasp of a man that it ultimately destroyed him, and there was talk of cases of pernicious malaria which speedily led to fatal results. This landscape of desolation and death was dominated by a luxuriant growth of vegetation. The most superb examples were the Ninfa district—well known to every painter—with its plants of every kind clambering over and adorning the ruins of a city suffocated by malaria ; and the Fogliano district, rich in palms, with an amazing growth of vegetation of the subtropical type.

Here began the apostolate of the doctor and the teacher. Angelo CELLI, a distinguished hygienist, to whom, in conjunction with Marchiafava, we are indebted for some very important discoveries in the biology of the malaria parasites, and Giovanni CENA, the poet of the desolate plains around Rome, undertook on foot a laborious tour of the *lestre* and the huts. The doctor carried, slung over his shoulders, a bag containing quinine, which he dispensed free of charge for purposes of prophylaxis and treatment. The poet had in his knapsack a little food and an elementary reader, and wherever he found children he stopped and gathered them round him to teach them to read and write, to relate in homely speech the history of Italy, and to tell them how to avoid malaria.

Faith in an idea is always man's most powerful force, because mind is greater than matter. Where Emperors and Popes had failed, the apostle and the poet—two dreamers, two seekers after Utopia—scored an initial success (Fig. 6). In 1908, the Italian Red Cross, financed by the Government, established on the deadly plain a steadily extending network of health services (Figs. 7 and 8).



Fig. 6. — CELLI AND CENA WITH A PEASANT FAMILY.

As early as 1904, the Italian Women's Union had founded schools in the country surrounding Rome for the children of the semi-nomadic shepherds and labourers. These schools were legally recognised in 1911, and collected around Cena a nucleus of volunteers forming an organisation under the name of "Peasant Schools", for the purpose of establishing the poet's personal work on a systematic and permanent basis, in order to carry education to places which the communal elementary school could not reach (Fig. 9). The two organisations combined to operate a regular medical and educational service in 1923, and continued the work

of civilisation after the two pioneers had disappeared from the human stage. Down to 1928, it is true to say that the small school and health-station buildings represented the sole germs of the new history that was preparing, and, in association with the general rise in the standard of living of the Italian people, which was felt even by the Pontine population, they achieved notable successes. The anophelines of the area were carefully studied, and FALLERONI distinguished new varieties and propounded notable theories, the importance of which was to be quickly recognised when, in the succeeding years, the scheme of comprehensive reclamation was organised. To take one instance: in this area the previous year's insects survive and sting men even in January and February, while the new generations begin to leave the egg in March, so that there is practically no break in the life-cycle of the vector insects, which explains the high malarial endemicity of the zone. The Pontine malaria parasites were also studied, and it was found that there was a great predominance of the dangerous *æstivo-autumnal* form, whose strains are even more virulent than those of Indian origin, as has lately been confirmed by JAMES's observations. Meanwhile, the semi-nomadic population of the *Agro* was brought under supervision; illiteracy was disappearing; the annual number of new cases—primitive forms—was reduced to less than 1 per cent of the population under observation; deaths from pernicious malaria became almost unknown; the shepherds and charcoal-burners, when they returned to the mountains in summer, were followed up and treated; and the rejections for the army on account of malaria were reduced to less than 5 per cent. Relapses, however, were still numerous, and endemicity persisted. With the return of confidence, attempts at rational cultivation were made; they were successful without any serious damage to health, by the unaided efforts of the peasants, in the tracts of land nearest to centres of population on the edges of the marsh. This applies especially to the planting of vineyards, under the stimulus of the high prices obtainable for grapes and wine, because viticulture requires the soil and waters to be kept in perfect order.

On the other hand, the attempts made in the heart of the marsh were unsuccessful, although considerable resources were employed. Some hundreds of hectares placed under rice yielded an excellent



Fig. 7. — THE RED CROSS DOCTOR AND SICK ATTENDANT ON THEIR ROUNDS IN THE FLOODED PLAIN.



Fig. 8. — MEDICAL CONSULTATION IN THE OPEN.

crop, but there were 100 per cent of malaria cases among the specialist labourers imported from areas in the Po Valley ; certain attempts to improve the land by the *métayer* system had to be abandoned, on account of the condition to which the labourers were reduced after their first few months on the dangerous ground. It was found, indeed, that, when the crops failed owing to bad weather, the *métayer* families were in serious financial position, and the quinine treatment of malaria cases had so little effect that there was talk of quinine-resisting forms. Yet as soon as an economical food kitchen was organised and diet thus improved, the drug took its usual decisive effect ; which is plain evidence of the close connection between medical questions and economic factors, and shows that malaria is undoubtedly to be classed as a social disease.

I advanced this conclusion at a meeting of farmers held at Foggia in 1928, using this very example of the *Agro Pontino*, and pointing out that here medicine had made every possible effort, and had obtained results that had perhaps never been secured before, inasmuch as deaths from pernicious malaria had been eliminated, original infections had been reduced to a minimum, and it had been made possible for the peasant to live. But things had come to a standstill, and it had been impossible to stamp out malaria, because that is beyond the power of medicine alone ; it can only be done by close co-operation between the hydraulic engineer, the farmer and the hygienist. These assertions were not remote visions, or predictions, but deductions from a plan that was already in full operation ; for, by a law of 1923, the Fascist Government had already extensively modified the traditional idea of "bonification" by including, among works having a claim to Government support, not merely hydraulic improvement works, but routes of access, housing schemes, peasants' villages and schemes for supplying electric power for agricultural machinery. It included also schemes for dealing with small drainage channels and pieces of swampy ground, which can easily be put right with a little spade-work and careful upkeep, no large hydraulic plant being required ; works of this kind are known as "minor improvement works" (*piccola bonifica*).

A law of 1924 gave the authorities power to make changes in the system of land tenure and to subsidise the work involved

because, owing to centuries of subdivision among heirs, the landed property in certain areas had become parcelled out into tiny portions on which it was impossible to carry out any rational cultivation or to arrange for drainage. It was therefore necessary to redistribute these properties on a new basis, if they were to be properly exploited and the causes of swamp-formation eliminated.

A law of 1928 defined the practical programme of "bonification" over a great part of the malarial area, and the Act of 1933

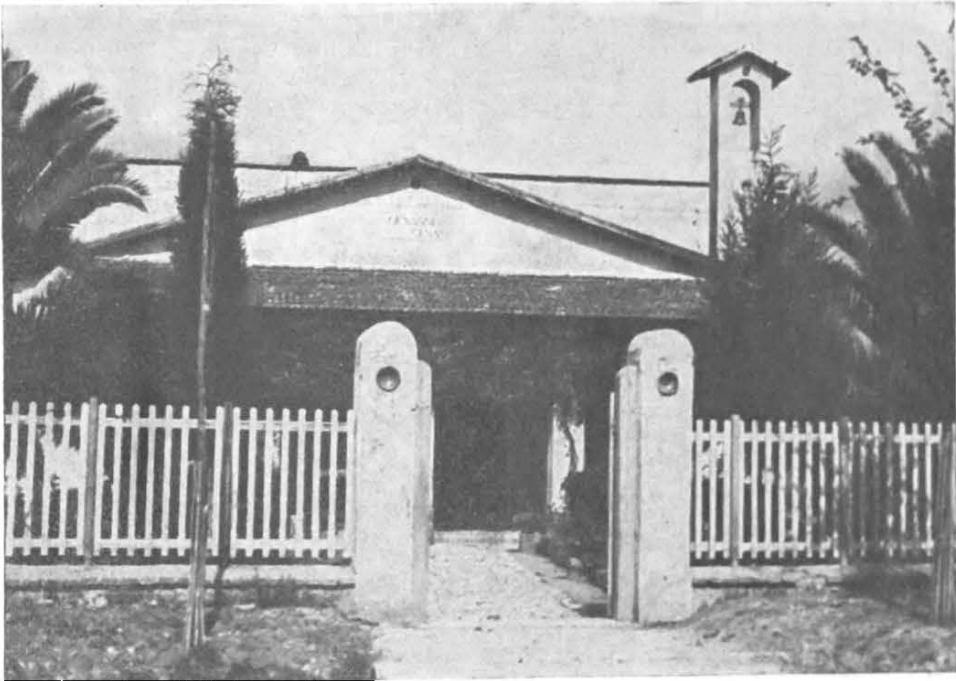


Fig. 9. — THE "GIOVANNI CENA" SCHOOL OPENED IN 1921 AT 11 KM. FROM CISTERNA.

consolidating the bonification laws combined all these provisions, and added the important principle that such schemes must cover the planning, financing and operating, not merely of the hydraulic and agricultural works, but also of the health services required to preserve the health of labourers, peasants, and superintending staff, without which every attempt must end in disaster. Such is the legal conception of the *bonifica integrale*. This comprehensive reconditioning of the land has been extended to parts of Italy which a tradition of dread had placed outside the human community; work has been made possible for the strong, numerous and sober

mass of Italian labourers, who no longer emigrate, but stay and cultivate the soil of their own country. An admirable practical example has been set by the National Ex-Servicemen's Association—an organisation formed with large resources during the concluding months of the war—which, during the last ten years, has been actively engaged in procuring land and employment for men who fought in the great war; it has acquired the ownership of unhealthy lands, reclaimed them, developed an excellent system of intensive cultivation, and distributed them in small holdings.

This historical and social panorama is the background against which the comprehensive reclamation of the *Agro Pontino* is proceeding.



The problem of the Pontine marshes has always been present in the minds of Italian statesmen, as is shown by the laws passed in 1899, 1909, 1912 and 1913. In these laws the draining of the marshes was assigned to the first category of important public works, to be carried out by associations of landowners, but with powerful financial support from the State. Before the war, up to the end of 1913, the Government grant was fixed at 7 million lire—*i.e.*, an average of less than 90 lire per hectare of land to be reconditioned. No provision was made for agricultural improvement—a matter left to the discretion of the owners—or for health services.

The basic survey which forms the foundation of the present drainage work in the Pontine region was made in 1918 by officials of the Office of Works (*Genio Civile*). It was seen that the Ninfa-Sisto stream divided the area into two sectors, each presenting different problems. The area lying between the southern two-thirds of the Monti Lepini and the left bank of this stream forms a huge irregular triangle, the base of which runs along the sandy shore at Terracina and the Canale delle Volte that follows the line of the coast. This sector was called the "Terracina bonification area" and later the "Pontine bonification area", and includes about 27,000 hectares. The rest of the plain forms the "Piscinara reclamation area", embracing 49,300 hectares, as defined in the 1933 law—*viz.*, between the northern part of the Monti Lepini in the direction of Cori, the right bank of the Ninfa-Sisto, and the coast

between the mouth of the Foce Verde and Torre Olevola, including the Monte Circeo massif. Work in both areas was begun by associations of landowners ; both were soon placed under one Government Commissioner, who became responsible for the work. The following are the main points of the Pontine bonification scheme :

Total area coming under the scheme, 27,000 hectares (area of natural drainage, 13,000 hectares ; area of artificial drainage, 14,000).

Classification of heights : from 20 metres to 6 metres, highlands and lands of medium altitude ; from + 6 metres to — 1.5 metre, lowlands.

Length of main drainage canals, 120 kilometres.

Length of secondary drainage canals, 250 kilometres.

Length of bonification roads, 250 kilometres.

Fourteen pumping-stations with a capacity of 50,000 litres a second.

Estimated cost, 300,000,000 lire.

Work began in 1924. By the end of 1933, all natural water-courses running through the region had been regulated.

There had been completed : 315 bridges and 120 kilometres of roads forming a three-kilometre-mesh network. When the work has been completed, each mesh will be one kilometre and a-half in breadth.

Eight pumping-stations had been erected for the draining of 4,500 hectares of lowland.

Three million cubic metres of earth had been displaced ;

Guard-houses, depots, workshops, garages, etc., had also been built.

The programme for the Piscinara sector is as follows :

Total area coming under the scheme, 49,300 hectares.

Area of natural drainage : upper waters, 9,600 hectares ; medial waters, 29,500 hectares ; lower waters, 8,700 hectares.

Area of artificial or mixed drainage, 1,500 hectares. Classification of heights : from 100 metres to 40 metres (including a few mountain zones) ; ground with natural drainage, from 20 metres to 8 metres ; ground with artificial drainage, from 1 metre to sea-level.

Length of main drainage canals, 150 kilometres.

Length of secondary drainage canals, 300 kilometres.

Length of bonification roads, 230 kilometres.

Workmen's villages, 7.

Four pumping-stations with a capacity of 8,000 litres a second.

Estimated cost, 300,000,000 lire.

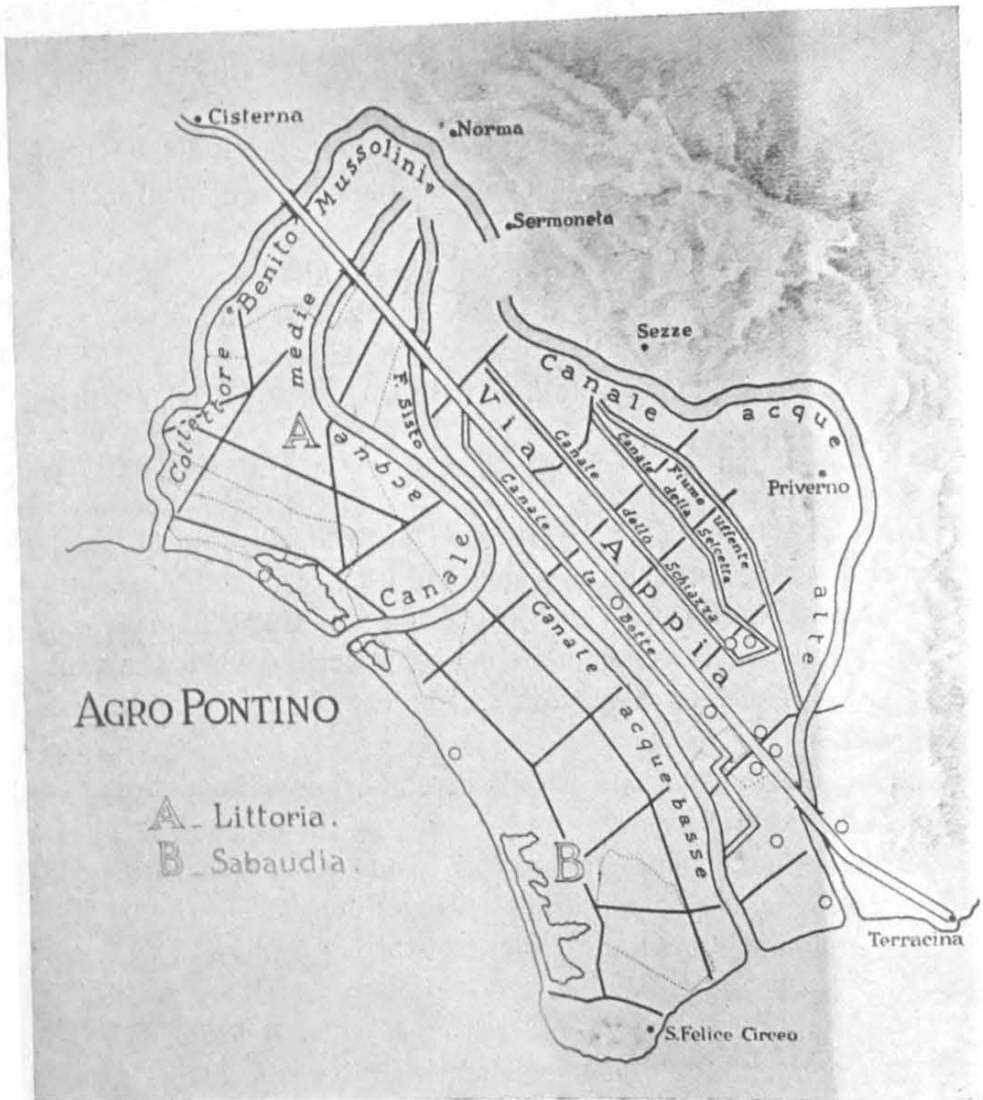


Fig. 10. — MAP OF THE BONIFICATION AREAS.

Work was begun in 1927. By the end of 1933, the network of open drains and main drainage canals for the upper and medial waters had been completed and the lower waters had been inducted

into the Sisto. Thus, throughout almost the whole region, floods and the formation of stagnant pools were eliminated, and it became possible to cultivate the land behind the quaternary dyke and between that dyke and the coast ridge and to found the town of Littoria. In the lowest-lying tract, behind the sand-dunes along the sea-coast, the small marshes are being either drained or filled in. The coastal lagoons are being left, but with their banks regularised and strengthened to prevent floods. When the



Fig. 11. — THE MUSSOLINI CANAL UNDER CONSTRUCTION, WITH ITS CENTRAL RUNNEL.

undertaking is completed, the spoil will total 20 million cubic metres ; at present, 150 kilometres of railway, including 30 kilometres of electrified line, are in operation. At the foot of the Monti Lepini there are perennial springs with an outflow of 20 cubic metres per second ; these will be used for irrigation during the dry season. Experience gained in similar undertakings in other parts of the country has shown that the system established for carrying off rain-water in the cold season can perfectly well be also used for irrigation purposes in the summer. Thus the ground

can be fertilised and utilised to its full extent without any danger of the breeding of anopheles and consequent malaria.

The cost of the work, which exceeds 5,000 lire per hectare, has, in view of the great sanitary and social benefits to be derived from the undertaking, been borne by the State. The owners of the land are required to pay only 30 lire per hectare over a period of thirty years—*i.e.*, 900 lire in all.

* * *

Novel and decisive action was taken by the Head of the Government when he called upon the National Ex-Servicemen's Association to carry out the programme of agricultural land improvement and the re-population of the zone. The owners of the land on which the drainage works were to be completed were either large estate-owners or collective entities, who hesitated to sink much capital in the inauguration of new farming methods and to win the land to productiveness by building farmhouses for the peasants and providing agricultural machinery, live-stock and selected seeds. The land uncovered was left as natural pasture, and no attempt was made to drain off rain-water or adduct it into canals. Consequently, owing to the nature of the soil, the humidity continued to be very great in the various sectors, small stagnant pools remained on the surface, and the anopheles continued to breed. A few isolated and unco-ordinated efforts were soon abandoned.

On August 28th, 1931, about 18,000 hectares of land were, by Royal decree, bestowed in full ownership on the National Ex-Servicemen's Association. This great public utility organisation had no need to concentrate upon sheer economy, except for seeing that the money was properly expended with a view to achieving final success. The association provided considerable funds and a still greater asset in the persons of technical experts of long experience, whose work had been crowned with success in other parts of Italy—men skilled in the art of planning, management and execution. On November 10th, when all formalities for the transfer of ownership had been completed, the laying-out of the first 10,000 hectares for agricultural purposes began. The first act was to clear the land of the stumps of brushwood, which made ploughing impossible.

This work, rapidly carried through by blasting, opened up 6,280 hectares for farming.

Most of this first parcel of land was situated within the Piscinara reclamation area, only 380 hectares falling within the limits of the Pontine sector, on the left bank of the Sisto. When the work began, the canalisation of the upper waters had already been completed. These waters were collected and brought down to the sea by the great Mussolini drainage canal, so that there can be no



Fig. 12. — SETTLERS' HOUSE.

backwash and consequent flooding. At that time also—the work was subsequently completed at a rapid pace—the medial waters were adducted into the old bed of the Rio Martino, which cuts through the quaternary ridge, and the lower waters were collected into the Sisto. When the brush had been cleared, the farmers had at their disposal a clay-limestone soil towards the hills and a clay-sandy soil towards the sea, thickly dotted with small swamps or ponds (*piscine*, from which the name of the region Piscinara derives) in slight depressions rendered impermeable by clay deposits.

The National Association first set about dividing the land into holdings, building 515 farmhouses and settling as many peasant families thereon, and instructing the peasants in rational farming methods, so that each family might become the owner of its farm, within the time-limit of one year set by the Head of the Government.

The average size of each holding was fixed at 10 hectares for the very fertile lands nearest to the Via Appia, and 25 hectares for the poorer lands towards the sea. The holdings were divided up in accordance with the boundaries formed by watercourses and the bonification roads. Inter-farm drains were adducted into the general drainage system under the scheme to drain such pools as could not be filled in, with subsidiary ditches every 40 metres, to ensure that the ground should be sufficiently dry to allow plants to grow. After the weeds and tree-stumps to a depth of 90 centimetres had been destroyed, powerful and deep-furrowing motor-ploughs were used to turn up the soil.

Each farm-building includes a dwelling-house built on a damp-course and comprising a ground-floor kitchen and storeroom and one upper story with three to five bedrooms and living-rooms, the doors and windows screened against flies and mosquitoes; a stable for eight to ten head of live-stock, in some cases built up against one wall of the dwelling; a chicken-run and pigsty; a well of fresh water for domestic use; a cesspool and a manure-heap.

There are also artesian wells—from 20 to 60 metres deep—for drinking-water, and plans are under consideration for the construction of a rural aqueduct.

The National Association bears the cost of preparing the soil of each farm, of buildings, live and dead stock, and the farm-tracks which form a very close network inside the wider network of roads constructed under the scheme. The farm is handed over to the peasant immediately all this work has been completed. Furthermore, the National Association has established five experimental farm centres to advise the peasants and direct their work.

The following figures for these first 10,000 hectares of reclamation works will give some idea of the vast preliminary labour involved :

Farmhouses, 515. Area covered, 10.5 hectares. Cubic space under roofing, 460,000 cubic metres. Walling, 71,100 cubic metres.

Roads : Main bonification roads, 11 kilometres. Inter-farm roads, 95 kilometres. Farm-tracks, 254 kilometres. Total, 360 kilometres.

Drainage canals : Main bonification canals, 52 kilometres. Secondary and tertiary canals, 358 kilometres. Total, 410 kilometres.

Constructional works : Manholes, 650. Foot-bridges, 87.

Material employed : For buildings and constructional works, 36,000 cubic metres. For roads, 800,000 cubic metres. For canals, 500,000 cubic metres. Total, 1,336,000 cubic metres.

| | Lire |
|--|------------|
| Cost of work contracted for by tender..... | 32,000,000 |
| Average cost of main bonification roads (per km.)..... | 75,000 |
| Average cost of farm-roads (per km.)..... | 3,000 |
| Average cost of canals (per km.)..... | 6,500 |
| Average cost of farm-buildings (each) | 40,000 |
| Cost of purchase and preparation per hectare : | |
| Average purchase price | 800 |
| Destruction of tree-stumps, clearing up, ploughing and levelling..... | 1,300 |
| Farm-houses and dependencies..... | 1,800 |
| Inter-farm roads and bonification roads | 325 |
| Drains..... | 175 |
| Total..... | 4,400 |

The first new buildings in the *Agro Pontino* were the workers' villages built by the authorities in charge of the hydraulic bonification works. The workpeople who built these villages were at first housed in the villages and hamlets along the slopes of the Monti Lepini, and were taken to their work in motor-coaches. When the houses had been built, the workmen lived in these until they had finished their work. They then handed them over to the settlers brought in to carry out the agricultural bonification. In 1929 and 1930, there thus sprang into existence the country townlet Doganella di Ninfa, near the rose-covered ruins of the ancient city destroyed by malaria, as well as the groups of houses in the more northerly part of the Piscinara sector, not far from the town of Cisterna.

The National Ex-Servicemen's Association needed a whole army of workmen to prepare the peasants' farms. On an average, 5,000 persons were employed for 1,500,000 days : navvies, levellers, masons, cement-workers, carpenters and joiners, ironwrights, carters, etc. The workmen are recruited and selected through the Labour Exchanges by a special body—the Commissariat for Internal Migration, attached to the office of the Prime Minister. The National Ex-Servicemen's Association takes them into its care and officers them with engineers, agricultural experts and tech-

nicians, to form the fighting units of this army of labour. In the early days, temporary hutments were put up by the contractors ; later, the Association itself undertook to construct huts for groups of from 500 to 2,000 workmen and to provide the elementary needs of life : damp-proof paved dormitories, each covering 140 square metres, with a glass surface of 40 square metres, windows and doors protected by wire netting, adequate ventilation and separate camp-beds ; common kitchen and dining-room ; bathrooms, douches and water-closets ; well, with raised reservoir and distribution conduits ; club-rooms for spare-time activities, in which the workmen could forgather and amuse themselves in their leisure hours.

Special squads are responsible for regular cleaning, protection against flies and the destruction of mosquitoes in the various premises. The vanguard constructed the huts ; the first batch on the spot were workmen who constructed the houses and prepared the farms. The dwellings are built along the roads in groups, and are named after the places in the mountains and along the rivers of Veneto which became famous during the war (Borgo Carso, Borgo Grappa, Borgo Piave, etc.), instead of the former ill-omened place-names of the Pontine district.

Then came the peasants ; the first nineteen families of war veterans took possession of the new farmsteads on October 27th, 1932, less than one year from the starting of the agricultural bonification.

Meanwhile, a town was growing up. On April 4th, 1932, the Head of the Government, present in person at the inauguration of the spring programme, announced the forthcoming creation of the Commune of Littoria. On June 30th, the foundation-stone of the town hall was laid. On December 18th, the new commune was officially constituted with appropriate ceremonial. The nearness of these dates is evidence of the rapidity of the work. In the centre of the town is the square, which was formerly one of the most malaria-ridden spots in the region. On November 1st, 1931, there were merely a few houses constituting a bonification-work village with 1,192 permanent and 821 temporary inhabitants ; when Littoria came into existence, it already had 6,308 permanent and 11,492 temporary residents.

In the speech which he delivered at the inauguration of the Commune of Littoria, the Duce explained to his hearers what still remained to be done. The following are the most noteworthy passages of the speech :

“This day is a red-letter day in the history of *Agro Pontino*. It is a day of triumph for the whole nation.

“What twenty-five centuries attempted in vain we now see accomplished before our eyes. At such a time we might well feel proud, and yet it is rather emotion that stirs our hearts ; as they march past the names that recall the Grappa, the Carso, the Isonzo and the Piave, those who lived through the great and tragic days of the victorious war feel old memories re-awakening.

“To-day, when officially inaugurating this new Commune of Littoria, we may tell ourselves that the first stage on our road is safely passed ; we have won our first battle, but our eyes are fixed steadfastly on the future.

“Until we have won the last battle of all, we shall not be entitled to claim final victory. Only when 5,000 houses stand where you see 500 to-day, only when to the present population of 10,000 we have added the forty to fifty thousand whom we intend to settle on this soil which was once the Pontine Marshes, can we proclaim to the country that our victory is complete.

“On October 28th, 1933, we shall inaugurate 981 new homes for settlers ; on April 21st, 1934, we shall inaugurate the new Commune of Sabaudia, and on October 28th, 1934, the third Commune—Pontinia.

“By then probably we shall have achieved our aim and carried through our plans to a successful issue.

“Formerly, to find work we had to pass the Alps or cross the ocean. Now the land is at our doors, within half-an-hour of Rome. It is here that we have conquered a new province, here that we have waged, and shall continue to wage, a real war, the kind of war we prefer.”

This first great success could never have been achieved, nor could the work have been continued, without adequate sanitary and medical services, the organisation of which was no easy task.

From 1920 onwards, there had been, in the *Agro Pontino*, five Italian Red Cross health stations for the treatment of all diseases, but primarily malaria, amongst the population of shepherds and charcoal-burners, whose numbers did not exceed 5,000 throughout the whole area in the winter and a few hundreds in the summer, all the others having migrated to the mountains. The Red Cross doctors also attended peasants from the communes bordering on the marshes—Nettuno, Cisterna, Norma, Sermoneta, Sezze,

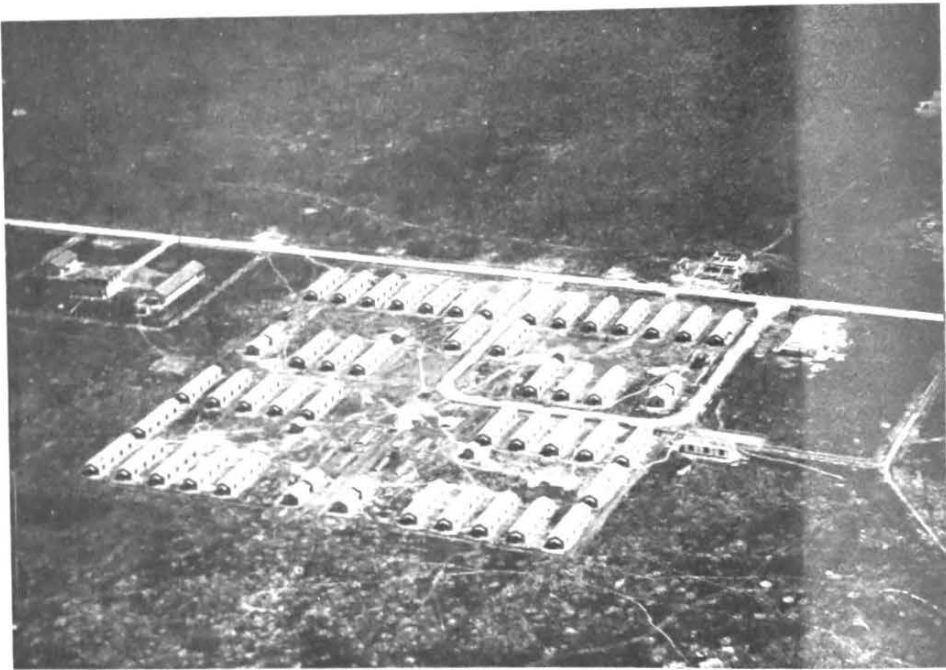


Fig. 13. — WORKERS' HUTMENT VILLAGE.

Priverno and Terracina—who ventured to come down from the highlands to cultivate the plain and were too far from their homes to obtain their usual medical aid. The stations were situated as follows : Acciarella, in the uncultivated region between Nettuno and Foce Verde ; Casale delle Palme, 11 kilometres from Cisterna, on the Via Appia ; Foro Appio, in the plain below Sezze, also on the Via Appia ; Pontemaggiore, 8 kilometres from Terracina, also on the Via Appia ; Fossanova, near the old abbey in the Priverno country. Every station had a doctor and sick-attendants in permanent residence throughout the year. Their duty was to seek out the sick, travelling through the marshlands by any means

of conveyance available—in small carts, in rafts or on horseback—and, if necessary, to bring them across to the Via Appia, whence they were conveyed in motor-ambulances to the neighbouring hospitals of Terracina, Sezze, Bassiano or Velletri, or else to Rome. As a piece of practical demonstration, they also organised a campaign against mosquitoes on the premises of the near health stations, and in the surrounding houses ; they carried out minor improvement works and destroyed larvæ ; they stocked the ponds with larvivorous fish within a radius of 500 metres around the station and the schools. This unassuming, devoted and undaunted mission succeeded in reducing the death rate from pernicious malaria to zero ; it also brought down the malaria morbidity rate and restored a certain amount of confidence among the peasants. Medicine alone could do no more, and there was some legitimate anxiety as to what would happen when large numbers of new workmen were brought to the marshes. The usual consequence of such action in malarial regions is common knowledge : fever suddenly breaks out, a very large number of workers die, the work slows down and is finally abandoned. This phenomenon has occurred so often that no particular example need be quoted. It was observed in the marshlands in the course of every attempt at cultivation made from 1920 to 1930—and that with the same characteristics : an average, but incomplete, resistance on the part of the native population already infected with malaria, due either to the persistence of a mild form of infection (allergy), or to a previous infection (immunity) ; 100 per cent infection rate among workers (labourers and settlers) brought in from outside resulting in a decrease and, finally, in the total loss of their working capacity.

In 1921, the “Company for the Reclamation of the Pontine Marshes” acquired part of the land between the Via Appia and the sea for the purpose of reclaiming and exploiting it. This land, which, after various financial vicissitudes, passed to other bodies, was finally assigned to the National Ex-Servicemen's Association, which triumphantly succeeded where others had failed. The company established an autonomous body, the Pontine Anti-malaria Institute, which set up a first health station at Colonia Elena (named after the Queen of Italy), between Terracina and Monte Circeo, and a second at Fogliano, near the coastal lagoon of the same name. These new stations, created in localities where

no medical aid had previously been available, led to the advent of a few farming enterprises and the settlement of some colonists. In 1929, the Red Cross opened its sixth health station at Doganella, the first workers' village established near the ruins of Ninfa. The success was complete from the health point of view, since, after 1932, no new case of malaria had broken out among the 500 persons who had come to live in the zone, while the surrounding country was transformed into a flourishing garden. Even the

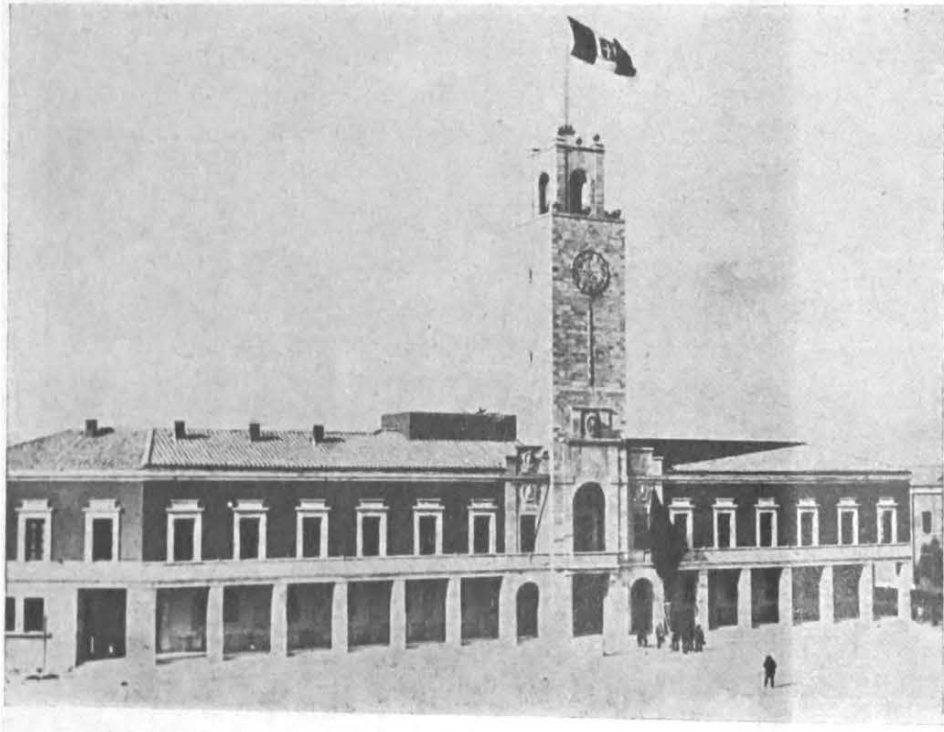


Fig. 14. — LITTORIA : THE TOWN HALL.

inhabitants of Sermoneta, a hamlet over 200 metres up on the mountain slopes, experienced the benefits of this activity, for whereas their splenic index had been 80 per cent in 1928, three years later there were practically no cases of malaria.

Since the agricultural bonification area entrusted to the Ex-Servicemen's Association embraced most of the area served by the Pontine Anti-malaria Institute, the Association concluded special agreements with this Institute for the year 1932, when the new work in full swing brought about a sudden increase of the population. The Institute added a third health station at Quadrato while the

town of Littoria was being built. In 1932, there were thus in operation in the *Agro Pontino* nine health stations in all, with infirmary wards for fifty beds, and three motor-ambulances. During the summer, patients were mainly taken to the hospitals in Rome, which had to organise new wards.

In 1933, all health services were placed under the Italian Red Cross, and were brought to the highest possible pitch of efficiency so that they might be able to cope with the situation created by an enormous increase in the population, both settled and temporary, due to the acceleration of the work. The following figures for one of the hot—and consequently, as regards malaria, more dangerous—months of the year will explain the magnitude of the task :

| | |
|---|--------|
| July 1924 : Number of persons resident in the <i>Agro Pontino</i> ... | 1,800 |
| July 1932 : Number of persons resident in the <i>Agro Pontino</i> ... | 12,090 |
| July 1933 : Number of persons resident in the <i>Agro Pontino</i> ... | 40,430 |

i.e., an increase of 2,300 per cent from 1924 to 1933. All these persons, both peasants and workmen, had come in from Italian districts immune from malaria and, before leaving their place of origin, had been medically inspected by officers of the Commissariat for Internal Migration. The details of the health organisation set up by the Italian Red Cross are as follows :

| | | |
|--|-----|-----------------------|
| Health stations in the <i>Agro Pontino</i> | 11 | |
| Infirmary beds | 360 | |
| Medical directors of stations | 11 | } 21 |
| Assistant medical officers | 8 | |
| Medical officers directing anti-mosquito squads..... | 2 | |
| Midwife | 1 | |
| Sick-attendants | 48 | |
| Anti-mosquito workers | 26 | |
| Chauffeurs | 16 | |
| Drivers | 4 | |
| Assistants | 22 | |
| Motor-cars for medical officers' visits | 11 | |
| Motor-ambulances for transporting patients | 8 | |
| Motor-vans for transporting anti-mosquito apparatus... | 3 | |
| Total annual cost | | about 4 million lire. |

These figures give some idea of the extent and complexity of the work of the health stations, but they only provide an impression of their means of action, and not of the enormous difficulties which have to be overcome in a very extensive area in process of transformation, among a highly active population, continually on the move and of very peculiar composition, consisting, on the one

hand, of settlers' families and, on the other hand, of an admixture of workmen of every age and trade. The activities of these services are as follows :

1. *Distribution of Quinine for Prophylaxis.* — This use of the drug, advocated thirty years ago by Angelo CELLI, is still in great favour ; the most recent observations show that, although it does not prevent infection, at any rate it secures prophylaxis, since, in many cases, the malarial parasite does not produce any morbid symptoms in persons thus treated ; it always prevents fever and, what is even more important, pernicious malaria. It should be remembered, however, that the climatic conditions obtaining in the *Agro Pontino* are dangerous almost throughout the year. It is impossible, therefore, to keep a composite mass of many thousands of men, women and children permanently and adequately dosed with quinine. Consequently, quinine prophylaxis is reserved for persons not permanently resident in the territory, and every facility for the purpose is afforded to those who desire it.

2. *Early Diagnosis and Treatment.* — Early diagnosis can only be secured by the periodical examination of the whole population in order to discover the initial symptoms of malaria. These are usually neglected because they are slight, but they may nevertheless lead to pernicious malaria after the first attacks. It is easy to organise the inspection of workmen housed in hutments and peasants living on farms ; but it is difficult to do so in the case of workmen who have entered the area of their own accord in search of work and are trying to escape notice in some part of this immense region, in order to evade the recruiting regulations of the Commissariat for Internal Migration and the rules laid down by law for the bonification area.

Out-patient and hospital treatment is provided for all cases of illness or accident, so that cases of malaria can be the more readily detected. During 1933, the capacity of the hospitals in the *Agro* was increased, and patients suffering from any acute form of disease can now be treated locally until they are completely restored to health, without having to proceed to neighbouring hospitals or to Rome. Patients are sent to these latter hospitals only when they are suffering from a disease which is bound to be very long-

drawn-out or necessitates some major surgical operation. The treatment is continued until a cure has been effected. This basic principle is very important where malaria is concerned, for, considering how easily relapses occur after shorter or longer periods, the multiplication of foci of infection is an ever-present danger in areas with a high anopheline density. After recovery, patients remaining in the area can be given follow-up treatment as out-patients, without interfering with their daily work. Those who return to their native places in distant communes are particularly



Fig. 15. — LITTORIA : HEADQUARTERS OF THE ORGANISATION FOR MATERNITY AND CHILD WELFARE.

dangerous, because many such places have still a fairly dense anopheline fauna and have been free from malaria only for a few years. These travelling carriers must be followed up and treated—as in fact they are—by the regular health authorities throughout the Kingdom.

3. *Destruction of Mosquitoes inside Dwellings.* — Imagoes are destroyed systematically every evening in the workmen's huts, which are so constructed as to offer no lurking-places for the

insects. One method followed is to explode smoke-bombs ; the mosquitoes are then caught in the wire netting of the windows and doors. Paraffin atomisers are also used, the paraffin containing pyrethrum powder in solution. In the settlers' houses, the families are told what to do, and provided with the necessary apparatus free of charge. Special officials visit the various farms at very short intervals to make sure that instructions are being carried out.

4. *Reduction of Anopheline Density in the Bonification Area.* — Anophelism, formerly very dense, was maintained by the marshes and aided in its development by domestic animals and small wild mammals which supplied the female with a blood meal during ovulation. *A. bifurcatus* was abundant in the woodlands ; in the more open parts of the country, in the neighbourhood of pastures, *A. superpictus* was common, though this variety comparatively seldom carries malaria parasites. *A. elutus* was found near the coastal lagoons ; not far from the Via Appia, several varieties of *A. maculipennis* were identified for the first time. These varieties, *basilii*, *messeæ*, *labbranchiæ*, are now universally recognised. Scientists are not yet agreed on the epidemiological importance of each variety : some regard *labbranchiæ*, which is not very long and is macrosplanchnic, as the most usual carrier, but FALLERONI, who discovered them, believes that all these varieties carry malaria to an equal extent. It was also in certain parts of the Pontine territory that zooprophylaxis was applied—with every success—for the first time, the houses being girdled with a protective ring of pigsties designed to attract the mosquitoes and so divert them from the human beings. This scheme has proved entirely successful. Proper drainage and the elimination of stagnant or sluggish water have already greatly restricted the breeding of anopheles. The present condition of the country may even have brought about some change in the respective proportions of the different varieties, though it is too soon to hope for any definite conclusions on this subject. Moreover, the increase in the number of live-stock due to the introduction of a rational system of husbandry has had the result that the cowsheds and pigsties attract the mosquitoes, which are, moreover, kept out of the human habitations by screening. Finally, a large amount of detailed work is carried out by the anti-mosquito squads directed by medical specialists. These squads

examine the country closely, report areas for draining, canals in need of repairs and marsh vegetation to be destroyed. They also spray, either with paraffin or a mixture containing Paris green, any pools which may happen to form. Their work ranges over the whole reclamation area, within a radius of 1,000 metres round all dwellings.

The results achieved by this health organisation may be judged by the fact that workmen and peasants have been able to continue

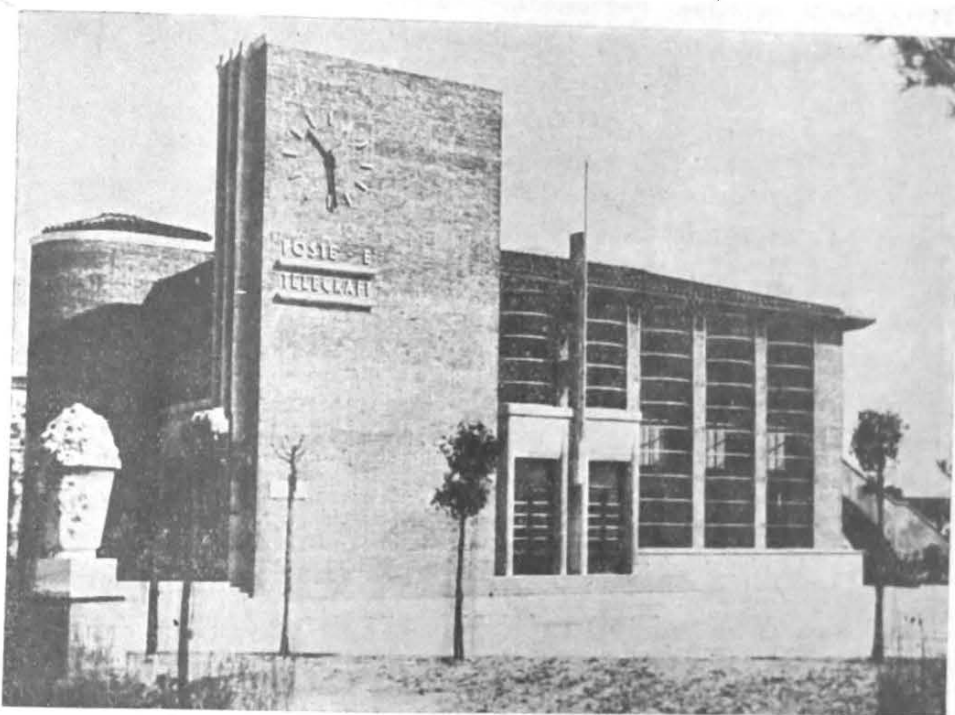


Fig. 16. — LITTORIA : THE POST-OFFICE. ARCHITECTONIC USE OF WIRE NETTING.

and intensify their work throughout the whole of the year, including the most dangerous periods. Consequently, the health question has ceased to be a hindrance to the work or a source of anxiety to the authorities. The number of cases of malaria must be considered in relation to the number of persons exposed to infection, which varies from month to month in relation to labour requirements and the arrival of new groups of settlers. We think it desirable to give the figures of the monthly maxima and minima throughout the year, comparing the data for 1930, when the region was still inhabited by the former population with only a slight addition of

labourers engaged on drainage work, with the data for 1932 and 1933, years of intensive colonisation.

A. Ratio between the Population in the Agro Pontino and Cases of Malaria.

| Year | Month | MINIMA | | | MAXIMA | | | |
|--------|----------|-----------------|-------|-----------------|---------|-----------------|-------|-----------------|
| | | Popu- lation | Cases | Per- centage | Month | Popu- lation | Cases | Per- centage |
| 1930.. | Feb. ... | 7,780 | 45 | 0.58 | July .. | 3,375 | 469 | 13.9 |
| 1931.. | Feb. ... | 6,000 | 73 | 1.2 | July .. | 3,420 | 239 | 7 |
| 1932.. | May ... | 12,700 | 73 | 0.58 | Oct. .. | 14,500 | 2,331 | 16 |
| 1933.. | Jan. ... | 30,000 | 300 | 1 | Aug. .. | 41,945 | 2,045 | 4.9 |

Monthly Average for Each Year

| Year | Popu- lation | Cases | Percent- age | Deaths from malaria | |
|------------|-----------------|-------|-----------------|---|--------------------------|
| | | | | Actual figures | Rate per 1,000 inhab. |
| 1930 | 5,500 | 185 | 3.3 | 5 | 0.9 |
| 1931 | 5,500 | 133 | 2.4 | — | — |
| 1932 | 14,106 | 683 | 4.8 | (27 within the area ; 20 after leaving the area) | 1.8 3.3 |
| 1933 | 41,026 | 860 | 2.09 | (3 within the area ; 11 after leaving the area) | 0.073 0.34 |

With the massing of workmen in 1932; the annual average endemicity rose to 4.8 per cent, with a maximum in October of 16 cases per 100 inhabitants, whether permanent or temporary. It should be borne in mind that the rate was previously very high. It has been said that in the commune of Sermoneta, whence the peasants came down to work in the nearest marsh, 80 per cent of the population suffered from splenomegaly due to malaria. Yet, with a fairly high morbidity rate, medical efforts were successful in keeping the death rate down to a very low figure ; for the rate reported (3 deaths per 1,000 immigrants in the area) includes also a few deaths which cannot with certainty be attributed to malaria, but which were included in the statistics in order to keep on the safe side. At all events, in the 1933 census, at a time when the number exposed to infection had trebled, the morbidity rate from malaria fell to 2.09 per cent, with a maximum of 4.9 per cent in August, and the death rate to 0.34 per thousand.

In addition to the monthly and annual rates, it is interesting to know the total number of malaria cases for each year, the number of deaths amongst malaria patients treated in the area, and, what

is most important, the number of cases of primary infection, it being remembered that these all relate to the tropical form.

B. *Malaria Cases and Deaths in the Agro Pontino.*

| Year | Cases | Deaths | Percent- age | Number of primary infections | Percent- age |
|------------|--------|--------|-----------------|------------------------------------|-----------------|
| 1930 | 2,035 | 5 | 0.24 | 590 | 29.0 |
| 1931 | 1,329 | — | — | 130 | 0.99 |
| 1932 | 8,193 | 27 | 0.32 | 3,435 | 41.7 |
| 1933 | 10,310 | 3 | 0.029 | 1,189 | 11.5 |



Fig. 17. — LITTORIA : HEADQUARTERS OF THE NATIONAL EX-SERVICE-MEN'S ASSOCIATION.

In addition to the maintenance of a very low death rate and the increase in the actual number of cases in 1933, due either to the fact that the number of inhabitants had trebled or to the existence of continued cases and relapses connected with the epidemic outbreak of 1932, the reduction in the number of primary infections is noteworthy, since it is a sure sign that the centres of infection are decreasing and that man is succeeding in his efforts to master and reduce the malarial endemicity of this region.

These figures are taken from an official report by Professor G. ALESSANDRINI, who was in charge of the health service in 1932 and 1933. It should be added that the data for 1930 and 1931 are incomplete, because the service had not at that time been centralised. The 1932 figures, moreover, relate only to the agricultural bonification area in the hands of the Ex-Servicemen's Association, whereas the figures for 1933 relate to the whole of the *Agro Pontino*, with the Red Cross health stations in those parts where there has not yet been any concentration of labour for colonisation purposes. Nevertheless, even allowing for these considerations, the figures are eloquent and should be taken in conjunction with the fact that no other infectious disease, nor any epidemic outbreak, has occurred among this enormous mass of people still living under provisional conditions. Final proof is afforded by the fact that primary malarial infections have occurred only amongst the workmen in hutments, whom it is more difficult to supervise, and who are exposed to infection in districts where the reclamation work is still incomplete. Out of nearly 10,000 people belonging to the families of settlers, on the other hand, there were, in 1933, only eleven cases of primary infections.

With the legal constitution of the commune of Littoria, a new health authority—the Communal Health Office—has begun to operate. This office started work with health supervision over drinks and foodstuffs, general hygiene and protection against common infectious diseases. As normal life becomes better organised, this office will take over the work of the health stations, and become a fighting unit which, with its doctors, will operate side by side with the bonification authorities and carry the campaign through to final success.



From the central zone of Littoria the agricultural bonification has spread in every direction. The lands of the first group in process of improvement and preparation have been followed by a further 11,796 hectares purchased or expropriated, and the second agricultural bonification sector has been extended to roughly 15,000 hectares, which, together with the 10,000 hectares of the first part, already represents nearly one-third of the entire area of the *Agro*

Pontino. The new land comprises two blocks. One is bounded by Littoria, the left bank of the river Astura and the coastal ridge—that is to say, it comprises the depression between the quaternary ridge and the sea, including the coastal lagoons; the other is between the river Sisto and the Via Appia. While hydraulic bonification schemes are being applied to the regulation of the surface waters—mostly by natural drainage, but with pumps at certain points—the National Association addressed itself in the first place to the business of putting up new hutment villages for workmen, turning its attention thereafter to the clearing of brushwood and tree-stumps over an area of 4,000 hectares, to the breaking-up by powerful ploughs and tractors of 14,100 hectares, which have lain uncultivated from time immemorial, to the drainage of the smaller swamps and surface-waters, to the construction of allotment roads and drains, of 850 farmhouses and eight agricultural centres, and the sinking of artesian wells. In this way, groups of farms have arisen bearing another series of famous war-time names: Borgo Ermada, Borgo Montello, Borgo Bainsizza, Borgo Sabotino, Borgo San Michele, etc.

On August 4th, 1933, a legislative decree was issued constituting the second commune in the *Agro Pontino*—Sabaudia—on a small peninsula projecting into the coastal lagoon of Paola, with an area of 14,427 hectares; it lies near the main motor-road, already nearly completed, which runs from Ostia to Anzio and Terracina, along the shore of the Tyrrhenian Sea. A bridge 200 metres long will join the end of the peninsula to the seashore, across the lake; near by is the wonderful forest of Terracina, which is being made accessible, while above looms the vast bulk of Monte Circeo. On August 5th, the Duce in person laid the first stone of the new town, after harvesting, in company with the farmers, the new wheat-crop wrung from the bosom of the conquered marsh. The chief buildings of Sabaudia will be ready and in use by April 21st, 1934, the anniversary of the foundation of Rome.

On the same day, the Duce inaugurated a seaside colony for the children of the Littoria settlers, at Torre Olevola, 3 kilometres from Terracina—a place which was formerly well known for its amazing marsh landscape of dead waters and gigantic water-lilies, and was completely in the grip of malaria. A number of excellent hutments erected by the Ex-Servicemen's Association had been handed over to the Italian Red Cross, which had fitted them up and received

400 of the children of the new settlers. Their presence in an area only just reclaimed was enough to allay any fears ; it was the Duce himself who insisted that the children should not be sent away from the land that their parents were conquering to luxuriously appointed watering-places, of which there is no lack in the neighbourhood of Rome. This profound ethical conception was crowned with complete success : the children immensely enjoyed their life in the colony ; a number of malaria cases were cured and no new cases occurred ; a small epidemic of scarlet fever was easily brought under control, which proves that the children's constitutions were in no way impaired.

On May 30th, 1933, His Majesty the King of Italy gave his august sanction to the first victories that had been gained, and a stimulus to further conquests. He visited the *Agro Pontino* and entered the new town by the Via Mussolini between a guard of honour of ex-servicemen, wearing their war medals and accompanied by their children.

Another event marks a step forward in history and reflects a tranquil certitude of victory, regardless of the difficulties to be overcome : the ancient, deadly *Agro Pontino* is to become the ninety-third province of Italy. By Legislative Decrees of September 7th and October 19th, 1933, a Royal Prefect is appointed Special Commissioner for the *Agro Pontino*, having under his jurisdiction the new communes of Littoria and Sabaudia, as well as the communes of Cori, Norma, Bassiano, Sermoneta, Cisterna di Roma, Sezze, Priverno, Terracina and San Felice del Circeo, which already existed on the edge of the Agro—a total area of 114,562 hectares, with a resident population of 85,907. The Commissariat is engaged in setting up its administrative services and establishing its health machinery : it has already a provincial medical officer and a provincial veterinary officer, and is organising anti-tuberculosis work, while the health services of the older communes, the health office of the Commune of Littoria and the Red Cross health stations are providing the groundwork of an organisation for protection from malaria and acute endemic infections, for the maintenance of healthy conditions in the soil and buildings and for the supervision of the trade in foodstuffs. On December 18th, 1933, the Duce, after laying the foundation-stones of other public buildings at Littoria, announced to the people of the town that it was to be the capital of the new province.

The ancient land of the Volsci has regained its unity ; it is to be restored to its former prosperity and perhaps raised to a height of greatness that it has never known in the past. Pliny the Elder wrote : "*Siccentur Pomptinæ paludes, tantumque agri suburbanæ reddatur Italiæ*". Nineteen centuries later, the command of our ancestors is being obeyed.



Fig. 18. — THE DUCE INAUGURATES A SEA-SIDE COLONY FOR CHILDREN AT TORRE OLEVOLA.

The reclamation of the *Agro Pontino* will be seen in its true significance only when it is regarded as part of a whole, as one factor in a comprehensive Governmental scheme.

The survey of the malarial zones throughout Italy was carried out chiefly during the period 1907 to 1912 ; it was completed after the war in respect of the annexed provinces, and yielded the following figures : out of a national territory of 31,013,669 hectares, the zones of endemic malaria represented in the aggregate 8,442,400 hectares, in 2,616 out of 8,362 communes in the Kingdom. The resident population of those zones was reckoned at 4 millions ; with the addition of the population on the edge of the zones and workers who migrated into them, there was a total of nearly 16 million persons exposed to malaria infection, and from 200,000 to 300,000

cases every year, quite apart from those that were not reported. The number of deaths from malaria had fallen from 23,000 per annum in 1887—the year in which complete statistics of causes of death for towns and rural areas were first compiled—to a little under 3,000 per annum.

In 1926, the great “back to the land” movement was initiated by the Duce, and the various laws enacted for the bonification of malarial land culminated in the Mussolini Act of December 24th, 1928, under which huge areas were to be comprehensively reclaimed at a cost of 7,000 million lire. Of this amount, more than half was to be paid direct by the State over a period of fourteen years (1929 to 1944). For purposes of comparison, it should be borne in mind that, between 1865 and 1928, 3,800 millions were expended on bonification works over 54 years—1,000 millions on works carried out direct by the State and 2,800 millions to contractors.

The works carried out under the above-mentioned Act may be summarised as follows :

| | |
|--|-----------|
| Hydraulic improvement works of the first class : | Hectares |
| Classified as such | 3,215,375 |
| Completed by July 1st, 1932 | 17,776 |
| In course of execution | 2,504,750 |
| Not yet begun | 692,849 |
| Lands of which the system of cultivation is to be changed for purposes of public utility : | |
| Classified and delimited as such | 3,923,400 |
| Classified and to be delimited | 471,000 |
| Conceded for execution of works | 615,000 |
| Mountain improvements for the regulation of catchment basins : | |
| Area to be improved | 8,750,803 |
| In process of improvement | 6,327,623 |
| Improvements not yet begun | 2,402,180 |

The regularisation of waters, the change in the system of cultivation and the improvement of mountain catchment basins are being extended beyond the limits of the malarial zones, because it is difficult to render those zones healthy without improving the hydraulic system in adjacent or higher areas, and because the purpose of those works is even wider than the stamping-out of malaria : it is to bring the land to the highest possible degree of productiveness, having regard to its natural conditions, in order to provide

bread for the workers. In consequence of this work, it was possible, between 1929 and 1933, to remove 161 communes, with a total area of 175,500 hectares, from the gloomy register of areas of endemic malaria.

The value of undertakings whereby man succeeds in changing the face of the land and the course of history can best be measured by comparison with other similar undertakings. I know of only two that can be approximated to the planting of a new civilised life in the malarial lands of Italy, and both belong to the twentieth century, though their development and aims are different. They are the reclamation of the Panama Canal Zone and the draining of the Zuider Zee.

* * *

Utopia is becoming a reality ; for to-day we are witnessing the realisation of that ultimate desire which Goethe puts into the mouth of Faust, and which he perhaps conceived when he crossed the Pontine Marshes in 1787 :

“A marsh spreads at the mountain’s foot, and poisons all that has already been won. To drain that pestilential fen would be the last and greatest victory. Wide lands I would open up for millions upon millions of men, lands where they could dwell, not in entire security perhaps, yet active and free, amid green fruitful fields—men and their herds, content upon the new-won land, sheltering under the lee of the sea-wall which industrious hands have built. Here, shrined within, a land of paradise ; there, let the stream without roar headlong to the very verge. But if it threaten to break in, all alike will speed to close the gap. Yes, that thought absorbs my being ; that is the final word of wisdom : he alone is worthy of liberty and of life who must win them anew day by day. Here, girt with peril, in childhood, in manhood, in old age, he strives and toils as the years pass. Would I might see that teeming host, and stand amid a free people in a free land ! At such a moment I could say : Stay yet a while, thou art so fair ! So would the vestige of my life upon earth remain in agelong memory.”

THE NATURAL TRANSMISSION OF MEDITERRANEAN LEISHMANIASIS

By

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Leishmaniasis are tending to occupy an increasingly important place in the human and veterinary pathology of Mediterranean countries. The more dangerous forms of leishmaniasis would seem to be spreading from east to west with growing impetus. New centres are coming into existence or are being discovered one after another ; at all events, the number of cases reported in certain localities grows year by year. Such a development cannot fail to be alarming, sufficiently so to call for the adoption of defensive health measures. Now, effective action against a communicable disease requires a knowledge of its origin and of the means of propagation. Our present aim is to summarise as succinctly as possible : (1) the present state of knowledge as regards the natural transmission of Mediterranean leishmaniasis and (2) the still unsolved problems of their ætiology—in other words, what is already known and what remains to be discovered.

*
* *

In current medical parlance, there are three varieties of Mediterranean leishmaniasis :

- (1) The cutaneous leishmaniasis of man, dogs and cats, commonly known as Oriental sore ;
- (2) The visceral (or internal) leishmaniasis of man (also known as infantile splenic anæmia, Mediterranean kala-azar, *ponos*, etc.) ;
- (3) The visceral leishmaniasis of dogs and cats.

It may be useful at the outset to consider whether this distinction is justified, to indicate the difference between the various forms of Mediterranean leishmaniasis and also their possible relationship one to the other and their affinities with the first visceral leishmaniasis known—namely, kala-azar proper.

I. THE VARIOUS FORMS OF LEISHMANIASIS.

A.—As their name indicates, all forms of leishmaniasis have this in common : they are caused by protozoa of the genus *Leishmania* Ross, 1903. From a morphological standpoint, *leishmania* are remarkably uniform ; in suitable culture media they develop into flagellates without any undulating membrane and are assimilable to *trypanosomidæ* of the genus *Leptomonas* Kent, 1880. It should be noted that *leptomonas* normally occur as parasites in the digestive tract of certain invertebrates and certain blood-sucking insects in particular.

B.—In spite of apparent similarities,¹ it is generally recognised to-day that the parasite of Oriental sore, *Leishmania tropica* (WRIGHT, 1903), is a species apart from the parasites of human visceral leishmaniasis and of canine visceral leishmaniasis. Oriental sore is accordingly regarded as an independent morbid entity. Certain clinical, epidemiological and experimental facts are advanced as affording adequate proof of this, the main evidence being as follows :

1. Oriental sore is a benign dermatosis having an ulcerating tendency which, throughout the whole of its course, retains the characteristics of a local lesion ; visceral leishmaniasis, on the contrary, are serious general infections from the outset.²

¹ *L. tropica* is scarcely distinguishable from the parasites of the various forms of visceral leishmaniasis, apart from the fact that it is slightly larger (Ch. NICOLLE and A. SICRE, *Arch. Inst. Pasteur, Tunis*, III, 1908, pages 117-125). Even this difference is hardly discernible, save in certain experimental lesions produced in dogs (L. PARROT, A. DONATIEN and F. LESTOQUARD, *Arch. Inst. Pasteur d'Algérie*, V, 1927, pages 120-130, and *Algérie médicale*, April 1932, pages 139-171).

² This clinical evidence cannot be countered by the argument that a general infection may be produced in white mice by subcutaneous, intradermal or peritoneal inoculation of *L. tropica*. The generalisation obtained in this case with a virus which always remains localised in its normal hosts merely proves the very high receptivity of the particular species of animal inoculated (PARROT,

2. The geographical distribution of Oriental sore does not everywhere coincide with that of the visceral leishmaniasis. Though there are countries (Greece, Southern Italy, Spain, the Algerian littoral) in which all three infections are met with, there are other regions in which—up to the present at any rate—only one form has been encountered; for instance, the visceral leishmaniasis have never been observed in the Algerian Sahara,¹ nor at Baghdad or Aleppo,² which are notoriously Oriental sore areas.

3. There is no cross-immunity between the Oriental sore and the various visceral leishmaniasis: Oriental sore immunises against Oriental sore, but not against the other leishmania infections. Visceral leishmaniasis sometimes immunise against Oriental sore—their virus behaving in this case towards *L. tropica* as a strong towards a weak virus,³ but sometimes they do not immunise at all or do so only incompletely.⁴ *L. tropica*, when injected intradermally into monkeys and dogs, reproduces Oriental sore with all its characteristics of an ulcerating lesion; when, however, viruses of visceral leishmaniasis are injected intradermally into the same animals, they cause the formation, *in situ*, of a hard, fibrous and non-ulcerating nodule.⁵

C.—The discovery of canine visceral leishmaniasis⁶ raised at the outset the problem of its specific identification: Was it or was it not due to the same parasite as visceral leishmaniasis in man? Most of the writers who have set out to solve this problem have,

DONATIEN and LESTOQUARD, *Algérie médicale, loc. cit.*). Similarly, the cutaneous ulcerations observed in canine visceral leishmaniasis have nothing in common with Oriental sore; they are not primitive and circumscribed lesions, but a sort of secondary and metastatic lesion which is the final phase of a diffuse parasitical infiltration of the tegument (ADLER and THEODOR, *Proc. Roy. Soc., B*, 110, 1932, pages 402-412) and which never constitutes the whole of the disease, as does Oriental sore.

¹ L. PARROT, A. DONATIEN and F. LESTOQUARD, *Algérie médicale, loc. cit.*

² S. ADLER and O. THEODOR, *Ann. Trop. Med. and Parasit.*, XXIII, 1929, pages 269-303.

³ Ch. NICOLLE and MANCEAUX, *Arch. Inst. Pasteur, Tunis*, VII, 1912, pages 219-224.

⁴ A. LAVERAN, *Leishmanioses*, Masson, Pub. Paris, 1917, page 423; L. PARROT, A. DONATIEN and F. LESTOQUARD, *Arch. Inst. Pasteur d'Algérie*, V, 1927, pages 120-130.

⁵ R. ROW, *Journ. Trop. Med. Hyg.*, XV, 1912, pages 327-328, and XVI, 1913, pages 1-2; A. LAVERAN, *loc. cit.*, page 421; L. PARROT, A. DONATIEN and F. LESTOQUARD, *loc. cit.*,

⁶ Ch. NICOLLE and Ch. COMTE, *C. R. Acad. Sc.*, April 6th, 1908.

like Ch. NICOLLE,¹ reached an affirmative conclusion, or at least hold this to be the most likely answer to the question.² In point of fact, there are many reasons to suppose that the agents are identical.

1. The parasite of Mediterranean visceral leishmaniasis in man and the parasite of visceral leishmaniasis in dogs resemble one another in every respect, in the *leishmania* as well as in the *leptomonas* form.

2. They are inoculable into the same animals and produce in these animals the same experimental lesions, whatever the mode and route of inoculation adopted.

3. Throughout the whole Mediterranean basin and as far as Turkestan, the two diseases are met with side by side. True, one or two exceptions to this rule have been cited. Canine visceral leishmaniasis exists, for instance, in Senegal,³ but human visceral leishmaniasis has not yet been observed there. In these matters, however, what is true to-day may not be true to-morrow. For instance, in Marseilles the first autochthonous human case was only noted eight years after the first canine case.⁴

4. The presence of an infected dog, or even cat,⁵ has often been noted in the immediate vicinity of persons suffering from visceral leishmaniasis. In certain localities of Sicily and Turkestan, the slaughter of dogs was followed by a considerable decrease in the incidence of the disease among humans.⁶

But it must be admitted that decisive proof of the ætiological identity of human visceral leishmaniasis and canine visceral leishmaniasis is still lacking. It will probably be long in coming, for it can scarcely be obtained otherwise than by the positive inoculation of man with the canine virus. Nevertheless, even in the present state of our knowledge, there are "so many, and often such complete,

¹ Ch. NICOLLE, *C. R. Congrès hyg. et démogr.*, Washington, 1912, C. M. WENYON, "Protozoology", London 1926, page 413.

² A. LAVERAN, *loc. cit.*

³ A. LAFONT and H. HECKENROTH, *Bull. Soc. path. exot.*, Vol. VIII, 1915, pages 162-164.

⁴ P. GIRAUD, *Bull. Soc. path. exot.*, Vol. XXV, 1932, pages 558-561.

⁵ Edm. and Et. SERGENT, G. LEMAIRE and QUILICHINI, *Ibid.*, Vol. V, 1912, pages 93-98.

⁶ C. BASILE, quoted by LAVERAN, *loc. cit.*; N. I. CHODUKIN, *Suppl. Pensée médicale, Usbékistan et Turkménistan*, Tashkent, 1928.

resemblances from a biological as well as from a morphological standpoint"¹ between the human and canine parasites that it would appear difficult, not to say unreasonable, not to assign them to the same zoological species—that is, to reject the view that, in the Mediterranean countries, there is only one visceral leishmaniasis, common to man, dogs and cats. In any case, it would be impossible at the present time to study the epidemiology or mode of propagation of one of the two infections independently of the other. A. LAVERAN's prudent advice has lost nothing of its force : " . . . it would be very unwise not to act on the assumption that human and canine leishmaniasis have now been proved to be identical."²

D.—The question of the relationship between Mediterranean visceral leishmaniasis and Asiatic kala-azar is more controversial. Ch. NICOLLE,³ A. LAVERAN,⁴ C. M. WENYON⁵ believe that the two diseases should be regarded as one, since their common characteristics are much more numerous than their points of dissimilarity ; the symptomology of both is the same and both are equally pathogenic for laboratory animals. An experiment in cross re-inoculation supports this view ; an ape which had acquired immunity against the Asiatic virus was refractory to the inoculation of Mediterranean virus.³ Consequently, *Leishmania infantum* Ch. Nicolle, 1908, the agent of infantile leishmaniasis, should be regarded as merely another name for *L. donovani* (Laveran and Mesnil, 1904), the agent of kala-azar proper. Without concluding that there are actually two kinds of visceral *leishmania*, F. MESNIL maintains, on the contrary, a distinction between *Indian leishmaniasis* and *Mediterranean leishmaniasis*, adducing, by way of argument, the biological "plasticity" of microbial species. The first is proper to man and attacks children and adults rather than infants, does not attack dogs and often occurs in an epidemic form ; the second, common to both man and dogs, prefers infants and only occurs in sporadic outbreaks.⁶

¹ A. LAVERAN, *loc. cit.*, page 299.

² *Loc. cit.*, page 277.

³ Ch. NICOLLE, VII^e Congrès Ital. Pédiatrie, Palermo, 1911.

⁴ A. LAVERAN, *Acad. Sc.*, Vol. CLVIII, 1914, page 1060.

⁵ C. M. WENYON, *loc. cit.*

⁶ F. MESNIL, *Premier Congrès intern. d'Hyg. méditerran.*, Marseilles, 1932, I, pages 385-387.

In any case, we may conclude that, in the part of the world which is here under review, the problem of the mode of transmission of the various kinds of leishmaniasis is confined to two forms—Oriental sore and human and canine visceral leishmaniasis.

II. MODE OF TRANSMISSION.

Many hypotheses have been advanced as to the way in which the various forms of leishmaniasis are transmitted. Most of these—and, in particular, those propounded before the exact nature of the pathogenic agents had been discovered—are of little more than historical interest and need not be enumerated here.

Nor do we propose to discuss again¹ suggestions, such as that of direct contagion in the case of Oriental sore, or contamination through the digestive tract in that of Mediterranean visceral leishmaniasis, which ignore the form of the evolutionary cycle of *leishmania*, and, curiously enough, the existence within that cycle of a *leptomonas* stage. It is hard to conceive, indeed, that *leishmania* should have two morphological aspects, two modes of multiplication, one of which was a useless luxury. MINCHIN wrote in 1912 that the transformation, in culture, of all *leishmania* into flagellates of the *leptomonas* type reflected with the natural development of the parasites in an invertebrate host.² Recent research into the behaviour of *leishmania* viruses in the organism of the phlebotomus has provided further evidence in support of this theory. Without concerning ourselves with the origin of *leishmania* and of *trypanosomidæ* in general—*i.e.*, without enquiring whether the first host is the vertebrate, as F. MESNIL believes,³ or the invertebrate, as E. BRUMPT⁴ maintains—we feel that there is good warrant for subscribing unreservedly to C. M. WENYON's preliminary stipulation—*viz.*, that no theory as to the transmission of leishmaniasis that fails to allow for the flagellate stage of *leishmania* can possibly be

¹ See on this subject, M. PARROT, "Soc. Biol.", C. 1929, page 467; L. PARROT, A. DONATIEN and F. LESTOQUARD, *Algérie médicale*, *loc. cit.*; Edm. and Et. SERGENT, L. PARROT and A. DONATIEN, *Bull. Soc. path. exot.*, LXXVI, 1930, pages 224-248.

² D. A. MINCHIN, "An Introduction to the Study of the Protozoa", London, 1912, page 318.

³ F. MESNIL, *Bull. Soc. path. exot.*, Vol. XXVI, 1933, pages 222-223.

⁴ E. BRUMPT, *ibid.*, pages 223-224.

correct. No satisfactory explanation of this stage can be given except by associating it with some insect or other invertebrate.¹

Finally, among the various blood-sucking arthropods which argument by analogy from the transmission of trypanosomiasis has successively brought under suspicion as possible vectors of leishmaniasis (phlebotomus, bugs, fleas, lice, mosquitoes, ticks, etc.), we will deal only with the species which have been incriminated with some apparent justification or, at all events, on the evidence of some positive experiment.

A. ORIENTAL SORE.

There can hardly be any doubt, after the researches conducted by the Institut Pasteur d'Algérie and the Microbiological Institute of Jerusalem University, that the phlebotomi, experimented upon for the first time as far back as 1904 by Edm. and Et. SERGENT² and incriminated, *inter alia*, by PRESSAT in 1905, are the agents responsible for the transmission of Oriental sore. We will review the positive facts which justify this assertion and will then state the unknown factors of the problem.

(a) *The Positive Facts.*

1. The inoculation into man, by scarification of the skin, of crushed phlebotomi (*Phlebotomus papatasi* (Scop.)) from a locality in which leishmaniasis is endemic (Biskra, Algeria) has produced Oriental sore (Edm. and Et. SERGENT, L. PARROT, A. DONATIEN and M. BÉGUET, 1921).³

2. The inoculation into various subjects, by scarification, of the digestive tract of phlebotomi of the same species taken from a locality in which cutaneous leishmaniasis is also endemic (Jericho, Palestine) and containing *leptomonas* forms, has produced Oriental sore (S. ADLER and O. THEODOR, 1925-1926).⁴

¹ C. M. WENYON, *Trans. Roy. Soc. Trop. Med. and Hyg.*, XXV, 1932, pages 319-348.

² Edm. and Et. SERGENT, *Soc. biol.*, LVII, 1905, page 673.

³ Edm. and Et. SERGENT, L. PARROT, A. DONATIEN and M. BÉGUET, *Acad. Sc.*, CLXXIII, 1921, page 1030.

⁴ S. ADLER and O. THEODOR, *Ann. Trop. Med. and Parasit.*, XIX, 1925, pages 365-371, and XX, 1926, pages 947-959.

3. *Phlebotomus papatasi* and another species, *P. sergenti* Parrot, easily become infected when fed on human Oriental sores, either natural or experimental,¹ or on Oriental sores experimentally produced in white mice.²

4. In the digestive tract of *P. papatasi* and *P. sergenti* thus infected, *Leishmania tropica* turn into *leptomonas* and multiply freely. The *leptomonas* forms become localised mainly in the anterior portion of the mid-gut, attach themselves by means of their flagellum to the gut epithelium and resist faecal evacuation. In some cases, they creep up through the oesophagus and the pharynx as far as the proboscis and thus come to occupy the very best position for infecting the cutaneous wound produced by the insect's bite. The behaviour of *L. tropica* in the organism of *P. papatasi* and *P. sergenti* is, in this respect, exactly similar to that of *L. donovani* of Asiatic kala-azar, in the organism of *Phlebotomus argentipes*, as the earlier research work of R. KNOWLES, L. E. NAPIER and R. O. A. SMITH on the one hand, and S. R. CHRISTOPHERS, H. E. SHORTT and P. J. BARRAUD on the other hand³ have revealed. It is evidence of the perfect adaptation of *L. tropica* to the phlebotomi in question.⁴

5. It has been possible to secure the infection of culture media by means of *P. papatasi* puncturing a shaved rabbit skin. In this case, the Oriental sore parasites contained in the proboscis were quite certainly ejected as and when the puncturing thrust was delivered.⁵

6. In nature, *Phlebotomus papatasi* harbouring parasitical *leptomonas* forms of *L. tropica* have been found to occur in the proportions of about one in a thousand at Jericho and Biskra, whilst infected *P. sergenti* occurred in the proportions of three per thousand specimens examined at Baghdad.⁶ As far back as 1911,

¹ S. ADLER and O. THEODOR, *loc. cit.*, *Ann. Trop. Med. and Parasit.*, XXIII, 1929, pages 1-18.

² L. PARROT and A. DONATIEN, *Bull. Soc. path. exot.*, XIX, 1926, pages 694-696; *Arch. Inst. Pasteur d'Algérie*, V, 1927, pages 9-21.

³ R. KNOWLES, L. E. NAPIER and R. O. A. SMITH, *Ind. Med. Gaz.*, December 1924, pages 593-597; S. R. CHRISTOPHERS, H. E. SHORTT and P. J. BARRAUD, *Ind. Journ. Med. Res.*, XII, 1925, pages 605-607.

⁴ Less perfect, however, than that of certain trypanosomes to the *glossinæ*; the *leptomonas* of Oriental sore do not, as a matter of fact, ever invade the salivary glands of the phlebotomi (S. ADLER, *Bull. Soc. path. exot.*, XXVI, 1933, page 220).

⁵ S. ADLER and O. THEODOR, *Nature*, CXXI, 1928, page 282.

⁶ S. ADLER and O. THEODOR, L. PARROT and A. DONATIEN, *loc. cit.*

C. M. WENYON¹ had noted the existence of similar forms in phlebotomi caught at Aleppo, a centre of Oriental sore. Our present knowledge justifies the belief that these too were natural *L. tropica* infections.²

7. The geographical distribution of Oriental sore coincides in Palestine and in Algeria with the distribution of *P. papatasi* and at Baghdad with that of *P. sergenti*.³

8. The usual localisation of Oriental sore on parts of the human body which are uncovered at night, accords with the habits of the phlebotomi, which are night-biting insects.⁴

To sum up, it is now fully established that *Phlebotomus papatasi* and *P. sergenti* are the natural hosts of *Leishmania tropica*. In nature, both are vectors of the virus in a form which is pathogenic for man.

(b) *The Unknown Factors.*

1. On the other hand, all attempts made by S. ADLER and O. THEODOR to produce Oriental sore in man or dogs through the bites of experimentally infected phlebotomi failed,⁵ as had the earlier attempts of Edm. SERGENT and H. FOLEY, and of Ch. NICOLLE, to transmit relapsing fever by lice-bites. Does this mean that we ought to revert to W. S. PATTON's hypothesis that infection takes place mechanically through the crushing of the insect on the skin and that, under the pressure, the *leptomonas* expelled from the mid-gut pass directly through the proboscis into the bite-wound, or are inoculated by subsequent scratching? It is certainly very easy to crush a phlebotomus while it is feeding, but such a mechanism can hardly be suggested in the case of very young children or dogs.

S. ADLER suggests that the process of infection may differ from country to country according to the varying degree of adaptation of *L. tropica* to the local phlebotomi: that it takes place by bites wherever the *leptomonas* forms regularly invade the most anterior

¹ C. M. WENYON, *Journ. Trop. Med. and Hyg.*, XIV, 1911, pages 103-109.

² L. PARROT, A. DONATIEN and F. LESTOQUARD, *Algérie médicale, loc. cit.*, S. ADLER, *Bull. Soc. path. exot.*, XXVI, 1933, pages 207-222.

³ S. ADLER, *ibid.*

⁴ Edm. and Et. SERGENT, H. FOLEY, L. PARROT, *Arch. Inst. Pasteur d'Algérie*, IV, 1926, pages 20-25.

⁵ S. ADLER and O. THEODOR, *Ann. Trop. Med. and Parasit.*, XXIII, 1929, pages 1-18.

portions of the digestive tract (pharynx and proboscis) of the invertebrate host (as at Baghdad, for instance), and that it is brought about mainly by crushing and sometimes by bites, in places where such invasion is less frequent (Palestine).¹

On this particular point of the mode of infection, the transmission of Oriental sore calls, therefore, for further research.² The fact that, up to the present, results have been negative does not in any way detract from the value of the positive epidemiological and experimental evidence; as E. HINDLE points out, no one doubts the part which mosquitoes play in spreading filariasis, though it has never been experimentally demonstrated.³

2. Is man the reservoir of virus of Oriental sore? In other words, is the origin of every human case of Oriental sore to be found in some previous human case on which the phlebotomus carrier infected itself? Observations conducted in Saharan centres of endemic leishmaniasis, where no developing Oriental sores are found during the breeding season of the phlebotomi, and reports of sporadic cases of cutaneous leishmaniasis in parts of Algeria where none had hitherto been noted, would seem to warrant a negative answer.⁴ The primary source of infection should, in that event, be sought elsewhere than in man. Various theories have been put forward incriminating the dog, the camel, the gecko, and *euphorbiaceæ*. All these have been refuted,⁵ but we will examine the case of the gecko on account of its speculative interest.

In 1914, Edm. and Et. SERGENT, G. LEMAIRE and G. SENEVET discovered in *Tarentola mauritanica* L., a gecko very common at Biskra, a blood flagellate of the *leptomonas* type, which was morphologically very closely allied to culture forms of *L. tropica*. Knowing, moreover, that certain phlebotomi of the *minutus* group fed on reptiles, the authors wondered whether these phlebotomi (*P. minutus* var. *Africanus* in this case) did not obtain the Oriental sore virus from the gecko in the first instance, thereafter inoculating

¹ S. ADLER, *Trans. Roy. Soc. Trop. Med. and Hyg.*, XXIII, 1929, pages 289-300.

² It will be seen further on how, according to S. ADLER's suggestion, it might be possible to elucidate the question of the mode of inoculation of leishmaniasis in general by phlebotomi.

³ *Trans. Roy. Soc. Trop. Med. and Hyg.*, XXV, 1932, page 349.

⁴ L. PARROT and H. FOLEY, *Bull. Soc. path. exot.*, XVIII, 1925, pages 485-495.

⁵ L. PARROT, A. DONATIEN and F. LESTOQUARD, *Algérie médicale, loc. cit.*

man.¹ It has since been found that the *leptomonas* of the gecko differs from *L. tropica*, in that it is pathogenic neither for man, nor for the ape, nor for the white mouse,^{1,2,3} and that the phlebotomi which, at Biskra, bite the gecko (*P. minutus*, *P. parroti*) do not bite man. If, therefore, they are infected by the former with leishmaniasis virus, they do not transmit it to man.⁴

But, though the gecko can now no longer be regarded as the reservoir of Oriental sore virus, the presence in this lizard of *leptomonas* forms—which certainly belong to the evolutionary cycle of a *leishmania* (*L. tarentolæ*, Wenyon, 1921)—“merits”, as S. ADLER⁵ observes, “the most careful attention of protozoologists”. There is, in fact, reason to suppose that the infection is communicated from gecko to gecko by *Phlebotomus minutus*.⁶ It could doubtless be established by experiment whether the gecko becomes infected by swallowing the insect (geckos being insectivora) or through the insect’s bite. This would help forward the solution of the general problem of the route of inoculation of *leishmania*.⁵ Personally, we think that this would only yield an indication significant if transmission were found to be by bite; of no evidential value if it were proved that infection is produced by ingestion.

In any case, it would seem that investigations with a view to discovering a reservoir of virus outside man should be studiously pursued.

3. With regard to American forest leishmaniasis, E. BRUMPT and A. PEDROSO have put forward the following hypothesis. There is, perhaps, no reservoir of virus in the strict sense. “Man and dogs may be the victims of a chance adaptation in their tissues of a harmless intestinal flagellate of some insect.”⁷ Extending this ætiological concept to *L. tropica* (and even to *L. donovani*), it might therefore be pertinent to ask whether, in the ordinary way, the parasite is not confined to phlebotomus as its only host. The

¹ Edm. and Et. SERGENT, G. LEMAIRE and G. SENEVET, *Ann. Inst. Pasteur*, XXIX, 1915, pages 309-312.

² E. CHATTON and G. BLANC, *Bull. Soc. path. exot.*, XI, 1918, page 595.

³ L. PARROT, *Arch. Inst. Pasteur d'Algérie*, VI, 1928, pages 453-464.

⁴ L. PARROT, *Bull. Soc. path. exot.*, XV, 1922, pages 80-92.

⁵ S. ADLER, *Bull. Soc. path. exot.*, XXVI, 1933, page 214.

⁶ L. PARROT, *loc. cit.*; S. ADLER and O. THEODOR, *Proc. Roy. Soc.*, B, 108, 1931, pages 447-463.

⁷ E. BRUMPT and A. PEDROSO, *Bull. Soc. path. exot.*, VI, 1913, pages 752-762.

preservation of the species would be ensured by the passage of the virus of one generation of insects to the following generation either by true hereditary transmission, or because the larva of phlebotomi become infected through ingesting excreta (as in the case of *Leptomona ctenocephali* of the dog flea), or eating the dead bodies of their parents. If so, the leishmania form of the virus would be an accidental aberration totally unrelated to the normal evolutionary cycle of the flagellate ; it would be the result of evolution gone off its course,¹ or, in the picturesque phraseology of Ch. ANDERSON, "one of nature's sideslips".²

These theoretical opinions do not fit in with the actual evolution of *L. tropica* in the digestive tract of the phlebotomi, or with their propensity to invade the pharynx and the proboscis as if these were their normal route of egress. Moreover, several attempts to infect phlebotomus larvæ with *Leishmania* cultures³ or to verify the passage of *L. tropica*⁴ from one generation to the following have given negative results. Still, they might perhaps be profitably repeated.

4. The only invertebrate hosts of *L. tropica* known at present—namely, *P. papatasi* and *P. sergenti*—are found wherever Oriental sore occurs ; but—so far as our present knowledge goes—Oriental sore does not occur wherever these hosts are present. Why is it that the *P. papatasi* and *P. sergenti* of certain regions are not infected or do not infect ? Is this owing to the absence of a reservoir of virus ? Do not phlebotomi of the countries in which cutaneous leishmaniasis prevails, other than *P. papatasi* and *P. sergenti*, which bite man, play any part in the propagation of the disease ? If not, why not ? These are so many unsolved problems, which still provide a vast field for investigators.

B. VISCERAL LEISHMANIASIS.

As regards visceral leishmaniasis in man, dogs and cats in the Mediterranean countries, we will only consider transmission by

¹ L. PARROT and H. FOLEY, *loc. cit.*, L. PARROT, A. DONATIEN and F. LESTOQUARD, *Algérie médicale, loc. cit.*

² Ch. ANDERSON, *Algérie médicale*, April 1932.

³ S. R. CHRISTOPHERS, R. O. SHORTT and P. H. BARRAUD, *Ind. Journ. Med. Res.*, XIV, 1926, pages 155-156.

⁴ L. PARROT, *Arch. Inst. Pasteur d'Algérie*, IX, 1931, pages 442-450.

fleas, ticks and phlebotomi, these being the only transmitters against whom evidence is adducible.

1. *Transmission by Fleas.*

C. BASILE, in Italy in 1911,¹ and Edm. SERGENT, A. LHÉRITIER and G. LEMAIRE in 1912,² reported positive observations of the experimental transmission of visceral leishmaniasis from an infected dog to an apparently healthy dog by the bite of the *Ctenocephalus canis*. Ch. NICOLLE's hypothesis that dog fleas acted as vectors³ would therefore seem to be correct. But similar experiments by W. E. MARSHALL,⁴ P. DA SILVA,⁵ C. M. WENYON,⁶ Ch. NICOLLE and Ch. ANDERSON⁷ yielded, on the contrary, a negative result.

NICOLLE and ANDERSON even conclude "definitely that the flea plays no part in transmission of kala-azar from dog to dog". More recently, S. ADLER and O. THEODOR failed to find a single *Ctenocephalus canis* harbouring parasitical *L. donovani* on dogs which were suffering from visceral leishmaniasis and were, at that time, infecting *Phlebotomus perniciosus* in the proportion of 65 per cent. This, they write in substance, once more confirms the fact that dog fleas have no connection with the transmission of kala-azar.⁷

2. *Transmission by Ticks.*

The dog tick, *Rhipicephalus sanguineus* Latreille, 1806, is, as a matter of common knowledge, very abundant throughout the whole Mediterranean basin. The idea that it might be the intermediary host for the parasite of canine leishmaniasis naturally occurred to the mind. C. BASILE, W. E. MARSHALL,¹ Ch. NICOLLE and Ch. ANDERSON² incline, after several negative experiments, to the view

¹ Quoted by A. LAVERAN, *loc. cit.*

² *Bull. Soc. path. exot.*, V, 1912, pages 595-597.

³ Ch. NICOLLE, *Bull. Soc. path. exot.*, I, 1903, pages 188-190.

⁴ W. E. MARSHALL, *Journ. Roy. Army Med. Corps*, XIX, 1912, page 276.

⁵ C. M. WENYON, *Journ. Lond. Sch. Hyg. and Trop. Med.*, II, 1912, pages 13-26, and *Trans. Roy. Soc. Trop. Med. and Hyg.*, VII, 1914, pages 97-111.

⁶ Ch. NICOLLE and Ch. ANDERSON, *Arch. Inst. Pasteur, Tunis*, XII, 1923, pages 168-198, etc., XIII, 1924, pages 155-164.

⁷ S. ADLER and O. THEODOR, *Proc. Roy. Soc.*, B, 110, 1932, pages 402, 412.

⁸ Ch. NICOLLE and Ch. ANDERSON, *Arch. Inst. Pasteur, Tunis*, XV, 1926, pages 114-117.

that this is not the case. In 1930, G. BLANC and J. CAMINOPETROS transmitted canine visceral leishmaniasis to the spermophile (*Citellus citillus*) by inoculating with crushed *Rhipicephalus sanguineus* previously fed either on spermophiles or infected dogs. In the tick, the virus passes from the larva to the nymph and from the nymph to the adult. There is, therefore, complete adaptation of *Leishmania donovani* to the *Rhipicephalus*; consequently, this tick is the natural intermediary host of the virus and must be regarded as the agent in the propagation of Mediterranean visceral leishmaniasis. Attempts at transmission by bites have been unsuccessful; it is not known in what form—whether flagellate or not—the virus persists in the organism of the tick during these evolutionary stages.¹

The interpretation placed by G. BLANC and J. CAMINOPETROS upon the result of their experiments has called forth serious objections: (1) the survival of a parasite in the digestive tract of an invertebrate does not necessarily prove that this invertebrate is its specific host, unless the parasite develops or behaves therein in some particular way,² “many germs may and do subsist in conditions absolutely foreign to those which ensure their ordinary propagation”³; (2) the virus of visceral leishmaniasis has not been found in its *leptomonas* form, nor, for that matter, in its *leishmania* form, in ticks taken from infected dogs; ⁴ therefore, it does not develop there; (3) transmission by ticks does not seem to be consistent with the epidemiological facts concerning visceral leishmaniasis—in particular, with the frequency of the disease among young children, because, if the tick fastened on to any part of their skin, it would certainly be noticed by the vigilant and anxious mother. No such case of previous parasitism has ever been reported.⁵ Finally, visceral leishmaniasis has been known to occur

¹ G. BLANC and J. CAMINOPETROS, *Acad. Sc.*, 191, 1930, page 800 and page 1162; *Soc. Biol.*, CVII, 1931, page 1493.

² C. M. WENYON, *Trans. Roy. Soc. Trop. Med. and Hyg.*, XXV, 1932, page 327.

³ Ch. NICOLLE and Ch. ANDERSON, *Arch. Inst. Pasteur, Tunis*, XVI, 1927, pages 228-232.

⁴ L. PARROT, A. DONATIEN and F. LESTOQUARD, *Arch. Inst. Pasteur d'Algérie*, IX, 1931, pages 438-441.

⁵ S. ADLER and O. THEODOR, *Proc. Roy. Soc.*, B, 110, 1932, pages 402-412.

• L. PARROT, A. DONATIEN and F. LESTOQUARD, *Algérie médicale*, loc. cit.

in valuable dogs which were kept indoors and had never had any ticks.¹

Nevertheless, several authors think it likely that human visceral leishmaniasis may be transmitted by ticks. P. GIRAUD points out that, in the summer, ticks are very abundant in gardens in the neighbourhood of Marseilles, where both human kala-azar and canine leishmaniasis are very frequent. Children playing on the ground offer an easy prey for the ticks, which they do not know how to keep off, so that they are frequently bitten.² To this it may be objected that the well-known elective localisation of visceral leishmaniasis in the neighbourhood of towns may be due to some other predominantly suburban vector—phlebotomus, for instance.³ Ticks do not bite with such surreptitious deftness that they are never found on the bodies of their victims. Finally, it is not at all usual to see six-months-old babies rolling about on the lawns. Such babies do, however, contract leishmaniasis.

3. *Transmission by Phlebotomus.*

Since 1924, as a result of the Algiers Pasteur Institute's work on Oriental sore, the search for the vector host of visceral leishmaniasis has been conducted mainly among phlebotomi, both in British India and in countries where so-called infantile kala-azar occurs. As regards the Mediterranean basin, as far back as 1925, J. A. SINTON indicated a particular species, *Phlebotomus perniciosus* Newstead, 1914,⁴ as being the probable vector, having regard to its geographical distribution. In point of fact, the area covered by *P. perniciosus* exactly coincides with the area of the human and animal disease in North Africa.⁵ Investigations have, therefore, been mainly concerned with this phlebotomus. Here, again, for the sake of convenience, we will draw a distinction between the

¹ Unpublished observations of our colleagues, A. DONATIEN and F. LESTOQUARD.

² P. GIRAUD, *Presse médicale*, February 17th, 1934, pages 272-274.

³ L. PARROT, A. DONATIEN and F. LESTOQUARD, *Arch. Inst. Pasteur d'Algérie*, IX, 1931, page 441; S. ADLER and O. THEODOR, *Bull. Entom. Res.*, XXII, 1931, pages 105-113, and *Proc. Roy. Soc.*, B, 108, 1931, page 474; L. PARROT, A. DONATIEN and F. LESTOQUARD, *Arch. Inst. Pasteur d'Algérie*, XI, 1933, pages 183-191.

⁴ J. A. SINTON, *Ind. Journ. Med. Res.*, XII, 1925, pages 701-709.

⁵ L. PARROT, *Congr. Ass. Franç. Avanc. sc.*, Constantine, 1927.

positive knowledge acquired and the problems which remain to be solved.

(a) *Facts established*.—1. *Phlebotomus perniciosus* infects itself easily on dogs, ¹ hamsters (*Cricetulus griseus*)² or man⁴ suffering from natural or experimental leishmaniasis. A variety of this species, the *lobbi*, found in Palestine and Persia,⁶ has also been infected by gorging according to HERTIG's method.⁶

2. In the organism of *P. perniciosus*, the parasite of Mediterranean visceral leishmaniasis behaves like the Indian kala-azar and like the Oriental sore parasite.⁷ It tends to invade the anterior parts of the insect's digestive tract; it is found in the proboscis up to the level of the barbs of the epipharynx; it can even emerge of itself, when the puncturing organs are inserted into a HERTIG capillary tube; it can therefore penetrate into the tegument of the bitten host without any active intervention on the part of the latter—i.e., without the crushing of the phlebotomus. The *leptomonas* forms developed in the digestive tract of the phlebotomus infect the hamster when inoculated by the peritoneal route.³

3. *P. perniciosus* has been found on several occasions naturally infected in kennels,¹ and once in a house at Catania,⁸ in which there were cases of human leishmaniasis.

4. *P. perniciosus* feeds on man and other domestic animals, but seems to prefer the latter⁹ and, above all, dogs to man.¹⁰

¹ L. PARROT, A. DONATIEN and F. LESTOQUARD, *Bull. Soc. path. exot.*, XXIII, July 1930, pages 724-725, and *Arch. Inst. Pasteur d'Algérie*, IX, 1931, pages 438-441.

² S. ADLER and O. THEODOR, *Proc. Roy. Soc.*, B, 110, 1932, pages 400-412.

³ S. ADLER and O. THEODOR, *Nature*, September 20th, 1930, page 437.

⁴ S. ADLER and O. THEODOR, *Proc. Roy. Soc.*, B, 108, 1931, pages 481-493.

⁵ After examining a collection of phlebotomi, kindly submitted to us by J. Caminopetros, we note that *P. perniciosus* var. *lobbi* also exists in Continental Greece and the Greek islands (an entirely new fact).

⁶ S. ADLER, O. THEODOR and M. LOURIE, *Bull. Entom. Res.*, XXII, 1931, pages 105-113.

⁷ L. PARROT, A. DONATIEN, and F. LESTOQUARD, *loc. cit.*; S. ADLER and O. THEODOR, *Proc. Roy. Soc.*, 108, 1931, pages 481-493; N. I. CHODUKIN, in Turkestan, has also observed the development of dog *leishmania* in the digestive tract of phlebotomi of an unknown species (*Suppl. Pensée méd. Usbékistan*, Tashkent, 1928). Similarly, SOFIEFF and SCHEWTSCHENKO in *P. papatasi* (*Pensée méd. Usbékistan*, 1929, No. 5, pages 48-55).

⁸ S. ADLER and O. THEODOR, *Proc. Roy. Soc.*, 108, 1931, pages 494-502.

⁹ S. ADLER and O. THEODOR, *ibid.*, pages 464-480.

¹⁰ L. PARROT, A. DONATIEN and F. LESTOQUARD, *Arch. Inst. Pasteur d'Algérie*, XI, 1933, pages 183-191.

5. Dogs suffering from visceral leishmaniasis which have lesions on the skin, whether ulcerated¹ or not (bald patches),² offer excellent conditions for the infection of the phlebotomus. It may perfectly well be that the dog acts as a reservoir of virus.

6. In the Sicilian centre of visceral leishmaniasis, so brilliantly studied by S. ADLER and O. THEODOR,³ as in North Africa, the distribution area of *P. perniciosus* coincides very closely with that of the disease. The disease is not met with in the higher parts of Sicily, where the insect is absent. Nevertheless, *P. perniciosus* is not in the Old World distributed over so wide an area as visceral leishmaniasis. In other places, therefore, transmission must be effected by different phlebotomi.⁴

7. In Sicily, as in North Africa, the other local species of phlebotomus (*P. papatasi*, *P. major*, *P. sergenti*) do not, in the light of epidemiological observation and experiment,⁵ seem to be responsible for the propagation of visceral leishmaniasis.

8. The existence of leishmaniasis and of *P. perniciosus* in a given spot are found to coincide with the presence of a fairly abundant vegetation (gardens, parks, open country). The fact is explained by the predilection of the larvæ of this species and of other phlebotomi for vegetable food (rotting leaves).⁴

(b) *Unknown Factors*.—1. The transmission of visceral leishmaniasis from dog to dog, or from any given infected animal, such as a hamster to a healthy animal, by the bite of *P. perniciosus*⁶ has not yet been achieved.

2. The species of phlebotomi which, outside the Western Mediterranean basin, might serve as propagating agents in places where

¹ A. DONATIEN, F. LESTOQUARD and L. PARROT, *Bull. Soc. path. exot.*, XXII, 1929, pages 252-253 ; L. PARROT, A. DONATIEN and F. LESTOQUARD, *ibid.*, XXIII, 1930, pages 724-725 ; *Arch. Inst. Pasteur d'Algérie*, XI, 1933, pages 183-191.

² S. ADLER and O. THEODOR, *Brit. Med. Journ.*, December 26th, 1931, page 1179 ; *Proc. Roy. Soc.*, B. 110, 1932, pages 402-412.

³ S. ADLER and O. THEODOR, *Bull. Entom. Res.*, XXII, 1931, pages 105-113 ; *Proc. Roy. Soc.*, B. 108, 1931, pages 447-502.

⁴ L. PARROT, A. DONATIEN and F. LESTOQUARD, *Arch. Inst. Pasteur d'Algérie*, XI, 1933, pages 183-191.

⁵ A positive experiment by N. I. CHODUKIN, M. S. SOPIEFF and F. J. SCHEWTSCHENKO does not seem to be conclusive, as the phlebotomi fed on a dog suffering from visceral leishmaniasis transmitted cutaneous leishmaniasis (*Arch. f. Schiffs- u. Tropenhyg.*, 35, 1931, pages 424-434).

P. perniciosus is not found are not known, or rather we do not know which species ought to be suspected most on account of their biology. These species probably belong to the *P. major* group, like *P. argentipes* (which is very probably the agent of the transmission of kala-azar in India), and like *P. perniciosus*.¹

* * *

Despite these lacunæ, which we would be the last to minimise, none of the hypotheses concerning the mode of propagation of Mediterranean visceral leishmaniasis has so many elements of probability in its favour as that of the transmission by phlebotomi. Future research will doubtless confirm this theory. In this connection, the recent successful work of SHORTT, SMITH, SWAMINATH and KRISHNAN, NAPIER, SMITH and KRISHNAN, who have on three occasions succeeded in infecting the hamster with the virus of Indian kala-azar by the bite of an infected *Phlebotomus argentipes*, warrant every hope.²

¹ The species known at present belonging to this group are : *P. major* and its variety *syriacus* ; *P. perniciosus* and its *lobbi* variety ; *P. ariasi*, *P. larroussel*, *P. canaaniticus*, *P. langeroni* and its *longicuspis* variety ; *P. perfiliewi*, *P. macedonicus*, *P. chinensis* and its *longiductus* variety.

² H. E. SHORTT, R. O. A. SMITH, C. V. SWAMINATH and K. V. KRISHNAN, *Ind. Journ. Med. Res.*, XVIII, 1931, pages 1373-1375 ; L. E. NAPIER, R. O. A. SMITH, and K. V. KRISHNAN, *ibid.*, XXI, 1933, pages 299-304.

RECENT TENDENCIES IN THE DEVELOPMENT OF GENERAL HOSPITALS IN ENGLAND¹

by

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Part I.

ADMINISTRATION.

One of the most remarkable social changes that has taken place in England in recent years is that in connection with the hospitals. In order fully to understand this change, it is necessary to sketch very briefly the method on which the hospital system in England has developed. In the Middle Ages, the sick and poor were looked after only by the monasteries. With the dissolution of the monasteries in the reign of Henry VIII, a large amount of the provision for the sick and destitute disappeared and consequently, in the reign of Elizabeth, we find the first Poor Law giving power to Local Authorities to provide relief for poverty and sickness. The work under various Poor Law Acts steadily increased and eventually included the care, not only of a large number of acute sick, but of the great majority of chronic cases of illness. The next development was the formation of the voluntary hospitals, mostly in the 17th

¹ The present report is based on a study of the hospital development in England only. Unfortunately, time did not allow of a visit to Scotland, where the hospital administration is distinct from that of England. The difference in the hospital administration in Scotland and the fact that this country did considerable pioneer work in connection with hospital development is sufficient to warrant a separate study.

In connection with the preparation of this report, the writer wishes to express his thanks for the assistance of the Ministry of Health and the London County Council. He wishes to acknowledge in particular the valuable help of Dr. Macewen and Dr. McIntosh, of the Ministry of Health, of Sir Frederick Menzies, of the London County Council, of Dr. Frazer, Medical Officer of Health of Liverpool, and Dr. Newsholme, Medical Officer of Health of Birmingham.

century, for the treatment of acute sick. Finally, after the industrial revolution and the passing of the Public Health Act in 1875, hospitals for infectious diseases only began to be created. Until the passing of the Local Government Act in 1929 there were therefore in England, broadly speaking, three entirely different groups of hospitals, administered by three different groups of authorities. In the first place, there were the Poor Law hospitals, dealing chiefly with chronic and senile cases, and commonly combined in the same building with accommodation for the destitute. Secondly, there were the voluntary hospitals, many of these having very old charters dating back 100 or 200 years, supported by voluntary contributions entirely and as such completely independent of any control either by the central Government or by any Local Authority. These hospitals were used to a great extent for the teaching of medicine as well as for the training of nurses. Thirdly, and finally, there were the hospitals for infectious diseases, which were administered by still another authority—*i.e.*, the local Municipal or District Council. These hospitals included accommodation for cases of infectious disease and later for tuberculosis, etc.

As the result of the passing of the Local Government Act, 1929, the first authorities—the Guardians of the Poor—ceased to exist and their functions were transferred to the County and County Borough Councils. At the present time, therefore, in England, speaking broadly, all hospitals¹ fall under one of two administrations. They may be voluntary or they may be administered by a Council, and as such constitute Municipal or Council hospitals. Further reference to the details of this change are given on page 255.

At the same time, there has been a greatly increased demand for hospital treatment generally during recent years for a number of reasons. With the rapid growth of complicated methods of diagnosis requiring special equipment, especially such facilities as X-rays, pathological laboratories, etc., the hospital has come to be an essential for all classes of the community and not for the poorer class only, as hitherto. The increasing tendency to live in

¹ It should not be forgotten that a very large amount of the medical and surgical work done in England is carried out in private nursing-homes. These cater generally for a different class of patients than those dealt with by the voluntary and Council hospitals but are required to be registered under a Local Authority under the Nursing-Homes Registration Act of 1927.

flats and in small houses has made the treatment of anything but the very mildest illnesses almost impossible at home. In addition, the increasing average age of the population has led to an increase in the hospital provision necessary for old persons. The rapid development of contributory schemes and the growth of the work of the National Health Insurance scheme has made the population much more "hospital-minded" than was previously the case. It is probable that the wide spread of unemployment has necessitated admission to hospital for a very considerable number of patients who would ordinarily have been treated at home. The improved roads and the development of the motor ambulance have enabled patients in remote country districts to be readily brought into hospital, so that the hospitals have been compelled to serve a much wider area than was previously the case. All these tendencies have resulted in a greatly increased demand for hospital accommodation. In addition, the increased call upon the municipal hospitals may to some extent be due to the inability of voluntary hospitals to extend in proportion to the call made upon them.

A specially interesting feature in England at the present time, therefore, is the rapid development of fully equipped general hospitals owned by the Municipality or County Council (hereafter referred to as Council hospitals) which are running parallel to, and in some cases closely collaborating with, the old system of voluntary hospitals. At the same time, some of the old Poor Law hospitals for chronic cases, with indifferent equipment, are being converted into modern fully equipped general hospitals, available not only for the destitute sick but also for all members of the community.

The Poor Law hospitals are now administered by a Local Authority in virtue of the Local Government Act of 1929. A summary of some of the points of interest in this Act is given as Appendix I. Briefly, this Act provided, not only for the new administration of the old Poor Law Institution, but in addition provided for consultation between the Local Authority and the voluntary hospitals in the district, gave power to County Councils to build new hospitals (other Local Authorities already had this power under the Public Health Act, 1875) and, finally, laid down the conditions under which the Council or County Borough should recover the cost of maintenance from a patient or those responsible for him. One of the principal objects of this Act was to co-ordinate

under the Local Authority all general health services, such as maternity and child welfare, school medical services, mental, the control of infectious diseases, venereal disease, and general hospital services. At the same time, the guiding principle in England appears to be so to develop the hospital services that they will meet the needs of the general practitioner in the treatment of his cases and, even in remote districts, the general practitioner should be able to benefit in his treatments by hospital facilities—operative, diagnostic, and special.

The conversion of the Council hospitals, together with the need of the voluntary hospitals for funds, has had a large number of unforeseen results, especially in connection with the development of the partial payment by the patient for the hospital services he receives. This has led to various forms of insurance, through contributory schemes or privately, to the development of the paying-bed system in voluntary hospitals, to the issue of debentures on paying-beds to provide for the construction of new voluntary hospitals, in the case of municipal hospitals to the legal right to make a charge to patients, to the consideration of the question of the remuneration of medical staff, to the study of problems connected with the nursing of the chronic sick and the grouping of hospitals for acute and chronic cases, and above all to the collaboration along various lines between the municipal and voluntary hospitals (cf. pages 225 and 226). Moreover, there has followed an increased growth of cheaper hospitals for convalescent cases and chronic cases, with the weeding of these cases out of expensive acute hospitals and the construction of hospitals outside the towns where land is cheaper.

Before describing the relationship existing between the Council hospitals and the voluntary hospitals, a note may be useful as to the different functions of these two groups of hospitals. The function of a voluntary hospital is comparatively simple, in that the work is to provide accommodation for one main class of case—viz., acute cases which require beds for a strictly limited time. There is a broad rule in many voluntary hospitals that a case staying in more than eight weeks is regarded as chronic and, where possible, accommodation is found for it elsewhere. With regard to the financial situation of the London voluntary hospitals, the report for 1932, in spite of a year of marked financial depression generally, shows that the voluntary gifts to hospitals other than legacies have increased, whilst the total running expenditure has been reduced,

although the services and equipment have been made available to other classes of the community requiring medical assistance.

The rapid development of contributory schemes (cf. page 254) has resulted in the great improvement in the financial position of the voluntary hospitals generally throughout the country. As a result, the voluntary hospitals are becoming more and more devoted to the treatment of the worker and his dependants, as the contributory schemes in general are not supported by the very poor. Voluntary hospitals have full power to admit or discharge whom they desire, without reference to any other authority. Their activities are limited only by the charter under which they exist in a number of cases, and it is interesting to note that, for private pay beds, it has been necessary to obtain in some cases a special Act of Parliament in order to get the necessary powers to make charges to patients. The voluntary hospitals enjoy a complete freedom from political supervision, as they are under no local government authority, as is the case with Council hospitals. A further characteristic of the voluntary hospitals is the fact that they serve to treat many patients resident far outside their area, whereas the Council hospitals primarily serve only residents in the district. Thus, in twelve teaching voluntary hospitals in London, of every eight patients treated three are not Londoners.

Both on general and economical grounds, it is generally considered undesirable for the voluntary hospitals to be absorbed in the Council hospitals. At present the large voluntary hospitals serve as teaching centres and almost all medical education in universities is given through them. Should such hospitals cease to be voluntary and become Council, the teaching of medicine would at once be placed under a local government body, which many consider highly undesirable. From the economic point of view, the immediate absorption of the voluntary hospitals would be reckless finance if effected suddenly at the present time.

Referring now generally by contrast to the Council hospitals, it must, in the first place, be pointed out that the Council hospitals are, under statutory obligations, bound to admit all cases which are "medically destitute", whether acute or chronic. The voluntary hospital, in view of the increasing demand for hospital accommodation, has failed to keep pace with the requirements, and in some areas it has been found, after careful surveys of many areas, that

there is a deficiency of hospital accommodation. The tendency is therefore for the municipal authorities to get more and more acute cases, on account of the delay in admission to the voluntary hospitals. Thus, in the case of Liverpool, the increase of patients' admissions to the municipal hospitals is 10 per cent per annum, and the type of patient now using the municipal hospital includes large numbers of the better-class working-man. In the contributory scheme in Birmingham, for instance, half of all the patients treated elected to go to Council hospitals and half to voluntary hospitals.

It is clear therefore that, from every point of view, a close collaboration should develop between the Council hospitals and the voluntary hospitals, and already much of the ground-work for this collaboration has been prepared. Thus, under the 1929 Local Government Act, provision is made for consultative committees for consulting with voluntary hospitals when making provision for further hospital accommodation. There appears to be some doubt in the minds of many as to whether simply consultative powers are sufficient or whether a joint executive committee should not be provided. A consultation is carried out with the voluntary hospitals local committee, representing the governing bodies of the voluntary hospitals and the medical staffs, and dealing with the provision of any hospital accommodation intended to be provided by the Council in the area concerned. Synchronously with these consultative committees of the Council, there is a general movement amongst the voluntary hospitals to form combined committees amongst themselves to co-ordinate and prevent overlapping—*e.g.*, recently in Leeds and Liverpool—and also for the purpose of meeting the consultative committee of the Council.

Collaboration between Voluntary and Council Hospitals.

The relationship of the work undertaken by the hospitals, whether acute or chronic, is determined locally. In some districts acute cases are dealt with by the local voluntary hospital, the Council hospital looking after convalescent and chronic cases, whilst in other districts voluntary effort is diverted into such other channels as after-care, district nursing, etc., the Council hospital dealing with the acute cases. In some cases, further collaboration is obtained by the Medical Officer of Health of the district being

made a member of the voluntary hospital committee. In a very large number of instances, work is carried out by voluntary hospitals on behalf of the Council hospitals, the Council paying the voluntary hospital for such service. Thus, financial arrangements are commonly made between Local Authorities and voluntary hospitals for the treatment of maternity cases, chiefly complicated cases and puerperal fever cases. Again, financial arrangements are entered into between Local Authorities and voluntary hospitals for the hospital treatment of tonsils and adenoids, the Council paying generally about 5s. a day or £1 11s. 6d. per case, unless the surgeon is paid separately. Under most of the contributory schemes throughout England, which were primarily started to maintain financially the voluntary hospitals, the contributors, through collaboration between the Councils and the voluntary hospitals, have the choice of admission to either a Council or a voluntary hospital bed. In connection with teaching, collaboration is developing. This is especially so in London, where each voluntary teaching hospital has been associated with a Council hospital or hospitals, for teaching purposes. At the same time, post-graduate teaching in both voluntary and Council hospitals is being co-ordinated. Again, in London, the London Voluntary Hospitals Committee has been formed as a representative body to be available for consultation with the London County Council under the Local Government Act of 1929. This Committee has existed for three years and served to link up the medical education of the undergraduate in the medical school hospitals with the Council hospitals, and has carried out a survey of existing voluntary hospital facilities in London synchronously with the London County Council, which has carried out a similar survey in the case of the Council hospitals.

The above are some of the more general lines upon which collaboration is developing, and the tendency appears to be for this to increase steadily in every direction. As pointed out by Sir George Newman, Chief Medical Officer of the Ministry of Health, in his report for 1929, it is hoped that co-operation between the Council hospitals and the voluntary hospitals will develop, particularly in connection with the following points :

- (a) The efficient general management of the Local Authority hospitals.

(b) Their suitable medical and surgical staffing and the relation of such staffing to :

- (1) The Medical Superintendent ;
- (2) The medical staff of the local voluntary hospital ;
- (3) The general practitioners of the area.

(c) Exchange of information.

(d) Availability of beds at public and voluntary hospitals and their economical use for the whole community.

(e) The measurement of the need for new beds (voluntary or municipal) and the source of capital expenditure for their establishment.

(f) Allocation of patients effectively and economically (according to disease, sex, age, social conditions).

(g) Methods and practice of admission to hospital.

It appears likely, therefore, that for some time, at any rate, efficiently organised and properly equipped Council hospitals will co-operate, on the one hand, with voluntary hospitals and, on the other, with the general body of the medical profession in the area. It will perhaps be of interest here to refer to the system envisaged by the British Medical Association, which in its publication of Hospital Policy, amended 1933, envisages a hospital system in which all hospitals in a given area will be grouped round a central or base hospital. Details of the Association's scheme are given in Appendix III.

Passing to the consideration of the functions of the various individual hospitals, accommodation is required in general hospitals for the following classes of patient :

(1) Patients acutely ill :

(a) Suitable for general wards ;

(b) Requiring special wards—*e.g.*, delirious, venereal disease, etc.

(c) Requiring special treatment—*e.g.*, orthopædic, ophthalmic, etc.

(2) Patients suffering from less serious acute diseases, or chronic diseases :

(a) Suitable for general wards ;

(b) Requiring special wards ;

(c) Requiring special treatment.

These again may be divided into those having a prospect of cure and return to their homes, and those without such prospect.

- (3) Sick children, (a), (b) and (c), as above, under (1).
- (4) Maternity patients :
 - (a) Normal ;
 - (b) Complicated, septic, venereal disease, etc.
- (5) Mental patients admitted for observation.

There is considerable discussion as to the desirability of complete segregation of chronic cases in special hospitals. A hospital for chronic cases can be much more economically run than a general acute hospital. The opinion is held that chronic cases in an acute hospital may be neglected as being less interesting and, it may be added, the custom of separation of chronic cases has always held in England and has worked very satisfactorily. On the other hand, the advocates of admitting chronic cases to general hospitals urge :

- (1) That this is less depressing for the chronic patient, who loses heart if relegated to a chronic hospital ;
- (2) It provides teaching facilities for medical students and nurses in chronic cases, which in later life commonly form the greater part of their practice ;
- (3) It obviates the difficulty that is experienced in staffing a chronic hospital, both from a medical and nursing point of view.

A further note of interest in connection with the classifying of cases in hospitals is the recommendation of the Departmental Committee on Maternal Mortality, which considered that new maternity accommodation, unless a very considerable amount was to be constructed, could most satisfactorily form part of a general hospital. The reason for this was partly economical and partly because the Committee felt "that a higher standard of obstetrics can be obtained where the resources of a general hospital and the services of a special staff, non-obstetric as well as obstetric, can be relied upon at any moment".

The value of providing adequate convalescent home accommodation is being more and more realised as economically sound in obviating the use of expensive acute hospital beds by patients who are in a state to be satisfactorily treated in a cheaper convalescent home.

Where possible, in large hospital groups, there appears to be a growing tendency to create special wards for nervous diseases, cancer, rheumatoid arthritis, epilepsy and orthopædic defects requiring prolonged treatment, and similarly the creation of special units in connection with the treatment of fractures, congenital deformities and plastic and thoracic cases. In connection with the provision of convalescent homes in order to reduce the pressure on acute hospital beds, mention should be made of the fact that in London, owing to the effective co-operation between the medical and district nursing services, there is some reversal of the usual tendency to seek hospital accommodation in sickness. The services of district nurses in reporting on the suitability of patients' homes for home nursing have also been of much assistance. More demand is being made for nursing in the home, and the resulting saving in hospital expenses must be set off against the cost of a larger home-nursing service.

Speaking generally, therefore, a common division in hospital accommodation in England appears to be :

- (a) General hospitals, to accommodate acute surgical and medical cases (male and female), with a proportion of chronic cases in special departments and special units for such cases as children, maternity, venereal disease, etc. ;
- (b) Convalescent hospitals, to relieve the pressure on acute hospitals and to provide open-air treatment ;
- (c) Hospitals for chronic cases ;
- (d) Special hospitals.

The latter class vary according to the size of the city concerned, but provide separate accommodation commonly for epilepsy, nervous diseases, etc. A further note on the classification of hospitals in London is given later on page 241, when the London County Council hospital service is discussed. Generally speaking, as far as possible, acute hospitals are placed either in the centre of the city or commonly within a short ambulance drive of the centre of the

city ; convalescent hospitals in the country or by the seaside ; and chronic hospitals in the suburbs, so as to allow of visiting.

It is not the custom in England to admit cases of infectious diseases to separate blocks in general hospitals, but to a special hospital for infectious diseases.

One of the most striking features in the last few years throughout England has been the great increase in the relative number of maternity beds in hospitals and the creation of ante-natal clinics in association with maternity hospitals or maternity blocks of general hospitals. A quarter of the total number of births in Liverpool, for example, now take place in maternity hospitals. Each hospital has a consulting ante-natal clinic, to which medical officers of the numerous district clinics can refer cases for advice. The consultant of the ante-natal clinic at the hospital has at his service all the pathological, radiological and other special aids which he may require, and he can, if necessary, admit the patient for observation to the ante-natal ward.

In addition to the great increase in beds for maternity and the rapid development of ante-natal clinics in connection with hospitals, a further interesting development in the organisation of maternity work is the provision for the treatment of puerperal mania. Cases of puerperal mania often recover rapidly, and it is therefore very undesirable to certify such persons as insane, and so stigmatise them permanently. Such cases are treated in special wards or cubicles as "temporary patients", under the provisions of the Mental Treatment Act which now extends the period of permissible detention in a general hospital, without certification under the Lunacy Act, from a maximum of seventeen days up to six months.

In connection with children's hospitals, or blocks for children's diseases in general hospitals, apart from new types of construction referred to in Part II of the present report, there are one or two recent developments of interest. There is an increasing tendency to isolate younger children on admission for at least forty-eight hours, or where possible for three or four days, in order to avoid the introduction of infectious disease. This has resulted in the construction of as many cubicles as can be conveniently provided, into which all admissions of younger children are taken. It appears likely that, in new hospitals, a still larger proportion of cubicles for admission and isolation will be provided.

An urgent problem in all children's hospitals is the future care of infants discharged from hospital after gastro-enteritis, marasmus, pneumonia, etc. Many deaths occur amongst children, who relapse after discharge from hospital. The custom is growing, therefore, of keeping children under observation after discharge, either in the "continuation clinic" of the hospital, or in other cases by means of the health visitor, who is notified forty-eight hours before the child is discharged. This allows of the home being visited on the day of discharge and the treatment being supervised.

The importance of the aseptic treatment of certain groups of infants' diseases is being more and more realised and practised. This particularly applies to young infants suffering from marasmus. Special wards are now provided for such cases, in which all the children are nursed virtually aseptically. Thus, the nurses, doctors, visitors, etc., all wear masks, and the nursing is done with rubber gloves. All bed-pans, washing bowls and food utensils are sterilised in three large sterilisers attached to the ward. Striking results have been obtained by this method of treating cases of marasmus, and special reference should be made here to the work of Dr. W. E. CROSBIE, at the Alder Hey Hospital, Liverpool. In another group of children's diseases—namely, orthopædic cases—it has been increasingly realised in recent years that a very large number of crippled children can be treated by the development of after-care clinics and home nursing, thus obviating the use of hospital beds. This has been strikingly shown in a memorandum prepared by the Committee of Management of the Edinburgh Hospital for Crippled Children. In connection with this hospital, a scheme of clinics to serve the hospital has been evolved for diagnosis, early treatment, minor treatment and after-care, and it has been estimated that, for every case needing admission to hospital, there are twenty which can be successfully treated as out-patients.

A further development in connection with children's hospitals has been the growth of consultation clinics in the out-patients departments, to which the private practitioner can refer cases for special investigation, advice, and, if necessary, treatment.

Closely connected with the collaboration between the Council and voluntary hospitals and the general accommodation provided is the method by which the needs of any district for hospital beds

is determined. The old method of estimating the number of beds required for different diseases in terms of a percentage of the population is falling into disrepute, owing to the enormous variations in the need for beds of different types amongst different classes of the population. The ordinary method employed is to determine the need for beds from :

(1) Hospital waiting-lists. In this connection, it should be noted that these may be deceptively short, owing to the growth of the belief that it is useless for patients to put their names down, owing to the difficulty of gaining admission. On the other hand, the waiting-list may be deceptively long, because of a temporary rush of urgent cases, and also from the fact that the names of patients who have obtained treatment elsewhere may still be on the list, as well as the names of patients who only require one or two days in hospital. Waiting-lists can only be used as a guide, and cannot be depended upon alone.

(2) A study of the number of vacant beds in the hospitals of the district or the amount of overcrowding. Such enquiries must extend over a period of years, so as to cover times of high and low pressure.

(3) Finally, useful information can be gained from the opinion of private practitioners as to the difficulty they experience in obtaining admission for cases, and also from clergymen and others concerned with the sick.

Allied with the question of the provision of hospital accommodation is that of the saving of existing beds. Increasing efforts are being made throughout England to segregate only the acute sick in the expensive acute general hospitals, and, by rapid diagnosis and adequate staff and facilities, to lessen the length of stay of each case in hospital. Convalescent hospitals serve to effect great economies in the cost of the acute hospitals, as do the development of the home-nursing services and the functioning of out-patients' departments as "continuation departments". Reference should also be made to the new continuation hospitals which are now being constructed in connection with a number of large acute hospitals, and serve for patients who, though too ill for convalescent homes, nevertheless require prolonged treatment which can be given in a

less expensive hospital than an acute general hospital. Continuation hospitals are commonly situated in the country, where sites are less expensive, and serve as an intermediate between the convalescent home and the acute general hospital.

Medical Staff of Hospitals.

In a considerable number of hospitals, the question of the alteration of the age-limit and the length of tenure of office is being considered, so as to provide for more practitioners to be appointed to the staff, and, where possible, arrangements for the admission of private patients, who can be attended by their own practitioners, are being made. At the same time, most hospitals feel it is too great a responsibility to allow any cases in hospital to be treated by any other practitioners than those appointed to the staff. Generally speaking, patients admitted to hospital can only be treated by the members of the staff appointed, both in the case of voluntary and Council hospitals, though exceptions occur, most commonly in connection with maternity cases.

A further point in connection with medical staffs that has arisen recently as a result of the development of contributory funds in connection with voluntary hospitals, and the appointment of salaried medical officers at Council hospitals, is the question of whether honorary staffs of voluntary hospitals should be paid from the contributory funds. The final report of the Voluntary Hospitals Commission recommended that, though the services of the staff, in the case of voluntary hospitals, are honorary, they obtain a valuable return in the form of surgical experience and the reputation as a member of the visiting staff of a big hospital. If the system of carrying over a percentage to a staff fund is confined to cases where the full cost is paid by the patient, including treatment, there is no objection, but any extension beyond these limits appears to endanger the future of voluntary hospitals. On the other hand, the British Medical Association suggests that a contributory scheme should be taken to cover the cost of maintenance and ordinary treatment of patients, and that therefore a percentage of all such receipts should be passed into a fund which is at the disposal of the honorary medical staff. Actually, the contributions to the newer contributory schemes are higher than to the older organised

workmen's collections, and it is now a common practice in cottage hospitals for medical officers to charge fees to the patients, as the schemes are only intended to cover cost of maintenance in hospital. The practice of the payment of the staff from contributory funds appears, however, to vary very much in different hospitals, and is discussed under "Contributory Schemes", pages 254-259.

Reference should here be made to the staffing of hospitals, as recommended by the British Medical Association, as given in Appendix IV. It appears to be generally held that the medical staff should have the sole word in the treatment to be given to each individual patient, but that the public authority employing a doctor should have the sole voice in his appointment. It is considered that there is no reason why a medical association should not advise about salaries and general conditions of employment, and even consult with the public authorities, but the final responsibility of the appointment must rest with the latter. The opinion is that the doctors or their representatives should have access to the administrators of the medical services, and that some channel should be afforded through which the medical officers can tender advice as to the development of the medical services to the administrators concerned.

As a result of the development of the Council hospital, with its salaried staff, and especially the gradual development of out-patient departments, not simply as treatment centres for large numbers of minor ailments but as consultative centres, there has been an increase in the demand for the service of consultants, especially by the class of patient who, whilst not able to bear the full ordinary consultant fee, is willing and anxious to pay a certain amount. In addition, there appears to be a growing desire to include a consulting service under the benefits of the National Insurance Act. The first list of consultants willing to accept a lower fee was set up recently in the Metropolitan area after consultation with the British Medical Association, in connection with the Hospitals Saving Association, referred to on page 257, in order that its members should have an opportunity of securing private consultations from consultants of repute at fees which the members could afford. The names of several hundred practitioners were included in the list, and the list was made available to members of the Hospitals Saving Association. This worked out so satis-

factorily in the Metropolitan area that the proposal to extend it to the provinces is under consideration. Consultant lists would be formed in the different provincial districts, but only if the consultants in each area concerned agreed to the establishment of such a list. In the case of the Metropolitan area, the consultants are available for :

- (a) Persons entitled to medical benefit under the National Health Insurance Act ;
- (b) Members of approved hospital contributory schemes ;
- (c) Members of approved medical services.

Any patient in these groups is now able to have a consultation for one guinea. There is a class of persons who previously only had the opportunity of a consultation at high fees, which they could ill afford, or else got advice free through hospitals, voluntary or municipal, and the arrangement for less expensive consultations, therefore, prevents patients from having to overcrowd the hospitals, and maintains a close relationship between patient and doctor.

Conditions under which a name should be added to the list of consultants when these have been created in each district have been laid down by the British Medical Association. A candidate for the list would have to show :

- (1) That he was holding, or had held, hospital or other appointments affording special opportunity of acquiring special skill and experience of the kind required for the performance of the service to be rendered, and that he had had recent experience in performing such service ; or
- (2) That he had made special academic or post-graduate study of the subject comprising the service to be rendered and had had actual recent experience in performing such service ; or
- (3) That he was generally recognised by other practitioners in the area as having special proficiency and experience in the subject comprising the service to be rendered.

The large number of appointments made to the new Council hospitals, both of medical and surgical specialists, has led to considerable discussion as to the terms and conditions of service of such consultants. The question of whether consultants should be appointed on a whole-time or a part-time basis has not yet been agreed upon, some authorities following the first practice, and others

the second. The London County Council (cf. page 241) has made appointments very widely on a sessional basis. On the other hand, in some big provincial cities, there is a feeling that better service is obtained by whole-time surgeons or physicians employed entirely by the authority. The advocates of the engagement of specialists on a sessional basis urge the possibility that this gives of securing the services of the very best type of consultant with an established name. In addition, it is pointed out that the whole-time appointments do away entirely with competition and with the necessity for keeping fully abreast with the specialist knowledge required. Such full-time appointments also provide little financial future for the candidates as compared with private surgical practice, and consequently are not likely to attract the best men, or, at any rate, will only be used as stepping-stones. On the other hand, it is pointed out by the opponents of the sessional basis that experience has shown in a number of cases that the part-time surgeon is very apt to systematically delegate much of his work to those members of the staff who are his juniors, and that, in practice, much more work relatively is obtained from the whole-time surgeon than from the part-time appointment. In this connection, it is interesting to note the recommendations of the British Medical Association to the London County Council, at the time when the appointments of specialists to the new London County Council hospitals were being made. The extent to which these recommendations were followed will be seen by reference to the later part of this report, when the conditions under which the appointments under the London County Council were made are set out in detail. The recommendations of the British Medical Association were :

- (1) That payment should be on a sessional basis ;
- (2) That there should be inter-availability between the groups of hospitals, so that the consultant at one hospital might obtain the opinion of the consultant at another ;
- (3) That consultants should be organised so as to work in teams or groups ;
- (4) In the case of surgeons, that a flat operating rate should be paid.

In order to ensure close co-operation between the Council and voluntary hospitals, it is clearly necessary that the same standards

of consultants should be maintained in both. Selection should be made by an advisory committee, consisting of men whose professional standard and contact with clinical medicine make them able to judge the worth of the candidates. Hospitals should be grouped on a geographical basis, and consultants appointed to the service as a whole, and attached to definite groups for service.

In connection with the staffing of hospitals, mention should be made of the growing opinion, in certain quarters, of the value of a special group of nurses for the nursing of chronic cases. It is pointed out that, in fact, at the present time, the greater proportion of the nursing of chronic cases is done by nurses who have failed to pass the examination for State registration as nurses. It is urged that it is unfair that nurses who can carry out satisfactorily the work of nursing chronic and senile cases, and whose sympathetic nature qualifies them particularly for this work, should not have a recognised diploma for this class of nursing. It will be recollected that special diplomas are given in connection with the nursing of infectious diseases, tuberculosis, etc., and it appears to many not irrational that a special diploma for chronic nursing should be given. Added to this is the fact that there is unemployment amongst trained nurses, suggesting the necessity of limiting the type of fully trained nurse, as the number is generally thought at present to exceed the demand.

Finally, it should be remembered that there are a large number of chronic cases in private homes who do not require to go to hospital and who cannot afford the services of a fully trained nurse and are not desirous of utilising the free services of a charitable nursing organisation. Such cases perhaps form the majority of cases for which home nursing is required in England, and it is felt by a large number of those qualified to judge that a "ward orderly", who could be obtained at a lower fee and who need not possess the high surgical training of the fully trained nurse, is an urgent necessity at the present time. It has been suggested either that the examination for such "ward orderlies" should be of a lower standard than that required for the fully trained nurse, or that the training should be the same in both cases, but the standard required at the final examination should be higher in the case of the fully trained nurse. The problem really appears to be, in the

chronic hospitals, whether it is better simply to accept failures as nurses, and to give no certificates, or whether it is not fairer to establish the position of such nurses by the granting of a special diploma for chronic nursing. At the same time, there is a strong feeling that should such a class be created, it is desirable to reserve the use of the word "nurse" for a fully certificated nurse and to designate others by some such term as "ward orderly". On the other hand, the whole question of the desirability of limiting the number of training-schools is one of great difficulty, as this would cause economic difficulties to hospitals, inasmuch as probationers in training are paid so much less than the fully trained nurses with whom it would be necessary to staff a hospital if there were not probationers in training. A further difficulty experienced at the present time is the trouble of getting fully trained nurses to accept service in country hospitals, though this is being met to some extent by the provision of higher salaries in order to compensate for the isolation.

Admission to Hospital.

The voluntary hospitals are under no obligations to receive any individual case, and the question of admission or non-admission lies entirely with the hospital authorities. In both the Council and voluntary hospitals, however, few are admitted to hospital purely on medical grounds, but generally partly on medical grounds and partly on home environment and financial position. In the case of the acute sick, the medical reasons generally predominate, and in the case of the chronic sick, it is generally the financial. It is clear that, as far as those responsible for the hospital are concerned, they must necessarily rely on the medical officer for advice as to the medical needs of the case, but as far as the decision to admit depends on the financial position and home environment, they must depend on their own judgment after hearing the report of an investigator. The Council hospital is statutorily responsible for the admission of the "medically destitute", and the determination of who is medically destitute lies with the Council and must, in fairness to the community, be carefully investigated. It is clear that a certain number of acute cases must be admitted urgently on the medical superintendent's instructions, and indeed there appears to be a

tendency for the admission generally of cases to be delegated more and more to medical superintendents. On the other hand, it is outside the scope of the medical superintendent's work to decide whether or not a case should be admitted upon financial grounds. The position has become more complicated in view of the increasing desire for admission to Council hospitals amongst a class of patients who have hitherto not applied for hospital treatment, and there is also the tendency of medical practitioners, working under the Insurance Act, to send patients to hospital as soon as possible. In actual practice, a common method adopted is the admission of cases by the medical superintendent at the request of the general practitioner concerned. The income of the patient is then assessed by a special investigating officer or almoner, and he or those responsible for his maintenance pay either in full or a proportion, determined upon a fixed scale, and depending upon his income. This assessment does not affect, in general, members of contributory schemes with which the Council have a special arrangement, either receiving so much per case or a block grant. Commonly, and approximately, of the admissions a third are sent by practitioners under the National Insurance Act; a third are recommended for public assistance from the relieving officer, and a third are sent by private practitioners.

Out-patients Departments.

A rapid change in the ideas with regard to the work of out-patients departments has occurred in the last few years. Hitherto the large out-patients departments have been connected with voluntary hospitals, and have served to treat very large numbers of trivial illnesses, many of which, it is now thought, should be treated by the general practitioner. It appears, however, that a change in the character of the out-patients departments is occurring in connection with the number of hospitals and that, "instead of being a place for the congregation of a miscellaneous group of chronic patients, whose complaints could be equally well treated elsewhere, it is becoming pre-eminently a consultative department for the provision of a second opinion, after careful and detailed examination and diagnosis, and also a place for the provision of specialised treatment".

In a number of hospitals, the work of the out-patients departments is gradually being limited to the following groups of cases :

- (1) Casualties and accidents ;
- (2) Continuation or after-treatment of former in-patients ;
- (3) Ante-natal and post-natal examinations and treatment ;
- (4) Consultation, examination and treatment, in special cases.

There is some feeling against these changes in the out-patients work on the part of the voluntary hospitals, on the following grounds :

- (1) The unwillingness of general practitioners to look upon themselves in the position of external checkers for the hospitals ;
- (2) The emotional appeal of the "ever-open door", providing, as it does, propaganda that the hospital is being utilised to the greatest possible extent ;
- (3) The reduction of the amount of available teaching material ;
- (4) That the new developments in out-patients departments will deprive a number of persons needing medical aid or treatment, because they are unable to pay for it.

It has been pointed out, however, that, with regard to (1), the general practitioner should be taught to regard the out-patients department as a place where he can obtain a second opinion without losing his patient. With regard to (3), it is urged that the reduction of the number of cases would allow for more individual study of cases and not tire the workers out, as is the case now, by endless trivial cases. With regard to (4), this does not appear to be important in practice, as the dependants of insured persons can often pay for trivial illnesses and others either obtain it through the National Insurance Act, or can apply to the Public Assistance Committee. In spite of the objections raised, the general tendency appears to be to develop out-patients departments on the lines mentioned above.

The question as to the need for a doctor's letter for out-patients has been the subject of much discussion. The British Medical Association urges that no person, except in cases of emergency, should

be accepted for treatment as an out-patient at a voluntary hospital unless he brings a recommendation from a private medical practitioner, a Provident or other dispensary, a public clinic or from the Public Assistance Officer of a Local Authority. Minor objections have been raised to this in view of the extra cost to the patient, and the fact that a considerable number of patients come because they are dissatisfied with their doctor. It does not, however, appear that these are serious objections. The Hospitals Saving Association (cf. page 257), with nearly one and a quarter million subscribers, strongly recommends that a doctor's letter be obtained, but cannot force this as many hospitals do not require it. The possession of a letter has the advantage that it enables the patient to go direct to the consultant concerned, thus saving congestion in the out-patients department, and, moreover, it puts the consultant directly in touch with the previous history of the case.

The general modern tendency in the administration of municipal hospitals may perhaps be best illustrated by detailed reference to the work of the London County Council in connection with the new Council hospitals transferred to them under the 1929 Act. On the last day of 1932, the London County Council was responsible for 30,609 patients in hospital, including sick-beds in both public health and public assistance institutions, this constituting the largest municipal hospital organisation in the world. During that year, no fewer than 260,000 patients were admitted to the Council hospitals in London. The following, taken from the Report of the Central Public Health Committee of the London County Council, summarises the steps that have been taken, since the passing of the Act in 1929, to develop the Council hospitals in London :

(1) For consultant purposes, the general hospitals have been divided into seven geographical groups, with affiliated special hospitals. The specialists attached are available for head office purposes in connection with the school, medical, and tuberculosis services, etc. Consultants are appointed to the services as required for a group of hospitals. At every hospital are available the specialist services of physician, surgeon, gynæcologist, ophthalmic surgeon, ear, nose and throat surgeon, orthopædic surgeon, dermatologist, paediatrist, neurologist, radiologist, obstetrician and tuberculosis expert.

The consultant and specialist service is on a sessional basis at groups of hospitals, it being considered that a part-time consultant service was better than a whole-time one. More than two hundred part-time consultant appointments have been made, and in selecting the consultants the Council had the valuable assistance of many eminent members of the medical profession.

(2) Wherever possible, smaller units of hospitals have been closed and the different diseases have been grouped in large hospitals. This applies particularly to cases for mental observation, post-encephalitic cases, epileptic cases, chronic patients, thoracic cases, goitres, congenital defects, plastic surgical cases, rheumatism, etc.

(3) There has been a further development of beds for the observation of mental cases.

(4) Out-patients are treated at the hospitals in the following cases :

- (a) Casualties and accidents ;
- (b) Continuation or after-treatment of former in-patients ;
- (c) Ante-natal and post-natal examinations and treatment ;
- (d) Consultation, examination and treatment in special cases.

(5) A central domestic supervisor has been appointed to improve the general feeding arrangements in the hospitals, and to secure more adequate supervision of the domestic work in the kitchens.

(6) A group of six State registered nurses has been sent for training to King's College of Household and Social Science. The courses are for the duration of one year, the first six months being spent at the College, and the second six months in the general and dietetic kitchens of a hospital. The nurses, having obtained a diploma in dietetics, will be appointed as dietitians to a hospital, and will be concerned, not only with the special diets of patients, but also with the organisation of the general feeding of the hospital concerned.

(7) There has been a large demand, which has been met, for increased maternity accommodation.

(8) Arrangements have been made for ante-natal clinics at all the London County Council maternity hospitals.

(9) To aid research work in puerperal fever, five cases are sent and maintained constantly in Queen Charlotte's Lying-In Hospital (this is a large voluntary hospital in London, used for teaching and research purposes). In addition, a puerperal fever unit has been created at the North Western Hospital.

(10) The demand for radium treatment, curative and palliative, is constantly increasing, and one hospital with a special unit has been provided for this purpose. It will be one of the best equipped in the Kingdom.

(11) A comprehensive and modern pathological service has been established and made available for all the hospitals, and a complete specialist and consultant service has also been organised for the hospitals.

(12) The standardisation and centralisation of the supply of medical and surgical requisites for the hospitals involved the setting-up of a special organisation for the purpose, the establishment of the closest co-operation between the Supplies and Public Health Department, and the settling of standards for contracts in place of the varying standards used up to now.

(13) Generally, if suitable, the patient's own clothing is worn in hospital, but where it is necessary to supply clothing for use in hospital, the recent tendency has been to supply brighter clothing of more pleasing style and variety as compared with the somewhat sombre garments previously issued.

(14) There has been in recent years a great development in the libraries in hospitals, many of which have persons voluntarily undertaking librarian's duties with great value.

(15) Uniform conditions of service and recruitment have been settled for the principal grades of staff, including medical, nursing and clerical.

The London County Council has given special attention to such work as :

(1) The further development of maternity services, including ante-natal and post-natal clinics ;

(2) The improvement of the equipment of hospitals ;

- (3) The further development of pathological laboratories ;
- (4) The construction of new operating theatres ;
- (5) The creation and development of special departments, such as X-rays, massage, out-patients, etc. ;
- (6) Improvements in nursing-homes and increase in nursing staff ;
- (7) Improvement in heating arrangements ;
- (8) Improvement in the laundries of hospitals ;
- (9) Increased provision of cold storage accommodation ;
- (10) Provision of sun balconies.

With regard to teaching, arrangements have now been made for the development of teaching facilities for both under- and post-graduates. Each voluntary teaching hospital in London has been associated with a Council hospital or hospitals and, in addition to arrangements being made for the teaching of medicine to students, classes in hospital administration in fever hospitals are also now given.

A new development by the London County Council is the creation, in conjunction with the Ministry of Health and the University of London, of the British Post-Graduate Hospital and Medical School. This is situated in the Council's hospital at Hammersmith, under a charter of incorporation granted in July 1931. The initial expenditure involved is a capital grant of £200,000, of which the Government contributed £100,000, and the school is to be opened early in 1935.

In conclusion, in view of the interest aroused by the terms of the appointments under which consultants have been appointed to the London County Council, it may be of interest to give one or two details as to the conditions under which these appointments were made.

It has been found difficult to estimate the number of sessions for neurologists and anæsthetists which would be required, and panels are therefore to be formed and the services of such consultants utilised as required, and paid for at a sessional rate. Consultants are appointed for a group of hospitals and are engaged on yearly salaries for which they work at different hospitals for a fixed number of sessions a week, at the same time doing any emergency work necessary. The salaries proposed cover the charges for doing

operations, and the period for which a consultant is appointed is normally two sessions a week. The salaries for part-time consultants and specialists are : £125 a year for one session a week, £200 for two sessions, £275 for three sessions, £350 for four sessions, £425 for five sessions, and £500 for six sessions, a session being about two and a half hours. For anæsthetists, the remuneration is 34s. a session, for neurologists 52s. 6d. a session, and for full-time consulting physicians and surgeons £1,250 a year, rising by increments of £50 to £1,500. The whole arrangement is for one year and will be completely reviewed in June 1934.

Accommodation for the Sick who are able to contribute the Whole or Part of the Cost of Their Maintenance and Treatment.

This is provided in England by the following means :

- I. Nursing-homes.
- II. Pay beds in voluntary hospitals or Council hospitals.
- III. Through the medium of various provident schemes.
- IV. By the development of local contributory schemes in connection with voluntary hospitals.

I. Nursing-Homes.

In 1927, the Nursing-Homes Registration Act was passed, which brought nursing-homes under a certain amount of control by the Local Authorities. Under this Act, a nursing-home means any premises used for the reception of, and providing the nursing for, persons suffering from any sickness, injury or infirmity. It includes a maternity home, but does not include : (a) any hospital controlled by a Government or Local Authority or by any other body constituted by a special Act of Parliament or incorporated by Royal Charter ; (b) any institution for lunatics under the Lunacy Act ; (c) any certified institution, certified house or approved home within the meaning of the Mental Deficiency Act, 1918. With the above exceptions, the keepers of all nursing-homes must be registered with the Local Authority and, in addition, Local Authorities may make bye-laws prescribing the records to be kept of the patients received into the nursing-home, of any miscarriages occurring in the home, of the children born therein and of the children so born

who are removed from the home otherwise than to the custody or care of any guardian, parent or relative. The bye-laws may also require notification of any death occurring in a nursing-home. The licence may be refused if the applicant or one of his employees is not considered "a fit person"; if the staffing, construction, situation, etc., render it improper or undesirable as a nursing-home, or if it is not under the charge of a medical practitioner or a qualified nurse who is resident in the home. The licence may be withdrawn upon adequate notice being given and upon a statement of the reasons for the withdrawal. The Act gives right of entry to the Medical Officer of Health or other officer authorised by the Local Authority and allows local authorities to exempt from registration any hospital or institution not carried on for profit. Regulations and bye-laws have been made by Local Authorities under the Act and a summary of those made by the London County Council for the registration of nursing-homes in the London area is given in Appendix II as an example.

II. *Pay Beds.*

There is a growing demand for suitable hospital accommodation for people who, while unable to pay the charges of a nursing-home, desire better accommodation or, at all events, more privacy than is provided in the ordinary wards and who are willing to pay for it according to their means and also to pay something for medical attendance. It is now usual for patients in the ordinary wards of voluntary hospitals to be asked to pay what they can towards the cost. Such voluntary contributions rarely exceed two guineas a week and, in the majority of cases, are much smaller, while patients who are really unable to make any payment are still admitted free. In the larger hospitals, the average cost of treatment, where separate rooms are provided, is now about £4 a week. Realising, however, the need for accommodation for those who are willing to pay more in order to secure more privacy, many hospitals have now made special provision for such patients, either in the form of single rooms, small wards for two or four persons, or cubicles. Medical and surgical fees are not, as a rule, included in the weekly charge, but it is usually contemplated that such fees will be on a modified scale and lower than

those charged to patients in a nursing-home. The amount of the fee is usually arranged between the patient and the consultant. These pay beds have increased in the London hospitals from 590 in 1920 to 1,667 in 1932 and further considerable additions to this number are under construction. A number of recommendations with regard to pay beds have been made by the Committee of the King Edward's Hospital Fund for London and serve generally as a basis, not only in connection with pay beds in London, but throughout England. The recommendations of this Committee include the following :

(1) Pay-bed accommodation should be provided at rates of charge which at least cover the current maintenance cost of all the pay beds in the hospital taken as a whole.

(2) The provision of special accommodation on a limited scale for patients of small means at rates which involve a charge on the general fund can legitimately be regarded as coming within the present extended function of the voluntary hospital system, provided that it is looked upon as a secondary part of that function and that the treatment of ordinary patients is maintained as a primary part. It is not, however, necessary that the weekly charges should cover interest on capital as well as current maintenance for the purpose of calculating the relation of charges to cost.

(3) It must be recognised that pay-bed patients who are merely paying their current cost are deriving benefit from funds contributed to the voluntary hospital system.

4. An efficient mutual insurance scheme should be organised for prospective pay-bed patients to make provision in advance, as has been done for ordinary hospital patients by contributory schemes like the Hospital Saving Association, and for middle-class patients by the British Provident Association.

5. On the question of pay-bed accommodation for the well-to-do, in view of the difficulty of obtaining full hospital facilities, this may well be furnished on a limited scale by voluntary hospitals, provided that the accommodation is not required for ordinary patients and that the charges to the well-to-do are sufficient to cover the whole cost of the beds provided for them, including rent and interest on capital, and to yield a profit available for other purposes of the hospital.

It is considered that a material extension of the provision of pay beds in London hospitals is urgently required to meet the existing demands. It is believed that the extension of the pay-bed system of the voluntary hospital would be of advantage to patients of all classes, to the individual hospitals and to the voluntary hospital system as a whole. The pay-bed patients of moderate means would benefit because they would obtain accommodation and treatment at charges within their means, especially if aided by a scheme of insurance to make provision in advance ; the well-to-do pay-bed patients would benefit because they would obtain facilities which can rarely be fully secured elsewhere, such as the constant presence of skilled medical and surgical attention in emergencies, a complete surgical organisation, and similar services. The ordinary hospital patients would have the use of beds in the general wards, which are now occupied as a matter of urgent necessity by patients who absolutely need the special facilities of a hospital, but who could and would pay extra for special accommodation if it was available. The hospitals would greatly extend their usefulness and it would be an advantage to them that all classes should come to recognise from personal experience the part which they play in the development of the most advanced forms of diagnosis and treatment.

Pay beds are commonly provided in single rooms, in cubicles or in small wards. There is generally no limitation in respect of income. In the majority of hospitals, the medical attendant must be on the staff of a general hospital or, in some cases, on the staff of the hospital concerned. Some hospitals, however, give free choice of medical attendant, especially in connection with maternity cases.

III. *Provident Schemes.*

As defined by the British Medical Association, the aim of a provident association is to develop a scheme for persons of the middle and professional classes on a mutual insurance basis and, in return for a definite premium, to offer to persons of defined income limits financial assistance in respect of (1) the cost of institutional accommodation, in private beds in voluntary or Council hospitals, or in nursing-homes, including all nursing, use of operating theatre, X-ray plant, laboratory, etc. ; (2) the cost of professional services.

A special committee of the British Medical Association has prepared a report setting out certain recommendations with regard to provident schemes. These recommendations serve to a great extent as a basis for the provident schemes in England and are referred to below. Some provident associations only desire to offer grants-in-aid, whilst others offer complete cover against serious illness. The British Medical Association report deals with the latter group and emphasises fundamentally that all provident associations should be actuarially sound. They should develop in close association with the medical profession and should not be restricted to a limited group of persons or in relation to a restricted group of medical practitioners. They should provide for the member free choice of approved institution and free choice of doctor. Patients should only be admitted to benefits on the recommendation of a private practitioner. Provident associations should be set up in an area with inter-availability of membership with other areas and all areas should be linked up in a National Federation of Approved Provident Associations. Provident associations should not be linked with definite hospitals or nursing-homes, but should remain separate financial and legal entities. The governing bodies of provident associations should include representation of subscribing members, area hospital services and the medical profession. Schemes should be administered through area associations and, pending the formation of a National Federation of Provident Associations, it is proposed to institute an Advisory Committee of Provident Schemes. This Committee would include representatives of the British Medical Association, the British Hospitals Association, the British Hospitals Contributory Schemes Association and any existing provident associations. The organisation of any scheme is dependent on the negotiating of agreed scales of fees for medical services and payment for institution accommodation. The following are the income limits suggested :

| | | |
|---|--------------------|------------|
| Members without dependants.... | £375 per annum.... | Class I. |
| Members with one dependant.... | £475 " " | Class II. |
| Members with more than one dependant..... | £550 " " | Class III. |

The annual rates of contribution suggested are :

| | |
|-----------------|---------|
| Class I | £1 18s. |
| Class II | £2 12s. |
| Class III | £3 |

On the basis of 10,000 membership, it is estimated that the average number of members claiming benefit would be 600 and the average cost per claim between £30 and £34. The annual income of 10,000 members is estimated at £22,000, of which £9,000 would go to hospitals and institutions for the maintenance and £10,000 in fees for medical services. Administrative expenses should not in the initial period of the scheme exceed ten per cent of the income. A "claims reserve fund" should be created and at least five per cent of the income should be transferred to this fund. It is recognised that experience of this type of insurance is extremely limited and it is necessary, therefore, to impose definite safeguards and limitations if the actuarial basis is to be preserved. It is suggested that surgical cases be paid for on the following schedule :¹

| | |
|---|------|
| Group I.—Major operations | £25. |
| Group II.—Intermediate operations | £15. |
| Group III.—Minor operations and investigations..... | £7. |

In medical cases and non-operative surgical cases, five guineas a week fee with a maximum fee of fifteen guineas. It is tentatively suggested that the hospital or nursing-home benefit should be at a rate not exceeding £5 per week for a maximum period of three weeks in any one year. The advice of the British Medical Association is available in the negotiation of the details of any provident schemes.

Closely associated with the recommendations with regard to provident schemes made by the British Medical Association and serving as a basis for the provident schemes generally in the country are the proposals of the British Medical Association for a general medical service. This would include the provision of hospital accommodation. The fundamental idea of a medical service for the community is to be based on the provision for every individual of a general practitioner or family doctor. A consultant service of all necessary specialist and auxiliary forms of diagnosis should be available for the individual normally through the agency of the family doctor. Those who need institutional treatment can

¹ The schedule of payments for operative and other work would be subject to the approval of the medical profession in the locality concerned; the scale given above is suggested for guidance only.

be divided into four classes under a medical service scheme, viz. :

- (1) Those who cannot afford to make any payment ;
- (2) Those who will pay by insuring themselves against risk of illness ;
- (3) Those who will use the institutions when they need and pay proportionate charges at the same time ;
- (4) Those who will use private nursing-homes.

This has led to the British Medical Association's suggestion that there is a need for the provision of "home hospitals" or nursing-homes, to which patients are admitted at very low rates, provided either separately or as individual blocks in a Council or voluntary hospital. The development of such home hospitals should, as far as possible, be guided by two principles. In the first place, the opinion is rapidly growing that the sole reason for admission to hospital should be the medical needs of the patients and not, as hitherto, his financial position. Secondly, it is argued that every effort should be made to provide hospital facilities where the family doctor can treat his own patients. In the British Medical Association scheme, the Medical Officer of Health would be administrative head and liaison officer between the profession and the authority which is responsible for the financing and general direction of those parts of the scheme on an insurance basis or provided by the community. The scheme should be administered under some committee the exact formation of which is not yet fixed, but should represent the Local Authority and include representatives of those bodies of persons who are rendering service under the scheme. Such a general medical service would be closely linked up with a local provident scheme on the lines given above.

In London alone, it is estimated that there are 600,000 families—*i.e.*, $2\frac{1}{3}$ million people-existing upon moderate means. To meet their needs in serious illness, 5,000 beds are required in suitable institutions. The need for more beds of this class is admitted to be urgent, and the problem is to provide the capital cost. In the case of paying hospitals, £1,000 is the average cost of a properly equipped hospital bed and one bed suffices for the average needs in any year of 100 families, thus giving £10 as the unit of contribution needed to provide the capital cost for the accommodation for a family. In order to raise the necessary capital and to make provision

generally for individuals of moderate means, the British Provident Association was founded. This aims at providing hospital and nursing-home beds at a reasonable charge, together with means whereby the cost of maintenance during serious illness can be substantially, if not wholly, covered through co-operative effort on the part of the people who are to benefit. The object was to benefit those classes midway between the working classes and the richest members of the community. The contributors to the British Provident Association, which has received the approval of an expert committee set up by the King Edward Hospital Fund, are divided into two groups. In the group known as "founders", each contributor pays £10 and is registered as a founder and becomes entitled to priority of call upon the founders' beds at professional rates of charges. The beds are provided out of founders' contributions, provided in or adjoining existing voluntary hospitals, or later, it is hoped, in separate institutions to be known as the British Provident Association Hospitals. The second group of contributors are known as the "subscribers". In the case of the subscribers, the benefit is paid direct to the subscriber and does not interfere in any way with the free choice of doctor. There are three schemes, depending upon the amount of the subscription, and any contributor can join whichever scheme he prefers.

Scheme I deals with provision for hospital and similar services. The annual rate of subscription is 1 guinea for a single person and 2 guineas for married couples with one or more children. The benefits are a grant not exceeding £5 per week for three weeks towards the cost of maintenance in a hospital or nursing-home, not exceeding 3 guineas per week up to three weeks towards the fees for a resident registered nurse at the patient's own home, not exceeding 3 guineas towards a fee for a consultation at the patient's own home, half the cost of treatment at the Radium Institute up to a maximum of £40, and not exceeding £1 towards the cost of ambulance service.

Scheme II. The annual subscription rate is £2 16s. for a single person up to £6 12s. for a married couple with one child. The benefits include all the benefits payable under Scheme I and in addition a contribution according to a fixed scale towards surgeons' fees up to a maximum of £100.

Scheme III. The rates of subscription and benefits secured are additional to the rates and benefits under Scheme I or Scheme II.

The additional subscription varies from 12s. 6d. in the case of a single person to £1 7s. 6d. in the case of a married couple with children. The additional benefits include contributions at the rate of 1 guinea per day up to a maximum of twenty days towards the fees of a consulting physician in daily attendance upon a case in a hospital or nursing-home.¹

A very large number of provident schemes and other methods for providing hospital accommodation for the middle class are rapidly developing in England at the present time. Reference may be made, in this connection, to the Oxford scheme, which includes :

- (1) A grant towards hospital expenses in the case of richer individuals ;
- (2) A provident scheme covering complete benefit on a fixed tariff for hospital and medical professional services ;
- (3) A contributory scheme for workers of less than a certain income. By this means, the whole population would be covered.

In Birmingham, again, there is no income limit to the contributory scheme, all those above a certain income receiving a grant-in-aid towards hospital expenses. This is discussed more fully below in connection with contributory schemes.

Finally, mention should be made of such developments as that exemplified by the new Manchester Middle-Class Hospital. The Manchester Royal Infirmary, which is a voluntary hospital, has launched a scheme to provide a middle-class hospital in the Infirmary grounds. Patients will pay from four to ten guineas a week, and will receive the benefits of the laboratories, X-ray and other departments of the hospital. Medical fees will be adjusted to the needs of each case. It is intended to construct the new building through the medium of a 4% loan and by gifts, but the interest on the loan will not be payable until 1935, to allow the hospital to be built. The loan certificates are from £10 to £1,000, and it is calculated that the hospital will pay its way, provide the interest on loans, and produce a sinking fund enabling the capital to be repaid in twenty-five years' time.

¹ The scale of payment for surgical operations and the general details of the conditions of the scheme can be obtained from the British Provident Association, 30, Lancaster Gate, London, W.2.

The brief reference to the British Medical Association Report on Provident Associations, the notes on the British Provident Association, and the references to the Oxford scheme, the development of contributory schemes as provident schemes, and the Manchester Middle-Class Hospital will serve to show the very great interest that the provision of medical attendance for the middle class is arousing in England at the present time. Great difficulty is experienced, especially in establishing provident associations on actuarial bases, in determining what benefits should be covered, in fixing what may be considered to be a middle-class income for a single person, a married person, and a person with children, etc.

IV. *Contributory Schemes.*

Contributory schemes are essentially different from provident schemes, in that the latter should pay their own way as compared with the contributory schemes, which do not. Provident schemes are to enable individuals whose incomes are above £200 or £300 a year to make provision for hospital treatment. Contributory schemes, on the other hand, carry with them certain privileges, but do not entitle the contributor to a bed in hospital unless one is available and the patient's medical condition gives him priority. The contributory schemes are run entirely in connection with the voluntary hospitals, and constitute a combination of self-help and charity. Contributors are asked to join a contributory scheme on one or more of the following grounds :

- (1) As an insurance against sickness and as a means at the same time of helping the hospital ;
- (2) On the ground that, when they need admission, contributors had paid towards it and will not be accepting charity ;
- (3) That the hospitals are principally for the use of wage-earners and their contributions should give them a sense of independence in using the hospitals ;
- (4) To assist hospitals in maintaining a regular source of income.

Such contributory schemes are springing up with mushroom rapidity in connection with almost all the voluntary hospitals in England. The schemes vary in the amount contributed and in the benefits received. It is clearly impossible to enter here into detailed

consideration of these points or of the relative merits of the various contributory schemes. A few general remarks will therefore be made regarding contributions and benefits, and three of the larger contributory schemes in England—viz., the Hospital Saving Association, the Birmingham contributory scheme and the contributory scheme of the Merseyside Hospitals Council—will be given in some detail as examples. Generally speaking, a clause is inserted that contributors will be admitted to hospital provided "that there is a vacant bed and that the case is one suitable for hospital treatment". The general opinion appears to be that about £312 a year should constitute a limit of income, the usual contribution being 2*d.* or 3*d.* a week. Contributory schemes are, in general, run by an outside body unconnected with a hospital, but there are a considerable number of exceptions to this rule. In the case of schemes run by outside organisations, a grant of about 10 per cent is commonly made to the auxiliary services, such as district nurses, ambulances, etc. The contributory schemes in England may be divided into two groups : (a) schemes under the control of hospitals, and (b) schemes not under the control of hospitals.

(a) *Schemes under the control of hospitals.*—In the majority of such schemes, the contribution is about £1 per annum, with a fixed income limit which varies with different hospitals from £300 to £500. The privileges vary from complete treatment to expenses of four weeks in hospital. In some cases, the benefit includes 50 per cent off the ordinary private ward charges ; sometimes the ordinary medical fees are covered, but in the great majority this is left to be arranged between the doctor and the patient.

(b) *Schemes not under the control of hospitals.*—The premium is generally about 1 guinea, but may be more, annually. In general, the schemes not under the control of hospitals have no income restrictions of any kind, the benefits vary much more, the arrangement of fees is invariably left to the doctor and the patient, the benefits are almost always a grant-in-aid or so many weeks in hospital, they are generally not limited to one hospital but to any of a number of approved institutions, and they, in some cases, include operations on a fixed scale of charges relative to the amount of the contribution and sometimes inclusive of consultant's fees.

With regard to Council hospitals and their relation to contributory schemes, it was laid down in the Local Government Act of 1929

that the Local Authority must recover from every hospital patient, or from any person legally liable to maintain the patient, the whole of the expense incurred in the maintenance of such patient, or such part of the expense as the Local Authority is of opinion that the patient or his liable relatives are able to pay. The Local Authority may, however, by agreement with any association or fund, such as a hospital savings association or a contributory fund, accept an agreed sum for the hospital expenses in respect of any member thereof. This has led to the development of contributory schemes of insurance for hospital treatment and to a closer co-operation between the voluntary and Council hospitals in an area. Upon the development of contributory schemes, the British Medical Association has kept a watchful eye and has outlined a number of points in connection with all contributory schemes, upon which it lays special stress. Thus it is felt strongly that schemes should not be organised by hospitals but by some outside organisation, that all schemes should make clear the exact limits of the benefits provided, that the contribution to be paid by a contributing agency is to be determined on a tariff agreed upon by the contributing agency of the hospital committee, that no preferential treatment is given to contributory cases, and that the sole reason for admission is to be on medical grounds. The question which the development of the contributory system in almost all the voluntary hospitals in England has raised is that of the payment of the voluntary staffs of the hospitals by contributory patients. The British Medical Association recommends that the contributory scheme should be taken to cover the cost of maintenance and medical treatment and a percentage of all such receipts should be passed to a fund which is at the disposal of the honorary staff of the hospital. Actually, the custom regarding the payment of honorary staffs from contributory funds varies. The majority of honorary staffs do not get any payment under contributory schemes, but, in some cases, are allowed to arrange moderate fees with contributory patients and, in other schemes, 20 per cent of the total amount is paid to the Medical Staff Fund. It is urged that the payment of the staffs of voluntary hospitals from contributory scheme funds is justifiable, in view of the fact that every extension of hospital services lessens the scope for specialists' practice outside the hospital.

(a) *The Hospital Saving Association.*—The unit of the Hospital Saving Association is a group of contributors formed in a place of employment or other centre, with a group secretary nominated by the group to act as a link with the Association. The group secretary is entrusted with a book of green vouchers, which may be issued to eligible contributors for presentation at any hospital on the list of the association. Holders of a green voucher are exempted at hospital from requests for payment for hospital services and from enquiries as to means. The Hospital Saving Association was established in view of the fact that the voluntary hospitals need a larger and more assured income and, at the same time, the wage-earner may need a hospital any day and does not want to make heavy payments at hospital at a time when he can least afford it, or else be dependent whilst in hospital on funds subscribed for the sick poor. The payment is a regular contribution of 3d. a week. In many cases, the weekly contributions are collected from the pay-roll when employees sign a request for this to be done. Some employers add 1d. per week voluntarily to the contributions of the employee. A contributor's income must be limited, if unmarried, to £4 a week or, if married, to a scale laid down and dependent on the number of children. The decision as to whether any case is suitable for hospital treatment and as to the order of priority under which applicants are admitted, whether contributors or not, lies entirely with the individual hospital. The Association does not deal with cases for which provision of treatment is made by the State, such as tuberculosis, mental, infectious cases, etc., though it does provide for such cases as tonsils, adenoids, rheumatism, etc., in spite of the provision made for these conditions by certain Local Authorities. The Association also pays the Local Authority for cases admitted to the authority's hospital. The growth of the Hospital Saving Association is shown by the following figures :

| | Number of contributors |
|------------|------------------------|
| 1924 | 62,390 |
| 1927 | 351,875 |
| 1930 | 810,144 |
| 1933 | 1,156,888 ¹ |

¹ Further details regarding the Hospital Saving Association can be obtained from the Hospital Saving Association, 30, Lancaster Gate, Paddington, London, W.2, by writing to Mr. F. B. Elliot, the Secretary.

(b) *Birmingham Contributory Scheme.*—The Birmingham Contributory Scheme is a purely voluntary effort, the subscription being 3d. per week, with no income limit. Contributions are commonly deducted from the pay-roll on the request of the employee. Contribution to the Association does not ensure admission to any hospital, but patients are admitted at the discretion of the medical staffs and in accordance with the accommodation available and the present practice of the hospitals. Contributors are, however, admitted free to both the voluntary hospitals and the Council hospitals if of the wage-earning class, and a limited grant-in-aid is given to contributors treated in the private ward of any of the voluntary or Council hospitals. The Association does not, however, assist contributors in meeting the cost of treatment received in a private nursing-home. During last year there were as many contributors treated in the Council hospitals as in the voluntary hospitals, the Contributory Scheme paying £1 per case to the Council hospitals at the present time and 27/- from the middle of this year. Ambulances for transport are run and owned by the Contributory Scheme and other benefits are available, such as nursing, supply of surgical equipment, etc. Thus, district nurses are paid 9d. a visit for each visit made to a contributor's home on a doctor's certificate, and, similarly, contributors requiring surgical appliances, glasses, etc., receive 20 per cent reduction, which is met by the Contributory Scheme. On applying for hospital treatment, a contributor must present a voucher showing that the payments are not in arrear and also a certificate from a general practitioner. Arrears are allowed up to three months, but there is an arrangement with the hospitals that, if the arrears are due to unemployment, the patient is taken in free. In Birmingham, with a population of about a million, the total number of contributors registered at the end of the year 1932, the last year for which figures are available, was 431,978, being an increase of 20,430 on the previous year. During 1932, the allocation to voluntary hospitals has enabled distributions to be made to these hospitals equivalent to 78 per cent of the cost of the treatment received by contributory patients.¹

¹ Further details regarding the Birmingham Contributory Scheme may be obtained from the Secretary, Mr. T. W. Place, Carlton House, High Street, Birmingham, 4.

(c) *Merseyside Hospitals Council Scheme*.—This is a 1d. in the £ contributory scheme—i.e., those earning under £2 a week pay 1d.; under £3, 2d.; under £4, 3d.; etc. The contributions are made through stamps purchased at various centres and fastened to a contribution card. Contributors are entitled to free maintenance on admission as in-patients and free out-patient service at the voluntary hospitals and, if admitted to the municipal hospital, free maintenance, provided the patient takes to the hospital an official letter of introduction from a general practitioner. In all cases recovering from serious illness, free maintenance is provided in a convalescent home, when this is considered necessary by the Council's medical referee. The scheme does not accept responsibility for medical fees in a private ward or nursing-home, tuberculosis, mental or infectious cases, or in chronic or senile cases. The income limit is £4 a week for single persons, and married persons with children £6 a week.¹

The rapid growth of contributory schemes throughout England has led to the formation of the British Hospitals Contributory Association, which is a national association formed by the affiliation of the various contributory hospital schemes in London and the provinces. The principal object of the Association is to co-ordinate the existing contributory schemes in various areas, so as to prevent overlapping and to allow of the interchange of treatment of patients between various districts. During 1932, seventy contributory schemes were affiliated to the national organisation, representing an approximate membership of 3,500,000.

The principal problems for the future with regard to contributory schemes are, first, how to make the contributory schemes actuarially sound, and, secondly, how to make them self-supporting. At the present time, benefits received are out of proportion to the amount contributed, the deficit being met by voluntary subscriptions in the case of the voluntary hospitals and out of the rates in the case of the Council hospitals.

¹ Details regarding the Merseyside Hospitals Council Contributory Scheme can be obtained from the Secretary, Mr. S. Lamb, Merseyside Hospitals Council, 87, Lord Street, Liverpool.

Part II.**HOSPITAL CONSTRUCTION.**

With regard to new municipal hospital buildings generally, the first step lies with the local Council. A new building is only decided upon when the need for it has been established and after the other available accommodation in the administrative area has been considered. From the earliest stages, the technical services of the experts of the Ministry of Health are available informally to any Council, either in the offices of the Ministry of Health itself or through the medium of a visit by a medical or other technical officer. In general, a large number of informal meetings and discussions take place between the officers of the Council and the technical officers of the Ministry of Health before the plans are formally submitted with an application for sanction to make a loan. A local Council is therefore enabled to benefit from the wide experience of the technical officers of the Ministry of Health at every stage in the construction of a new hospital, from the preliminary determination of the necessity for building to the final consideration of the plans. It should be mentioned, however, that, in England, the great majority of hospitals now under the Councils were taken over as existing hospitals under the Poor Law, and the great mass of work has been the conversion of these buildings to serve the needs of a modern hospital and the provision of modern equipment, rather than the actual building of a large number of new hospitals.

In England, a general hospital is ordinarily accepted as having the following departments :

- (1) Admission and out-patients' department.
- (2) Ward blocks.
- (3) Isolation block.
- (4) Theatre block.
- (5) X-ray department.
- (6) Resident quarters for medical officers and nurses.
- (7) Laundry.
- (8) Kitchen.

- (9) Mortuary, pathological laboratories, etc.
- (10) Boiler- and power-house.
- (11) Administrative block.

There is a growing feeling that the old method of estimating the cost of a hospital on the "cost per bed" method is unsatisfactory, as this varies so greatly with such considerations as the cost of the site, the proximity of water, electricity and gas, the amount of road-making necessary and the general lay-out of grounds, the loss of interest during construction, and the fees of the architect. The modern method is to determine the cost by means of a cost-sheet classifying the costs under each part of the hospital. By so dividing up, through the medium of costing-sheets, the total cost of the hospital, it is possible to compare the expenditure on each section of the hospital with that being incurred in other hospitals. Under the old system of "cost per bed", for the reasons given above, it was exceedingly difficult to compare fairly the costs of two hospital buildings. In the actual construction of walls, etc., cost is now commonly compared per cubic foot, per square foot, or per foot of wall.

Much discussion is taking place as regards the relative desirability of the construction of hospitals in two or more storeys. In cities, the question of the high value of the site is commonly sufficient to determine unequivocally the building of a many-storied structure. In the suburbs of a city, or in the country, where the cost of the site is not a determining factor, there are strong supporters of both forms of building. The advantages of the one-storied building are that they allow of the construction of verandahs, and lessen the risk of fire. In addition, they can be more easily extended and they obviate the somewhat costly installation of lifts. It does not appear to be certain whether or not the several-storied buildings cost less initially, but it appears likely that their cost of maintenance is less than the single-storied building. The advantages of the vertical type are the economy in construction of foundations, the saving of piping in connection with heating and particularly the great saving on drainage, and, generally, the greater possibility of providing for the engineering services of the hospital economically. In addition, there is less distance for the staff to walk, for the carrying of food, etc., and the supervision of patients is easier.

It needs hardly be added that a vertical building is only satisfactory if there is adequate lift accommodation and if adequate steps are taken to provide, by means of fire-proof staircases, for the escape of patients in case of fire. In the vertical buildings, the whole of the structure is made fireproof.

Closely connected with the problem of the horizontal versus the vertical hospital is the question of the material of which the walls are constructed. This, in its turn, is related to the problem of the permanent versus the semi-permanent building. Bearing in mind the rapid changes constantly occurring in the development of medical and surgical practice, there are many in England who strongly advocate the semi-permanent building, and, in any case, the general opinion appears to be that a hospital building needs last only sufficient time to cover the period of the loan. The advocates of the permanent buildings, on the other hand, point out that there is not more than 10 per cent of difference in cost between permanent and semi-permanent buildings and that, in using a light construction, it is only on the shell of the building that a saving is made, as practically everything within the walls is the same as in more permanent buildings. Finally, it is urged that nothing is cheaper than brick, especially when the cost of maintenance is taken into account.

With regard to the actual material used for the walls there appears to be considerable variation, according to the building material existing locally. Bricks are almost universally available, and their use in 9-inch brick walls is probably the cheapest suitable walling at the present time and has the advantage that they require no skilled labour for erection. The whole steel-framed building, with a relatively thin outer walling of possibly hollow construction, in two thicknesses of brick or concrete slabs, is now a good deal in favour. This is fire-resisting and can be rapidly erected. The life of such a building is generally considered to be not less than sixty years. Walls of this type, if constructed of concrete, have the disadvantages invariably associated with this material—viz., the liability to crack and to sweat. They are, however, strong and appear to be adequate, with sufficient steel framework, for many-storied buildings. In some cases the concrete used is reinforced, thus doing away with the liability to crack, but increasing

the cost of construction. The strength of a steel framework has the great advantage that it allows of the construction of a much greater window area than is possible with the older form of brick construction. Hollow brick walls are being used to some extent and, in some cases, the hollow is filled in with concrete. It is doubtful, however, if these are economical. Another type of wall construction in use is that of cavity-brick walls with a steel framework allowing of greater speed in construction and effecting a definite economy. A full description of the materials commonly used at the present time in England in the walls of hospitals is given in a number of the *Architects' Journal* issued in June 1932.

Generally speaking, the tendency appears to be to cover the internal surface of the walls with Portland cement, finished with Keene's cement, the whole wall being then painted with several coats of paint. Tiles are not in favour, owing to the rough areas between the individual tiles, as every effort is made to get as smooth a surface as possible. In the sanitary annexes terrazzo is commonly used, as also in the waiting-room, kitchen, mortuary, etc.

In order to obviate the cost of rounding of the walls at the floors, wooden fillets are now commonly fixed, which are definitely cheaper to construct than rounded joints.

Roofs.

The question of the flat roof versus the pitched roof is still undecided. The flat roofs have the advantage that they can be converted into sun-rooms for convalescents and also they allow more easily of extension upwards at a later date. The pitched roofs, on the other hand, give air space between ceiling and roof and are more commonly employed in country hospitals. The defect of the flat roof is the tendency to crack, caused by contraction and expansion owing to variation of temperature. In actual cost the difference is not great, but the flat roof is fire-proof and, as far as maintenance is concerned, costs less. A new form of flat roof has been recently introduced in country hospitals, consisting of wooden joists, boarding, and a layer of cork covered with rubberoid, or similar material. In the Lord Mayor Treloar's Hospital at Alton, an annex has been built consisting of five cubicles with sliding roofs of vita-glass and windows on the south aspect which can be completely open. When the roof is raised and the windows are

opened, the patients are exposed to fresh air and sunlight and are still completely isolated. They may be sheltered at once if rain falls and the cubicles can be kept warm, well-ventilated and dry under all conditions. This has the great advantage that the patient does not require to be moved. This appears to be likely to be developed very much in the future.

Verandahs.

Verandahs are of great value but are apt to restrict the free access of sunlight and air to the wards. There is a tendency to increase the verandah accommodation in hospitals to provide for open-air nursing.

Floors.

The perfect hospital flooring for wards does not yet appear to have been invented. Linoleum cracks, cork lino is too soft for bed traffic, terrazzo is apt to crack, tiles are noisy, cement is dusty, and asphalt, which is quieter and cheap, has not a very good appearance. On the whole, wood-block floors appear to be the most generally adopted. Flooring is commonly of pitch pine, oak, or maple, in 3-inch widths, or a thick linoleum laid on ordinary white pine flooring. Magnesite has been tried but is not satisfactory, owing to its tendency to retain grease. Floors of hospital rooms at ground-floor levels have a ventilating space between the floor and the surface concrete to prevent the penetration of the moisture of the sub-soil through the concrete. Linoleum laid direct on concrete allows condensation, with the consequent growth of fungus between the covering material and the concrete. On the other hand, wood blocks laid in concrete are not ideal, owing to the large number of joints, and boards fixed either on fillets or in mastics are liable to rot if the upper part is polished. According to general opinion, ordinary hard-wood boards, carefully tongued, grooved and polished, make the best floors, if laid upon concrete with an air space. The best wood-blocks for hospitals appear to be teak, as it is practically the only wood that does not warp in panel-heated buildings. A number of other hard-woods from Australia and West Africa are now commonly used. If there is no panel heating, an oak-block floor appears to be satisfactory, and for

living-rooms, nurses' bed-rooms, etc., soft-wood blocks are satisfactory.

Tiles are commonly used for the floor of kitchens, sculleries, etc., as they are less expensive than terrazzo. In stairs it is advisable to form treads with a sinking for the insertion of patent treads, as the stone or concrete steps have a much shorter life.

Rubber is being used in a number of hospitals, but has certain disadvantages, particularly : (1) the difficulty in getting rubber to stick satisfactorily to the floor itself ; (2) the tendency to buckle ; (3) the tendency to be greatly affected by variation of temperature ; (4) the expense ; and (5) the difficulty of keeping clean. When rubber is used satisfactorily, it appears to be essential that it should be at least $\frac{3}{16}$ of an inch thick. It should not be laid on concrete until the concrete is thoroughly dry, and should not be laid on wood, as it prevents ventilation. Care must be taken with new wooden floors, owing to the practical impossibility of obtaining in these days wood that is thoroughly seasoned. Generally speaking, no trouble need be anticipated with sub-floors, whether of wood or concrete, which have been in existence for some time and are well seasoned and mature.

With regard to the flooring materials for open-air wards, again nothing really satisfactory has been invented. Terrazzo is perhaps the best, but it is cold and liable to crack. Oak or teak flooring is satisfactory but expensive, as is cork composition matrix.

Cubic Space and Floor-area per Bed.

Little accurate information is available as to the amount of cubic space required per bed. There is the well-known work of GLOVER during the war,¹ who showed that, in the case of soldiers in army huts, the carrier rate for meningococcus varied with overcrowding. He showed that, by lessening the distance between the beds, the carrier rate increased, and that a distance of three feet between the edges of the beds of soldiers appeared to be sufficient to prevent the spread of cerebro-spinal meningitis. This work, of course, concerns only healthy soldiers and dealt with the spread of a particular disease. A certain amount of work in connection with droplet infection has been done, notably by DUDDLEY,

¹ Medical Research Council, Special Report Series, No. 50.

who showed that a danger of overcrowding is an increase in the incidence of pneumonia.¹ In addition, a large number of observations have been made in connection with the possibility of cross-infection in infectious disease wards, where barrier nursing is carried out. But no definite facts appear to have been established as to the distance required to prevent droplet infection in cases of infectious disease. The tendency appears to be at present to neglect, to a considerable extent, height, and to determine standards on the square area per bed, while the distance adopted ordinarily in English hospitals between bed heads appears to be empirical. It must also be remembered that the distance between beds must be sufficient to provide for the working space round the bed for nursing. The modern practice appears to be to aim at securing for the patient a frequent change of air, and to abandon all attempts to fix standards upon percentages of carbon dioxide, etc. The whole position is complicated by the fact that there is some evidence to show that, according to the modern views of a number of physicians, patients may benefit by an actual current of fresh air. The modern custom as regards ventilation is to rely entirely on ventilation by natural means in the wards, etc., and to use mechanical ventilation only in the operating theatres, kitchens, laundries, X-ray department, etc. The definite standards recommended by the Ministry are 8 feet between the bed centres, with a square area per patient of 96 feet, and a cubic space for each patient of 1,056 feet. These figures are those obtaining for ordinary wards. The general opinion appears to be that 10 feet constitutes a minimum height, that less than this is undesirable and that a greater height is of much less importance than the floor area as far as ventilation is concerned and simply increases the cost of heating. The actual question of cubic space for beds is generally considered to be much less important than the provision of proper sunlight and an adequate amount of fresh air. This, in its turn, depends on the amount of ventilation that can be obtained naturally through the medium of windows.

¹ Medical Research Council, Special Report Series, No. 111.

Parallel Beds.

In some new general hospitals in England, the system of placing the beds parallel to the wall is being adopted, constituting a so-called "shallow" type of ward. This enables an adequate distance between the heads of the beds to be readily obtained and, at the same time, allows of a narrower ward, which is commonly not more than 20 feet across. The "shallow" ward has the further advantages that it can readily be converted into a verandah in fine weather and also the patients are not lying constantly facing the window and looking straight into the light. It appears, however, that the "shallow" type of ward requires more staff, commonly estimated at one nurse extra to every thirty beds, and the cost of maintenance of these ward blocks is therefore increased. The new Sussex Hospital for Women and Children, in Brighton, is an example of a hospital built on these lines and was fully described in *The Lancet* of June 30th, 1931. The beds are placed on each side of the ward parallel with the outside wall, adjacent head-ends being separated by glazed screens running out at right angles from the wall. Each patient thus lies sideways to the light, privacy being secured by the ease by which curtains can be drawn across the foot of the bed and on the corridor side. Screens of polished plate-glass are fitted in the upper half and panels below the level of the bed-head rail. Screens are connected by rods carrying curtains, thus saving the bother of portable screens. There is a space of 1 foot between the bottom of the screens and the floor and 6 inches between the jamb and the wall to which it is fixed to allow of cleaning. The wards have a cheerful appearance and every bed retains its own light and ventilation, even when screened. Radiators beneath the windows are situated nearer to the foot than the head of the beds, giving a diffused warmth instead of striking the patients' heads first.

Reference should also be made to Mr. Elcock's article in *Nosokomeion* of October 1931, in which the construction of the new Hertford County Voluntary Hospital is described. The wards are 20 feet wide and the beds are arranged in groups of four, parallel to the long axis of the ward, the groups being separated by transverse glass screens and the service gangway being at the side of the ward. The ward thus consists of a series of beds separated by screens, the beds being arranged with their heads against the

ward and, indeed, there is a definite tendency for physicians to keep patients at a definitely lower temperature than used to be the case. The most commonly adopted form of heating at the present time appears to be low-pressure forced circulation hot-water systems with independent boilers, or central boilers. This has been adopted on both economical and practical grounds as being satisfactory. The use of steam, either independently or centrally, whether of high or low pressure, appears to be dropping into disrepute owing to the difficulty of regulating the heat, the higher maintenance costs, and the danger to patients of touching the radiators. Hot-air heating, with a system of mechanical ventilation, is generally being confined to special cases, such as operating theatres, where a high temperature is required for only a few hours and supplements the ordinary heating.

One of the newest developments of heating is in connection with the use of the so-called "panel" system of heating. Panel heating depends on radiators, which are sunk into the wall and which actually heat the fabric of the building, converting it into a large radiator emitting radiant heat. These radiators may be heated by low-pressure hot-water systems or, sometimes, by electricity. The use of panel heating still appears to be regarded as being in an experimental stage. A more general heating of the ward is obtained and there is economy in fuel. The panel radiators can also be used as a cooling system in hot weather. On the other hand, the panel system has a number of very definite drawbacks. The plaster is very liable to crack badly, though it appears that a coating of Portland cement, finished with Keene's cement, lessens the risk of cracking very considerably. The inaccessibility of the pipes and the difficulties of carrying out repairs are definite drawbacks. To meet these difficulties to some extent, the so-called radiant radiator has been employed recently. This consists of a metal plate with the hot-water pipes attached at the back. The plate is put in flush with the wall or the ceiling, as the case may be, and the pipes at the back are embedded in recesses in the wall. Such a design makes for greater accessibility and a more uniform temperature is obtained. One of the difficulties being experienced with panel heating is to correlate the temperature in the room with that of the outside, should a considerable change of outside temperature occur. In other words, there is a considerable lag in panel-heated wards, as

compared with those heated by ordinary radiators. Experience so far has shown that copper pipes must be used for panel heating, owing to the liability of other pipes to fur and the danger of nails being driven through softer alloys if used for the piping. From the point of view of economy, the cost of the installation of either panel-heating or radiator systems appears to be about the same, but in an existing building radiators are cheaper. As previously remarked, there is a definite economy of fuel in the panel system.

Electric heating has every advantage except that of economy. It is easily controlled, is free from dirt, and does not call for skilled engineering supervision once it is installed. In the great majority of cases, however, the cost of electricity is prohibitive.

A new and very interesting development in connection with the heating of wards is the use of thermostatic control. It particularly lends itself to cases where electricity is used as a source of heating. Studies are also being carried out with regard to the possibility of building walls of less-conductive material and lining the internal surfaces with materials which would conserve the heat, thus very considerably reducing both the cost of installation and maintenance of the heating plant. Generally speaking, for the kitchen and for the central heating system coal or coke is the cheapest fuel in England. It should be remembered, however, that rapid developments are being made in the use of oil fuel, with its great advantages in requiring less staff and causing less dirt. Oil fuel is now being extensively used for both heating and cooking. Mention should here be made of the rapidly developing practice of fitting a number of wards with steam jets for tracheotomy and other cases.

Domestic Hot Water.

There appears to be a consensus of opinion that there are great disadvantages in having the domestic hot-water supply drawn off from the central heating apparatus.

There are, however, two interesting developments in connection with the domestic hot-water supply of hospitals. The first is based on the fact that water is only required for general hospital purposes at tepid heat (about 100°—120° Fahrenheit), except in the kitchens for washing up greasy utensils. Rather than raise the general temperature of the water in the whole hot-water system

to the temperature required in the kitchen, a small tank is installed in the main kitchen, fitted with a heating battery of steam pipes, by which sufficient water for the kitchen purposes is raised to a higher temperature. Secondly, there is a growing practice to deliver tepid water to the hand-basins in cubicles, instead of hot and cold as hitherto. This requires only one set of pipes and economises in the plumbing fittings.

A modern practice is to install hot-water meters, in order to avoid waste.

A considerable amount of saving is affected in hospitals by the introduction of water-softening apparatus, with its consequent saving of soap and protection of the pipes from furring, which may more than counterbalance the cost of installation.

Electricity.

One of the striking recent developments in hospitals is the increasing use of electricity, especially in connection with reading-lamps, wireless, internal telephones, lifts, etc. The modern practice appears to be to provide a light at the head of each bed, as well as to duplicate considerably the number of controls. There has been great development in the use of electric power, not only for cooking but also for refrigerators, which are now commonly installed in the ward kitchens, the main kitchens, and the mortuary. Finally, the rapid development of electro-medical therapeutics has greatly increased the amount of electricity used. There has been, too, a rapid development of automatic telephones in hospitals, which, though more expensive to install, save in the cost of staff. These are commonly combined with a system of electric-light signals or call-bells, so as to establish communication at once with medical officers or other officials of the hospital. Owing to their silence, electric lifts are installed as far as possible. A recent development, too, is the fitting of synchronised clocks. These are somewhat expensive to install, but have the great advantage of saving the time of staff. With regard to wireless, it appears to be generally the practice in the London hospitals to provide loud-speakers in wards occupied by patients who are not in bed, in staff common rooms, and in the children's wards. In the wards for the acutely sick, head-phones are fitted.

Lighting.

An interesting report has been published by the Joint Committee of the Royal Institute of British Architects on the orientation of buildings, and includes the establishment on a scientific basis of the calculation of insolation and orientation. In this report, the heliodon is described, and with this instrument it is possible to reproduce exactly the incidence of sunshine upon a building for any given conditions, while the daily period of sunlight exposures can be obtained by rotating the instrument and noting the time at which the sun begins and ceases to shine on the model. With regard to the orientation, the maximum amount of sunlight appears to be obtained if the axis of the building lies north and south. For four months in winter, the maximum entry of sunlight is obtained by an east-by-west axis, but in summer a north-by-south axis gives the maximum result. The usual practice in England is to have the main axis of the wards from north to south, with the beds at right angles to the external walls.

A recent definite trend has been the greatly increased proportionate amount of window space in wards, which has, during the last few years, increased to more than 50 per cent of the wall area. This is in spite of the increased cost of cleaning, the loss of heating during winter, and the necessity for protecting patients from the sun with screens during summer.

The use of the steel window-frame, as opposed to the wood, is steadily increasing. The window generally preferred appears to be the ordinary sash window with, or without, a hopper. The Austral type of window is also being extensively used and appears to give satisfactory ventilation and lighting.

With regard to artificial lighting, the modern practice is to fit centre lights in the wards, with a bracket light over each bed. Special lighting is required for the operating theatre, where a shadowless lamp is fitted, with a number of lights for general lighting and a system of emergency lighting which comes into action automatically if the normal electricity supply fails. For the latter, alkaline batteries are commonly used, as these allow of complete discharge without damage to the accumulator. Similar emergency lighting is being commonly fitted in the sterilising room, in the anæsthetic room and in the labour wards. In order to avoid the strain of

reflected light, green sheets are now being used in a number of operating theatres. Mention should here be made of a development of the epidiascope, which is now frequently fitted into operating theatres. By means of this instrument, the whole of the proceeding in the theatre is reflected and thrown into another room, for the use of students, thus obviating the necessity for on-lookers to be actually in the theatre.

Construction of the Ward Unit.

The general tendency in modern hospital construction in England is towards a reduction in the number of beds in the main ward and the provision of beds in smaller wards or separate cubicles. This is due partly to the increased demand for accommodation for patients willing to pay and anxious for separate accommodation, and partly to the facility which it provides for isolation of cases, either on grounds of infection or for any other reason. A common arrangement appears to be a large ward with eighteen beds, two smaller wards of four beds and four single-bed cubicles. There is a further modern tendency to divide the large ward more or less completely into separate cubicles.

The general opinion appears to be that a ward unit should consist of about thirty beds, as being the number which can be fairly looked after by one sister.

Much discussion is taking place in England as to what rooms should be included as ancillary to the ward unit. The following appear to be commonly considered essential :

- (1) Sisters' duty room, for sisters' clerical work, poison cupboard, etc.
- (2) Ward kitchen, with larder adjacent, including facilities for keeping food warm and simple cooking, and fitted with a refrigerator.
- (3) Storage accommodation for ward furniture, such as food trollies, stretchers, invalid chairs, etc.
- (4) Linen room and blanket drying and warming room, fitted with hot pipes.
- (5) Foul linen store.
- (6) Blanket drying and warming room, fitted with hot pipes.

- (7) Clinical room for carrying out tests.
- (8) Sterilising room.
- (9) Cleaners' room, provided with water supply, sink and storage for pails, etc.

Additional rooms which are sometimes considered essential in a ward unit are :

Day-rooms.

Examination room.

A room for patients' clothing.

A visitors' room.

A room for the medical visiting staff.

Operating Theatre.

The modern tendency appears to be to group the operating theatres together, so as to economise in the construction of sterilising and washing-up rooms. The theatres are commonly placed on the top floor, where the top light is available when required. In some of the newer hospitals, the various theatres are one above the other, the upper one being stepped back, so as to give direct sky-light to the lower. Mention should be made of the growing custom of providing an increased proportionate accommodation of operating theatres, owing to the large increase in the number of operations now undertaken. A recent trend appears to be the use of artificial light more and more for operating, especially since the introduction of the shadowless lamp. Glass appears to be an ideal material for the walls of operating theatres, but the difficulties of fixing, owing to contraction and expansion, have not yet been overcome. Recent operating theatres constructed in England commonly have the whole wall in terrazzo, owing to the liability of paint to crack with repeated washings. The question as to whether ether has any definite deteriorating effect on paint is being investigated at present. The floors are commonly of terrazzo and the ceiling of any material which does not allow condensation. The lighting of the operating theatres has been already mentioned, but reference must be made to the darkening of operating theatres for special cases. Nothing quite satisfactory yet appears to have been installed, and the common practice is to use the operating theatre for such

cases after dark. In at least one hospital, however, a double glazing of the roof of the theatre, with a spring-blind between, has been fitted and is said to work satisfactorily. With regard to the heating of operating theatres, the modern practice appears to be to maintain the temperature about 60° Fahrenheit when the theatres are not in use, by means of a low-pressure steam-heated plenum and extraction ventilating plant, with air-filtering screens and humidifiers to provide eight to ten changes of air per hour and to raise the temperature to 70°-75° Fahrenheit when the theatres are in use. The common practice appears to be to use steam for sterilising, as gas is dangerous from the point of view of explosions, and electricity is expensive.

Children's Section.

The modern tendency is to treat children, as far as possible, on open-air lines and consequently to put the section for children on the top floor in a many-storied building, in order to provide the possibility for open-air treatment on the flat roof. The protection of acutely sick children from noise is very important, but at the same time provision is made for them to see other children by means of the use of glass partitions. Stress is being laid at present particularly on the method of admission of children, so as to prevent, as far as possible, the introduction of infectious disease. Broadly speaking, older children are admitted direct into the wards, but the tendency is to isolate younger children for at least forty-eight hours after admission and, where accommodation allows of it, for several days. This necessitates the construction of a considerable number of cubicles. These are commonly placed in one ward and all children below a certain age, and any others suspected of having been exposed to infection, are kept in this ward for four to five days or longer before proceeding into the general children's wards. A new cubicle ward of this type at Alder Hey Hospital, Liverpool, contains fifty-six cubicles and embodies modern ideas of barrier nursing. A triple equipment of steam sterilisers for all food utensils, washing-bowls and bed-pans is provided and there is an "infected" and a "clean" kitchen attached to the ward, so that dishes, plates, remains of food, etc., coming from the ward go direct into the "infected" kitchen and all the utensils in the "clean" kitchen have passed through the steam steriliser between it and the

"infected" kitchen. The standards at present in vogue for accommodation for sick children are as follows :

| | |
|-----------------------------|---------|
| Space between bed centres.. | 7 feet. |
| Super area | 77 " |
| Cubic space | 847 " |

Isolation Section.

The modern practice is to provide isolation accommodation to serve the general wards of the hospital. This isolation accommodation is sometimes in the form of a separate small block of cubicles, or may consist of one or more cubicles opening off the main ward blocks.

Laboratory.

The recent tendencies have been to increase considerably the pathological laboratory provision in hospitals, in view of the increasing importance of pathology in connection with treatment.

X-Ray Department.

As far as possible, X-ray work, and, in particular, specialist X-ray work, such as thoracic examinations, etc., is being undertaken in one central hospital of a group of hospitals. In the construction of the X-ray room itself, the recommendations of the British X-Ray and Radium Protection Commission are followed, as adopted by the Third International Congress on Radiology, Paris, July 1931. The recommendations of the Commission defined the hours to be worked in X-ray departments. In addition, it laid down general instructions with regard to equipment, screens, etc., and protection against high-tension wires. It also dealt with the question of the storage of films and protection against radium emanations. It urged the necessity for the operator to work completely outside the X-ray room in the case of X-ray treatment and behind a protective wall of a minimum lead equivalent of 2 millimetres. It emphasised the necessity for deep X-ray therapeutic work concentrated at certain hospitals to serve those groups of hospitals where the highly specialised and expensive apparatus and protection needed, together with skilled personnel, are not available. It further emphasised the precaution of surrounding the X-ray bulb as completely as possible with adequate protective material, except for an aperture of minimum size for the emergence of the

rays. In addition, regulations have been outlined by the British X-ray and Radium Protection for the handling and storage of celluloid X-ray films in October 1929. Regulations have also been issued by the Home Office as regards the handling and storing of celluloid films. The international standard of protection which has been generally adopted in England is 1.5 mm. of lead against 100,000 volts and 4 mm. against 200,000 volts. X-ray departments where screening is done and the rooms in which deep therapy is being carried out must be insulated by sheets of lead in the floor, walls and ceiling, or by the application of barium cement. Lead-headed nails are used for fixing the lead sheets. Doors and their frames are similarly treated, and the glazing of the windows is such as prevents scattered radiation. This applies also to openings formed for observation between deep-therapy units and the outside control-room for the protection of the operator. The construction of all X-ray departments in general hospitals is allocated to specialists in this subject.

Kitchen.

The best position of the kitchen in vertical buildings is under discussion. Those in favour of its position on the top floor urge the necessity for avoiding smell. On the other hand, kitchens placed on the top floor monopolise the finest floor in the building and one which is commonly used either for operating theatres or for children's wards, or others requiring open-air treatment. This floor has the best air and the largest amount of sunshine. Furthermore, the high position of the kitchen necessitates the placing of all kitchen stores on the same floor and also the staff dining-rooms. Finally, nurses, whether on duty or off, have to be conveyed to the top floor of the building, which is uneconomical both in time and cost of lifts. It appears that, with good ventilation, it is possible to obviate kitchen smells and, if so, the opinion generally appears to be that there is no objection to a ground-floor kitchen.

With regard to the actual cooking, electricity is generally prohibitive on account of cost, but otherwise is the most convenient. Most commonly, coke-fired ovens are being fitted. There are a number of types of such ovens being used, from the steam-pipe draw-plate oven, with its high cost of instalment but low maintenance costs and ease of operation, to the Portway oven, with its

low cost of installation but higher cost of repairs and the difficulty of maintaining the same uniformity of heat. The tendency is to provide specially heated frying-pans in a compartment screened off from the kitchen. The pans most commonly used for cooking are generally cast-iron, heated by steam, although aluminium-lined or enamel-lined pans are desirable for milk and porridge. These cost more, and actually cast-iron pans appear to function satisfactorily. Copper inner pans, requiring frequent re-tinning, and iron-enamel pans are liable to crack and splinter. Where possible on grounds of cost, the tilting iron pan is used, owing to the great facility that this offers for cleaning. The cost of installation, however, is definitely greater. Refrigerating has of recent years become of increasing importance in the equipment of hospitals, and it is now customary to provide refrigerators in the main stores, the main kitchen, the ward kitchens, and the mortuary. In recently constructed kitchens, the following mechanical apparatus is commonly installed :

| | |
|------------------------|-------------------------|
| Food-mixing machines | Potato-paring machines |
| Meat-slicing ,, | Bread-cutting ,, |

A dietitian's kitchen is commonly provided, attached to the main kitchen for the training of nurses in sick-room cooking.

Laundry.

A number of hospitals still find it cheaper to send out their laundry, but the practice which is most economical is that of having a central laundry for a group of hospitals.

Nurses' Homes.

In connection with nurses' homes in general hospitals, the following appear to be the chief modern tendencies :

(1) The conversion of the nurses' bedroom into a bed-sitting-room or study, as in practice it is found that the common rest-rooms or reading-rooms are little used and that nurses prefer the privacy of their rooms for their off-time and for study. This has led to a change in furnishing and particularly, in certain cases, to a tendency to provide a settee convertible into a bed for night rather than a fixed iron bedstead.

(2) There is a tendency to provide for the heating of the bed-rooms by small radiators in each room, rather than by

simply heating through hot air admitted from the corridor through fan-lights.

(3) The instalment of fixed lavatory basins in nurses bedrooms is becoming more common. These have obvious advantages and do not appear to cost very much more than the common lavatories hitherto provided.

(4) The custom of providing ample recreation facilities for the nursing staff is steadily growing.

(5) The use of the spray-bath in nurses' homes is growing in popularity, as sprays allow for rapid bathing and there are no baths to clean after use. The nozzles are arranged at a height which obviates the possible wetting of the hair.



Mention may be made here of the custom of providing flats in hospitals for married medical officers. This arrangement is increasing, as it promotes continuity of service.

Out-patients' Department.

The accommodation commonly provided in a modern out-patients' department includes a number of consulting and examination rooms, a casualty and receiving section, with one or two single-bed wards, a minor operation room, ante-natal and venereal diseases sections, a room for medical officers, offices for the almoner, sanitary provision, etc. In addition, special departments, such as massage, light treatment, ophthalmic, may be added.

Fire.

Opinion appears to be divided as to the necessity for fire-resisting floors throughout hospitals, especially whether these are necessary in such buildings as the nurses' home. Another question is that regarding the necessity for the ceiling below the roof being fireproof, though opinion generally appears to consider this necessary, especially in view of the fact that electric cables, etc., are commonly laid through the roof.

It is considered satisfactory for the domestic main to serve for fire purposes. The objections to a separate fire main are the stagnation of the water, with the resulting corrosion of pipes and

deposit of sediment. The modern practice in London hospitals appears to be to provide a number of hand fire-extinguishers in place of internal hydrants for immediate use, and possibly one or two external hydrants, but generally to rely on the fire brigade and the public water-mains.

Standardisation of Central Purchasing.

There has been rapid development in English hospitals in connection with the standardisation of furniture, textiles, crockery, surgical materials, laundry materials, etc. The value of appointing an expert purchaser has been realised and such an appointment has already been made in a number of hospitals. Purchasing by groups of hospitals has developed, especially in Liverpool, Newcastle, and Leeds. The object of standardisation is to secure a better article by incorporating the best features of many types in an agreed specification. This obviously must result in a lower price, owing to the increased demand. Standardisation must be elastic and continually changing, in order to keep pace with the experience of the users and the new requirements of medical work. As far as possible, all requirements are grouped so as to require as small a group as possible of expert buyers. The British Engineering Standardising Association has prepared standard specifications for many articles, and a number of Government departments have also standardised a large amount of their general equipment. In addition, a number of individual trades have standardised their articles. Central purchasing has long been used by Government departments and has gradually extended to railway companies and other large commercial concerns. It increases efficiency, is more economical, facilitates rapidity of supply, and acts as safeguard against waste. One of the principal points to be watched in connection with central purchasing is the possibility of the overhead charges for the staff, including the expert buyers, being unduly high. In addition, there is the cost of storage accommodation and, commonly, transport from the stores to the individual hospital. It appears that, whilst in larger units a very great economy is effected, the question of central purchase with smaller units is one which must be carefully considered from the financial point of view. It must be remembered, too, in connection with central purchasing, that, if unduly pushed, it may drive manufacturers too far and result in the formation of

rings. An economy that may be mentioned in connection with central purchasing is the fact that, owing to present trade conditions, there is a tendency for the middle man to disappear and manufacturers will commonly now sell direct to the consumer. For instance, it is now possible to obtain direct from manufacturers orders of not less than 5,000 yards of cloth. The tendency appears to be for commercial managers to be appointed to local authorities, and for hospital stores and equipment to be supervised by stewards who have been trained in business and often in the technical side of some of the trades concerned with the production of the articles. Purchases may be made by tender, or by quotation. Where the market is at all unstable and where the amount of the requirement is not absolutely defined, a quotation for a single purchase is commonly the method employed. In cases, however, where the market is stable and the requirements are exactly known, the method of tendering for a contract lasting for some time is the most economical. It is interesting to compare this work with that of the committees on simplification and standardisation of the American and German hospital associations. One of the difficulties in connection with standardisation that has been met with is the opposition from local tradesmen, as standardisation tends to do away with competition in connection with tenders.

Closely connected with standardisation is the publication by the Ministry of Health of analysed costing returns for all the principal institutions for the treatment of the sick, which are administered or used by Local Authorities. The principal object of these returns is to assist Local Authorities in the economical administration of the institutions under their control. The first of these returns was published in 1931. The first group of columns gives the locality of the hospital, the number of beds graded for men, women and children, the average number of medical, surgical, and maternity beds occupied, number of discharges, deaths, etc. A second group of columns gives the cost per patient per week of administrative services—*e.g.*, salaries, etc., medical cost, cost of nursing and other staffs, food, drugs, fuel, light, laundry, renewals and painting of buildings, ambulance charges, rent, taxes and insurance, loan charges, etc.

The best example of standardisation and central purchase is that developed by the London County Council, and it may be of interest

to add some of the details of the work of this body. The department of the London County Council for standardisation and purchasing is divided into two sections : (1) an administrative section which deals in the ordinary way with contracts, tenders, accounts, etc. ; (2) a technical and supply section, including technical staff from the trades concerned. This section has to do with the standardisation of all equipment as far as possible. The object is not to set up new standards, but to make available to all the standards already accepted by expert buyers. Practically all the ordinary articles of furniture, textiles, clothing, cleaning materials, hardware, paints, engineering requisites, etc., are now determined by standard specifications in the London County Council. Two sample rooms have been provided at the County Hall, in one of which standard surgical and other appliances and in the other furniture, furnishings and clothing are available for inspection by medical superintendents and others. The experience gained soon enabled improvements in supplies to be effected, with great benefit to efficiency and the achievement of economy.

Practically all the ordinary articles of equipment and clothing have now been standardised and satisfactory substitutes, which comply with official formulae, have been found for costly proprietary preparations. Whenever possible, articles in unbreakable material are being supplied to replace those of glass and earthenware. Standardisation of instruments has enabled the replacement of scalpels, forceps, etc., to be made from circulating stocks in the sample rooms, while the instruments are being repaired. The more expensive and unusual instruments are kept in the sample room available on loan, thus avoiding expensive purchases for each hospital. Media for pathological laboratories are standardised and distributed in airtight bottles. Centrifuges, ampoules, etc., are standard, and all technicians are trained on a standard microscope. Experimental work is constantly being undertaken by those responsible for standardisation, and new products and equipment are tried out. A recent development in this connection has been the testing and final adoption of standard non-inflammable films for all X-ray work.

Another development in connection with standardisation and central purchasing in the London County Council has been the construction of large refrigerating plants at each hospital, so as

to allow of whole carcasses being bought. A number of men have been trained in each hospital in the cutting-up of carcasses and the meat is now bought in this form. Attention is also drawn, by means of a pamphlet, to the best use to which each and every part of the carcass can be put. A great economy has been secured, which will shortly more than repay the cost of installation of the refrigerating plants.

Appendix I.

LOCAL GOVERNMENT ACT, 1929.

The Council, in preparing an administrative scheme, shall have regard to the desirability of securing that, as soon as circumstances permit, all assistance which can lawfully be provided otherwise than by way of poor relief shall be so provided But nothing in this sub-section shall diminish or otherwise affect the duty of a Council under the Poor Law Act, 1927, to provide relief for the poor.

The Council of every County and County Borough shall, when making provision for hospital accommodation consult such Committee or other body as they consider to represent both the governing bodies and the medical and surgical staffs of the voluntary hospitals providing services for the benefit of the County or County Borough as to the accommodation to be provided and as to the purposes for which it is to be used.

The Local Government Act, 1888, shall have effect as if, amongst the powers conferred by that Act on County Councils, there were included the like powers with respect to the provision of places for the reception of the sick as are conferred on Local Authorities by the Public Health Act, 1875, amended by the Public Health Act, 1925.

The Public Health Act, 1875, as so amended, shall, in its application to County Councils and County Borough Councils, have effect as if the power to provide places for the reception of the sick included power to provide places for the reception of pregnant women.

On the appointed day, the functions of each Poor Law authority shall be transferred to the Council of the County or County Borough comprising the poor law area for which the poor law authority acts

As from the appointed day, it shall be the duty of the Council of every County and County Borough and of every other Local Authority to recover from any person who has been maintained by them in any institution, other than a person who has become an inmate of an institution for the purpose of receiving treatment for infectious disease, or from any person legally liable to maintain that person, the whole of the expenses incurred by the Council or authority in

the maintenance of that person or, if the Council or authority are satisfied that the persons from whom the expenses are recoverable cannot reasonably, having regard to their financial circumstances, be required to pay the whole of those expenses, such part, if any, of the expenses as they are, in the opinion of the Council or authority, able to pay; provided that any such Council or authority may, by agreement with the Governing Body of any association or fund established for the purpose of providing benefits to members or other beneficiaries thereof, accept from the association or fund, in respect of the expenses incurred by the Council or authority in the maintenance of any member or beneficiary of the association or fund, payment of such sums as may be provided by the agreement, in lieu of recovering the whole or any part of the said expenses from the member or beneficiary or from any person legally liable to maintain him.

Appendix II.

REGULATIONS OF THE LONDON COUNTY COUNCIL FOR THE REGISTRATION OF NURSING-HOMES, UNDER THE NURSING-HOMES' REGISTRATION ACT, 1927.

Structural.

Proper provision for escape in case of fire, including the provision of self-closing doors. Removal of bars from window-opening, etc.

General precautions against fire covering electrical installations, heating and electric apparatus in operating theatres, gas appliances and services, domestic hot water and central heating, boilers, storage of inflammable liquids and celluloid films. Certificate of registration not transferable.

Superintendence.

A nursing-home must be under the charge of a person who is either a duly qualified medical practitioner or a qualified nurse, and who is resident in the home. This individual will be responsible for :

- (1) The nursing of the patients in the home ;
- (2) The adequacy of the nursing staff for day and night nursing, in accordance with such requirements as may be considered necessary by the Council ;
- (3) Adequacy of equipment, in accordance with the minimum standard approved by the Council ;
- (4) Cleanly conditions of the premises ;
- (5) The comfort of, and the catering arrangements for, the patients and nursing staff.

Nursing Staff.

Numbers of trained and untrained nursing staff required will depend upon the number and type of patients accommodated. While each case must therefore be dealt with on its merits, it is considered that, in the ordinary mixed type of home, there should be, as a rule, one day nurse and one night nurse for every six patients. Arrangements must be made for at least one nurse to be on night duty whenever there are four or more patients in the home, or whenever any patient is acutely ill. It is undesirable for ordinary nursing-homes to take infectious cases, and such cases must be notified to the Borough Medical Officer of Health.

Particulars of any patient who suffered from an infectious disease while in the home must be entered in the register of patients, together with the nature of such disease and the action taken.

The Council will not, as a general rule, object to the accommodation of surgical cases in the same nursing-home as maternity cases, subject to suitable precautions, but when a room contains two or more beds and one of such beds is occupied by a maternity case, the remaining bed or beds must not be utilised for medical or surgical cases.

If two or more maternity cases are to be accommodated in one ward, a separate room must be provided as a labour room and another separate room as an isolation room. An operating theatre is required in all homes which were not in existence on July 1st, 1928, at which surgical cases are accommodated.

Appendix III.
GENERAL SCHEME OF HOSPITAL GROUPING.

Extract from the British Medical Association's Report on Hospital Policy.

The Association envisages a hospital system in which all hospitals in a given area will be grouped round a central or base hospital. In the existing state of affairs, the central or base hospital will generally be one of the larger voluntary hospitals. This may or may not be the locus of a medical school, but will, in any case, be expected to set the standard of hospital practice in the area and be the chief centre of education and research.

Central or Base Hospital.

Before a hospital could be said to occupy the position of a central or base hospital, it should fulfil one or other of the following conditions :

- (1) It should be a hospital with which a recognised medical school (under-graduate or post-graduate) is associated ; or

(2) It should be a general hospital (voluntary or Council), other than one associated with a medical school, which :

- (a) Has outstanding advantages as regards staff and equipment, and is of sufficient size ;
- (b) Acts as a consultative centre ;
- (c) Deals with the investigation of the more difficult cases ; and
- (d) Undertakes the more specialised methods of treatment.

Where a district is considered to be suitable for a grouped area but cannot be said to have a hospital fulfilling the necessary conditions, then the central or base hospital should be developed from the most suitable hospital available, a necessary condition, however, being an adequate and efficient staff.

No class of case, other than infectious and certifiably insane, should be excluded from the central or base hospital. Certain categories of cases might, however, according to local circumstances, be allocated to other hospitals of the area, provided they were still available for teaching purposes when necessary.

It is inevitable that some Local Authorities will have more than one base hospital in their area and some base hospitals will have to deal with more than one Local Authority (especially in the case of county council and county borough councils in the same county). In order to facilitate co-ordination, the boundaries of hospital areas should, however, as far as possible, coincide with those of Local Government areas.

Other Hospitals.

All the other hospitals in the area, including special and cottage hospitals, should be grouped round the central or base hospital and be co-ordinated with it.

The Council hospital, as the hospital under the control of the Local Authority, which has a direct responsibility for providing institutional treatment when necessary, must provide accommodation for those cases which are outside the province of the voluntary hospitals. Where the voluntary hospital is already holding the leading position and is progressive and locally supported, it should maintain this position, and any further developments which are necessary in the area should be made in co-operation with it. The Council hospital, where not itself the central or base hospital, should develop, not in wasteful competition with, but in co-ordination and co-operation with the voluntary hospital.

Necessity for Clearing-House.

A "clearing-house" (*i.e.*, a central bureau) to co-ordinate the distribution of cases requiring admission to the various hospitals and to provide information as to where and when special forms of treatment and other forms of diagnostic help are available, would be desirable under a system of co-ordination of grouped hospitals. It should work in close connection with the central or base hospital, and be situated near it, or even within it. It should also co-ordinate the hospital ambulance transport of the area.

Appendix IV.**COUNCIL HOSPITAL POLICY.**

Extract from the British Medical Association's Report on Hospital Policy.

The continued provision of services for those types of illness which form the bulk of cases dealt with in poor-law hospitals is now a primary function of Council hospitals. Increased hospital provision for acute medical and surgical cases, however, will be found necessary within their areas by most Local Authorities. In the more populous centres, it will probably be agreed that the acute class of case such as now constitutes the majority of the patients of a large voluntary hospital is best dealt with in separate wards, blocks or institutions.

The responsibility for the treatment of certain types of case will doubtless remain as at present with the whole-time resident staff. In some units, the present mode of staffing with free use of a consultant visiting staff will be economical and efficient. It is advisable, however, to ensure full co-operation with the voluntary hospitals, wherever large numbers of acute cases have to be dealt with, by having a part-time visiting staff of similar status and in similar numbers to those of the large voluntary hospitals.

The medical staffing of Council hospitals should therefore be on the following alternative lines :

(1) A whole-time Medical Superintendent (resident), in full administrative control, responsible to the Local Authority, whose duties should be :

- (a) The general administration of the hospital ;
- (b) The determination of the admission and discharge of patients ;
- (c) The supervision of the work of resident assistant medical officers, house physicians and house surgeons ;
- (d) In some circumstances, the responsible charge of some branches of professional service, the demands of which are not incompatible with his administrative duties.

(2) A whole-time resident staff :

- (a) Senior, with responsibility for various classes of patients, according to the size of the institution ;
- (b) Junior, with responsibility similar to that of house physicians and house surgeons in the larger voluntary hospitals.

(3) A part-time consultant visiting staff, whose duties should be (subject to the administrative control of the Medical Superintendent) :

- (a) In certain instances, to have responsible charge of beds, and also to be available for consultant service to all cases in the hospital at the request of the Medical Superintendent ;
- (b) In other instances, to be available for consultant services when required by the Medical Superintendent.

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(4) Clinical assistants, appointed from amongst the practitioners of the area.

or

(1) A Medical Superintendent, whose duties and responsibilities should be as defined under 1 (above) ;

(2) A whole-time resident staff, with responsibility similar to that of house physicians and house surgeons in the larger voluntary hospitals ;

(3) A part-time consultant visiting staff, as defined under 3 (above);

(4) A part-time general practitioner visiting staff (subject to the administrative control of the Medical Superintendent), to have responsible charge of beds and clinics ;

(5) Clinical assistants, appointed from amongst the practitioners of the area.

The medical staffs of Council hospitals should be remunerated either by fixed salary or by payment for definite services and responsibility.

In any Council hospital for general cases, special accommodation should be available for contributing and private patients admitted on the recommendation of their own practitioner, who should there be able to attend these patients, subject always to the administrative control of the Medical Superintendent.

Council hospitals should be controlled by a committee on which there should be a small but definite representation of the local medical profession.

THE PARTICIPATION OF THE PUBLIC HEALTH SERVICE IN THE CIVIL WORKS PROGRAMME FOR THE RELIEF OF UNEMPLOYMENT IN THE UNITED STATES OF AMERICA

By

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As the economic depression in the United States of America became more acute in 1932, the individual States found themselves unable to meet the sudden and unprecedented demand for relief of the destitute without assistance, and it became necessary for the Federal Government to supplement State and local relief funds through grants-in-aid to the State relief organisations. Provision for Federal participation in State and local relief work was made in the Act creating the Reconstruction Finance Corporation, one of the first of the emergency organisations set up by the Federal Government to further national recovery. In the spring of 1933, the Congress made additional provision for the relief of distress on a nationwide scale by creating the Federal Emergency Relief Administration and setting aside a sum of \$500,000,000 to finance participation of the Federal Government in relief activities within the States.

The desirability of affording relief beneficiaries an opportunity to work for the aid given to them was recognised with the beginning of the relief programme, and this method of administering relief to certain classes of beneficiaries had come into general use throughout the country in the summer of 1933.

In a further effort to relieve unemployment and stimulate the recovery of private industry, the Congress, in 1933, created the

Public Works Administration and appropriated a special fund to be used for the construction of additional public buildings for the Federal Government and for loans to States and municipalities for local construction projects ; the necessary delays incident to the examination of proposed construction projects prevented, however, the beginning of actual construction on a large scale as early as had been hoped for. With the end of the agricultural season, the unemployment situation became more acute and some other means of supplying work quickly had to be considered. Accordingly, the President decided to set aside from the Public Works appropriation the sum of \$400,000,000, to be allotted direct to the States for immediate expenditure on local work projects which could be easily and quickly undertaken and which were not considered suitable as public works projects. To administer this programme, there was set up, as an adjunct to the Federal Emergency Relief Administration, an organisation designated as the Civil Works Administration.

In planning the work programme to be undertaken in the several States, the Civil Works Administration considered it desirable that the projects undertaken be in the interest of the public welfare and community improvement as far as possible. Accordingly, the Public Health Service was asked, along with other Federal agencies, to suggest projects on which beneficiaries of the Civil Works Administration might be profitably employed. Four projects were recommended by the Public Health Service—namely, *an intensive malaria-control drainage programme in the fourteen States where malaria has prevailed most extensively ; the construction of sanitary privies in the small towns and villages and in the unsewered outskirts of larger cities ; surveys to determine the extent of endemic typhus fever in rodents in important seaports and in certain inland areas where the disease now prevails ; and the sealing of abandoned coal-mines to reduce the acid wastes being discharged into streams used for water-supplies.*

In order that these projects might be given proper technical direction, they were placed under the general supervision of the Public Health Service, and the health officers of the States participating in the several programmes were made the agents of the Public Health Service for technical supervision of the work. Special allotments of funds were reserved for the Public Health Service

projects out of the funds given to the several States for the employment of labour. The amounts set aside amounted to approximately \$1,500,000 for malaria control, \$5,000,000 for community sanitation, 1,000,000 for typhus-fever surveys, and \$1,500,000 for sealing abandoned coal-mines.

A brief description of each of the projects carried on under the supervision of the Public Health Service follows.

COMMUNITY SANITATION PROJECT.

The community sanitation project had for its immediate objective the removal of a health menace to communities through the elimination of insanitary disposal of excreta. This was to be accomplished by the removal of insanitary privies and the construction of sanitary fly-tight privies or septic tanks, or by sewer extensions, where such extensions might be economically advisable, to include flush toilet installations. The work was confined, however, largely to the installation of sanitary privies.

The decrease shown in the death rate from typhoid fever and the dysenteries in States where extensive sanitary privy construction has been carried on, as compared with the death rates for these diseases in neighbouring States where less has been accomplished in this field, is striking. In the following table, death rates are shown for typhoid fever in two Southern States ("A" and "B") where little had been done in the way of sanitation, as compared with the rates for another State ("C") in which an extensive State-wide sanitation programme was undertaken in 1920 and consistently carried forward :

*Typhoid-fever Deaths per 100,000 Population for the Years
1920 to 1931.*

| | 1920 | 1921 | 1922 | 1923 | 1924 | 1925 | 1926 | 1927 | 1928 | 1929 | 1930 | 1931 |
|--------------|------|------|------|------|------|------|------|------|------|------|------|------|
| State "A" .. | 18 | 22 | 19 | 15 | 22 | — | 23 | 20 | 18 | 14 | 17 | 17 |
| State "B" .. | 19 | 27 | 24 | 20 | 22 | 22 | — | — | 14 | 12 | 17 | 17 |
| State "C" .. | 12 | 12 | 11 | 10 | 10 | 10 | 10 | 8 | 6 | 6 | 4 | 5 |

The rates shown for State "A" and State "B" are more or less typical of the prevalence of typhoid fever in most of the Southern States.

The work was carried on in the following States : Alabama, Arkansas, Florida, Georgia, Illinois, Indiana, Kansas, Kentucky, Louisiana, Maryland, Michigan, Mississippi, Missouri, North Carolina, Ohio, Oklahoma, South Carolina, Tennessee, Texas, Virginia, West Virginia, Delaware, Pennsylvania and Washington. The health officers of all the States were informed of the possibility of using work-relief labour on privy construction and were given an opportunity to signify their willingness to participate in the project. The States selected were those which responded to the invitation.

The programme in each State was set up under, and administered through, the State Department of Health. The supervisory personnel consisted of a State director, in general field charge of the whole programme ; district supervisors selected from the State re-employment rolls, each having responsibility for the work in a group of counties ; and a county supervisor for each county, selected from the local re-employment rolls. It was the function of this force to promote local adoption of the programme, sell the project to individuals, and train and supervise labour engaged in construction. Labour was assigned for the construction of sanitary privies only where materials were furnished by the property-owner or by some public agency such as the County Board of Education, county supervisors or the municipal government. Some municipalities purchased the materials in one lot for the sanitation of the entire community, the privies constructed being regarded as a public utility. Others purchased the materials and offered to furnish what was needed for the installation of a sanitary privy in any home in the community where the property-owner would pay a certain proportion of the cost. Others have purchased the material in order to take advantage of wholesale prices and expedite the work, and assessed the cost against the property on which the sanitary privies were erected, or provided other means for reimbursing the municipality. In some sections the labour was used to construct privies for farm-homes throughout the county, but for the most part the work was confined to unsewered towns and villages, and the unsewered sections surrounding the sewerred areas of the larger communities. The work was concentrated in these more congested areas because the health menace of an insanitary privy is proportionate to the number of persons who live within

fly range of it, because typhoid fever is most prevalent in small towns and villages, and because more effective supervision could be exercised where the labour could be worked in large groups.

Only a small number of men could be used at the very beginning, because materials for the project could not be furnished from Federal funds. However, the number employed increased steadily from the time the work was begun in December, reaching a total of 35,000 at the peak of activities. All material had to be furnished by individual property-owners or local public agencies. It was therefore necessary to make arrangements for materials, and to develop sufficient interest in each community to create a demand for the work, in advance of the assignment of labour. The local interest that developed in this programme exceeded the most optimistic expectations. At the peak of activities, there were enough materials on hand and commitments made by property-owners to furnish materials to make work for at least five times the number of labourers available.

Accomplishments.

1. Incomplete reports show 200,000 privies constructed. It is believed that the complete report will show at least 25,000 more constructed or partially completed by the end of March 1934.

2. While it will be impossible for some time to measure the result of the work in terms of actual prevention of disease, it is believed that there will be both immediate and remote benefits which will thoroughly justify the undertaking.

(a) As to immediate benefits, in communities where the programme proceeded far enough to effect complete elimination of insanitary privies, it is expected that a noticeable reduction in the prevalence of excreta-borne diseases will occur.

(b) As to future benefits, even in communities where the programme did not proceed far enough to accomplish a complete or almost complete elimination of insanitary privies, the community has been made "sanitation conscious", and there has been provided a standard of sanitation which will induce further progress on the part of both the public and the local governmental agencies. Modern standards of sanitation have been introduced into hundreds of communities and in several States which heretofore have given little attention to practical sanitary privy construction.

3. The supplying of materials by property-owners and local governmental agencies has helped private industry. These purchases of materials by private individuals and agencies other than the Federal Government involved a total expenditure at least equal to the amount paid by the Civil Works Administration to labour employed on this project. It is estimated that the materials purchased included approximately a hundred million board feet of lumber ; forty thousand barrels of cement ; a million pounds of nails ; six million square feet of roofing, mostly metal roofing ; three million pairs of hinges ; and half a million bolts.

Most of the materials were purchased from local dealers.

MALARIA CONTROL.

When the Civil Works programme was inaugurated, malaria control by permanent drainage immediately presented itself as a feasible work project for the purpose of furnishing employment to a large number of people. It was believed that measures directed towards the reduction of malaria in the fifteen States in which the disease is most prevalent would react more beneficially on the population of those States than would any other single public health measure.

In each of the States selected, malaria is the major public health problem in much of their territory. In the malarious sections of these States, the school-child infection rate (the rate for the only accurately measured group) varies from 10 per cent to 60 per cent, and in some places is as high as 95 per cent. There are approximately two million cases of malaria each year and the annual loss is estimated at half a billion dollars. Although the death rate from malaria is not high in comparison with the rate for some other diseases, it does, in a number of States, exceed the death rate for typhoid fever and causes more deaths than smallpox.

The programme was inaugurated in early December and was approaching its maximum of development by early January 1934. When the work commenced, the malaria projects were designated as Federal projects and an allotment of labourers was made for this purpose to each State. At the height of labour employment (January 20th, 1934) there were 28,000 labourers at work daily on Federal projects. The work proved so popular and the benefits accruing

from it were so apparent that the State directors of the Civil Works Administration supplemented the Federal projects by creating State and local projects of similar type. At the labour peak, reports showed the employment of 53,000 people on State and local projects—a total actually greater than the number on the Federal projects. The reported number at work on malaria drainage at the height of employment was therefore over 80,000 labourers.

The results of the work can only be estimated. Drainage commenced after the last malaria transmission season had ended, and the new season has not yet arrived. We cannot at this time even approximate the number of persons living within possible flight-range of those areas now drained which heretofore have produced anophelines. However, it is conservatively estimated that not less than one-fifth of the population will be removed from the hazard of malaria if the drainage effected should be properly maintained in the future. It is believed the economic benefit from the removal of this hazard will represent an annual saving of not less than \$100,000,000. A project for establishing the malaria index in the areas where the work has been carried on, by blood examination, is now under way. This will furnish a "base-line" for measurement of the results of the work in the future.

TYPHUS-FEVER CONTROL.

While there have been few outbreaks of the classical "Old World" typhus in the United States in recent years, a milder form of the disease has prevailed constantly in many of our cities and, to a lesser extent, in rural areas, especially in the south. This mild type, known as "endemic typhus", was first recognised as a distinct clinical entity by a New York physician. Medical officers of the Public Health Service identified this new disease in other sections of the country and demonstrated the existence of a rodent reservoir in which "endemic typhus" is maintained by the agency of external parasites which act as vectors in the transmission of the infection from one animal to another. The most important animal harbouring this infection in nature is the Norway rat. The rat flea transmits the infection from animal to man.

Although formerly not an important cause of illness, during the past three years the disease has been increasing steadily in

prevalence. While, in 1931, only 332 cases were reported in the entire country, the number rose to 995 in 1932, and to 2,043 in 1933. This increasing prevalence had emphasised the necessity that measures be undertaken for reduction of the spread of the disease.

At the request of the Civil Works Administration, the Public Health Service indicated areas harbouring the greatest amount of infection. The Biological Survey undertook a campaign of destruction of the rats in these areas by means of trapping and poisoning. At the same time, it was planned that groups of men recruited from the ranks of the unemployed and working under the supervision of the Public Health Service would *test* the efficacy of these control measures and make tests on new areas to ascertain where additional control measures would be required.

At the height of the work, a total of 3,757 men were employed, and the control work was carried on in three Southern States and preliminary surveys made in thirty seaports.

In spite of the very short time of unrestricted operations (one month from the time of approval of the project), it is felt that some worth-while results have been accomplished. In several communities where rapidly mounting sickness had created widespread apprehension on the part of the citizens, it was possible to locate the exact sources of infection and promptly institute intensive control measures. The work has been of substantial educational value, and the people have been awakened to the need of continued effort on their own part, if a permanent reduction in the incidence of this disease is to be effected.

SEALING ABANDONED COAL-MINES.

This project was undertaken to provide work for unemployed miners and for the purpose of protecting the public health through the safeguarding of water-supplies from the effects of acid mine drainages. The action of oxygen, pyrites and water in abandoned or idle bituminous coal-mines brings about the formation of acid salts and sulphuric acid. In many sections, the amount of acid thus formed and discharged to streams is sufficient to bring about an acid condition in these streams and in the larger rivers to which they discharge. This condition has been increasing in intensity

in recent years and is materially affecting the efficiency of treatment of many public water-supplies and has made the use of the water for some of the smaller supplies impossible.

This problem has been one of considerable concern to the health authorities for many years in several of the soft-coal-mining States where little had been done to care for sections of mines as they became worked out.

Experimental work by the U.S. Bureau of Mines and the State Health Department of Pennsylvania had demonstrated that, if air could be eliminated from abandoned workings, oxidation would cease, and the water in and flowing from these openings would remain alkaline.

Two methods were possible by which this could be brought about :

1. Flooding of the workings, and
2. Air sealing.

In either method the flow of water would not be interrupted. Certain dangers existed in the flooding method which made it practicable only under certain conditions. Air-sealing in general appeared more satisfactory, although requiring more careful attention to ensure that all openings, however small, were closed.

Funds were made available by the Civil Works Administration for the actual starting operations on December 17th, 1933, for carrying on the project in ten States.

In Pennsylvania, West Virginia and Alabama, where certain information was already available, permitting work in certain sections to start immediately, a considerable amount of actual sealing was effected. In other States, surveys were completed and work had just been started on the sealing when the restrictions on the employment of labour became effective on January 19th.

While it was not possible to complete the project as planned, sufficient work was done to accomplish the following results :

Furnishing of records to State Departments of Health covering the location of mines discharging acid water and the extent of this discharge ; demonstrating the practicability of air-sealing for control of acid mine water ; development of methods for air-sealing under varying conditions ; the training of a considerable group of coal-mining engineers and others in the methods of acid mine water control ; and creating the interest of mine operators in the work.

The work as a whole was classed as quasi-hazardous, with some part of it hazardous. It is very gratifying to note that loss-of-time accidents were practically nil.

The maximum number of persons employed was during the week ending February 15th, when 2,927 men and 24 women were on the pay-roll. Of this number, approximately 2,700 were employed in Alabama, Pennsylvania and West Virginia.

At the termination of the work on February 15th, 1934, approximately 7,000 openings of various types had been closed and several hundred additional openings were being closed.

FLY-FREE MANURE HEAPS

By

Edm. and Et. SERGENT,
of the Pasteur Institute of Algeria.

Two types of manure-containers which preclude the breeding of flies have been tested by the Algiers Pasteur Institute.

I. URBAN TYPE.

The twin manure-container built by the Algiers Pasteur Institute in 1912, in the middle of the town, has been in use for twenty-two years without having constituted a breeding site for fly larvæ.

The underlying principle is this : *flies only lay eggs on fresh manure.*

Therefore, we argue, let the manure be placed in an airtight container as soon as produced, and let it not be withdrawn for removal to the fields until it has completely fermented and decomposed and has so become an unsuitable medium for the growth of fly larvæ. To that end, instead of a single container, we built a double container consisting of twin chambers to be used alternatively. First one is loaded and, when filled, is closed and left, whereupon the second is brought into use. When this in turn is full, the first is opened and emptied, and the cycle begins again.

The twin chambers, which are of cubic shape with a capacity of 14 cubic metres apiece, are built of reinforced concrete against an abutment wall, and are raised on pillars so designed that a cart can be placed under the chambers. Each has two horizontal

trapdoors on the top and a vertical door in front ; these openings are closed with an overlapping cover of sheet iron (Fig. 1).

Twice a day the stable manure is discharged by barrow-loads through the upper trap-door of one of the chambers—*e.g.*, container A. The fermentation of the manure in such a well-closed



Fig. 1.—TWIN MANURE-PIT. URBAN TYPE.

space engenders a high temperature (maximum recorded by a thermometer placed in the centre of the container = $94^{\circ}\text{C}.$). After ten or fifteen days container A is full. It is closed tight and left, while container B is being filled in the same way. When container B is full—*i.e.*, after some ten days—manure in container A is discharged into a cart backed in between the supporting pillars and brought directly below the vertical door. According to the gardeners, this manure, after remaining only eight days in the container,

is well matured and very good. The liquid manure is drained off from the floor of each container through a pipe into a closed pit, whence it can be removed at will.

Effective obturation of the openings prevents the flies from gaining access to the containers. Moreover, the heat developed inside by fermentation is fatal to insects. No eggs or larvæ are found inside the chambers, except, on occasion, along the bottom rim of the vertical sheet-iron covers which serve as doors, as these are cooler than the other parts of the container. We were desirous, however, of ascertaining how flies behave towards the manure as discharged from the containers. In September and October, a heap of warm, damp, black manure just removed from a container was exposed to the air. Flies came, but no batches of eggs could be found.

To sum up, by using two closed chambers alternatively, the whole of the fresh manure is removed from exposure to the air as and when it is produced, and only well-matured manure, unsuitable as a fly-breeding medium, is handed over to be spread on the fields.

The construction, on these lines, of a manure-container with twin chambers for alternative use is specially advisable in towns. The design may be modified to suit local conditions. At the Pasteur Institute we turned the declivity of the ground to account, but elsewhere we were able to build these twin-chambered containers on flat ground.

II. RURAL TYPE.

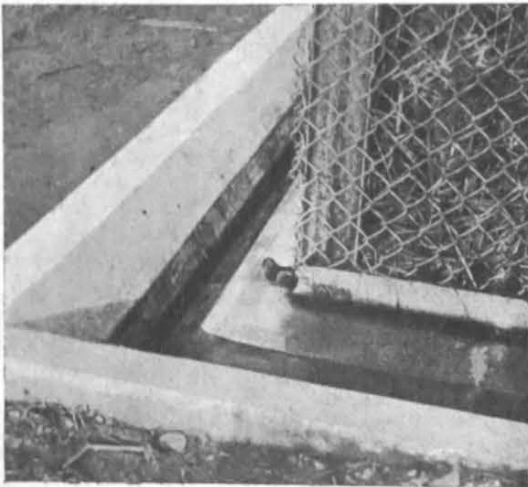
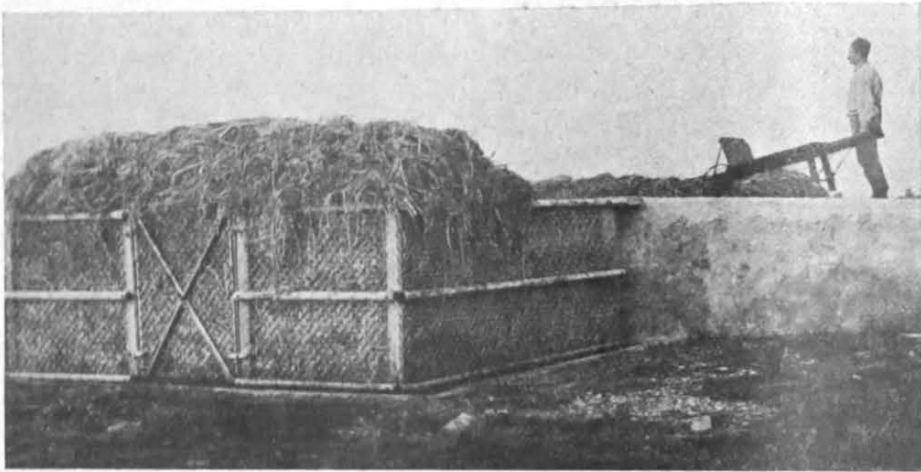
This manure platform was built at the Rural Experimental Centre of the Algiers Pasteur Institute, on the model of Riber's "manure enclosure with larva trap", as described in documents which we owe to the kindness of Professor Dr. T. J. Oudestepoort.

The underlying principle is this: *fly larvæ need dry soil in which to burrow for the process of pupation. Larvæ which pupate consequently leave the fermenting manure and seek the ground.* The idea was conceived of setting a "trap" or "net" which they necessarily follow.

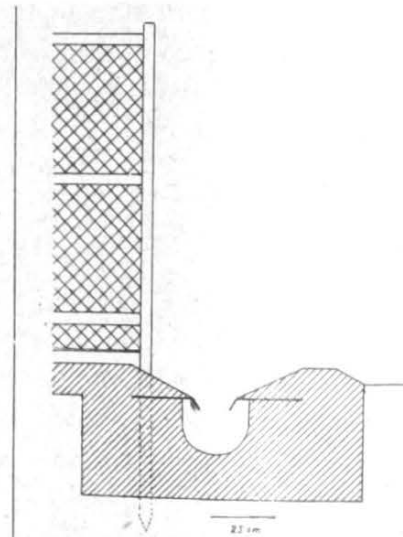
A square concrete manure platform, 3 metres by 3 metres was built, fenced in with stout wire netting frames 2.5 metres by 2.5 metres.

surrounded by an unbroken masonry gutter some twenty centimetres wide and deep (Fig. 2). The novel feature of the manure-pit is the construction of this gutter.

Fig. 2.—MANURE PLATFORM WITH FLY-TRAP.



THE FLY-TRAP.



CROSS SECTION OF GUTTER.

Along both edges of the gutter a narrow strip of sheet iron is fitted, with the inner edge folded down so as to lie at an acute angle to the side of the gutter.

The manure is discharged on to the concrete platform. It is stacked against the netting, watered and rammed tight so as to facilitate fermentation. Fly larvæ which have hatched out and remained in the upper layers of the heap try instinctively, when pupation is imminent, to leave the fermenting mass and pupate in dry soil. They drop into the gutter and cannot crawl out, owing to the down-turned edge of the sheet-iron strip, the top surface of which they cannot reach. The larvæ thus die in the liquid manure in the gutter or are eaten by farm-yard or other birds.

We recommend the construction of such platforms in twos (at least), so that they can be operated on the alternative principle, and that, when one is emptied, the manure removed to be spread on the fields may be completely mature and unsuitable for fly-breeding.

This type of rural manure platform has given excellent results and is inexpensive to instal, so that it can be brought into general use on all farms.

FLY CONTROL IN DENMARK

By

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[Abridged text.]

The investigations which have been carried out in Denmark into the biology of flies and the practical possibilities of fly control were originally started on the recommendation of the Danish delegates to the European Rural Hygiene Conference held at Geneva under the auspices of the League of Nations in 1931.

The idea of developing improved methods of stable hygiene and, in particular, of perfecting measures of fly control, was warmly welcomed by all concerned, stock-breeding and dairy experts and hygienists alike. In 1932, Dr. Th. MADSEN, President of the League of Nations Health Committee, secured from League funds a grant-in-aid for a series of investigations, which the Danish Government, in turn, also helped to finance.

As these studies are to be continued throughout 1934, it would be rash at this stage to try and draw any final conclusions. There is reason to believe, however, that, though the conclusions so far reached may be somewhat modified, they will in the main be confirmed.

THE COMMONEST SPECIES OF FLIES.

1. THE HOUSE-FLY (*Musca domestica*).

This is by far the commonest of the fly species to be found in most human dwellings, in which it represents up to 90 per cent of the total fly population. It is easily distinguishable from kindred

species by its size, colour and wing veins. The colour may vary, especially on the abdomen, but it is always recognisable by the wing, one of the longitudinal veins of which takes a sharp turn, so that it nearly meets the next vein at the wing margin (see Plate I).

The larva (Plate IV*b*) is creamy white or light yellow and very mobile. The young puparia are creamy in the early stages, but change rapidly through yellow to a reddish brown, whilst the older puparia become very dark (Plate VI).¹

In addition to living-rooms and kitchens, the house-fly also haunts stables, byres, pig-sties and other animal sheds. It also has a predilection for human excreta and every kind of filth. In warm and sunny weather it takes to the open, whilst in rainy or cloudy weather it seeks shelter in the houses.

2. THE STABLE-FLY (*Stomoxys calcitrans*).

Unlike the house-fly, this is a blood-sucking fly, distinguishable from the former by its slender pointed proboscis and its more greyish colour with conspicuous dark spots on the abdomen (Plate II).

The larva resembles that of the house-fly, but may be identified by means of the posterior spiracles (Plate IV*a* and Plate XI). The puparium is shown on Plate VI*d* and the egg on Plate IX*c*.

This species does not frequent houses except in rare instances, when it is usually found on verandas and similar places, and inflicts extremely irritating bites. Its real home is the byre. When not sucking blood from the cattle, it will settle on the ceiling and the upper part of the walls, where the air is warmest. It may also be found in stables, but in smaller numbers; it will sometimes invade the stables when the cows are taken out of the byre and pester the horses. It is fairly infrequent in pig-sties, for it has a marked preference for cattle, which it sometimes follows out to pasture; it is, however, but rarely seen in the open, and then only in small numbers and in immediate proximity to the farm buildings.

¹ Cf. C. G. HEWITT, *The House-Fly*. University Press, Cambridge, 1914. E. E. AUSTIN, *The House-Fly*. British Museum (Natural History), Economic Ser. No. 1*a*, third edition, London, 1928.

3. THE HORN-FLY (*Lyperosia irritans*).

This species is smaller than the preceding one ; it is more uniformly coloured and lacks the dark spots on the abdomen. It is marked on the thorax, however, with somewhat indistinct dark stripes (Plate IIIb). The proboscis is shorter than that of *Stomoxys* and is completely covered by the palpi. The larva resembles that of *Musca*, but is smaller, yellower and different in certain structural details, more especially the shape of the spiracles (Plates Vb and XIId). In the height of the summer, these flies are to be found in large numbers sucking the blood of grazing cattle. They are more stationary and more pronouncedly parasitic than *Stomoxys*. Unlike the latter, which seeks the shelter of cattle-byres, *Lyperosia* is an outdoor insect, to be found in byres only when the cattle are brought in to be milked or for the night. It is most frequently found on the back of the animals out of reach of the tail, legs or ears. When the animal shakes itself a swarm of *Lyperosia* rises into the air but soon settles back on to the skin again. The flies which are not sucking remain on the animal, preferably around the base of the horns. Hence the American term "horn-fly". The eggs are laid in freshly dropped cow-dung, in which the larvæ subsequently develop. Pupation takes place in the soil under, or close to, the cow-droppings.

Control of this species consequently calls for measures other than those which may be suitable for *Musca domestica* and *Stomoxys*. We have made no experiments in this direction, but it would seem natural to use washes giving off a repelling odour, or spraying liquids which kill outright.

4. *Hæmatobia stimulans*.

In point of size and appearance, this species (Plate IIIa) occupies an intermediate place between *Stomoxys* and *Lyperosia*. The larva (Plates Va and XIc) closely resembles the *Stomoxys* larva.

Though its economic significance in Europe is just as great as that of *Lyperosia*, it has not received anything approaching the attention it deserves. In fact, whilst the three species already

mentioned have been studied by many investigators, the Russian PORTSHINSKY is the only author who has published some observations on the biology of *Hæmatobia*.

In Denmark, *Hæmatobia stimulans* was particularly abundant in the autumn of 1933, especially in September and in the beginning of October, when it ousted, as it were, the *Lyperosia*, which had occurred in large numbers in July and August, but decreased heavily with the increase of *Hæmatobia*. Our investigations show that the habits of *Hæmatobia* are similar to those of *Lyperosia*. *Hæmatobia* is found on grazing cattle, sucking their blood. We counted upwards of 200 *Hæmatobia* per cow in sheltered woodland clearings. Its abundance in 1933 is doubtless attributable to the exceptionally mild and dry weather prevailing during the summer and autumn.

The eggs are laid in fresh cow-droppings.

A small number of *Hæmatobia* were found on horses ; but, like *Lyperosia*, they have a marked preference for cattle.

* * *

These four species by no means exhaust the *Muscidæ* fauna to be found in human habitations, stables or farm outhouses, or on grazing cattle, manure or rotting refuse. Compared, however, with the species already discussed, the others are of very minor significance. Clouds of small flies, which may, to an untrained eye, appear to be young house-flies, are sometimes seen to rise from dung-heaps, when they are disturbed. These small flies, *Borboridæ*, *Sepsidæ*, etc., hardly ever enter dwelling-houses and are hence probably quite harmless and of no interest to us. It may be well to point out that flies, like other insects, do not grow after reaching the imaginal stage. Growth is confined to the larval stage, which is also the principal (and sometimes the exclusive) phase of food absorption, whilst the pupal stage is a phase of immobility and the imaginal stage the phase of procreation.

Such differences in size as may be observed in individuals belonging to the same species are ascribable to the conditions—especially nutritional—experienced in the larval stage ; they are never made good by subsequent growth in the imaginal stage.

Several other species of the *Muscidæ* are very similar in appearance to the house-fly and may easily be confused with it. When

such species occur in large numbers in places where attempts have been made to fight the house-fly methodically, doubts will often arise as to the practical importance of the method recommended. In such cases it is important to have the flies identified by an expert. A species frequently mistaken for the house-fly is the "cluster-fly" (*Pollenia rudis*), which may, however, be distinguished by a peculiar golden-yellow silky hair covering on the thorax, by the position of the wings at rest, practically superimposed, and by the slow and sluggish movements. This fly is sometimes to be found in considerable numbers—indeed, in regular clusters—in houses, where it seeks shelter in the autumn and winter to hibernate, on window-sills, frames and panes and behind the shutters of unoccupied rooms. KEILIN has demonstrated that the larvæ develop as internal parasites of earth-worms, more particularly of the species *Allobophora chlorotica*, which is common in Europe and North America.

Other species of flies which may enter houses in large numbers for purposes of hibernation are the *Musca autumnalis*, which is closely related to the house-fly, but breeds in cattle-droppings in the fields, *Limnophora humilis* and *Chloropisca notata*.

BREEDING-PLACES OF HOUSE-FLIES AND STABLE-FLIES.

The first question to be asked when the practical problem of fly control is approached is : Where do the flies breed ? Where are the larvæ to be found ? It will be evident at once that measures directed exclusively to the destruction of adult flies are doomed to failure owing to the tremendous fertility of the species. WARDLE calculated that, if a female fly lays 120 eggs during her lifetime—and this is clearly too low an estimate—and if seven generations develop during the summer, a single pair of flies may in one summer have a progeny of 5,598,720,000.

ROUBAUD, who bases his calculations on a larger number of eggs, arrives at truly astronomical figures.

Fortunately, in nature, living creatures do not propagate their kind according to the rules of mathematics ; there is always a considerable mortality at all stages of development. Actual observations are therefore likely to be of greater interest than theoretical

calculations. By way of example, I indicate below the number of *Musca* larvæ produced in a 70 to 80 kg. barrowload of pig-dung on a farm outside Copenhagen during the month of July 1933 :

| | July | | | |
|------------------------|--------|--------|---------|--------|
| Date of exposure | 5 | 6 | 7 | 8 |
| Number of larvæ | 30,000 | 26,000 | 124,000 | 48,000 |

Even if all the larvæ should not become adult flies, the figures are enough to show how enormous is the multiplication of flies during the warm months. To quote another instance, we may mention that, in 1932, 50,000 adult flies were hatched out in a smaller quantity of pig-dung exposed to egg-laying for twenty-four hours. When the daily increase reaches such proportions as this, the utter hopelessness of attempting fly control by the mere process of killing adult individuals will be self-evident.

It is common knowledge that the house-fly breeds in manure. But what kind of manure? So far, writers on the subject have taken the view that horse-manure is the principal breeding medium. Other kinds of manure, if referred to at all, are mentioned but incidentally and as being of a minor importance. ROUBAUD, for instance, asserts quite definitely that the part they play is practically nil.

The only author who advances a different opinion is MADSEN-MYGDAL, formerly Principal of Dalum Agricultural School, who described the breeding conditions of the flies on Danish farms in an article published in a Danish agricultural periodical, *Vort Landbrug*, for 1915.

MADSEN-MYGDAL's fundamental discovery is that, in Denmark, the principal breeding-place of the house-fly is fresh pig-dung. "In a heap of several kinds of manure", he writes, "pure unmixed cow-dung and dung mixed with a good deal of straw hardly ever contain larvæ so long as fresh pig-dung is available as well. Larvæ may be found in horse-manure, but generally in small numbers only."

This striking discrepancy between the views of MADSEN-MYGDAL and those of foreign investigators induced us to select this particular point as the first one for study. The investigations into the breeding habits of flies which we conducted on more than a hundred farms led us to the same result as MADSEN-MYGDAL—namely, that

on Danish farms—in midsummer at all events—pig-dung is the principal breeding-place of the house-fly.

The figures quoted above are in themselves indicative of this fact. As regards cow-dung, our observations corroborate MADSEN-MYGDAL's conclusion that *Musca* larvæ are practically never found in such dung. This is a fact of obvious practical significance, seeing that cow-dung frequently makes up the bulk of the manure. We often found considerable numbers of *Musca* larvæ in horse-manure; but, as in the farm dung-heaps, there is usually much less of this than of pig-dung—especially in the summer, when the horses are out at pasture—it is but of minor importance compared with pig-dung. No house-flies breed in the horse-droppings in fields and on the roads, but they will often hatch out in chicken-dung and in rabbit-dung. The reason why investigators in other countries have underestimated the importance of pig-dung is that in practically every case their investigations were carried out in towns or in military stables, where the dung is mainly horse-manure.

EXPERIMENTS IN CONNECTION WITH OVIPOSITION.

We carried out certain experiments in connection with egg-laying. Containers of equal size were filled with different kinds of manure and exposed to egg-laying. The surface area of dung thus exposed in each container was 500 sq. cms. After twenty-four hours at most, they were covered with gauze and removed to the laboratory, where the larvæ were allowed to develop. The flies hatching out were removed day by day, counted and kept. Four series of experiments were carried out in this way, sixteen containers being used in each series. Eight containers—consisting of four sets of two, filled respectively with pig, horse, cow and calf dung—were exposed to egg-laying on a dung-heap swarming with house-flies. A second lot of eight containers similarly filled were exposed in a calf-byre, where *Stomoxys* was present in large numbers. This experiment served to show which kind of dung each species prefers for oviposition.

The following graph shows the result of the first two experiments. In the first, the horse-manure yielded the largest number of house-flies—i.e., 1,485 in the container exposed in the open, and 951 in

that placed in the calf-byre ; whilst the yield from pig-dung is nothing like so great. On the other hand, an appreciable number of *Stomoxys* hatched out in horse-manure and even in the calf-dung, which contained practically no *Musca domestica* larvæ. It should be noted that not a single fly of either species hatched out in the cow-dung.

The second experiment produced a much higher yield of flies and, so far as can be judged, a far more typical distribution picture. The pig-dung container exposed in the calf-byre yielded 8,891 house-flies and that exposed in the open 2,437. The horse-manure container took second place with 2,118 flies in the container exposed in the calf-byre, and 387 in that exposed in the open. Stable-flies were found almost exclusively in the calf-dung, and in much smaller numbers than house-flies in pig-dung and horse-manure (210 and 111) The cow-dung yielded no flies at all.

These experiments show that the house-fly has a marked predilection for pig and horse manure, though it is impossible to tell with certainty which of the two it prefers. It breeds to a lesser extent in calf-dung but not at all in cow-dung.

The stable-fly lays its eggs in calf-dung and horse-manure but not in pure pig-dung or pure cow-dung. Its favourite breeding place is in calf-stalls, though stable-fly larvæ *may* also occur in cow-dung mixed with straw and urine, more particularly in corners and cracks where some sweepings may have been left. It has sometimes been found in pig-dung mixed with straw or in old mixed dung.

Both species of flies discriminate definitely between cow-dung and calf-dung. The explanation may lie in the milk diet of the calves and the resultant difference in the composition of the dung, or in its processes of fermentation. On many occasions, the temperature of calf-dung has been found to be higher than that of cow-dung, and Professor CHRISTIANSEN demonstrated some years ago that, whilst strongly fermenting *B. coli* are abundant in calf-dung, they are comparatively infrequent in cow-dung, where other species of bacteria, especially *Micrococcus*, predominate. This fact does not appear to be widely known. It might be argued that *B. coli* fermentation, besides engendering a higher temperature—which is certainly a factor in inducing oviposition—produces certain substances whose smell is attractive to the flies.

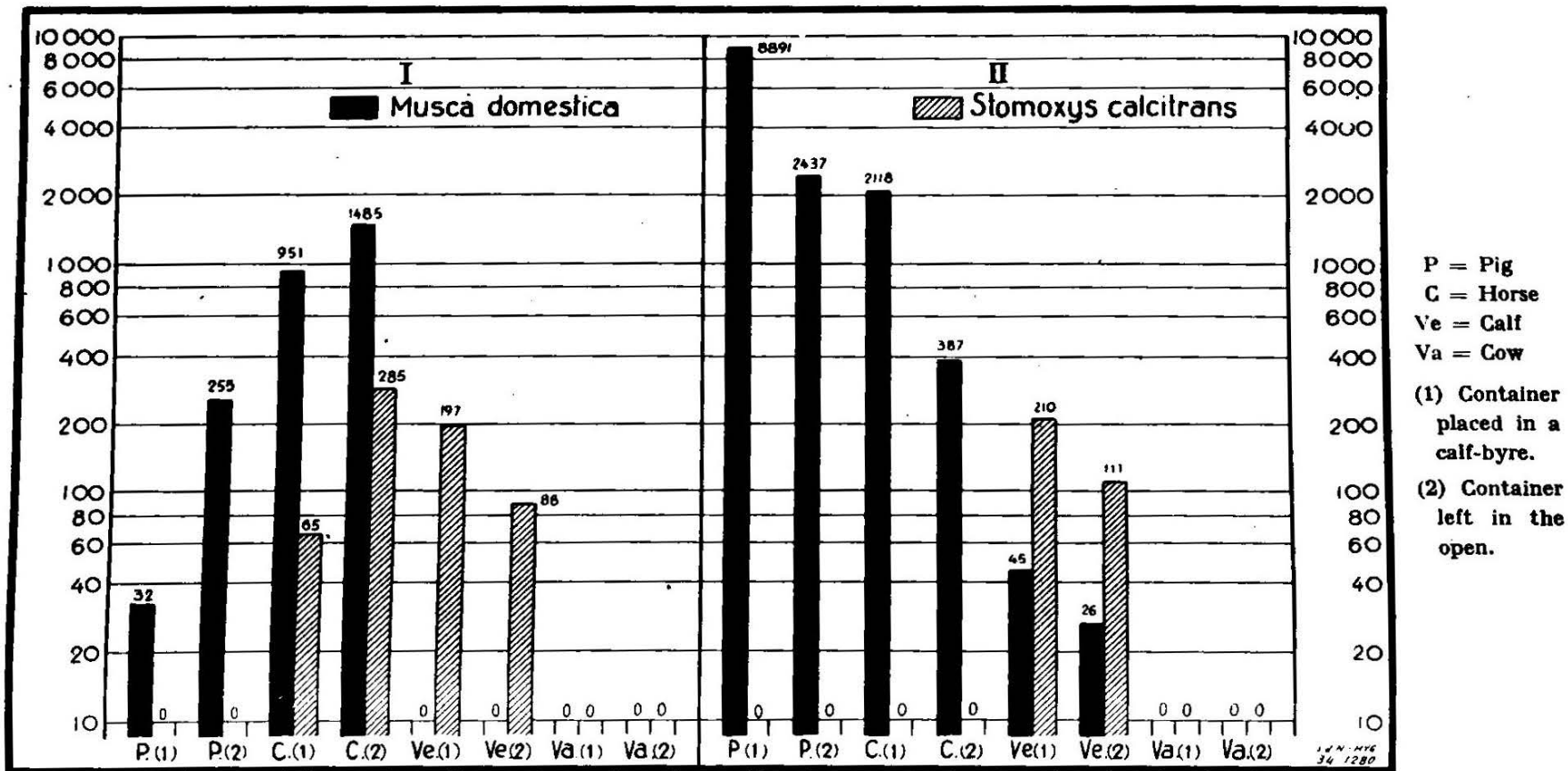


Figure 1. EXPERIMENTS ON OVIPOSITION.

There can be no doubt that the diet of domestic animals may considerably affect the properties of the dung, and hence the flies' reaction to it. Certain observations, which have not yet been experimentally confirmed, make it appear possible that feeding pigs on milk makes the dung more attractive to flies.

It will be observed that, in the first experiment, the containers exposed in the open on the heap of pig-dung yielded the largest number of house-flies, but that, in the second experiment, those exposed in the calf-byre gave the largest number. The difference is presumably due to the weather conditions; but the practical inference to be drawn is that oviposition *may* take place inside sties, stables or byres before the dung is removed to the dung-heap. Whilst there are many observations to confirm this fact, its practical importance is limited, owing to the daily cleaning out of animal-sheds, which is current routine on most Danish farms, and by the difficulty of undisturbed oviposition of the flies.

Our findings concerning the breeding habits of the two most important fly species to be found in Danish farms may be summarised as follows :

(a) The *house-fly* breeds in pig-dung, horse-manure and calf-dung. In the summer, the principal breeding medium is the pig-dung deposited on the manure-heap, whilst, in other seasons, most of the flies hatch out in calf-stalls, horse-stalls and other like places.

(b) The *stable-fly* breeds in calf-dung and horse-manure and, to a lesser extent, in cow-dung mixed with moist straw. The bulk of flies is produced, in the course of the year, in calf-stalls in which dung is allowed to accumulate for some length of time.

INFLUENCE OF TEMPERATURE ON THE DEVELOPMENT OF FLIES.

A fairly considerable literature is available on the subject, but there is no record of systematic investigations into the development of larvæ in thermostats, though this would be the one method likely to yield accurate data, since the temperature of manure-heaps is known to be liable to considerable variations.

With special reference to the house-fly, we have carried through a considerable number of experiments, with the results shown in the following table :

Musca domestica.
Duration of

| The egg stage | | The total period of development | | |
|--------------------|-------|---------------------------------|------|-------|
| Degrees centigrade | Hours | Degrees centigrade | Days | Hours |
| 16 | 46 | 16 | 34 | |
| 18 | >33 | 19 | 23 | |
| 22 | 19.15 | 25 | 12 | |
| 25 | 14.35 | 30 | 9 | |
| 30 | 10.45 | 33 | 7 | 4 |
| 33.5 | 8.45 | 35 | 7 | 18 |
| 36.5 | 7.45 | 40 | 9 | |
| 40 | 8.40 | | | |

It appears from the work of KROGH, PEAIRS, BLUNCK and others that, within the temperature limits of normal development, the curve of the ratio between temperature and duration of the process of development of certain animals coincides with a symmetrical hyperbola. Such a hyperbola can be constructed as soon as two of its points are known, and this has been done in the subjoined figure on the basis of the two values 30°-9 days and 16°-34 days.

The curve having been drawn, the experimentally determined values were then plotted. It will be seen that they coincide fairly well with the theoretical curve. A marked difference is noticeable, however, in the higher temperatures, which indicates that some detrimental influence was at work. This will be clearly seen from the value at 40°, which shows the same speed of development as appears for 30°; besides this, a heavy mortality was recorded. The shortest period of development so far observed is 7 days 4 hours, but a few investigators (ROUBAUD, AUSTIN) claim to have observed cases in which it was reduced to six days (in strongly fermenting horse-manure). If this is correct, it is to be presumed that, in our cultures, some other factors are not optimal at higher temperatures. We shall endeavour to force down the time of development still further, but for the present we may conclude that, under the best possible conditions, one week represents the shortest duration of the developmental stages (egg, larva and pupa). The dotted line in the graph represents the so-called zero of development, the limiting temperature below which all development ceases. Empirically it cannot be exactly determined, but theoretical computations fix it at 10 to 11°.

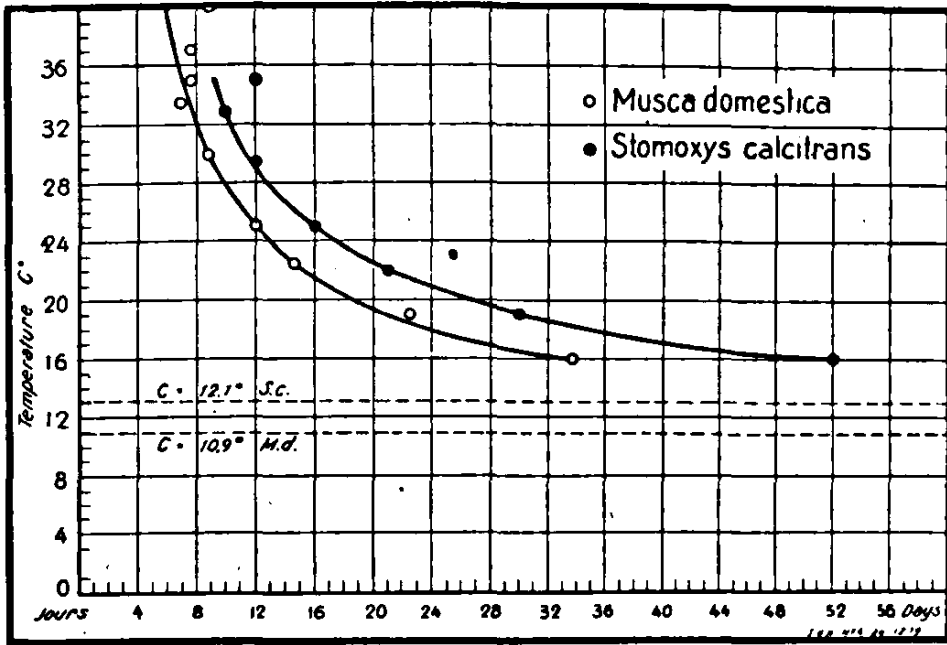


Figure 2. TEMPERATURE AND DURATION OF THE PROCESS OF DEVELOPMENT.

For *Stomoxys*, the curve has been similarly constructed. It shows that, at equal temperature, *Stomoxys* requires much longer for its development than *Musca*. The following are the figures which have been worked out up to the present ; we give them, without committing ourselves, however, as to their entire reliability :

| Degrees centigrade | Days |
|--------------------|------|
| 16 | 42 |
| 19 | 30 |
| 22 | 21 |
| 25 | 16 |
| 29 | 12 |
| 33 | 10 |
| 35 | 12 |

When emerging from the puparium, the fly is not immediately capable of laying eggs. The length of this pre-oviposition period is, of course, influenced both by the temperature and by other factors. In flies kept in the laboratory at a temperature of 20° to 22° C. and fed on milk our experiments showed that this period lasted five or six days.

FLY CONTROL.

As already emphasised, measures of fly control must be directed in the main, not against the adult fly, but against its progeny—*i.e.*, eggs, larvæ and pupæ. The use of "tangle foot" and spraying fluids in stables, sties, byres and living-rooms is none the less extremely useful as a supplementary measure.

1. CHEMICALS.

Experiments have been made all over the world, with numberless chemical products, to destroy the larvæ in manure. American investigators in particular have tested a large number of compounds for their larvicidal power. The resistance of larvæ to the action of chemicals is extraordinary, but they can be killed by certain compounds. The Americans specially recommend borax, or, alternatively—since large quantities of borax may make the manure injurious to the crops—hellebore (powdered root of *Veratrum viride* and *Veratrum album*). After testing a certain number of compounds, we came to the conclusion that, though a few may be used with advantage, the application of chemicals to manure cannot be advocated in a general way, and is practicable only in cases where expense is no consideration.

2. HOT WATER.

A cheaper method than chemical destruction is the use of water at 70-90°C. as recommended by MADSEN-MYGDAL. For the successful application of this method to the ordinary manure-heap, the pig-dung—preferred by the egg-laying flies—should be kept separate, constituting, as it were, a bait, so that only a comparatively small part of the surface of the heap has to be treated. MADSEN-MYGDAL emphasises the need for studying the "geography" of the manure-heap and the behaviour of the flies, so that all clusters of eggs, maggots and pupæ may be located and treated.

In the hands of a capable and conscientious man, this method will undoubtedly yield good results, especially where the daily quantity of manure is comparatively small and where hot water is readily available. But most farmers to whom we suggested this method rejected it out of hand as too exacting. It would doubtless be difficult to train stock-breeders to the use of this method, but, as a supplementary measure, it may be distinctly valuable.

3. ROUBAUD'S BIOTHERMIC METHOD.

ROUBAUD proposed to make use of the fermentation heat of the manure itself to destroy larvæ and pupæ.¹

The temperature of fermenting manure may rise to 70° or even higher, a temperature absolutely fatal to flies at all stages of development. ROUBAUD has proposed several variations of the method—for instance, that the fresh manure from the stable should, every morning, be buried in the warmer inner layers of the manure-heap; or that the fresh manure be deposited on the surface as usual every morning, while in the evening the top layer containing the day's egg-layings, together with the eggs and maggots from the stable, be scraped off and buried in the warmer inner layers.

Prima facie, this method seems to be a simple solution of the problem, but, on a practical test, it does not prove suitable under the conditions prevailing in Denmark. It is based on the assumption that horse-manure is the only kind of manure in which an appreciable number of flies hatch out, and, further, that the bulk of the eggs are laid inside the stables, byres, pig-sties, etc. As previously explained in this report, however, horse-manure forms only a small part of the manure-heaps of most Danish farms, which are mostly made up of cow-dung and pig-dung, the last-named being by far the most important fly-breeding medium.;

¹ E. ROUBAUD : "Études biologiques sur la mouche domestique : Méthode biothermique de destruction des œufs dans le tas de fumier" ; *Compte-rend. Soc. Biol.*, Vol. 78, 1915. "Production et autodestruction par le fumier de cheval des mouches domestiques" ; *Compte-rend. Acad. Sci.*, Paris, Vol. 161, 1915, page 325.

Though the temperature of pig-dung may rise to a degree which is fatal to the larvæ, cow-dung never reaches such temperatures; it is "cold dung", and an admixture of cow-dung to other kinds of dung will tend to lower the general temperature and thus to make Roubaud's method impossible. Even if the pig-dung is kept apart, the method is impracticable—first, because the temperature does not rise sufficiently if the pig-dung is somewhat wet, and, secondly, because the flies will lay their eggs on the surface of the heap of pig-dung even if the fresh dung is buried and only dung a few days old is exposed on the surface.

Roubaud's method may, therefore, be successfully applied to a heap of pure horse-manure, but not to dung-heaps consisting mainly of pig-dung or cow-dung.

4. COVERING METHODS.

The observed preference of the flies for fresh pig-dung suggested to us the idea of trying to cover this with other materials in order to prevent, or at least reduce, oviposition. This is a preventive technique as distinct from most others, which aim at killing the flies before or after hatching. The egg-laying experiments already described led us to try *cow-dung as a covering*, seeing that, for all practical purposes, flies do not lay eggs in cow-dung. Further, the use of cow-dung offers the great advantage that this material has to be deposited on the dung-heap anyhow, so that no expenses are incurred. The dung-heap is carefully covered with fresh cow-dung, which, in its ordinary semi-liquid form, rapidly cakes on the surface and prevents the smell of pig-dung from exercising its influence on the flies.

Towards the end of the summer of 1932, we carried out a few preliminary trials with this method at Aarslev experimental station. The results were not decisive, but on the lines expected. In 1933, we carried out a second, successful, series of experiments at a farm near Copenhagen.

Particulars of the experiments are given in the table on page 319.

NUMBER OF MAGGOTS (*Musca domestica*) DEVELOPED IN PIG-DUNG.
(July 1933.)

| Date of exposure of heap | Deviation of mean temperature from the normal | Rainfall in mms. | Number of maggots | |
|--------------------------|---|------------------|-------------------|--------------|
| | | | Uncovered heap | Covered heap |
| July | Degrees C. | | | |
| 5 | + 6.0 | 0 | 30,000 | |
| 6 | + 5.4 | 0 | 26,000 | |
| 7 | + 4.2 | 0 | 124,000 | |
| 8 | + 7.1 | 0 | 48,000 | |
| 10 | + 4.4 | 0.5 | | 7,550 |
| 11 | + 1.1 | 13.5 | | 6,110 |
| 12 | + 0.4 | 5.2 | | 720 |
| 13 | — 0.9 | 12.2 | 20 | |
| 14 | + 0.3 | 10.4 | (not counted) | |
| 15 | + 1.4 | 6.2 | 17,200 | |
| 16 | + 2.0 | 0.2 | | 0 |
| 17 | + 0.3 | 0.8 | | 300 |
| 18 | — 1.5 | 0.2 | | 50 |
| 19 | + 0.4 | 0.2 | 1,640 | |
| 20 | + 1.1 | 0 | 7,120 | |
| 21 | + 2.0 | 0 | 1,140 | |
| 22 | + 1.4 | 5.0 | | 50 |
| 23 | + 1.6 | 0 | | 0 |
| 24 | + 1.9 | 0 | | 0 |
| 25 | + 1.1 | 18.8 | 500 | |
| 26 | + 1.6 | 0 | 7,280 | |
| 27 | + 3.2 | 0 | 38,000 | |
| | | | 300,900 | 14,780 |

From July 5th to 27th, part of the fresh daily sweepings from the pig-sty was exposed to egg-laying flies on the ground outside the buildings. During the first four days, the heaps were left uncovered and eggs were deposited in abundance. On the following three days, they were immediately covered with a layer of cow-dung (15 to 20 centimetres). During the next three days, the dung was again left uncovered and this alternation was continued up to July 27th. Throughout the experiment, the other pig-dung produced on the farm was covered daily with cow-dung to prevent the mass from attracting flies. After exposure for a number of days, the heaps were carefully examined and the number of larvæ (*Musca domestica*) counted.

During the first four days, the weather was unusually warm and dry, with temperatures of 4 to 7 degrees above normal, thus affording the best possible conditions for oviposition, as shown by the enormous number of larvæ found in the uncovered heaps. In the cow-dung covered heap of July 10th, the number hatching out is markedly smaller, but still above 7,000 ; the cow-dung was thus not entirely effective in preventing the smell of pig-dung from passing through. The weather on that day was still fine and favourable to egg-laying, but, on July 11th, a period of unsettled showery weather set in, which lasted until July 15th, after which there was another fine spell, interrupted, however, by a few rainy days.

Weather conditions have certainly influenced the experiments, for, on rainy days, flies remain under shelter and egg-laying in the open is that much reduced. The fluctuations in the number of larvæ do not, however, tally exactly with rainfall variations, owing to the fact that conditions favourable to egg-laying may yet have prevailed for several hours a day during stormy spells. Moreover, the temperature and rainfall records were not made at the farm itself, but at the nearest meteorological station.

Taken as a whole, the experiment may be said to have been particularly satisfactory. More than 300,000 larvæ hatched out in the uncovered heaps, and something over 14,000—*i.e.*, less than one-twentieth—in the heaps covered with cow-dung, the great bulk being assignable to the first two days (July 10th and 11th). It is obvious that, if this method were applied from the beginning of the summer, the fly population would at no time be as large as it was during this experiment.

We had certain practical trials carried out on a number of farms.

At the Tune Agricultural School, from May 1st, the dung on the manure-heaps was carefully stacked into compact rectangular blocks, well above a man's height ; every morning the pig-dung was stacked on the dump first, packed as close as possible and then covered with a thick layer of cow-dung. In this way, the number of flies hatching out up to the end of July was greatly reduced in comparison with previous years and the heap contained, moreover, but a very few maggots. On one or two occasions, however, when the covering was discontinued for a couple of days, a fair number of larvæ were immediately found. From July 4th, as the cows

were not brought in for milking, there was no cow-dung available and the dung had to be covered instead with a layer of old dung, a mixture of pig-dung, cow-dung and horse-manure. This soon proved inadequate ; and, towards the end of July, the number of flies gradually increased, without, however, reaching really serious figures, whilst the larvæ similarly became more numerous.

The method was also applied, with excellent results, on a farm in North Jutland. There, as the cows were brought under shelter every night throughout the summer, according to the usual Jutland practice, there was never any lack of fresh cow-dung. Plate XII (b) shows the wire netting applied to keep the farmyard hens from scratching the surface layer. We found that there were exceedingly few flies in the pig-sty, and no maggots to be seen in the manure-heap. The farm people were extremely satisfied with the results and considered the method both easy and practical. According to the local veterinary surgeon, no other farm in the district had so few flies. That same day, we visited another farm, more modern and with a manure-heap unusually well arranged, but not covered with cow-dung. It was thick with maggots and the living-rooms were swarming with flies.

Covering manure-heaps with cow-dung seems to be an efficient method of reducing the numbers of flies. The only drawback is that there is sometimes a lack of fresh cow-dung when the cows are out at pasture, and that old mixed dung and old pig-dung, which have been tried as substitutes, have not proved effective. This difficulty might be overcome by storing up a certain amount of cow-dung in the spring.

We have therefore endeavoured to devise some other method which would enable cow-dung to be dispensed with, and have recently tried another simple measure—namely, *covering with tarpaulins*, made of the discarded nitrate bags which are available on all farms in Denmark. As they are made of fairly stout material and lined with tarred paper, they form a good fly-proof cover, provided the sacking is carefully arranged with plenty of overlap all round [Plate XII (c)]. The dung must, of course, be stacked as carefully as in the previously described method, and be kept permanently covered.

This method enables the fermentation heat of the manure to permeate the topmost layer. With pure and very liquid pig-dung,

the temperature rarely rises above 35 to 40°C. But if such dung contains a certain amount of straw or of horse-manure, it reaches 50°C. or more at the surface and 60 to 70° at a depth of 15 cms. The dung deposited in the morning may, under favourable conditions, reach these high temperatures by 5 or 6 o'clock in the evening of the same day or at latest by the next day. Slight compression seems to promote the rise of temperature. Moreover, all the eggs deposited on the surface of the sacking by flies attracted by the smell of pig-dung will perish,

We do not yet know how long the dung must be kept covered before the tarpaulin can be removed without risk of egg-laying by flies. It might possibly be found useful to cover the completed stack with a layer of earth, peat litter or fresh cow-dung.

If stables and sties were conscientiously cleaned out every day, the number of eggs involved would be far less than those laid in the manure-heap, and, if the latter is covered with cow-dung or other material throughout the fly season, the number of flies which succeed in developing during the year should be comparatively small.

The raising of the fermentation heat by tarpaulin-covering acquires special practical importance when byres and sties are not cleaned out daily. Fly maggots dislike temperatures above 40° and will move to cooler parts of the manure-heap—*i.e.*, the surface. If the surface is covered with sacking so that the temperature under the sacking is still 50° or more, many of the larvæ will be killed by the heat. Thus, in the course of our experiments, we found large masses of dead larvæ on the surface of the heap when we removed the sacking [Plate XIII (b)].

The lack of oxygen and the generation of poisonous gases may also contribute to the destruction of larvæ. To kill those which manage to slip out at the sides of the heap, where the temperatures usually remain below lethal point, it will suffice to stack another rectangular block up against the exposed side before the pupae have time to develop.

We did not begin to try this method until towards the end of the summer, so that we can make no definite statement as to its practical value ; but the results achieved are promising, and we intend to pursue our experiments in 1934. The sacking method is a combination of the preventive method with the biothermic method, for, when it is properly carried out, not only is oviposition prevented,

but any maggots and pupæ already present in the dung removed from the byres will be killed.

5. OTHER MEASURES.

An essential requirement, if the fly population of a farm is to be kept down to a tolerable minimum, is the regular cleaning of animal-sheds, in particular, calf-stalls and horse-stalls, in which, owing to the very common practice of allowing the dung to accumulate for months, thousands of house-flies and the bulk of stable-flies breed. Our observations show that the dung layer on the floor of such stalls generally has a temperature of 20 to 25°C. Now, at 25°C., *Stomoxys* requires sixteen days to complete its life cycle and *Musca* only twelve; it follows, therefore, that such stalls should be cleaned out every week—at any rate, during the summer.

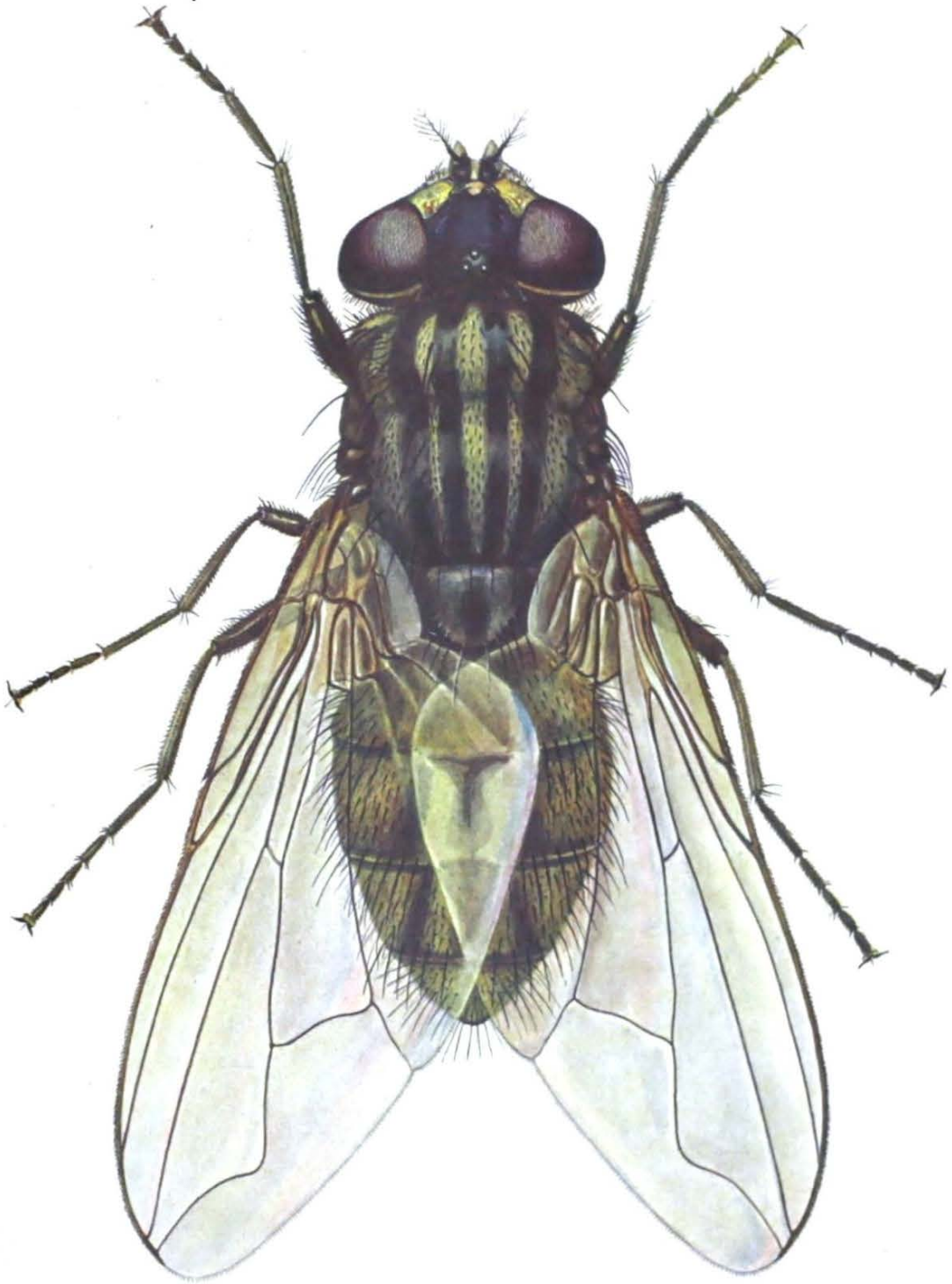
The removed dung may be covered with sacking or—if it is only a small quantity—it may be buried in the warm part of the dump, provided the temperature is sufficiently high to kill maggots and pupæ.

If none of the covering methods mentioned here are regarded as suitable—and simpler methods of control can hardly be conceived—the only thing left is to remove the dung every day or every few days to a manure-heap out in the fields, well removed from the farmhouse. The observations we made on a few farms in Denmark indicate that the fly nuisance can be considerably abated in this way, since flights from the manure-heap to the house and back are thus checked. This is certainly the simplest of all measures, but it does not represent actual control, for the flies breed anyhow and, in districts where farms lie close together, it simply means driving them over to the neighbours.

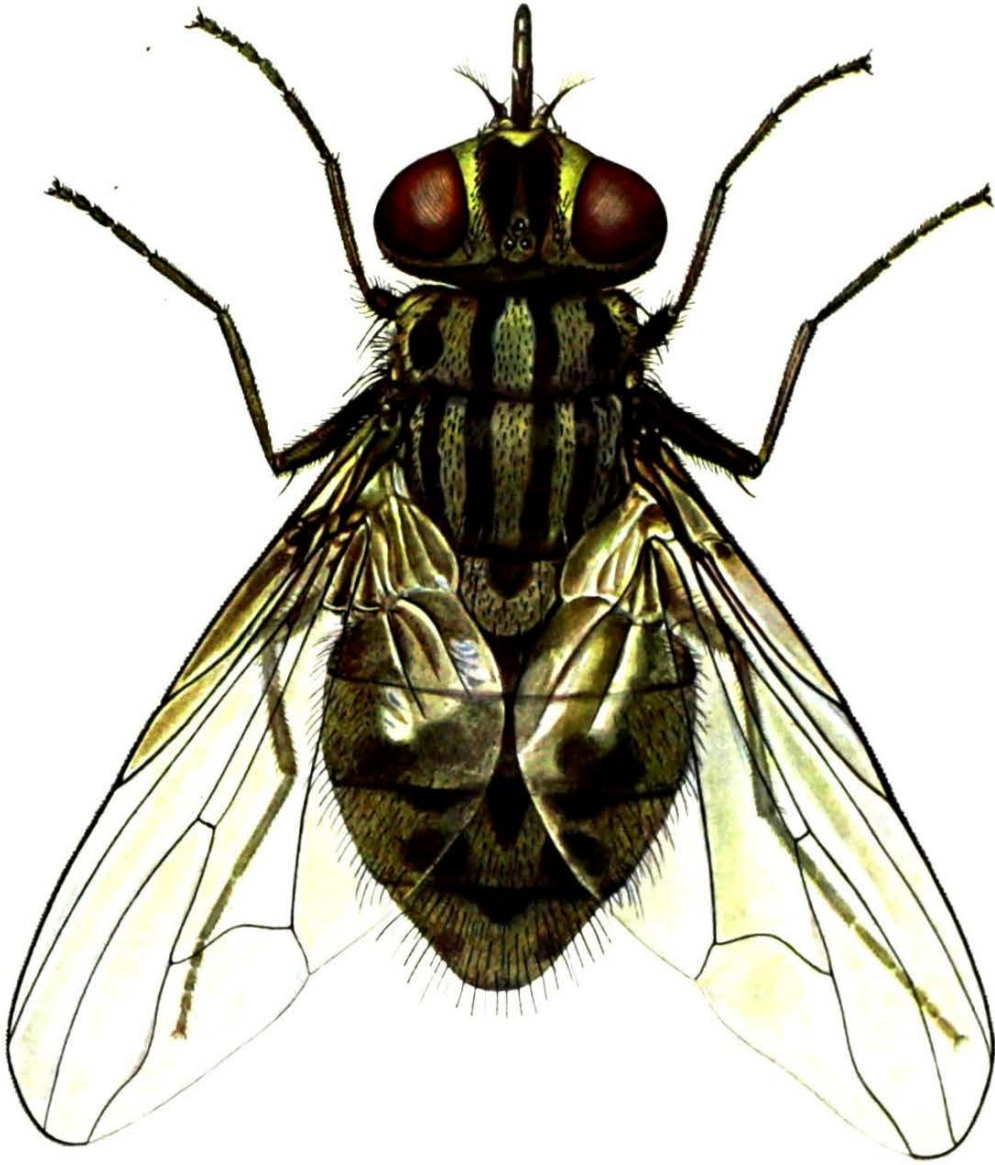
To sum up, the periodical and conscientious cleaning-out of all animal-sheds during the summer and the covering with cow-dung or sacking of the fresh pig-dung and horse-manure constitute the most practical means of dealing with the fly nuisance on Danish farms. We cannot, of course, completely exterminate flies, but it is possible at any rate to keep the numbers down to a bearable minimum, and farmers should realise that it is just as shameful to be infested with flies as with any other kind of vermin.

There can obviously be no question of applying direct to other countries in which conditions are different the methods which have proved successful in Denmark. In that country, where the fly nuisance is attributable mainly to the large number of pigs kept, the principal question is that of the manipulation of the pig-dung, and the high standard of stock-breeding technique warrants the hope that measures of fly control will be successfully applied.

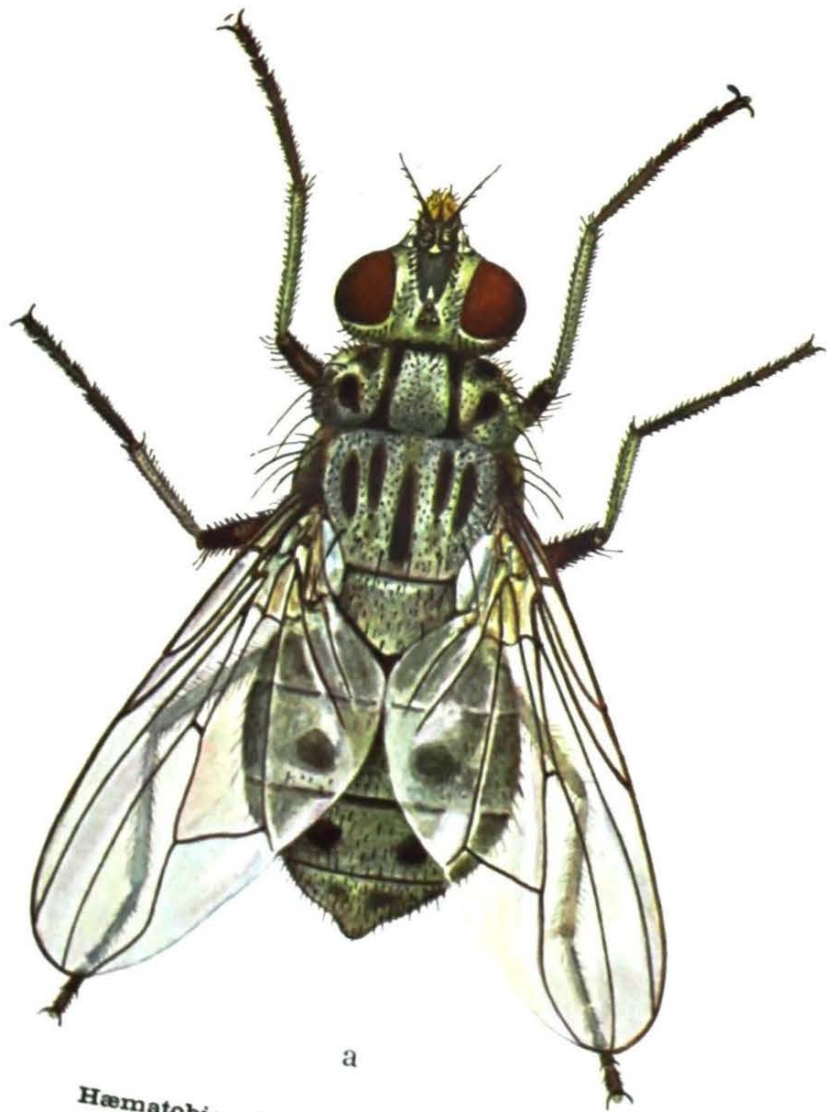
We can only hope that the results of our investigations can be adjusted to suit the needs of other countries and that they will, at all events, focus public interest upon the important problem of fly control.



Musca domestica. Female, × 15.

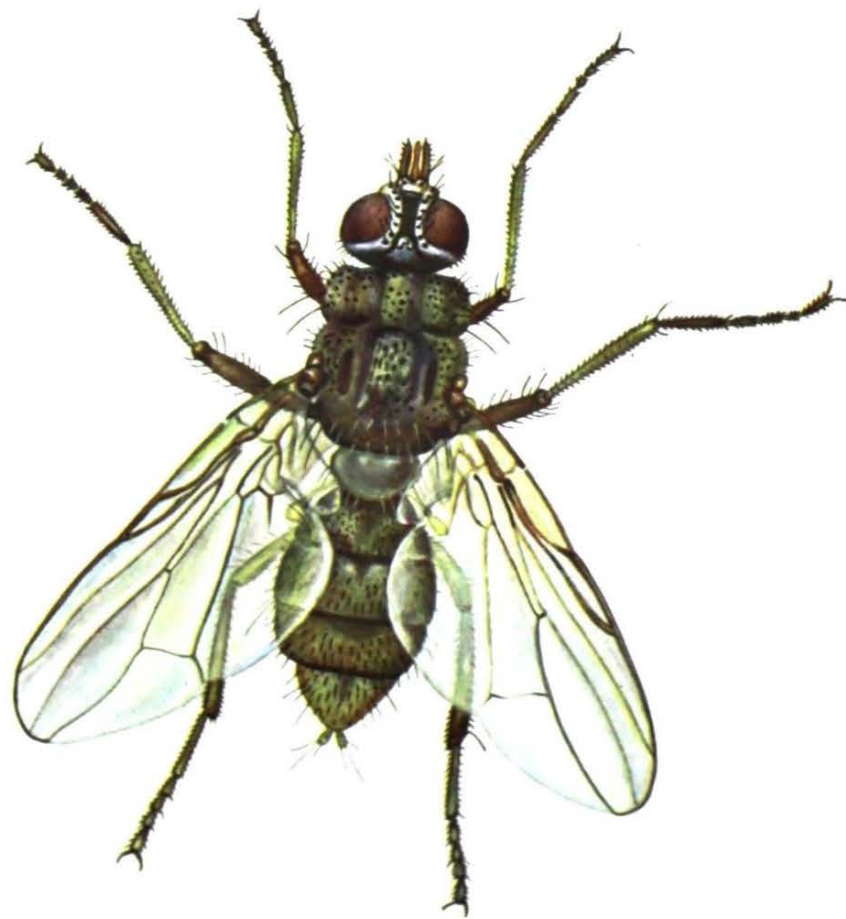


Stomoxys calcitrans. Female, $\times 15$.



a

Hæmatobia stimulans. Female, $\times 15$.



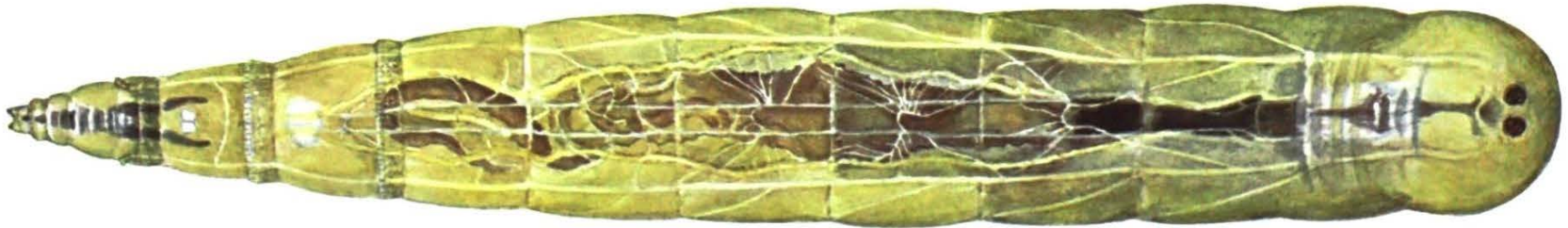
b

Lyperosia irritans. Female, $\times 15$.



a

Larva of *Stomoxys calcitrans*, $\times 15$.



b

Larva of *Musca domestica*, $\times 15$.



Larva of *Hæmatobia stimulans*, $\times 15$.



Larva of *Lyperosia irritans*, $\times 15$.



d

Puparium of *Stomoxys calcitrans*.



c

Older puparium of *Musca domestica*.



b

Puparium of *Musca domestica* a few hours old.



a

Puparium of *Musca domestica* immediately after pupation.



a

Larva of *Musca domestica* in manure.



b

Collection of *Musca domestica* as found in the outer layer of straw at the base of manure heaps.



a

Batch of *Musca domestica* eggs produced by a single female in a single oviposition, $\times 12$.

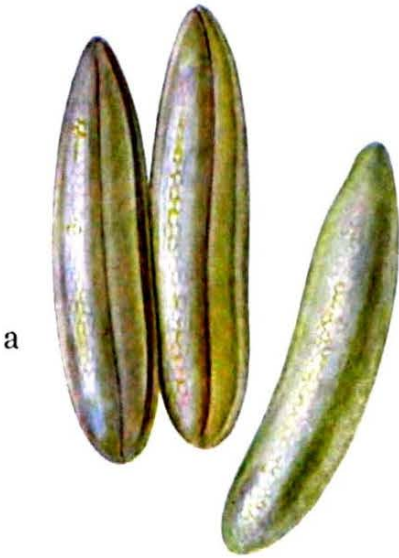


b

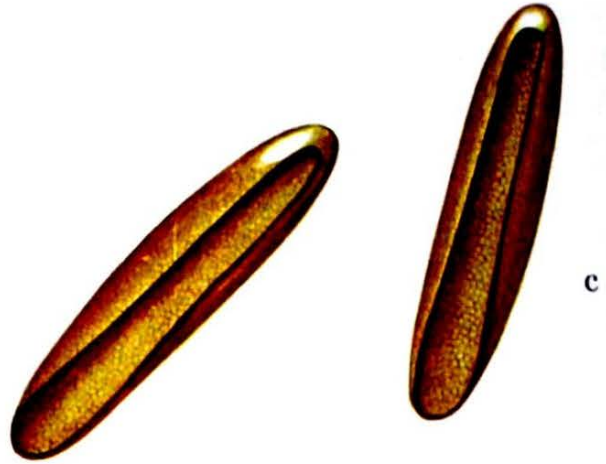
The pupa proper of *Musca domestica* dissected out of the puparium. Below the eye, the left spiracle (brown) is visible. $\times 15$.

Eggs of various species of flies.

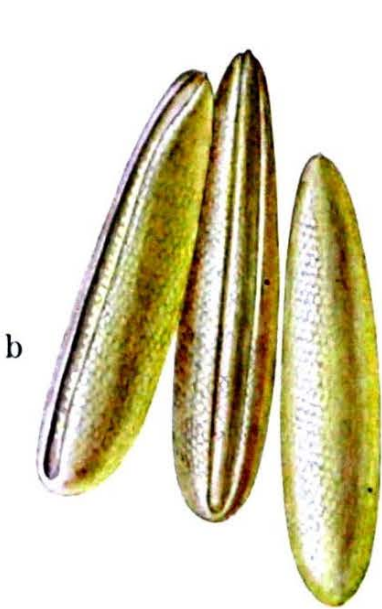
× 50.



Musca domestica.



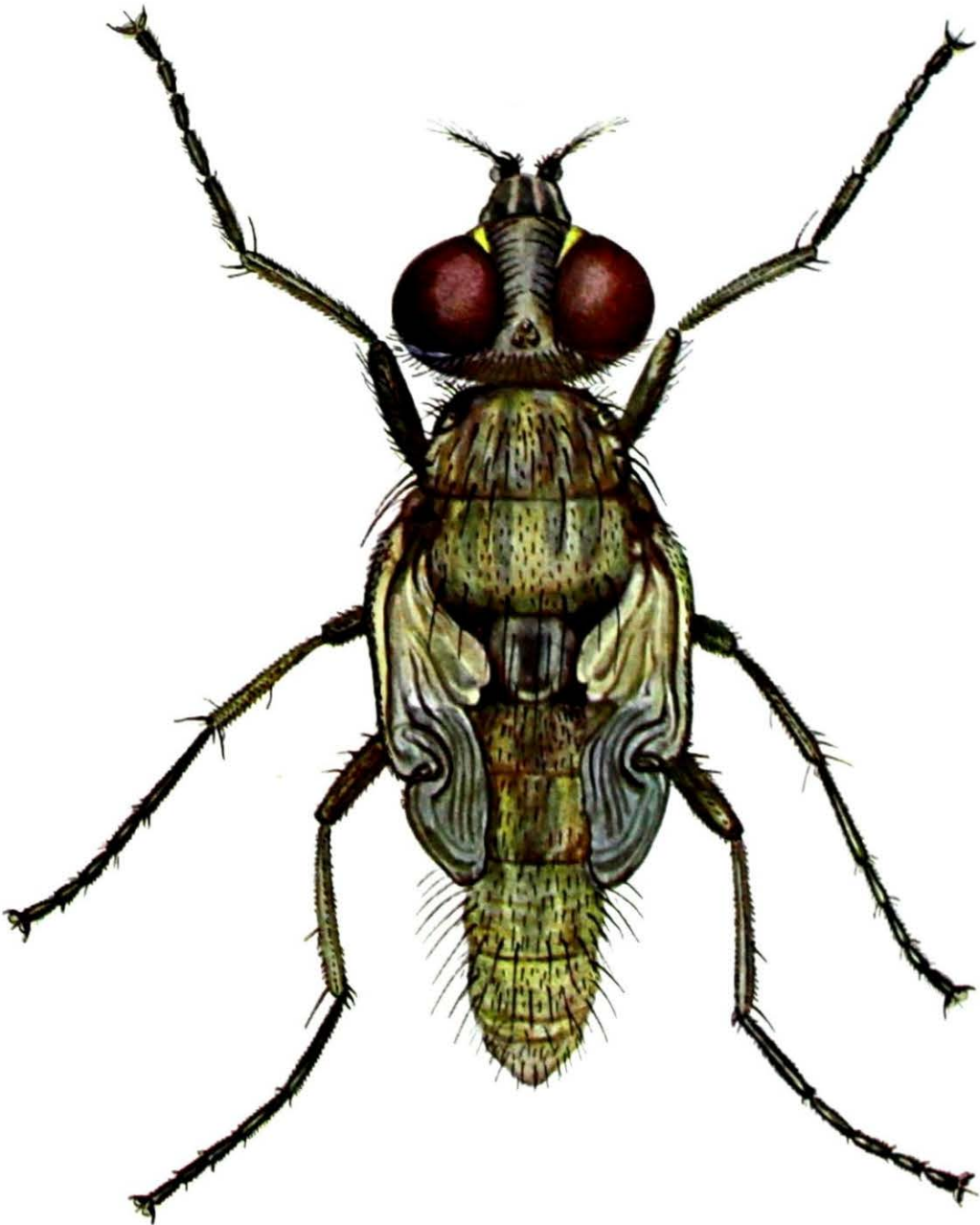
Lyperosia irritans.



Stomoxys calcitrans.



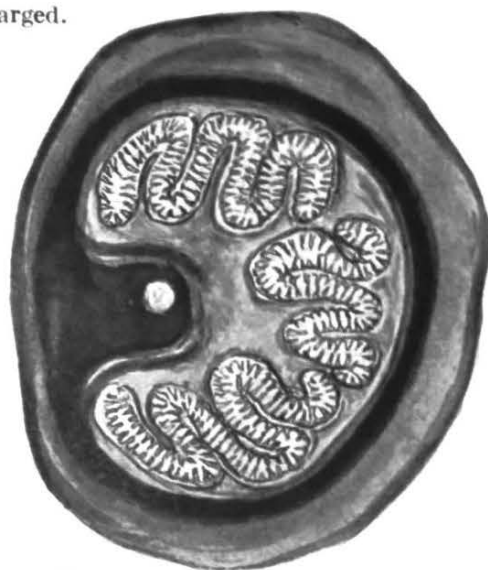
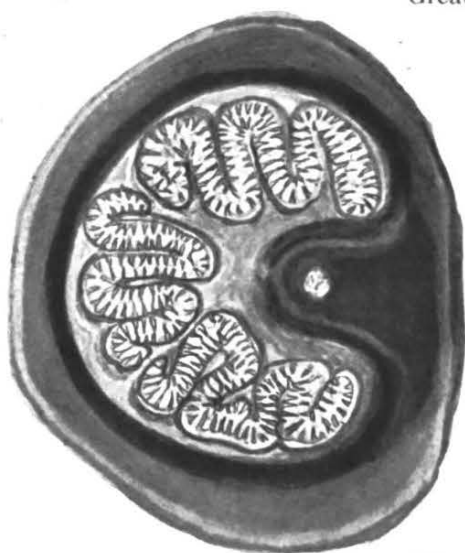
Hæmatobia stimulans.



Musca domestica freshly emerged from puparium, wings still folded, $\times 15$.

Posterior spiracles of various fly larvæ.

Greatly enlarged.



a

Musca domestica.



Stomoxys calcitrans.



b



Hæmatobia stimulans.



c



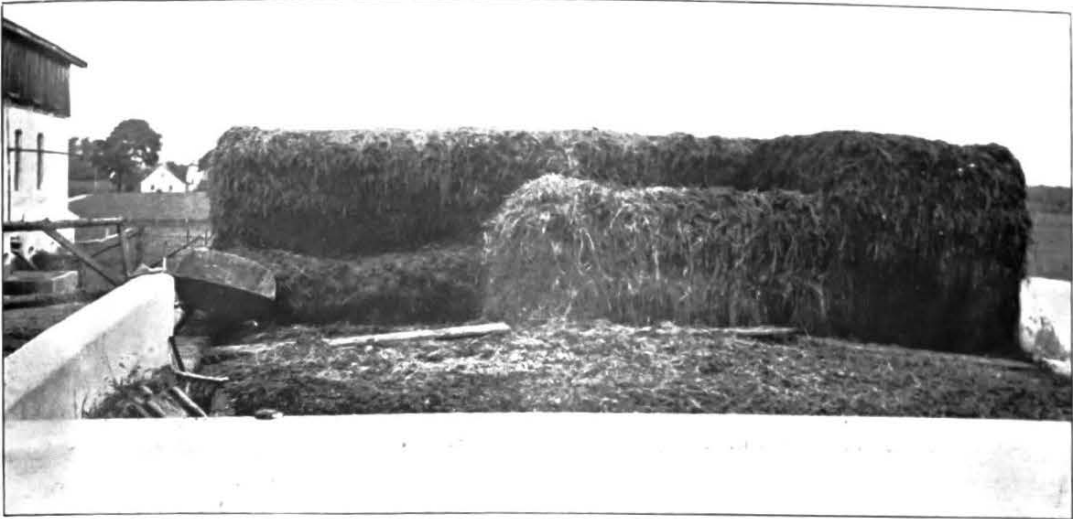
d

- (a) Manure stacked in compact rectangular blocks ; pig-dung first deposited and covered with cow-dung.**

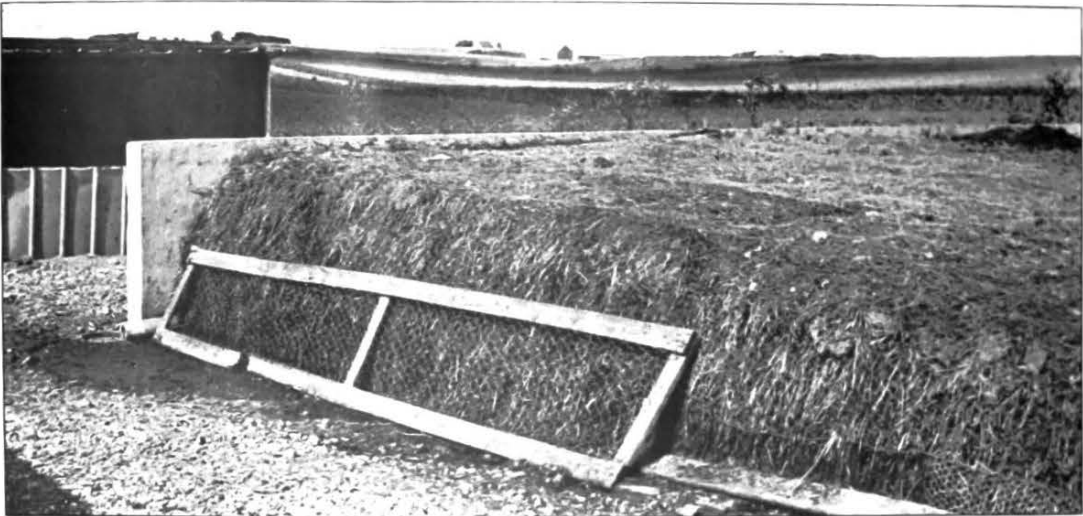
(Tune Agricultural School, July 1933).

- (b) Manure dump on a farm in North Jutland. Stacking into compact rectangular blocks and daily covering of the pig-dung with cow-dung reduces loss of nitrogen and makes the heap unsuitable as a breeding-place for the house-fly. Wire netting prevents the hens from pecking the surface.**

- (c) Heap of pig-dung covered with sacking. A metal tube is inserted in the dung to measure temperatures of deeper layers.**



a



b



c

(a) A heap of pig-dung unsatisfactory from the economic and sanitary points of view. The large surface allows of a maximum loss of nitrogen and affords an ideal breeding-place for house-flies.

(b) The sacking of the dump shown on plate XII, fig. c, is folded back to show collection of maggots killed by fermentation heat.



a



b

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Authors are alone responsible for views expressed in signed articles.

THE THERAPEUTIC EFFICACY OF TOTAQUINA
IN HUMAN MALARIA

The present report marks an important stage in the history of the Malaria Commission, the concluding phase of its effort to find some drug that would be at once effective against malaria and less expensive than quinine. Ever since its inception, in 1923, the Malaria Commission has, in fact, included the problem of the treatment of malaria patients among its subjects of enquiry.

Most of the countries in which malaria is rife—especially in the tropics—have a population which lives under very precarious economic conditions ; large numbers of malaria patients receive no treatment.

Only ten years ago "malaria treatment" was synonymous with "quinine treatment". Now, quinine is expensive, very expensive even, where its trade is not strictly controlled.

It was thus natural to argue that, if it proved possible to reduce the price of quinine, more patients could be treated. The reduction of the price of quinine was an economic problem ; price control, the distribution of the drug at reduced prices or free of charge in malarious countries was a matter both of economics and of internal policy. There was, however, one purely medical field whose exploration might conduce

to the achievement of the objects in view: research with a view to discovering a cheaper drug than quinine. There was the precedent of British India, which was using *cinchona febrifuge*, a mixture of the residual alkaloids of quinine, with the addition of a certain amount of quinine. And it was pertinent to ask whether this experiment might justify the advocacy of a mixture of alkaloids as a medicament for the treatment of malaria.

The Commission instructed a Sub-Commission to Investigate the question of quinine in its three aspects: botanical, chemical and pharmacological. Co-ordinated tests, carried out under its guidance in various countries with a view to determining the therapeutic action of cinchonine and mixtures of alkaloids comparatively to that of quinine, demonstrated the fact that the efficacy of certain mixtures of total alkaloids of cinchona bark was equivalent to that of quinine. There remained but to standardise these mixtures, to lay down the mode of preparation and chemical and biological analysis in order to reduce them to identity. In 1931, the Commission gave the name of Totaquina to the new standard preparation thus recommended.

There was no suggestion of replacing quinine by Totaquina. It was intended, however, that the use of mixtures of alkaloids should enable treatment to be extended to the masses just as the use of cod-liver oil has enabled preventive antirachitic action to be undertaken on a wider scale. These mixtures are, in fact, less expensive than quinine, for they are obtained either by adjusting the residual products of quinine manufacture to the standard specification by the addition of quinine, or by the extraction of all the alkaloids from the bark of the least expensive species of cinchona, such as *C. robusta* and *C. succirubra*. It is a well-known fact that the rationalisation of quinine production has led to the selection of that species of cinchona whose bark has the highest quinine content—*C. ledgeriana*, a very delicate species which only flourishes in areas satisfying certain special conditions as regards altitude, soil, temperature and moisture. The circumstance that only *C. ledgeriana* is at present employed for the manufacture of quinine gives the producing countries a practical monopoly and thereby influences the prices of quinine.

The two other species—*C. robusta* and *C. succirubra*—which are much less delicate, can be grown in most tropical countries, for which reason their bark is cheaper. Whilst they contain less quinine, their total alkaloid content may be higher even than that of *C. ledgeriana*.

Finally, the manufacture of Totaquina with such barks is much more economical than the process of quinine extraction, seeing that the various alkaloids are not separated.

In order to facilitate the adoption of Totaquina by the pharmacopœias of various countries, the Commission instructed experts to work out methods of analysis, and communicated these to the national pharmacopœia committees of malaria-infested countries. It should be added, in conclusion, that certain factories prepared the various samples of Totaquina which were used in the clinical tests whose results are set forth below.

* * *

The Health Committee, at its twenty-first session, May 1934, adopted the following resolution of the Malaria Commission :

“The Malaria Commission,

“Having noted the therapeutical experiments carried out with Totaquina and having studied Dr. William Fletcher’s report thereon :

“Considers that Totaquina seems able to fulfil the purpose for which it was intended, since, having regard to its efficacy—equal to or only slightly less than that of quinine—, facility of preparation and cost price, its use would enable malaria treatment to be extended over a wider field ;

“Recommends that the report, together with an introductory note, be distributed to Health Administrations in malarious countries ;

“And requests the Health Section to assist Health Administrations who wish to employ this remedy in the treatment of malaria and to hold itself at the disposal of any institute which might continue this research work.”

I. Clinical Tests carried out under the Auspices of the Malaria Commission

by

E. J. PAMPANA, M.D., D.T.M. & H.,

Member of the Health Section of the Secretariat of the League of Nations.

Definition of Totaquina.

"Totaquina" is the name given by the Malaria Commission to a new standard preparation consisting of the total alkaloids of cinchona bark.

According to the definition of the Malaria Commission, Totaquina should contain 70 per cent of crystallisable alkaloids and not less than 15 per cent of quinine. It should not contain more than 20 per cent of amorphous alkaloids, or more than 5 per cent of water, and the mineral ash content should not exceed 5 per cent, and if possible 3 per cent.

Types of Totaquina used in the Tests.

Type I (made direct from the bark of *Cinchona succirubra*) :

1. *B. & W.* — made by Messrs. Burroughs, Wellcome and Company, London ;
2. *Madras*—prepared by the Madras Government Factory.

Type II (made from residues of quinine extraction, and adjusted to the Malaria Commission's standard specification) :

3. *Turin II A* }
4. *Turin II B* } made by the Turin State Quinine Factory.
5. *Howards*—made by Messrs. Howards, London.

With the exception of the *Howards* product, which was supplied directly by the producers, the various preparations were distributed by the Health Organisation to the following workers :

Dr. BORČIĆ, Central Field Health Station, Nanking, and
Dr. CHEER, the Central Hospital, Nanking ;

Dr. E. DE BUEN, Malaria Institute, Naval Moral de la Mata, Spain ;
 Colonel S. P. JAMES, Horton Hospital, Epsom, England ;
 Dr. A. Neave KINGSBURY, Institute for Medical Research, Kuala Lumpur ;
 Dr. H. KUSAMA, Central Health Bureau, Tokyo ;
 Professor E. MARCHOUX, Pasteur Institute, Paris ;
 Professor G. MEMMI, Regio Ospedale della Misericordia, Grosseto, Italy ;
 Professor D. MEZINCESCU, Institute of Hygiene, Bucarest, and Professor
 A. SLATINEANU, Institute of Hygiene, Jassy ;
 Professor W. MOLLOW, Alexandrovsk Hospital, Sofia ;
 Professor Ed. SERGENT, Pasteur Institute of Algeria, Algiers ;
 Lt.-Col. J. A. SINTON, Malaria Survey of India, Kasauli.

Composition of the Products employed in the Test.

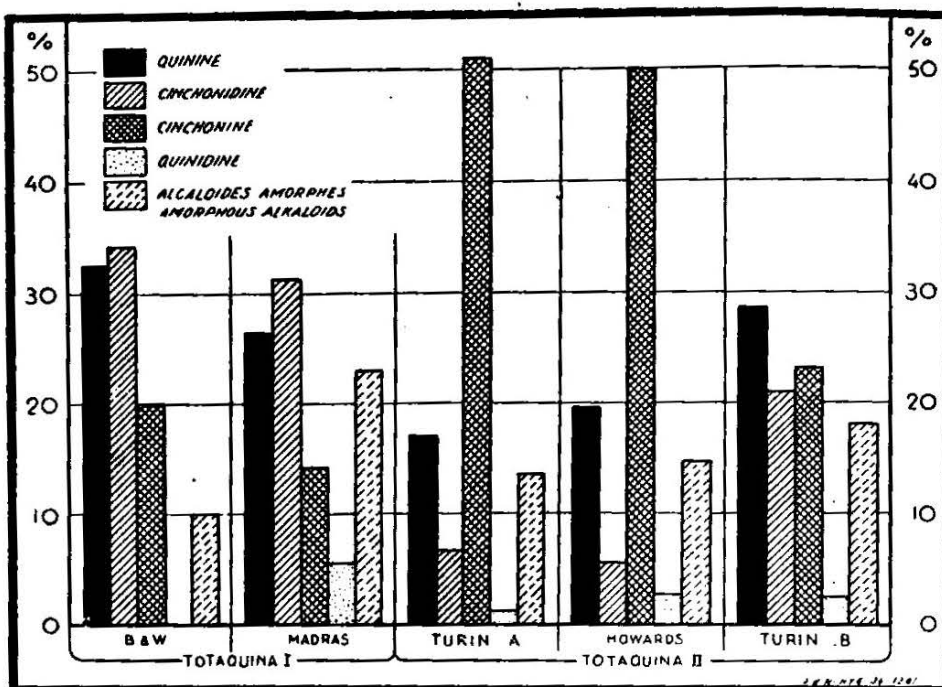
Dr. T. A. HENRY, Director of the Wellcome Chemical Research Laboratories (W.C.R.L.), arranged to have the *Madras, Turin II A* and *Turin II B* products analysed in his laboratory by the "B Method" (see Annex), which was also adopted by the Madras Laboratory ; the Turin Laboratory, on the other hand, carried out its analyses by the "A Method" (see Annex) ; finally, the *II Howards* preparation used at Kuala Lumpur was analysed by Byron and Simpson by a third method.

Table 1 and Graph 1 give results of these analyses.

Table 1.

COMPOSITION OF THE SAMPLES OF TOTAQUINA USED FOR THE CLINICAL TESTS.

| | TYPE I | | | TYPE II | | | | |
|--------------------------------------|-------------|--------------|-------------|--------------|-------------|--------------|-------------|------------------------------|
| | B. & W. | Madras | | Turin II A | | Turin II B | Howards | |
| | Analysis by | | | Analysis by | | | | |
| | W. C. R. L. | Fac- tory | W. C. R. L. | Fac- tory | W. C. R. L. | Fac- tory | W. C. R. L. | I. M. B., Kuala Lumpur |
| Quinine | 32.5 | 32.0 | 26.1 | 15.84 | 17.0 | 26.90 | 28.5 | 19.3 |
| Cinchonidine ... | 34.2 | 30.0 | 31.2 | 7.91 | 6.6 | 25.58 | 21.1 | 5.3 |
| Cinchonine | 20.1 | 10.5 | 14.1 | 55.12 | 50.9 | 25.12 | 23.2 | 49.9 |
| Quinidine | — | 0.8 | 5.7 | 0.27 | 1.1 | 5.40 | 2.6 | 2.8 |
| Total crystalli- sable alkaloids. | 86.8 | 73.3 | 77.1 | 79.14 | 75.6 | 83.00 | 75.4 | 77.3 |
| Amorphous alka- loids | 9.9 | 15.0 | 23.1 | 12.67 | 13.5 | 15.30 | 18.2 | 14.7 |
| Moisture | 2.6 | 4.8 | — | 3.28 | 3.0 | — | — | 2.3 |
| Ash | 0.2 | 4.5 | 0.7 | 3.94 | 4.3 | — | trace | 1.8 |



Graph. I. — COMPOSITION OF THE SAMPLES OF TOTAQUINA USED FOR THE CLINICAL TESTS.

Table 1 shows that *Turin II B*, though manufactured from the residues of quinine extraction, possesses the characteristics of a Type I Totaquina—that is to say, a product prepared direct from the bark of *Cinchona succirubra*: high content of quinine and cinchonidine, comparatively low content of cinchonine; and that it proves very similar to the first experimental sample of Totaquina extracted from *C. succirubra*, which was analysed by Dr. HENRY in 1932 (see *Transactions of the Royal Society of Tropical Medicine and Hygiene*, volume XXVI, page 112).

As regards the two types of Totaquina II, prepared by the State Quinine Factory at Turin, the Director of that establishment wrote to us in the following terms on July 15th, 1933:

“If the tablets of *Turin II A* have not given very satisfactory results (*in respect of their disintegration in water*), it is certainly due to the fact that they were composed of pure Totaquina without the addition of any substance to render them friable. The alkaloids in the form of free bases, when compressed into tablets, are not very soluble, even in dilute acids, whereas in powder form they are easily soluble. The

therapeutic action of the drug would certainly be very much increased if the alkaloids were given in the form of hydrochlorides or sulphates."

Dr. FIELD, of Kuala Lumpur, informs us, however, that the compressed tablets of *Turin II B*, which are similarly manufactured by the Turin Factory, but made up with an excipient designed to make them friable, easily break up and can be kept for long periods under tropical conditions without special precautions.

The results of analyses carried out both by the manufacturers and by the Wellcome Chemical Research Laboratories show on the whole "as good an agreement as can be expected" (Dr. Henry).

The results of the manufacturers' analyses differ considerably from those of the Wellcome Chemical Research Laboratories so far as concerns the quinine content of the *Madras* sample (factory : 32.0; W.R.C.L. : 26.1) and the crystallisable alkaloid content of the *II B* (factory : 83.0; W.C.R.L. : 75.4); it should be observed, however, that the samples analysed by the W.C.R.L. were already mixed with starch in readiness for compression into tablets, and that the addition of this substance distorted the results of the analyses. In the *Turin II A* (without addition of starch) the content of matter insoluble in alcohol was 2.58 per cent as against 26.13 per cent in the *Madras* and 26.90 per cent in the *Turin II B*. It being impossible to determine how, in the last two specimens, the moisture, the ash and the matter other than starch insoluble in alcohol should be apportioned between the Totaquina and the added starch, the W.C.R.L. worked, not direct on the supplied samples, but on their alcohol-soluble extracts. The analyses of these two products are therefore liable to indicate an unduly high alkaloid content, since moisture, organic matter insoluble in alcohol and possibly part of the mineral matter have been eliminated.

Technique of Clinical Tests.

These tests were carried out during the 1933 malaria season in Algeria, Bulgaria, China, France, Italy, the Federated Malay States, Morocco, Roumania and Spain. In order to standardise so far as possible the technique of the experiments and to prevent any selection of cases likely to give misleading results, a special record card was drawn up and sent to all workers.

The present report covers a total number of 1,144 cases including 1,055 treated by Totaquina and 89 quinine-treated controls (see Table 2).

These cases are distributed as follows among the various hospitals which took part in the tests :

| | |
|--|-------|
| Algiers, Marengo Hospital | 19 |
| Arcos de la Frontera, Spain, Malaria Dispensary..... | 29 |
| Fez, Morocco, Cocard Hospital | 62 |
| Grosseto, Italy, Regio Ospedale della Misericordia | 29 |
| Gurbanesti, Roumania, Malaria Experimental Station..... | 28 |
| Jassy, Izolarea Hospital | 244 |
| Jassy, Military Hospital | 212 |
| Kuala Lumpur, F.M.S., Malay Hospital and District Hospital. | 158 |
| Nanking, Central Field Health Station..... | 63 |
| Navalmoral de la Mata, Spain, Institute of Malariology | 54 |
| Paris, Asile Ste. Anne | 5 |
| Sofia, Bulgaria, Hôpital Alexandrovska | 23 |
| Tomesti, Roumania, Rural Health Centre | 218 |
| | 1,144 |

Table 2.

NUMBER OF CASES TREATED WITH EACH PRODUCT.
(Distribution according to the kind of parasite.)

| | P. vivax | P. falciparum | P. malariae | P. vivax + P. falciparum | P. vivax + P. malariae | P. malariae + P. falciparum | Undetermined forms | All forms of malaria |
|------------------------------|------------|---------------|-------------|--------------------------|------------------------|-----------------------------|--------------------|----------------------|
| TOTAQUINA I. | | | | | | | | |
| B. & W. | 165 | 113 | 10 | 4 | 1 | — | 4 | 297 |
| Madras | 30 | 75 | 12 | 5 | — | 1 | 1 | 124 |
| Total type I | 195 | 188 | 22 | 9 | 1 | 1 | 5 | 421 |
| TOTAQUINA II. | | | | | | | | |
| Turin A | 159 | 86 | 3 | 3 | 1 | 1 | — | 253 |
| Turin B | 104 | 107 | 9 | 2 | — | 1 | — | 223 |
| Howards | 41 | 101 | 15 | 1 | — | — | — | 158 |
| Total type II ... | 304 | 294 | 27 | 6 | 1 | 2 | — | 634 |
| All Totaquinas .. | 499 | 482 | 49 | 15 | 2 | 3 | 5 | 1,055 |
| QUININE SULPHATE..... | 47 | 35 | 6 | 1 | — | — | — | 89 |

Table 3.

MEAN DOSE OF TOTAQUINA PER KILOGRAMME OF BODY WEIGHT.

| | PLASMODIUM VIVAX | | | PLASMODIUM FALCIPARUM | | |
|--|--------------------|-------------------|-------------|-----------------------|-------------------|-------------|
| | Cases | ctg. ratio kg. | | Cases | ctg. ratio kg. | |
| | | Mean | Extremes | | Mean | Extremes |
| Totaquina I B. & W., Izolarea | 31 | 1.1 | 0.52 — 3.70 | 27 | 2.5 | 1.78 — 5.88 |
| • I Madras | — | — | — | 38 | 2.45 | 1.60 — 5.33 |
| • II Turin A | 38 | 1.45 | 0.88 — 4.0 | 14 | 3.4 | 1.99 — 5.01 |
| • II Turin B | 12 | 1.01 | 0.84 — 1.77 | 34 | 2.3 | 1.20 — 7.06 |
| • I B. & W., Tomesti | 73 | 0.83 | — | 18 | 1.76 | — |
| • II Turin A | 41 | 1.13 | — | 24 | 1.82 | — |
| • II Turin B | 11 | 1.23 | — | 15 | 1.75 | — |
| • II Turin B, Arcos de la Frontera. | 27 | 1.32 | — | | | |
| • II Howards, Kuala Lumpur | 41 | 2.75 | 2.00 — 4.40 | 101 | 2.9 | 2.20 — 4.40 |
| | PLASMODIUM MALARIE | | | | | |
| • II Howards, Kuala Lumpur | 15 | 3.7 | 2.20 — 4.40 | | | |

Dosage.

The model case-record card prescribed a dose of 0.60 gramme of Totaquina per 70 kilogrammes body weight in cases of benign tertian and 1.20 gramme in cases of malignant tertian or quartan, the $\frac{\text{ctg.}}{\text{kg.}}$ ratios being thus respectively 0.85 and 1.71.

An examination of the record cards disclosed the not unexpected fact that these ratios have in many cases not been rigorously observed. The administration of a drug in tablet form does not, in fact, allow of the exact adjustment of dose to body weight. In practice, moreover, where the dose prescribed for an adult is 1 gramme, for instance, such a dose is administered irrespectively of the patient's body weight. The dose of Totaquina actually given appears, generally speaking, to have been higher than that prescribed by the Commission.

We give on Table 3 the average daily dose in centigrammes per kilogramme of body weight for those series of cases in which the available information enabled it to be computed.

The particulars of all the case-record cards have been collated and tabulated in such a way as to show the number of daily doses required to bring about the disappearance of fever, schizonts and gametocytes (Table 4). From this table, we then computed the percentages, which, though they have no absolute value, will none the less facilitate the comparison of the products (Table 5 and Graph 2). We have not, in these tables, taken account of cases in which the medicament produced toxic phenomena, since the proportion of such cases for the same drug varies very considerably from one centre to another. A critical analysis of such cases appears in Dr. W. Fletcher's report, on page 344.

Method of Classification of Cases in the Statistical Tables.

We have proceeded from the assumption that the disappearance of any symptom was due to the drug administered, the last dose considered to have taken effect being that administered about twenty-four hours, or, in exceptional cases, eight or even six hours, before the disappearance of the symptom.

The symptoms of which account has been taken are the following : fever, the presence of schizonts and trophozoites, the presence of gametocytes and spleen enlargement.

In Table 4, the headings "fever", "schizonts" and "gametocytes" are subdivided into eight columns numbered 0, 1, 2, 3, 4, 5, 5+ and D. Columns 1 to 5 give the cases in which the symptoms disappeared after the administration of from 1 to 5 daily doses ; column 0 gives the cases in which the symptom was absent at the beginning of treatment. Column 5+ gives the cases in which the symptom persisted after the fifth daily dose—*i.e.*, was still reported on the sixth day (or exceptionally, as, for instance, in the Algiers Marengo Hospital series, six hours after the fifth dose, the last examination being made in the afternoon of the fifth day instead of the morning of the sixth). Finally, column D (doubtful) gives cases in which data concerning the symptoms were not furnished or in which treatment was not continued for five days.

In working out Table 5, the *percentages* were computed relatively to the total number of cases, less the cases recorded in columns 0 (symptom absent at the beginning of treatment) and D (insufficient particulars).

Table 5.

RATE OF DISAPPEARANCE OF FEVER AND PARASITES AND OF REDUCTION OF SPLENIC ENLARGEMENT ACCORDING TO THE NUMBER OF DAILY DOSES ADMINISTERED (in percentage)

| Plasmodium vivax. | FEVER | | | | | Cases considered | SCHIZONTS | | | | | Cases considered | GAMETOCYTES | | | | | Cases considered | Percentage in which the spleen was reduced after treatment |
|---|------------------|---|------|------|------|------------------|--|------|------|------|------|------------------|---|------|------|------|------|------------------|--|
| | Cases considered | Percentage in which the fever disappeared after doses : | | | | | Percentage in which schizonts and trophozoites disappeared after doses : | | | | | | Percentage in which gametocytes disappeared after doses | | | | | | |
| | | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | | | |
| a. Totaquina I, B. & W. | 110 | 44.5 | 88.5 | 96.5 | 99.5 | 99.5 | 40.5 | 86 | 96 | 99 | 99.5 | 138 | 19.5 | 58 | 90 | 97 | 98 | 122 | 35.5 |
| b. " " I Madras (1) | | | | | | | | | | | | | | | | | | | |
| c. Total for Totaquina I | 130 | 43 | 83.5 | 95.5 | 99.5 | 99.5 | 40 | 85.5 | 96 | 99 | 99.5 | 164 | 22 | 59.5 | 89.5 | 97 | 99 | 144 | 36 |
| d. Totaquina II Turin A | 106 | 38.5 | 69 | 95.5 | 98 | 99 | 25 | 60.5 | 83.5 | 94 | 98 | 142 | 22 | 50.5 | 78 | 89 | 97 | 106 | 27 |
| e. " " II Turin B | 57 | 98 | 99 | 98 | 98 | 98 | 33.5 | 83 | 95 | 99.5 | 100 | 83 | 35 | 69 | 87 | 97.5 | 100 | 61 | 54 |
| f. " " II Howards (1) | | | | | | | | | | | | | | | | | | | |
| g. Total for Totaquina II | 163 | 46 | 72 | 92 | 98 | 99 | 24.5 | 65.5 | 85.5 | 94.5 | 99 | 248 | 26 | 56 | 80 | 91 | 97 | 167 | 27 |
| Plasmodium falciparum. | | | | | | | | | | | | | | | | | | | |
| A. Totaquina I, B. & W. | 66 | 41 | 80 | 91 | 97 | 100 | 20 | 55 | 73.5 | 86.5 | 92 | 51 | — | — | — | — | 37 | 70 | 50 |
| I. " " I Madras | 56 | 43 | 80.5 | 94.5 | 96.5 | 96.5 | 39 | 78 | 98.5 | 98.5 | 98.5 | 37 | — | — | — | — | 40.5 | 51 | 61 |
| J. Total for Totaquina I | 122 | 41.5 | 80 | 93 | 96.5 | 98.5 | 28 | 64.5 | 84 | 91 | 95 | 88 | — | — | — | — | 39 | 121 | 50.5 |
| k. Totaquina II, Turin A | 64 | 22 | 57.5 | 81 | 84.5 | 94 | 17 | 49 | 63 | 83 | 92 | 48 | — | — | — | — | 27 | 52 | 29 |
| l. " " II Turin B | 74 | 51 | 78.5 | 89 | 96 | 98 | 34 | 76 | 87 | 93.5 | 97 | 64 | — | — | — | — | 39 | 77 | 46.5 |
| m. " " II Howards | 96 | 26 | 52 | 89.5 | 85.5 | ? | 10 | 34.5 | 64.5 | 80 | ? | 65 | — | — | — | — | ? | 7 | ? |
| n. Total for Totaquina II | 234 | 33 | 62 | 79 | 89 | ? | 20.5 | 53 | 72 | 85.5 | ? | 177 | — | — | — | — | — | ? | ? |
| Total for Totaquina I & II : | | | | | | | | | | | | | | | | | | | |
| o. P. vivax | 337 | 44.5 | 76 | 93.5 | 96.5 | ? | 31 | 73 | 90 | 96 | ? | 412 | 24 | 57 | 83.5 | 93 | ? | ? | ? |
| p. P. falciparum | 356 | 36 | 63 | 84 | 92 | ? | 23 | 57 | 78 | 83 | ? | — | — | — | — | — | ? | ? | ? |
| q. P. malariae | 32 | 18.5 | 53 | 68.5 | 84.5 | ? | 9.5 | 44 | 60 | 75 | ? | 26 | 10.5 | 32.5 | 39 | 61 | ? | 25 | 16 |
| Total pour Quinine : | | | | | | | | | | | | | | | | | | | |
| r. P. vivax | 35 | 48.5 | 94 | 100 | 100 | 100 | 40.5 | 81 | 98 | 98 | 100 | 41 | 36.5 | 78 | 97.5 | 100 | 100 | 39 | 54 |
| s. P. falciparum | 32 | 34 | 78 | 97 | 100 | 100 | 28 | 53 | 94 | 100 | 100 | 24 | — | — | — | — | 37 | 35 | 21 |

(1) The small number of cases of benign tertian treated with "Madras" or "Howards" does not allow of expressing percentages.

The "cases considered" are those in which fever, schizonts, gametocytes (in the thin smears) or an enlarged spleen were present at beginning of treatment and regarding which sufficient data are available.

* Calculated for sake of uniformity in spite of the very small number of cases.

Fever.

An analysis of the record cards discloses certain slight rises of temperature (37.2 to 37.4°C.) which do not appear, clinically speaking, to be attributable to malaria. We felt that to record every rise of temperature above 37°C. as "fever" would, especially for certain series, unduly prolong the recorded period of fever: we accordingly raised the minimum limit to 37.5°C. and prepared our tables according to the number of daily doses necessary to stabilise the temperature below that limit. In the Kuala Lumpur series, the limit has been set somewhat lower—*i.e.*, at 99°F. (37.22°C.).

Observation of Temperature.

The temperature was taken four times a day at the Izolarea Hospital at Jassy and at the Gurbanesti Experimental Station; four times, three times, or twice a day at the Jassy Military Hospital, the Ospedale della Misericordia at Grosseto, and the Institute of Malariology of Naval Moral de la Mata; twice or once a day at the dispensary of Arcos de la Frontera and at the Nanking Central Field Health Station.

Under the heading "Fever" of Tables 4 and 5, no account is taken of cases in which the temperature was taken but once a day.

Generally, the observation of temperature is continued to the sixth day—*i.e.*, twenty-four hours after the last daily dose; but certain institutes (Tomesti, Kuala Lumpur) discontinued it on the fifth day, with the result that the effect of the fifth dose cannot be gauged. If there was no more fever on the fifth day, the disappearance of the fever is regarded as having occurred after four doses, the assumption being that, if the fever had returned on the sixth day, it would have been recorded on the cards. If there was still fever on the fifth day, we have proceeded on the same argument and have classified the case in column 5, using italics.

Parasites.

The distinction between schizonts and trophozoites provided for in the case-record cards was omitted from the tables, which only discriminate between schizonts (including therein young trophozoites) and gametocytes.

The number of parasites has also been omitted from the tables.

The case-record cards advocated a standard method of count over a hundred microscopic fields, the blood sample to be taken at the time of administration of the drug and all smears to be examined by the same person. At the Izolarea Hospital and at the Tomesti Health Centre, the examination of smears was conducted strictly on standard lines. Elsewhere (Gurbanesti), although the examination was made over a hundred fields, there was no count. Several centres (Jassy Military Hospital ; Marengo Hospital, Algiers ; Hôpital Cocard, Fez ; Alexandrovska Hospital, Sofia ; Central Field Health Station, Nanking) were not content merely to use the advocated technique, but proceeded also to thick-drop examinations.

Other centres made examinations more frequently than our method required. At Gurbanesti, the blood was examined three times, on the first, third, and fifth day of treatment. At Kuala Lumpur, the blood was frequently examined seven days after the beginning of treatment. At Nanking, an attempt was made to mobilise the parasites by an injection of ephedrin given during the afternoon of the sixth day. In order to preserve the uniformity of our work, we have left aside these additional examinations, whatever their value. At the same time, if we had only included the cases examined by our method, we should have had to discard the following :

Grosseto : 29 cases examined sometimes by smears and sometimes by the thick-drop method.

Navalmoral de la Mata : 27 cases in which the data concerning the disappearance of schizonts are based upon thick-drop examinations.

Kuala Lumpur : 158 cases in which the blood examination was carried out by Sinton's method.

By accepting these, we have embodied in our tables 214 cases in which the blood examinations were carried out more elaborately than in other series and in the quinine-treated controls, and are hence liable to show a greater persistence of parasites than if they had been examined by our standard method. If they somewhat modify the results of our analysis, they do so rather in a manner unfavourable to Totaquina.

We have disregarded the temporary disappearance of parasites during the five days treatment. If, therefore, the schizonts

disappear after the second or third dose and recur after the fourth, in order to disappear again on the sixth day, they are recorded as having disappeared after the fifth dose.

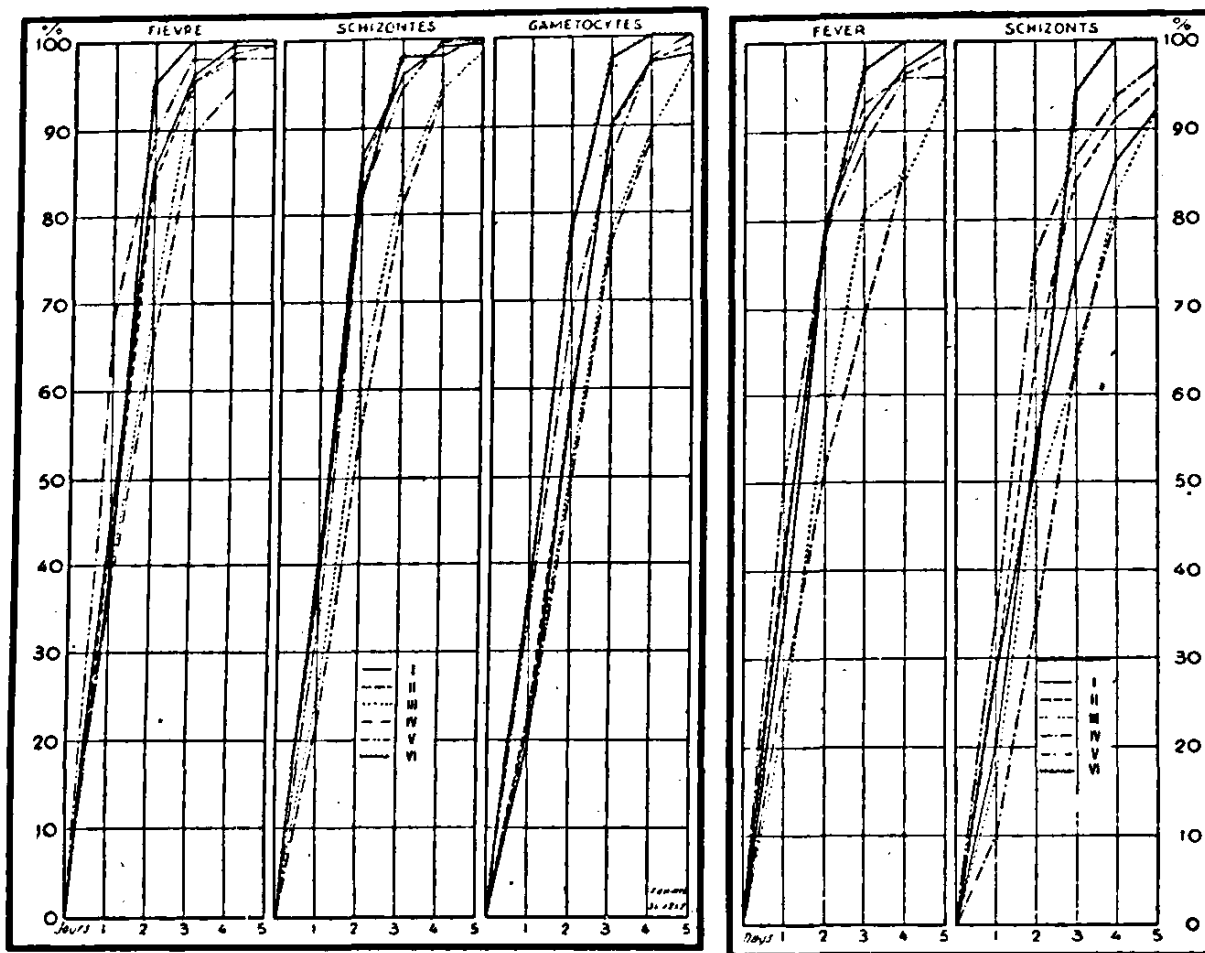
Owing to the fact that alkaloids of cinchona produce no effect upon the gametocytes of malignant tertian, we felt that no useful purpose would be served by determining the rate of disappearance of such forms after each dose. In Table 5, we have indicated these rates at the end of treatment, and in Graph 3 we have omitted them.

Spleen Enlargement.

Several centres give no particulars as to the size of the spleen. Such particulars as have been furnished have not been reported in a uniform manner. Whilst the Roumanian figures indicate the position of the lower edge of the spleen relatively to the costal border and the umbilicus according to Schüffner's system, which is the method adopted by the Malaria Commission, the Spanish hospitals followed Boyd's method, whilst the Chinese hospitals state in centimetres the distance which the lower edge of the spleen projects below the costal border. These differences of methods are, however, immaterial to our compilation, since Table 4 is not intended to show the amount of spleen retraction following treatment, but merely indicates, in cases where splenomegaly was present at the beginning of treatment, whether the spleen had been reduced in the course of treatment or not. In one single case, treated at Nanking, the spleen seems to have increased in volume after treatment.

Plasmodium vivax

Plasmodium falciparum



- I. Totaquina I B. & W.
- II. Totaquina I B. & W. et Madras.
- III. Totaquina II Turin A.
- IV. Type II Turin A et Howards.
- V. Type II Turin B.
- VI. Sulfate de quinine.

Graph 2. — RATE OF DISAPPEARANCE OF FEVER AND SCHIZONTS AFTER 1 TO 5 DAYS OF TREATMENT.

ANNEX.

CHEMICAL ANALYSIS OF TOTAQUINA.

PROCESS A.

Total Alkaloids.

Dissolve 1.55 gramme of Totaquina in 75 cc. of warm alcohol (96 per cent), cool the solution, filter, evaporate the filtrate to dryness and weigh the residue (a). Dissolve the residue in 10 cc. of normal hydrochloric acid, add 20 cc. of distilled water, filter the solution and wash the filter paper with distilled water until the filtrate measures 75 cc. ; warm the filtrate and neutralise exactly with half-normal caustic soda solution, using litmus paper as indicator. Each cc. of normal hydrochloric acid is equivalent to 0.31 gramme of total alkaloids.

Quinine and Cinchonidine.

Evaporate the solution, prepared as described above, to 50 cc, and set aside for two hours ; filter. Wash the filter paper with sufficient distilled water to bring the volume of the filtrate to 100 cc., evaporate again to 50 cc. and, while still warm, add 10 cc. of a 40 % solution of sodium tartrate ; render the mixture faintly acid by the addition of a few drops of a 10 % solution of tartaric acid and allow to stand overnight.

Collect the precipitated quinine and cinchonidine tartrates on a filter, wash with small quantities of cold distilled water, until the combined filtrate and washings measure 80 cc., then dry the precipitate at 105° C. for three hours and weigh. Add to the weight 60 milligrammes as a correction for the solubility of quinine and cinchonidine tartrates.

The relative proportions of quinine and cinchonidine in this precipitate may then be determined from the following data :

Quinine tartrate, dried at 105° C., is represented by the formula $(C_{20}H_{24}N_2O_6)_2$, $C_4H_6O_4$, H_2O , contains 79.41 per cent of quinine base and, under the conditions described below, has an observed rotation of -8.85° .

Cinchonidine tartrate, dried at 105° C., is represented by the formula $(C_{17}H_{21}N_2O)_2$, $C_4H_6O_4$, contains 79.68 per cent of cinchonidine base and, under the conditions described below, has an observed rotation of -5.48° .

Each unit per cent of quinine tartrate present in the precipitate therefore augments the observed rotation of cinchonidine tartrate by $8.85^\circ - 5.48^\circ / 100 = -0.0337^\circ$.

Dissolve 0.5 gramme of the dried tartrate precipitate in 3.75 cc. of normal hydrochloric acid, dilute with distilled water to 25 cc., add 25 milligrammes of decolorising charcoal, shake well, filter into a 2-decimeter tube and observe the rotation for sodium light in a suitable polarimeter.

Example : 1.55 gramme of a sample of Totaquina gives 1.2 gramme of tartrate precipitate, whose rotation, determined as described above, is -7.20° . The proportion of quinine tartrate present in the precipitate is given by the expression $\frac{7.20-5.45}{0.0337} = 51$ per cent and that of cinchonidine tartrate, by difference, is 49

per cent. From these figures the amounts of quinine and cinchonidine in the sample of Totaquina can be readily calculated thus :

$$\frac{51 \times 1.2 \times 79.41}{100 \times 100} = 0.486 \text{ gramme of quinine} = 31.35 \% ;$$

$$\frac{49 \times 1.2 \times 79.68}{100 \times 100} = 0.468 \text{ gramme of cinchonidine} = 30.20 \text{ per cent.}$$

For the determination of quinine and cinchonidine by the polarimetric method, it is essential that the precipitated tartrates should be clean and of pale colour. If not, they should be re-precipitated by dissolving them in a solution of tartaric acid, warmed to boiling and while at this temperature solution of ammonia or caustic soda should be added until the reaction is just alkaline. The precipitate is left to stand overnight and then filtered, washed, dried, etc., as already described.

Quinine and Cinchonidine by Methoxyl Determination.

Since quinine contains one methoxyl group and cinchonidine contains none, it is also possible to estimate the proportion of quinine in the mixed tartrate precipitate by a methoxyl determination by the Zeisel method. For this purpose, the mixed tartrates dried at 105°C . may be used direct, or the mixed bases regenerated from the tartrate precipitate may be employed. Although there is no unanimity as to the merits of this method, it has been considered desirable to draw attention to it, as a permissible alternative to the polarimetric method.

Cinchonine.— Shake the filtrate of 80 cc. from the tartrate precipitate with 70 cc. of chloroform and 10 cc. of a 16 per cent solution of caustic soda. Separate the chloroform and repeat the agitation with a second 70 cc. of chloroform. Mix the two quantities of chloroform, evaporate to dryness, dry the residue (*b*) and weigh. This residue contains cinchonine, quinidine, amorphous alkaloids and the bases from 60 milligrammes of tartrates of quinine and cinchonidine (solubility correction).

Dissolve the residue (*b*) in 15 to 25 cc. of warm alcohol (96 per cent), cool, add an equal volume of distilled water and allow to stand overnight to complete the separation of cinchonine, filter, wash with 25 cc. of alcohol (50 per cent), dry at 105°C . and weigh. Add a correction of 1 milligramme of cinchonine for each cc. of alcohol used.

Quinidine.— Warm the filtrate from the cinchonine on a water-bath until the alcohol is evaporated, neutralise with hydrochloric acid, filter, add 5 grammes of sodium iodide and allow to stand overnight to complete precipitation of the alkaloidal hydriodides. Filter, wash the residue with a little water and finally with two portions each of 5 cc. of alcohol (94 per cent). Dry the quinidine

hydriodide at 105° C. and weigh, adding a correction of 0.8 milligramme for each cc. of alcohol used. The corrected weight \times 0.717 gives the amount of quinidine.

Amorphous Alkaloids.

The quantity of amorphous alkaloids is given by the difference between the weight of residue (*b*) (see page 340) and the sum of the weights of cinchonine and quinidine found.

Alternative Process for Cinchonine and Quinidine.

The filtrate and washings from the precipitated tartrates are run into a separator containing 80 cc. of alcohol-free ether and an excess of solution of sodium hydroxide and shaken. The aqueous layer is run off into a second separator and shaken with two further portions of 80 cc. of ether, each portion of ether being returned to the first separator. The combined ethereal extracts (usually containing cinchonine in suspension) are washed with a little water, and the alkaloids extracted from the ether by shaking with 10, 10 and 5 cc. of normal sulphuric acid and finally with 10 cc. of water. The combined acid and aqueous liquids are run into a separator containing 25 cc. of ether (alcohol-free) and 30 cc. of normal sodium hydroxide solution, shaken and allowed to stand 1 hour. The precipitated cinchonine is filtered off, a little water being used to facilitate the complete transfer of the precipitate to the filter; the ether is separated from the filtrate and again run through the precipitate on the filter. The aqueous liquid is again shaken with two separate portions of 25 cc. of ether and these ethereal washings are used to wash the precipitate. The precipitate is dried at 100° and weighed, 0.08 gramme being added (correction for solubility of cinchonine in ether).

The filtrate from the cinchonine is run into a separator, the filter-flask washed out with a little water and ether, and added to the liquid in the separator. The aqueous layer is removed and the alkaloids extracted from the ether by shaking with 10, 10, 5 and 5 cc. of 10 % acetic acid, which have been previously used to wash out any alkaloid remaining in the filter-flask or in the stem of the funnel. The combined acid solution is raised to boiling point, neutralised with 10 per cent ammonia solution and 5 grammes of potassium iodide added; allow to stand overnight. The clear supernatant liquor is poured off through a filter, the residue warmed with 5 cc. of 50 % alcohol, the liquor filtered, and the crystalline precipitate washed on to the filter with 5 cc. of 50 % alcohol. The precipitate is dried at 100° and weighed, 0.008 gramme being added as correction for solubility of quinidine hydriodide. The weight multiplied by 0.717 gives the weight of quinidine.

PROCESS B.

MODIFIED PROCESS FOR TOTAQUINA, TYPE II.

In the case of Totaquina of type II, which may be more highly coloured than those of type I and contain much cinchonine, it is desirable to eliminate the

cinchonine first. For this purpose, dissolve residue (a) (page 339) in 25 cc. of alcohol (96 per cent), cool the solution, add 25 cc. of distilled water, set aside overnight, filter, wash with 25 cc. of alcohol (50 per cent), dry and weigh. The filtrate from this cinchonine is then treated as described above for residue (a) for the estimation of quinine, cinchonidine and quinidine.

ALTERNATIVE TO PROCESS B.¹

10 grammes of Totaquina are dissolved in 50 cc. of dilute hydrochloric acid (10 %), and transferred to a large separating funnel containing about 750 cc. of washed ether. Excess of ammonia solution (s.g. = 0.959) is added after shaking vigorously, and then again shaken about 50 times. Allow to settle and filter off the rough cinchonine alkaloid at the filter-pump. This crude cinchonine is washed on the pump with 50 % alcohol until the filtrate runs through fairly colourless, and is then given washes with acetone until the filtrate again runs nearly colourless. The filtrate is evaporated to dryness in a beaker, and is practically all amorphous alkaloid. The washed cinchonine is dried and weighed.

Return the filtrate from the crude cinchonine to a second separator (the bulk of the first ether being left in the first separator) and shake well with another 500 cc. ether. Allow to settle and run off aqueous portion (reserve this). Bulk the two ethers and wash out with 100 cc., 50 cc., and 20 cc. consecutively of 5 % tartaric acid solution, allowing each acid wash to settle thoroughly before running off into a basin. Bring the combined acid liquor to the boil and neutralise with 20 % sodium hydroxide solution, using litmus paper as indicator. Allow the mixed quinine and cinchonidine tartrates about 18 hours to crystallise. This mixed tartrate is filtered off, given two small water washes (cold), dried and weighed. This mixed tartrate is then recrystallised (see page 340) and estimated polarimetrically.

The filtrate is transferred to a separator containing about 500 cc. washed ether, excess of 10 % ammonia added, and the mixture shaken thoroughly. After settling, the aqueous layer is run off into another separator containing 500 cc. washed ether, and again shaken. The aqueous portion is added to that reserved from the primary extraction. The two ethers are bulked and washed out with 80 cc., 40 cc., and 30 cc. of dilute sulphuric acid (2.5 %). The acid washings are transferred to a smaller separator, about 50 cc. of washed ether and excess of 10 % ammonia solution added, and the whole well shaken. Allow to stand twenty-four hours, when a further small quantity of cinchonine crystallises out. This is filtered off, dried and weighed, and the weight added to that of the first crop of cinchonine.

The filtrate is shaken with two successive lots of 500 cc. of ether, and the aqueous portion added to the other two alkaline liquors. The two ethers are

¹ The following process for the examination of Totaquinas of type II has been communicated to the Sub-Commission by Mr. Bernard Howards and has been tried and found satisfactory in the laboratory of one member (Dr. Henry) of the Sub-Commission.

bulked and washed out with 50, 40 and 30 cc. dilute sulphuric acid (2.5 %), the acid solution brought to the boil and neutralised with 20 % sodium hydroxide to litmus paper. Excess of potassium iodide (about 10 grammes) is added and the precipitate allowed to stand overnight. The liquid is poured off (reserve this) and about 20 cc. of 50 % alcohol added to the precipitate, warmed to about 50° C. and stirred to dissolve amorphous hydriodide. The crystals of quinidine hydriodide are filtered off on the pump and washed with two or three small lots of warm 50 % alcohol, until all amorphous hydriodide is dissolved out. The quinidine hydriodide is dried and weighed (weight \times 0.717 = quinidine).

The alcohol is evaporated, the filtrate then added to the other alkaline liquors and the whole extracted with benzolated amylic alcohol (British Pharmacopœia 1914), the solvent being then taken to dryness and the residual alkaloid weighed, the weight being added to the previous weight of amorphous alkaloid obtained.

II. Critical Analysis of the Results achieved

by

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I have examined the records of cases treated with Totaquina which were handed to me by Dr. Pampana, and I have checked my results by the statistical tables which he generously placed at my disposal. Both he and I have had some difficulty in deciding how to deal with doubtful or faulty returns, such as those where essential details have been omitted or where there has been a wide departure from standard practice. My figures differed very little from his and, as I know the lines on which he made his decisions, I have adopted his figures concerning the numbers of the returns from each centre which should be accepted for consideration. As regards the cases found "positive" on the day after the last, that is the fifth, dose of Totaquina, *I have included a few not admitted by him, because I was anxious not to weigh the scales in favour of the drug.*¹ I have, however, given the hospital numbers of such "positive" patients in order that they may be easily checked. I have excluded from my survey the mixed infections with more than one species of parasite, because such cases are comparatively few in number and are scattered among the different treatment centres. For the same reason, I have omitted quartan malaria, except in the Kuala Lumpur series, which includes a group of 15 cases.

The surest indicator of the efficiency of a drug in the cure of malaria is its effect upon the parasites, and this I have adopted as the criterion; fever I have considered only in those cases where parasites persisted at the end of the course of treatment. Totaquina has no direct action upon the gametocytes of *P. falciparum*, and the records from some centres show that they were more numerous at the end than at the beginning of treatment; consequently, I have neglected them when assessing the value of Totaquina in subtertian

¹ The cases not admitted in Dr. Pampana's statistical tables as positive after the fifth dose are starred, thus *.

malaria. One or two of the observers at the different treatment centres have remarked on the diminution in the size of enlarged spleens during treatment with Totaquina, such as would be expected with a drug which destroys the parasite ; but records of the size of the spleen over a short period of six days, especially when they are made by different people at a number of different stations, are unlikely to be of much value as a measurement of the efficiency of treatment.

A striking feature which is brought out by a study of the records is the difference in the condition of the patients in one group and in another, at the beginning of treatment ; for example, among the 53 patients who were given Totaquina at Navalmoral in Spain none vomited ; but, at Nanking, 25 patients vomited out of 61 who were treated. Another striking difference is the response of the patients to treatment ; this was noticeably more prompt in the Roumanian centres than elsewhere. Neither the same kinds of Totaquina nor the same doses were used at all the different centres ; the form known as Type I, *Madras*, was used in comparatively few places, and at Navalmoral almost only Type II was employed. This lack of uniformity would have mattered less if a control series had been treated with quinine at each centre ; unfortunately, this was done only in Roumania and the Federated Malay States. On these grounds, it seems to me a sounder method to discuss the results of Totaquina treatment in various groups of centres rather than to consider them all together and, for this purpose, I have divided them into four sections : (1) the four Roumanian centres, 661 records ; (2) Kuala Lumpur, 157 records ; (3) Nanking, 61 records ; (4) the remaining European and the North-African centres, 199 records. Though, as a whole, they cannot be considered as the records of an accurate scientific investigation, they give a good idea of the value of Totaquina in hospital and dispensary practice.

Roumania.

The Roumanian group includes the following centres : (a) Hôpital Izolarea, Jassy, 229 cases ; (b) Hôpital militaire, Jassy, 195 cases ; (c) Centre d'hygiène rurale, Tomesti, 212 cases ; (d) the Experimental Malaria Station, Gurbanesti, 25 cases. The treatment was carried out with the following samples of Totaquina : Type I, *B. & W.* and *Madras* ; Type II, *Turin A* and *Turin B*.

Tables I and II show the results compared with those obtained by treating a control series with quinine. All the samples of Totaquina, except *Turin A*, appear to have been as effective as quinine. In 212 cases of benign tertian malaria treated with Totaquina (excluding *Turin A*), parasites were found in only 19 on the day following the third dose, and in not a single one after the fifth dose. In 47 controls treated with quinine, parasites were found in 2 after the third dose, and in none after the fifth. The results in subtertian malaria were almost as successful: in 197 cases treated with Totaquina (excluding *Turin A*), asexual parasites were found in 12 after the third dose, and in 2 (1)¹ (Izolarea No. 83, Vasile, and Gurbanesti No. 32 Nikolae*) after the fifth dose. Vasile was an obstinate relapsing case and was treated three times in close succession, Nikolae was a child of twelve; neither of them had fever on the sixth day. Vasile was treated with *B. & W.*, and Nikolae with *Turin B*. In a control group of 35 cases of subtertian malaria treated with quinine, parasites were present in 2 after the third dose, and in none after the fifth. The striking success of treatment with both Totaquina and quinine is probably to be explained by the immunity of the Roumanian population to which Professor CRUCA has repeatedly drawn attention.

Totaquina *Turin A* was not so effective; in 108 cases of benign tertian malaria, parasites were found in 27 after the third dose, and in 4 after the fifth dose. (Izolarea No. 20; Hôpital militaire No. 71**; Gurbanesti No. 14 and No. 19). None of them, however, had fever at the end of the treatment. The results were still worse in subtertian; asexual parasites were present in 22 out of 62 patients after the third dose, and in 9 (6) they persisted after the fifth dose (Hôpital militaire, Nos. 160*, 165*, 166*, 168*, 171, 176; Tomesti, No. 125; Gurbanesti, Nos. 22, 24). The temperature had become normal on the sixth day in all except 4, Nos. 166, 171, 176, 22.

¹ The figures in brackets are those given in Table 4 (inset between pages 336 and 337).

* Not admitted in Table 4. (Asexual parasites were still present in specimens taken only four hours after the administration of Totaquina, but there were none eight hours after the drug was given. (Note by the Editor.)

** No. 71.—After the fifth dose, the blood was negative for parasites in thin films, positive in thick drops; Nos. 160-165-166-168.—After the fifth dose the blood was negative for asexual parasites in thin films, positive in thick drops. No. 176 was given two separate courses of treatment, with blood still positive in both cases, after the fifth dose. (Note by the Editor.)

The doses of Totaquina for adults were, for the most part, at the rate of either 0.6 gramme or 1.2 gramme daily ; the smaller dose for benign tertian and the larger for subtertian, but there were deviations from this practice. The average weight of the patients in the military hospital was about 60 kilogrammes. Smaller doses were given to children, many of which were treated at Tomesti and Gurbanesti. The weakness of this group as a test for Totaquina is the trivial nature of many of the infections (in numbers of cases, the recorded temperature was never above 38° C., or 100.5° F.), and the very ready response to treatment.

Table I.

BENIGN TERTIAN MALARIA. ROUMANIA.

Treatment with Totaquina and Quinine compared.

| Place | Drug | Number of patients treated | With parasites after three doses | With parasites after five doses |
|-----------------------|------------|----------------------------|----------------------------------|---------------------------------|
| Izolarea | B. & W. | 31 | 1 | 0 |
| Hôpital militaire ... | " | 16 | 0 | 0 |
| Tomesti | " | 73 | 7 | 0 |
| Gurbanesti | " | 5 | 0 | 0 |
| | Total | 125 | 8 | 0 |
| Izolarea | Madras | 6 | 1 | 0 |
| Hôpital militaire ... | " | 17 | 0 | 0 |
| Tomesti | " | 6 | 2 | 0 |
| Gurbanesti | " | 0 | 0 | 0 |
| | Total | 29 | 3 | 0 |
| Izolarea | Turin A | 38 | 9 | 1 (2) |
| Hôpital militaire ... | " | 22 | 8 | 1 (0) |
| Tomesti | " | 41 | 6 | 0 |
| Gurbanesti | " | 7 | 4 | 2 |
| | Total | 108 | 27 | 4 |
| Izolarea | Turin B | 12 | 1 | 0 |
| Hôpital militaire ... | " | 31 | 2 | 0 |
| Tomesti | " | 11 | 2 | 0 |
| Gurbanesti | " | 4 | 3 | 0 |
| | Total | 58 | 8 | 0 |

Note. — The figures in brackets are those given in Table 4 (inset).

| Place | Drug | Number of patients treated | With parasites after three doses | With parasites after five doses |
|-----------------------|------------|----------------------------|----------------------------------|---------------------------------|
| Izolarea | Quinine | 14 | 1 | 0 |
| Hôpital militaire ... | " | 18 | 1 | 0 |
| Tomesti | " | 15 | 0 | 0 |
| Gurbanesti | " | 0 | 0 | 0 |
| | Total | 47 | 2 | 0 |

Table II.

SUBTERTIAN MALARIA. ROUMANIA.

Treatment with Totaquina and Quinine compared.

| Place | Drug | Number of patients treated | With parasites ¹ after three doses | With parasites ¹ after five doses |
|-----------------------|------------|----------------------------|---|--|
| Izolarea | B. & W. | 27 | 2 | 1 |
| Hôpital militaire ... | " | 17 | 3 | 0 |
| Tomesti | " | 18 | 3 | 0 |
| Gurbanesti | " | 1 | 1 | 0 |
| | Total | 63 | 9 | 1 |
| Izolarea | Madras | 38 | 0 | 0 |
| Hôpital militaire ... | " | 17 | 0 | 0 |
| Tomesti | " | 2 | 0 | 0 |
| Gurbanesti | " | 0 | 0 | 0 |
| | Total | 57 | 0 | 0 |
| Izolarea | Turin A | 14 | 2 | 0 |
| Hôpital militaire ... | " | 20 | 11 | 6 (3) |
| Tomesti | " | 24 | 6 | 1 |
| Gurbanesti | " | 4 | 3 | 2 |
| | Total | 62 | 22 | 9 (6) |
| Izolarea | Turin B | 34 | 1 | 0 |
| Hôpital militaire ... | " | 24 | 0 | 0 |
| Tomesti | " | 15 | 1 | 0 |
| Gurbanesti | " | 4 | 1 | 1 (0) |
| | Total | 77 | 3 | 1 (0) |
| Izolarea | Quinine | 15 | 0 | 0 |
| Hôpital militaire ... | " | 13 | 2 | 0 |
| Tomesti | " | 7 | 0 | 0 |
| Gurbanesti | " | 0 | 0 | 0 |
| | Total | 35 | 2 | 0 |

¹ Asexual parasites only.

Kuala Lumpur.

The series of records from the Federated Malay States is particularly valuable as a demonstration of the action of Totaquina in malaria ; first, because the number of parasites per cubic millimeter was estimated every day by Sinton's method, and, secondly, because a control group of patients was treated with quinine. The number of parasites, which was sometimes a hundred thousand or more at the beginning, rapidly dwindled to nothing, or was reduced to a few scanty remnants of the former hosts (see Table III). The case records of the control series treated with quinine are not available, but, fortunately, tables embodying the results are given in the Annual Report of the Institute for Medical Research, Federated Malay States, 1932, and in the *Notes on Totaquina*¹ by Dr. J. W. Field. Dr. Field, as the result of an examination of 236 patients treated with Totaquina (including the series reviewed here) and a control group of 181 treated with quinine, found that there was little difference in the therapeutic efficiency of the two drugs, but that the parasites disappeared rather more quickly with quinine. The investigation was begun by Dr. Field, who is Malaria Research Officer at the Institute for Medical Research, in August 1932, and, as it was well under way before the request to test Totaquina was received from the Malaria Commission of the League of Nations, no change was made in the procedure which had been adopted, and consequently it did not altogether conform to the standard methods. The sample of Totaquina employed was type II *Howards*, and it was given in doses rather larger than those given in other centres. The daily dose in the majority of cases was either one or two grammes per 100 lb. body weight, which is 2.2 or 4.4 centigrammes per kilo. This corresponds to 24 or 48 grains for a man weighing 11 stones (70 kilos). None of the Kuala Lumpur patients weighed nearly as much as this, only 2 of the 157 patients weighed as much as 60 kilos, and less than a third of them weighed over 50. The actual dose given to most of the adults was 15 or 30 grains (1 or 2 grammes). The results obtained were excellent and, speaking with a long experience of the two hospitals where these tests were made and of the

¹ A précis of this paper, which is about to be published in the *Malayan Medical Journal*, was submitted with the case records from Kuala Lumpur.

types of patients which are treated there, I can say without hesitation that they are as good as those obtained with quinine given in the same doses. The records do not show that the larger dose had any definite advantage over the smaller ; but Dr. Field, as the result of treating a larger series of patients, concludes that the optimum dose lies between the two.

The results of five days' treatment with Totaquina were briefly as follows : in 41 cases of benign tertian malaria, parasites persisted on the sixth day in 1 ; in 15 cases of quartan, in 3 ; in 101 cases of subtertian, in 8 (7) ; all examinations were made with thick drop preparations.

In greater detail, the results were as follows :

Benign tertian, 41 cases ; the numbers of the parasites decreased rapidly under treatment with Totaquina and, after the third dose, they could be found in only 13 cases ; after the fourth dose scanty parasites were still found in 6 cases ; two of these (Nos. 36 and 42) were not re-examined after the fifth and final dose, but parasites were found in only 1 (No. 38) of the remaining 4 cases on the sixth day. The temperatures of Nos. 36 and 38 had come down to normal ; that of No. 42 was 99.6° F. on the fifth day ; it was not recorded on the sixth.

Quartan, 15 cases. Parasites were present in 10 after the fourth dose. Three of these (Nos. 1, 6, 15) were not re-examined ; three (Nos. 2, 7, 10) of the remaining 7 were still positive on the sixth day, and No. 2 had slight fever.

Subtertian, 101 cases ; asexual parasites were present in 35 after the third dose, and in 20 after the fourth dose (Nos. 4, 7, 8, 9, 43, 48, 48, 59, 61, 61, 61, 62, 66, 70, 81, 89, 89, 92, 99, 99), though in very small numbers. Four of these cases (Nos. 70, 89, 89, 92) were not re-examined after the fifth dose ; but, of the remaining 16, scanty parasites persisted in 8 (7) (Nos. 4*, 7, 48, 48, 59, 61, 66, 99). Some of the patients in whose blood parasites persisted seem to have been particularly prone to relapse and difficult to cure ; Nos. 48, 59, 61, 66, 89 and 99 appear from two to four times each in the records examined. In all the eight patients with persistent parasites, the temperature was normal on the fifth day.

* No. 4 is reported as negative for asexual parasites after the fifth dose—*i.e.*, on the sixth day—but a subsidiary examination was performed on the seventh day, with positive result. (Note by the Editor.)

Table III.

ILLUSTRATING THE ACTION OF TOTAQUINA HOWARDS II ON THE ASEQUAL PARASITES OF SOME CASES OF SUBTERTIAN MALARIA TREATED IN KUALA LUMPUR BY DR. J. W. FIELD.

The figures are the numbers of asexual parasites per cubic millimetre.

| Case No. | 59 | 65 | 67 | 70 | 78 |
|--------------------|--------|--------|--------|---------|--------|
| Day of treatment : | | | | | |
| First | 55,000 | 24,000 | 16,000 | 370,000 | 32,000 |
| Second | 38,000 | 600 | 24,600 | 500 | 10,000 |
| Third | 24,000 | 200 | 2,000 | 103,000 | 9,200 |
| Fourth | 100 | 140 | 300 | 1,200 | 20 |
| Fifth | 20 | 0 | 0 | 50 | 0 |
| Sixth | 50 | | | | |

Central Field Health Station, Nanking.

The Nanking series, which comprises 61 records of benign and tertian malaria, is reviewed separately from the European groups because nearly half the Chinese patients were troubled by vomiting, a symptom which occurred very rarely in Europeans. This series is not combined with the Kuala Lumpur group, because the form of Totaquina used in Kuala Lumpur differed from that used in any other centre. Another point in which the Nanking series differs from the others is the special method by which the final examination of the blood was made on the day after the fifth dose ; an ordinary, thin-film examination was usually made about eighteen hours after the last dose and, six hours later, three more examinations were made at intervals, after an injection of ephedrine. As this series is considered separately, I have decided to accept the results of these four examinations which were made on the sixth day.

Eighteen cases of benign tertian malaria were treated with Totaquina, B. & W., with the result that parasites persisted in 6 twenty-four hours after the last dose—viz., Nos. E. 102, 111, 118, 119, 120, 121—but none of them had any fever. Twenty-eight cases of tertian were treated with the same drug, and parasites persisted in 6 (5)—Nos. E. 105, 116, 122, 123,* 139, 163—without fever (see Table IV).

* Case No. 123 was negative for parasites according to the routine specimen taken twenty-four hours after the fifth dose : became positive after an injection of ephedrine. (Note by the Editor.)

Six cases of benign tertian were treated with *Turin A*, with the result that, in 3 cases—Nos. E. 201, 202, 203—parasites persisted after the fifth dose, but without fever. Nine cases of subtertian were treated with the same drug; asexual parasites were found in 2 cases after the third dose, but in none after the fifth dose (see Table V).

The infections in this series of cases were not heavy; in only 10 of the 61 cases were as many as a hundred parasites counted in a hundred fields of the microscope, and in only 3 was the number above 200, excluding crescents. The temperature of most of the patients was normal at the beginning of the treatment; in only 24 was it above 37.8° C. (100° F.), and in only 8 was it above 39° C. (102.2° F.). No control group was treated with quinine, and it would be difficult to assess the value of Totaquina from this series alone. The results, on the whole, were not very good; possibly the frequent occurrence of vomiting was responsible for this, but, in the absence of examination of the urine for the presence of alkaloids, it is impossible to say whether the Totaquina was absorbed in every case, or not.

Table IV.

NANKING PATIENTS TREATED WITH TOTAQUINA I, B. & W.

| | Number of patients | Number with parasites after third dose | Number with parasites (excluding crescents) after fifth dose |
|---------------------|--------------------|--|--|
| Benign tertian | 18 | 6 | 6 |
| Subtertian | 28 | 13 | 6 (5) |
| | <hr/> 46 | <hr/> 19 | <hr/> 12 (11) |

Table V.

NANKING PATIENTS TREATED WITH TOTAQUINA II, TURIN A.

| | Number of patients | Number with parasites after third dose | Number with parasites (excluding crescents) after fifth dose |
|---------------------|--------------------|--|--|
| Benign tertian | 6 | 4 | 3 |
| Subtertian | 9 | 2 | 0 |
| | <hr/> 15 | <hr/> 6 | <hr/> 3 |

Other Centres in Europe and North Africa.

I have considered the remaining centres as a single group of 199 cases. The numbers at some of them are too small to be dealt with separately. The centres are: Instituto de Malariologia, Navalnoral de la Mata, Spain; Dispensary of Arcos de la Frontera,

Spain ; Asile Ste. Anne, Paris ; Regio Ospedale della Misericordia, Grosseto, Italy ; Hôpital de Marengo, Algiers ; Hôpital Cocard, Fez, Morocco ; Hôpital Alexandrovska, Sofia. The results are an indication of the therapeutic efficiency of Totaquina, but they cannot be regarded as a test of the relative value of the different samples of the drug, for one was used in one centre and another in another—for example, almost only Type II was used at Navalморal and only Type I at Marengo—and no control group was treated with quinine. The interesting temperature chart of a patient undergoing malaria therapy¹ at the Asile Ste. Anne (Case No. 4. Kral) demonstrates graphically the immediate effect of Totaquina in a woman who was having regularly-spaced tertian paroxysms before its administration. The doses in these centres were about 0.6 or 1.2 gramme daily, with smaller doses for children.

The results of Totaquina treatment in this group are set out in Table VI ; briefly, they were as follows : in 113 cases of benign tertian, parasites were found after the third dose in 19, and after the fifth dose in only 4 cases—*viz.*, Sofia, No. 1 ; Navalморal, No. 23 ; Grosseto, Nos. 12 and 22. No. 22 had slight fever, the temperatures of the other patients were normal. In 86 cases of subtertian, asexual parasites were found after the third dose in 16, and after the fifth dose in 4 cases—*viz.*, Marengo, No. 2 ; Navalморal, Nos. 24 and 41 ; Grosseto, No. 28. Grosseto, No. 22 and No. 28 had slight fever, but the remainder had none.

Table VI.

SHOWING RESULTS OF TREATMENT WITH TOTAQUINA IN THE GROUP CONSISTING OF THE NORTH-AFRICAN CENTRES, AND THE EUROPEAN CENTRES, OTHER THAN THOSE IN ROUMANIA.

| <i>Benign Tertian.</i> | | | |
|------------------------|----------------------------|--|--|
| Sample of Totaquina | Number of patients treated | Number in which parasites found after 3rd dose | Number in which parasites found after 5th dose |
| Type I B. & W. . . . | 22 | 4 | 1 |
| Type I Madras | 1 | 0 | 0 |
| Type II Turin A. . . . | 45 | 11 | 3 |
| Type II Turin B. . . . | 45 | 4 | 0 |
| Total | 113 | 19 | 4 |

¹ Therefore not included in the statistical tables.

| <i>Subtertian.</i> | | | |
|------------------------|----------------------------|--|--|
| Sample of Totaquina | Number of patients treated | Number in which parasites found after 3rd dose | Number in which parasites found after 5th dose |
| Type I B. & W. . . . | 22 | 2 | 0 |
| Type I Madras | 18 | 2 | 1 |
| Type II Turin A. . . . | 15 | 4 | 1 |
| Type II Turin B. . . . | 31 | 8 | 2 |
| Total | 86 | 16 | 4 |

THE TOXICITY OF TOTAQUINA.

The reports from the different centres are not unanimous with regard to the toxic effects of Totaquina, and consequently each group is dealt with separately under this heading. The observations made here are limited to the objective signs—vomiting and albuminuria—unless some other symptom was particularly prominent.

The Roumanian Group.—No symptoms which can be regarded as due to the toxic action of Totaquina were observed in this group of patients.

At Izolarea, neither vomiting nor albuminuria was noted in 53 cases treated with *Turin A*, or in 49 cases treated with *Turin B*. Albumin was found in 2 cases out of 59 treated with *B. & W.* and in 2 out of 52 treated with *Madras*; but the albumin was present at the beginning of treatment in all four cases and it had either disappeared, or diminished in quantity, by the end of the five-days course.

The cases treated at the Military Hospital, Jassy, were also free from toxic symptoms. Many of them were recorded as having traces of albumin in the urine at the beginning of treatment, and, in a few, it persisted to the end; but these results were possibly due to the use of very sensitive reagents in the examination of the urine, for traces of albumin were found with equal frequency (9 out of 35 cases) in the control group which was treated at this centre with quinine.

No toxic symptoms were noted among the patients treated at the Tomesti and Gurbanesti centres. A trace of albumin was found at the beginning of treatment in one of the Gurbanesti patients, but it had disappeared at the end.

The daily doses given at these Roumanian centres were about 0.6 gramme (9.25 grains) in benign tertian and 1.2 gramme (18.5

grains) in subtertian. Smaller doses were given to children ; for example, at Tomesti, where there were many, 0.3 gramme was given to children, and 0.15 gramme to infants.

The Kuala Lumpur Group.—Vomiting was remarkably common among the patients treated at this centre with Totaquina *Howards*, and occurred in no fewer than 65 out of a total of 158. This symptom appears to have been due to the malaria rather than to the Totaquina, because the case sheets show that it decreased during treatment instead of becoming worse, as it would have done had it been due to poisoning. This view is confirmed by additional evidence from this centre, for Dr. Field states that, in a series of 236 patients treated with Totaquina and 181 treated with quinine, 103, or 25 per cent, were vomiting at the beginning of treatment, but only 12, or 3 per cent, at the end ; in addition, the patients in the quinine group suffered as much from vomiting as those in the Totaquina group. Again, in the Annual Report of the Institute for Medical Research, Federated Malay States, 1932, the cases treated with Totaquina *Howards*, at Kuala Lumpur, are compared with an approximately equal number of cases treated with quinine, and the conclusion is reached that, as regards toxicity, there was no difference between the two drugs. The daily doses given in Kuala Lumpur were either 1 gramme or 2 grammes per 100 lb. body-weight—which is, roughly, 15 or 30 grains for the average Asiatic patient. These doses are larger than those generally used at the other centres.

The Nanking Group.—A striking feature of the 63 case records received from this centre is the large number of entries made in the columns reserved for toxic symptoms. Vomiting is noted as occurring in 27 cases, discoloration of the skin in 26, and cyanosis of the lips in 18 ; but closer scrutiny shows that (except in one case, E. 151) the symptoms were present when treatment was begun, and that they generally disappeared a day or two later. Consequently, they were not due to Totaquina. The samples of Totaquina used were *B. & W.* and *Turin A* ; they were given in doses of 0.6 or 1.2 gramme.

Other Centres in Europe and North Africa.

Grosseto.—Nine cases were treated with Totaquina *B. & W.* and 13 with *Turin A* ; but, except that one patient vomited on a

single occasion, no toxic symptoms were noted. The daily dose was usually 0.6 gramme.

Fez.—Twenty-one cases were treated with *B. & W.*, and 19 with *Turin A*; with the result that, excluding three patients who vomited once or twice, there were no toxic symptoms. Twenty-two cases were treated with either *Madrás* or *Turin B* with very different results; none of them vomited, but *tinnitus* and *vertigo* were so severe that some of the patients were unable to raise themselves in bed. Dr. FLYE SAINTE-MARIE, who treated them, was therefore unwilling to continue giving either *Madrás* or *Turin B* to any more of his patients. The daily dose was 1.2 gramme; this cannot be considered large, because the patients were mostly men who weighed between 60 and 70 kilos. The analysis of the different types of Totaquina used in this enquiry shows that *Madrás* and *Turin B* resemble one another rather closely in composition, and that they contain more amorphous alkaloids than the other types. This is very clearly demonstrated in the graph on page 330.

Hôpital de Marengo, Algiers.—Eight patients were treated with *B. & W.* In 1 case it was necessary to stop the drug because of "gastric intolerance", and atebirin was substituted. Two other patients vomited. Eleven patients were treated with *Madrás*; 4 vomited. The daily doses were 1.2 gramme.

Navalmoral de la Mata, Spain.—Thirty cases were treated with *Turin A*, and 23 with *Turin B*. The daily doses were 0.6 to 1.25 gramme, with smaller doses for children. Although *Turin B* was found very toxic at Fez, no toxic symptoms were noted here.

Arcos de la Frontera.—Twenty-nine cases were treated with daily doses of 0.6 gramme of *Turin B*, but, again, no toxic symptoms were noted.

Alexandrovská Hospital, Sofia.—Fourteen patients were treated with 0.6 gramme daily of *B. & W.*, and 9 patients with *Turin B*. No toxic symptoms were noted, except that three patients who were taking *B. & W.* vomited at the beginning of treatment.

Paris.—There were no toxic symptoms in 9 cases treated with *B. & W.*, but one patient out of two treated with *Turin A* began to purge and vomit at the end of the five-days treatment.¹

¹ Six of the 11 patients treated in Paris were cases of therapeutic artificially-induced malaria and are therefore not included in the statistical tables.

THE METHOD OF ADMINISTERING TOTAQUINA.

Totaquina was given in the form of tablets, cachets or powder at all the centres except Kuala Lumpur, where it was given, for the most part, in solution. This was necessary because the doses were graduated for each patient according to his weight, but the general use of such solutions is undoubtedly responsible for much of the unpopularity of the cinchona alkaloids ; their bitter taste is enough to make many healthy people vomit, let alone those ill with malaria. The use of solutions of cinchona alkaloids in preference to tablets or capsules is, I believe, peculiar to British medical men, and possibly dates from the days of long voyages in sailing-ships, when quinine pills were kept in stock for months or years and became as useless as pebbles. The tablets which are made to-day by reputable firms disintegrate quite easily when they are swallowed and afford a most trustworthy method of giving the alkaloids. The analysis of a large number of quinine mixtures in India showed how often the high price of quinine proved too great a temptation for the compounder and how seldom the mixtures contained the correct quantity of quinine. It is strange that medical men who have a strong prejudice against prescribing quinine in solid form have no objection to tablets of atebirin or plasmquine, or even to tablets containing quinine when it is mixed with another drug, as in Plasmoquine Compound. Fluid mixtures of Totaquina are even more disgusting than those containing quinine, because it is not so readily soluble. The solutions used by Dr. Field in Kuala Lumpur were made with great care, but, unless they were filtered, a little of the powder remained in suspension. Any doubt as to the absorption of tablets or capsules can be quickly settled by testing the urine.

CONCLUSIONS.

The results of this trial of five different samples of Totaquina show that they are all good remedies for malaria, but possibly they are not equally good. For example, the results in Roumania with the sample *Turin A* were not so good as those obtained with the other kinds, though its composition is almost the same as that of the sample *Howards* which was used in Kuala Lumpur and found as effective as quinine. Again, the results of treatment with the

sample *B. & W.* were very poor in Nanking, though they were excellent in all other centres where it was used, and the probable explanation in this case is that the Chinese patients did not absorb the drug because they vomited. This question could have been settled very easily by testing the urine for quinine; this would have occupied very little extra time, since the urine was examined for albumin in almost every case. As regards toxicity, the case records contain no cogent evidence that Totaquina is more toxic than quinine in the doses given, but it is not easily soluble and should not be given in a fluid mixture.

To sum up, the records of the cases treated at the different centres show clearly that Totaquina acts like quinine as a potent remedy in all forms of malaria; but it must be remembered that a field trial of this kind is not a carefully controlled experiment and, when it comes to deciding whether Totaquina is a little better than quinine or not quite so good, one is on less sure ground and, in the absence of adequate controls treated with quinine, the yard-stick needed for more exact measurements is lacking. Similarly, the observations made at the different centres were not sufficiently precise and unanimous to warrant a final decision on the relative merits of the different samples of Totaquina.

Table VII.

SHOWING THE RESULTS OF TREATMENT WITH THE DIFFERENT TYPES OF TOTAQUINA IN EACH GROUP.

| PLACE | SAMPLE OF TOTAQUINA | | | | |
|----------------|-------------------------|------------------------|-------------------------|------------------------|------------------------------------|
| | Type I B. & W. | Type I Madras | Type II Turin A | Type II Turin B | Type II Howards |
| Roumania ... | B.T. 125-0 M.T. 63-1 | B.T. 29-0 M.T. 57-0 | B.T. 108-4 M.T. 62-9 | B.T. 58-0 M.T. 77-1 | |
| Nanking | B.T. 18-6 M.T. 28-6 | | B.T. 6-3 M.T. 9-0 | | |
| Kuala Lumpur | | | | | B.T. 41-1 M.T. 101-8 Q. 15-3 |
| Other places.. | B.T. 22-1 M.T. 22-0 | B.T. 1-0 M.T. 18-1 | B.T. 45-3 M.T. 15-1 | B.T. 45-0 M.T. 31-2 | |

The first figure of each pair is the number of cases treated; the second figure is the number in which parasites persisted after treatment.

B.T. = benign tertian; M.T. = malignant tertian; Q. = quartan.

STOCKHOLM GARDEN SETTLEMENTS

By

Senator C. LINDHAGEN,

former Mayor of the City of Stockholm.

At the end of 1933, the Swedish capital had 522,000 inhabitants. With three subsidiary towns and other suburbs situated outside the city's jurisdiction, the total population was 662,000 (Greater Stockholm).

Stockholm is a fine city ; it is built on seven islands and a hilly mainland. It lies like a golden jewel set in the Malar and Baltic Archipelagoes. The city is surrounded and honeycombed by fjords, streams, bays, and canals.

The beauty of the city thus consists in the great variety of its aspects. This beauty is the city's inheritance and possession, and has been its stamp of nobility throughout the ages. It can be enhanced, but it can likewise be destroyed or impaired, by building.

But the natural outlines have been too powerful to be fundamentally spoilt by the hand of man. Not even the modern machine age has achieved this result.

This outward beauty must reflect an inward inspiration. Only the soul can breathe life into matter. The structural unnaturalness of great cities raises the question of the return of inspiration. The social city will succeed to the wilderness of bricks and mortar through the instrumentality of town planning, the object of which is to make provision for all social interests which have their roots in the earth.

THE RETURN TO NATURE.

In the midst of life's struggles, there is still a solid rock, which is called the law of nature. Everything that has gone astray is

ultimately found to be in conflict with nature and is commonly called unnatural. All culture, both spiritual and material, comes from nature's rich and generous bosom.

In the past, when artificiality went too far in the work of man, the cry "back to nature" always arose as a saving message. When burdens have become too heavy and illusions have failed, philosophers and statesmen have found rest and regeneration by retiring to cultivate their gardens.

When, as at present, the fires of industry are burning out and unemployment makes the masses hopeless, the only way out that they can see is "Back to the land".

It is thus a sign of a return to what was of lasting value in the good old days. In those days, most of the Swedes lived on agriculture and their small communities were garden cities. Even then, of course, the people had to contend with difficulties from outside, and were hampered by their own frailties. But the conditions of life compelled them then more than at present to enrich their lives with love for the soil, and this tendency was fostered by the nature of the land. People were obliged to seek their food and clothing from the soil. The woods and streams gave them shelter, tools, heat, light and power, fruit, fish, game, and beauty.

The Swedes have therefore inherited the desire to till the land and exploit the forests. When, after a life of toil, they went to their last rest, three spadefuls of earth were thrown on their coffins, with the words : "from earth thou camest and to earth thou shalt return".

Thus the earth dominated the Swedes, until a revolution took place and man became master over new, and hitherto latent, natural forces. Great technical discoveries followed one another in rapid succession. Machines were invented and were taken into the service of companies as soulless as they. Industrialism arose, and cities grew up in its wake.

THE CITY.

This was the beginning of a new era, when the old idyllic life disappeared. Fierce competition arose for the profits which the machines offered, and the land became its prime battlefield. There was a ruinous flight from the land to the opportunities and

allurements of the towns. The price of building-land increased, and the cities, those stony deserts, came into existence. The debit and credit of this movement may be set down as follows :

The city attracts with its life and movement and its alternation of work and play. It satisfies the human need of communal life, which increases in proportion as the inner life loses its influence. The city seems to be the centre of spiritual and material culture,



Stockholm—Bird's-eye view.

from whence all the driving force originates and whither all threads run together.

This brilliant surface hides an underworld. The city is also the offspring of industrial decadence, a cancer in the body of society, the concentration-point of destitution and malnutrition, the abuse of alcohol, hatred, disease and crime. The city is a furnace that consumes human fuel. Nothing proves its essence more clearly than the necessity for sending city children to summer camps or elsewhere in the country for the sake of their moral and physical health.

The continual growth of the city is the expectation and aim of its municipal policy. The Swedish capital is no exception to this rule. Although it is realised that, if any defect arises in the machinery, the city will be without food, heating or light, that the city is

the main starting-point of the increase in the cost of living, and that it affords an all-too propitious environment for our latent tendency to plunder our neighbours and to debase our own characters, yet we continue to work thoughtlessly and hopefully on top of this volcano so that, year by year, the wild venture may be carried ever further afield.

THE SOCIAL CITY.

In the meantime, the unnaturalness of factories and deserts of bricks and mortar began to become evident. The instinct of self-preservation made the Swedes long to return to nature. City-dwellers and factory-workers began to settle in homes of their own with gardens, or to take refuge during the summer in garden settlements.

The Stockholm Town-planning Committee of 1866 was a symptom of this movement. (The Chairman was the writer's father, Albert LINDHAGEN, Counsellor at the Supreme Court.) It put forward a plan for the re-organisation of the inner city, and made the following prophecy regarding the garden city :

"One of the most effective ways of counteracting the harmful influence of the towns is to give the inhabitants as large a share as possible of the country's rich supply of light and fresh air and to bring the country into the towns by laying out spacious gardens and parks, and thus to banish from town dwellings and their surroundings darkness, congestion, foul air, and other unnatural conditions of life—in a word, all the disadvantages which generally accompany city life and undermine physical health while contaminating and dulling the mind."

One of the guiding principles in the return to nature must be that the land shall be used for its proper object and not become an article of commerce.

Something of the kind is not wholly foreign to existing social conditions even in large towns. Parks appear in the town plans as shrines of ideal values. All thought of selling them for profit has vanished. Why should not the dwelling-places of the citizens

at some future time enjoy the same peace under the law ? Why cannot one imagine a town community where the public buildings and the private gardens with their own houses or summer colonies, forming a supplement to hired dwellings should have a permanent and secure place on the land without regard to their situation and be entirely exempt from brutal economic valuation and land usury ?

International housing congresses now generally demand humanitarian arrangements in the building of great towns. A new idea of the form of the large town has been gaining support. It is urged that a number of independent communities should be allowed to grow up round the old town as a centre of administration. They should be separated from the centre and from each other by free zones serving for agriculture, forestry, industry, garden settlements, games, amusements and relaxation. The suburbs in the periphery should retain their present rustic character.

The nuclei and extensions of suburbs should be surrounded by fields and a system of garden settlements.

GARDEN CITIES.

The real fundamentals of life are first laid bare in the lives of the common folk who dwell and toil on the land. It is in relation to such a life of simple needs and endeavour that the social city was planned, in Stockholm as elsewhere.

The inner town of tenement houses continued on the whole to represent unnaturalness and homelessness, even when health conditions could be improved by esplanades and parks and the town was brightened by numerous streams with their opportunities for boating excursions.

In the first place there was a popular revolt against the homelessness of flat life. People longed for their *own home*. Garden cities arose around the town. When the land was privately owned, the developments took place unfortunately as a speculation.

There were also garden cities laid out by the town. With wise foresight the municipality had purchased large tracts of property inside the town for town regulation and, subsequently, on the initiative of the municipal engineer Herman Ygberg, it had acquired extensive estates in the dutlying areas with a view to providing

for future urban development. A special Board was set up to administer the latter quite independently of the mercantile property within the town itself. This Board had powers to propose town plans, to carry them out, to experiment with various types of dwellings, to provide for all other land interests and, for a time also, to organise communications. The writer was Chairman of this Board and it was one of his most instructive experiences.

The greatest importance was from the outset attached to the creation of individual homes. They were arranged as one-family houses in their own grounds. The Swedes have from old times had a predilection for privacy. They do not feel that they have a real country home and garden unless they can walk right round the house. Rows of houses are not in favour. This tradition has hitherto been a protection against the spoiling of the social town by the construction of high tenement houses. But space had also to be set aside for low apartment houses of at most two or three storeys. These were also built for preference as detached houses and surrounded by trees and sometimes by gardens for the use of the tenants.

On these country estates the town generally retains the ownership of the land. It is let on building lease, the terms of which do justice both to the individual and to the community. As a rule, the payments to the town represent merely the actual cost. The leases are granted, not to the highest bidders, but to the first applicants. The profit-making system is for the most part excluded.

The estates at present consist of 5,767 hectares, of which 1,812 are arable land and 3,955 forest land. Of this area, 1,436 hectares are included in the town plan.

GARDEN SETTLEMENTS.

The town's land policy, as stated above, also provides for other social needs. One of its principal features is the garden settlement schemes, which also originated in the above-mentioned popular movement. This institution struck root in the Swedish towns and the capital led the way.

The garden settlement movement is a monumental expression of popular revolt against the industrial, mechanical and mercantile

character of our time. It reflects the aspiration of the common people to freedom and light, health and beauty, repose and reflection. It is an expression of the human instinct to seek spiritual regeneration by a return to nature. It is a striving for a constructive supplement to the wretched home in the tenement city. It is the way in which people of small means can take their recreation



Garden city in the neighbourhood of Stockholm.

in the summer without holidays or money. It represents an indictment by rural culture of urban culture with its destruction of man's community with nature, which is the source of his livelihood.

This movement was received by the Rural Property Administration of Stockholm with open arms. For a short time it also found a haven in the parts of the city area which were not yet built over. Its future on the rural estates, where the principal settlement sites must be sought, is now under consideration.

GARDEN SETTLEMENTS AND TOWN PLANS.

The nature of the countryside in and near the capital imprints a very varied and unique appearance upon the towns. The numerous watercourses form natural fresh-air channels and separate the blocks of buildings from each other. The mainland, with its variety of fields, valleys and wooded hills, lends itself to "homestead" schemes which suitably combine all the various desiderata and are gradually created as geographical units as the estates come under exploitation.

The land is portioned out in each case in accordance with the purposes for which it is required : apartment houses — communal, co-operative or speculative—individual homes with gardens, garden settlements and parks. In addition, areas are allotted for industries and crafts, public buildings and establishments, athletic and sports grounds, shops, etc. At the main traffic junctions, small urban centres develop with low houses containing apartments and shops. The family houses, garden settlements and parks alternate according to the nature of the soil. The uniform garden cities of the European continent and North America, which are laid out in squares on the flat land, find little counterpart in Stockholm, where the ground is broken up by water, hills and valleys.

It is to be expected that more apartment houses will have to be built on the rural estates on account of the scarcity of building space inside the town. A number of people who will not or cannot tie themselves to the one-family house have a right to rent an apartment in the garden city. The following building programme should therefore be established :

In each centre, apartment houses are built of at most three storeys and may be tastefully laid out in groups. Small cultivated or wild parks are laid out in the immediate vicinity of the apartment houses. Beyond these come the one-family houses, either the smaller and larger separately or the two types alternating with each other. Beyond the one-family houses come the garden settlements. A "homestead" scheme centre of this kind is surrounded by woodland in the form of a park connected with the garden settlements, and these may also be partly situated in the park itself. Each centre could therefore be said to consist of three parts : the apartment house city, the garden city and the allotment city.

THE EVOLUTION OF THE GARDEN SETTLEMENTS.

The garden settlement movement in Stockholm began to develop in 1904, when work commenced on a definite plan. During the first two years, the settlements were created without any special organisation on the initiative of the writer's sister, Anna Lindhagen, Child Welfare Inspector. Interest in the movement grew rapidly and, in January 1906, the Association of Stockholm Garden Settlements was formed, and various other plans came to fruition. The land used was principally communal but, to some extent, State land and land belonging to a number of foundations. After 1910, when the town began to exploit extensive tracts of its rural estates, the movement assumed large proportions. It was further stimulated during the crisis which followed the war, when there was an extensive cultivation of foodstuffs even in the town.

At the beginning, the members of the Association were persons who supported it by their work or capital. The settlers were, as a rule, not members and therefore had no direct influence on the management. The Association, by its form of organisation, exercised a good influence on the development of these areas. The Stockholm garden settlements achieved a high reputation. As the activity developed, various difficulties arose as a result of conflicting interests and the economic connection between the various settlements. Although, as a rule, the movement could be carried on with profit, it suffered from a lack of capital. In 1918, therefore, the Association received a grant of 10,000 Kronor from the town in return for planting land with potatoes and the organisation work carried out in the settlements.

At the same time, the settlers expressed a desire for economic self-government. In some districts they demanded the right to take over the land direct from the town without the intermediary of the Association, and to carry on the work on a co-operative system. The town acceded to these desires by letting fresh land direct to the settlers or to groups of settlers. In a number of these areas, the town made experiments with co-operative groups and in most cases these experiments were successful.

When allotting the land, care was taken to allow, to the utmost possible extent, for the permanence of the settlements concerned,

although in this there was bound to be some element of uncertainty. They represented a new departure in the field of social welfare which could hardly be expected to rouse general interest at once, or to be judged, until it had stood the test of experience.

As far back as 1909, however, the Rural Estates Board made the following pronouncement in connection with the inclusion of garden settlements in a certain town plan : "Experience has constantly shown the importance which such well-arranged garden settlements may acquire. They give the settlers both healthy recreation and an economic return. They are also of great value from the point of view of health, and it is said that many who have been in a position to lease such garden plots have regained their health. Garden settlements should therefore be given adequate space in the town plans and thereby obtain a permanent position, and not be constantly moved on as at present."

In view of the extent to which garden settlements subsequently developed, it became desirable that the town should place them under uniform administration. The Rural Estates Board therefore decided in January 1918 to appoint a Garden Settlements Council with detailed instructions.

In 1918, however, a change took place in the town's land policy, in connection with the proposed re-organisation of the administration of the capital. It was decided to combine the administration of municipal property in the inner city, as conducted on commercial lines, with the administration, on social principles, of estates in the outlying districts.

The joint administration was created and began work in 1919.

In view of the existing conditions, the Garden Settlement Association in January 1919 proposed that the town itself should take over the garden settlement areas on land rented by the Association from the town.

Negotiations were now started regarding the land taxes and the transfer of the movement from the town to a co-operative organisation, or a system of direct lease to each settler. The latter was, and is still, a thorny question. The co-operative holders desire that a private settler may not obtain a lease direct from the town but should receive it indirectly from the administration of the co-operative areas. The Association for its part expressly desired that, before it transferred contracts to the town, a suitable

number of plots should be leased to settlers who did not wish to enter a co-operative society but preferred to rent their plots direct from the town.

The Association further pointed out that, in the agreement with the co-operative societies, a provision should be included forbidding a group of settlers to form a co-operative society and subsequently letting plots to other holders. The Association also considered that the town should retain the right to give a private holder notice



Garden-settlement cottage.

to leave his allotment even if the competent settlement association did not consider that such action was required.

Since so many new co-operative societies were to be formed, the Association expressly desired to urge the necessity for the town to organise more powerful and effective machinery to draw up and maintain a building plan which would be satisfactory from an æsthetic and practical point of view.

The chief town authority—*i.e.*, the Municipal Council—now proposed to confirm the agreement regarding the transfer of the garden settlement movement from the Association to the town.

On February 21st, 1921, the Municipal Council approved the agreement, specifying, however, that the Joint Estates Board would administer the garden settlement movement on self-supporting lines.

This was a first sign of the difficulty of joint administration. It was a hint of the psychology of the mercantile community, which, as might be expected, felt somewhat dubious about social values which cannot be expressed in terms of money except indirectly.

UNDER THE PROTECTION OF THE COMMUNITY.

After the community had thus taken over the administration of the garden settlement movement, the attitude adopted towards the question underwent an immediate change. Land was no longer allotted from the town's property for laying out new settlement areas, and allotment holders even received notices to quit. This was done inside the town in order to build apartment houses on the property, and the settlers' resistance was finally of no avail. Outside the town it was done in order to make new roads, which were indispensable. At the same time there were cases even here where the settlement areas had to make room for apartment houses.

In consequence, a motion was proposed in the Town Council in 1923 with a view to including settlement areas in the town plan, allotting further areas for settlements and paying reasonable compensation to settlers under notice to leave. No decision has yet been taken on this motion.

In the meantime, the Town Planning and Property Office has drawn up a plan for the settlement movement on the rural estates. It is proposed that, of the 5,285 plots on the town land in 1918, 3,243 plots should sooner or later make way for other buildings in addition to 828 plots which have already been abolished. It is only proposed to include 1,214 plots in the town plan. It has been proposed to allot fresh land in compensation, but the area is somewhat smaller than that occupied by old allotments which are to be abolished. This site is at a greater distance from the town, the accommodation of which it is intended to supplement. It requires expensive and laborious adaptation of new land and plantations, together with the removal of the buildings.

This change in municipal policy coincides with the re-organisation of the property administration, which was decided on in 1918.

In reality, the new policy is not merely due to a change in views. It is also explained by the annual increase in the population. In recent years there has been an influx of 10,000 to 15,000 new

inhabitants, while the figures of deaths and births have been roughly identical. The unbuilt property in the town is coming to an end. It is therefore argued that space must be found for the inhabitants, not only on the unexploited land belonging to the State and private people, but also, in particular, on the town's rural estates.

Here, the social and mercantile views are in conflict. Some parties urge that the new apartment houses should be allotted space lying beyond the existing garden settlements. Up to the present, this has been the case. Others consider that the apartment houses have a better right than the allotment gardens to be situated as near as possible to the centre of the town, where the tenants mainly work. The garden settlements are considered a secondary matter and a primitive method of utilising the soil, which must give way before what are called higher, or at any rate more inescapable developments. In addition, the building costs on garden settlement land are lower than they are when most of the apartment houses have to be erected on rocky soil, as in the centre of the town.

The latter view is supported to some extent by a powerful organisation called the Tenants' Building Society, which builds large blocks of houses every year for its members. In the centre of the town, under the influence of the growing "functionalism" in architecture, it has been permitted to construct high buildings, while abolishing the system of interior courtyards. In Building Society circles, it has been remarked on occasion that, if the buildings are to be situated on the rural estates, the land belonging to the garden settlements would be the most suitable.

This raises the possibility of high buildings, which are now being erected up to eleven storeys in the town. Hitherto such buildings have not been allowed on the rural estates, and applications to build apartment houses of a greater height than three storeys have recently been refused in the immediate vicinity of the two main exits from the town to the rural estates.

At the beginning of 1933, the prophet of the school of "functionalism", the Swiss Le Corbusier, came to Stockholm with his gospel. He said he loved the green fields and the light of heaven. He called his city of the future the green city or the radiant city

and wanted it to be filled with verdure. He must, he said, clear away all the conglomeration of hovels in which people felt as if they were prisoners in a stony desert instead of free creatures. The houses were not to be built on a single pattern but according to the conditions of each district and town. He was enthusiastic about Skansen, the hilly peoples' park in Stockholm, with its old-fashioned peasants' houses.

Thus there appear to be prospects that the new school of architecture and the association of tenants will finally reconcile themselves with the garden settlements and, as sometimes happens, even become adherents of this movement.

It is, however, still not clear whether apartment houses should rise in towering piles with multitudes of small apartments or should be lower-built and more individualised. No doubt people can live and die in both kinds of buildings. As far as I can understand, the individual is a world in himself. At the same time, according to the Swedish rural tradition, the ideal dwelling is the detached house. Such a house, with its own garden, adds in the greatest measure to the amenities of life.

The democratic form adopted for such houses in Stockholm is the so-called "small cottage". It contains a permanent dwelling for the whole year and has not less than two rooms and a kitchen on the ground floor and, in certain cases, two rooms on the upper floor together with a cellar and bathroom. The house often has a garage. In addition, it is surrounded by a small garden. Experiments have been carried on with various types and sizes.

The principle of the small cottage is that it is built by co-operation between the person seeking accommodation and the town. The former, assisted by his family, carries out a considerable part of the building work in his spare time, and workmen in various trades help each other. The town sells the building material at cost price, including standardised parts for dwelling-houses which can be erected in one day. In addition, it gives technical advice and credit against security according to the law on building leases, most of the security being represented by the dwelling-house.

These measures, which have aroused the admiration of foreign experts and are even described as a solution of the housing question, provide a family with a much roomier, healthier and cheaper dwelling than it possessed in the town. It is now the favourite

form of building in the municipal property administration. It is argued that the garden settlements must be supplanted by the small cottages. On the other hand, those who are most interested in the apartment houses regard small cottages and garden settlements alike with disfavour. It is absurd, they state, to allot land for such building when it could provide space for innumerable flats and give accommodation to many more people.



Garden-settlement cottages.

The small cottage schemes are, however, sturdily standing out against the inroads of tenement-house building. They and their supposed rivals, the settlement cottages, are being warned of many dire calamities which are alleged to await them. In the end, all the contending parties may become good friends.

THE GARDEN SETTLEMENTS' CONTRIBUTION TO CULTURE.

The garden settlers in Stockholm and their adherents regard the garden settlement as an integral part of a social town plan. So

long as towns exist which are dreary wastes of buildings, it is a distinct gain for the tenants to remove during the summer to a garden settlement.

This need is common to most countries inhabited by the white race, whose technical inventions have engendered the progress and the troubles of modern times. In the north, this desire is great on account of the short but bright summers. In Sweden and especially in Stockholm, according to the reports of observers, the settlements are particularly developed as a result of the industry of the people, the extension of cottage building and the organisation of the movement.

The first object of the settlements is to offer a healthy alternative to the unsatisfactory town dwellings for persons of small means. This is all the more important in the northern countries on account of the length of the cold season. A garden plot is a boon to flat dwellers in the modern town houses, with their cramped rooms in mercantile surroundings. The settlements are therefore intended primarily for the tenants of town apartment houses. As the outer districts are progressively built over with apartment houses, it should not be impossible to arrange for the leasing of such plots to their inhabitants. On the other hand, the old idea of placing garden land next to the apartment houses for leasing to the tenants has, on the whole, proved unsuccessful in Stockholm.

The garden settlements also contribute to the maintenance and improvement of the physique of the population from generation to generation, and thereby result in savings on medical attendance and poor relief. Official circles are reluctant to admit this and reticent on the point. Hygiene is still insufficiently developed on the side of preventive medicine, and steps are taken only when disease has broken out. On the other hand, enormous institutions are built for the care of the sick and poor. The garden settlers are in the front rank of those by whose action this system will be reformed.

One of the means of self-preservation of the town population is to send the poorer families' children to summer or holiday camps. The garden settlements of a town contribute even more powerfully to the improvement of the public health. They benefit the entire family and their effect is permanent. One good thing should not exclude another. Statistics sometimes try to show that health

conditions are now better in the towns than in the villages, but no one has yet heard of country children being sent to the towns for the sake of their health.

Moreover, the settlers make by their work a valuable contribution to their own maintenance and the town food supply. The value of their produce in 1926 in Stockholm was calculated at not less than 2 million Kronor, and for all towns with over 10,000 inhabitants, at $9\frac{1}{2}$ million Kronor.

It is obviously important to maintain and develop the garden settlements in order to give the unemployed, who now are always with us, an opportunity of working and growing their own food. This applies particularly to times of depression.

THE SITING OF GARDEN SETTLEMENTS.

We now come to the siting of the garden settlements on the land. The soil must be suitable for gardening. For this reason, settlers should not be arbitrarily evicted from cultivated land and offered in exchange, for instance, heavy clay soil which involves fresh expenditure and labour in order to adapt it to the delicate work of gardening.

As the settlement is also to be a summer resort, it should not be relegated to some desolate district with surroundings already spoiled by industrialism.

Marshy lands should not be selected ; in the northern countries they cause frost and prevent growth. For the same reason, the plots should be to some extent protected from the cold northern winds.

The effect is unæsthetic and a good deal of the pleasure is lost if the plots of land are not of moderate width and situated close to the edge of a wood, but are laid out in patches like a box of bricks on an open plain. The best situation is at the edge of wild parks. Then they constitute an object lesson and a useful reminder to the city of what has at all times been the slogan of Swedish rural civilisation—namely, the tilling of the soil and the care of the woodlands.

Lastly, it should be remembered that the garden settlements are intended particularly for flat dwellers from the centre of the town. The nearer the settlements lie to the town supplement the better

do they fulfil their object. They need not satisfy a condition suggested in Germany that they should be situated "within perambulator range" of the ordinary dwelling. This can rarely be feasible in Sweden. In our opinion, the settlements should be situated in rural surroundings. The cottages should be of such a size that, as in the case of Stockholm, the whole family may move out into the country. But the breadwinner must be able to go to and from his work within a reasonable time and without undue cost.

THE RELATION OF THE SETTLEMENTS TO THE ONE-FAMILY HOUSE AND THE APARTMENT HOUSE.

In addition to the settlement movement, there is in Sweden a healthy tendency which is supported by the State and communes for providing the town-dwellers with their own homes in which they can live both summer and winter.

One of the main objects is to relieve the town-dwellers from the homelessness of life in hired apartments, from the leasing of dwellings merely for one year at a time, from notices to quit, increases in rent and burdensome rents. Instead of being merely tenants, they will become masters of their own homes.

In Stockholm, these evils are to a great extent overcome by leasing municipal one-family houses and by the creation of co-operative dwellings. In both cases, the dwellings are leased in principle at cost price and notices to quit are seldom given.

Another object, in some cases, is akin to the one underlying the garden settlement movement—namely, a return to nature.

A third object is the provision of accommodation for an increasing population. As mentioned above, this necessity adds greatly to the difficulties of the Stockholm housing problem. Many ways of meeting it have been suggested, but, in any case, it reduces the old inhabitants' prospects of obtaining cheap and spacious accommodation. A dwelling consisting of one room with kitchen or kitchenette at a heavy rental is the highest standard that can be attained by many of the Stockholm families.

A further consequence of this state of affairs is that other problems which may be quantitatively matters of minor concern but are qualitatively of no less importance are liable to be overlooked.

This applies particularly to the garden settlements ; and yet they do serve a useful purpose even here, if only by offering a haven of refuge to some of the unfortunate house-hunters.

The garden settlements are also required for persons who may be in a position to secure a small home of their own but do not do so because their work does not permit it, because they are likely to be transferred elsewhere, because the business which employs them may be wound up, etc.



Garden-settlement.

The view is now being advanced in the administration that the settlers should instead obtain a small cottage in which they can live the whole year. The commune should, however, take care not to induce persons to acquire their own home if they cannot afford it or do not dare to bind themselves on account of the uncertainty of their prospects. The town is overcrowded with such families. It should not be imagined that such families, from whom the settlement movement is mainly recruited, will cease to exist or leave the town for the allurements of a cottage of their own.

The garden settlement is therefore an intermediate type between apartments in the town and one-family houses in the suburbs.

During the winter, the family lives in a town flat for which it pays the whole year, but in the summer, at any rate in Stockholm, it usually lives in the settlement. The size of the cottages is suitable for summer residence. It is interesting to see how practically the families adjust themselves to the small space. This is facilitated by the fact that house and garden form a closely connected whole in which the garden is indeed the main consideration. The settler lives the open-air life, in community with nature.

The settler is nothing less than the smallholder of the large town. He belongs to an élite of the population which is driven to the settlement, among other reasons, out of interest and comprehension for the cultivation of the soil. The plot is, moreover, not so large that the family cannot devote its spare time to intensive market gardening or what is known as Chinese agriculture. The family does not seek a dwelling in the ordinary sense of the word, for the cottage is too small for that purpose. It is, as it were, the blending of the cottage life with the cultivation of the soil which makes up the sum total of the benefit which the family derives from the allotment as a summer residence.

The problem is different for families looking for a permanent dwelling for the entire year in a home of their own in rustic surroundings. For them the house is the main consideration and they wish to increase its value by beautifying the plot surrounding it. The gardens are therefore sooner or later given up to terraces or greenery arranged so as to require little attention. There are lawns, perennial plants, with attractive flowers which can be put in vases, a few bushes and one or two fruit trees and wild trees. Sometimes, of course, the owner has a natural love for gardening, but the above is the general tendency and must be so in the nature of things, whether the house is large or small. To a great extent, therefore, the ground which is in demand and is supplied for large country houses is situated on hilly forest land, while the small cottages are built for preference on arable land.

It is also a striking fact that settlers who wish to remain in their cottages over the winter and can, with difficulty, be persuaded to leave their dwellings, which, though cheap, are hardly suitable for winter use, belong to the class which attaches more importance to the dwelling than to the garden. As a rule, they care little or insufficiently for the cultivation of the ground. Such plots easily

become dilapidated and real settlers are unwilling to take over land which has been so neglected.

Another difference between those who merely want a dwelling and the real garden settlers is the effect exercised by the different types of property on the character of the families' children, especially the boys. In a garden settlement, it is stated, the children never steal produce from other settlements. The swarms of children who



A typical garden settlement.

live in the apartment houses and have no roots in the Swedish soil are, on the other hand, dangerous neighbours for the garden settlements. Children from one-family houses are better, but they, too, are not always little angels.

THE SIZE OF THE PLOTS, LENGTH OF LEASE.

In Stockholm, the garden settlement plots have an average area of about 325 square metres and vary from about 200 to 480 square metres. The cottages cover an average area of about 15.5 square metres and vary in size from 6 to 22 square metres.

As a rule they contain one room, a small cooking arrangement and a tiny entrance. The shortest leases granted are for one year, automatically renewable for a further year unless notice is given. They are usually let for five to ten years with subsequent renewal for one year at a time if notice is not given.

As a rule, the families move out to the country at the beginning of spring and remain there until harvest-time. The breadwinners and the grown-up sons and daughters go to their work in the morning and return in the evening.

In addition to the house, there are summer houses, arbours and the like where the family spends the greater part of the day in fine weather. Great attention is also paid to comfort, order, good taste and ingenuity in the sleeping arrangements.

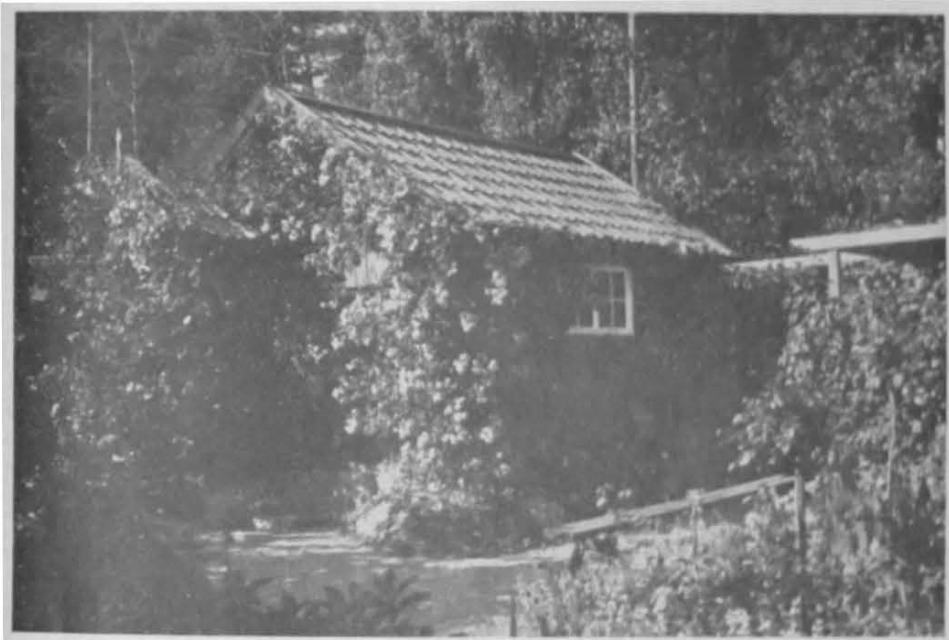
To a great extent the high cultural level of the Stockholm settlements is a result of the efforts made from the outset by the leaders of the movement, who insisted that the cottages should be erected on a certain artistic plan. The opposition aroused at first by this attack on "freedom" was often considerable. The importance of such a principle from the point of view of comfort and character formation is now universally realised. It has been calculated that, in the capital, some 28,000 people have adopted this means of seeking physical and spiritual improvement and of indulging their love for the soil.

THE GARDEN SETTLEMENTS' STRUGGLE FOR EXISTENCE.

The shortness of the leases and the demand that the settlements should give way for other buildings are a sign that, in Stockholm, as in many other places, they are regarded by many in the town-planning department and property administration as no-man's land or unexploited property. There is an incipient tendency to regard land as suitable for almost any purpose but its own ; for instance : for apartment houses, one-family houses, especially small cottages, parks, sports grounds, etc., or what is known as "vital housing interests". As mentioned above, no new leases have been granted for a long time, so that the movement has been unable to grow. It is even said now and again that garden settlements are an antiquated institution.

As against this tendency, the opposite view is making headway with the settlers themselves at the head. The general public is sympathetic, and the movement has allies in the Press regardless of parties.

In view of this feeling on the part of settlers, who have had notice to leave their plots in the town, land has been recently prepared and leased in a district called Riksby. This new area for garden settlements was included in the 1931 town plan. The



Garden-settlement cottage.

plots are let on building lease, the system which the town applies to one-family houses. The lease is for forty years as against sixty years for one-family houses, and gives a preferential right to a fresh lease at the end of the period.

In this area, however, the town has applied the commercial principle that the whole of its outlay must be covered by the settlers. The payments are higher than for the old settlements. This and certain other stipulations have made the areas less desirable and less accessible to people of small means.

At the same time, the municipal administration was demanding a final decision on the principle of gradually abolishing a large

number of settlement areas. The writer submitted a memorandum on the Stockholm garden settlements to the town councillors at the end of 1931. The impending action against the garden settlements was then checked for the moment. No decision has yet been taken on the representations made in 1923 and 1931 in favour of the settlement movement.

The problem has been kept to the fore in Stockholm and the entire country, thanks to the international organisation of the movement. The settlers organised themselves into associations, a national council and an international union. In Sweden, the local associations combined to form the Swedish Garden Settlement Council. The largest local association is that at Stockholm. At the International Garden Settlement Union's Congress in 1917, certain principles were laid down as regards legislation governing the activities of the garden settlements. Among other things, the Congress demanded that existing garden settlements should be included permanently in town plans, that sufficient ground should be reserved in the town plans for parks and garden settlements and that every new area leased for garden settlements be guaranteed to be permanently assigned for this purpose.

GARDEN SETTLEMENTS ON STATE LAND AND PRIVATE LAND.

Opportunities for the acquisition of garden settlement lots by town dwellers must be extended to all the surroundings of the town. In the near future, the line of development for Stockholm lies towards the south and west, where the necessary land has, in the main, been purchased by the town. This is not the case in the north and east, where the principal owners are the Crown and private persons.

In 1932, the writer proposed a motion in the Riksdag for furthering the garden settlement movement by State legislation and colonising on the State land. The matter was entirely new to the Riksdag and, as is often the case, the first attempt was unsuccessful.

In the meantime, the pioneers of the movement, in particular Miss Anna Åbergsson, when they were at the head of the movement, endeavoured by private representations to persuade the State

administration, and to some extent private persons, to let land for the garden settlement movement. In these areas in 1932, 40.7 hectares, making 1,245 plots, were allotted, most of them on State land. At Stockeby there are thirty settlement plots on State land, which have even been included in the town plan. This, the first official town plan for garden settlements in Sweden, was established in 1928 and comprises a little more than 2 hectares. The plots are sold with right of ownership. This is a unique



Bergshamra settlement.

example. The garden settlements are less advantageous on private land. On the State land, the organisation and size of the plots are approximately the same as on the town land. The settlement at Bergshamra is a particularly well-arranged settlement area on State land.

TRANSITIONAL AREAS.

There is a difference of opinion in Stockholm administration as to whether the garden settlements subserve purposes which are still

of importance and should accordingly be permanently included in the new social town plans, or whether they must be regarded as hindering the erection of dwellings habitable throughout the year and should therefore be abolished or continually moved out so as to keep them on the periphery of the town area.

Those who take the latter view have, *inter alia*, suggested that garden settlements should, in future, to a certain extent or without exception, be so laid out that the holders can convert them into cottage areas and erect new buildings suitable for permanent habitation throughout the year. These areas have been called transitional areas.

The idea is, as stated, that the settlers in these areas should have the right to erect in due course a permanent home of the cottage type. A cottage plot at present averages 500 square metres and a settlement plot about 300 square metres. Presumably, therefore, the plots in a transitional area would be between these two sizes. Hitherto, only one such area has been officially contemplated and is known as "Riksby B". It is said to consist of 390 plots of an average size of 450 square metres. New settlement areas have now been proposed to take the place of those that have been abolished. Some of them have been planned as transitional areas. Three of them have plots of an average of 370, 310 and as low as 300 square metres.

This proposal abandons the settlement idea. There is obviously no objection to such an intermediate form in addition to the garden settlement areas. But it must be made a condition that the garden settlements continue to have sufficient land of good quality and in a suitable position. They should not be hindered in any way by the new departure.

It would no doubt be the simplest and best way to plan each type separately for its own particular purpose. If a settler desires a home of his own on the rural estates, he will have to apply for a plot in an area set aside for the purpose. This is the present practice. Any person who removes to a cottage plot sells his allotment in a settlement to a family living in an apartment house and therefore requiring it. A transitional area presumably involves greater cost than a pure garden settlement area. This takes us a step along the by no means unfamiliar road of the increasing exclusion of the poorer classes.

All that is new in the proposal is that houses of the small cottage type are built on even smaller plots than hitherto. But should land be assigned to such schemes out of hand in order to bring the opportunity of possessing a separate home within reach of lower strata of the population? This is the question which should first be discussed. It would seem that the proposal might lead to a motley collection of buildings of an undesirable kind. A similar course, we are told, was tried in Denmark with poor results. Cottages packed close together like boxes are a sorry sight.

The stony wastes of the large cities will certainly exist for a long time to come. The main object of the settlements—namely, to supplement the wretched homes in the town—will subsist for as long. Settlement areas which turn into building areas are thus antagonistic to the underlying idea of the settlement movement. They are not genuine garden-settlement areas and at the same time represent a muddled form of organisation.

COMPENSATION FOR SETTLEMENT PLOTS, THE TENANCY OF WHICH HAS BEEN TERMINATED, OR WHICH HAVE BEEN ABOLISHED.

The settlement plots must give way for the construction of main roads. When the massed masonry of the city advances against them, they cannot withstand the encroachment, and this in itself is one of the reasons why settlements have to be abandoned.

The question then arises whether settlers should be granted compensation by the landowner. On this subject there are great differences of opinion in the Stockholm administration. In the proposal submitted to the town councillors in 1923, compensation was recommended. No decision has yet been taken on the subject.

This brings us to the historical problem: legal rights or justice. There is a temptation to interpret the laws literally. "Summum jus, summa injuria" was an acknowledged maxim of Roman jurisprudence.

The settlements represent a social institution which has a bearing on the housing question and public health. The town encouraged the movement by the leasing of land and other measures, and finally took over the administration. The settlers were entitled to believe that the public authorities would defend their own work and the achievements of individual sacrifice. For even the loans which

the town had granted for the settlements had in many cases been issued with an amortisation period longer than the duration of the leases.

The settlers thus possess a moral right to compensation and this is the highest legal right. Moreover, the amounts involved are small in comparison with other items of communal expenditure incurred for the advantage of the town population or certain sections of it.

The settlers are also warranted in making certain comparisons. When the commune enforces expropriation laws, repurchase rights or conditions for the withdrawal of building rights, full compensation is ordered. The settlers have no right to compensation under the law. They are compelled to take the land on the terms on which it is offered.

Some settlers receive their allotments as permanent property while others are compelled to give them up. Many of the latter obtain no compensation for the reason that, with that very object in view, the town gave them notice in proper time. Others obtain compensation because no obligation to vacate their plot is incumbent upon them at the particular time when the State thinks it requires the land. It does not appear to the writer that there is any sort of patriarchal justice behind such an arrangement.

The town which is built up on a mercantile system must obviously plead legal rights. The town built up on social principles cannot be unmindful of circumstantial justice, otherwise known as equity.

CONDITIONS FOR THE LEASING OF LAND.

When the garden settlements are allotted on a permanent basis, the conditions are important. A payment of 10 öre per square metre was fixed for certain settlers who had removed from a settlement area which had been abolished in the town. Other settlers pay 20 öre per square metre. In addition, there are administrative charges of 4 to 5 öre per square metre. The settlers have appealed against the payment of 20 öre, which, they state, is more than they can pay. They also complain that it is illegal to fix different payments for different settlers.

It is a very open question whether the land should be granted on a building lease or an ordinary lease. The former gives greater security as its duration may be for more than twenty-five years,

which is the maximum for ordinary leases. A building lease can also be given as security for a loan. On the other hand, building leases are likely to convert the property into independent estates with appreciating land values. In the case of building leases, the condition might therefore be inserted that the property should not be pledged as security.

One of the conditions in any case should be that the settler has a preferential right to a fresh lease at any future time. He should also be entitled to dispose of the rights of usufruct.

Opinions vary as to the method of administration. Some prefer the system of leases granted by the town to private persons, without any obligation to enter into a co-operative association (Malmö system). Others urge that the town should also lease plots direct to private persons, but that the latter must combine to form an association which is entitled to receive applications and to grant the right to allotments.

SUMMARY.

The conflict between the mercantile city and the social city still goes on, and the influx of newcomers is a source of trouble to both. The growth of the large town is fraught with danger.

The scientists' and politicians' one-sided zeal for large towns, industry, a growing population and national economic interests, should be subjected to careful examination and scrutiny. The politics of daily life neglect the relations between country and town, agriculture and industry, the increase in the population and the country's resources.

Last, but not least, this applies particularly to the relations between economic values and human values ; the question is, whether material advantage expressed in money at market rates is the most important factor in the social question, as modern statecraft is apt to teach, or whether the inner development of the personality, expressed in spiritual values which cannot be bought and sold, is equally a factor to be considered in dealing with the social question. The garden settlements represent a human value of this kind for the towns, and in particular for the large towns.

INVESTIGATIONS ON HEAVY MUSCULAR WORK

By

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1. INTRODUCTION.

A rapidly growing interest in athletic sports and games was apparent all over the world even before the great war, and in many countries support was given to such activities out of public funds, perhaps because it was hoped to obtain better human material for military service, or, more generally, because athletics were believed to improve the health of the people.

Since the war, sporting enthusiasm has grown to an extraordinary degree. The man who runs 100 metres in x seconds or throws a discus y metres is celebrated as a national hero.

One consequence of this popular interest is that the sums spent upon athletic sports have grown enormously. Public opinion demands that the clubs and organisations concerned shall be supported out of public funds. Very few people or authorities, indeed, venture to raise the question whether the money voted for athletics is well spent or the contrary.

Anyone who has been present at an international competition when the Marathon runners come in, and seen the runners draw themselves one by one across the line, drop down in a fit of hysterical weeping, be posed amid general applause before a camera and finally led away in a more or less miserable plight—anyone who has

witnessed such scenes may justifiably doubt whether such exertions improve the health of the runners, which is, of course, the final criterion for the value of athletic sports. As entertainment *only*, they scarcely deserve support out of public funds.

We wish to make it clear that we do *not* think it significant in this connection that occasional, even serious, accidents take place. It is in the nature of several sports to demand a certain amount of courage and involve a certain amount of danger. It cannot, for example, be counted seriously against football that the percentage of broken legs among football players is larger than among people remaining indoors. The pleasure, if nothing more, derived from the play more than counterbalances the risk. But it would be a serious indictment should it be the case that the players become less fit for their regular occupation than others who do not play, whether on account of chronic fatigue due to overtraining, or from some other cause, or if it should turn out that active sportsmen are more liable to heart failure, or other organic diseases, or to the complaints of old age. That would mean that, from the point of view of the community, the sportsmen were below par, and support out of public funds would be definitely against the public interest.

One would therefore expect that public authorities would have proceeded cautiously and required some evidence that the money spent upon athletic sports is really well spent. It is to be admitted, however, that such evidence, whether for or against, is difficult to obtain and may only gradually be forthcoming.

LINDHARD has repeatedly insisted that a comprehensive and critical study by statistical methods will be required finally to settle the problem whether the various athletic sports, as indulged in by single individuals, will in the long run be of mainly beneficial or mainly detrimental effect on the organism.

The materials for such a study are as yet scarcely available, but something can be accomplished even now by laboratory studies of the processes taking place in the organism under the heavy strain of athletics.

In view of the dogmatic dicta concerning the beneficial effects of athletics which have for many years been vouchsafed us, it is a remarkable fact that the processes taking place in the organism when subjected to maximal athletic strain are still largely unknown,

while the limits within which such strains can be imposed without undue risk are for that very reason not well defined.

It is evidently important to try and find out by systematic and carefully controlled investigation what does happen in the organism when subjected to maximal strain, what changes, both immediate and gradual, take place, what are the limits of safety and why they are there, etc.

The importance of such studies increases *pari passu* with the active interest in athletic sport itself, and is further enhanced by the information they will provide regarding the physical effects of hard manual labour, which is still a factor in certain industries.

Studies such as those outlined above must be carried out under well defined and controlled conditions, available only in laboratories, by persons well versed in the various complicated experimental procedures of modern physiological science.

The Health Organisation of the League of Nations, aware of the importance of the issues involved, appointed a number of experts who met in Copenhagen in January 1931. These included several physiologists who had contributed to the study of muscular work (DURIG, LILJESTRAND, LINDHARD, LOEWY). The meeting agreed to ask the Health Organisation to initiate and supervise a study of problems connected with the physiology of athletics and maximal muscular work. It was recommended :

(1) That investigations in different countries should be carried out as far as possible under similar and well-controlled conditions ;

(2) That the methods employed should conform to the exacting demands of modern physiology so as to ensure results from which general conclusions could be drawn.

As a practical solution, it was recommended that laboratories of acknowledged standard should be approached with a view to the investigations desired.

A study of the following functions, during and after maximal muscular work, was suggested : metabolism, respiration, circulation, blood, renal function, heat regulation and fatigue.

The Laboratories of Zoophysiology and of the Theory of Gymnastics in Copenhagen University have done work along these lines for

upwards of twenty years, but until lately the main interest of these laboratories has lain on muscular work of a moderate type. Shortly after the Copenhagen meeting, a unique opportunity presented itself of extending our studies to the heaviest type of work. Three young men, who were trained athletes and at the same time well versed in the experimental work concerned, consented to work in the above-mentioned laboratories for two years as experimenters and as subjects, thereby ensuring an amount of co-operation which could scarcely have been attained in any other way. A programme for the experimental studies proposed was accordingly drawn up and submitted to the Health Committee of the League of Nations, which was asked to support the work financially.

The main lines of the proposed investigation were the following :

1. A study of the alveolar air with analyses of CO_2 and O_2 , during very heavy work combined with an investigation of the possible effects of breathing oxygen mixtures on the circulation rate and the maximum output of work, and also with determinations of the diffusion coefficients of the lungs of the subjects.

It was considered probable that determinations of the oxygen content of the arterial blood during work would have to be carried out.

2. A study of the respiratory exchange and the R.Q. as compared with the values during rest. This was to form an extension of an investigation, formerly carried out by KROGH and LINDHARD, to muscular work of a much heavier type and should show what—if anything—is to be gained by a regulation of the diet. We propose further to study the effect of sugar—and possibly alcohol—administered just before or during the work. This study will include determinations of blood sugar (and blood alcohol) during the work and should throw light on the problem whether general fatigue can be brought about by a lowering of the blood sugar.

3. We propose, finally, to study the mechanism and after effects, including the circulation rate, of work continued for a long time each day under varied conditions of diet and supply of suitable foodstuffs just before and during the work.

Methods.

Special methods will be briefly mentioned in their place in the discussion of results, but we want to emphasise here certain general considerations which we hold to be very important :

1. When there is no special reason to the contrary, all experiments are made in the morning and with the subjects fasting, in order to obtain the most uniform conditions.

2. The muscular work is invariably carried out on the electric brake cycle ergometer described by KROGH, the subjects pedalling at a constant rate prescribed by a metronome. On this machine the work can be measured with great accuracy ; it can be varied within very wide limits, and it can be reproduced at any time with great precision, an essential point for the control of training and comparisons between different subjects.

3. All determinations and samplings referring to the working state are made while the work is actually in progress. The minute volume of the heart, pulse rate, blood sugar level, etc., change so rapidly on transition from work to rest that determinations just after work can never represent working conditions. It is necessary to make a sharp distinction between functions measured *during* work and *after* work.

2. THE HEAT REGULATION.¹

In previous studies by one of us (HOHWÜ CHRISTENSEN, 1931), it was shown that the body temperature during heavy muscular work may rise to definitely dangerous heights and may become one of the limiting factors for the continuation of work. The present studies demonstrate the existence of individual differences in the power of temperature regulation during work, differences which are inconspicuous during rest, but come out very clearly during work, when the quantity of heat to be eliminated is increased ten to twelvefold.

¹ Based mainly upon studies by M. NIELSEN.

Heat is eliminated mainly by radiation from the body surface, by convection and by evaporation of water. While radiation is, during rest, generally responsible for the major part of the heat loss, we find that, during work, the elimination through convection and especially through evaporation may be greatly increased. We cannot yet make up a *complete* balancesheet for the production and elimination of heat, though most of the material is available. Continuous records of rectal and skin temperatures are necessary for this, and a special technique has had to be worked out to determine the effective temperature of the radiating surface.

The following example will illustrate what has been accomplished. The three subjects *O.H.*, *O.B.* and *M.N.* perform work on the ergometer under exactly similar conditions, doing 1,080 kg.-m.-minute. *O.H.* works for 180 minutes, *O.B.* and *M.N.* for 160 minutes each. After an hour, the rectal temperature of *O.H.* has risen 1.85°C. from 36.80° to 38.65°C., and during the next two hours the temperature remains constant : equilibrium between production and elimination has been reached. Not so with the two others. The temperature of *O.B.* continues to rise during the period of work and is 39.10°C., corresponding to a rise of 2.14°C., when work is discontinued after 160 minutes. The rectal temperature of *M.N.* rises in two hours 2.87°C. to 39.70°C., and at this high level equilibrium is attained between heat production and elimination, the temperature remaining constant during the last forty minutes. The temperature of 39.7°C. is very near the limit which the organism will stand, and heat stroke would probably have supervened if the conditions for eliminating heat had suddenly become unfavourable —*e.g.*, by a rise in temperature or vapour pressure in the room.

The following figures from the heat balance can be given. *O.H.* produced in 180 minutes a total of 2,465 Cal. (calculated from the oxygen intake). Of these, 472 Cal. were converted into mechanical work, taken up by the cycle ergometer ; 107 Cal. served to heat the subject from 36.80° to 38.65°C. The remainder (2,465 - 472 - 107 = 1,886) the subject was able to eliminate ; 1,089 Cal. served to evaporate water. The subject lost 1,900 grammes of water and powerful fans secured the evaporation of the total perspiration directly from the skin. This corresponded to 956 Cal., while 133 Cal. were given off by evaporation from the air passages. Of the remaining 797 Cal. a small

fraction (about 6 Cal.) served to heat the inspired air (about 8,500 litres) and the remainder was eliminated by convection and radiation.

The heat loss (or gain) by radiation depends upon the temperature difference between the skin and the solid surroundings. It is increased by lowering the room temperature and by a rise in skin temperature. In the resting subject the skin temperature is increased when conditions demand by an increased blood flow through the skin, which can be heated in this way to very near the general body temperature. It was natural to assume that a similar increase would take place during heavy muscular work when the amount of heat to be dissipated was unusually large. The measurements show, however, that skin temperatures do not rise along with the rectal temperature during work. They may even become lower during heavy work than in rest. This is due partly to the cooling effect of the high rate of evaporation, but in part probably to the fact that the working muscles require all the blood they can get, and there is not enough left for a generous supply to the skin. The supply of oxygen is more important than the heat regulation.

The heat eliminated by convection depends upon the temperature difference between the skin and the air coming in contact with it, and, since the latent heat of air is small only, it is greatly increased by wind. In the experiments described the air temperature was kept constant at 19°C. and two powerful fans were employed to facilitate the heat elimination by convection and evaporation. In the example given above, 790 Cal. were eliminated by radiation and convection, and, of these, some 650 must be due to convection.

When the amount of work is increased further, the percentage heat eliminated by evaporation rises. In work of 1,800 kg.-m.-minute—approaching the maximum possible—the subject *O.H.* gave off 80 per cent of the heat by evaporation, and, of the 20 per cent remaining, the larger part was lost by convection.

We may sum up as follows : While during rest about 75 per cent of the heat produced in the body is eliminated by radiation and convection and 25 per cent by evaporation, the ratio may be reversed when the large amounts produced during work have to be eliminated.

Optimum conditions for strenuous athletic exercise include dry air in constant movement relative to the bodies of the athletes.

Sporting contests requiring long spells of strenuous exercise should not be held when the temperature and the percentage saturation of the air with moisture are both high. The danger of fatal increases in body temperature is in such conditions considerable.

3. THE RESPIRATORY METABOLISM.¹

The problem of determining the substances which serve as sources of energy for muscular work is of fundamental importance alike from a practical, nutritional and theoretical point of view.

The classical researches of ZUNTZ showed conclusively that fats and carbohydrates and not the proteins, as formerly believed, are the main sources of energy. Later KROGH and LINDHARD concluded from accurate determinations of the respiratory quotient before and during muscular work that fats and carbohydrates are utilised in very nearly the same proportions during work as in a previous period of rest, the actual proportion depending upon the available stores and, therefore, upon the proportions in the diet of the preceding period.

HILL and his school, on the other hand, conclude that the energy of muscular work is derived mainly from the combustion of carbohydrate.

One might expect the solution of this problem to be a simple matter, because—assuming constant protein metabolism—the respiratory quotient (R.Q.) will show the relation between fats and carbohydrates katabolised at any time in the organism. An R.Q. of 1.00 corresponds to a combustion of carbohydrate, of 0.71 to fat, and any intermediate value to the combustion of both in a proportion which can easily be calculated.

It is, however, by no means a simple matter to determine the true quotient of combustion during muscular work. The R.Q., as directly determined from the gas analyses, is a valid indicator only in so far as the CO₂ expired during a given period of time corresponds exactly to the CO₂ produced, which means that the large store of CO₂ always present in the organism must remain unaltered.

In the transition from rest to fairly heavy work and during the first minutes of such work, the store of CO₂ usually becomes more

¹ Based mainly upon studies by O. BÖJE and O. HANSEN.

or less reduced, more CO_2 being expired than is produced. This is shown by simultaneous determinations of the CO_2 in the blood, which decreases rapidly. In this period, therefore, the R.Q. found is too high and cannot give us any definite information concerning the character of the metabolism.

Further, it may happen that later in an experiment the quotient, as directly determined, may be vitiated by accidental changes in ventilation, which result in changes in the store of CO_2 in the body.

We have had these difficulties constantly in mind. We have closely followed the blood CO_2 , and endeavoured by our experimental technique to keep it as constant as possible, and the determinations from which our conclusions are drawn were all made during constant work after the known period of change in the store of CO_2 .

For the determination of metabolism and R.Q., two different techniques were utilised. In one, the subject respire through a mouthpiece and suitable valves, and the expired air is collected in large rubber bags (DOUGLAS). In the other, the head of the subject is enclosed in a helmet (BENEDICT) through which outside air is drawn at a suitable rate—reaching 1,000 litres per minute—by means of a large motor-driven gas meter. Gas analyses of special accuracy (KROGH), combined with the readings of the carefully calibrated meter, allow the determination of oxygen intake and CO_2 output, and, when the blood CO_2 remains constant, conclusions regarding the substances katabolised are valid.

Control experiments have shown that the DOUGLAS technique, to give reliable results, requires that the subjects should be specially practised, while the valves and tubing must be wide enough to give no perceptible resistance. Otherwise the type of breathing is often affected and the quotients distorted accordingly. Large series of comparisons have shown, however, that, with proper precautions, the technically simpler DOUGLAS method will give the same results as the more difficult helmet method, and this latter is therefore to be preferred only when quotient determinations of the highest possible precision are essential.

In experiments carried out by the methods described, only the CO_2 expired through the lungs is obtained. There is, however, according to some workers, a significant exhalation of CO_2 , also from the skin, especially when it is moistened by perspiration. Figures amounting to 5 per cent of the total CO_2 elimination have

been published, and, if these were correct, we would have to take them into account in our determinations of the R.Q., especially since there is general agreement that practically no oxygen is absorbed through the skin.

The published determinations are not, however, convincing, and we have therefore made special control experiments by means of a respiration chamber containing the subject working on the ergometer, while the breathing took place from and to the outside air through tubing and valves. At intervals during the work, samples for analysis were taken from the air in the chamber, and these experiments definitely established the fact that the CO_2 eliminated through the skin is insignificant in amount and need not be taken into account even in very precise determinations of the respiratory quotient.

As mentioned above, CO_2 determinations on the blood must be made regularly along with the respiration experiments proper to control the validity of the R.Qs. as determined from the expired air. These determinations were made as follows: The blood was taken from a finger after keeping the hand in water of 47°C . for at least five minutes. The heating produces a very pronounced hyperæmia and the "capillary" blood obtained in these conditions is practically identical with arterial blood with regard both to oxygen and carbon dioxide. The taking of samples during continuous work proved very difficult at first, but we finally succeeded by means of a technique introduced by the Groningen Institute of Physiology and suitably modified in our laboratories. The CO_2 determinations, requiring a blood sample of about 0.5 cc., were carried out according to a method worked out recently by KROGH and REHBERG.

The determinations show that a washing out of CO_2 —a depletion of the store carried by the organism which is many times larger than the quantity found in the blood—takes place as a rule during the first 10 to 15 minutes of work. In highly trained subjects doing light or moderate work this depletion is small and does not take long. With very heavy work in all subjects and on untrained subjects even with moderate work the CO_2 content of the blood may be reduced by about one-half. While this depletion takes place it is, of course, impossible to determine the true respiratory quotient. The CO_2 eliminated does not correspond to the quantity

produced. The figures found will be too high and may considerably exceed unity. All such values are spurious, and only when the CO_2 content of the blood remains constant—at any level—is the CO_2 expired equivalent to the CO_2 produced.

It will be convenient to discuss briefly at this point the possible mechanisms for the washing out of CO_2 , which takes place during the initial stages of work.

The CO_2 content depends upon two factors—viz., the pulmonary ventilation and the CO_2 capacity of the blood.

When the ventilation is increased without a corresponding increase in metabolism, the alveolar CO_2 tension will gradually become reduced, and more CO_2 will be given off from the blood to the alveolar air until equilibrium is reached at a lower level of CO_2 content.

A reduction of the CO_2 capacity of the blood will take place when other acids (*e.g.*, lactic acid) accumulate in the blood and take the place of carbonic acid in combination with the blood alkali.

Both these mechanisms may come into play during the first minutes of work. At the transition from rest to work the ventilation has to change from one level to another, perhaps ten to twenty times higher. While this change is in progress it is very usual, especially when the amount of work demanded is exceptional, to find that the ventilation rises considerably beyond the final level corresponding to the CO_2 production, and with fairly heavy work a considerable reduction of the CO_2 capacity will also take place during this initial period, because large quantities of lactic acid enter the blood from the working muscles. Simultaneous determinations of CO_2 and lactic acid have shown that the liberation of lactic acid is chiefly responsible for the reduction in CO_2 content, while over-ventilation plays in most cases the minor part.

Our determinations of the respiratory exchange and R.Q. on trained subjects doing *light* or *moderately heavy* muscular work agree completely with the views of KROGH and LINDHARD that the same proportions of fat and carbohydrate are katabolised as during the previous period of rest.

In *very heavy* work, on the other hand, a definite and real rise in quotient will take place as compared with the previous period of rest. The organism will utilise more and more carbohydrate to cover the energy requirements.

Comparing the R.Q. in two subjects, one trained and one untrained, doing the same fairly large amount of work, we find that the untrained will work on a higher quotient—that is, he will use more carbohydrate in proportion.

Such a comparison is valid only when the resting quotient is the same in the two and this can be accomplished by means of the diet. By suitable adjustment of the diet, we can produce variations in the R.Q. within wide limits from a little over 0.7 to very near 1.

Working near the limit of his capacity, any person will show a rise in quotient, indicating a relative increase in carbohydrate utilisation, from which it seems legitimate to conclude that carbohydrate is preferable as a source of muscular energy.

Several facts can be adduced as contributory to this preference on the part of the organism.

(1) Disregarding the points at issue between the various theories of muscular contraction, it seems fairly certain that carbohydrate transformations constitute an integral part of the chemical mechanism.

(2) KROGH and LINDHARD showed that about 10 per cent more energy was utilisable for work from carbohydrate than from fat, and our experiments fully bear this out.

(3) The caloric value of oxygen used for the combustion of carbohydrate is higher in the proportion of 5.0 to 4.7 as compared with the combustion of fat.

Points 2 and 3 indicate a reduction of about 15 per cent in the oxygen required for a certain amount of work when done exclusively on carbohydrate instead of exclusively on fat.

One might ask here : If it is so much cheaper for the organism to work on carbohydrates, why is this not done during light or moderate work ? The reason is no doubt this : If the organism utilised only carbohydrate in moderate work, the stores of glycogen in the liver and muscles would be exhausted. The total amount of energy available as glycogen is small compared with that stored as fat, and the stores of carbohydrate have the further function of maintaining the blood sugar at a suitable level, a function of paramount importance, since a reduction of the blood sugar below a certain level has very serious consequences, as will be shown below.

4. THE INFLUENCE OF DIET ON THE CAPACITY FOR WORK.¹

Detailed experiments were made to study the influence of the diet upon the amount of work performed. The three subjects *O.B.*, *O.H.* and *M.N.* lived alternately (1) on an ordinary mixed diet, (2) on a diet extremely rich in carbohydrate and poor in fat and, conversely, (3) on a diet very rich in fat and poor in carbohydrate. The quantity of protein was kept low in all diets, being generally between 50 and 60 grammes per day. The transition from one diet to another took place gradually to avoid digestive disturbance and the extreme diets were taken only for a couple of days at a time.

The capacity for work was studied by means of the cycle ergometer and, in order to minimise the effects of training which had been very troublesome in KROGH's and LINDHARD's experiments, the subjects had been training on the ergometer for a long time previous to this series of experiments. They worked during the experimental period either each day or on alternate days doing 1,080 kg.-m.-minute for one or two hours. On the last day of taking each diet, each subject would work at the same rate, but carry on for the longest possible period. Because these subjects were themselves very deeply interested in the experiments, it became possible to realise total amounts of work and degrees of exhaustion to which paid subjects would scarcely have submitted.

In accordance with some observations by KROGH and LINDHARD, we found a very pronounced difference in the capacity for work on the different diets. On a fat diet, the subject would be able by the utmost mental effort to carry on for about ninety minutes, when he would reach such a degree of exhaustion that he could no longer follow the metronome, and the rate of pedalling would slow down and become more or less irregular.

On a carbohydrate diet, on the contrary, the two subjects *O.H.* and *M.N.* were able to carry on for over four hours (at 1,080 kg.-m.-minute). When, finally, they had to give in this was not due to exhaustion of the same type, but to a gradually increasing stiffness in the muscles and joints. After such prolonged periods of uninterrupted activity, the joints, and especially the knees, seem to require some

¹ Based mainly upon studies by O. HANSEN.

rest, a fact which is not, perhaps, surprising considering the heavy strain to which they have been exposed.

Some explanation can be given why the capacity for exhausting work should be at a maximum after a diet rich in carbohydrate.

During work the organism will always—even at the lowest quotients—use up a certain amount of carbohydrate as shown by the following examples from actual experiments. In ninety minutes' work (1,080 kg.-m.-minute) on a fat diet, at an R.Q. of 0.745, 30 grammes of carbohydrate were katabolised.

On a carbohydrate diet the R.Q. was 0.900, and in ninety minutes 180 grammes of carbohydrate were katabolised.

The total amount of carbohydrate used up in four hours' work, during which the R.Q. would fall from 0.910 to 0.820, was 400 grammes.

When the stores of carbohydrate have run very low, the normal blood-sugar level cannot be maintained, and when the blood sugar (determined by the HAGEDORN-JENSEN method) falls to about 60 mg. p.c. hypoglycæmic symptoms usually become pronounced.

In one experiment on *M.N.*, the blood sugar after an extreme fat diet came down to about 40 mg. p.c. The symptoms were a feeling of ravenous hunger, exhaustion, tremor and cyanosis of the hands. Finally, when in spite of every effort it became impossible to pedal in keeping with the metronome, there were subjective visual phenomena and the mind became obscured. At this stage, the subject took in 100 grammes of glucose, continuing work all the time. During the first minutes no effect could be observed, but in ten to fifteen minutes the hypoglycæmic symptoms, including the exhaustion, disappeared, and the subject was able to work for sixty minutes more and to finish without being absolutely exhausted.

In all these experiments, not only the blood sugar, but also the respiratory metabolism was determined at suitable intervals, and it will be convenient here to discuss the change in metabolism during such a spell of work. We select a couple of experiments on *M.N.* and begin with an experiment after an extreme carbohydrate diet in which the R.Q. during rest was at 0.93. The subject had been working every day on the ergometer, and it is interesting to note that, when this is done, we have not found it possible to obtain quotients above 0.94. Higher quotients were obtained, however, when the subject was allowed a rest of one or two days.

This can mean only that the daily period of work prevented the complete filling up of the glycogen stores.

In the experiment under discussion, the work was done at first with a slight change only in the R.Q., which decreased from 0.93 to 0.90. The work was carried on by combustion of fat and carbohydrate in nearly the same relative proportions as during rest, but at a greatly increased rate, corresponding to an oxygen intake of 2.5 litres per minute.

During the four hours' work, a slow rise in metabolism and a gradual decrease in R.Q. was observed. The rise in metabolism is due apparently to : (1) the rise in body temperature, which automatically increases metabolism, (2) the decrease in quotient, and (3) the increasing fatigue which will cause the subject to use fresh units of musculature which are less suited to the task in hand.

The decrease in R.Q. means that, as the work progresses, more and more of the energy is derived from fat. The organism does not spend freely from the carbohydrate stores, but appears to save them up as much as possible. In this experiment, the R.Q. went down during the four hours' work from 0.90 to 0.80.

In experiments on a fat diet we have observed a characteristic difference between two of our subjects. One (*O.H.*) will show from the start a very low R.Q. (0.75) and thereby save his carbohydrate stores as much as possible. The other (*M.N.*) will start work on a much higher quotient (0.82), which results in a rapid fall of the blood sugar.

As mentioned above, a dose of glucose was given in such an experiment during the work. This caused the blood sugar to rise promptly, reach the resting level in ten minutes and continue to rise considerably above that. It is a remarkable fact, however, that the muscles did not, at least during the sixty minutes through which the determinations of metabolism were continued, show any definite utilisation of the sugar ingested. The R.Q. kept on falling for twenty minutes, in spite of the rise in blood sugar, indicating an increasing utilisation of fat, and did not in sixty minutes reach the value observed before the sugar was given.

This result, which was confirmed in other experiments, is of considerable theoretical significance. It seems to show that the muscles are unable directly to utilise the glucose circulating in the blood, which will probably have to undergo some conversion, perhaps

to glycogen. It shows, further, that the beneficial effect of the sugar is not brought about through metabolic changes, but depends probably on conditions in the nervous system. Just as the normal function of the central nervous system requires a certain fairly high oxygen tension, there appears to be a certain critical blood-sugar level for the higher nervous functions.

A further point of considerable importance was revealed by continued experimentation with the fat diet. When the resting quotient was brought down to a low level by several days on fat, and work was performed on a few days in succession, the resting quotient would remain constant, while the R.Q. during work would begin by being a few units higher and decline day by day towards the quotient during rest. This must mean either a gradual adaptation to the peculiar dietary conditions or a progressive exhaustion of the carbohydrate stores of the organism.

The practical results of our studies on the influence of the diet on muscular work can be summarised as follows :

Trained subjects will do light and moderate work by katabolising both carbohydrate and fat in proportions determined by the preceding diet and nearly the same as during rest. In heavier work an increasing percentage of carbohydrate is katabolised. The reason for this appears to lie in a better utilisation of carbohydrate and a higher caloric value of the oxygen utilised for carbohydrate combustion compared with fat combustion. The oxygen requirement is reduced by 15 per cent, and this in its turn reduces the strain on the heart.

When long-continued severe work is to be performed the preceding diet must provide ample energy, mainly in the form of carbohydrate, to fill up the stores of glycogen. When the absolute maximum of work is to be attained—*e.g.*, in sporting contests—about two days' rest is required to secure a complete filling up of the glycogen stores, and it appears that this cannot be done by taking large amounts of carbohydrate just prior to the work.

In athletic sports requiring long continued severe work, the same person ought not to take part in several contests in immediate succession, but periods of two days' rest ought to be interposed. This holds, of course, also for games like football, where the rule is often disregarded to the certain detriment both of players and of play.

5. THE BLOOD SUGAR DURING WORK.¹

As mentioned above, the blood sugar was closely followed in a large number of experiments.

A short spell of light work does not produce any significant change in the blood-sugar level, while a short spell of maximal work will sometimes produce a fall, sometimes a rise. As a rule, a rise is observed just *after* the work, but we have found no relation either between the blood-sugar values and the power to perform maximal work of short duration or between fatigue and blood sugar.

During prolonged work, of such severity that trained subjects are able to continue for some hours (about 1,000 kg.-m.-minute), a gradual fall in blood sugar will usually begin after one or two hours. As mentioned above, we correlate this fall with the gradual depletion of the glycogen stores, because we find it to begin earlier when these are known to be small. In work of this type a definite correlation is observed between the subjective symptoms of fatigue and the blood-sugar level. This level can be raised by taking sugar, and simultaneously the symptoms will disappear and the power for work become definitely increased.

The HAGEDORN-JENSEN method for blood-sugar estimation employed by us determines, like most other methods, the reducing substances in the blood after removal of the proteins. Glucose is certainly the main reducing substance, and it is generally assumed that the residual reduction due to other substances amounts only to about 5 per cent. Recent investigations put the residual reduction at a much higher level, even up to 30 mg./p.c. Should this turn out to be the case and the high figures be valid also for our experiments, our low values of 50-40 mg./p.c. would indicate extremely low concentrations of glucose. It has therefore been decided to make a special investigation of the residual reduction during rest and work.

¹ Based mainly upon studies by O. BOJE.

6. THE LACTIC ACID IN THE BLOOD.¹

Being closely related both to the metabolism of muscles during work and to carbohydrate metabolism, lactic acid is of interest in the present study, and, in many of the experiments, serial determinations of blood lactic acid were therefore made. New methods, based mainly on the work of WIDMARK and ÖRSKOV, in which "capillary" blood was utilised, had to be worked out, because those generally accepted, requiring large amounts of blood, were not available when the subject was doing heavy work.

Working on "capillary" blood it became possible to follow the changes in lactic acid through every stage of severe work; new and rather surprising results have thereby come to light.

1. In moderate work, which the subject is fully able to perform for a long time without fatigue, lactic acid shows a sharp rise during the first five to ten minutes and then a gradual decrease going on until the resting level is reached.

2. In heavier work, we also find the sharp rise and gradual fall; but when fatigue sets in there is a secondary, somewhat irregular, rise.

3. In very severe work, which the subject is unable to continue for any prolonged period, lactic acid continues to rise throughout.

4. The decline in lactic acid found in moderate work is independent of the work. If the work is discontinued the decline goes on just as before. This points to the initial increase as due to causes which act only during the initial stage, and most probably to an insufficient supply of oxygen during this stage, for which there is other independent evidence.

The secondary rise, observed in heavier work when fatigue begins, may possibly be due to fresh groups of muscles taking over part of the work. When fresh muscles are deliberately set in action, a rise in lactic acid has been demonstrated.

5. The maximum lactic acid concentration reached depends upon the severity of the work, but is independent of the duration or the total amount of work.

¹ Based mainly upon studies by O. BANG.

The rise in lactic acid brought about by work of definite severity (kg.-m.-minute) becomes less for the subject in better training, and this holds both in comparisons between different subjects and for the same subject before and after a period of training.

6. In experiments of short duration some relation appears to exist between the rise in lactic acid and fatigue, but in prolonged work the rise in lactic acid as a cause of fatigue can be definitely ruled out.

There seems to be some relation between the point of time in the work when lactic acid begins to decrease and the so-called "second wind", but no causal relationship can be established as several changes take place at that time.

7. THE RESPIRATION.¹

It was mentioned above (section 4) that the respiratory metabolism during prolonged muscular work shows a gradual rise, even when the external work per minute is kept absolutely constant. This rise we expected to account for (1) by a rise in body temperature causing increased standard metabolism, (2) by a decrease in R.Q., which reduces the coefficient of utilisation, (3) by an increase in ventilation causing increased work for the respiration muscles and (4) by fatigue which will bring new and less efficient muscles into play.

1. Special experiments to study the relation between standard metabolism and body temperature show a rise of about 8 per cent for 1°C. increase in body temperature. These determinations were carried out during absolute rest, and the heating of the body was brought about by universal diathermy. In the work experiments, body temperature was recorded throughout, and we are able, therefore, to calculate the resulting rise in metabolism—on the assumption that the mechanical efficiency of the work is not affected by the temperature changes.

2. From the decrease in R.Q. we can calculate the increase in metabolism due to the increased proportion of fat katabolised,

¹ Based mainly upon studies by M. NIELSEN.

the net efficiency on carbohydrate being 10 per cent better than on fat.

3. The information available in the literature, especially the study undertaken by LILJESTRAND, shows that an increase in ventilation will give rise to an increase in metabolism due to the work of the respiration muscles.

The "cost of ventilation" does not increase in strict proportion to the ventilation, but an increase of a certain magnitude (litres per minute) will cost more when the rate of ventilation is high beforehand. We were unable to obtain the absolute figures required in our work from LILJESTRAND'S experiments, because most of these were made on one single subject having a rather small vital capacity. It is natural to expect that the vital capacity will be an important factor in connection with the cost of ventilation, especially at high rates. We therefore found it necessary to make new experimental determinations of the cost of ventilation.

Experimental determinations of the cost of ventilation are made by producing isolated variations in ventilation and making simultaneous determinations of metabolism. When we have changes in ventilation alone, the changes in metabolism observed must be a measure of the cost of the ventilation differences.

Variations in ventilation were produced by adding CO_2 to the air inspired. Each experiment begins with a determination of the standard metabolism of the subject made by the DOUGLAS method with inspiration of pure air. Next, the subject is supplied with a mixture of CO_2 in air from a large spirometer. This increases the ventilation more and more with rising CO_2 percentage up to about 10 per cent. Any further increase reduces the ventilation, probably on account of a narcotic effect on the respiratory centre. When the ventilation has become constant, corresponding to the CO_2 percentage supplied, one or more determinations of respiratory metabolism are made and will give higher figures for the oxygen absorption than the standard, and, since we may assume that CO_2 in the concentration employed does not affect the tissue metabolism, the increase can be taken as a measure of the cost of increased ventilation.

This technique may appear simple, but, in reality, it is very difficult to obtain reliable determinations, especially for the smaller rates of ventilation and for slight increases in these, mainly because

the differences to be measured are extremely slight and the accuracy of the determinations must be correspondingly great. On highly practised subjects and by a very careful technique, we have succeeded nevertheless in determining the cost of ventilation during rest and even during muscular work.

The determinations during work are made in the same way as during rest, with the difference only that the subject is performing work at a constant rate all the time.

Determinations were made on five subjects having vital capacities from 3.1 to 5.3 litres.

It turned out to be impossible to increase the ventilation beyond 60-70 litres per minute by means of CO_2 , although several of the subjects reached ventilations of 100-120 litres per minute during heavy muscular work. The mechanism of the increase during work is not simply an increase in CO_2 but, as maintained long ago by KROGH and LINDHARD, is partly brought about by an increase in the sensitivity of the respiratory centre, for which the central nervous system seems to be mainly responsible.

The four subjects having vital capacity of 4.5 to 5.3 litres show practically the same "cost" for the same ventilation, but for the one with a vital capacity of 3.1 litres the cost is greater. For the subjects studied, the cost is, on the whole, independent of the depth or rate of respiration, and is determined by their product, the rate of ventilation (litres per minute) exclusively.

When the respiration becomes very deep, however, approaching the figure for the vital capacity, the cost becomes increased with depth.

The cost of ventilation in normal quiet breathing (5-10 litres per minute) during rest is very small, and we can confirm LILJESTRAND'S determinations of 0.5 cc. O_2 per litre or 1.4 per cent of the standard metabolism. When the ventilation is increased to 60 litres per minute the cost per litre is about 1.7 cc. O_2 .

During work on the ergometer, the cost of ventilation, measured at the same rate, is somewhat greater than during rest and may reach 2.3 cc. O_2 per litre for a ventilation of 60 litres. This is probably due to a certain fixation of the thorax caused by the pull of muscles from the arms.

When the work increases, the cost of ventilation becomes an increasing percentage of the total metabolism, and in maximal

work it approaches 10 per cent of this total. It is, therefore, a factor of considerable importance in the total metabolism during work.

In all the experiments the rate and depth of respiration have been spontaneously adopted by the subject, and we find that our subjects, when starting on *light* work (700 kg.-m.-minute) will mainly increase the depth of respiration. This depth will then be approximately maintained even up to very large ventilations, which are brought about chiefly by increasing the rate. The depth of respiration adopted during work seems to be "optimal" and to depend upon the vital capacity of which it is from 40 to 60 per cent.

When the depth is increased further, the cost of ventilation is definitely increased. The adoption at once of the optimum depth reduces the cost by reducing the influence of the "dead space" of the air passages and thereby reducing the total ventilation necessary.

A single example may serve to illustrate how the increase in metabolism in an experiment of long duration is brought about. The metabolism of the subject *M.N.* rose from 13.0 Cal. per minute in the thirtieth minute of work to 13.8 Cal. 100 minutes later, a rise of 0.8 Cal. per minute. The increase in body temperature will account for 20 per cent of this (0.16 Cal.). The decrease in quotient (increasing combustion of fat) covers 35 per cent (0.28 Cal.), and 10 per cent (0.08 Cal.) is due to increased cost of ventilation. The remaining 35 per cent (0.28 Cal.) we must put down as due to "fatigue".

The mechanism of the large increase in ventilation during muscular work is still an open problem. According to one view, the ventilation is regulated through the p_{H^+} of the blood; while, according to the other, the CO_2 tension of the blood is the main stimulating factor.

We have a number of experiments showing that neither of these factors will explain the actual increases in ventilation during work. One of us (LINDHARD) has shown that it is possible to express quantitatively the change in sensitivity of the respiratory centre which we find it necessary to postulate, and with this as the starting-point a renewed study is in progress.

8. THE OXYGEN SUPPLY IN WORK OF MAXIMUM INTENSITY.¹

In work of maximal intensity, the oxygen supply becomes the limiting factor for the duration of the work. An insufficient supply leads to an accumulation of lactic acid in the working muscles, which may be the factor immediately responsible for putting a stop to the work.

The factors influencing the oxygen supply are mainly the following: (1) the pulmonary ventilation, (2) the rate of diffusion of oxygen from the alveolar air to the blood, (3) the minute volume of the heart, (4) the rate of blood flow through the muscles, and (5) the conditions for O₂ diffusion from the muscle capillaries to the tissue.

1. In maximal work, the ventilation in our trained, athletic subjects will rise to 100-120 litres per minute. The upper limit attainable during work on the ergometer seems to be 120 litres per minute. Should this ventilation be insufficient to maintain a normal oxygen tension in the alveoli, it must be considered as a limiting factor for the work; but *whether* such a condition is practically possible we are at present unable to decide. There is no doubt, however, that ventilation at such a rate produces a subjective feeling of heavy strain and is very fatiguing. When the ventilation can be reduced below 100 litres per minute, a definite feeling of relief is brought about. Such a reduction can be effected by breathing an oxygen-rich mixture as observed in work experiments with breathing of 45 per cent oxygen which caused a very definite relief.

2. The rate of diffusion from the alveolar air to the blood depends upon the mean difference in the tension of the gas in question between the blood and the alveolar air, on the diffusion coefficient, and on the total area of the alveolar membranes. The individual "diffusion constant" was defined by A. and M. KROGH as the number of cubic centimetres of a gas which will diffuse from the alveolar air into the blood per minute and per millimetre tension difference. The diffusion constant can be determined for carbon monoxide, and the corresponding diffusion constant for oxygen is calculated on certain assumptions which, though probable, have not so far been definitely proved.

¹ Based mainly upon studies by O. BÖJE, O. HANSEN, and M. NIELSEN.

The studies of M. KROGH showed that the diffusion constant is higher during work than in the resting condition, and we have repeated these experiments and extended them to higher rates of work in order to obtain information concerning the very high oxygen absorption found in maximal work.

The results obtained confirm those of M. KROGH, showing (1) that there are large individual differences with regard to the diffusion constant during rest, while the same individual will show little change even over a period of many years ; (2) that the diffusion constant increases with increasing rates of work, probably in relation to the increased circulation ; (3) that the maximum oxygen diffusion calculated for a normal pressure and composition of the inspired air is about 5 litres per minute and that this would involve a definitely incomplete saturation of the arterial blood with oxygen. The maximal absorptions directly observed are from 4 to 4.5 litres per minute and it was natural to assume therefore that an increase in O_2 tension might increase the absorption of oxygen and render possible even higher rates of work.

Experiments to settle this problem have been made before ; we refer especially to those undertaken by A. V. HILL and his collaborators. These workers found a very definite increase in the maximal O_2 absorption when the subject breathed 50 per cent oxygen instead of atmospheric air. In our opinion, HILL's experiments are not quite conclusive, and they cannot be reproduced, because no measurements were made of the work performed.

We therefore considered it necessary to undertake renewed experimentation on this problem. Our preliminary experiments yielded the following results :

1. The O_2 absorption and the rate of maximal work can be increased by breathing 45 per cent oxygen.

2. As shown before by LINDHARD, the " oxygen " respiration reduces the rate of ventilation, which may go far to explain the increase in rate of work through the reduced cost of ventilation and the subjective feeling of diminished strain.

3. *The effect of oxygen does not become apparent in very brief spells of work of one minute or less, but in work which can be kept up for two, three or more minutes.* The explanation of this rather surprising result appears to be that it takes two minutes or more for the circulation rate to become maximal, and up to that time

the circulation rate constitutes the limiting factor for the supply of oxygen to the tissues.

4. *The maximal oxygen absorption both on air and on "oxygen" is obtained when the subject starts doing submaximal work.*

When, for instance, *O. II.* begins work at 1,700 kg.-m.-minute and works at this rate for five minutes the oxygen absorption will be just under 4 litres per minute. The work is now increased to 2,000 kg.-m.-minute and the O_2 rises to 4.6 litres per minute. In a final spurt the rate is increased to 2,500 kg.-m.-minute and the oxygen will get above 5 litres per minute. When starting at 2,000 kg.-m.-minute, *O. II.* is able to work at this rate only for about two minutes before he has to stop, absolutely unable to carry on. The reason is that in the two minutes the circulation rate cannot become maximal, and the lack of oxygen in the muscles has become so serious—probably much lactic acid has been produced—that the muscles are unable to function. When, on the other hand, work at a somewhat slower rate has allowed the circulation to get into full swing an adaptation to increased demands can take place with greater rapidity, and the oxygen supply can become sufficient before the subject has to stop.

5. The respiratory quotient in severe work is lower on 45 per cent O_2 than on air.

This point is of considerable importance theoretically. We have pointed out that the R.Q. increases with increasing rate of work above a certain rate and that, other things being equal, the trained subject will work at a certain rate on a lower quotient. These points, taken in combination with the oxygen effect upon the R.Q., indicate a close relationship during heavy work between the supply of oxygen and the substances katabolised to supply energy. When the oxygen fails, the organism has recourse to carbohydrate. We have shown that the combustion of carbohydrate results in a higher efficiency because the caloric value of oxygen is then at its maximum.

The experiments on the influence of oxygen upon the capacity for maximal work are to be continued. The results require some further control, and experiments are to be made with lower oxygen concentrations.

9. KIDNEY FUNCTION AND MUSCULAR WORK.¹

It is well known that even perfectly healthy athletes may have albumen in their urine after strenuous exercise. This indicates that maximal work must have some disturbing influence upon the function of the kidneys. In spite of its importance, systematic experiments dealing with this problem are lacking. Most observers have examined the urine only after the cessation of work. It seemed valuable, therefore, to include renal function in our study of the effects of muscular work on the organism.

Our investigations take as their starting-point the filtration-reabsorption theory of renal function proposed by CUSHNY and further elaborated especially by REHBERG.

According to this theory, a very copious filtration from the blood takes place in the kidney glomeruli. The filtrate is blood plasma minus the colloidal proteins. The quantity of filtrate, which can be measured independently of the quantity and concentration of the urine, will increase with a rise in blood pressure and become diminished by a rise in the colloid osmotic pressure of the blood. Any considerable decrease in the circulation rate through the kidneys will reduce the rate of filtration.

The filtrate passing through the renal tubules is concentrated by active reabsorption of most (99 per cent) of the water and finally leaves the kidneys as urine, from which also the so-called threshold substances, including sugar, are removed by active reabsorption, while substances such as creatinine and urea are not absorbed. The total amount of creatinine present in the filtrate is retained in the urine, while the final quantity of other substances, like urea, is reduced by diffusion back to the blood through the somewhat permeable walls of the tubules.

The diffusion of urea depends upon the concentration difference set up between the urine and the blood and upon the permeability of the tubules for urea. When for some reason the urine becomes highly concentrated by absorption of water, a large quantity of urea will diffuse back into the blood.

¹ Based mainly upon studies by F. GRANDE COVIAN.

Applying the theory briefly summarised here to the conditions during work and comparing always with conditions during rest we have found the following :

Filtration (F) is maintained unaltered during work up to about 1,000 kg.-m.-minute. At higher rates of work, the F values show a rapid decline. At 1,620 kg.-m.-minute F was found to be only 35 per cent of the resting value. During restitution, F rises rapidly to the resting value or even somewhat above.

Diuresis (D) decreases greatly with increasing work and was in one experiment at 1,620 kg.-m.-minute found to be only 20 per cent of the value during rest. During restitution, also, D is lower than before work. The fall in diuresis finds a natural explanation in the loss of water by perspiration stimulating tubular reabsorption. During work of 720 kg.-m.-minute, *O.H.* lost 400 cc. of water per hour by evaporation, and during work of 1,800 kg.-m.-minute the loss amounted to 1,100 cc. per hour.

The elimination of urea decreases with an increasing rate of work. At 1,620 kg.-m.-minute only 20 per cent of the excretion during rest was observed. We had to expect—according to our theory—that the urea should show a decline corresponding to the increase in urine concentration. A quantitative calculation, however, shows the urea elimination to be even lower than can be accounted for by the increase in concentration. This is taken to mean that something has happened to the walls of the tubuli, increasing their permeability to urea.

The reason for increased permeability might be lack of oxygen in the kidneys. Several observations, and especially the large fall in filtration rate, point to a reduction in the blood supply to the kidneys when the work becomes heavy. Lack of oxygen in some of the glomeruli may also be responsible for the albuminuria of heavy work by increasing their permeability. Albuminuria is produced only at high rates of work—in our trained subjects above 1,500 kg.-m.-minute. This probably means that at these rates the supply of blood to the kidneys, which is normally very high, becomes reduced in relation to the demands of the working muscles.

The sweat excreted during work will contain from 300 to 600 mg. urea per litre and will therefore compensate to a considerable extent for the decrease in excretion of this substance through the kidneys. In our experiments the blood urea remained practically at the normal level during the long periods of work.

From the above it is concluded that kidney function is distinctly affected by muscular work, but seriously affected only when the work is very heavy.

10. TRAINING AND FATIGUE.

On the basis of the studies here recorded and certain earlier investigations carried out in our laboratories, we are able to make a few suggestions for the rational training of the human organism to perform heavy or maximal muscular work.

From the point of view of training we have to distinguish between brief spells of maximal effort and work which is to be sustained during prolonged periods.

For *maximal efforts*, during, say, three to four minutes, a maximal efficiency of the respiration and circulation systems is of prime importance, on a par with the muscular force itself. In individuals in perfect health, the simultaneous development of these functions can be attained by rational training.

The essential point is to increase the demands on the organism steadily, but not too rapidly. Only in this way can circulation and respiration be developed *pari passu* with the muscles directly concerned in the work.

The training effect manifests itself in an increase in muscular force, a slowing of the pulse rate and deep and slow respiration. The slow pulse is correlated with an increase in size and weight of the heart, which adapts itself by growth to *increasing* demands, but stops growing on constant demands.

When we remember that in maximal work each half of the heart has to deliver at least thirty litres of blood per minute as against four during rest, it is easy to understand that such heavy demands cannot be met without careful preparation.

The vital capacity of the lungs becomes increased during training.

In long-continued training on short spells of maximal work the organism develops a power of rapid adjustment of ventilation and circulation as expressed by the absorption of oxygen, which will rise abruptly to the maximum level.

During the period of training, intermissions of two or more days should be frequent. In some of our experiments the subject did maximal work for one minute a day for several days in succession

resulting in a decline of the amount of work performed. This "negative training" effect was evidently due to imperfect restitution in twenty-four hours after one minute *maximal* work. Similar observations were made also on five- to eight-minute spells of work.

The character of the diet is not, apparently, of any importance. On any diet a surplus of carbohydrate will be available for a short spell of maximal work.

Training for *heavy work of several hours' duration* involves different considerations.

For long-continued work, the preceding diet is very important. Effective work at the lowest cost to the organism can be done only on well-filled carbohydrate stores, as obtained by a diet rich in calories and carbohydrate. In the last few days before an athletic contest, heavy work should be avoided to allow the maximal filling of the stores.

In training, not less than in contests, regard should be paid to the external temperature and especially to the moisture of the air, because work in hot and moist air may easily cause a dangerous rise in body temperature.

During a period of training, the rate of work should occasionally exceed that demanded in the contest in order to train the heart and respiratory organs to become superior to the final demands and thereby provide a margin of safety.

The limiting factors so far brought to light for long-continued heavy work are high body temperature and low blood-sugar values, but there is no doubt that other factors also come into play, such as "fatigue" in the central nervous system and various processes occurring in the muscles and articulations.

Training carried out with due precautions does not appear to present any danger to the healthy organism. The experience of the athletic world shows, however, that an athlete can remain at his best only for a very brief space of years.

With increasing age and at a comparatively speaking very early age the maximum achievement is reduced.

Those athletes who never attain to the first rank within their branch of sport will have to content themselves with the personal pleasure derived from the sport and with the feeling of well-being which should be the corollary of every rational form of athletics.

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INTERNATIONAL STUDY OF THE STATISTICAL RESULTS OF RADIOLOGICAL TREATMENT OF CANCER OF THE UTERUS

Report of the Conference of Experts

Held at Zurich, July 21st-23rd, 1934.

PRELIMINARY NOTE.

In 1928, the Health Committee's Cancer Commission, as it existed from 1924 to 1930, was called upon to consider a proposal that an international study be made of the radiotherapy of cancer. With this object in view, a Sub-Commission of radiotherapists and gynaecologists was set up under the chairmanship of Professor Cl. REGAUD.

The reports of this Sub-Commission, published in 1929 (document C.II.788) dealt with the question of uterine cancer. Definitions were given for the four stages into which cancer of the cervix uteri should be classified when the results of radiotherapy are assessed or tabulated—definitions which have since been widely adopted. The Sub-Commission recommended that the Health Organisation should collect data from leading radiotherapeutic institutes and clinics in various countries. If these data were to be of use, it was essential that they should include a record of the after-histories of the treated cases, for a period of years. The Sub-Commission considered that five years was the desirable minimum and that, at the date of its report, there was therefore no immediate need to enter fully into the question of tabulation and presentation of the results.

In October 1933, the Health Committee, on the advice of its Bureau, decided to convene former members of the Radiological Sub-Commission and a number of other experts, who have taken part in the work since

1929, in conference at Zurich on the occasion of the International Radiological Congress held in that city in July 1934.

The Conference was asked to review the progress of the enquiry, as set forth in the documents previously circulated, and advise as to the lines on which further action should be pursued. The Health Committee requested its Vice-President and rapporteur on cancer, Sir George BUCHANAN, to preside over this Conference, which sat from July 21st to July 23rd inclusive, immediately before the opening of the Congress, and was attended by :

Sir COMYNS BERKELEY, Radium Centre, London County Council ;
 Dr. E. BERVEN, Radiumhemmet, Stockholm ;
 Professor G. FORSELL, Radiumhemmet, Stockholm ;
 Dr. J. HEYMAN, Radiumhemmet, Stockholm ;
 Dr. J. W. F. HEUKENSFELDT JANSEN, Institut du Radium,
 Amsterdam ;
 Dr. A. LACASSAGNE, Institut du Radium, Paris ;
 Professor J. MURDOCH, Centre anticancéreux de l'Université libre,
 Brussels ;
 Colonel A. B. SMALLMAN, Ministry of Health, London ;
 Professor A. H. M. J. VAN ROOY, Wilhelmina Gasthuis, Amsterdam.

Professor REGAUD was unfortunately prevented from being present at the Conference and at the International Radiological Congress.

The first act of the Conference was to pay a tribute to the memory of Madame CURIE, whose death is so greatly mourned by the whole scientific world and by all those who have benefited from the discovery and therapeutic use of radium.

Turning then to the business on its agenda, the Conference began by considering the question of maintaining the classification by stages of cancer of the cervix uteri, as laid down by the Sub-Commission in 1929. On this point, a draft prepared by Professor VAN ROOY was adopted and its terms embodied in the recommendations.

The Conference then examined the question of the rules for the tabular statements it had decided in principle to recommend, and instructed a small committee, under the chairmanship of Dr. LACASSAGNE to work out the details. Its findings were similarly embodied in the report of the Conference, which has now been forwarded to the Health Committee.

RECOMMENDATIONS OF THE CONFERENCE.

1. The Health Organisation should for the present limit its collection of statistical data to cancer of the *cervix uteri*. Consideration should be given at a later stage to the need for including in the statistical presentation of results data relating to the body of the uterus and vagina. Consideration should similarly be given to the application of the system followed in the case of cancer of the cervix to cancer of other sites, beginning where possible with definition of stages of cancer at those sites, as has been done for the cervix.¹

2. The Health Organisation should aim at producing annual statistical statements regarding five years' results (and possibly results for later years) of radiotherapy of cancer of the cervix. An agreed table for this purpose, which may be termed the "Survival Table", is annexed, with relevant notes.

As is shown below, the work put in hand by the Health Organisation, and by those who have collaborated with it since the report of the Radiological Sub-Commission of 1929 was made, will permit a statistical statement to be made in 1936 in respect of cases whose treatment began in 1930. Attention can then be given to cases whose treatment began in 1931, 1932, 1933 and 1934 respectively and statements regarding them can be prepared annually between 1937 and 1940. It is well, however, to envisage this system of regular annual statistical statements without fixing a date at which they will necessarily end. If the utility of the earlier annual statements is established, the system can readily be applied in subsequent years.

¹ As to the definition of stages of cancer of the cervix, the Conference is of opinion that, for the purpose of statistical statements regarding the results of radiotherapy—and radiotherapy is used here to cover röntgentherapy, etc.—:

- (a) The subdivision into four groups should be maintained for the enquiry begun in 1930;
- (b) The advisory body referred to on page 4 should in a few years consider whether that subdivision should be revised, either in the light of the experience gained in the enquiry or in consideration of new scientific knowledge;
- (c) Cases in which the primary origin of the cancer (*corpus uteri*, or *cervix uteri*) is doubtful should be dealt with separately and a statement relating to them should be added to the form, and their numbers given.

3. The annual statistical statement would comprise statements supplied :

- (a) By the "national correspondents" of those countries in which information from the most important institutes can be effectively collected and submitted by a single correspondent ;
- (b) Where that is not possible, or in special circumstances, by an "institutional correspondent".

4. The Health Organisation should take the further steps necessary to arrange for the effective collaboration of national and institutional correspondents on this basis. To aid it in the preparation of its annual statistical statement, and for other purposes referred to below, the Organisation should obtain the aid of a small body of experts.

It will be remembered in this connection that the institutes and administrative officers who have been collecting material for the Health Organisation of the League during the past three years have done so in consequence of the decision of the then Health Committee to give effect to the scheme proposed by the Radiological Sub-Commission in its report of 1929. But in 1930, when a new Health Committee was appointed, the work recommended on the expert authority of the Radiological Sub-Commission had been started and it was not thought necessary to re-nominate that Sub-Commission, particularly since its parent body, the Cancer Commission, was not being re-appointed. It seems essential, however, that at the present stage, if the proposal of this Conference for continuous annual statistical statements is adopted, the Health Organisation should possess an expert advisory council or committee for the purpose of its radiological investigations. This advisory body would, in particular, guide the Organisation on the nature of the commentary or explanatory observations which should accompany the annual statistical statements and as to any special reports which might be added to them.

5. The primary object of the proposed annual statistical statement is to provide a convenient work of reference for those who need to know what can be said statistically in regard to the results obtained by the application of radiotherapy to patients

suffering from cancer of the *cervix uteri*, when the agreed rules for the setting-up of statistics have been observed and full account is taken of the following-up of treated cases and the records of their after-histories.

This is an object sufficiently important in itself and, in furthering it, the Health Organisation can render a very valuable service. To remove any ambiguity, the Conference adds that it does not propose to the Health Organisation that the data obtained should be analysed with the intention of declaring that any one technique of radiotherapy should be given preference over others on account of its possessing a favourable statistic. This is a matter on which international pronouncements, based only on statistical evidence, would be unprofitable.

6. The material now available or being obtained would permit the preparation of the first annual statement at an early date ; its appearance in 1936 seems practicable and desirable.

The material for the first annual statement would consist in part of data from institutions which have complied with the request made to them by the Health Section of the League as a result of the report of the Radiological Sub-Commission in 1929. At these institutions, the special case-record books for cases of cancer of the cervix with duplicate sheets, provided by the Health Section have been regularly used. In part also, it would consist of information from particular institutes which are in a position to make a return to date, on the lines of the standard "survival table", even though they have not used the individual case-record books supplied by the Health Section.

7. On this proposal it would be necessary, in certain cases, to invite the national correspondent to arrange for the collection and tabulation of the results which, since 1930, have been recorded in the special case-record books provided by the Health Section. It will be remembered that these special case-record books were originally designed with the intention that all the duplicates should be sent for analysis and tabulation to the Health Section at Geneva, or to some central authority determined by the Health Organisation. In these circumstances, the Health Organisation has special reason to consider the ways in which it may be able to assist the national correspondent to undertake the duty of supplying "survival tables".

based on the case-record books which have been kept in their countries.

8. The above recommendations are necessarily in general terms. The discussions at the Conference have shown that, even under the simple system proposed, doubts will arise about the tabulation of particular cases or as to the interpretation of the rules suggested for the keeping of the survival tables. They have also shown that provision must be made for considering the application of the statistical statements to new knowledge obtained in the future. In so far, however, as such questions require expert opinion, they can be dealt with as they arise, with the aid of the expert advisory body which has been proposed above.

NOTES ON THE SURVIVAL TABLE.

I.

1. A general statistical table should be prepared covering the total of all patients considered for treatment (column 2 *a*) and containing all particulars required for the computation of the *absolute* survival rate.

2. Separate statistical tables should also be prepared in respect of treated cases (column 3) in stages I, II, III and IV as defined in the rules already adopted (see Radiological Sub-Commission's report 1929—document C.H.788). The particulars given in these tables are those required for the computation of *relative* survival rates.

3. In column 3 a discrimination should be made as between cases of cancer histologically confirmed and those not histologically confirmed.

4. The general principles of the methods of treatment applied should be briefly described where shown on form (10).

II.

Column 2 comprises all cases examined at the clinic for radiological treatment (*vide* document C.H.788, page 14, section C).

Column 3. This column will include only new cases—*i.e.*, patients who have not previously been treated elsewhere, either by hysterectomy or by radiotherapy.

Column 4 comprises patients known to be alive whether the disease continues or not in the primary site or as metastases. *In this and the subsequent columns, the years refer to anniversaries dating from the beginning of the treatment.*

Column 5 comprises patients known to be alive and *clinically* free from the disease in the organ for which treatment was given or from metastases. The existence of a proved second primary growth—*e.g.*, a carcinoma of the breast arising during observation after treatment for a carcinoma of the uterus—is disregarded.

Column 6 includes patients who died of cancer in the organ for which treatment was given or of metastases. It also includes those dying during or as a result of treatment (patients dying of a proved second primary growth are entered in column 8).

Column 7 comprises patients whose histories at the expiry of the period of observation are not definitely known.

Column 8 includes patients dying of accident, other disease, etc., during the period of observation. It also includes those dying of a proved second primary growth.¹

Column 9. When data are set out in the way indicated in the tabular statement, it becomes practicable to calculate the survival rates, as provided for in columns 9*a* and *b*.

Column 9a. An "absolute" survival rate based on column 2*a* may be arrived at either for survivors (column 4) or for survivors who are clinically free from the disease (column 5).

Column 9b. Similarly, "relative" survival rates based on column 3*a* may be calculated.

Difference of practice occurs in the way the cases in columns 7 and 8 are dealt with. One method is to regard the patients as dying from cancer, but this is considered to under-state the survival rate seriously. Another method is to deduct such cases wholly from the sample, basing the percentage of survivors on the number of cases treated in column 2*a* or 3*a* less those in columns 7 and 8. This is regarded as being sufficiently accurate for practical purposes.

¹ A list of the patients included in this column may usefully be appended to the Survival Table showing the stage of the disease when treatment began, the date of beginning treatment, the date of death and the condition which caused death.

SECOND CONFERENCE ON VITAMIN STANDARDISATION

held in London from June 12th to 14th, 1934.

PRELIMINARY NOTE.

An International Vitamin Conference, attended by most of the experts responsible for the present report, was held in London in June 1931 under the auspices of the Permanent Commission on Biological Standardisation of the League of Nations Health Organisation. The report of the earlier Conference,¹ published in 1931, recommended for international adoption standards and units for vitamins A, B₁, C and D, which were to be "provisional for two years". Since certain of the standard preparations recommended for adoption were not available for general use until 1932, the second Conference was postponed until 1934, at which date two years' experience of the practical application of the provisional standards was available.

The following report should therefore be regarded as a revision of the report of the 1931 Conference. In making its decisions, the present Conference had also at its disposal the results of many important new investigations connected with vitamin standardisation. It is to be noted that, in this report, the standards and units recommended are no longer termed "provisional". While the advance of scientific knowledge may at some future date make changes in the adopted standards and units desirable, it was not felt necessary, as before, to assign provisional periods for their use.

The time may shortly arrive when the cumbrous method of comparing the vitamin activity of test materials with the activity of a chosen standard will be obsolete, and vitamin potency will be expressed in terms

¹ "Report of the Conference on Vitamin Standards". Publications Department of the League of Nations No.C.H.1055 (1), Geneva 1931.

of the exact amount of pure active vitamin present. The Conference, however, considered it desirable that, for the present, vitamin potency should, in the case of all the vitamins dealt with in its report, continue to be estimated by means of biological tests in comparison with a chosen standard, even in those cases in which pure substances possessing high vitamin potency have been isolated, thus making it possible to estimate with considerably accuracy, by chemical and physical methods, the amount of these substances present in materials under test.

As in the 1931 Report, standards and units are recommended for only four of the known vitamins—namely, vitamins A, B₁, C and D. Consideration was given to the possibility of adopting standards for vitamins B₂ and E, but it was felt that our knowledge of the nature and possible complexity of these vitamins, and of the pathological results to which their absence gives rise, is still insufficient to justify the adoption of standards and units for them.

The standards for vitamins A and C have been altered. Those chosen for these vitamins in 1931 were found to have certain defects which impaired their usefulness ; the substitution of more clearly defined and more easily reproducible chemical substances is a definite step in advance. No change has been recommended in the standards for the vitamins B₁ and D. The former has proved highly convenient in practice—of all the standards chosen by the 1931 Conference the vitamin B₁ standard has perhaps proved most satisfactory—and a large stock, sufficient to last for many years, is available at the central distributing institution, the National Institute for Medical Research, London. In view of all the circumstances, its replacement by a purer vitamin B₁ preparation does not seem at present desirable. The vitamin D standard also remains unaltered, with the proviso that it may be replaced when exhausted (or if it should become for any reason unsatisfactory) by crystalline vitamin D in suitable solution. Large quantities of the original standard solution of irradiated ergosterol are still available. Certain recently observed anomalies, in the anti-rachitic action on certain species, of different substances containing equal numbers of international vitamin D units, to which brief reference is made in the report, suggest that a re-examination of the suitability of the present vitamin D standard may become necessary at some future date.

The units of vitamin activity remain the same in all cases. Where a change has been made in the standard material, the old units have

been re-stated in terms of the newly chosen substance. The desirability of leaving the original units unaltered is emphasised by the fact that certain of the units recommended by the 1931 Conference have been adopted in the pharmacopœias of certain countries.

The majority of the members of the Conference have in recent years carried out experiments bearing directly on problems of vitamin standardisation, the results of which proved to be of the greatest value to the Conference. In addition to the members of the Conference, many workers in different countries, whose names do not appear in the Report, helped to carry out the recommendations for research made by the 1931 Conference, and placed valuable information at the disposal of the present meeting. Thanks are due to such workers, without whose active and untiring co-operation the Conference could not have undertaken the task set before it.

REPORT OF THE CONFERENCE.

List of Participants.

- Chairman : Dr. E. MELLANBY, Secretary, Medical Research Council of Great Britain, London.
- Professor J. C. DRUMMOND, Professor of Biochemistry, University College, London.
- Professor H. v. EULER, Professor of Biochemistry, University of Stockholm.
- Professor L. S. FRIDERICIA, Director, Institute of Hygiene, University of Copenhagen.
- Professor B. C. P. JANSEN, Professor of Physiological Chemistry, University of Amsterdam.
- Professor P. DE MATTEI, Director, Institute of Pharmacology, University of Pavia.
- Dr. E. M. NELSON, Senior Chemist, Bureau of Chemistry and Soils, U. S. Department of Agriculture, Washington, D. C.
- Professor E. POULSSON, Director, State Vitamin Institute, Oslo.
- Mme. RANDOIN, Directeur du laboratoire de physiologie de la nutrition à l'École des Hautes-Études, et Ministère de l'Agriculture, Paris.
- Professor H. STEENBOCK, Professor of Agricultural Chemistry, University of Wisconsin, Madison, U. S. A.

Professor A. SZENT-GYÖRGYI, Institute of Medical Chemistry,
University of Szeged, Hungary.

Dr. H. CHICK, Lister Institute of Preventive Medicine,
London.

Dr. W. R. AYKROYD Health Section, League of Nations }
Secretariat, Geneva. } Technical Secretaries

The following also were present :

Dr. M. H. BROWN, Connaught Laboratories, Toronto, Canada.

Dr. K. H. COWARD, Laboratory of the Pharmaceutical Society of Great Britain,
London.

Sir Henry H. DALE, Director, National Institute for Medical Research, London.

Dr. P. HARTLEY, National Institute for Medical Research, London.

Miss E. M. HUME, Lister Institute of Preventive Medicine, London.

Dr. A. JUNG, Institute of Physiological Chemistry, University of Basle.

Dr. Ch. LORMAND, Directeur du Laboratoire national de contrôle des médicaments, Paris.

Dr. R. MENDEZ, Technical Institute of Pharmacy and Biology, Madrid.

Dr. R. A. MORTON, Department of Chemistry, University of Liverpool.

Dr. R. A. PETERS, Professor of Biochemistry, University of Oxford.

Dr. O. ROSENHEIM, National Institute for Medical Research, London.

Dr. M. TSURUMI, Member of the League of Nations Health Committee (Japan).

Mr. T. A. WEBSTER, National Institute for Medical Research, London.

Dr. S. S. ZILVA, Lister Institute of Preventive Medicine, London.

The meeting was opened by Sir George BUCHANAN, who welcomed the members on behalf of the Health Committee of the League of Nations, after which Sir Henry H. Dale gave a brief review of the present position with regard to international vitamin standardisation.

I. VITAMIN A.

(a) *International Standard.*

The Conference recommends that pure β -carotene be adopted as the International Standard for Vitamin A. The Standard Preparation shall conform to the requirements stated in Note 1 in regard to its chemical and physical constants.

(b) *Definition of Unit.*

The Conference recommends that the unit for Vitamin A provisionally adopted at the 1931 Conference shall be maintained. It has been established that one such unit is contained in 0.6 microgram (0.6 γ) of pure β -carotene.

The International Unit for Vitamin A recommended for adoption shall be defined as the Vitamin A activity of 0.6 microgram (0.6 γ) of the International Standard Preparation.

Daily doses of 2 to 4 International Units of Vitamin A, when administered to young rats suitably prepared on a Vitamin A-deficient diet, have been found adequate to restore growth ; somewhat larger doses are required for the cure of xerophthalmia.

(c) *Mode of Preparation.*

It is recommended that the Health Organisation of the League of Nations shall be requested to obtain a sample of β -carotene as defined by the Conference (see Note 1), and that the National Institute for Medical Research, London, *acting for this purpose as central laboratory on behalf of the Health Organisation of the League of Nations*, shall undertake the care, storage and distribution of the International Vitamin A Standard so obtained.

(d) *Mode of Distribution.*

The Conference recommends that the International Standard Preparation shall be issued in the form of a standard solution in oil, the strength of the solution being such that 1 gramme contains 500 International Units, or 300 micrograms (300 γ) of β -carotene. (See Note 2.)

(e) *Adoption of a Subsidiary Standard of Reference.*

The Conference recommends that a sample of cod-liver oil, the potency of which has been accurately determined in terms of the International Standard Preparation of β -carotene, shall be provided as a Subsidiary Standard of Reference.

In view of the fact that the Reference Cod-liver Oil of the United States Pharmacopœia, which has been accurately assayed in terms

of the provisional International Standard adopted in 1931, has been in effective use in the United States of America for some time, the Conference recommends that the Board of Trustees of the United States Pharmacopœia be approached and invited to place a quantity of their Reference Cod-liver Oil at the disposal of the Health Organisation of the League of Nations, with a view to its adoption for international use as a Subsidiary Standard for Vitamin A.

In the event of the Reference Cod-liver Oil of the United States Pharmacopœia not being available for international adoption, the Conference recommends that another sample of cod-liver oil be selected, its potency in terms of the International Standard Preparation of β -carotene accurately determined by biological comparison and independently by spectrophotometric measurements (see (f) below), and that this selected sample be then adopted as a Subsidiary International Standard for Vitamin A.

(f) *Spectrophotometric Test for the Assay of Vitamin A in Liver Oils and Concentrates of High Potency.*

It has been found that, within certain defined conditions, measurements of the coefficient of absorption (E) at 328 $m\mu$ affords a reliable method for measuring the Vitamin A content of liver oils and concentrates. As a means of converting values obtained for $E \frac{1\%}{1 \text{ cm.}}$ 328 $m\mu$ into a figure representing the International Units of Vitamin A per gramme of the material examined, the factor 1600 is recommended for adoption. (See Note 3.)

Note 1.

Properties of Pure β -Carotene ($C_{40}H_{56}$).

(a) Melting-point, 184-184.5°C., corrected.

(b) Optically inactive.

(c) Absorption spectrum showing bands—

in carbon disulphide at 519, 485.5 $m\mu$

in chloroform at 495, 465 $m\mu$

in cyclohexane at 486, 456 $m\mu$

Note 2.

Nature of the Oil to be used as Diluent.

The oil used for the preparation of the standard solution of β -carotene, and for the further dilution of the standard and for use in the biological assay of

Vitamin A, shall be a colourless, Vitamin A-free, vegetable oil, from which the dissolved carotene can be properly absorbed from the alimentary canal of the test animals. 0.01 per cent of hydroquinone shall be added to the oil to prevent oxidation and ensure stability.

In order to establish its suitability, the oil to be used as diluent for the above-named purposes must be submitted to the following test. A 0.003 % solution of β -carotene in the oil is prepared, and the colour of the solution compared with that of a 0.5 % solution of potassium bichromate; about 6 cc. of the carotene solution in oil are placed in a flat-bottomed tube (5 cm. \times 2 cm.), which is closed with a hard cork so as to leave an air space of about 6 cc. capacity. The tube is then maintained at a temperature of 37°C. in the dark for seven days, and the colour of the solution again compared with that of the standard solution of potassium bichromate. An oil may be considered satisfactory for the purposes indicated if the loss in colour does not exceed 10 per cent. Some samples of cocoa-nut oil have been found to fulfil the requirements of the above test.

Note 3.

The Spectrophotometric Test.

(a) The measurement must be made on the unsaponifiable fraction, unless the material is of potency greater than 10,000 International Units per gramme.

Method of saponification. Since the error associated with the saponification may be considerable, the following method is recommended, as yielding trustworthy results.

One gramme of oil is saponified with 10 cc. N/2 freshly prepared alcoholic KOH, by boiling until clear (time needed about 5 minutes). 20 cc. water are added, the whole transferred to a small separator and extracted with two quantities of 25 cc. ether (peroxide-free). The ethereal extracts are washed first with water (10-20 cc.), then with 10-20 cc. N/2 KOH, and again with water, while rotating gently without shaking. The ethereal solution is then shaken thoroughly with two quantities of 10 cc. water, after which it is filtered into a flask, the ether evaporated almost to dryness and the residue dissolved in ethyl alcohol or cyclohexane and made up to the concentration required for the particular instrument in use. A preliminary test on the original oil will indicate the amount both of oil and of solvent which will be necessary.

(b) Pure ethyl alcohol or cyclohexane must be the solvent used. Pure cyclohexane, suitable for spectrographic examination, should have the following properties: $d_{4}^{20} = 0.7784$; B.P. 81.4°C; F.P. 6.5°C; it should be almost completely transparent in the region of 328 $m\mu$. and exhibit no trace of discontinuous absorption.

(c) The intensity of absorption at 328 $m\mu$ may be determined to within \pm 2.5 per cent by any of the recognised methods of spectrophotometry.

(d) The factor, 1600, is the average figure derived from a series of comparative and independent tests on the unsaponifiable fractions of liver oils and on concentrates of high potency. It is desirable that, when a figure expressing the biological potency of a preparation has been derived by the use of this calculation, the fact should be stated.

II. VITAMIN B₁.

(a) *International Standard.*

The Conference confirms the adoption, as International Standard, of the adsorption product of Vitamin B₁ prepared in the Medical Laboratory, Batavia (Java), by the method of Seidell, as described by Jansen and Donath.

(b) *Terminology.*

The International Standard Preparation shall be known as the "standard adsorption product of Vitamin B₁".

(c) *Method of Preparation.*

The International Standard was prepared by extracting rice polishings with water, sufficient sulphuric acid being added to make the pH 4.5. Salicylic acid to a concentration of 0.2 per cent. and toluene were then added to prevent bacterial decomposition. The process of extraction was continued for two days, after which the solution was filtered. For each 100 kg. of the original rice polishings, 3 kg. of fuller's earth (specially selected for its adsorptive powers) were added to the solution, which was then stirred for twenty-four hours. Subsequently, the solution was filtered off and the fuller's earth, after being washed with water and alcohol, was dried; 3 kg. of the fuller's earth adsorbate represents the Vitamin B₁ from 100 kg. of rice polishings.

(d) *Definition of Unit.*

The International Unit recommended for adoption is the Vitamin B₁ activity of 10 milligrammes of the International Standard adsorption product.

A daily dose of 10 to 20 milligrammes of this preparation is required to maintain normal growth in a young rat on a diet deficient in Vitamin B₁ but complete in all other respects. The curative "day dose" for a pigeon (300 grammes weight) exhibiting head retraction on a diet of polished rice is about 10 to 30 milligrammes (method of Kinnersley and Peters). The Standard contains Vitamin B₁, but relatively small amounts of Vitamin B₂.

(e) *Mode of Distribution.*

The International Standard adsorption product of Vitamin B₁ is kept at the National Institute for Medical Research, London, acting for this purpose as central laboratory on behalf of the Health Organisation of the League of Nations.

No special precautions are necessary in keeping this preparation, except that it should be stored in a dry place. In the presence of moisture, bacterial decomposition readily takes place.

(f) *Recommendations for Future Research.*

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. The following, who have isolated such crystalline preparations, should be asked to make this comparison, employing the biological methods usual in their own laboratories:

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.

In further research, the comparative effect of parenteral and oral administration should be examined. In the case of the standard adsorption product, the preparation of suitable extracts should be investigated.

III. VITAMIN C.

(a) *International Standard.*

The Conference recommends the adoption of *l*-ascorbic acid as International Standard. The Standard Preparation shall conform to the requirements stated in Note 4, below, in regard to its chemical and physical constants.

(b) *Definition of Unit.*

The unit recommended for adoption is the Vitamin C activity of 0.05 milligramme *l*-ascorbic acid.

This is about 1/10th of the daily dose necessary to prevent development of gross macroscopic scorbutic lesions in a young guinea-pig maintained on a scurvy-producing diet.

(c) *Mode of Preparation.*

It is recommended that the Institute of Medical Chemistry, Szeged, should be asked, through Professor SZENT-GYÖRGYI, to prepare a batch of 500 grammes of the Standard Preparation, and that Professor W. W. HAWORTH, University of Birmingham, be invited to co-operate in controlling the purity of the standard material.

(d) *Place of Distribution.*

It is recommended that the National Institute of Medical Research, London, acting for this purpose as central laboratory on behalf of the Health Organisation of the League of Nations, shall be requested to undertake the storage and distribution of the Vitamin C standard.

(e) *Method of Use.*

The standard may be kept at room temperature in a sealed tube or in an evacuated desiccator, and the required amount must be dissolved in freshly boiled and cooled glass-distilled water, immediately before daily administration to the test animals.

Note 4.

Properties of the Vitamin C Standard.

The Standard Preparation of *l*-ascorbic acid should have the following characteristics :

(a) Melting-point 192° C., uncorrected, taken in an open capillary, without appreciable darkening before melting.

(b) Specific rotation $[\alpha]_D^{20} = + 20.0^\circ$ in water (conc. 14.0 g. per 100 cc. solution)

$[\alpha]_D^{20} = + 22.4^\circ$ in water (conc. 2.2 g. per 100 cc. solution).

(c) The absorption spectrum in slightly acid aqueous solution is characterised by a single intense band with head at 245 m μ . The molecular extinction coefficient for a solution containing 20 milli-

grammes per litre is 10,000. (The ascorbic acid is to be dissolved in freshly distilled water to which 0.1 cc. N/1 sulphuric acid has been added for every 100 cc. water).

- (d) 10 milligrammes *l*-ascorbic acid should require 11.4 cc. N/100 aqueous iodine, the titration being carried out with starch as indicator.
- (e) The substance must be ash-free and its elementary analysis must agree with the figures for $C_6H_8O_6$. It normally crystallises in rectangular plates which show straight extinction with high birefringence. [n_{α} (D line) 1.47 ± 0.005 ; n_{β} (D line) 1.68 ± 0.005].

IV. VITAMIN D.

(a) *International Standard.*

The Conference recommends that the standard solution of irradiated ergosterol, prepared at the National Institute for Medical Research, London, and at present issued as International Vitamin D Standard, shall be retained.

When the present International Standard Solution is exhausted, or if it should become unsatisfactory for any reason, the Conference recommends that it should be replaced by an equivalent solution of pure crystalline Vitamin D in olive oil, of such strength that 1 milligramme contains 0.025 micrograms (0.025 γ) of crystalline Vitamin D. (For a definition of crystalline Vitamin D, see Note 5 below.)

(b) *Definition of Unit.*

The Unit of Vitamin D recommended for adoption by the 1931 Conference shall remain unaltered : namely, the Vitamin D activity of 1 milligramme of the international standard solution of irradiated ergosterol, which has been found equal to that of 0.025 micrograms (0.025 γ) of crystalline Vitamin D.

The assay of materials for Vitamin D content should be carried out by comparative tests on rats, and their value in international units should be derived from the results of such tests. If other species are employed for these tests, the values cannot be expressed in international units (see (d) below).

(c) *Mode of Distribution.*

The National Institute for Medical Research, *acting for this purpose as central laboratory on behalf of the Health Organisation of the League*

of Nations, shall be asked to continue the storage and distribution of the International Vitamin D Standard. The mode of distribution recommended by the 1931 Conference shall remain unaltered either in the case of the existing standard solution, or the solution of crystalline Vitamin D by which it may be replaced in future.

(d) *Recommendations for Further Research—Cod-liver Oil as Subsidiary Vitamin D Standard.*

The Conference recognises that amounts of cod-liver oil and irradiated ergosterol which contain an equal number of Vitamin D units, as determined by tests with rats, may not possess equal anti-rachitic activity when tested on certain other species—*e.g.*, poultry. The utility of cod-liver oil as a secondary standard of reference is obvious, and such standard cod-liver oils are at present distributed in several countries. In view of the fact that inconveniently large quantities of cod-liver oil would have to be handled for international purposes as Vitamin D Standard, thereby giving rise to storage problems, the Conference does not recommend the adoption of a sample of cod-liver oil as a subsidiary International Standard for Vitamin D.

The Conference recommends, however, that national centres of distribution should prepare subsidiary reference samples of cod liver oil, of known Vitamin D activity, for distribution to workers in the countries concerned. In order to preserve a uniform value for the International Unit, the Vitamin D activity of such oil should be compared with that of the International Standard by means of tests on rats and their potency should be stated in International Units. It is recommended that the experience gained with such subsidiary cod-liver oil standards should be devoted to an attempt to elucidate the questions involved in the anomalous action on certain species of different sources of Vitamin D, and that members of the Conference be asked to co-operate in these investigations in their respective countries.

(e) *Biological Methods for Estimation of Vitamin D.*

In using the International Standard Solution for the determination of the anti-rachitic potency of unknown preparations, it is recommended that not fewer than twenty similar rats (preferably

more) be used for a determination, half of these to receive the standard and the remaining litter-mates the unknown substance. Provided this precaution is observed, it is considered permissible to use either prophylactic or therapeutic methods of investigation.

Note 5.

Properties of Crystalline Vitamin D (Calciferol or Vitamin D₂), C₂₈H₄₄O.

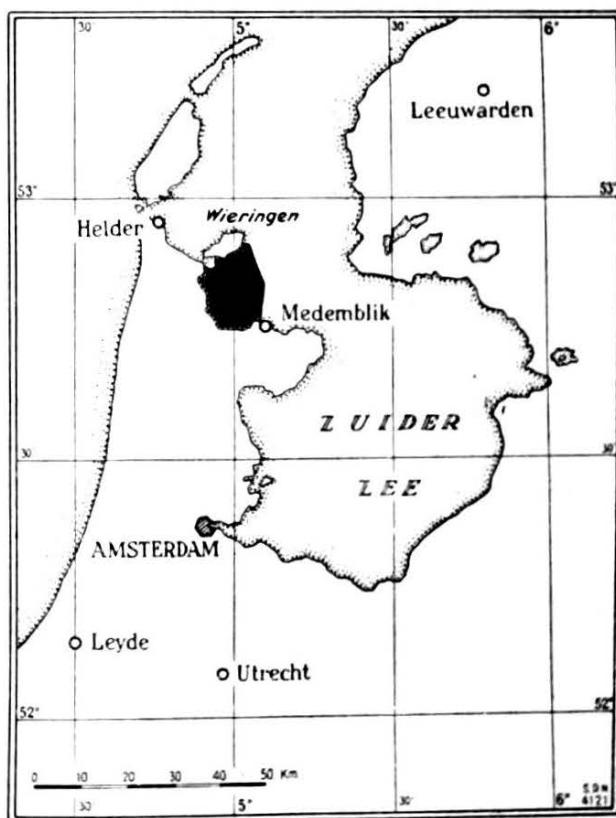
- (a) Colourless acicular crystals, odourless ; melting-point, 114.5-117°C. (open capillary).
- (b) Specific rotation :
 - in alcohol $[\alpha]_D^{20} = + 101^\circ$ to $+ 102.5^\circ$; $[\alpha]_{5461}^{20} = + 119^\circ$ to $+ 122^\circ$
 - in chloroform $[\alpha]_D^{20} = + 52^\circ$; $[\alpha]_{5461}^{20} = + 62^\circ$
- (c) Absorption spectrum : in alcohol or other suitable non-absorbing solvent, a smooth curve with a maximum at 265 m μ ($E_{1\%}^{1\text{cm}} = 470$ to 485).

OBSERVATIONS ON THE INVASION OF THE WIERINGERMEERPOLDER BY ANOPHELES MACULIPENNIS¹

by

N. H. SWELLENGREBEL and J. A. NYKAMP,
Zoological Laboratory, Royal Colonial Institute, Amsterdam.

Map 1.
SITE
OF THE
NEW WIERINGER
POLDER.



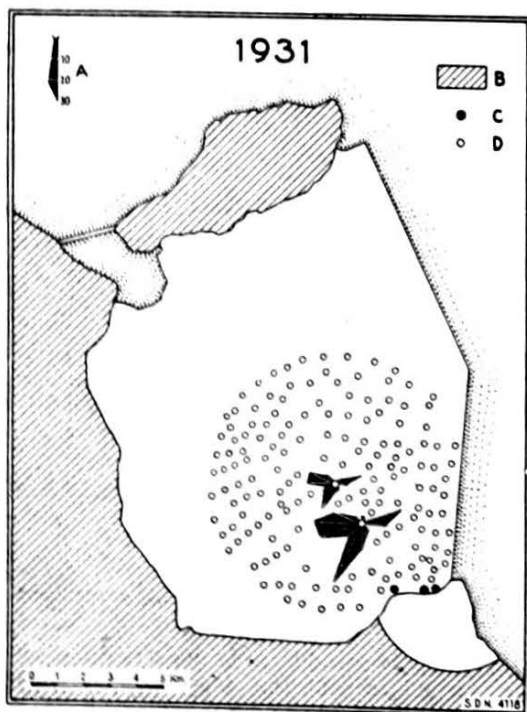
¹ The investigations on which this paper is based have been carried out with the financial support and under the auspices of the International Health Division of the Rockefeller Foundation.

All sea-polders (*i.e.*, polders directly reclaimed from the sea) which we observed during the process of desiccation had this common feature, that anopheles never commenced to breed immediately after the reclamation of the land. One year at least elapsed before this stage was reached. In the small experimental polder near Andyk, reclaimed in 1927, no larvæ were found till the summer of 1929. On the mudbanks in the estuary of the River Scheldt, reclaimed by protecting them from the floods by means of embankments, no breeding occurred till several years after the reclamation had been completed. On the contrary, polders reclaimed from fresh water immediately start breeding anopheles.

All the newly reclaimed polders we have examined up to the present were of small size and it was a new experience to watch a large polder being gradually invaded by anopheles.

In August 1930, the polder was reclaimed; as at that time the anopheline season was too far advanced to allow of anything important happening that year, our regular observations did not commence until the next year.

CONDITIONS IN 1931.



Map 2.

- A. Scale of the compass-cards.
- B. Old land.
- C. Breeding-places.
- D. Areas free from breeding-places.

The centre of the two compass-cards indicates the position of stables "3 km." and "5 km."

No Larvæ.

In 1931, no anopheline breeding-places were found. There was plenty of water, however, and not only in the big canals and in the ditches ; the whole polder was a quagmire comparable to an area freshly reclaimed by hydraulic filling where the water has not yet run off. We are acquainted with this state of things from descriptions by old writers of conditions they found in newly reclaimed polders in the 18th and 19th centuries, conditions they designated by the name of the "quagmire stage". The new polder had to pass through this stage before more normal conditions could be attained. The old writers had been taught to associate it with the unavoidable bad health of the workmen occupied with the work of land reclamation and of the first settlers. If this unhealthy condition was due to the presence of malaria — and we have no doubt it partly owed its origin to that source — it is difficult to understand it in the light of modern epidemiological knowledge. That is, if we only direct our attention to the *breeding* of anopheles.

Our statement that no anopheline larvæ were found in the new polder may raise some doubts. We should add, therefore, that we do not rely on our experience gained since 1925 in other sea-polders during the first year after their reclamation. On the contrary, our statement is justified by an extensive and often repeated examination, continued during the whole of the breeding season within the area indicated on map 1, where not a single collection of water escaped our attention. In that area we found larvæ three times, in water containing 1,600-2,400 mgr. of chlorine per litre. These breeding-places were found only in the southern extremity of the new polder, near the former coast-line. Outside this area they *may* have occurred—*e.g.*, at the northern fringe of the new polder, where we found them next year. But, within the precincts of the area surveyed, we are sure they were absent all the year.

The absence of anopheline larvæ is readily explained by the water in the ditches being too brackish. Our "short-wing" anopheline larvæ can stand a good deal of salt, but 7,000 mgr. of chlorine per litre is about the limit, and the average salinity of the ditches in the area surveyed was 8,000 or more.

Adult Anopheles in Experimental Stables 3 and 5 Kilometres from the Breeding Area.

Absence of larvæ, however, did not imply absence of adult anopheles in the new polder. In September 1930, we did not, however, find any in some labourers' barracks and houseboats near the locality named "Terp" (*cf.* maps 3 and 4) in the centre of the polder. In 1931 we built two experimental stables (Nos. 1 and 2 on map 3) with two pigs each, at a distance of 3 and 5 kilometres from the nearest point of the old land (Medemblik). We did so for the purpose of securing two stations to catch anopheles, as no such stations were otherwise to be found in the new polder. But the erection of the stables served another object also. They stood within the area we knew to breed no larvæ. Consequently, all adults we might detect in these stables would be sure to have got there either from the old land or (unlikely, but still possible) from some part of the new polder outside the area surveyed, but at any rate from a point at least 3 kilometres distant from the one stable and 5 kilometres from the other.

We were already aware of the long flights our short-winged *A. maculipennis* (practically the only one present in those areas) is able to perform. We had proved this by liberating stained anopheles 3 kilometres outside Medemblik and recapturing them within that town if the wind was favourable (*i.e.* blowing in the direction of the town). Experiments like these, however, prove only that anopheles *can* cover this distance, flying or in some other fashion, at one stretch or by a series of short flights. But they do not prove that anopheles *habitually* makes such long tours, and that is the point which should be settled, as it is the rule and not the exception that the hygienist is concerned with. It is particularly difficult to prove that these long-range flights are a habit of anopheles. As a rule, the position of the breeding-places around a catching station is such as to preclude the possibility of ascertaining whether anopheles caught in that station came from afar or not.

Our experimental stables in the new polder were in the exceptional position of permitting us to settle that particular point beyond any doubt, because they stood within an area of new land completely devoid of breeding-places.

In these stables we daily caught and counted all anopheles from June 1st till September 15th, 1931, and we found new ones almost every day. In other words, almost every day there were anopheles covering the distance of 3 and 5 kilometres to these stables, for in that flat uninhabited land without animal or plant life there existed no other shelters. The average daily catch was small : 13 anopheles with 2 males in the stable "3 kilometres" and 7 anopheles with 1 male in the stable "5 kilometres".

The invariable presence of males deserves some attention because it contradicts the widespread opinion that the presence of males in a catching station denotes the near presence of breeding-places, as males do not fly far from them. If an area protected by anti-larval measures is still found to harbour anopheles, the sanitary inspector may be excused on the plea that these mosquitoes have arrived there by long-range flights. But this excuse is not tenable in the case where the anopheles caught are males. In future, we shall have to admit the excuse in any case, at least with regard to short-winged maculipennis.

Where the Adult Anopheles in the Stables came from.

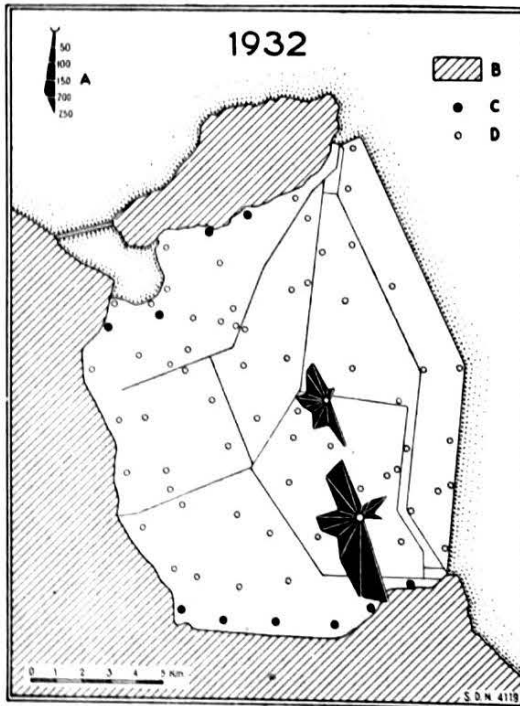
On map 2, showing the conditions found in 1931, the position of the two stables is shown as the centre of a diagram shaped like a compass-card with rays of unequal length. The length of each ray records the average daily catch of anopheles on days following evenings when a wind was blowing from the direction in which the ray is pointing. We took account of the wind blowing on the preceding evening, because it particularly aided or impeded the progress of those groups of anopheles we caught in the experimental stables next day. The ray pointing in a south-west direction is the longest, which signifies that anopheles were most numerous in the stables on days following evenings with a south-west wind.

The old land on map 2 is hatched as an indication that it is a practically continuous breeding area. From it must have come the anopheles we found in our experimental stables ; most of them from the south-west where the old land is nearest. The peninsula of Medemblik is nearer still and should have been foremost in stocking our stables with anopheles, but the area around Medemblik was subjected to measures of antilarval control and so produced

no anopheles in 1931. For that reason, this area has been left unshaded.

We are ignorant of the ways and means by which the adult anopheles contrived to reach our stables. This much we can say, that the new polder was far too swampy to allow of any traffic passing through it except along a canal from Medemblik to "Terp" (map 4), passing our stables at no great distance. It is difficult to believe that the boats plying on this canal conveyed the anopheles to the stables, as they never stopped near them. The rare specimens of anopheles, however, we caught in a canteen and a chicken pen at "Terp" may reasonably be supposed to have been transported in this fashion.

CONDITIONS FOUND IN 1932.



Map 3.

A. Scale of the compass-cards.
 B. Old land.
 C. Breeding-places.
 D. Water collections under observation and proved to be free from larvæ.

The centre of the two compass-cards indicates the position of stables "3 km." and "Terp"; the compass-card for stable "5 km." has been left out for want of space; it would have the same shape as that for stable "3 km."

Adult Anopheles in the Experimental Stables.

In 1932, the experimental stables were no longer considered useful for the purpose of estimating the range of flight of anopheles,

as it was taken for granted that the mosquitoes would commence breeding in the new polder. We therefore abandoned the plan of keeping under observation all collections of water within a limited area of the polder, as we had done in 1931. Instead, we selected eighty ditches spread over the whole polder with the object of watching the advent of the larvæ. Nevertheless, we continued to utilise the experimental stables as a gauge of the number of adults, and erected another at "Terp", 10 kilometres distant from Medemblik (map 4). We noticed a marked increase in the number of adults: the average daily catch in the stables "3 kilometres" and "5 kilometres" was 110 and 113 anopheles respectively against 13 and 7 in the previous year. In the stable "Terp" it was 69.

Breeding-places.

Contrary to our expectation, the breeding area showed but little extension. Ten out of 80 observational ditches bred larvæ once; rarely more. Five of these breeding-places were situated along the former sea-coast in the southern extremity of the new polder. The salinity there was fairly low (about 2,000 mgr. chlorine per litre) and the larvæ were numerous (14 per dip). The others likewise occurred near the former sea-coast along the western and northern boundaries of the new polder. The salinity there was higher (about 5,000 mgr. chlorine per litre) and the larvæ few in number (0.7 per dip). Map 3 shows the position of these breeding-places. The greater part of the polder breeds no anopheles.

Cause of the Increase of the Number of Adults.

As a consequence, the considerably greater number of anopheles in the experimental stables cannot be explained by an extension of the breeding area, and it must be dependent on an invasion from without. This invasion, so much greater than last year, is explained by changes occurring in the old land near Medemblik. Around that town the anti-larval measures had been discontinued in 1932 and, as a consequence, the number of anopheles had been much increased (see the diagram, page 458). The peninsula of Medemblik now became the nearest breeding area to replenish the stables in the new polder. The compass-card on map 2, the centre of which

indicates the position of the stable "3 kilometres",¹ has assumed a shape entirely different from that observed in 1931. Its longest ray points towards Medemblik, which signifies that anopheles were most numerous on days following evenings when a wind was blowing from that direction. In 1931, that south-easterly ray was among the shortest. Stable "Terp", at a distance of 10 kilometres from Medemblik, has a compass-card of similar shape, its longest ray likewise pointing towards Medemblik; but here another one of almost equal length is pointing in the direction of the breeding-places in the northern extremity of the polder, to which stable "Terp" is so much nearer than the other two.

Comparison of the Anopheline Density in the New Polder with that prevalent in Medemblik during the Period it was protected by Anti-larval Measures.

Although the anopheline density had been greatly increased in the new polder since 1931, it still remained much below that in the old land. This can be demonstrated by comparing it with anopheline catches in experimental stables around Medemblik, identical in every respect with those in the new polder, except for the catches not being performed daily, but once a week only during the height of the anopheline season (July and August). For the purpose of comparison, we shall take account of those catches in the new polder only which were carried out on the same dates as the catches around Medemblik.

Accordingly, we counted in the experimental stables around Medemblik in 26 catches 20,044 anopheles, or 771 per catch, and in the new polder in 18 catches 2,925 anopheles, or 162 per catch. Consequently, the proportion of the anopheline density around Medemblik and in the new polder is as 4.7 to 1. This ratio is a remarkable one, as it is almost identical with the one we found in Medemblik at the time that town was still protected by anti-larval measures, when comparing the anopheline density in Medemblik with that in the area outside the boundary of anti-larval operations (at a distance of 3-5 kilometres from the town). In the following

¹ The compass-card of stable "5 kilometres", which has the same shape as that of stable "3 kilometres", had to be left out for want of space. For the same reason, the compass-cards in map 2 have been drawn on a smaller scale than in map 1.

table, the anopheline density (denoting the quantity of anopheles in stables of various sizes divided by their area in square metres¹) is given for Medemblik and the area not affected by larval control.

| Year | Anopheline density : | | Proportion |
|---------------------|----------------------|--|------------|
| | In Medemblik | 3-5 kilometres outside Medemblik | |
| 1927 | 14 | 59 | 1 to 4.2 |
| 1928 | 26 | 121 | 1 to 4.6 |
| 1929 | 51 | 218 | 1 to 4.3 |
| 1930 | 26 | 120 | 1 to 4.6 |
| 1931 | 5 | 29 | 1 to 5.8 |
| Average 1927-1931 . | 24 | 109 | 1 to 4.5 |

In other words : man's interference by means of Paris green and oil and nature's by means of salt have both kept the anopheline population within a definite area low. Man, working within a radius of 3 kilometres, reduced the anopheline population to from a quarter to a fifth of normal. Nature scored no better results than man although it had extended its field of action to a radius of 10 kilometres.

Stabular Deviation.

In June 1932, the first village in the new polder ("Slootdorp", maps 3 and 5) was completed and soon after was occupied by a group of settlers. This afforded us the opportunity to study conditions no less exceptional than the land without breeding-places in 1931—viz., man living in a rural area in the midst of anopheles, but unprotected by stables occupied by animals of any size above rabbits or poultry.

The condition we are accustomed to in the rural areas around Medemblik, Amsterdam, Alkmaar and Zaandam is characterised by anopheles being much more numerous in occupied (usually by pigs) stables than in human dwellings. Around Amsterdam, the proportion of their numbers in stables and houses is some 200 to 1.

¹ For the purpose of estimating the number of anopheles in stables unsuitable for counting the mosquitoes directly (because of the size of the stable) we proceeded as follows : The stable was closed, a sheet of 3.7 square metres was spread on the floor ; the interior of the stable was sprayed with an insecticide containing an extract of pyrethrum dissolved in kerosene ; the mosquitoes dropping down on the sheet were counted and the figure obtained in this fashion was multiplied by a factor denoting the proportion of the area of the whole stable to that of the sheet.

Roubaud drew attention long ago to the epidemiological consequences of this "stabular deviation".

These consequences can best be appreciated by following the various movements of an anopheles which acquired a malarial infection on visiting a house during the summer. It has to leave this house for the sake of oviposition. Afterwards, it returns from the breeding-places in search of blood. Evidently, there is a much greater chance of its alighting in a stable than in a house, for the presence of an overwhelming majority of anopheles in stables can have no other meaning than that they are more attracted by animal than by human dwellings. So the malaria-infected anopheles probably alights in a stable and there wastes the sporozoites developing in its salivary glands by feeding on animals. As a consequence, in Holland there is but a small chance for an anopheles to transmit malaria during the summer months—much less than during autumn; for in autumn it develops no more mature eggs, although it continues to take blood; so it is no longer forced to leave the house where it acquired its infection and it can quietly await the maturing of its sporozoites and the occasion which it is sure to find to inject them into the body of one of the human inmates. Accordingly, we find the majority of infected anopheles in houses during autumn and winter. This statement does not imply that they are absent in summer, but only that they are not found at that time because they are in the stables. It should be understood, moreover, that the phenomena described here are governed by chance: it is improbable, not impossible, that malarial transmission occurs in summer, even in areas where stabular deviation exerts its influence. It becomes not only possible but even probable in rural areas where stabular deviation is absent or poorly developed.

Little Stabular Deviation in the New Polder.

In the new polder, the correctness of this last statement has not been proved by direct evidence, but it has been possible to collect circumstantial evidence in its favour; first, by the remarkably high average number of anopheles in the houses in Slootdorp, notwithstanding the fact that they were screened, although insufficiently. In August and September 1932 we counted an average of 21 anopheles per house in thirty-three houses. This would be

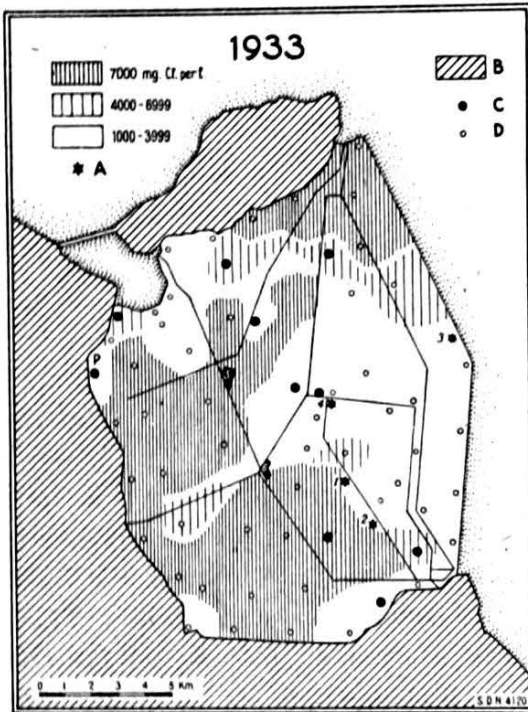
considered a high figure, even in an area teeming with breeding-places, like the environments of Amsterdam and Medemblik. But it is preposterously high if compared with the small numbers of anopheles found in animal dwellings (rabbits and poultry) erected near the house. In 10 animal dwellings (or groups of them) belonging to 10 of the above houses, we counted on an average 123 anopheles per animal dwelling (or group of them if more than one belonged to one house). So the proportion of the number of anopheles in human and animal dwellings is as 1 to 6. Here, consequently, a malaria-infected mosquito leaving a house to visit the breeding-places has a much greater chance to return to a house than in an area where this proportion is as 1 to 200.

In the first paragraph of section 1, we mentioned the old experience that reclaimed land was most unhealthy during the "quagmire stage". We pointed out that this unhealthy condition could not be explained by an excessive breeding of anopheles, because no breeding whatever is going on at that stage, at least not in seapolders. In the light of the recent findings in the new polder, it is probable that this old experience is to be interpreted, not in terms of anopheles breeding, but of stabular deviation. In old times, a polder in the "quagmire stage" was as little appropriate for cattle-farming as it is now, and so we may take it that the labourers completing the work of land reclamation and the first settlers in the new land were menaced more by a small anopheline population than they would have been by a numerous one in an area where stabular deviation was well developed.

CONDITIONS IN 1933.

Breeding-places.

Breeding-places were hardly more developed in 1933 than they were in the previous year. Out of 70 ditches we watched regularly, 10 only showed any larvæ. Most of them were confined to the edges of the new polder, though a few were found in its centre. The average salinity (4,000 mgr. chlorine per litre) was somewhat higher than last year and the average number of larvæ (0.7 per dip) much less than in 1932 (6 per dip). Map 4 shows the extent of the area of high salinity in the new polder.



Map 4.

A. Experimental stables :

1. Stable "5 km."
2. Stable "3 km."
3. Stable "Oude Zeug".
4. Stable "Terp".
5. Village of Slootdorp.
6. Village of Middenmeer.

B. Old land.

C. Breeding-places.

D. Water collections under observation and proved to be free from larvæ.

P. Spot where stained mosquitoes were liberated on July 10th.

Adult Anopheles in the Experimental Stables.

Notwithstanding the breeding of anopheles being seriously impeded, the anopheline density in our experimental stables had risen again since 1932. The average daily output was :

| | 1931 | 1932 | 1933 |
|--------------------------------------|------|------|------|
| "3 kilometres" (No. 2 on map 4)..... | 13 | 110 | 443 |
| "5 kilometres" (No. 1 on map 4)..... | 7 | 113 | 391 |
| "Terp" (No. 4 on map 4)..... | — | 69 | 528 |
| "Oude Zeug" (No. 3 on map 4)..... | — | — | 100 |

This marked increase, bearing no relation to the local production of anopheles, runs parallel with the greatly increased anopheline density in the old land outside the polder (*cf.* diagram, page 458). Breeding within the new polder is no more responsible for it than it was for the stocking of the stables with anopheles during the first year of our observations. In 1933, as in 1931 and 1932, the anopheline population consisted mainly of immigrants—a small minority only were natives.

Experimental Stable "Oude Zeug".

In the preceding table and on map 3, mention has been made of a new experimental stable "Oude Zeug". It was a small one only, containing one goat, which accounts for the comparatively small daily output. This stable was erected to serve a special purpose. To explain this, it is necessary to return to the compass-cards (on maps 2 and 3), with their rays, each of which indicates by its length the number of anopheles considered to have been taken to the stable by an evening wind blowing from the direction to which the ray is pointing. Up till now we only considered the longest ray, pointing south-west in 1931 and south-east (Medemblik) in 1932. But there were others : one pointing to the old land in the west, a third one to the breeding-places along the northern edge of the polder and the adjoining former island of Wieringen. This is as might have been expected. But there was another ray still pointing north-east in a direction where there were no breeding-places. In 1932, we tried to explain this fourth ray by the help of a small settlement (a few house-boats and a labourers' barrack) situated on the spot where stable "Oude Zeug" was erected next year. This settlement was the only place affording shelter to anopheles. We assumed that anopheles, flying from the west or south-west and chancing to miss the stables on passing through the new polder, would alight at that settlement and would return to the stables, starting afresh from that point. In that fashion, the easterly ray might be accounted for.

To justify this assumption, we erected the stable "Oude Zeug", by which this much was proved at least, that anopheles can penetrate so far and in fairly large quantities. In order to prove that they actually can get there straight from the old land, the following experiment was carried out.

Long-range Flying over Distances of 9 and 14 Kilometres.

On July 18th, 1933, at 9-9.30 p.m., a soft wind blowing from W.N.W. (changing to W.S.W. in the course of the night), 3,000

stained anopheles (including 700 males) were liberated at a spot marked "P" on map 3.¹

On July 19th-21st (with weak N.E. evening winds) we caught anopheles in the localities marked on map 3 as Nos. 1-5 :

| | |
|---|---|
| Animal dwellings, No 5. | 495 anopheles, no stained ones. |
| Stable No. 2 ("3 kilometres"). | 872 anopheles, no stained ones. |
| Stable No. 1 ("5 kilometres"). | 987 anopheles, no stained ones. |
| Stable No. 4 ("Terp"), 9 kilometres distant from "P". . . . | 1,468 anopheles, one male stained. |
| Stable No. 3 ("Oude Zeug"), 14 kilometres distant from "P". | 374 anopheles, one male and one female stained. |

These findings prove that anopheles from the most distant parts actually reached stable "Oude Zeug". Moreover, they suggest that many of the long-range flyers went straight to that stable instead of alighting in stables nearer by. This supports our view that the rays of the compass-cards (maps 1 and 2) pointing east in 1931 and 1932 owed their origin to the return-flight of anopheles, which lost their way and came to alight in the shelters near to the spot occupied in 1933 by the stable "Oude Zeug".

Quite apart from the special point it served to elucidate, this experiment is interesting as a fresh evidence of the long flights of our micropterous race of *A. maculipennis*, males as well as females. It should be noticed that the conditions of our present experiment were particularly favourable for recapturing the stained mosquitoes : the land was like a desert—few houses, no trees—and all the stables offering a fair chance of recapture were in our own keeping.

Stabular Deviation.

The numerical proportion of house and stable anopheles had not changed since 1932, as there were no stables occupied by animals

¹ They had been sprayed in the laboratory with a 1 % aqueous solution of methylene blue till they dropped down. Those which recovered had been transported to spot "P" and were set free there. The mosquitoes caught on the ensuing days were tested for the presence of the dye on their bodies by putting them separately into a drop of liquid (composed of equal parts of glycerin, alcohol and chloroform) placed on a slab of milk-glass. If the mosquito is dyed, little clouds of stain are seen detaching themselves from the insect's body and dispersing into the liquid.

larger than rabbits and poultry except for our own stables, which were a long way distant from the centres of human habitation.

From June 15th till September 30th, we found 862 anopheles in 88 houses of the two villages (one more had been erected since 1932) in the new polder—*i.e.*, an average of 10 per house. In 172 animal dwellings belonging to these houses, we found 7,215 anopheles—*i.e.*, an average of 42 per animal dwelling (or group of animal dwellings if more than one belonged to one house), or 4 anopheles in stables to 1 in houses in the new polder.

During the same period we found, in and around Medemblik, in 36 houses 784 anopheles—*i.e.*, an average of 22 per house. In 56 stables or groups of stables (pigs, horses, cattle, goats) belonging to these houses, we found 537,163 anopheles¹—*i.e.*, an average of 9,592 per stable (or group of stables if more than one belonged to one house). So we found over 400 anopheles in stables to 1 in houses in the old land.

In the new polder, consequently, an anopheles leaving a house where it acquired a malarial infection in summer has a chance of re-entering another house on its return from the breeding-places a hundred times greater than in the environments of Medemblik. Of course the chance of its transmitting malaria in summer is increased in the same proportion.

Results of Anopheles Destruction in September.

By the end of August 1933, a couple of cases of malaria suddenly occurring in the new polder came very near offering us a practical demonstration of the above and it is only thanks to the activity of the inhabitants that they did not. This activity consisted of a systematic destruction of all adult anopheles both in human and animal dwellings by means of insecticides containing pyrethrum. We were able to estimate the result of this activity during our subsequent inspections, as is shown in the next table.

| | Average number of anopheles per house | | |
|-----------------------------------|---------------------------------------|------|----------------------|
| | New polder | | Old land (Medemblik) |
| | 1932 | 1933 | 1933 |
| Two inspections in July..... | — | 8 | 7 |
| Two inspections in August..... | 18 | 23 | 24 |
| Two inspections in September..... | 31 | 2 | 26 |

¹ For our method of estimating these numbers, see footnote on page 449.

The catches in September 1933, following on the alarm raised by the end of August, show a marked reduction of anopheles, wholly absent in the old land and likewise in the new polder during the same period of 1932. This is a useful demonstration of what can be accomplished by villagers roused by a sudden alarm. Without this stimulus, however, it is difficult to obtain anything beyond a more or less regular killing of anopheles in the bedrooms, and it is more than doubtful whether this is of any real value.

Our investigations have permitted us to gather some information regarding this point, showing that the results of this simple method of personal prophylaxis are not to be despised.

The Effect of catching Mosquitoes in Houses on the Number of Anopheles in the Bedrooms.

When we investigated the stabular deviation in the new polder in 1932, we simply counted the anopheles present inside the houses, without catching them. In 1933, however, we proceeded in a different way, by catching all mosquitoes for the purpose of determining the kind of blood they had imbibed. This cannot be done without taking the housewife into one's confidence. She is constantly made aware of the fact that here is one mosquito and there another which is left undisturbed because it is a *Culex* or a *Theobaldia* and there again a third one which has to be captured because it is an *Anopheles*. Without knowing it, she picks up a good deal of practical knowledge and soon cannot help feeling interested. Moreover, this search for mosquitoes in her house takes her to all manner of nooks and corners hardly known even to her.

The effect of these explorations was forced upon our attention on our second tour of inspection in 1933. Houses we knew of, since 1932, as particularly neglected by housewifely cares and where we felt sure of a rich catch whenever we entered them, we found cleansed and well kept, and everywhere the inhabitants took a pride in telling us that they had learnt now to identify the "malaria mosquitoes" and that they killed them regularly.

This was done in the bedrooms more than anywhere else. On our first tour of inspection we found 13 anopheles per house and 44 per cent of the total we captured in the bedrooms. On our second tour, the average per house had dropped to 3 and the

proportion found in bedrooms to 21 per cent. On our third round, the average per house had risen as high as 32, but the proportion found in bedrooms had decreased still further to 8 per cent.

In Medemblik, where the population is long since accustomed to malaria and where they show but small interest in mosquitoes, conditions are entirely different : 60-80 per cent of the anopheles collected in houses come from the bedrooms ; and in 1932, the new polder was likewise different, because, at that time, we were conducting our investigations in a fashion so as to attract little or no attention : between August 23rd and September 22nd, 1932, the proportion of house-anopheles found in the bedrooms was 58 per cent, in the same period of 1933 it was 21 per cent.

There is nothing very surprising in the fact that anopheles are rarely found in the bedrooms, since they are regularly killed there, while other parts of the house are neglected. We would not have ventured to draw attention to this effect of a very simple measure of personal prophylaxis if we had not found it accompanied by another one which is less obvious.

Influence of catching Anopheles in Bedrooms on the Proportion of Anopheles containing Human Blood.

We expected to find a greater proportion of carriers of human blood among anopheles caught in human dwellings in the new polder than in the environments of Medemblik. For in the new polder every fourth mosquito entering a house may be expected to have come from another house (by way of the breeding-places, of course), whereas around Medemblik it is most probable that it came from a stable.

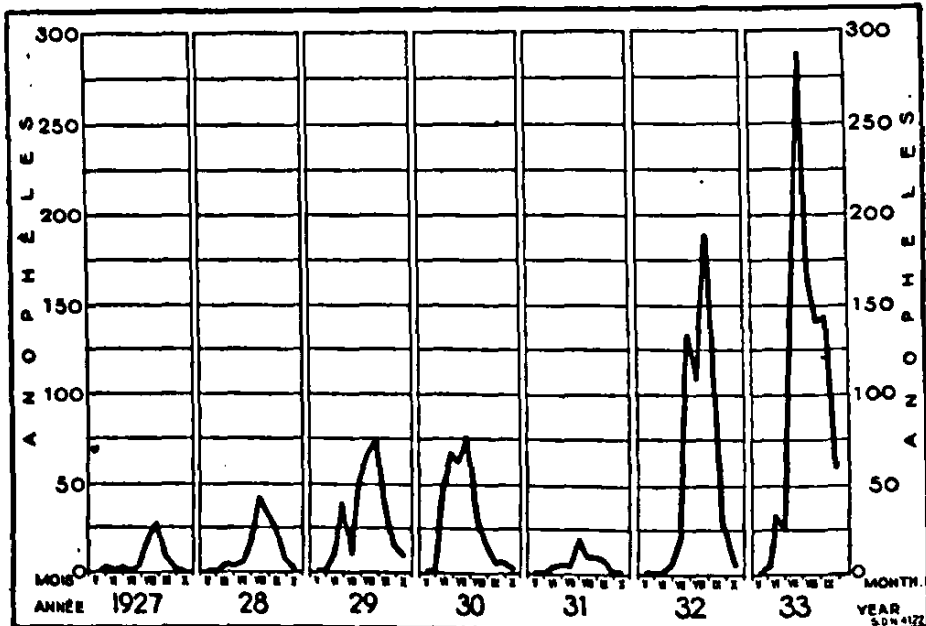
On our first tour of inspection, we found our expectation fully confirmed : 60 per cent (33 out of 55) of the anopheles in the houses of the new polder were carrying human blood, whereas on all our tours in Medemblik we found 16 per cent only (varying from 4 to 31 per cent on our various rounds).

But our remaining tours in the new polder revealed an entirely different situation. The percentage of carriers of human blood dropped to 13 per cent (varying from zero to 22 per cent), a figure lower even than in Medemblik.

Nothing had been changed since our first round except for one thing : the interest awakened among the inhabitants of the houses we were visiting and the consequence of this interest—killing anopheles, by preference in the bedrooms. This preference was fatal to just those anopheles which had the best chance of ingesting human blood. In this way, the number of anopheline carriers of human blood was kept low and so the difference between the new polder and the old land (Medemblik) we expected to find (and actually found on our first tour) was obscured.

Prophylactic Value of catching Mosquitoes in Bedrooms.

So we have to admit that we completely failed in obtaining the information we had been looking for, except for our first round. We had vitiated our results by under-rating the effect of making the inhabitants take notice of the anopheline inmates of their dwellings.



RESULT OF THE CATCHES OF ANOPHELES IN AN UNINHABITED SHELTER ON THE OUTSKIRTS OF MEDEMBLIK FROM MAY TO OCTOBER OF THE YEARS 1927 TO 1933. AVERAGE DAILY CATCHES FOR HALF-MONTHLY PERIODS.

But we believe this failure is of greater interest than the information we wanted to collect, for it shows that regular destruction of anopheles in the bedrooms is most important. The reduction

of the number of anopheles carrying human blood shows that this form of anopheles control tends to loosen the contact between mosquito and man—*i.e.*, tends to reduce the chances of malaria transmission, even when there is no reduction of the anopheles present in other parts of the house. On our first round there were 13 anopheles per house, on our third and fourth rounds nearly twice as many (22) ; but on our first round 60 per cent carried human blood and 44 per cent were found in the bedrooms, whereas on our third and fourth rounds we found 15 per cent only carrying human blood and 11 per cent only in the bedrooms.

The result of this unpremeditated experiment was a surprise to us and we considered it of an importance sufficient to justify this somewhat elaborate description.

CONCLUSIONS.

1. During the years of observation, settlement of anopheles larvæ in the new Wieringermeerpolder was greatly impeded by the high salinity of the water. For that reason, the greater part of the adult anopheline population consisted of immigrants, hailing from the old land, more particularly from the environments of Medemblik. The anti-larval operations of 1931 conducted in that area favourably influenced anopheline conditions in the Wieringermeer, as became apparent on their being discontinued in 1932.

2. Man, working around Medemblik, demonstrated on a small scale what results may be obtained in this country by carrying out anti-larval operations. In the Wieringermeer, nature has repeated this experiment on a far larger scale. In both cases, it has been found possible to reduce the numbers of anopheles to a quarter or a fifth of the anopheline density in the surrounding areas, where breeding goes on freely.

3. The salutary effect to be expected from the small anopheline population in the Wieringermeer was more than counterbalanced by the lack of "stabular deviation"—*i.e.*, the condition characterised by mosquitoes being very numerous in human dwellings (even as compared with houses in areas where anopheles breed freely), but comparatively rare in stables. This condition is due

to the absence of stables sheltering live-stock of any size above rabbits and poultry.

4. The effect of the lack of stabular deviation, a menace to the health of the new polder, was compensated to some extent by the inhabitants regularly destroying anopheles in their bedrooms. This simple activity resulted in decreasing the number of anopheles having ingested human blood—*i.e.*, of the potential malaria vectors. The total number of anopheles found in each house was hardly reduced in this way.

5. A sudden alarm, arising from malaria making its appearance in the new polder, had the effect of stimulating the inhabitants to much greater activity, and to a wholesale destruction of the domestic anopheline population by means of pyrethrum sprays. The effect was so striking that it is well to bear in mind : (1) that the inhabitants were thoroughly prepared by an energetic propaganda ; (2) that the bedrooms were protected by wire gauze which, although insufficient by itself, helped to keep anopheles away ; (3) that the new polder sheltered an immigrant anopheline population only. It would have been quite another matter to get rid of native mosquitoes.

6. The high salinity of the water in the new polder, which at present is preventing anopheles from breeding freely, may be expected gradually to come down to normal. Unless normal stabular deviation be established simultaneously, malaria conditions in the new polder will tend to become worse than in the old land.

THE EFFECTS OF THE ECONOMIC DEPRESSION ON THE POPULATION OF VIENNA

By

A. GÖTZL, W. KORNFELD and E. NOBEL.

A. RESULTS FROM THE POINT OF VIEW OF SOCIAL HYGIENE.

1. SCOPE AND ORGANISATION OF THE ENQUIRIES.

Although, generally speaking, the investigations undertaken in Vienna were conducted in accordance with the guiding principles laid down by the Health Organisation,¹ it was found necessary to depart from these principles on some points of detail in order to meet local circumstances.

The urgency of the work, together with the scarcity of available funds, made it impossible to extend the enquiries to the 1,000 families which were rightly regarded as an absolute minimum. As the unemployed, and even more so the employed, were reluctant to come forward for examination in the numbers desired unless they were offered some *quid pro quo*, the number of cases to be investigated had to be restricted at the outset. Consequently the investigation covered only 558 families of unemployed, comprising a total of 2,729 persons. The cases were selected by the anti-tuberculosis centres in the various districts, a course which was justified by the fact that these centres are in touch with a great many persons who, though not suffering from the disease, apply for advice on a variety of matters, usually of a social character. It must therefore be

¹ "The Most Suitable Methods of detecting Malnutrition due to the Economic Depression." (Report of the Conference held in Berlin in December 1932.) *Quarterly Bulletin of the Health Organisation*, Vol. II, No. 1, March 1933.

emphasised that, although this category of persons investigated was reached through the anti-tuberculosis centres, they were all, by medical—or at least by practical—standards, healthy subjects.

Greater difficulties were experienced in getting in touch with those still in employment, whom it was necessary to examine for purposes of comparison. In this matter, the Workers' and Employees' Chamber and the trades unions afforded valuable assistance, but, in spite of their efforts, only 152 families in this category, comprising 543 persons, could be induced to submit to investigations. Thus, the undoubtedly justified recommendation that the families investigated for purposes of comparison should be as numerous as those of the unemployed could not be carried out. Nor was it possible to comply with the recommendation that control investigations should be carried out on the same scale as the principal enquiries, since the observation period would have been far too short to yield figures disclosing statistically significant differences, as distinct from mere chance variations. A further factor was the circumstance that people broken by daily want could not be expected to submit to repeated investigations without the distribution of assistance in kind on a comparatively large scale. In these circumstances, the investigators had to be satisfied with the investigation of control cases selected at random. An examination of the forms reproduced in the annexes, which analyse the physical condition and general circumstances of each individual and also the factors common to all the members of the various households, will show what criteria were considered important for the purposes of the enquiry. It should further be noted that, as was only to be expected, not all the questions were answered by every individual or family and also that not all the individuals could be induced to submit to the original investigations or subsequent re-check, so that the percentage figures do not exactly correspond to the basic figures previously given. The original investigations in regard to the unemployed were carried out in April and May of 1933, while those relating to the employed took place in June and July ; the control examination was carried out some five or six months later.

The sharp distinction made between the unemployed and employed, which is no doubt fully justified in theory, is only partly so when applied to the examination of families from the point of

view of public health. For such purposes, the only possible criterion must be whether the person responsible for the maintenance of the family is employed or unemployed within the meaning of the law on the date of the investigation. In families which include children old enough to work, the latter may contribute to the maintenance of the family, even when the father is out of work ; conversely, children who are unemployed may add greatly to the family burden of fathers who are in employment ; in the last place, it is possible that all the employable members of the family are either working or unemployed together. The position of the wife of the head of the family also calls for special consideration in this respect, as she too is sometimes employed and sometimes unemployed within the meaning of the law, while, in a third category of families, she confines herself to purely household duties. In the last place, there is the case of work done at home, which was met with in forty of the families investigated. In the large towns, however, such work is generally only casual in character and, for that reason, cannot be regarded as forming a normal part of the process of production but must be considered as merely supplementary. As a rule, moreover, such work is done by the family as a whole rather than by individual members. From these considerations and the results of practical experience, it is therefore clear that the classification of families according to whether the head of the family is employed or not is not reliable in every respect. It must also be remembered that there are many families in which the chief wage-earner is not a man (for example, the families of widows living upon casual earnings of the most varied kinds, the families of divorced women with children not in receipt of alimony, etc.). To what extent the subdivision into "unemployed" and "employed" groups is justified will be clear from the following data regarding the period extending from January 1st, 1930, to April-May 1933. There had been the following periods of unemployment at the time of the investigation :

| | One person | | | | | | Two persons | | | | | | |
|--------------------------------|--------------------|-------------|--------------|--------------|--------------|--------------|--------------|---------------------|--------------|--------------|--------------|--------------|--------------|
| | Less than 6 months | 6-12 months | 12-18 months | 18-24 months | 24-30 months | 30-36 months | 36-48 months | Less than 12 months | 12-24 months | 24-36 months | 36-48 months | 48-72 months | 72-90 months |
| Families of the unemployed. | 12 | 26 | 42 | 49 | 70 | 75 | 108 | — | 5 | 6 | 13 | 29 | 6 |
| Families of the employed . . . | 11 | 7 | 6 | 4 | 4 | 4 | 5 | 3 | — | 2 | — | 2 | — |

Furthermore, in the group of the "unemployed", there were six families, each of which included three persons out of work, totalling 23, 43, 45, 67, 75 and 105 months' unemployment respectively. In the "employed" group, there were also two families, each with three members out of work, the periods of unemployment involved being 37 and 65 months respectively. In the unemployed group, two families were found with four unemployed members totalling 72 and 85 months' unemployment, similar conditions being noted in two families in the employed group, the total unemployment being 10 and 123 months respectively. As shown by the table, the temporary unemployment of one individual (up to six months) was found to exist in both groups to almost exactly the same extent. The same applies to the families in which there were four persons unemployed at the same time: the absolute figures regarding the maximum period of unemployment for one person in a family (40 months) naturally differ widely. Percentage figures which would give a faithful picture of the situation cannot be established with such limited material at our disposal. The absolute figures quoted show that there is no clear-cut difference between the position of the "unemployed" and that of the "employed".

2. HOUSING CONDITIONS.

Leaving rooms which are sub-let out of account, the dwellings visited were distributed as follows:

| Number of rooms ¹ | | Percentage of total |
|------------------------------|---|---------------------|
| 0.5 | (1 small closet) | 3 |
| 1 | (kitchen or bedroom) | 3 |
| 1.5 | (kitchen or bedroom and small closet) | 5 |
| 2 | (kitchen, bedroom or kitchen, 2 small closets) | 47 |
| 2.5 | (kitchen, bedroom, small closet) | 28 |
| 3 | (kitchen, 2 bedrooms; or kitchen, bedroom, 2 small closets) | 11 |
| 3.5 | (kitchen, 2 bedrooms, small closet) | 3 |
| 4 | (kitchen, 3 bedrooms, 1 small closet; or kitchen, 2 bedrooms, 2 small closets)..... | — |

¹ For the sake of uniformity, small closets have been counted as half a living-room each and kitchens as entire living-rooms; entry-halls and balconies, on the other hand, have not been included at all.

The percentage figures for the above categories of dwellings do not show any difference between the "employed" and "unemployed" groups; it should be noted, however, that four-room dwellings were only met with in the case of three families in the "employed" group.

The following is a table of the amount of house-room occupied by the various households investigated; in compliance with the usual practice, two children below the age of 14 have been counted as equal to one adult.

| Persons | Unemployed | | | | | | | Employed | | | | | | | |
|---------|--|---|-----|-----|-----|----|-----|--|---|-----|----|-----|---|-----|---|
| | Dwellings classified according to number of rooms: | | | | | | | Dwellings classified according to number of rooms: | | | | | | | |
| | 0.5 | 1 | 1.5 | 2 | 2.5 | 3 | 3.5 | 0.5 | 1 | 1.5 | 2 | 2.5 | 3 | 3.5 | 4 |
| 1 | — | — | — | — | — | — | — | — | 1 | — | — | — | — | — | — |
| 1.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 2 | 2 | 2 | 2 | 13 | — | 1 | — | 3 | 4 | 4 | 13 | 2 | 1 | — | 1 |
| 2.5 | — | 5 | 2 | 13 | 3 | 1 | 1 | 2 | 2 | 2 | 14 | 7 | — | 1 | — |
| 3 | 4 | 4 | 10 | 100 | 45 | 7 | — | 1 | 2 | 2 | 16 | 6 | 1 | 1 | 1 |
| 3.5 | 4 | 1 | 6 | 55 | 40 | 16 | 3 | — | — | 2 | 11 | 5 | — | 3 | — |
| 4 | 1 | — | 2 | 35 | 16 | 11 | 1 | — | — | 1 | 10 | 8 | 2 | 1 | — |
| 4.5 | — | 1 | 1 | 17 | 15 | 16 | — | — | — | — | — | 3 | 2 | 1 | — |
| 5 | — | — | 1 | 11 | 12 | 2 | — | — | — | — | — | 2 | 2 | — | — |
| 5.5 | — | — | — | 3 | 5 | 3 | 4 | — | — | — | 2 | 4 | — | — | 1 |
| 6 | 1 | — | — | 3 | 3 | 2 | — | — | — | — | 4 | 1 | 1 | — | — |
| 6.5 | — | — | — | — | 4 | 2 | — | — | — | — | — | — | 1 | 1 | — |
| 7 | — | — | — | — | 1 | — | — | — | — | — | — | — | — | — | — |
| 7.5 | — | — | — | — | 1 | — | — | — | — | — | — | — | — | 1 | — |
| 8 | — | — | — | — | 1 | — | 1 | — | — | — | — | — | — | — | — |
| 10 | — | — | — | — | — | — | — | — | — | — | — | 1 | — | — | — |

It is also clear that there are no serious differences as regards the number of persons per room in the various categories of dwellings, since, in families of the sizes which are most frequently met with (2.5, 3 and 3.5 persons), the distribution among the most common types of dwelling (kitchen, small closet; kitchen, bedroom; kitchen, bedroom, small closet) is approximately the same among employed and unemployed.

Noteworthy differences were, however, brought to light in regard to the number of beds in relation to the size of the family, irrespective of the age of its members. The following are the results of the investigation, among the unemployed and employed respectively.

| | Unemployed | Employed |
|--|--------------|----------|
| | (Percentage) | |
| Number of beds = number of persons | 23 | 43 |
| 1 bed short | 36 | 21 |
| 2 beds short | 24 | 19 |
| 3 and more beds short | 17 | 17 |

The proportion of families with one bed per person in the "employed" is almost twice that found among the "unemployed". A shortage of one or two beds, moreover, is more frequently met with in the "unemployed" families than among the "employed". A different impression is, however, gained if the families with 3 or more children, in both groups, are singled out for consideration :

| | Unemployed | Employed |
|--|--------------|----------|
| | (Percentage) | |
| Number of beds = number of persons | 10 | 11 |
| 1 bed short | 26 | 24 |
| 2 beds short | 32 | 27 |
| 3 and more beds short | 32 | 38 |

It should be borne in mind that there are only 236 such families comprising 1,384 members among the "unemployed" and 40 families with 256 members among the "employed". The basic figures are therefore so small that the calculation of comparative percentage figures would scarcely seem justified.

Similarly, it was found that there was no appreciable difference between the two principal categories in the matter of household cleanliness for which the various families were classified as very good, good, fair and bad. If the first two of these classes are combined and ranked as "good" and the last two as "bad", the first category is found to include 82 per cent of the "unemployed" and 84 per cent of the "employed", while 18 per cent of the "unemployed" and 16 per cent of the "employed" fall into the second category. Among families with numerous children (three or more), the investigations revealed a high level of household cleanliness in the case of 72 per cent of the "unemployed" and 60 per cent of the "employed" families, while conditions were bad in 28 and 40 per cent respectively. This difference may perhaps be due to the fact that, in the "unemployed" families, more time can be devoted to the care of the house. It is, however, more probable that this is a fortuitous result due to insufficient material.

As regards the amenities of the dwellings, about one-fifth included an entry hall and the number of dwellings with balconies was negligible. As regards water-supply and privies, it may be noted that in 44 per cent of the cases these were inside and in 54 per cent outside the dwellings visited ; in the remainder the water-supply was inside and privies outside, or *vice versa*.

3. INCOME.

In order to simplify as far as possible our account of income, which, among the unemployed, is often a highly complicated question, we first took the families without lodgers, subtracted the rent from total income and divided the result by the number of persons in the family, children under 14 again being counted as half an adult. The deduction of rent from total income was prompted by the consideration that the important point was to discover how much remained available for food and other necessaries. It is of course well known that a number of families pay no rent, but it has been, in spite of the most painstaking inquiries, impossible to ascertain exactly how many. Working on these lines, the results of our investigations were as follows :

| Monthly income per person | Families of the unemployed | Families of the employed |
|--------------------------------|----------------------------------|--------------------------------|
| | (Percentage) | |
| Ten schillings or under | 11.8 | — |
| From 10 to 20 schillings | 30.2 | 1.2 |
| From 20 to 30 schillings | 38.6 | 4.5 |
| From 30 to 40 schillings | 10.6 | 8.3 |
| From 40 to 50 schillings | 5.4 | 16.7 |
| From 50 to 60 schillings | 1.7 | 15.5 |
| From 60 schillings | 1.7 | 53.8 |

It should further be mentioned that, in 12 per cent of the "employed" families, it was found that the available monthly income exceeded 100 schillings per person and that the proportion of "unemployed" families with a monthly income not exceeding 30 schillings per person is almost as great as the proportion of "employed" families with a monthly personal income of over 40 schillings (80 as against 86 per cent).

Among families with three or more children—236 among the unemployed and 40 among the employed—the pecuniary situation is naturally even more unsatisfactory, as the proportion of families

with the lowest monthly income is higher. In 49.8 per cent of the "unemployed" large families, the monthly income does not exceed 20 schillings per head, while even among "employed" families the proportion is as high as 5 per cent; only a third of the latter are in receipt of a monthly income of 60 schillings per head.

The following table shows what percentage of the total family income of each group of 100 families goes in rent :

| | 0-10 | 10-20 | 20-30 | 30-40 | 40-50 | 50-75 | 75-100 | Over 100 |
|------------------------------|------|-------|-------|-------|-------|-------|--------|-------------|
| Families of the unemployed . | 17 | 46 | 19 | 7 | 5 | 4 | 1.5 | 0.5 |
| Families of the employed .. | 80 | 17 | 3 | — | — | — | — | — |

Rent does not therefore appear to play a very important part in the household budget of the "employed" families. In 80 cases out of 100, it does not exceed 10 per cent, but a similar proportion of "unemployed" is not reached until those paying up to 30 per cent are added in. That, in the case of one-tenth of the "unemployed" families investigated, rent was calculated to absorb one-half or more of the family income will therefore cause no surprise. A small income—derived, in the main, from relief—combined with relatively high rent can only too easily produce such percentages. But the foregoing calculations must not be confused with the question of the amounts actually paid in rent. Enquiries on this point would undoubtedly have led to regrettable, but justified, consequences in a large number of cases.

It was particularly important to ascertain the various sources from which families derived their total income. For this purpose, it was only logical to divide the family income considered into the three following groups : (a) wages ; (b) relief out of public funds (unemployment relief, allowances of various kinds, maintenance grants, sickness insurance, etc.); and (c) assistance out of private funds (including food, income from lodgers, etc.). Leaving out of account those families a part of whose income is derived from sub-letting, the total monthly income was distributed among the three groups as follows :

| | (a) | (b) | (c) |
|----------------------------------|-----|-----|-----|
| Families of the unemployed | 33 | 61 | 6 |
| Families of the employed | 95 | 3 | 2 |

Even in the families of the "unemployed", there may be a not inconsiderable income from work which sometimes accounts for as much as one-third of the total income. But, while two-thirds of

the income of such families was derived from a wide variety of forms of relief, the latter only accounted for one-twentieth of the income of the families of those in employment. The average monthly income of all the "unemployed" families, not including those taking in lodgers, amounted to 98.3 schillings, while the average for all "employed" families—again excluding those taking in lodgers—was 239 schillings. Paying lodgers were found in the homes of 40 "unemployed" and 19 "employed" families. In the former cases, the sums received from lodgers represented the same proportion of the total income as wages (16 per cent), while, in the case of the latter, it represented approximately the same percentage as the assistance received out of public funds (4 as compared with 3 per cent). For "unemployed" families, it is therefore of the highest importance to secure a paying lodger. If the income from lodgers is included in that part of the total income which is represented by column (c), the only result would be slight changes in regard to the "unemployed" families. The income in (a) and (b) would be reduced in each case by 1 per cent, while that in (c) would be increased by 2 per cent of the total income. In the case of the families of the employed, there would be no difference capable of statistical expression, the material being insufficient. If the families with lodgers are included and income from this source added to the total income, the latter is increased to a monthly average of 98.9 schillings in the families of the unemployed and 241 schillings in the families of those at work.

The degree of hardship which the above figures reveal is brought into even higher relief when it is realised what a multitude of heavy charges have to be met out of such an income. Investigations on this aspect of the question are very difficult. Mistrust, shyness and fear that their statements might be improperly used lead those concerned either to refuse information altogether or to make statements which are not true; occasionally, it is possible to detect exaggerations prompted by the hope that, in this way, some kind of relief might be obtained. Thus, a complete and reliable reply to all the questions which it would be desirable to put on this point is absolutely impossible to obtain. The figures given above must therefore certainly be regarded as a minimum.

First and foremost among the regular charges in question comes rent. Of the other charges, maintenance allowances, the repayment

of loans, and school fees play such a small part in the budget of the families investigated that they can well be left out of account. In regard to debts and transactions with pawnbrokers, on the other hand, the position revealed by the enquiries was truly appalling. Even among those in employment, 63 families, or approximately one-third, were in debt, though the exact amount of their indebtedness was impossible to ascertain. Among the unemployed, a total indebtedness of 42,527 schillings was owned to by 356 families (64 per cent), making an average of 119 schillings per family. If the total income of these families is calculated proportionately to the total income of all the families of the unemployed (55,133 schillings), their acknowledged indebtedness alone must stand in a ratio of approximately 6 : 5 to their total income (an indebtedness of 42,527 schillings against a monthly income of 35,237 schillings). But that is not all. Pawning transactions still open at the date of the enquiries were admitted by 349 families of the unemployed and 45 families of those in employment, but forfeited pledges worth several thousand schillings had to be left out of account through lack of trustworthy information. The open transactions represented similar amounts in both categories of families—*i.e.*, approximately 99 schillings per family. It would therefore appear that by far the heaviest charge on the budget of the "unemployed" families covered by the enquiry with an income of approximately 100 schillings a month was their indebtedness of, on an average, 119 schillings and payments due to pawnbrokers representing an average of 99 schillings. Even among the families of the employed, the indebtedness—if one may judge by the number of families which admitted debts—is far from small ; the amount of their indebtedness to pawnbrokers was also much the same as in the case of the unemployed. And again it must be emphasised that, as a guide to the distress from which these families are suffering, the amounts reported can only be regarded as a minimum.

As against this picture of want, the extent to which it was found that these families were in receipt of assistance in kind is of some importance. A total of 179 children was receiving school meals (in schools or kindergartens). It was also found that, in eight families, even the adults were being fed, while to 232 others parcels of food were being distributed ; 55 were in receipt of other provisions, 79 were being provided with fuel and 24 with clothing. In many

families, it was naturally found that assistance was being received in a variety of forms, so that assistance in kind only applies to a small section of those who need help. Among the families of the employed, only five children were found to be in receipt of school meals, and only one family was receiving provisions.

B. RESULTS OF MEDICAL EXAMINATION.

The foregoing explanations show that it is not always possible to draw a clear distinction between the families whose breadwinner is unemployed and the families of employed persons. Nevertheless, from a material point of view, in the vast majority of the families studied, a very appreciable difference is noticeable between the families of unemployed persons and those of persons in employment. Although the number of families studied was too small to allow of the solution of certain problems, there was reason to hope that the results of the enquiry would throw light on some fundamental points requiring elucidation which may be stated as follows : Is it possible to prove objectively that unemployment among the population of Vienna has affected the state of nutrition and the physical development of the families concerned ? In what age-groups are these effects most noticeable ? Is one sex affected to a greater degree than the other ? What methods of investigation bring out these differences (if any) most clearly ? What sources of error have been noted during the investigation ?

We think that the last two questions are very important because, owing to the economic situation, it is unfortunately quite likely that, in the near future, it may be found desirable to institute further similar enquiries, not only in Austria, but in most other civilised countries, and because we ourselves have often had to gain the necessary experience empirically and then to undertake a further series of enquiries in the light of the experience gained.

FIRST SERIES OF INVESTIGATIONS.

Our first series of investigations was organised as follows : From the registers of the tuberculosis centres of five Vienna municipal districts we selected a fairly large number of families whose father,

or other breadwinner, was unemployed, but in which no case—or at any rate no serious case—of tuberculosis had been discovered. Visiting nurses first conducted enquiries in these families by visiting them in their homes, the results being set down in special questionnaires. Facts concerning the whole family were noted on a family questionnaire which served as cover for the other questionnaires (see Annex 1). In this cover were placed, for each member of the family, two sheets : a personal questionnaire (Annex 2) containing other information of social interest to be obtained by the visiting nurse and which referred solely to the person concerned, and an individual medical questionnaire (Annex 3), on which the results of the medical examination were entered. In connection with all these questionnaires, provision had been made for an examination for control purposes some time after the first enquiry. After the enquiries conducted in their homes, the families were invited to come, by groups, to the consulting-rooms of the five anti-tuberculosis centres ; 558 families, including in all 2,729 individuals, complied with this invitation and were examined in April and May 1933.

Subsequently, in June, in order to ensure a certain degree of comparability with other families belonging roughly to the same social stratum, but whose breadwinner was in employment, 152 families, including in all 543 persons, were examined according to the same plan.

A summary examination of the completed medical questionnaire first confirmed the fact that the members of the families designated by the anti-tuberculosis centres were not sick people. Apart from disease due to age, such as arterio-sclerosis, emphysema, etc., which occur fairly frequently in the questionnaires of persons over a certain age, the number of chronic cases of disease was not higher than is generally met with in fairly large groups in populous towns. The same remark applies in general to acute diseases, such as angina, bronchitis, etc., which were sometimes noted, and to infectious diseases of children. We were therefore able to concentrate our attention on such data as were likely to throw light on the problems mentioned above. The facts noted in this connection were : height, weight, blood content of the skin and visible mucous surfaces according to subjective estimates and the Pelidisi index.

Table I shows the number, average height and average weight of the persons examined, classified according to sex and age and

TABLE I.
AVERAGE FIGURES OF HEIGHT AND WEIGHT REGISTERED IN
FAMILIES OF UNEMPLOYED AND OF EMPLOYED.

A. MALES.¹

| Age groups (Years and months) | Height | | | Weight | | |
|----------------------------------|-----------------|------------|--------|-----------------|-----------|--------|
| | Unem- ployed | Employed | Normal | Unem- ployed | Employed | Normal |
| 0 ; 8 | 60.9 (15) | — | — | 6.7 (16) | — | — |
| 1 | 71.7 (10) | 73.0 (2) | 76 | 9.3 (11) | 10.4 (2) | 10.2 |
| 1 ; 6 | 79.1 (14) | 77.7 (3) | 82 | 11.0 (14) | 11.1 (3) | 11.3 |
| 2 | 85.6 (18) | 85.3 (3) | 87 | 12.4 (18) | 12.6 (3) | 12.7 |
| 3 | 90.9 (38) | 93.3 (6) | 95 | 14.2 (38) | 14.4 (6) | 14.5 |
| 4 | 100.1 (32) | 100.7 (6) | 102 | 16.3 (32) | 17.1 (6) | 16.5 |
| 5 | 105.5 (39) | 107.7 (7) | 108 | 17.7 (39) | 18.6 (7) | 18.5 |
| 6 | 111.4 (58) | 112.1 (16) | 114 | 19.2 (58) | 18.7 (16) | 20.5 |
| 7 | 117.7 (75) | 116.4 (5) | 119 | 21.3 (75) | 21.5 (5) | 22.5 |
| 8 | 122.1 (74) | 122.9 (7) | 124 | 23.5 (74) | 23.7 (8) | 24.5 |
| 9 | 127.4 (73) | 126.7 (16) | 128 | 25.6 (73) | 25.9 (16) | 26.7 |
| 10 | 133.0 (98) | 136.8 (11) | 132 | 28.9 (98) | 31.2 (11) | 20.0 |
| 11 | 136.1 (76) | 138.4 (18) | 137 | 30.2 (76) | 31.8 (18) | 31.8 |
| 12 | 141.6 (85) | 141.4 (10) | 142 | 33.8 (85) | 35.0 (10) | 35.0 |
| 13 | 146.2 (55) | 152.3 (6) | 148 | 36.9 (55) | 41.0 (6) | 38.0 |
| 14 | 150.9 (40) | 151.0 (8) | 154 | 40.9 (40) | 39.6 (8) | 43.0 |
| 15 | 158.1 (23) | 158.7 (3) | 160 | 47.4 (23) | 46.0 (3) | 48.0 |
| 16 | 162.1 (9) | 171.5 (2) | 165 | 52.2 (9) | 64.6 (2) | 53.0 |
| 17 | 165.2 (17) | 167.0 (3) | 168 | 54.8 (17) | 60.5 (3) | — |
| 18 | 167.0 (12) | 152.0 (1) | 169 | 59.7 (12) | 47.5 (1) | — |
| 19 | 164.4 (10) | 175.7 (4) | 169 | 58.1 (10) | 64.2 (4) | — |
| 20 | 165.2 (12) | 161.0 (1) | 170 | 57.3 (12) | 51.0 (1) | — |
| 21-24 | 169.3 (27) | 165.3 (9) | 170 | 60.2 (27) | 62.3 (9) | — |
| 25-29 | 167.3 (27) | 168.6 (10) | 170 | 60.3 (27) | 60.7 (10) | — |
| 30-34 | 166.6 (77) | 167.0 (34) | 170 | 61.0 (77) | 61.9 (34) | — |
| 35-49 | 165.7 (283) | 167.7 (70) | 170 | 61.5 (283) | 62.9 (70) | — |
| 50-59 | 164.7 (58) | 166.2 (17) | 169 | 61.3 (58) | 67.4 (17) | — |
| 60- | 162.3 (15) | 163.7 (3) | 168 | 60.2 (15) | 52.8 (3) | — |

B. FEMALES.

| | | | | | | |
|-------|-------------|------------|-------|------------|-----------|------|
| 0 ; 8 | 64.5 (4) | 58.0 (3) | — | 6.2 (6) | 5.0 (3) | — |
| 1 | 71.6 (5) | — | 75 | 9.6 (7) | 8.1 (1) | 9.8 |
| 1 ; 6 | 79.8 (5) | — | 81 | 11.2 (5) | — | 10.9 |
| 2 | 83.7 (19) | 90.0 (2) | 86 | 11.9 (19) | 13.1 (2) | 12.2 |
| 3 | 90.8 (18) | 90.0 (6) | 94 | 13.5 (18) | 12.0 (6) | 14.0 |
| 4 | 98.0 (36) | 101.0 (2) | 101 | 15.6 (36) | 18.2 (2) | 16.0 |
| 5 | 105.2 (55) | 102.9 (8) | 107 | 17.4 (55) | 17.0 (8) | 18.0 |
| 6 | 110.8 (40) | 111.6 (8) | 113 | 19.0 (40) | 18.8 (8) | 20.0 |
| 7 | 116.5 (54) | 118.2 (12) | 118 | 20.9 (54) | 21.4 (12) | 22.0 |
| 8 | 121.7 (72) | 122.7 (11) | 123 | 23.1 (72) | 23.3 (11) | 24.0 |
| 9 | 126.6 (64) | 126.9 (7) | 127 | 25.2 (64) | 24.3 (7) | 26.0 |
| 10 | 131.2 (80) | 130.7 (12) | 132 | 27.3 (80) | 27.0 (12) | 28.5 |
| 11 | 137.5 (61) | 133.4 (7) | 138 | 30.5 (61) | 27.8 (7) | 31.5 |
| 12 | 145.3 (54) | 143.4 (10) | 144 | 36.1 (54) | 34.1 (11) | 35.0 |
| 13 | 148.6 (60) | 147.2 (10) | 149 | 39.5 (60) | 40.7 (10) | 38.5 |
| 14 | 154.1 (29) | 150.0 (2) | 154 | 45.0 (29) | 47.0 (2) | 43.0 |
| 15 | 153.7 (18) | 156.2 (4) | 157 | 47.8 (18) | 53.2 (4) | 47.5 |
| 16 | 155.0 (15) | 163.0 (2) | 158.5 | 51.3 (15) | 48.5 (1) | 52.5 |
| 17 | 156.3 (12) | 156.0 (5) | 159.5 | 50.5 (12) | 52.5 (5) | 55.5 |
| 18 | 154.9 (13) | 152.0 (4) | 160 | 51.7 (13) | 48.5 (4) | 57.0 |
| 19 | 159.4 (24) | 154.0 (1) | 160 | 53.9 (24) | 50.0 (1) | — |
| 20 | 155.8 (8) | 162.0 (1) | 160 | 51.8 (8) | 55.2 (1) | — |
| 21-24 | 155.0 (25) | 157.7 (10) | 160 | 50.4 (25) | 53.8 (10) | — |
| 25-29 | 153.2 (54) | 157.0 (22) | 160 | 54.1 (54) | 58.9 (22) | — |
| 30-34 | 155.5 (123) | 156.7 (31) | 160 | 56.8 (123) | 60.9 (31) | — |
| 35-49 | 154.6 (354) | 154.9 (72) | 160 | 59.1 (354) | 63.2 (72) | — |
| 50-59 | 150.1 (27) | 161.0 (7) | 159 | 58.6 (27) | 63.4 (7) | — |
| 60- | 151.1 (9) | 157.0 (3) | 158 | 53.3 (9) | 62.1 (3) | — |

¹ The figures in brackets indicate the number of persons examined.

according to whether they are members of families of employed or unemployed persons respectively. For purposes of comparison we have added, in each age-group of children and adolescents, figures which, in the light of recent investigations, we regard as the normal figures for our population. These figures have also been taken as a basis in the new edition of PIRQUET's scale of values which we have followed.² In the case of adults, we have adopted 170 cm. as the normal height for men, and 160 cm. for women. The men's weights were calculated according to a table practically identical with HASSING's table.³ The only changes made were such as would eliminate certain slight irregularities to be noted when HASSING's values tables, particularly in the lowest height groups, are plotted out in the form of graphs. For women, we had first to establish a corresponding table and then ascertain whether it was in fact suitable for our enquiry. We decided to allow 700 grammes additional weight for each additional centimetre of height and—as regards age—an increase of 1 kg. for each additional five years. Furthermore, in constructing graphs from the values shown in our tables, we made use of certain standard curves as guidance. On the lower portion of the graphs showing the height and, approximately, the progression of weight in the age-group, including the youngest individuals (18 to 20 years), we used BACH-ROTH's values (see *Tabulæ biologicæ*, Volume III) ; for the age-group 25 to 30 we took HAUTMANN's "Normal values", and for the 40 to 50 group we referred to KELLOG's normal weights for women of different heights.

As the groups given in Table I, particularly of children and adolescents, are generally too small to be of statistical value, the same data have been set out in Table II for wider age-groups, but without the youngest group. In order to facilitate comparison between the various groups, we have also given, for each group, the average age of the persons examined. The figures in this table allow us first to draw the following conclusions regarding height.

The average height of adults over 20 years of age, both men and women, and in almost all age-groups is distinctly greater among the

¹ KORNFELD, W. (1933) : "Ueber Normalwerte für Grösse und Gewicht bei Kindern und Jugendlichen", *Wiener klin. Wochenschr.*, 46, page 683.

² S. BRUGSCH-LEWY, 1926, *Biologie der Person*. Vienna, Urban & Schwarzenberg.

TABLE II.
AVERAGE FIGURES FOR HEIGHT AND WEIGHT IN LARGER
AGE GROUPS.

| Age groups (Years) | Unemployed | | | Employed | | |
|--------------------|----------------|--------------------------------|-------------------------------|----------------|--------------------------------|-------------------------------|
| | Average height | Average age (Years and months) | Normal height for average age | Average height | Average age (Years and months) | Normal height for average age |
| A. MALES. | | | | | | |
| <i>Height.</i> | | | | | | |
| 7-8 | 119.9 | 7 ; 6 | 121.5 | 120.2 | 7 ; 8 | 122.5 |
| 9-11 | 132.3 | 9 ; 11 | 132.0 | 131.0 | 10 ; 0 | 132.0 |
| 12-14 | 144.5 | 12 ; 8 | 146.0 | 147.3 | 12 ; 11 | 147.5 |
| 15-16 | 159.1 | 15 ; 1 | 160.5 | 163.8 | 15 ; 5 | 162.0 |
| 17-20 | 165.5 | 18 ; 3 | 169.0 | 168.6 | 18 ; 4 | 169.0 |
| 21-29 | 168.3 | 25 ; 0 | 170.0 | 167.6 | 25 ; 2 | 170.0 |
| 30-49 | 165.9 | 38 ; 11 | 170.0 | 167.5 | 37 ; 10 | 170.0 |
| 50- | 164.2 | 55 ; 9 | 170.0 | 165.8 | 56 ; 3 | 170.0 |
| <i>Weight.</i> | | | | | | |
| | Average weight | | Normal weight for average age | Average weight | | Normal weight for average age |
| 7-8 | 22.3 | 7 ; 6 | 23.5 | 22.9 | 7 ; 8 | 23.8 |
| 9-11 | 28.3 | 9 ; 11 | 29.0 | 29.4 | 10 ; 0 | 29.0 |
| 12-14 | 36.3 | 12 ; 8 | 37.3 | 38.0 | 12 ; 11 | 38.1 |
| 15-16 | 48.8 | 15 ; 1 | 47.0 | 53.5 | 15 ; 5 | 52.0 |
| 17-20 | 57.1 | 18 ; 3 | 62.0 | 59.6 | 18 ; 4 | 62.0 |
| 21-29 | 60.2 | 25 ; 0 | | 61.5 | 25 ; 2 | |
| 30-49 | 61.4 | 38 ; 11 | | 62.3 | 37 ; 1 | |
| 50- | 61.1 | 55 ; 9 | | 65.0 | 56 ; 3 | |
| B. FEMALES. | | | | | | |
| <i>Height.</i> | | | | | | |
| | Average height | | Normal height for average age | Average height | | Normal height for average age |
| 7-8 | 119.7 | 7 ; 6 | 120.5 | 120.3 | 7 ; 4 | 120.0 |
| 9-11 | 131.6 | 9 ; 11 | 131.5 | 130.4 | 9 ; 10 | 131.5 |
| 12-14 | 148.5 | 12 ; 9 | 148.0 | 146.2 | 12 ; 6 | 146.5 |
| 15-16 | 154.3 | 15 ; 4 | 158.0 | 158.5 | 15 ; 4 | 158.0 |
| 17-20 | 157.2 | 18 ; 5 | 160.0 | 154.9 | 17 ; 8 | 160.0 |
| 21-29 | 153.8 | 25 ; 9 | . | 157.2 | 25 ; 3 | . |
| 30-49 | 154.5 | 38 ; 1 | . | 155.5 | 38 ; 1 | . |
| 50- | 153.2 | 56 ; 0 | . | 159.8 | 57 ; 4 | . |
| <i>Weight.</i> | | | | | | |
| | Average weight | | Normal weight for average age | Average weight | | Normal weight for average age |
| 7-8 | 22.2 | 7 ; 6 | 23.0 | 22.3 | 7 ; 4 | 22.7 |
| 9-11 | 27.6 | 9 ; 11 | 28.4 | 26.5 | 9 ; 10 | 28.2 |
| 12-14 | 39.3 | 12 ; 9 | 37.5 | 38.1 | 12 ; 6 | 36.7 |
| 15-16 | 49.4 | 15 ; 4 | | 52.2 | 15 ; 2 | |
| 17-20 | 52.4 | 18 ; 5 | 51.4 | 51.0 | 17 ; 8 | 50.0 |
| 21-29 | 53.0 | 25 ; 9 | | 57.3 | 25 ; 3 | |
| 30-49 | 58.5 | 38 ; 1 | | 62.5 | 38 ; 0 | |
| 50- | 57.9 | 56 ; 0 | | 63.0 | 57 ; 4 | |

members of employed families. The differences between the average figures vary for men, between 0.4 and 2 cm.; for women, between 0.3 and 0.9 cm. True, the larger differences would seem to be attributable to chance errors due to the fact that the number of individuals examined was not large enough. There is one exception in the case of men from 20 to 24 years of age, in which the figure for twenty-seven unemployed persons (average figure 169.3 cm.) comes very close to the normal figure of 170 cm. (the highest average figure in each group). The males in the families of employed persons only reached the relatively low average of 165.3 cm. ; but, in view of the very small number of individuals examined (nine), no great importance need be attached to this figure. The same remark applies to figures concerning the families of persons in employment, particularly as regards children and adolescents; the figures are merely of use as a sort of preliminary indication. The results set out in the tables are made clearer by Graphs 1 and 2.

In order to explain the singular fact that there would appear to be such marked differences in the height of adult members of families of employed persons and of unemployed persons respectively, we are first tempted to conclude that this is not a consequence of unemployment, but rather some phenomenon due, in the first place, perhaps, to the way in which the families examined were chosen. It is very unlikely that a sort of "downward" selection took place among the unemployed convened by the anti-tuberculosis centres. Among the employed persons who voluntarily presented themselves for examination, a sort of "downward" selection from among the total of the families of the employed might have occurred more easily. It is just possible that the families which came forward for the enquiry were precisely those which feared that their members' health was in danger or those which, as a result of frequent illnesses, were particularly willing to be examined. To some extent this "inverted" selection might also be due to the greater frequency of unemployment in families that are already psycho-physically impaired. Members of such families are more likely to fall victims to unemployment than members of entirely sound families. This problem is of very great interest from the standpoint of social medicine, but we do not know whether any concrete material has been collected up to the present with a view to its solution. Another possible explanation occurs to the mind : the grouping might have

acquired a certain bias owing to the fact that the unemployed, even if they are not primarily constitutionally unsound, mostly come from social surroundings where conditions were less favourable from the outset.

But if all these possibilities are taken into account, we think it very probable that some portion at least of the differences between the average height of the adults observed by us must be regarded as a result of unemployment. As in adults of a certain age unemployment can exercise no further influence on growth, it is highly probable that bad living conditions and also an unfavourable mental condition have contributed to the development of a stoop, in some cases over many years. This stoop has gradually become permanent and makes the adults of unemployed persons' families appear to be shorter. A loss of elasticity and, consequently, of recuperative capacity in the intervertebral cartilage of the spinal column as a result of poor general health is also a possibility.

In the case of young persons, in so far as we have obtained individual figures of some value by combining larger age-groups, we also observe differences in average height. These differences between persons belonging to employed families and unemployed families are shown to be quite regular in the male sex, both in the groups from 15 to 16 years and those from 17 to 20 years. In the female sex, on the other hand, we find the corresponding differences only in the age-group of 15 to 16 years ; while, in the group from 17 to 20 years, fifty-seven girls belonging to unemployed families have an average height of 157.2 cm., and thus come considerably nearer the premised normal height of 160 cm. than the group of girls belonging to employed families. In the latter case, again, the number of persons in the group (eleven) is so small that it is hardly possible to ascribe any significance to the small average height of 154.9 cm. thus obtained.

On passing to the lower age-groups, we again find the typical difference among boys in favour of the working families. In the group from 12 to 14 years, the average height of the boys of employed families exactly corresponds to the premised normal height for the average age of this group, while the average height of boys of unemployed families is 1.5 cm. below this standard. In the age-group from 9 to 11 years, on the other hand, the average height of children of unemployed persons corresponds to the normal height,

while the average height of children of working families is definitely above normal. In the age-group from 7 to 8 years, the difference disappears ; but in this group, according to our data, the average growth is below normal, not only in the case of children of unemployed, but also of children of employed families.

In the case of girls of school age, we find the typical differences in height only in the youngest group. In the other groups, on the other hand, the position is in some cases even reversed. This is probably again due to the small number of children examined and, in particular, of children belonging to employed families. In the group from 12 to 14 years, the average height in unemployed families exceeds the normal height by 0,5 cm., while, in the families of employed persons (where the average age is, however, somewhat lower), the average height is still 0.3 cm. below the normal height for the corresponding average age. In the age-group from 9 to 11 years, we again find that the average height of girls belonging to unemployed families corresponds to the standard for the age in question, while that of the girls belonging to employed families is 1.1 cm. less. As regards infants and small children, the measurements are too few to permit of reliable conclusions. There are, however, definite differences in height in the case of boys from 3 to 6 years. In the age-groups from 3 to 6 years, the figures for boys belonging to employed families are slightly below normal. These deficiencies are more pronounced among children belonging to unemployed families. In the case of girls belonging to these low age-groups, no regular differences have been found, and, in view of the small number of cases examined, no conclusions can be drawn from the differences which appear to exist.

The differences in weight are still more striking than the differences in height, since (as is well known) the state of nutrition revealed by the plumpness of the body follows the fluctuations in external conditions much more rapidly than the development in height which, genotypically, is more definitely fixed (Graphs 3 and 4).

For instance, in the case of adults, we observe considerable regularly recurring differences in the average body weight between employed families and unemployed families in all the age-groups of some size, both in the case of men and of women. These differences show that fluctuations in the state of nutrition determined by exogenous factors are more pronounced in women than in men.

In the case of young people from 17 to 20 years, the difference is 2.5 kg. for males ; among girls of these age-groups the average weights of unemployed persons reach the comparatively high figure of 52.4 kg. and thus exceed by 1.4 kg. the average weight for young persons belonging to employed families. In the age-group from 15 to 16 years, we observe a typical difference of 4.7 kg. in the male sex and a similar difference of 2.8 kg. in the female sex.

We find among boys of school age typical differences of 1.7 kg. in the group from 12 to 14 years, 1.1 kg. in the group from 9 to 11 years, and 0.6 kg. in the group from 7 to 8 years. In the case of girls, on the other hand, we find an excess weight of 1.2 kg. in the group from 12 to 14 years for children belonging to unemployed families, a similar excess of 1.1 kg. in the group from 9 to 11 years, and the same average weight in the group from 7 to 8 years. As regards young children, in so far as the scanty individual figures enable an opinion to be formed, there are both among boys and girls only slight and irregular differences. A comparison with the normal figures shows that the latter are in many cases also not attained by children and young people belonging to employed families. In some age-groups, however, the average figures of weight approach the normal, both in unemployed and employed families. In a few age-groups, the figures for the employed families slightly exceed the normal. What would, however, be noteworthy in any case is the fact that the distinct differences noted in the case of adults, young people and the older schoolchildren show a tendency to disappear in the younger children. This fact would have to be regarded as evidence of the remarkable spirit of self-sacrifice with which the adults, even under extremely difficult material conditions, endeavour to supply their children, at any rate in their earliest years, with what is necessary for maintaining a satisfactory state of nutrition. That it has often been possible to attain this object in spite of the most difficult conditions is, no doubt, to a great extent due to the application of measures of social assistance, and it is obvious that any diminution of this social assistance would, under such circumstances, have serious effects. In a later section we shall show, with the help of the results of a further series of investigations, that, on examining a greater number of persons in the winter of 1933-34, it has been definitely found, even among young persons and children of school age, that the general physical

development was sensibly impaired in unemployed families. These investigations even reveal more marked effects among the younger schoolchildren than among the older children and young people.

To conclude our examination of the figures for height and weight obtained during the first series of investigations, we give in Table III and in Graphs 5 to 8 a comparison of these figures in respect of children and young people. We have compared the figures for employed families and unemployed families with the figures obtained by NOBEL and PIRQUET¹ in examining children and young people at Vienna in the years 1920 and 1923 ; the tables and graphs also give the normal figures. This comparison shows that, in spite of the harmful effects brought about clearly in some cases by the economic situation, the present figures relating to schoolchildren are all considerably higher than those obtained by PIRQUET in 1923. This applies both to the height and weight, and to boys and girls. Even in the case of young people of the male sex, the figures relating to height and weight are all still considerably higher than those obtained by NOBEL in 1923, which, in turn, were definitely higher than his figures for 1920. In the case of young people of the female sex, the position is similar in the age-groups from 15 to 16 years and, in respect of weight, in the age-groups of 17 and 19 years. On the other hand, the height figures for girls of 17 and 18 years, and the weight figures for girls of 18 years, are somewhat lower than the figures recorded by NOBEL in 1923. In the main, the examination of these persons belonging principally to the unemployed class also confirms the fact that the height of children and young people has continued to increase since the war.

In order to determine the state of nutrition of individual cases, we have used, on the one hand, PIRQUET's Pelidisi index,² and, on the other hand, the difference between the actual weight and the normal weight, calculated in the case of children in relation to the height, and in the case of adults in relation to age and height. We have been surprised to find that the Pelidisi index did not show the differences in the state of nutrition as clearly as we had expected

¹ *Zeitschrift für Kinderheilkunde*, Vol. 36, 1923.

² Cf. NOBEL (1933) : VON PIRQUET's "Sacratama" and "Pelidisi" methods, *Quarterly Bull. of the Health Org.*, 2, page 127.

in view of our previous experience of this index (Table IV and Graphs 9 and 10).

In order to explain the irregular figures of the Pelidisi index, we must bear in mind in the first place the average difference in height

TABLE III.

AVERAGE FIGURES OF HEIGHT AND WEIGHT OF CHILDREN AND YOUNG PEOPLE OF ALL THE FAMILIES EXAMINED IN 1933, AS COMPARED WITH (1) THE FIGURES SHOWN BY NOBEL AND PIRQUET IN 1920 AND 1923, AND (2) THE FIGURES ADOPTED AS NORMAL (KORNFELD, 1933).

| Age (years) | Height (cm.) | | | | | Weight (kg.) | | | | |
|-------------|--------------|-------|-------|-------|--------|--------------|-------|------|------|--------|
| | Pirquet 1923 | Nobel | | 1933 | Normal | Pirquet 1923 | Nobel | | 1933 | Normal |
| | | 1920 | 1923 | | | | 1920 | 1923 | | |
| 6 | | | | 111.6 | 114.0 | 18.8 | | | 19.1 | 20.50 |
| 7 | 115 | | | 117.6 | 119.0 | 20.3 | | | 21.3 | 22.50 |
| 8 | 120 | | | 122.2 | 121.0 | 22.5 | | | 23.5 | 24.50 |
| 9 | 125 | | | 127.3 | 128.0 | 24.5 | | | 25.7 | 26.70 |
| 10 | 130 | | | 133.4 | 132.0 | 27.0 | | | 29.1 | 29.00 |
| 11 | 134 | | | 136.6 | 137.0 | 29.4 | | | 30.4 | 31.80 |
| 12 | 137.5 | | | 141.6 | 142.0 | 32.7 | | | 34.0 | 35.00 |
| 13 | 142.5 | | | 146.8 | 148.0 | 35.2 | | | 37.3 | 38.50 |
| 14 | 147 | | | 150.9 | 151.0 | 39.6 | | | 40.7 | 43.00 |
| 15 | | 151.7 | 151.2 | 158.2 | 160.0 | | 42.4 | 44.6 | 47.2 | 48.00 |
| 16 | | 155.2 | 158.2 | 163.8 | 165.0 | | 45.8 | 48.8 | 54.5 | 53.00 |
| 17 | | 158.4 | 162.5 | 165.5 | 168.0 | | 48.6 | 52.5 | 55.6 | 57.00 |
| 18 | | 159.8 | 164.2 | 165.8 | 169.0 | | 50.1 | 54.4 | 58.7 | 60.50 |
| 19 | | | 166.4 | 167.6 | 169.5 | | | 55.8 | 59.8 | 62.00 |
| 20 | | | | 164.8 | 170.0 | | | | 56.8 | 64.00 |

A. MALES.

B. FEMALES.

| | | | | | | | | | | |
|----|-----|-------|-------|-------|-------|------|------|------|------|-------|
| 6 | | | | 110.9 | 113.0 | 17.8 | | | 19.0 | 20.00 |
| 7 | 114 | | | 116.8 | 118.0 | 19.4 | | | 21.0 | 22.00 |
| 8 | 119 | | | 121.8 | 123.0 | 21.3 | | | 23.2 | 24.00 |
| 9 | 124 | | | 126.6 | 127.0 | 23.5 | | | 25.1 | 26.00 |
| 10 | 129 | | | 131.1 | 132.0 | 25.9 | | | 27.3 | 28.50 |
| 11 | 134 | | | 137.1 | 138.0 | 28.4 | | | 30.2 | 31.50 |
| 12 | 138 | | | 145.0 | 144.0 | 31.9 | | | 35.7 | 35.00 |
| 13 | 146 | | | 148.4 | 149.0 | 37.0 | | | 39.7 | 38.50 |
| 14 | 151 | | | 154.2 | 154.0 | 43.6 | | | 45.2 | 43.00 |
| 15 | | 151.2 | 153.3 | 154.2 | 157.0 | | 44.3 | 47.4 | 48.8 | 47.50 |
| 16 | | 152.8 | 154.4 | 155.9 | 158.5 | | 46.4 | 49.2 | 51.2 | 52.50 |
| 17 | | 153.8 | 156.9 | 156.2 | 159.5 | | 48.3 | 50.8 | 51.1 | 56.00 |
| 18 | | 153.8 | 155.6 | 154.2 | 160.0 | | 48.7 | 52.3 | 51.0 | 57.00 |
| 19 | | | 155.1 | 159.2 | 160.0 | | | 53.3 | 53.7 | |
| 20 | | | | 156.4 | 160.0 | | | | 52.2 | |

in children of the same age-groups, as a result of which the Pelidisi index necessarily gives a relatively higher figure for the families of unemployed persons when the average height is smaller and the state of nutrition is the same. In addition, in the families of unemployed persons the bad carriage, which has already been taken as an explanation of the difference in height, might also play a part, especially in the case of adults. In this point, also, the third series of investigations, which relates to a larger number of persons, clearly shows, at any rate for children and young people, the inferior conditions of nutrition in the families of unemployed persons. The fact that, in the first series of investigations, the difference in the state of nutrition is not shown by the Pelidisi index must therefore be attributed, at any rate in the case of children and young people, partly to the small number of persons examined.

TABLE IV.

AVERAGE FIGURES OF THE PELIDISI INDEX.

| Age-groups (years and months) | Males | | Females | |
|--|----------|------------|----------|-----------------|
| | Employed | Unemployed | Employed | Unem- ployed |
| 0-8 | 97.7 | — | 100.5 | 103.0 |
| 1 | 99.5 | 102.0 | 98.8 | 103.0 |
| 1;6 | 99.9 | 101.0 | 100.6 | — |
| 2 | 98.2 | 96.5 | 97.5 | 98.0 |
| 3 | 97.3 | 95.8 | 99.1 | 95.2 |
| 4 | 97.1 | 95.8 | 97.3 | 95.5 |
| 5 | 96.0 | 94.6 | 97.0 | 98.5 |
| 6 | 94.6 | 95.0 | 95.3 | 95.0 |
| 7 | 93.5 | 95.8 | 94.2 | 94.6 |
| 8 | 93.4 | 93.6 | 95.1 | 93.4 |
| 9 | 94.1 | 95.1 | 93.5 | 94.1 |
| 10 | 94.3 | 94.0 | 93.9 | 93.8 |
| 11 | 93.9 | 93.7 | 93.0 | 94.1 |
| 12 | 94.0 | 96.1 | 93.2 | 93.5 |
| 13 | 94.6 | 93.0 | 93.3 | 93.5 |
| 14 | 94.3 | 93.5 | 93.8 | 95.5 |
| 15 | 96.7 | 94.7 | 95.9 | 98.5 |
| 16 | 96.4 | 96.5 | 98.9 | 91.0 |
| 17 | 94.7 | 97.0 | 95.4 | 98.5 |
| 18 | 95.6 | 94.0 | 96.1 | 94.2 |
| 19 | 94.9 | 92.5 | 96.9 | 97.0 |
| 20 | 95.8 | 93.0 | 98.5 | 94.0 |
| 21-24 | 95.0 | 96.6 | 96.2 | 97.2 |
| 25-29 | 97.0 | 96.3 | 100.1 | 99.4 |
| 30-34 | 97.5 | 97.2 | 100.2 | 100.5 |
| 35-49 | 98.4 | 98.0 | 102.1 | 103.4 |
| 50-60 | 98.9 | 100.6 | 106.0 | 104.0 |
| 60- | 99.6 | 95.7 | 102.6 | 104.6 |

The typical distribution according to age-groups (see Table V and Graph 11) and the regular difference between the average Pelidisi figures of persons of the male and female sex, which is shown especially in Graph 12, prove that, even for the persons in question, the Pelidisi figures show marked regularity. This difference is clearly seen in all the age-groups. With one exception, the average figures for persons of the female sex are definitely higher than those for the male sex. This exception, which relates to the age-group from 11 to 14 years, is explained by the fact that this is the period of development in which girls, on account of their approaching puberty, temporarily surpass the boys in growth.

Tables VI and VII show the individual differences in height in relation to the normal height for the respective ages, and the differences in weight in relation to the normal weight determined by reference to height and also, in adults, to age. These tables, particularly when one considers large age-groups (Tables VIII to XI), reveal very strikingly the considerable preponderance of minus differences in the height of adults, adolescents and children in the families of unemployed persons as compared with families which are employed, and the relatively more frequent plus differences in the latter. This is particularly clear in the graphs showing the percentage of plus and minus differences for these two categories of families (Graph 13). True, if the figures are divided according to sex, this difference is not clear in all the age-groups. Among males, irregularities are found in the younger adults; among females, both in the children of elementary-school age and in the older children, the exception already pointed out (page 478) to the above-mentioned rule is found, to be explained in all probability by the fact that an insufficient number of cases were examined. The physical deficiency in members of families of unemployed persons (Graph 14) appears again in the *distribution of plus and minus differences in weight in adults*. Tables X and XI prove, however, that the figures in the Table of Concordance for adult women of the population of Vienna were clearly too low, since plus differences in weight predominate on the whole for adult girls and married women in both employed and unemployed families; but it is in women and girls in families of employed persons that these plus differences in weight are relatively most marked.

TABLE V.
AVERAGE PELIDISI FIGURES IN LARGER AGE-GROUPS.

| Age-groups (years and months) | Males | | Females | | Both sexes | | Males | Females |
|-------------------------------------|------------|----------|------------|----------|------------|----------|-------------------------------------|---------|
| | Unemployed | Employed | Unemployed | Employed | Unemployed | Employed | Employed and unemployed together | |
| 0 — 1 ; 0 | 99.0 | 101.5 | 99.9 | 103.0 | 99.2 | 101.2 | 99.2 | 100.5 |
| 1 ; 10 — 5 ; 5 | 97.0 | 95.4 | 97.5 | 97.0 | 97.2 | 96.1 | 96.8 | 97.4 |
| 5 ; 6 — 10 ; 5 | 94.0 | 93.0 | 94.3 | 94.2 | 94.1 | 93.6 | 93.8 | 94.3 |
| 10 ; 6 — 14 ; 5 | 94.1 | 94.1 | 93.3 | 93.8 | 93.7 | 94.0 | 94.1 | 93.3 |
| 14 ; 6 — 18 ; 5 | 95.9 | 95.8 | 96.6 | 96.9 | 96.2 | 96.4 | 95.9 | 96.7 |
| 18 ; 6 — 20 ; 5 | 95.4 | 92.6 | 97.3 | 95.5 | 96.5 | 93.4 | 94.9 | 97.2 |
| 20 ; 6 — 29 ; 5 | 96.0 | 96.4 | 98.9 | 98.7 | 97.7 | 97.9 | 96.1 | 98.8 |
| 29 ; 6 — 34 ; 5 | 97.5 | 97.2 | 100.2 | 100.5 | 99.2 | 98.8 | 97.5 | 100.3 |
| 34 ; 6 — 49 ; 5 | 98.4 | 98.0 | 102.1 | 103.4 | 100.5 | 100.8 | 98.3 | 102.3 |
| 50 — 60 | 98.9 | 100.6 | 106.0 | 104.0 | 101.1 | 101.6 | 99.3 | 105.5 |
| 60 — | 99.6 | 95.7 | 102.6 | 104.6 | 100.7 | 100.2 | 98.9 | 103.1 |

TABLE VI.
INDIVIDUAL DIFFERENCES IN HEIGHT AS COMPARED WITH
NORMAL HEIGHT.

| Age-groups (years) | Unemployed | | | | Employed | | | | | |
|-----------------------|-----------------|--------------------------|----|-----|-----------------------|-----------------|--------------------------|---|----|-----------------------|
| | Average age* | Number of differences | | | Average difference | Average age* | Number of differences | | | Average difference |
| | | + | = | - | | | + | = | - | |
| 1 | 0 ; 6.7 | 3 | 2 | 10 | -1.7 | — | — | — | — | — |
| 1 | 1 ; 0.3 | — | — | 10 | -4.0 | 1 ; 0.5 | — | — | 2 | -3.5 |
| 1½ | 1 ; 5.8 | 2 | — | 12 | -2.4 | 1 ; 5.7 | — | 1 | 2 | -3.8 |
| 2 | 2 ; 2.2 | 4 | 2 | 12 | -2.5 | 2 ; 1.7 | — | 1 | 2 | -2.3 |
| 3 | 2 ; 10.8 | 5 | 4 | 29 | -2.9 | 2 ; 11.2 | 2 | — | 4 | -2.7 |
| 4 | 4 ; 0.2 | 9 | — | 23 | -1.9 | 3 ; 11.2 | 2 | — | 4 | -0.8 |
| 5 | 4 ; 11.8 | 7 | 3 | 29 | -2.3 | 4 ; 11.1 | 2 | — | 4 | +0.9 |
| 6 | 5 ; 11.3 | 18 | 1 | 39 | -2.2 | 5 ; 10.8 | 5 | 2 | 9 | -1.0 |
| 7 | 6 ; 11.6 | 25 | 3 | 47 | -1.2 | 6 ; 10.8 | 1 | 1 | 3 | -1.9 |
| 8 | 7 ; 11.6 | 29 | 1 | 44 | -1.4 | 8 ; 1.4 | 3 | 1 | 3 | -1.3 |
| 9 | 8 ; 11.0 | 33 | 6 | 34 | -0.3 | 8 ; 11.0 | 7 | 2 | 7 | -0.6 |
| 10 | 9 ; 11.2 | 53 | 7 | 38 | +1.2 | 10 ; 0.2 | 10 | — | 1 | +5.0 |
| 11 | 10 ; 11.7 | 30 | 6 | 40 | -0.6 | 10 ; 11.1 | 10 | 3 | 5 | +1.6 |
| 12 | 11 ; 10.9 | 35 | 5 | 45 | +0.1 | 11 ; 10.6 | 5 | 1 | 4 | +0.1 |
| 13 | 12 ; 11.4 | 19 | 4 | 32 | -1.3 | 13 ; 1.5 | 5 | — | 1 | +3.7 |
| 14 | 13 ; 11.9 | 16 | — | 24 | -3.2 | 13 ; 11.9 | 2 | 1 | 5 | -2.6 |
| 15-16 | 15 ; 1.4 | 12 | 2 | 18 | -1.0 | 15 ; 4.8 | 3 | 1 | 2 | +0.7 |
| 17-18 | 17 ; 3.4 | 7 | 6 | 16 | -2.4 | 17 ; 2 | 1 | — | 3 | -4.5 |
| 19-20 | 19 ; 5.0 | 3 | — | 19 | -4.6 | 19 ; 3 | 3 | — | 2 | +2.8 |
| 21-24 | 22 ; 4.6 | 12 | 1 | 14 | -0.6 | 22 ; 8.1 | 2 | 1 | 6 | -3.4 |
| 25-29 | 27 ; 8.1 | 7 | 3 | 17 | -2.6 | 27 ; 5.6 | 5 | — | 5 | -1.1 |
| 30-34 | 32 ; 2.2 | 22 | 5 | 50 | -3.4 | 31 ; 11.6 | 8 | — | 26 | -2.8 |
| 35-49 | 40 ; 9.9 | 59 | 22 | 202 | -4.1 | 40 ; 8.6 | 26 | 2 | 42 | -2.0 |
| 50-60 | 53 ; 2.7 | 12 | 2 | 44 | -5.1 | 53 ; 5.9 | 4 | 1 | 12 | -3.7 |
| 60- | 64 ; 8.3 | 1 | — | 14 | -7.6 | 71 ; 8 | — | — | 3 | -6.0 |

A. MALES.

B. FEMALES.

| | | | | | | | | | | |
|-------|-----------|----|----|-----|-------|-----------|----|---|----|------|
| 1 | 0 ; 5.2 | 1 | 3 | 0 | +0.2 | 0 ; 3.3 | 1 | — | 2 | -1.7 |
| 1 | 0 ; 10.4 | — | 2 | 3 | -1.7 | — | — | — | — | — |
| 1½ | 1 ; 7.4 | — | — | 5 | -2.3 | — | — | — | — | — |
| 2 | 2 ; 1.5 | 5 | 1 | 13 | -3.1 | 2 ; 3 | 1 | — | 1 | +2.2 |
| 3 | 2 ; 10.9 | 3 | 3 | 12 | -1.8 | 3 ; 0.8 | — | — | 6 | -4.5 |
| 4 | 3 ; 11.5 | 13 | — | 23 | -3.0 | 4 ; 2.3 | 1 | 1 | 1 | -0.2 |
| 5 | 4 ; 11.9 | 17 | 4 | 34 | -1.7 | 4 ; 11.3 | 1 | 2 | 4 | -3.6 |
| 6 | 5 ; 11.3 | 13 | 2 | 25 | -1.8 | 6 ; 0.5 | 3 | — | 5 | -1.4 |
| 7 | 6 ; 11.1 | 22 | 4 | 28 | -1.6 | 6 ; 11 | 6 | — | 6 | +0.6 |
| 8 | 7 ; 11.3 | 24 | 8 | 40 | -0.8 | 7 ; 10.9 | 4 | — | 7 | -0.5 |
| 9 | 8 ; 10.9 | 25 | 8 | 31 | -0.1 | 8 ; 11.4 | 4 | 1 | 2 | -0.1 |
| 10 | 9 ; 11.7 | 34 | 1 | 45 | -0.7 | 9 ; 11.1 | 7 | — | 5 | -0.8 |
| 11 | 10 ; 11.5 | 23 | 4 | 34 | -0.4 | 10 ; 11.9 | 1 | 1 | 5 | -4.1 |
| 12 | 12 ; 0.1 | 27 | 4 | 23 | +2.8 | 11 ; 11.2 | 6 | — | 4 | -0.1 |
| 13 | 12 ; 11.3 | 27 | 4 | 29 | -0.1 | 12 ; 11.6 | 3 | — | 7 | -1.6 |
| 14 | 13 ; 9.6 | 18 | — | 11 | +1.3 | 13 ; 11.5 | 1 | — | 1 | +1.5 |
| 15-16 | 15 ; 4.4 | 8 | 1 | 24 | -3.1 | 15 ; 2.2 | 4 | — | 1 | +3.7 |
| 17-18 | 17 ; 5.6 | 3 | 2 | 20 | -4.0 | 17 ; 4.1 | 2 | 1 | 6 | -5.5 |
| 19-20 | 19 ; 4.9 | 11 | 1 | 20 | -1.5 | 19 ; 3.5 | 1 | — | 1 | -1.7 |
| 21-24 | 22 ; 2.4 | 4 | 1 | 20 | -4.9 | 22 ; 2.9 | 3 | 1 | 6 | -2.1 |
| 25-29 | 27 ; 4.7 | 9 | 2 | 43 | -6.9 | 26 ; 7.7 | 7 | — | 15 | -2.8 |
| 30-34 | 32 ; 1.1 | 26 | 9 | 88 | -4.4 | 31 ; 1.3 | 12 | — | 19 | -3.1 |
| 35-49 | 40 ; 1.6 | 56 | 22 | 276 | -5.3 | 40 ; 3.4 | 16 | 1 | 55 | -5.0 |
| 50-60 | 53 ; 2 | — | — | 27 | -10.8 | 52 ; 3.6 | 3 | 1 | 3 | +1.0 |
| 60- | 64 ; 4.6 | — | — | 9 | -8.9 | 62 ; 2.7 | 1 | — | 2 | -3.2 |

* Calculated in years and months, to one decimal point.

TABLE VII.

INDIVIDUAL DIFFERENCES IN WEIGHT
AS COMPARED WITH NORMAL WEIGHT.

| Age-groups (years) | Unemployed | | | | Employed | | | |
|-----------------------|-----------------------|----|-----|-----------------------|-----------------------|---|----|-----------------------|
| | Number of differences | | | Average difference | Number of differences | | | Average difference |
| | + | = | - | | + | = | - | |
| A. MALES. | | | | | | | | |
| ½ | 11 | 1 | 3 | + 0.45 | — | — | — | — |
| 1 | 8 | — | 2 | + 0.26 | 1 | — | 1 | + 0.95 |
| 1½ | 8 | — | 6 | + 0.14 | 2 | — | 1 | + 0.53 |
| 2 | 8 | 2 | 8 | + 0.07 | 2 | — | 1 | + 0.40 |
| 3 | 26 | 4 | 8 | + 0.64 | 2 | — | 4 | + 0.15 |
| 4 | 17 | 3 | 12 | + 0.33 | 3 | — | 3 | + 0.38 |
| 5 | 18 | 3 | 18 | — | 4 | — | 3 | + 0.07 |
| 6 | 12 | 10 | 36 | — 0.52 | 2 | 3 | 11 | — 1.33 |
| 7 | 18 | 9 | 48 | — 0.81 | 3 | 1 | 1 | — 0.12 |
| 8 | 26 | 7 | 41 | — 0.51 | 2 | — | 5 | — 1.13 |
| 9 | 16 | 8 | 49 | — 1.00 | 5 | — | 11 | — 0.48 |
| 10 | 33 | 8 | 57 | — 0.71 | 3 | — | 8 | — 1.29 |
| 11 | 16 | 5 | 55 | — 1.37 | 2 | 2 | 14 | — 1.34 |
| 12 | 21 | 5 | 59 | — 1.12 | 1 | 1 | 8 | + 0.03 |
| 13 | 20 | 4 | 31 | — 1.14 | 1 | — | 5 | — 1.37 |
| 14 | 11 | 6 | 23 | — 0.67 | 2 | 1 | 5 | — 1.78 |
| 15-16 | 17 | 2 | 13 | + 0.11 | 3 | — | 2 | + 0.42 |
| 17-18 | 8 | 2 | 19 | — 2.38 | 2 | 1 | 1 | + 3.27 |
| 19-20 | 5 | 2 | 15 | — 3.02 | — | — | 5 | — 5.34 |
| 21-24 | 10 | 1 | 16 | — 2.97 | 5 | 3 | 1 | + 0.74 |
| 25-29 | 5 | 3 | 19 | — 4.08 | 1 | — | 9 | — 4.77 |
| 30-34 | 13 | 4 | 60 | — 4.53 | 8 | — | 26 | — 3.75 |
| 35-40 | 61 | 11 | 211 | — 5.28 | 15 | 2 | 52 | — 4.05 |
| 50-60 | 10 | 1 | 47 | — 6.26 | 8 | — | 9 | — 1.28 |
| 60- | 3 | 1 | 11 | — 5.81 | — | — | 3 | — 14.20 |

B. FEMALES.

| | | | | | | | | |
|-------|-----|----|-----|--------|----|---|----|--------|
| ½ | 2 | — | 2 | + 0.20 | 1 | — | 2 | — 1.70 |
| 1 | 4 | 0 | 1 | + 0.62 | — | — | — | — |
| 1½ | 2 | — | 3 | + 0.64 | — | — | — | — |
| 2 | 13 | 1 | 5 | + 2.95 | 2 | — | — | + 0.51 |
| 3 | 7 | 4 | 7 | + 0.21 | 2 | — | 4 | — 1.02 |
| 4 | 17 | 4 | 15 | + 0.46 | — | 1 | 2 | — 0.50 |
| 5 | 19 | 6 | 30 | — 0.08 | 3 | — | 4 | + 0.26 |
| 6 | 11 | 4 | 25 | — 0.47 | — | 1 | 7 | — 0.92 |
| 7 | 15 | 5 | 34 | — 0.58 | 3 | 1 | 8 | — 0.82 |
| 8 | 22 | 5 | 45 | — 0.52 | 1 | 1 | 9 | — 1.73 |
| 9 | 12 | 7 | 45 | — 0.70 | 1 | — | 6 | — 1.73 |
| 10 | 20 | 5 | 55 | — 0.83 | 4 | — | 8 | — 0.98 |
| 11 | 13 | 1 | 47 | — 1.10 | — | — | 7 | — 1.66 |
| 12 | 19 | 4 | 31 | — 0.68 | 4 | — | 6 | — 0.62 |
| 13 | 30 | — | 30 | + 0.25 | 4 | 2 | 4 | + 1.07 |
| 14 | 15 | — | 14 | — 0.08 | 1 | — | 1 | + 1.35 |
| 15-16 | 25 | — | 8 | + 4.30 | 3 | — | 2 | + 3.22 |
| 17-18 | 13 | 2 | 10 | + 1.54 | 5 | — | 4 | + 2.20 |
| 19-20 | 15 | 2 | 15 | + 0.89 | 1 | — | 1 | + 2.00 |
| 21-24 | 11 | 1 | 13 | — 0.57 | 4 | 1 | 5 | + 0.90 |
| 25-29 | 32 | 4 | 18 | + 2.90 | 14 | — | 8 | + 4.74 |
| 30-34 | 61 | 9 | 53 | + 2.30 | 21 | 1 | 9 | + 5.46 |
| 35-40 | 216 | 12 | 126 | + 3.78 | 52 | — | 20 | + 7.48 |
| 50-60 | 20 | — | 7 | + 6.04 | 5 | — | 2 | + 2.64 |
| 60- | 4 | — | 5 | — 0.28 | 2 | — | 1 | + 3.77 |

TABLE VIII.
POSITIVE AND NEGATIVE DIFFERENCES IN HEIGHT IN LARGER AGE-GROUPS.

| Age-groups (years) | Employed | | | Unemployed | | | Employed | | Unemployed | |
|-----------------------|----------------|---|----|------------|----|-----|----------|------|------------|-------|
| | Actual figures | | | | | | % | | | |
| | + | = | - | + | = | - | + | - | + | - |
| A. MALES. | | | | | | | | | | |
| — 5 | 6 | 2 | 18 | 30 | 11 | 125 | 23.1 | 69.3 | 18.1 | 75.3 |
| 6 — 10 | 26 | 6 | 23 | 158 | 18 | 202 | 47.3 | 41.8 | 41.8 | 53.4 |
| 11 — 14 | 22 | 5 | 15 | 100 | 15 | 141 | 52.4 | 35.7 | 39.1 | 55.1 |
| 15 — 20 | 7 | 1 | 7 | 22 | 8 | 53 | 46.7 | 46.7 | 26.5 | 63.9 |
| 21 — 34 | 15 | 1 | 37 | 41 | 9 | 81 | 28.3 | 69.8 | 31.3 | 61.8 |
| 35 — 49 | 26 | 2 | 42 | 59 | 22 | 202 | 37.1 | 60.0 | 29.8 | 71.4 |
| 50 — | 4 | 1 | 15 | 13 | 2 | 58 | 20.0 | 75.0 | 17.8 | 79.5 |
| B. FEMALES. | | | | | | | | | | |
| — 5 | 4 | 3 | 14 | 39 | 13 | 90 | 19.0 | 66.7 | 27.5 | 63.4 |
| 6 — 10 | 24 | 1 | 25 | 118 | 23 | 169 | 48.0 | 50.0 | 38.1 | 54.5 |
| 11 — 14 | 11 | 1 | 17 | 95 | 12 | 97 | 37.9 | 58.6 | 46.6 | 47.5 |
| 15 — 20 | 7 | 1 | 8 | 22 | 4 | 64 | 43.7 | 50.0 | 24.4 | 71.1 |
| 21 — 34 | 22 | 1 | 40 | 39 | 12 | 151 | 34.9 | 63.5 | 19.3 | 74.8 |
| 35 — 49 | 16 | 1 | 55 | 56 | 22 | 270 | 22.2 | 76.4 | 15.8 | 78.0 |
| 50 — | 4 | 1 | 5 | — | — | 36 | 40.0 | 50.0 | — | 100.0 |

TABLE IX.
POSITIVE AND NEGATIVE DIFFERENCES IN WEIGHT IN LARGER AGE-GROUPS.

| Age-groups (years) | Employed | | | Unemployed | | | Employed | | Unemployed | |
|-----------------------|----------------|---|----|------------|----|-----|----------|------|------------|------|
| | Actual figures | | | | | | % | | | |
| | + | = | - | + | = | - | + | - | + | - |
| A. MALES. | | | | | | | | | | |
| — 5 | 14 | — | 13 | 96 | 13 | 57 | 51.9 | 48.1 | 57.8 | 34.4 |
| 6 — 10 | 15 | 4 | 36 | 105 | 42 | 231 | 27.3 | 65.5 | 27.5 | 61.1 |
| 11 — 14 | 6 | 4 | 32 | 68 | 20 | 168 | 11.3 | 76.2 | 26.6 | 65.6 |
| 15 — 20 | 5 | 1 | 8 | 30 | 6 | 47 | 35.7 | 57.1 | 36.1 | 56.6 |
| 21 — 34 | 14 | 3 | 36 | 28 | 8 | 95 | 26.4 | 67.9 | 21.4 | 72.5 |
| 35 — 49 | 15 | 2 | 52 | 61 | 11 | 211 | 21.7 | 75.4 | 21.6 | 71.6 |
| 50 — | 8 | — | 12 | 13 | 2 | 58 | 40.0 | 60.0 | 17.8 | 79.5 |
| B. FEMALES. | | | | | | | | | | |
| — 5 | 8 | 1 | 12 | 64 | 15 | 63 | 39.1 | 57.1 | 45.1 | 41.1 |
| 6 — 10 | 9 | 3 | 38 | 80 | 26 | 204 | 18.0 | 76.0 | 25.8 | 65.8 |
| 11 — 14 | 9 | 2 | 18 | 77 | 5 | 122 | 31.0 | 62.1 | 37.7 | 58.0 |
| 15 — 20 | 9 | — | 7 | 53 | 4 | 33 | 56.3 | 43.7 | 58.9 | 36.7 |
| 21 — 34 | 39 | 2 | 22 | 104 | 14 | 84 | 61.9 | 31.9 | 51.5 | 41.6 |
| 35 — 49 | 52 | — | 20 | 216 | 12 | 126 | 72.2 | 27.8 | 61.9 | 35.6 |
| 50 — | 7 | — | 3 | 24 | — | 12 | 79.0 | 30.9 | 66.7 | 33.3 |

TABLE X.

POSITIVE AND NEGATIVE DIFFERENCES IN HEIGHT AND WEIGHT
IN ALL THE FAMILIES EXAMINED (EMPLOYED AND UNEMPLOYED).

| Age- groups (years) | Height | | | | | Weight | | | | |
|---------------------------|----------------|----|-----|------|------|----------------|----|-----|------|------|
| | Actual figures | | | % | | Actual figures | | | % | |
| | + | = | - | + | - | + | = | - | + | - |
| A. MALES. | | | | | | | | | | |
| — 5 | 36 | 13 | 143 | 18.7 | 74.5 | 110 | 13 | 70 | 57.0 | 36.3 |
| 6 — 10 | 184 | 24 | 225 | 42.5 | 52.0 | 120 | 46 | 267 | 27.7 | 61.7 |
| 11 — 14 | 122 | 20 | 156 | 40.0 | 52.3 | 74 | 24 | 200 | 24.9 | 67.1 |
| 15 — 20 | 29 | 9 | 60 | 29.6 | 61.2 | 35 | 7 | 55 | 36.1 | 56.7 |
| 21 — 34 | 50 | 19 | 118 | 30.4 | 64.1 | 42 | 11 | 131 | 22.8 | 71.2 |
| 35 — 49 | 85 | 24 | 244 | 24.1 | 69.1 | 76 | 13 | 263 | 21.4 | 74.7 |
| 50 — | 19 | 3 | 73 | 20.0 | 76.8 | 21 | 2 | 70 | 22.6 | 75.3 |
| B. FEMALES. | | | | | | | | | | |
| — 5 | 43 | 16 | 104 | 26.4 | 63.8 | 72 | 16 | 75 | 44.2 | 46.0 |
| 6 — 10 | 142 | 24 | 194 | 30.4 | 53.9 | 89 | 29 | 242 | 24.7 | 67.2 |
| 11 — 14 | 106 | 13 | 114 | 45.5 | 48.9 | 86 | 7 | 140 | 36.9 | 60.1 |
| 15 — 20 | 29 | 5 | 72 | 27.4 | 67.9 | 62 | 4 | 40 | 58.5 | 37.7 |
| 21 — 34 | 61 | 13 | 191 | 23.0 | 72.1 | 143 | 16 | 106 | 54.0 | 40.0 |
| 35 — 49 | 72 | 23 | 331 | 16.9 | 77.7 | 268 | 12 | 146 | 62.9 | 34.3 |
| 50 — | 4 | 1 | 41 | 8.7 | 39.1 | 31 | — | 15 | 67.4 | 32.6 |

TABLE XI.

POSITIVE AND NEGATIVE DIFFERENCES IN HEIGHT AND WEIGHT
IN LARGER AGE-GROUPS (BOTH SEXES).

| Age- groups (years) | Employed | | | Unemployed | | | Employed | | | Unemployed | |
|---------------------------|----------------|---|----|------------|----|-----|----------|------|------|------------|---|
| | Actual figures | | | | | | % | | | | |
| | + | = | - | + | = | - | + | = | - | + | - |
| A. HEIGHT. | | | | | | | | | | | |
| — 5 | 10 | 5 | 32 | 69 | 24 | 215 | 21.3 | 68.1 | 22.4 | 69.8 | |
| 6 — 10 | 50 | 7 | 48 | 276 | 41 | 371 | 47.6 | 45.7 | 40.1 | 53.9 | |
| 11 — 14 | 33 | 6 | 32 | 195 | 27 | 238 | 46.5 | 45.1 | 42.4 | 51.7 | |
| 15 — 20 | 14 | 2 | 15 | 44 | 12 | 113 | 45.2 | 48.4 | 26.0 | 66.9 | |
| 21 — 34 | 37 | 2 | 77 | 80 | 21 | 232 | 31.9 | 66.4 | 24.0 | 69.7 | |
| 35 — 49 | 42 | 3 | 97 | 115 | 44 | 478 | 29.6 | 68.3 | 18.1 | 75.0 | |
| 50 — | 8 | 2 | 20 | 13 | 2 | 94 | 26.7 | 66.7 | 11.9 | 86.2 | |
| B. WEIGHT. | | | | | | | | | | | |
| — 5 | 22 | 1 | 25 | 160 | 28 | 120 | 45.8 | 52.1 | 51.9 | 39.0 | |
| 6 — 10 | 24 | 7 | 74 | 185 | 68 | 435 | 22.9 | 70.5 | 26.9 | 63.2 | |
| 11 — 14 | 15 | 6 | 50 | 145 | 25 | 290 | 21.1 | 70.4 | 31.5 | 63.0 | |
| 15 — 20 | 14 | 1 | 15 | 83 | 10 | 80 | 46.7 | 50.0 | 48.0 | 46.2 | |
| 21 — 34 | 53 | 5 | 58 | 132 | 22 | 179 | 45.7 | 50.0 | 39.6 | 53.8 | |
| 35 — 49 | 67 | 2 | 72 | 277 | 23 | 337 | 47.5 | 51.1 | 43.5 | 52.9 | |
| 50 — | 15 | 0 | 15 | 37 | 2 | 70 | 50.0 | 50.0 | 33.9 | 64.2 | |

In *adolescents* and *children*, on the other hand, we find, surprisingly enough, exactly the opposite, whether we consider the sexes together or separately (Table XI). The graphs again show very clearly the curious predominance of plus differences in children and adolescents of families of unemployed persons and the predominance of minus differences in those of families who are employed. Presumably, the inadequacy of the weight of children of families of unemployed persons, as it appears from Tables I and II, represents, in part, not a relative inadequacy of weight with reference to height, but a lack of physical development accompanying shortness of stature. Since, in addition to differences of height, an examination of the absolute figures often brings out also differences of weight in groups of children in which a study of weight in relation to height reveals no difference of this kind, or may even indicate the contrary, the explanation here must be, not a relative inadequacy of weight due to malnutrition, but simply general backwardness of growth.

In order to make this perfectly clear, we have also calculated the *differences of weight in relation to the normal weight corresponding to the age of the children and adolescents*. These results as a whole, taken by fairly big age-groups, show very clearly, both in the form of a table (Table XII) and, better still, in the graphic representation of percentage differences (Graph 15), the predominance of plus differences in families of employed persons and that of minus differences in families of unemployed persons for all ages in childhood and adolescence. Thus, the results of this first series of researches establish beyond dispute the fact of retarded general development in children and adolescents in families of unemployed persons, just as the data previously examined proved backwardness in the physical constitution of the adults.

It may be well, again, to examine here another phenomenon indicative of a pathological state from which families of unemployed persons suffer as compared with families of employed persons—a state which is not to be taken as directly parallel with malnutrition. The phenomenon concerns the blood-content of the skin and visible mucous membranes, considered subjectively. In determining the blood-content of the skin, PIRQUET'S "Sacratama" method was followed. With this method, four criteria are used to describe the general state: the blood-content of the skin, the condition of the subcutaneous fat layer, the skin tension and the condition of the

TABLE XII.

POSITIVE AND NEGATIVE DIFFERENCES IN WEIGHT
WITH REFERENCE TO HEIGHT IN CHILDREN AND ADOLESCENTS.

| Age- groups (years) | A. BOTH SEXES. | | | | | | | | | | | |
|---------------------------|----------------|----|----|------------|----|-----|-------------|------|------|------------|------|------|
| | Employed | | | Unemployed | | | Employed | | | Unemployed | | |
| | Actual figures | | | | | | % | | | | | |
| | + | - | — | + | = | — | + | = | — | + | = | — |
| | - 5 | 16 | 10 | 23 | 88 | 81 | 144 | 32.7 | 20.4 | 46.9 | 28.1 | 25.9 |
| 6-10 | 35 | 13 | 58 | 189 | 84 | 402 | 33.0 | 12.3 | 54.7 | 28.3 | 12.5 | 59.6 |
| 11-14 | 29 | 6 | 37 | 161 | 30 | 266 | 40.3 | 3.3 | 51.4 | 35.2 | 6.6 | 58.2 |
| 15-18 | 11 | — | 12 | 46 | 9 | 64 | 47.8 | 0.0 | 52.2 | 38.7 | 7.6 | 53.8 |
| | B. MALES. | | | | | | C. FEMALES. | | | | | |
| | Employed | | | Unemployed | | | Employed | | | Unemployed | | |
| | + | - | — | + | = | — | + | = | — | + | = | — |
| - 5 | 11 | 5 | 11 | 45 | 46 | 76 | 5 | 5 | 12 | 43 | 35 | 68 |
| 6-10 | 23 | 5 | 28 | 101 | 40 | 226 | 12 | 8 | 30 | 88 | 44 | 176 |
| 11-14 | 15 | 5 | 22 | 79 | 18 | 157 | 14 | 1 | 15 | 82 | 12 | 109 |
| 15-18 | 6 | — | 3 | 28 | 6 | 27 | 5 | — | 9 | 18 | 3 | 37 |

muscles. All four criteria were employed in our researches, but only the results relating to the blood-content of the skin will be examined here. We have grouped the results in Table XIII.

We have attempted also to establish a relationship between the state of health noted and various factors relating to environment. With this object, we classified the families according to their housing conditions, and then compared *inter se* the most striking physical characteristics of the persons thus grouped (differences in height, in weight, blood-content of skin, etc.). To begin with, the total number of families was divided into two groups, the first consisting of those living in cellars, basements and ground-floor premises, and the second of those living on upper floors. Table XIII (*d*) shows that families living on the ground-floor exhibit, as regards height, more plus differences and fewer minus differences, and, as regards weight, more minus differences and fewer plus differences than

TABLE XIII.

DETERMINATION OF THE BLOOD-CONTENT OF THE SKIN
AND VISIBLE MUCOUS MEMBRANES.

A. ALL AGES.

| Blood-content | Males | | | | Females | | | |
|--------------------|----------------|------|----------------|------|----------------|------|----------------|------|
| | Unemployed | | Employed | | Unemployed | | Employed | |
| | Actual figures | % | Actual figures | % | Actual figures | % | Actual figures | % |
| 1. Excellent | 1 | 0.1 | — | — | 1 | 0.1 | — | — |
| 2. Very good..... | 12 | 0.9 | — | — | 11 | 0.8 | 3 | 1.1 |
| 3. Good | 729 | 53.3 | 197 | 69.6 | 722 | 53.8 | 176 | 66.7 |
| 4. Fair | 62 | 4.5 | 20 | 7.1 | 50 | 3.7 | 23 | 8.7 |
| 5. Bad | 551 | 40.2 | 61 | 22.6 | 541 | 40.3 | 61 | 23.1 |
| 6. Very bad | 14 | 1.0 | 2 | 0.7 | 16 | 1.2 | 1 | 0.4 |

B. BY AGE-GROUPS : MALES.

| Age groups (years) | Families of unemployed: Blood-content | | | | | | Families of employed: Blood-content | | | | | |
|--------------------|---------------------------------------|---|-----|----|-----|---|-------------------------------------|---|----|----|----|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 1 | 2 | 3 | 4 | 5 | 6 |
| — 6 | — | 1 | 112 | 14 | 93 | 6 | — | — | 20 | 10 | 11 | — |
| 7 — 14 | — | 8 | 226 | 47 | 285 | 7 | — | — | 46 | 10 | 25 | 1 |
| 15 — 19 | — | — | 45 | 1 | 24 | 1 | — | — | 12 | — | 1 | — |
| 20 — 29 | — | — | 40 | — | 26 | — | — | — | 16 | — | 4 | — |
| 30 — 49 | 1 | 2 | 254 | — | 102 | — | — | — | 87 | — | 17 | — |
| 50 — | — | 1 | 52 | — | 20 | — | — | — | 16 | — | 3 | 1 |

C. BY AGE-GROUPS : FEMALES.

| | | | | | | | | | | | | |
|---------|---|---|-----|----|-----|----|---|---|----|----|----|---|
| — 6 | — | 2 | 85 | 9 | 87 | 2 | — | — | 15 | 6 | 9 | — |
| 7 — 14 | — | 1 | 191 | 39 | 232 | 10 | — | 1 | 41 | 14 | 16 | — |
| 15 — 19 | — | — | 58 | 1 | 23 | — | — | — | 12 | 1 | 3 | — |
| 20 — 29 | — | 1 | 64 | 1 | 21 | — | 1 | — | 23 | — | 10 | — |
| 30 — 49 | 1 | 5 | 304 | — | 164 | 4 | — | 2 | 81 | 2 | 18 | — |
| 50 — | — | 2 | 20 | — | 14 | — | — | — | 4 | — | 5 | 1 |

D. HEIGHT, WEIGHT, AND BLOOD-CONTENT, ACCORDING TO POSITION OF DWELLING.

| Dwelling | Number of differences | | | | | |
|---------------------|-----------------------|------|------|----------------|------|------|
| | + | | | - | | |
| | Actual figures | % | | Actual figures | % | |
| 1. Height : | | | | | | |
| Ground-floor* | 286 | 76 | 538 | 31.8 | 8.4 | 59.8 |
| Upper floors | 690 | 175 | 1197 | 29.2 | 7.2 | 63.4 |
| 2. Weight : | | | | | | |
| Ground-floor* | 304 | 78 | 518 | 33.8 | 8.7 | 57.5 |
| Upper floors | 905 | 186 | 1271 | 38.3 | 7.4 | 51.3 |
| 3. Blood-content : | | | | | | |
| | very good | good | bad | very good | good | bad |
| Ground-floor* | 4 | 529 | 367 | 0.4 | 58.8 | 40.8 |
| Upper floors | 24 | 1295 | 1043 | 1.0 | 54.8 | 44.2 |

* Including cellars and basements.

those living higher up. In particular, children living on the ground-floor are of course more out of doors and have more exercise, and—though they are probably less well fed—they seem to be better off, as regards stature, than children living on upper floors, who do not get out so much. As regards the blood-content of the skin, specially satisfactory results are rather more numerous in dwellings situated on upper floors, but there again we find fewer good and more fair or bad results, while in ground-floor dwellings, where the occupants get out more, there are fewer pale-faced persons and more with a healthy colour. The results in regard to skin-tension, the subcutaneous fat layer and the condition of the muscles did not reveal any special difference. These findings are substantially the same when the results obtained are classified according to employed and unemployed families.

Again, we established two groups, the first consisting of families occupying dwellings with balconies and the second of families which had no balcony. The chief difference resulting from this division concerned the blood-content of the skin, which was classified as good or very good in 56.2 per cent of cases for occupants of dwellings without balconies and in 64.7 per cent of cases for occupants of dwellings with balconies. No difference was found in the figures relating to height or weight, but there was a difference in the subjective estimate of the condition of the subcutaneous fat layer, which was classified as good or very good for 55.4 per cent of the persons occupying dwellings with balconies, but only for 46.9 per cent of those who had no balcony. This difference is obviously not due simply to the existence or non-existence of the balcony ; generally speaking, the fact of there being a balcony also means that the dwelling is healthier in other respects, and probably, in the large majority of cases, that it is situated in a modern building.

Lastly, we attempted to classify families as units according to the state of health of all the members of the family who were examined, and sometimes also with reference to data concerning any diseases, for persons not present at the inspection. In this way, we obtained the following list, which comprises nine separate categories for the state of health, differentiated according to individual stature and weight, the findings by the "Sacratama" formula, any other data concerning physical defects, symptoms of disease,

etc. These various categories may be distinguished according to the following criteria :

Categories of state of health :

1. State of health and state of nutrition particularly good in all members of the family ; no disease or unfavourable indication.
2. Intermediate degree.
3. General state and state of nutrition generally good or very good ; sometimes an isolated case of disease.
4. Intermediate degree.
5. General state and state of nutrition satisfactory or good in the majority of the individuals ; a few favourable or unfavourable exceptions.
6. General state and state of nutrition good in some persons and bad in others, the results being, in the majority, barely satisfactory ; sometimes a few cases of serious disease.
7. State of health and state of nutrition bad in the majority of persons.
8. Intermediate degree.
9. State of health and state of nutrition bad or very bad in all members of the family ; sometimes numerous pathological symptoms.

The intermediate degrees 2, 4, 6 and 8 were utilised whenever a difficulty was experienced in deciding between the principal categories 1, 3, 5, 7 and 9, which have more definite characteristics. The following diseases were noted : rickets, tuberculosis, frequent catarrh, as well as affections of the glands, or scrofula having necessitated sanatorium treatment, etc. In doubtful border-line cases, note was also taken of the state of the teeth and other indications of the state of health less important in themselves. Obviously, a classification of this sort cannot be hard and fast : all that was aimed at was an approximate general survey. The results were more pronounced than we had expected when we examined the material. The comparative tables are as follows :

| Categories | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|------------------|-----------------------|---|-----|------|------|------|-----|---|---|
| | Actual figures | | | | | | | | |
| Employed | 0 | 0 | 9 | 22 | 68 | 51 | 0 | 0 | 0 |
| Unemployed | 0 | 0 | 4 | 46 | 171 | 304 | 29 | 0 | 0 |
| | Percentages | | | | | | | | |
| Employed | 0 | 0 | 6.0 | 14.8 | 45.3 | 34.0 | 0 | 0 | 0 |
| Unemployed | 0 | 0 | 0.7 | 8.3 | 30.9 | 54.9 | 5.2 | 0 | 0 |

The general state and state of nutrition of families of unemployed persons, considered as units, were thus good far more rarely, and bad far more often, than in the case of families of employed persons examined for purposes of comparison. It may be noted, further, that even these families of employed persons certainly do not

represent a "picked lot" of particularly fit and physically well-developed persons.

SECOND SERIES OF INVESTIGATIONS.

Partly to check the accuracy of the results obtained and partly in order to ascertain whether, after a brief interval, the cases observed by us already exhibited marked changes, we summoned all the families examined for re-examination five or six months after the first series of inspections. Unfortunately, only a comparatively small proportion of the persons in question responded to this invitation. Only 48 of the employed families (153 persons) and 151 of the unemployed families (757 persons) presented themselves the second time.

Nevertheless, even this small number of cases enabled us to prove in one definite respect a clear and striking difference in the state of the two groups during that brief space of time. An examination of the average change in weight gives the following results for the big age-groups :

*Average Changes in Weight between the First and Second Series of Inspections
(Interval of Time : about Six Months).*

| Age-group (years and months) | Families of unemployed persons | | Families of employed persons | |
|------------------------------------|-------------------------------------|---------------------------------------|-------------------------------------|---------------------------------------|
| | Number of persons re-examined | Change in weight in kilogrammes | Number of persons re-examined | Change in weight in kilogrammes |
| — 5 6 | 65 | + 1.14 | 10 | + 1.54 |
| 5 7 — 13 6 | 326 | + 1.94 | 53 | + 2.21 |
| 13 7 — 19 6 | 61 | + 2.58 | 11 | + 2.59 |
| 19 7 — 34 6 | 84 | + 0.43 | 25 | + 1.72 |
| 34 7 — 49 6 | 187 | + 0.19 | 50 | + 0.90 |
| 49 7 — | 34 | + 0.16 | 4 | + 1.32 |

These figures point to the conclusion that, except for young persons from 14 to 19 years of age, all the big age-groups exhibit marked differences as regards weight. As a general rule, the average increases in weight in families whose breadwinners are working are much higher than in families of unemployed persons. But these data are not sufficient to permit of a more exhaustive analysis or a statistical study of results.

THIRD SERIES OF INVESTIGATIONS.

Since we found, when considering the results of our first series of investigations, that the insufficient number of children and adolescents examined rendered it difficult to draw proper conclusions on some points, we decided to undertake a third series of investigations. This was, however, organised differently. In this case, two groups of children and adolescents were merely to be compared with each other, without any further differentiation, by means of special social investigations; in one group, the breadwinner was unemployed, while the other group comprised all the children and adolescents of families where the father or other breadwinner was in employment. Special account was to be taken of the weight in relation to height, and of the Pelidisi index.

For this purpose, children and adolescents were examined in accordance with the plan shown in Annex 4 during the months of January to March 1934 in a number of schools (*Volksschulen, Hauptschulen, Fortbildungsschulen*). The original plan was curtailed on account of the fact that, after the disturbances which broke out in Vienna in February, we were no longer able to obtain permission in time from the new management of the continuation schools to carry on the investigations in those schools. Consequently, the returns for adolescents were limited to a small group of male apprentices numbering all together 366. The investigation of female adolescents was abandoned and, in view of the small number of male apprentices examined, it was impossible to divide up the investigations in the continuation schools according to the trade group of the apprentices and the occupation of the father, as was originally proposed.

In describing the results of this series of investigations we will confine ourselves, for the sake of clearness, to comparing the physical development and state of nutrition of the two groups (Graphs 16 to 21 and Tables XIV to XVII).

Graph 16 shows the percentage distribution of the divergencies of height from the average height. On grouping together all the children, it is quite clear that the plus differences in the case of children of employed families are more frequent than in the case of children of unemployed families, while, on the other hand, the minus differences are throughout more frequent in the case of

TABLE XIV.

DISTRIBUTION OF SCHOOL-CHILDREN ACCORDING TO DIFFERENCES IN HEIGHT AS COMPARED WITH NORMAL HEIGHT.

1. Boys.

A. Actual figures.

| cm. | Volksschulen | | Hauptschulen | | Fortbildungs- schulen | | All boys | |
|----------|---------------|-----------------|---------------|-----------------|--------------------------|-----------------|---------------|-----------------|
| | Em- ployed | Unem- ployed | Em- ployed | Unem- ployed | Em- ployed | Unem- ployed | Em- ployed | Unem- ployed |
| +++V 10 | 105 | 26 | 147 | 43 | 36 | 7 | 288 | 76 |
| +++V 9.5 | 249 | 66 | 200 | 97 | 49 | 10 | 498 | 173 |
| +++V 9 | 251 | 101 | 220 | 91 | 64 | 13 | 535 | 205 |
| ++H 9.5 | 67 | 37 | 65 | 34 | 18 | 11 | 150 | 82 |
| ++H 9 | 127 | 85 | 146 | 76 | 58 | 16 | 331 | 177 |
| ++V 9.5 | 59 | 44 | 91 | 63 | 46 | 9 | 196 | 116 |
| ++V 9 | 6 | 7 | 37 | 23 | 19 | 10 | 62 | 40 |
| | 864 | 366 | 906 | 427 | 290 | 76 | 2,060 | 869 |

B. Percentages.

| | | | | | | | | |
|----------|------|------|------|------|------|------|------|------|
| +++V 10 | 12.1 | 7.1 | 16.2 | 10.1 | 12.1 | 9.2 | 14.0 | 8.7 |
| +++V 9.5 | 28.8 | 18.0 | 22.1 | 22.7 | 16.9 | 13.2 | 24.2 | 19.9 |
| +++V 9 | 29.1 | 25.8 | 24.3 | 21.3 | 22.1 | 17.1 | 26.0 | 23.6 |
| ++H 9.5 | 7.8 | 10.1 | 7.2 | 8.0 | 6.2 | 14.5 | 7.3 | 9.4 |
| ++H 9 | 14.7 | 23.2 | 16.1 | 17.8 | 20.0 | 21.1 | 16.1 | 20.4 |
| ++V 9.5 | 6.8 | 12.0 | 10.0 | 14.8 | 15.8 | 11.8 | 9.5 | 13.3 |
| ++V 9 | 0.7 | 1.9 | 4.1 | 5.4 | 6.6 | 13.2 | 3.0 | 4.6 |

2. GIRLS.

A. Actual figures.

| cm. | Volksschulen | | Hauptschulen | | All girls | | All children | |
|----------|---------------|-----------------|---------------|-----------------|---------------|-----------------|---------------|-----------------|
| | Em- ployed | Unem- ployed | Em- ployed | Unem- ployed | Em- ployed | Unem- ployed | Em- ployed | Unem- ployed |
| +++V 10 | 84 | 8 | 153 | 40 | 237 | 48 | 525 | 124 |
| +++V 9.5 | 163 | 25 | 272 | 114 | 435 | 139 | 934 | 312 |
| +++V 9 | 119 | 24 | 234 | 94 | 353 | 118 | 889 | 323 |
| ++H 9.5 | 40 | 10 | 72 | 32 | 112 | 42 | 262 | 124 |
| ++H 9 | 71 | 22 | 218 | 84 | 289 | 106 | 621 | 283 |
| ++V 9.5 | 19 | 12 | 79 | 65 | 98 | 77 | 294 | 193 |
| ++V 9 | 6 | 3 | 30 | 18 | 36 | 21 | 98 | 61 |
| | 502 | 104 | 1,058 | 447 | 1,560 | 551 | 3,620 | 1,240 |

B. Percentages.

| | | | | | | | | |
|----------|------|------|------|------|------|------|------|------|
| +++V 10 | 16.6 | 7.7 | 14.5 | 8.9 | 15.2 | 8.7 | 14.5 | 8.7 |
| +++V 9.5 | 32.5 | 24.0 | 25.7 | 25.5 | 27.9 | 25.2 | 25.8 | 22.0 |
| +++V 9 | 23.8 | 23.1 | 22.1 | 21.0 | 22.6 | 21.4 | 24.5 | 22.7 |
| ++H 9.5 | 7.9 | 9.6 | 6.8 | 7.2 | 7.2 | 7.6 | 7.2 | 8.7 |
| ++H 9 | 14.3 | 21.2 | 20.6 | 19.0 | 18.6 | 19.2 | 17.1 | 19.9 |
| ++V 9.5 | 3.8 | 11.5 | 7.5 | 14.5 | 6.3 | 14.0 | 8.1 | 13.6 |
| ++V 9 | 1.2 | 2.9 | 2.8 | 4.0 | 2.3 | 3.8 | 2.7 | 4.3 |

TABLE XV.

DISTRIBUTION OF SCHOOL-CHILDREN ACCORDING TO DIFFERENCES IN WEIGHT AS COMPARED WITH NORMAL WEIGHT.

1. Boys.

A. Actual figures.

| kg. | Volksschulen | | Hauptschulen | | Fortbildungsschulen | | All boys | |
|---------|---------------|-----------------|---------------|-----------------|---------------------|-----------------|---------------|-----------------|
| | Em- ployed | Unem- ployed | Em- ployed | Unem- ployed | Em- ployed | Unem- ployed | Em- ployed | Unem- ployed |
| + > 10 | 22 | 1 | 43 | 9 | 39 | 5 | 104 | 15 |
| + 5-9.9 | 77 | 8 | 70 | 35 | 44 | 11 | 191 | 54 |
| + 1-4.9 | 228 | 76 | 194 | 88 | 57 | 21 | 479 | 185 |
| + 0.9 | 256 | 125 | 174 | 99 | 34 | 10 | 464 | 244 |
| - 1-4.9 | 265 | 147 | 365 | 163 | 55 | 15 | 685 | 325 |
| - 5-9.9 | 14 | 9 | 54 | 30 | 43 | 10 | 111 | 49 |
| - > 10 | 2 | 1 | 6 | 2 | 18 | 4 | 26 | 7 |
| | 864 | 367 | 906 | 426 | 290 | 76 | 2,060 | 860 |

B. Percentages.

| | | | | | | | | |
|---------|------|------|------|------|------|------|------|------|
| + > 10 | 2.5 | 0.3 | 4.7 | 2.1 | 13.4 | 6.6 | 5.0 | 1.7 |
| + 5-9.9 | 8.9 | 2.2 | 7.7 | 8.2 | 15.2 | 14.5 | 9.3 | 6.2 |
| + 1-4.9 | 26.4 | 20.7 | 21.4 | 20.7 | 19.7 | 27.6 | 23.3 | 21.3 |
| + 0.9 | 29.6 | 34.1 | 19.2 | 23.2 | 11.7 | 13.2 | 22.5 | 26.0 |
| - 1-4.9 | 30.7 | 40.0 | 40.3 | 38.3 | 19.0 | 19.7 | 33.3 | 37.4 |
| - 5-9.9 | 1.6 | 2.5 | 6.0 | 7.0 | 14.8 | 13.1 | 5.4 | 5.6 |
| - > 10 | 0.2 | 0.3 | 0.7 | 0.5 | 6.2 | 5.3 | 1.3 | 0.8 |

2. GIRLS.

A. Actual figures.

| kg. | Volksschulen | | Hauptschulen | | All girls | | All children | |
|---------|---------------|-----------------|---------------|-----------------|---------------|-----------------|---------------|-----------------|
| | Em- ployed | Unem- ployed | Em- ployed | Unem- ployed | Em- ployed | Unem- ployed | Em- ployed | Unem- ployed |
| + > 10 | 20 | 2 | 88 | 27 | 108 | 29 | 212 | 44 |
| + 5-9.9 | 68 | 8 | 185 | 57 | 253 | 65 | 411 | 119 |
| + 1-4.9 | 162 | 25 | 271 | 124 | 433 | 149 | 912 | 334 |
| + 0.9 | 123 | 30 | 147 | 66 | 270 | 96 | 734 | 330 |
| - 1-4.9 | 121 | 38 | 250 | 118 | 371 | 156 | 1,056 | 481 |
| - 5-9.9 | 7 | 2 | 87 | 41 | 94 | 43 | 205 | 92 |
| - > 10 | — | — | 31 | 13 | 31 | 13 | 57 | 29 |
| | 501 | 105 | 1,059 | 446 | 1,560 | 551 | 3,620 | 1,420 |

B. Percentages.

| | | | | | | | | |
|---------|------|-------|------|------|------|------|------|------|
| + > 10 | 4.0 | 1.9 | 8.3 | 6.1 | 6.9 | 5.3 | 5.9 | 3.1 |
| + 5-9.9 | 13.6 | 7.6 | 17.5 | 12.8 | 16.2 | 11.8 | 12.3 | 8.4 |
| + 1-4.9 | 32.3 | 23.8 | 25.6 | 27.8 | 27.8 | 27.0 | 25.2 | 23.5 |
| + 0.9 | 24.5 | 28.6 | 13.9 | 14.8 | 17.3 | 17.4 | 20.3 | 23.2 |
| - 1-4.9 | 24.2 | 36.12 | 23.6 | 26.5 | 23.8 | 28.3 | 29.2 | 33.9 |
| - 5-9.9 | 1.4 | 1.9 | 8.2 | 9.2 | 6.0 | 7.8 | 5.7 | 6.5 |
| - > 10 | — | — | 2.9 | 2.9 | 2.0 | 2.4 | 1.6 | 1.4 |

TABLE XVI.
DISTRIBUTION OF SCHOOL-CHILDREN ACCORDING TO THE VALUE OF THEIR PELIDISI INDEX.

| PELIDISI | A. Boys | | | | | | B. GIRLS | | | | | | | |
|----------|--------------|------------|--------------|------------|---------------------|------------|----------|------------|--------------|------------|--------------|------------|-----------|------------|
| | Volksschulen | | Hauptschulen | | Fortbildungsschulen | | All boys | | Volksschulen | | Hauptschulen | | All girls | |
| | Employed | Unemployed | Employed | Unemployed | Employed | Unemployed | Employed | Unemployed | Employed | Unemployed | Employed | Unemployed | Employed | Unemployed |
| 115 | — | — | — | — | — | — | — | — | — | — | 1 | — | 1 | — |
| 114 | — | — | — | — | — | — | — | — | — | — | — | — | 1 | — |
| 113 | — | — | — | — | — | — | — | — | 1 | — | — | — | 1 | — |
| 112 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 111 | 1 | — | — | — | 1 | — | 2 | — | — | — | — | — | 1 | — |
| 110 | — | — | — | 1 | — | — | — | 1 | — | — | — | — | — | — |
| 109 | 1 | — | 1 | — | — | — | 2 | — | 1 | — | 1 | — | 2 | — |
| 108 | 2 | — | 3 | 1 | 1 | — | 6 | 1 | — | — | 2 | 1 | 2 | — |
| 107 | 1 | — | 2 | — | — | — | 3 | — | 3 | — | 2 | 1 | 2 | — |
| 106 | 4 | 1 | 3 | 1 | 2 | — | 9 | 2 | 4 | — | 9 | 1 | 13 | — |
| 105 | 2 | 2 | 5 | 1 | — | — | 7 | 3 | 5 | — | 8 | 3 | 13 | — |
| 104 | 7 | — | 9 | 1 | 1 | — | 9 | 1 | 10 | — | 13 | 4 | 23 | — |
| 103 | 12 | 1 | 9 | 1 | 2 | — | 17 | 2 | 6 | — | 17 | 8 | 23 | — |
| 102 | 20 | — | 12 | 6 | 1 | — | 23 | 6 | 15 | 2 | 23 | 6 | 38 | — |
| 101 | 13 | 3 | 17 | 5 | 4 | — | 33 | 8 | 8 | 3 | 28 | 6 | 36 | — |
| 100 | 16 | 7 | 27 | 9 | 5 | 1 | 48 | 17 | 23 | 2 | 42 | 13 | 65 | 15 |
| 99 | 37 | 4 | 36 | 15 | 5 | 3 | 78 | 22 | 24 | 2 | 64 | 24 | 88 | 26 |
| 98 | 48 | 16 | 54 | 28 | 18 | 4 | 119 | 48 | 44 | 6 | 68 | 20 | 112 | 35 |
| 97 | 56 | 27 | 74 | 29 | 17 | 8 | 147 | 64 | 48 | 10 | 77 | 30 | 125 | 40 |
| 96 | 83 | 34 | 79 | 38 | 24 | 7 | 186 | 79 | 51 | 9 | 99 | 44 | 150 | 53 |
| 95 | 94 | 37 | 116 | 59 | 32 | 8 | 242 | 104 | 47 | 12 | 114 | 46 | 161 | 58 |
| 94 | 115 | 58 | 144 | 57 | 38 | 9 | 297 | 124 | 60 | 12 | 117 | 40 | 177 | 61 |
| 93 | 120 | 46 | 111 | 60 | 42 | 11 | 273 | 117 | 51 | 15 | 96 | 53 | 147 | 68 |
| 92 | 106 | 58 | 78 | 51 | 30 | 8 | 124 | 117 | 38 | 11 | 113 | 48 | 151 | 59 |
| 91 | 53 | 40 | 65 | 36 | 28 | 10 | 146 | 86 | 25 | 7 | 76 | 33 | 101 | 40 |
| 90 | 39 | 20 | 29 | 11 | 21 | 4 | 89 | 35 | 19 | 4 | 37 | 21 | 56 | 25 |
| 89 | 27 | 9 | 22 | 10 | 11 | 2 | 60 | 21 | 10 | 2 | 23 | 14 | 33 | 16 |
| 88 | 5 | 3 | 5 | 2 | 4 | — | 14 | 5 | 4 | 2 | 12 | 7 | 16 | 9 |
| 87 | 1 | — | 3 | 3 | — | — | 4 | 3 | 1 | — | 4 | 1 | 5 | 1 |
| 86 | — | — | 2 | — | 1 | — | 3 | — | — | — | 2 | — | 2 | 1 |
| 85 | — | — | — | — | — | — | — | — | 1 | 1 | 2 | — | 3 | 2 |
| 84 | 1 | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 83 | — | — | — | — | — | — | 1 | — | — | — | 1 | — | 1 | — |
| 82 | — | — | — | — | — | — | — | — | 1 | — | — | — | — | — |

TABLE XVII.

DISTRIBUTION OF SCHOOL-CHILDREN ACCORDING TO THE VALUE OF THEIR PELIDISI INDEX (LARGER GROUPS).

| PELIDISI | Boys | | | | | | GIRLS | | | | | | All children | | | | |
|----------|--------------------|-----------------|--------------|-----------------|--------------------------|-----------------|----------|-----------------|--------------|-----------------|--------------|-----------------|--------------|-----------------|----------|-----------------|---|
| | 1. Actual figures. | | | | | | | | | | | | | | | | |
| | Volksschulen | | Hauptschulen | | Fortbildungs- schulen | | All boys | | Volksschulen | | Hauptschulen | | All girls | | | | |
| | Employed | Un- employed | Employed | Un- employed | Employed | Un- employed | Employed | Un- employed | Employed | Un- employed | Employed | Un- employed | Employed | Un- employed | Employed | Un- employed | |
| 110-115 | 1 | — | — | 1 | 1 | — | 2 | 1 | 1 | — | — | 3 | — | 4 | — | 6 | 1 |
| 105-109 | 10 | 3 | 14 | 3 | 3 | — | 27 | 6 | 13 | — | 25 | 9 | 38 | 9 | 65 | 15 | |
| 100-104 | 68 | 11 | 74 | 22 | 13 | 1 | 155 | 34 | 62 | 7 | 209 | 37 | 185 | 44 | 340 | 78 | |
| 97-99 | 141 | 47 | 164 | 72 | 40 | 15 | 345 | 134 | 116 | 18 | 223 | 83 | 325 | 101 | 670 | 235 | |
| 94-96 | 292 | 129 | 339 | 154 | 94 | 24 | 725 | 307 | 158 | 33 | 330 | 139 | 488 | 172 | 1,213 | 479 | |
| 91-93 | 379 | 144 | 354 | 147 | 100 | 29 | 633 | 320 | 114 | 33 | 285 | 134 | 399 | 167 | 1,032 | 487 | |
| 88-90 | 71 | 32 | 56 | 23 | 36 | 6 | 163 | 61 | 33 | 8 | 72 | 42 | 105 | 50 | 268 | 111 | |
| 82-87 | 2 | — | 5 | 3 | 1 | — | 8 | 3 | 3 | 3 | 9 | 1 | 12 | 4 | 20 | 7 | |
| | 804 | 366 | 906 | 425 | 288 | 75 | 2,058 | 866 | 500 | 102 | 1,056 | 445 | 1,556 | 547 | 3,614 | 1,413 | |

2. Percentages.

| | | | | | | | | | | | | | | | | |
|---------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| 110-115 | 0.1 | — | — | 0.2 | 0.3 | — | 0.1 | 0.1 | 0.2 | — | 0.3 | — | 0.3 | — | 0.2 | 0.1 |
| 105-109 | 1.2 | 0.8 | 1.5 | 0.7 | 1.0 | — | 1.3 | 0.7 | 2.6 | — | 2.4 | 2.0 | 2.4 | 1.6 | 1.8 | 1.1 |
| 100-104 | 7.0 | 3.0 | 8.2 | 5.2 | 4.5 | 1.3 | 7.5 | 3.9 | 12.4 | 6.9 | 11.6 | 8.3 | 11.9 | 8.0 | 9.4 | 5.5 |
| 97-99 | 16.3 | 12.8 | 18.1 | 16.9 | 13.9 | 20.0 | 16.8 | 15.5 | 23.2 | 17.6 | 19.8 | 18.7 | 20.9 | 18.5 | 18.5 | 16.6 |
| 94-96 | 31.8 | 35.2 | 37.4 | 36.2 | 32.6 | 32.0 | 35.2 | 35.5 | 31.6 | 32.4 | 31.2 | 31.2 | 31.4 | 31.4 | 33.6 | 33.9 |
| 91-93 | 32.3 | 39.1 | 28.0 | 34.6 | 34.7 | 38.7 | 30.8 | 37.0 | 22.8 | 32.4 | 27.0 | 30.1 | 25.6 | 30.5 | 28.6 | 34.5 |
| 88-90 | 8.2 | 8.7 | 6.2 | 5.4 | 12.5 | 8.0 | 7.9 | 7.0 | 6.6 | 7.8 | 6.8 | 9.4 | 6.7 | 9.1 | 7.4 | 7.9 |
| 82-87 | 0.2 | — | 0.6 | 0.7 | 0.3 | — | 0.4 | 0.3 | 0.6 | 2.9 | 0.9 | 0.2 | 0.8 | 0.7 | 0.6 | 0.5 |

children of unemployed families than of employed families. In this respect, the differences are smaller only in the case of the very young children. The extreme minus differences are therefore shown to be due less to exogenous causes than the other groups of minus differences. In the case of the plus differences, on the other hand, we also observe a strongly marked preponderance of children of employed persons in the groups containing the greatest divergencies. We must conclude from this that, unlike the extreme minus differences, which are obviously due to constitutional causes, the plus differences are due to exogenous factors which extend to the maximum differences noted. The same phenomenon is also apparent when all the returns are divided according to sex. In the case both of boys and girls, we notice more frequent minus differences in unemployed families and more frequent plus differences in the children of employed parents. On further dividing up the figures according to the grade of school (Graph 17), we notice that, in the case of the pupils of elementary schools (*Volksschulen*), who range from 6 to 10 years of age, the differences are even more marked than in the total returns. In the *Hauptschulen*, where the pupils range from 11 to 14 years, the difference between boys and girls is still distinct, though no longer so marked as in the younger grades. In the continuation schools (*Fortbildungsschulen*), where the ages range from 14 to 20 years, the difference is hardly observable except in the case of the plus variants. The difference in the extreme groups is very marked in the case of pupils of both sexes in the *Volksschulen* and *Hauptschulen*. This difference between the extreme groups may possibly be expressed as follows : The smallest individuals are cases of hypoplasia due to constitutional causes which are probably, in the main, degenerative, whilst the tallest subjects present a physical development which results from the operation of extraneous causes and is reflected in part even in their stature. The latter phenomenon apparently does not occur in the unemployed families.

Graphs 18 and 19 are based on the figures recorded in Table XV. They contain the percentage distribution of the various divergencies from the normal weight in relation to the height. On grouping together all the children examined and on comparing all the boys and girls, we again observe that the minus variants predominate in children of unemployed while the plus

variants predominate in the children of employed persons. We also again observe that the difference in the extreme minus variants disappears while the difference in the extreme plus variants is maintained. The difference which was noticed in the case of stature as between the values for constitutionally degenerative hypoplastic subjects at one end of the scale, and the effect of extraneous factors upon physical development observable up to the extreme values at the other end of the scale, can thus also be detected in the case of weight. On dividing up the returns according to the grade of school, marked differences are observed in the elementary schools between the children of unemployed and employed persons ; in the *Hauptschulen*, these differences are still evident in the case of girls, but are hardly noticeable in the case of boys, and there are no appreciable differences among the pupils of the continuation schools.

Lastly, Graphs 20 and 21, which are based on the figures contained in Tables XVI and XVII, show the distribution of the Pelidisi figures in the various groups of children. For all the children together, we again observe quite clearly the predominance of the minus variants among children of unemployed persons and the relative predominance of the plus variants among the children of employed persons. The difference is maintained when dividing the returns according to sex. On dividing the returns according to the grade of school, the difference between the children of unemployed and of employed persons in the elementary schools is again particularly marked ; in the *Hauptschulen* it is still clear, though not so marked, and in the continuation schools it is no longer observable. The extreme figures of the Pelidisi index do not show any certain differences between the two main groups of children, either for the plus variants or for the minus variants. The extreme plus variants, therefore, also appear to be to a great extent due to endogenous causes. In this connection, it should be borne in mind that the causes for the extreme height of the Pelidisi figures are partly to be found, not only in abnormal development of adipose tissue, but also in unusual physical proportions (squat figures).

CONCLUSIONS.

1. The enquiries have revealed that there is no difference between the families of employed and unemployed persons as regards housing, particularly in the case of families with three or more children. The pecuniary situation of the unemployed is in itself sufficient evidence of their extreme poverty, which is further increased by debt. But even the families of employed persons are frequently in debt. Consequently, public and private relief acquires great importance.

2. The *average height* of adults, both male and female, is greater in families whose breadwinner is working than in the families of the unemployed.

3. The *average weight* is also greater for adults, both male and female, in the families of employed persons. The difference is more noticeable in women than in men.

4. The differences of height and weight noted among adults, both male and female, are also apparent among *boys and youths*, according to whether the parents are employed or unemployed.

5. Among *girls*, these differences were less regular in the first series of enquiries, the difference being sometimes even in the contrary direction. But investigations among larger numbers of children (third series) showed that these irregularities in the results for the first group of girls were due to errors caused by the examination of too few individuals.

6. If account is taken of all the persons examined in the first series of investigations, it will be seen that the *average height and weight* of the children and adolescents in these families also were considerably greater than those of the persons examined by NOBEL and PIRQUET in 1920-1923.

7. In the *Pelidisi index*, the differences of physical constitution were hardly noticeable in the first series of investigations. But the results of the third series show that, in the case of children and adolescents, this was also due in part to the examination, on the first occasion, of an insufficient number of individuals in this age-group. In the case of adults, this remarkable result would seem

to be due to two causes : small average height and more negligent carriage among members of the families of unemployed persons.

8. The contrast from the point of view of physical constitution between the two groups of families examined is brought out very clearly and definitely *when the plus and minus divergencies in height are compared by age-groups.*

9. In adults, a similar contrast also appears on comparing *the plus and minus divergencies in weight in relation to age and height.* For children and adolescents, on the contrary, a comparison of the plus and minus divergencies in weight in relation to height within the group of the first series gives opposite results. This fact is explained on comparing the plus and minus divergencies in *weight* in relation to age, among children and adolescents. This comparison again clearly demonstrates the defective physical development of unemployed persons' children. The contrast *proves that the effect of unemployment on Viennese children has hitherto been not so much to hinder the proper development of fatty tissue (as a result of mal-nutrition) as generally to retard physical development (owing to unsatisfactory living conditions).*

10. Very marked differences to the advantage of the families of employed persons are also noted in the blood-content of the skin and visible mucous membranes.

11. *Housing conditions* also affect growth, the development of fatty tissue and blood-content of the skin, as can definitely be proved. Upper-storey flats tend to encourage the development of fatty tissue, while ground-floor flats (including dwellings in cellars and basements) tend rather to stimulate growth and, to a certain extent, increase the blood-content of the skin (it being easier for the children to get into the open). Similarly, we noted that the presence of balconies tends to increase the blood-content of the skin, and possibly the development of fatty tissue.

12. A second series of investigations showed that the *average alterations in weight*, during the first six months following the first series of enquiries, were all to the advantage of families of employed persons, both children and adults of all ages. Only among adolescents could no difference be detected.

13. *A third extensive series of investigations gave further results as regards schoolchildren.* On comparing the various divergencies, we noted very marked differences between the children of the unemployed and the employed, with regard both to height and to weight in relation to height, as well as to the Pelidisi index. Generally speaking, these differences are much more noticeable in the youngest children (6 to 10 years) ; they are less pronounced in the following age-group (11 to 14 years) and almost entirely undetectable in the 14 to 18 years group.

Appendix.

When the above enquiries had been completed, a further statistical survey was made of the results of the third series of investigations ; this survey related to the three categories of schools : *Volksschulen*, *Hauptschulen* and *Fortbildungsschulen*. The main object was to enable these figures to be further checked by means of certain very valuable but hitherto little known statistical data collected between 1920 and 1922, when the American children's relief organisation was at work in Vienna. At that time, more than 140,000 children were repeatedly examined in all the Viennese *Volksschulen* and *Hauptschulen* under the direction of PIRQUET and NOBEL. The results of these enquiries, the statistics of which were prepared by A. FESSLER, were published in the bulletins of the American " Save the Children Fund " in Vienna, in the *Zeitschrift für Kinderheilkunde*, Vol. 36, in 1923, and in the *Wiener klinische Wochenschrift*, in 1921.¹ Tables XVIII to XX first of all show the average figures for height, weight and the Pelidisi index for the boys and girls examined during the third series of investigations. They reveal very appreciable differences in all the age-groups between the children of persons in work and out of work respectively. The difference in average height is in most age-categories about 1 to

¹ PIRQUET, C. (1921) : " Die Amerikanische Schulausspeisung in Oesterreich ", *Wiener klin. Wochenschr.*, 34, page 323.

NOBEL, E. (1921) : " Einiges über die Amerikanische Kinderausspeisung in Wien und Niederösterreich ", *Wiener klin. Wochenschr.*, 34, page 325.

2 centimetres for both boys and girls. The difference in weight usually averages 2 kilogrammes. The average Pelidisi index figures are about 1 Pelidisi degree higher among children of employed persons in most year groups. These differences in the average figures confirm, in the main, what we previously said when discussing the various groups of divergencies and distribution curves relating to height, weight and Pelidisi index in the two categories of families under consideration.

TABLE XVIII.

HEIGHT OF THE CHILDREN OF VIENNA :
RESULTS OF EXAMINATIONS IN 1920, 1922 AND 1934.

| Age | Children of unemployed* | Children of employed* | Vienna 1920 | Vienna 1922 | Pirquet- Camerer | Normal 1933 |
|------------|----------------------------|--------------------------|----------------|----------------|---------------------|----------------|
| | 1934 | | | | | |
| A. BOYS. | | | | | | |
| 6-6½ years | 115.8 (22) | 117.5 (41) | — | — | — | — |
| 7 | 119.2 (74) | 122.0 (157) | — | 116 | 115 | 110 |
| 8 | 125.2 (76) | 127.5 (190) | — | 119 | 120 | 124 |
| 9 | 130.1 (103) | 131.6 (246) | — | 124 | 125 | 128 |
| 10 | 134.3 (98) | 137.1 (260) | — | 128 | 130 | 132 |
| 11 | 140.6 (91) | 140.5 (214) | — | 134 | 135 | 137 |
| 12 | 143.9 (118) | 145.5 (233) | — | 138 | 140 | 142 |
| 13 | 148.8 (117) | 150.7 (256) | — | 142 | 145 | 148 |
| 14 | 153.7 (95) | 155.1 (173) | — | 145 | 151 | 154 |
| 15 | 162.8 (28) | 161.0 (76) | 151.7 | 152.2 | 157 | 160 |
| 16 | 161.5 (18) | 165.2 (81) | 155.2 | 158.2 | — | 165 |
| 17 | 164.3 (17) | 167.3 (73) | 158.4 | 162.5 | — | 168 |
| 18 | 166.6 (7) | 165.8 (20) | 159.8 | 164.2 | — | 169 |
| B. GIRLS. | | | | | | |
| 6-6½ years | 119.7 (4) | 119.1 (19) | — | — | — | — |
| 7 | 119.4 (27) | 121.8 (81) | — | 114 | 113 | 118 |
| 8 | 125.4 (20) | 127.7 (168) | — | 119 | 118 | 123 |
| 9 | 127.1 (26) | 131.5 (134) | — | 124 | 123 | 127 |
| 10 | 137.4 (40) | 137.2 (196) | — | 129 | 128 | 132 |
| 11 | 140.5 (107) | 141.2 (307) | — | 134 | 133 | 138 |
| 12 | 145.0 (128) | 147.5 (274) | — | 139 | 139 | 144 |
| 13 | 151.2 (114) | 152.2 (240) | — | 145 | 146 | 149 |
| 14 | 153.7 (80) | 154.2 (186) | — | 148 | 153 | 154 |

* The figure in brackets is that of the children examined.

But these tables, and the curves in Graphs 22 to 27, also allow of comparisons between our figures and those obtained by the American "Save the Children Fund" in Vienna in 1920-1922. Here also we find very striking differences. Among boys and girls, and in all age-groups, the height is now appreciably greater than then, the difference exceeding in almost all cases 5 cm. The same

is true of weight in relation to age : here the difference amounts to from 2 to 4 kilogrammes in most age-groups. These facts concord with similar changes noted elsewhere, mainly in Germany, in the physical condition of children during post-war years.¹ But a most interesting point is the comparison of the children's state of nutrition as shown by the Pelidisi index. Both for boys and girls, the average figures of this index are distinctly higher than in 1922 in all age-groups, the difference amounting, in most groups, to from 2 to 4 Pelidisi degrees.

TABLE XIX.

WEIGHT OF THE CHILDREN OF VIENNA ;
RESULTS OF EXAMINATIONS IN 1922 AND 1934.

| Age | Children of unemployed | Children of employed | Vienna 1922 | Pirquet- Camerer | Normal 1933 |
|-----------|---------------------------|-------------------------|----------------|---------------------|----------------|
| | 1934 | | | | |
| A. Boys. | | | | | |
| 7 years | 22.5 | 24.7 | 20.7 | 23.0 | 22.5 |
| 8 " | 25.1 | 27.4 | 22.8 | 25.0 | 24.5 |
| 9 " | 27.6 | 29.1 | 24.9 | 27.5 | 26.7 |
| 10 " | 30.1 | 32.9 | 27.1 | 30.0 | 29.0 |
| 11 " | 33.2 | 34.6 | 29.2 | 32.5 | 31.8 |
| 12 " | 35.9 | 37.7 | 30.8 | 35.0 | 35.0 |
| 13 " | 39.6 | 41.6 | 33.4 | 37.5 | 38.5 |
| 14 " | 43.7 | 44.3 | 35.4 | 41.0 | 43.0 |
| 15 " | 52.6 | 54.7 | | 45.0 | 48.0 |
| 16 " | 51.6 | 55.6 | | — | 53.0 |
| 17 " | 56.8 | 59.6 | | — | — |
| 18 " | 56.4 | 58.7 | | — | — |
| B. GIRLS. | | | | | |
| 7 years | 22.6 | 24.9 | 20.4 | 21.0 | 22.0 |
| 8 " | 26.1 | 27.7 | 22.2 | 23.0 | 24.0 |
| 9 " | 25.9 | 30.7 | 24.3 | 25.0 | 26.0 |
| 10 " | 31.9 | 33.3 | 26.9 | 27.0 | 28.5 |
| 11 " | 34.4 | 35.5 | 29.7 | 29.0 | 31.5 |
| 12 " | 37.5 | 40.1 | 32.7 | 32.0 | 35.0 |
| 13 " | 43.1 | 45.0 | 38.1 | 37.0 | 38.5 |
| 14 " | 45.1 | 47.5 | 40.7 | 43.0 | 43.0 |

Graphs 28 and 29, indicating the percentage distribution of the Pelidisi figures for boys and girls, show that the American relief workers had already, in 1922, noted a marked improve-

¹ KORNFIELD, W. (1933) : " Ueber Normalwerte für Grösse und Gewicht bei Kindern und Jugendlichen ", *Wiener klin. Wochenschr.*, 46, page 683.

TABLE XX.

PELIDISI INDEX OF THE CHILDREN OF VIENNA :
AVERAGE FIGURES IN 1934 AND IN 1922.

| Age | Children of unemployed | Children of employed | Vienna 1922 |
|-----------|---------------------------|-------------------------|----------------|
| | 1934 | | |
| A. Boys. | | | |
| 7 years | 94.7 | 95.0 | 91.4 |
| 8 " | 93.7 | 95.1 | 91.5 |
| 9 " | 93.9 | 94.3 | 92.1 |
| 10 " | 93.8 | 95.1 | 92.2 |
| 11 " | 93.9 | 95.0 | 92.1 |
| 12 " | 94.6 | 95.1 | 91.5 |
| 13 " | 94.7 | 95.1 | 91.1 |
| 14 " | 94.3 | 94.8 | 91.1 |
| 15 " | 94.9 | 94.3 | |
| 16 " | 93.8 | 93.8 | |
| 17 " | 94.6 | 93.8 | |
| 18 " | 92.4 | 94.0 | |
| B. GIRLS. | | | |
| 7 years | 94.3 | 95.5 | 94.2 |
| 8 " | 95.0 | 95.5 | 92.1 |
| 9 " | 93.9 | 96.4 | 91.5 |
| 10 " | 93.7 | 95.4 | 91.7 |
| 11 " | 95.2 | 95.3 | 92.1 |
| 12 " | 94.6 | 95.1 | 92.8 |
| 13 " | 95.3 | 95.5 | 92.9 |
| 14 " | 94.8 | 95.9 | 94.4 |

ment as compared with 1920. Our latest figures show a further and very appreciable improvement, even among children of the unemployed, as compared with the generality of individuals in the earlier period. The distribution of the Pelidisi figures indicates an even more striking amelioration in the development of the tissues in children whose parents are in work.

Assuming, as in 1920-1922, a Pelidisi index of 94.5 as the outside figure for a normal state of nutrition, we now find, among the male children of the unemployed, 58.5 per cent weighing less than normal and, among the male children of employed parents, 53.5 per cent. In the case of girls, these percentages are 51.6 and 44.5. The American investigators working on the same system found a weight deficiency in 1920 in 89.2 per cent of the boys and 84.6 per cent of the girls, and, in 1922, in 81.6 per cent of the boys and 77 per cent of the girls.

TABLE XXI.

DISTRIBUTION OF PERCENTAGES OF *PELIDISI* FIGURES IN 1920, 1922 AND 1934.

| PELIDISI degree | 1920 | 1922 | 1934 | |
|-----------------|------|------|------------------------|----------------------|
| | | | Children of unemployed | Children of employed |
| A. Boys. | | | | |
| 82 — 87 | 4.6 | 2.3 | 0.3 | 0.4 |
| 88 — 90 | 30.2 | 22.3 | 7.0 | 7.9 |
| 91 — 93 | 45.2 | 44.9 | 37.0 | 30.8 |
| 94 — 96 | 17.3 | 25.0 | 35.5 | 35.2 |
| 97 — 99 | 2.4 | 4.7 | 15.5 | 16.8 |
| 100 and over | 0.3 | 0.7 | 4.7 | 8.9 |
| B. GIRLS. | | | | |
| 82 — 87 | 6.2 | 3.6 | 0.7 | 0.8 |
| 88 — 90 | 29.4 | 22.3 | 9.1 | 6.7 |
| 91 — 93 | 40.2 | 40.3 | 30.5 | 25.6 |
| 94 — 96 | 18.7 | 24.4 | 31.4 | 31.4 |
| 97 — 99 | 4.4 | 7.2 | 18.5 | 20.9 |
| 100 and over | 1.1 | 2.2 | 9.6 | 14.6 |

On comparing the average figures in the tables here reproduced with the figures obtained from the first series of enquiries (among families), we see that the average figures of height and weight are higher in the third series than in the first. This seems to bear out the theory we put forward tentatively above, that the families of the employed persons taken for purposes of comparison in this category were among the least healthy of their category. They came forward voluntarily for medical examination precisely because they felt it was necessary in their case ; in other words, they regarded their state of health as unsatisfactory, or perhaps, being in need of relief, they thought that the examination might help them to obtain it.

The only other recent data for the Viennese population available for comparison with the results of our enquiries refer to a very restricted age-group—namely, children from 13 to 16. With regard to this age-group, PELLER has recently published¹ certain average

¹ PELLER, S. (1933) : "Wirtschaftskrise und körperliche Entwicklung der Kriegsgeborenen, derzeit im Pubertätsalter stehenden Jugend", *Klinische Wochenschr.*, 12, page 673.

figures for height and weight. In the case of girls of 14, these are practically the same as our own figures for schools ; in the case of boys they are slightly lower. But, in the higher age-groups, PELLER's figures are much lower for boys than ours. Perhaps this is due to the fact that PELLER's material was obtained from the City of Vienna Occupational Advice Centre. It is probable that, of the subjects of his enquiry, only the children of about 14 represented the normal composition of the population ; the young persons who came to the Occupational Advice Centre at a somewhat later age would be representative, in many cases, of a process of "downward" selection. PELLER's data go down to 1932. They seem to show, as compared with the years 1929 to 1931, an improvement in weight and height which is, however, so slight that it comes within the margin of error. It may, however, be real, and may correspond to the gradual change in the post-war years to which we have referred above. Perhaps it continues to be reflected in the differences between PELLER's figures for 1932 and ours for 1934.

In short, we may draw the satisfactory conclusion that, considering the entire population of Vienna, the children's growth and increase in weight and the conditions of nutrition, as shown by PIRQUET's index, afford evidence of a striking improvement as compared with early post-war years. The condition of these children varies, however, very greatly according to whether the supporter of the family is unemployed or employed.

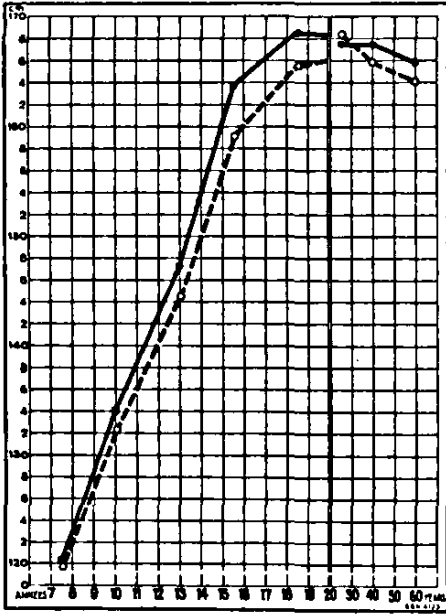
GRAPHS.

Unless otherwise stated, in all the following graphs, a continuous line (——) stands for employed and a broken line (— — —) for unemployed persons.

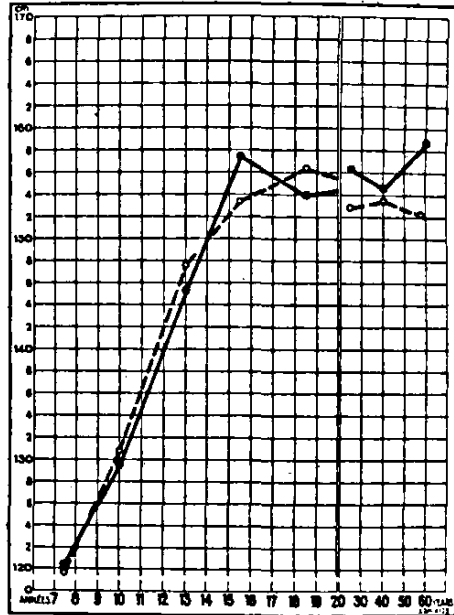
AVERAGE HEIGHT (1933).

Males.

Females.



1

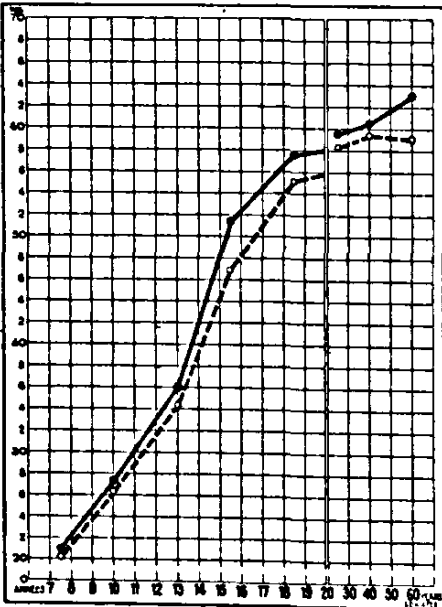


2

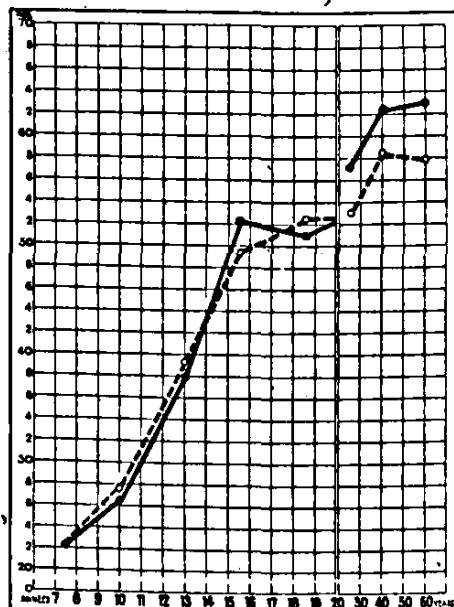
AVERAGE WEIGHT (1933).

Males.

Females.



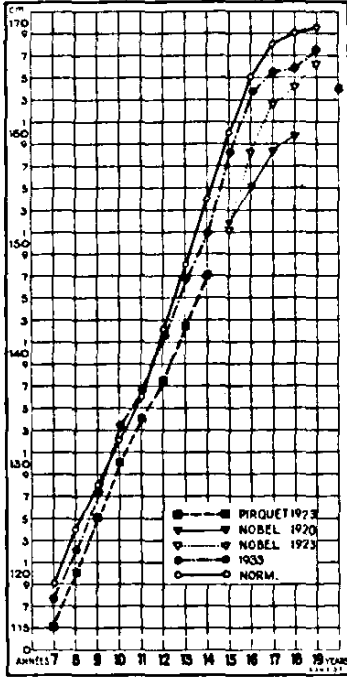
3



4

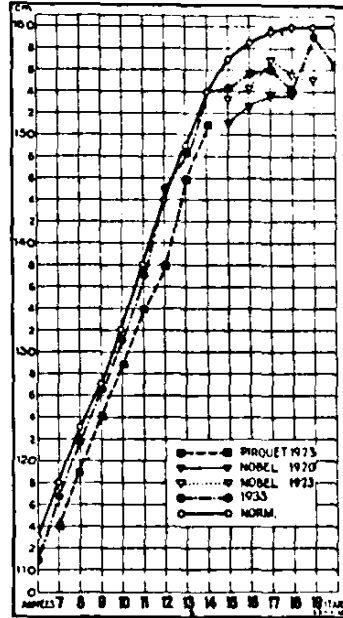
HEIGHT OF CHILDREN EXAMINED IN 1933 AS COMPARED WITH (1) THE NORMAL HEIGHT AND (2) THE FIGURES SHOWN BY NOBEL AND PIRQUET IN 1920 AND 1923.

Boys.



5

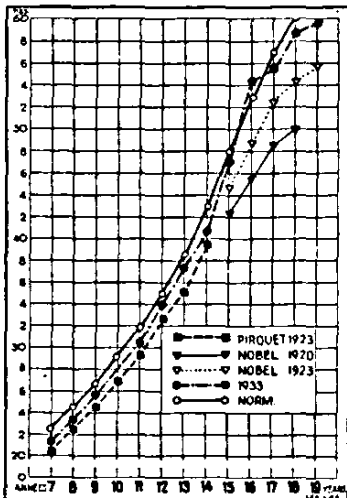
Girls.



6

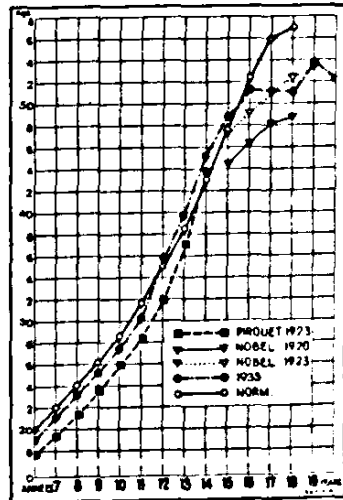
AVERAGE WEIGHT OF CHILDREN EXAMINED IN 1933 AS COMPARED WITH (1) THE NORMAL WEIGHT AND (2) THE FIGURES SHOWN BY NOBEL AND PIRQUET IN 1920 AND 1923.

Boys.



7

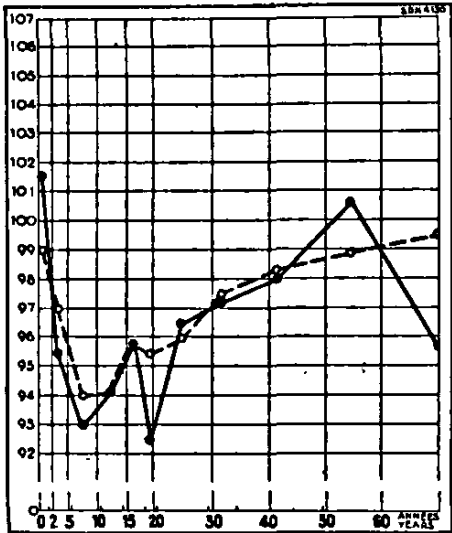
Girls.



8

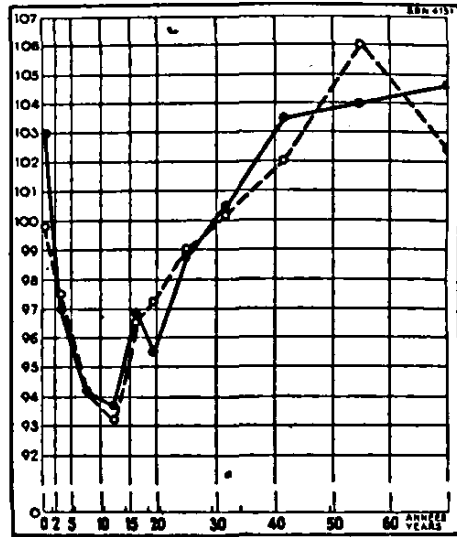
AVERAGE FIGURES OF THE PELIDISI INDEX BY AGE-GROUPS.

Males.



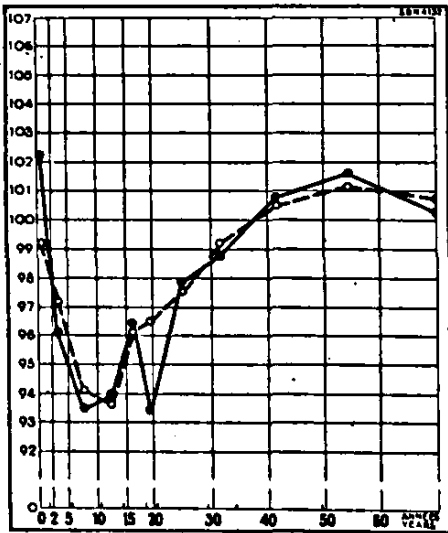
9

Females.



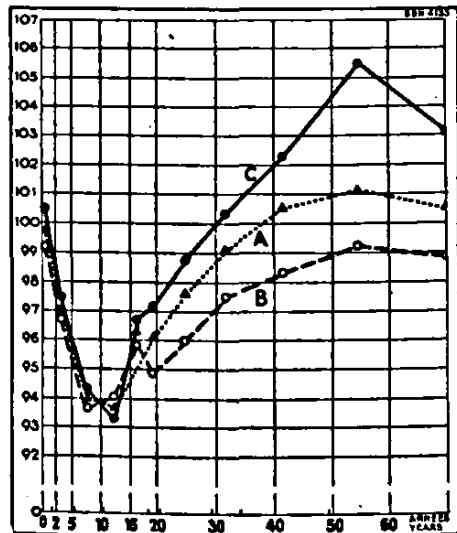
10

Both sexes.



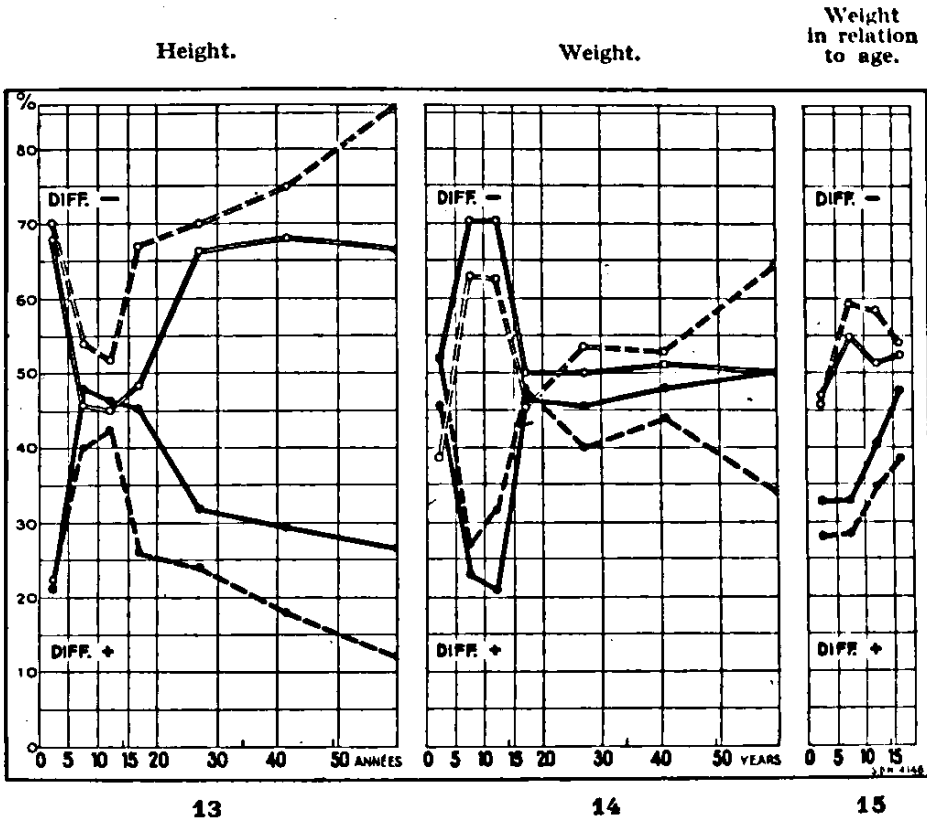
11

Employed and unemployed : both sexes (A) ; males (B) ; females (C).

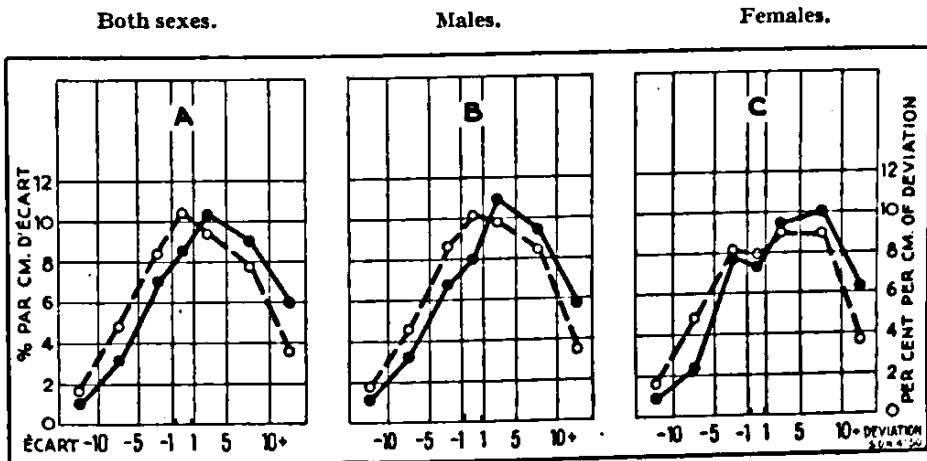


12

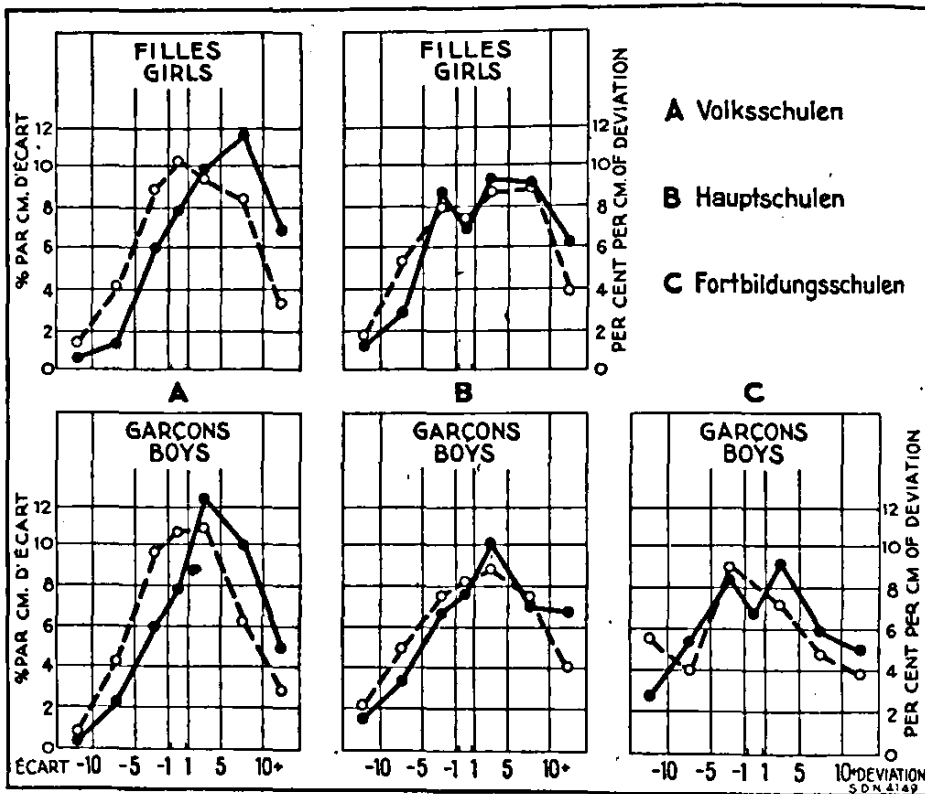
PERCENTAGE OF PLUS AND MINUS DIFFERENCES IN FAMILIES OF EMPLOYED AND UNEMPLOYED AS REGARDS :



PERCENTAGE DISTRIBUTION OF DIFFERENCES FROM THE AVERAGE HEIGHT IN FAMILIES OF EMPLOYED AND UNEMPLOYED.



PERCENTAGE DISTRIBUTION OF DIFFERENCES FROM THE AVERAGE HEIGHT IN THE CASE OF PUPILS OF VOLKSSCHULEN (A), HAUPTSCHULEN (B) AND FORTBILDUNGSSCHULEN (C).

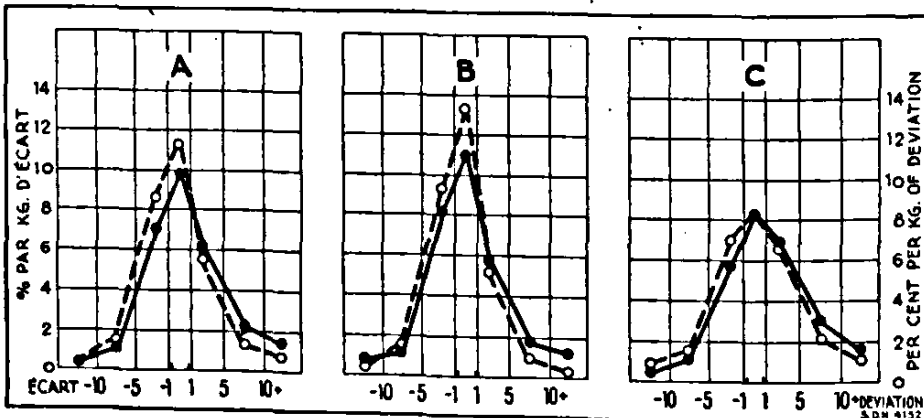


PERCENTAGE DISTRIBUTION OF DIFFERENCES IN WEIGHT AS RELATED TO HEIGHT FROM THE NORMAL WEIGHT IN THE CASE OF PUPILS OF PRIMARY AND SECONDARY SCHOOLS.

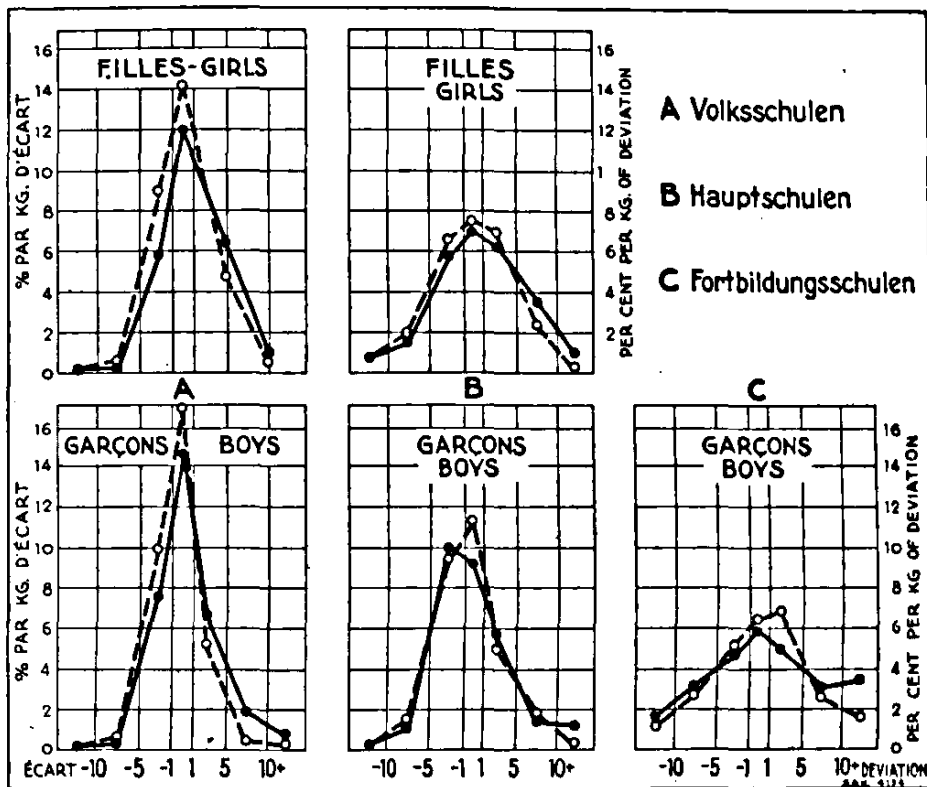
A. Boys and girls.

B. Boys.

C. Girls.



PERCENTAGE DISTRIBUTION OF DIFFERENCES IN WEIGHT FROM THE NORMAL WEIGHT IN RELATION TO HEIGHT IN THE CASE OF PUPILS OF VOLKSSCHULEN (A), HAUPTSCHULEN (B) AND FORTBILDUNGSSCHULEN (C).



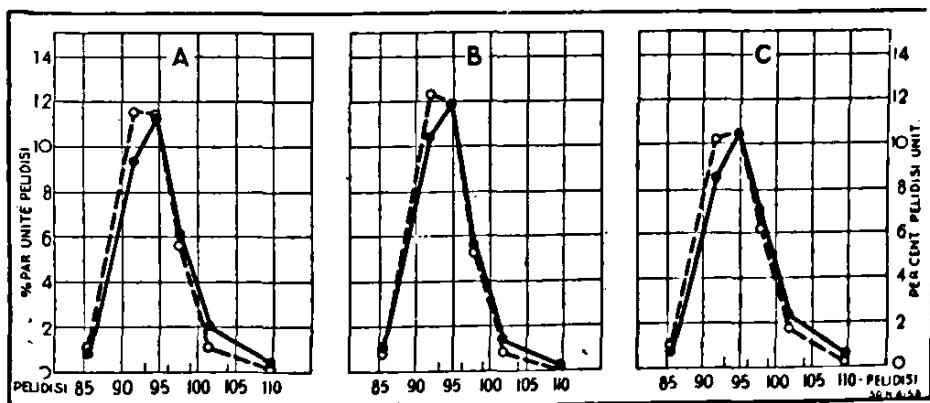
19

PERCENTAGE DISTRIBUTION OF THE PELIDISI FIGURES IN THE CASE OF PUPILS OF PRIMARY AND SECONDARY SCHOOLS.

A. Boys and girls.

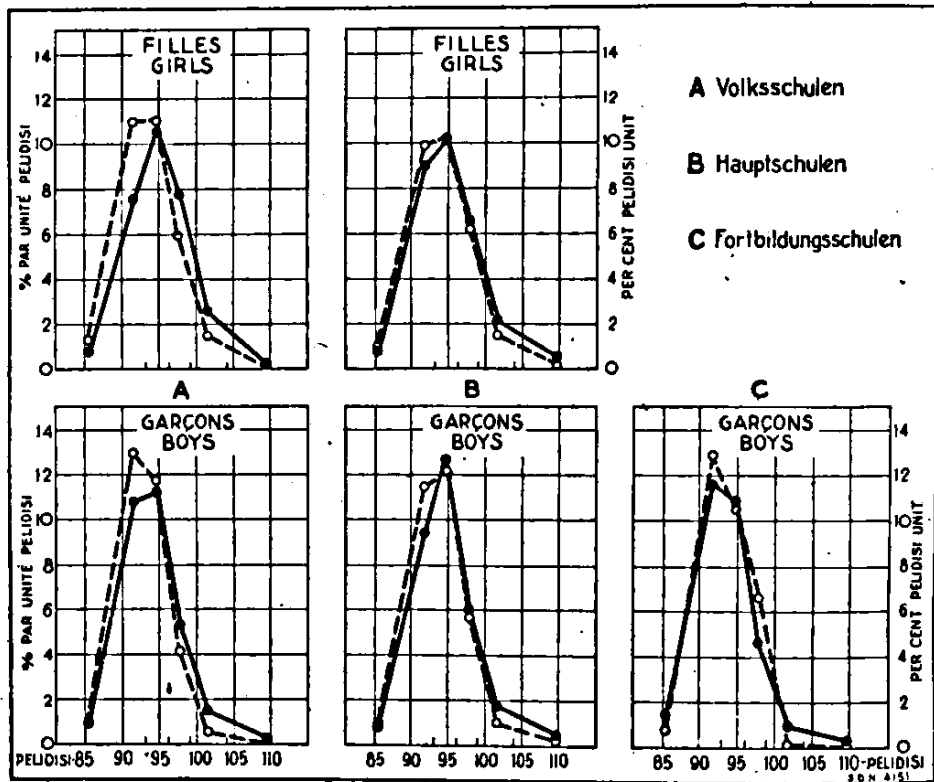
B. Boys.

C. Girls.



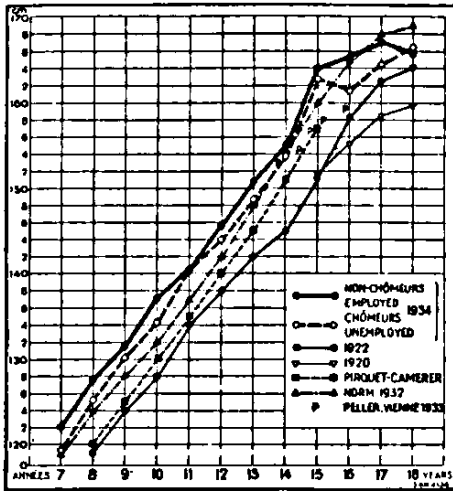
20

PERCENTAGE DISTRIBUTION OF THE PELIDISI FIGURES IN THE CASE OF PUPILS OF VOLKSSCHULEN (A), HAUPTSCHULEN (B) AND FORTBILDUNGSSCHULEN (C).



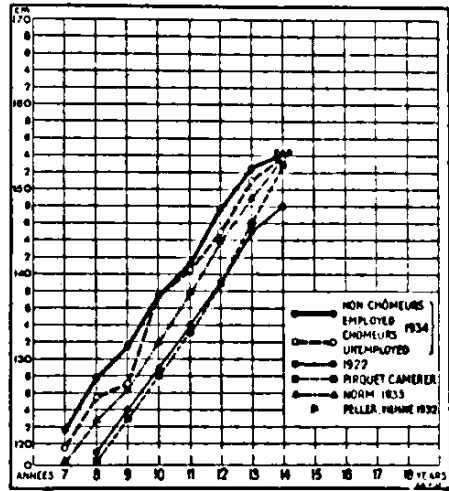
HEIGHT OF PUPILS OF PRIMARY AND SECONDARY SCHOOLS.

Boys.



22

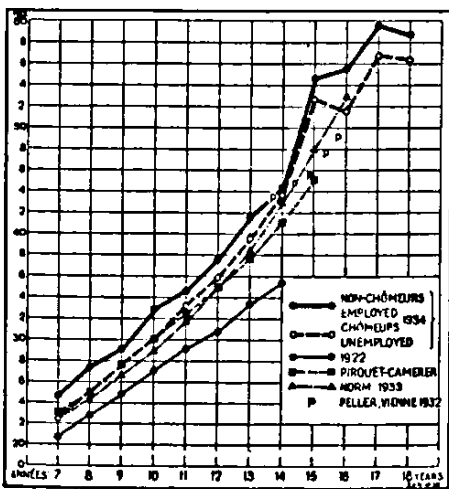
Girls.



23

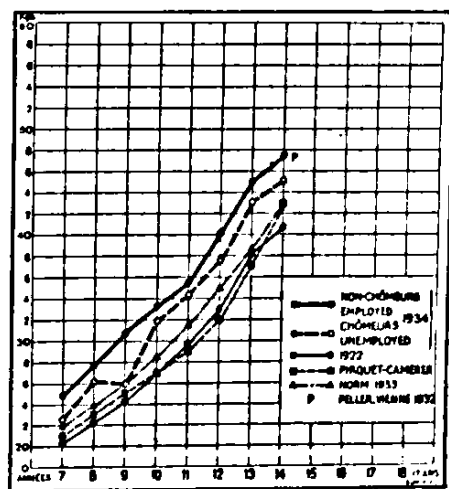
WEIGHT OF PUPILS OF PRIMARY AND SECONDARY SCHOOLS.

Boys.



24

Girls.

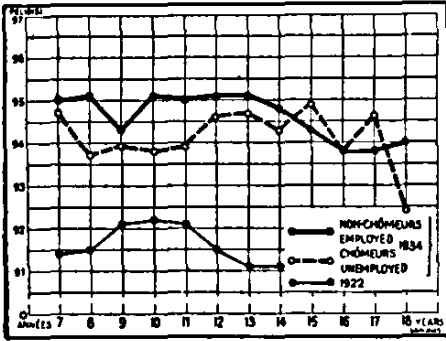


25

DISTRIBUTION OF THE PELIDISI FIGURES IN THE CASE OF PUPILS OF PRIMARY AND SECONDARY SCHOOLS. COMPARISON OF THE FINDINGS OF THE THIRD SERIES OF INVESTIGATIONS (1934) WITH THE FIGURES FOR 1920 AND 1922.

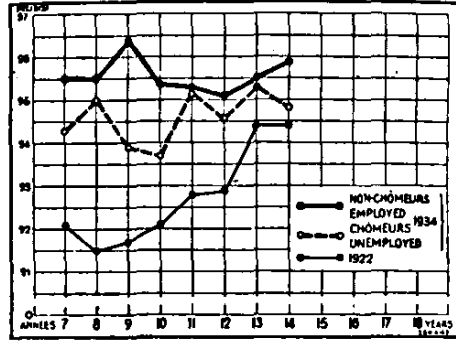
(a) Actual figures.

Boys.



26

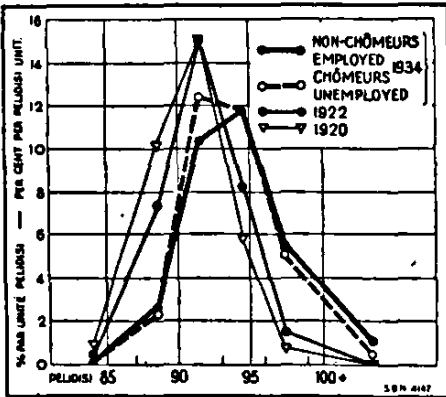
Girls.



27

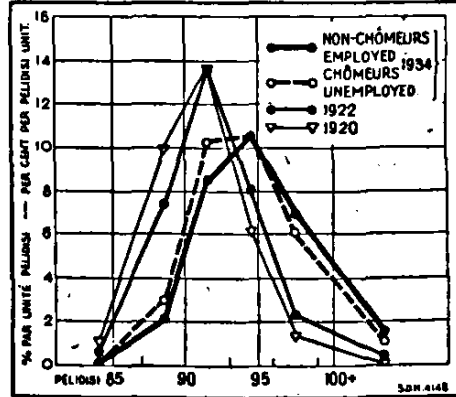
(b) Percentages.

Boys.



28

Girls.



29

[ANNEX 1. (The original form serves as cover for the three others.)]

No.....

I. — FAMILY CARD.

Locality : *Date of enquiries* : I..... II.....

Name : *Address* :

Size of dwelling :kitchen,room,small room,hall,balcony,outhouses.

W.C. in apartment : yes, no.*

Water pipes in apartment : yes, no.*

Situation of the apartment : Cellar, basement, ground-floor, floor, attic, overlooking road, courtyard, alley, garden. Garden, playground adjacent to house : yes, no.*

Occupants : adults, infants, young children, children of school age,adolescents; subtenants (see No.) : yes, no*; number, age

Condition of dwelling : very good, good, passable, bad.*

Number of beds :

Water supply : good, passable, bad.*

Lighting by day : natural lighting : good, passable, bad* ; artificial light : yes, no.*

Lighting by night : nature ; good, passable, bad.*

Heating : what kind ; absence of heating, passable heating, satisfactory heating.*

Ventilation : what kind ; ventilation good, passable, bad, impossible.*

Work at home : yes, no* ; nature of work :

Rent : schillings per week, per month, per quarter.*

Special remarks (including any changes during the period of observation) :

Total income (monthly) :

(a) Earnings schillings ; number of persons

(b) Public or private assistance schillings.

(Signature)
 Investigator (Social Assistant).

* Underline what applies.

[ANNEX 2.]

No. /

II. — INDIVIDUAL CARD "A".

Locality : *Address* : *Date of enquiries* : I. II.*Name* :*Sex* : male, female*; *Civil status* : unmarried, married, widowed, divorced.**Date of birth* *Present occupation**Professional training* (trade learnt)*Education* : elementary school ; primary school ; professional school ; secondary school ;
higher educational establishment.**Breadwinner of a family* : yes, no.**Living in the family or living alone*.**Income* (net income during the month in question) :

- | | | |
|--|--------------|----------|
| (a) Present regular earnings (per month, per week*) | Sch. I. | II. |
| (b) Occasional income (per day, week, month*) . . . | Sch. I. | II. |
| (c) Unemployment dole (per week) | Sch. I. | II. |
| (d) Sickness allowance (per day) | Sch. I. | II. |
| (e) Maintenance allowance, old-age pension (per month) | Sch. I. | II. |
| (f) Pension (monthly) | Sch. I. | II. |
| (g) Maintenance allowance (monthly) | Sch. I. | II. |
| (h) Other regular income in cash (such as assistance from members of the family, proceeds of sub- letting, etc.) (per month) | Sch. I. | II. |
| (i) Income from immovable property | Sch. I. | II. |

Assistance in kind :

- | | |
|--|----------------------------|
| (a) School meals : yes, no.* | (d) Other food ; yes, no.* |
| (b) Meals served to adults : yes, no.* | (e) Coal : yes, no.* |
| (c) Food parcels : yes, no.* | (f) Clothing : yes, no.* |

Regular charges :

- | | |
|--|---|
| (a) Rent : monthly, weekly.* | (d) Repayment of advances : yes, no.* |
| (b) Maintenance allowances : yes, no.* | (e) Current expenditure on education yes, no.* |
| (c) Debts : yes, no. * | |

Pawning : yes, no.*

Number of articles pawned

Total value of articles pawned

Occupation or unemployment during the last few years (number of months) :

| | 1930 | 1931 | 1932 | 1933 |
|-------------------------------------|-------|-------|-------|-------|
| Work | | | | |
| Unemployment with dole | | | | |
| Unemployment without dole | | | | |

Special remarks (including any changes during the period of observation) :

.....

.....

.....

.....

.....

(Signature)

Investigator (Social Assistant).

* Underline what applies.

[ANNEX 3.]

No.....

II. — INDIVIDUAL MEDICAL CARD "B".

Name Date of examination : I II.....

Age I. Years Months.... II. Years ... Months

Height I.cm. (—cm.) II.cm. (—cm.)

Weight I.kg. (—kg.) II.kg. (—kg.)

Height (sitting position) I.cm. II.cm.

Pelidisi I. II.

Blood content of the skin (S). I. i, e, a, o, u. II. i, e, a, o, u.

Turgescence of the tissues (Cr). I. i, e, a, o, u. II. i, e, a, o, u.

Condition of the subcutaneous fat layer (T) I. i, e, a, o, u. II. i, e, a, o, u.

Condition of the muscles I. i, e, a, o, u. II. i, e, a, o, u.

Bone structure : I. Strong, medium, weak, slight rickets, severe rickets, other pathological modifications.
II. Strong, medium, weak, slight rickets, severe rickets, other pathological modifications.

Glands I. II.

Teeth I. Looked after, not looked after, neglected, treated, not treated, decayed : yes, no.
II. Looked after, not looked after, neglected, treated, not treated, decayed : yes, no.

Thyroid gland I. normal, hypertrophied 1, 2, 3, goitre : yes, no.
II. normal, hypertrophied 1, 2, 3, goitre : yes, no.

Lungs I. Heart and blood-vessels
II. Heart and blood-vessels

Abdomen I. Sensory organs
II. Sensory organs

Suffering acute disease I. since..... Diagnosis
II. since..... Diagnosis

Suffering from chronic disease : I. since..... Diagnosis
II. since..... Diagnosis

In the case of women, any menstruation troubles I.
II.

Other remarks I.
II.

Doctor conducting examination :
.....

[ANNEX 4.]

No.

.....CLASS IN ELEMENTARY — PRIMARY — SECONDARY SCHOOL : FOR BOYS — GIRLS.

District : Street :

Date of examination :

| Serial No. | Parent or breadwinner* | | | Number of children | Surname and christian names | Born on | Age | S | Cr | T | M | Height in standing position | | Height in sitting position | | Weight | | Pelidisi | | Observations | |
|------------|------------------------|------------|-------------------|--------------------|-----------------------------|---------|-----|---|----|---|---|-----------------------------|------------------------|----------------------------|------------------------|---------------|------------------------|---------------|------------------------|--------------|--|
| | Employed | Unemployed | Duration (months) | | | | | | | | | Actual figure | Difference from normal | Actual figure | Difference from normal | Actual figure | Difference from normal | Actual figure | Difference from normal | | |
| | | | | | | | | | | | | | | | | | | | | | |
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| | | | | | | | | | | | | | | | | | | | | | |

* (1) workman ; (2) private employee ; (3) public official ; (4) working on his own account ; (5) liberal profession.

522 THE ECONOMIC DEPRESSION AND THE POPULATION OF VIENNA

CURRENT NOTES ON THE WORK OF THE HEALTH ORGANISATION.

DEATH OF PROFESSOR JEAN CANTACUZÈNE AND PROFESSOR LÉON BERNARD.

Since the publication of our last *Current Notes*, the Health Committee has suffered a cruel loss through the death of two of its most distinguished members, Professor Jean CANTACUZÈNE and Professor LÉON BERNARD.

The career of these two outstanding scientists has been described elsewhere and we shall therefore confine ourselves here to a brief account of the part which they played in the work of the Health Organisation.

Professor CANTACUZÈNE first became a member of the Health Committee in 1924, when he was appointed to represent the Joint Commission of the International Red Cross Committee and the League of Red Cross Societies. It was, however, apparent at the very outset that his activities were not to be restricted to that field and that the Health Committee should be able to avail itself of his extensive scientific culture and authoritative opinion—witness the outstanding part which he played in the activities of the Malaria Commission, and more especially in the investigation of anophelism in deltas.

CANTACUZÈNE was first and foremost a biologist, and it was therefore only natural that he should interest himself in the activities of our Commission on Biological Standardisation, to whose work he made important contributions on the unification of anti-dysentery serum. He also took part in research work on immunisation against diphtheria and scarlet-fever and also on the B.C.G., in which he was passionately interested and of which he became, as it were, the pioneer in Roumania. He was, in addition, a member of our Commission for the Teaching of Hygiene.

Professor LÉON BERNARD was one of the Health Committee's pioneers ; even in the distant days of 1921, he was already playing an active part in drawing up the rules and defining the field of activities of the future Health Organisation. It was, however, in regard to tuberculosis that his personal influence on the Health Committee made itself most strongly felt, and it was at his instance that the

enquiries on the subject of this disease were set on foot in 1924. In 1928 he played an active part in the Conference for the Study of Anti-Tubercular Vaccination by the B.C.G. When the Greek Government asked the Health Committee to co-operate in health reorganisation in Greece, it was Léon BERNARD who drew up a scheme for the anti-tuberculosis campaign.

As a professor of public health, it was only to be expected that he should become the moving spirit of the Commission for the Teaching of Hygiene and actively promote international co-operation between schools of hygiene.

As President of the French Supreme Health Council, he was largely instrumental in assuring the success of the collective study tour in France which took place in 1930 under the auspices of the Health Organisation.

Léon BERNARD was a confirmed believer in international co-operation, and he was a shining example of what he preached, both at Geneva and in the numerous international congresses, in which he stood out as the eloquent spokesman of French science.

A tribute was paid to the memory of these great scientists in the Council of the League of Nations, which conveyed to their families and collaborators the expression of its warmest sympathy.

AWARD OF THE DARLING FOUNDATION PRIZE.

The Darling Foundation Prize was instituted to perpetuate the memory of Dr. Samuel T. DARLING, who met his death on August 21st, 1925, in a motor accident while travelling in Syria in the service of the Malaria Commission.

The prize, which is to be given to the author of an unpublished work, or a work published within the last five years, on the pathology, ætiology, or prevention of malaria, was recently awarded for the first time. The recipient was Colonel S. P. JAMES, of the British Ministry of Health. The prize was officially presented to him at a public meeting at which M. PILORRI, Deputy Secretary-General of the League, and the members of the Health Committee were present.

The ceremony was opened by the President of the Health Committee, Dr. MADSEN, who traced Dr. Darling's scientific career in the following terms :

"Samuel Taylor DARLING was a native of New Jersey, where he was born in 1872. He had graduated in 1903 at Baltimore, and had stayed on for another two years studying histology and pathological anatomy.

"The year 1906, when he started work in the Panama Canal Zone, marks the beginning of his connection with the tropics which was to afford such full scope to his enterprising qualities. Some little time before, in 1904, the United States had taken over the Zone, and were resuming the work abandoned by the French. In those days, tropical countries still had the reputation of being 'the white man's grave', and the Isthmus of Panama was among the worst examples of the kind. During the summer of 1905, the work had been practically brought to a standstill by the high death-rate among the workers. It was then that the great figure of GORGAS emerged into prominence. Darling was instructed by him to organise a

The Darling
Medal.



The first
recipient,
Col. S.P. James.

laboratory and to define the part it should play in the solution of the grave health problems attendant upon the cutting of the Canal. From 1906 to 1915, Darling lived in the Zone as chief of the Canal Commission Laboratory, working at the 'Ancon Hospital', at the summit of a high hill overlooking the Pacific. Under his guidance, the Ancon Hospital developed into a research centre for an area which had so far had no institution of that kind. Malaria in all its aspects, from pathological anatomy to epidemiology, from therapeutics to entomology; Panama recurrent fever, bacillary and amœbic dysentery, leishmaniasis—all these came within the purview of his research. New diseases were described, such as histoplasmosis; affections never till then encountered in Central America were diagnosed, such as recurrent fever and leishmaniasis; and in the veterinary field Darling established the ætiology and prophylaxis of an enzootic disease of horses and mules: derrengadera, caused by *Trypanosoma hippicum* Darling.

"In 1913 we find him still working with General Gorgas, and accompanying him on a trip to South Africa to study the causes of high mortality among the miners of the Transvaal.

"When he returned to Panama, the Canal was about to be opened. It is too easily forgotten that some engineering works, some industrial or agricultural schemes, which have developed the tropics, could never have been put through but for the aid of the medical man. The Panama Canal is a case in point, and side by side with the Canal builders, General Gorgas and Darling have, too, their rightful claim to the remembrance of posterity.

"During his stay in the Isthmus, Darling's health had been seriously impaired, but the opening of the Canal marked the end of his mission. Having been appointed in 1915 a member of the International Health Board of the Rockefeller Foundation, he left for the Far East at the head of a medical mission sent to study the causes of the widespread anæmia among the populations of the Malay States, Java, and the Fiji Islands.

"It will soon be a hundred years ago that DUBINI discovered the *Ancylostoma* at Milan ; later, in Switzerland, during the construction of the St. Gothard tunnel, PERRONCITO connected this parasite with the ætiology of certain kinds of anæmia. Only since Darling's visit to the Far East, however, has the problem of uncinariasis been given its due epidemiological and social importance. Darling's research work led immediately to a distinction between infestation and disease as a result of his method of hæmatode counts.

"To be a carrier of *Ancylostoma* is not in itself sufficient to entail ancylostomiasis, for the anæmia characteristic of the disease depends upon the number of parasites. The recognition of this very simple fact made possible a refinement of the diagnosis of tropical anæmia, the identification of true ancylostomiasis, and the assignment of other forms of anæmia to other causes such as malaria, malnutrition, or overstrain.

"On his return from the Far East in 1918, Darling was appointed Professor of Hygiene at the São Paulo Faculty of Medicine. Here he continued his work on ancylostomiasis, and thereby claimed a place among the benefactors of mankind. Instead of the delicate and ineffectual treatment with thymol, he advocated oil of chenopodium, determined its dosage and demonstrated that two administrations of this drug were sufficient to eliminate 95 per cent of the parasites. A very powerful weapon was thus placed in the hands of the medical practitioner, and Darling, quite logically, ranked this above every other preventive measure, advocating mass treatment with unshakable faith in its value. Up till then, it had been a regular rule never to treat without first establishing a microscopic diagnosis, and, in such circumstances, any attempt at mass treatment was bound to involve a costly and intricate organisation. Darling had the courage to propound a rule that must have struck his hearers as something like blasphemy, and to rule out stool examination as superfluous whenever enquiries had shown infestation to be widespread. Such an attitude appeared at first sight unscientific, and aroused much criticism, but it ultimately overbore opposition, and redounded to the advantage of the health of many millions.

"In 1921, still poor in health, Darling left the tropics for the United States, where he was appointed Professor *honoris causa* at the Johns

Hopkins University School of Hygiene and Public Health. In 1922 the Rockefeller Foundation gave him the directorship of its malaria research laboratory at Leesburg in Georgia, a post he was to hold until his death. This enabled him to take up once more the research work he had started 16 years earlier, and to enter upon it again with interest unabated. He is perhaps the first malariologist to begin to study malaria in the United States after acquiring a well-nigh universal knowledge of the disease in every latitude and clime.

"Darling's findings rank nowadays among the established and unchallenged facts of our knowledge. Following CARTER and others, Darling confirmed that the only important vector of malaria in the south is *A. quadrimaculatus*. He succeeded in discrediting the anamnesis method as a means of conducting malaria surveys, and in substituting investigations into the spleen rate of children as affording an indication of the degree to which the population was infected with malaria. Thereafter he adapted this same method to the conditions prevalent in the United States, where splenomegaly is usually but very slight. Even now, if we examine the plan of work he drew up at Leesburg some ten years ago, we shall be struck by its modern quality. As early as 1924 he was studying experimental malaria by means of malariatherapy, the conditions governing the experimental infection of mosquitoes, and the morphology of anopheles eggs."

It rested with the Chairman of the Malaria Commission, Dr. A. LUTRARIO, to outline the scientific achievements of Colonel JAMES.

After referring to the important position occupied by the prizewinner in the Malaria Commission, whose last two general reports bore the imprint of his work, Dr. Lutrario demonstrated how Colonel James, by exploring the experimental field offered by malariatherapy, had increased the sum of knowledge on the subject of the pathogenesis of malaria. His researches have thrown light on such questions as the transmission of the infection from man to the mosquito and from the mosquito to man, the period of incubation of the disease, the influence of the number of mosquito-bites, the seasonal incidence of primary attacks, and the periodicity of relapses.



Colonel S. P. JAMES.

It is not only the knowledge of malaria, however, that has profited by his researches; malariatherapy as a system of treatment has also benefited greatly.

Colonel James was the first to use the mosquito-bite process for infecting the patient, and to fix the technique ; it was he who advocated the use of the different plasmodia, including *P. falciparum*, as agents of infection.

After thanking the Darling Foundation Committee for the honour conferred upon him, Colonel JAMES referred to his friendship with Darling, whom he had known and appreciated 22 years before in Panama, where he himself had been sent by the Government of India to study yellow fever in the Canal Zone. Darling, who was studying the transmission of malaria, had then already established the relative importance of the different species of carriers by original processes which 20 years later were successfully employed by the members of the Malaria Commission in different parts of the world. He possessed in high measure the qualities of perseverance, determination, and endurance which make a pioneer and a scientist. He had a constructive mind, and was not devoid of critical sense, and it was because he had been able to judge at the outset what might be expected in given circumstances from different methods of fighting malaria that his advice had been so useful to the Malaria Commission during the journey in Syria in the course of which he lost his life.

FOUNDATION OF A LÉON BERNARD PRIZE.

In order to perpetuate the memory of Professor Léon BERNARD, various members and ex-members of the Health Committee have proposed to open an international subscription with a view to the creation of a fund for the periodic award of an international prize for social medicine ; the award would be made by the Health Committee and would bear the name of the LÉON BERNARD PRIZE.

This suggestion has been warmly welcomed in all quarters. A subscription list for the collection of the capital required to create this foundation is now open ; subscriptions may be paid in to the " Fondation Léon Bernard " account at Lloyds and National Provincial Foreign Bank Ltd., Geneva.

RIO DE JANEIRO INTERNATIONAL LEPROSY RESEARCH CENTRE.

The Rio de Janeiro International Leprosy Research Centre, which was inaugurated on April 20th, 1934, was founded by the Brazilian Government under the auspices of the League and with the aid of grants from the League, the Brazilian Government, and M. Guilherme GUINLE, a Rio philanthropist. Its governing body is the Health Committee of the League, and there is on the spot a Board of Management consisting of M. GUINLE, Chairman ; the Director of the Federal Public Health Department ; the Director of the Oswaldo Cruz Institute ; Dr. P. BALIÑA, Professor in the University of Buenos Aires ;

DR. E. RABELLO, Professor in the University of Rio de Janeiro ; DR. A. HERRERA RESTREPO, Director of the Colombian National Leprosy Department ; and DR. E. BURNET, Secretary of the League of Nations Leprosy Commission, who was appointed by the Secretary-General of the League. The Director is Professor CARLOS CHAGAS, Director of the Oswaldo Cruz Institute and member of the Health Committee.

The objects of the centre are : (1) leprosy research : clinical, epidemiological, biological, and therapeutical ; (2) specialised instruction available to scientists, medical men, and public health experts from all countries ; (3) the development of world-wide co-operation in the campaign against leprosy.

It meets the same need in South America as is admirably met by similar institutions in the Far East ; hence the seventh Pan-American International Conference (Montevideo, December 1933) passed a resolution inviting the countries of the two Americas to co-operate with the new institution at Rio by sending specialists there and to contribute to it financially ; a specialised theoretical and practical course will be given there to enable them to train medical men and public health experts in leprosy prevention.

The centre is temporarily housed in the Oswaldo Cruz Institute, and its Board of Management is arranging for new laboratories to be fitted up.

The work is divided into four branches : (1) clinics and epidemiology ; (2) bacteriology and immunology ; (3) therapeutical chemistry ; (4) ætiology and pathogenesis.

The centre possesses the following facilities :

Leper colonies : The new leper colony at Curupaity, near Rio, and the up-to-date leper colony of Santa Isabel, near Bello Horizonte, accommodating about 1,500 lepers in all.

Clinic : At Curupaity, a pavilion with about 50 beds, specially constructed for clinical and therapeutical research.

Laboratories : The Oswaldo Cruz Institute and the Curupaity leper colony.

Epidemiology : The Federal Department of Health co-operates with the centre (inspection ; dispensaries).

While retaining its independent organisation, the State of São Paulo Leprosy Department is prepared to welcome workers recommended to it by the centre. The State will place at their disposal its central organisation (prophylaxis service, dispensaries) and its five up-to-date leper colonies, which will have accommodation for at least 4,000 lepers by the end of 1935. An inspectorate of epidemiology and prophylaxis is attached to each of the four most important colonies.

The League of Nations will shortly select two leprologists from Europe or the United States to take part in the researches proceeding at the Rio centre.

LEAGUE OF NATIONS
QUARTERLY BULLETIN
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Authors are alone responsible for views expressed in signed articles.

THE PERILOUS THRESHOLD OF LIFE

Being a Description of
the Demographic Setting of Infant Mortality

by

K. STOUMAN,

Former Chief Statistician of the Health Section, League of Nations Secretariat.

INTRODUCTION.

Infant mortality is the price of adaptation paid by each generation when entering life, just as the settlement of a new country takes its toll from its immigrants. It must therefore be a matter for great comfort and rejoicing, especially at a time when mankind is suffering severe defeats in the economic field, to find that a large part of the world has become infinitely less hostile than formerly to young human life.

Realising the historical importance of the reduction within a single generation of the infant mortality by one-half or two-thirds in so many countries, and confident that further reduction could be secured even where the fall of the rate had been greatest, the Health Committee of the League of Nations decided in its sixth session

of April-May 1926 to undertake an intensive study of the infant mortality in selected areas. This study was carried out during the subsequent years in seven European and four South American countries under the auspices of the respective national health services. The results have now been published by the Health Organisation of the League.¹

The present analysis is not presented as a new study of this material, but is meant to supplement it by an attempt to assign to the problem of infant mortality the place it should occupy in the framework of the great demographic change that has characterised the last generation or two.

History furnishes many examples of an increase or a decrease of the population over large areas resulting from changes in economic and social conditions. Movements of a different origin, such as those due to unusual epidemic prevalence, have also been frequent. As a result of these movements, whatever their cause, the areas of high pressure of population have frequently changed, thereby provoking migrations which have deeply affected the destiny of mankind.

The demographic changes which have occurred during the last half-century are probably more profound than any of the earlier ones because of the greatly increased rapidity of social and economic development resulting from an avalanche of technical inventions. Changes which formerly required centuries are now accomplished in decades, almost from year to year, and the movement of the population is quickly reacting to the new accelerated tempo of events.

At the same time, a new and important factor in the demographic balance, negligible in earlier centuries, has made itself felt—namely, sanitation and preventive medicine. The rapid development of these sciences enables us to foresee the possibility of a directed demography as counterpart of a directed economy. Such achievement is, however, hardly within the realm of immediate possibili-

¹ See, particularly, League of Nations, Health Organisation : Memorandum relating to the Enquiries into the Causes and Prevention of Still-births and Mortality during the First Year of Life ; Geneva, 1930, document C.H.820. Consult also the various national memoranda and Robert DEBRÉ, Pierre JOANNON and M. T. CRÉMIEU-ALCAN : *La Mortalité infantile et la Mortinatalité*. Masson et Cie, Paris, 1933.

ties, largely because of the difficulty in disentangling the various influences of which statistics reveal only the combined result.

It is in infancy that the reduction of mortality has been greatest, because it was at this age that life was most lavishly wasted. It is also against the dangers threatening infant life that medical and sanitary science has been most successful. The further reduction of infant mortality largely depends, apart from social and economic conditions, upon the general application of already well-established principles.

The reduction of infant mortality raises many important demographic questions, among which its relation to the unprecedented fall of the birth rate is of great interest. The coincidence of the two has resulted in a far greater demographic efficiency than at any previous time in history. The new generation is produced and an increase of population maintained with a far smaller effort than before : fewer pregnancies and child-births but more babies surviving. It is a process of rationalisation which results, first of all, in an amelioration of the social position of woman, but also in an important diminution of the dead charges upon the family and the community.

The degree of interdependence between the fall of the birth rate and the fall of the infant mortality rate has been the subject of much discussion. It will be dealt with in the following pages. The effect on infant mortality of urban and rural conditions, so important on account of the increasing urban concentration of the population, constitutes another problem of equal importance. The chief object of the following pages is to present a statistical documentation capable of throwing some light upon these problems.

I. THE GREAT DEMOGRAPHIC CHANGE.

1. FALL OF THE BIRTH RATE.

We know little about fluctuations of the birth rate in earlier centuries, although there is some evidence of their existence ; but their magnitude has undoubtedly never been comparable to those now in process in most countries inhabited by European races. In

so far as Europe is concerned, the decline of the birth rate began in Normandy at the very beginning of the nineteenth century and spread slowly to other parts of France, notably the Garonne valley. It was remarked in Scandinavia shortly after the middle of the century, in the United Kingdom and in Central Europe, after a temporary increase, in the 'eighties, and in Southern Europe in the 'nineties. In the 'eighties, most European countries still had birth rates well over 30 ; only in France, Ireland, Sweden and Switzerland were they below 30, and nowhere below 20 (see Map 1). A similar

1. BIRTH RATE PER 1,000 INHABITANTS IN EUROPEAN COUNTRIES, 1871-1880.

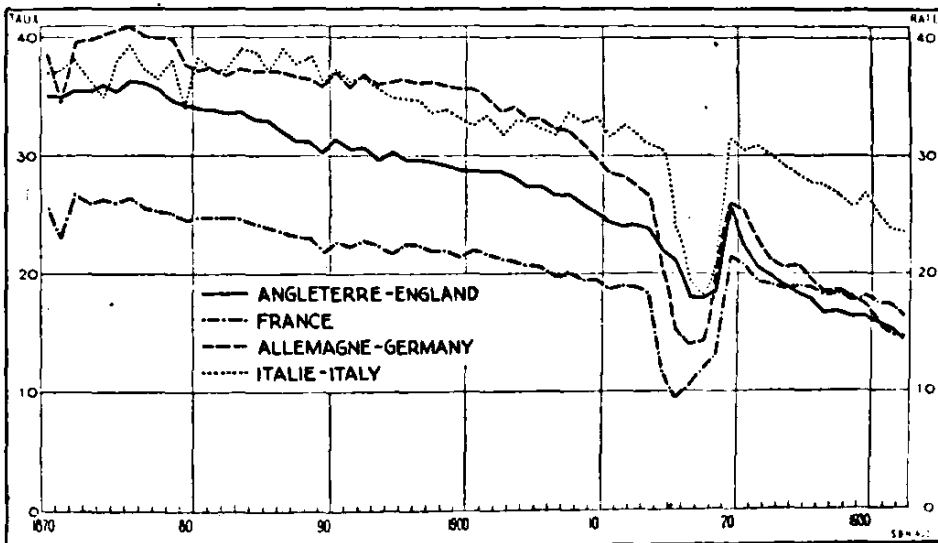


Note : The number of births is available for Russia, but not that of the population.

decrease occurred also in countries outside Europe inhabited by people of European origin. In Massachusetts, the decrease set in in the 'sixties, in Australia in the 'seventies and in New Zealand in the 'eighties. The fall is consequently not due to the increase of population pressure in Europe. There is, on the other hand, no indication of this fall having extended in the nineteenth century to Asiatic or African peoples.

The downward trend of the birth rate in most countries inhabited by people of European origin continued fairly regularly up to the outbreak of the war. From 1915 to 1919, the birth rate dwindled to about half of its pre-war level in the belligerent countries. After a temporary increase lasting only a couple of years, the birth rate resumed its downward trend, which has not yet been interrupted (see Diagram 2). There is no sign, so far, of this fall slowing up. On the contrary, the arrival at marital age of the young people born during the lean war years will soon result in excessively low birth rates in many countries.

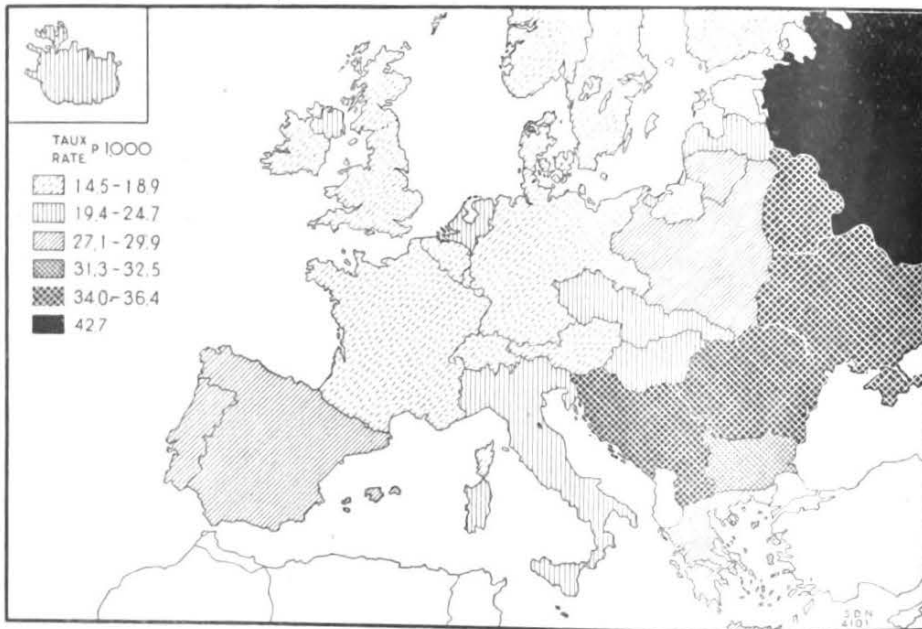
2. BIRTH RATE PER 1,000 INHABITANTS IN ENGLAND AND WALES, FRANCE, GERMANY AND ITALY, 1870-1933.



A map of the present distribution of the birth rate in Europe shows but little resemblance to what it had been half-a-century ago. France and Ireland were then the only countries having a low birth rate, while the rate was highest in Central Europe. The low Irish birth rate, however, was entirely due to the peculiar age distribution of the population resulting from very heavy emigration, the standardised rate being equal to that of England. In 1932, on the contrary, the area of very low birth rate comprised nearly all of

Northern, Central and Western Europe (see Map 3). Six countries had in that year a lower birth rate than France—namely (in inverse order of their rate), Sweden, Germany, Austria, England and Wales, Norway and Switzerland. Birth rates, hitherto unheard-of for a country as a whole, were reported in several countries in 1933, such as 13.7 in Sweden, 14.4 in England and Wales and 14.7 in Germany. Birth rates exceeding 30 are now encountered, as far as Europe is concerned, only in Eastern Europe and in the Balkans. It should be noted that there are very considerable differences in the height of the birth rate from one area to another inside each country.

3. BIRTH RATE PER 1,000 INHABITANTS IN EUROPEAN COUNTRIES IN 1932.



Note : The data for the Ukraine refer to 1929, those for the remainder of the U.S.S.R. to 1928.

Important differences between urban and rural birth rates have existed in most countries at least since their fall began. The lower birth rates on the whole prevailing in the towns, together with the high urban death rates of the nineteenth century, have had a considerable demographic importance by increasing the quota required from the rural population in order to maintain the excep-

tionally rapid industrial development of the last half-century. There is now in most countries, however, evidence of a rapid decrease of natality in rural districts, which may lead to an approximate equality of urban and rural birth rates.

In 1933, urban and rural birth rates in England and Wales were about equal. In Ireland and Scotland, urban rates were higher than those of the rural districts, but it must be added that the age constitution of the town population, owing to immigration from the country of young people, favoured a higher birth rate.

On the European continent, urban birth rates were, during the same year, wherever information is available, lower than rural rates, but the latter were also rapidly decreasing. In Germany, for example, the urban birth rate was 10.9 per 1,000 as against 14.7 for the country as a whole. In the Netherlands, the corresponding figures were 17.4 and 20.8 ; in Switzerland, 11.3 and 16.4 ; and, in Spain, 23.7 and 27.8.

Much has been written about the differences of natality among the various social classes. It is certain that, in most countries, the fall of the birth rate has been heaviest among the fairly well-to-do part of the population. The rate is usually lowest among intellectuals. Investigations made at Stockholm¹ furnish, however, some evidence to the effect that the fall is now equally pronounced among the poorer classes of the population and that the social differences tend to disappear.

These various differences of the height of the birth rate are important in connection with an interpretation of the infant mortality, but it should not be forgotten that we are here in the presence of movements in rapid progress. There is, therefore, as yet, no stability in the relative position of the various rates of incidence which should rather be considered as consecutive phases of a vast radiating movement than as stable characteristics of the various national, urban or social groups. We are naturally bound to find similar features in an analysis of the infant mortality.

An important feature in the fall of the birth rate which has hitherto been rather neglected is the diminution of the age of

¹ See "The Fertility of the Social Classes in Stockholm in the Years 1919 and 1929", by K. A. EDIN in "Problems of Population" (International Union for the Scientific Investigation of Population Problems). G. Allen Unwin Ltd., London, 1932.

mothers. It is obvious that the fall of the birth rate means a diminution of the size of families, which again means that the births late in life are becoming rare. Hence, a considerable diminution of the average age of child-birth.

Still another factor is at work in this sense. It is found that, at the same time as the birth rate is rapidly falling away at ages over 30, it is actually increasing for very young mothers. It is only when the birth rate reaches a very low level that the rate for young mothers declines. This fact is best shown by the Swedish statistics (see Diagram 4 on page 539), which have specified the age of the mother since the early part of the nineteenth century. We find similarly in France that the birth rate of very young mothers is higher in districts of low natality than in areas of large families, such as Brittany. It is significant that, in Prussia, where the fall of the natality has been heaviest, the birth rate of women under 20 remains particularly high (see Diagram 5 on page 539).

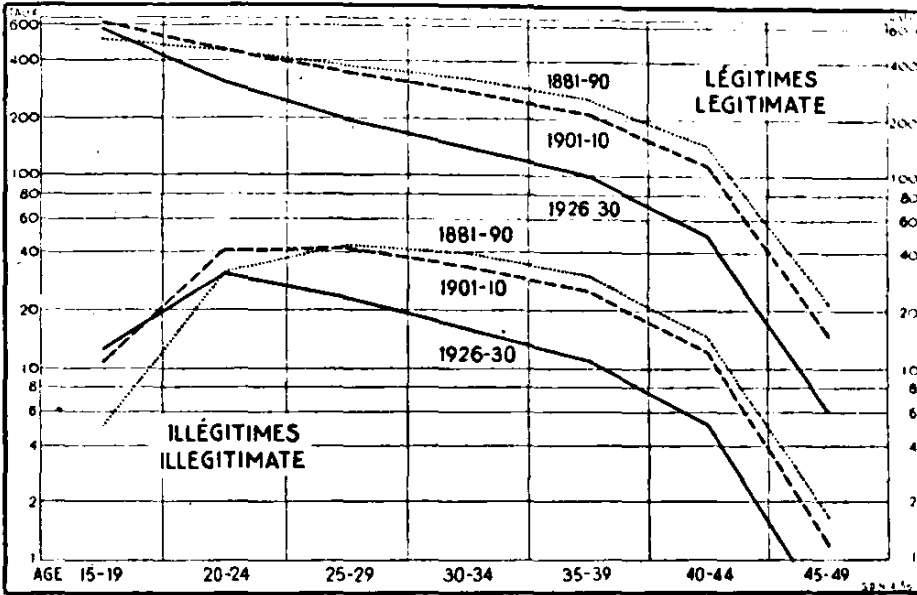
The demographic effect of this change is notably to quicken the succession of the generations in spite of the lengthening of life. It is likely to exercise an influence also upon the infant mortality.

2. FALL OF THE DEATH RATE.

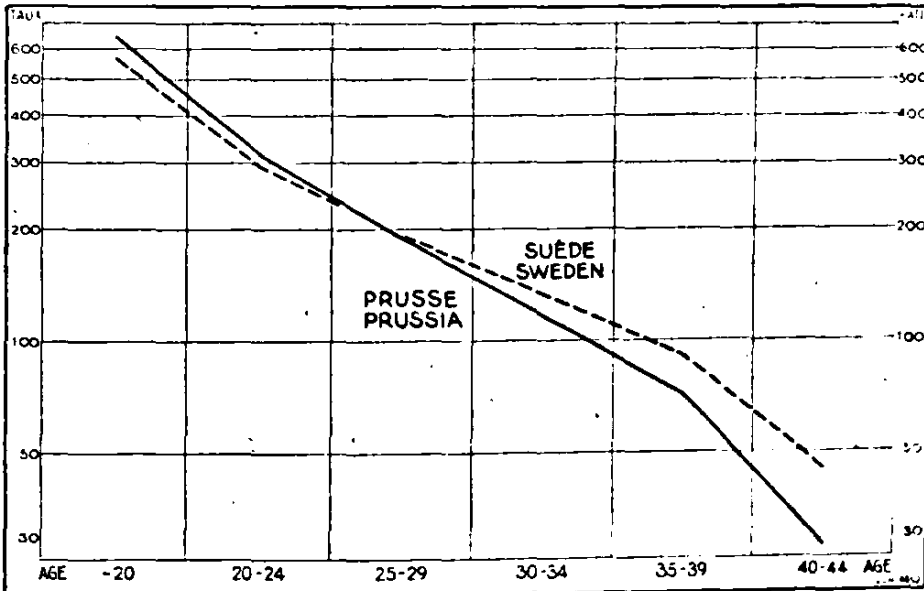
The fall in the death rate preceded and outstripped in most countries the decrease of the birth rate almost until the outbreak of the war. In recent years, it has slackened in the countries where the rate was already low, and it must eventually come to a standstill, inasmuch as life cannot be extended much beyond the proverbial four score of years and owing to the increased average age of the population. The general death rate is now from 8 to 12 per 1,000 in the most healthy countries, but in a large part of Europe it still exceeds 15. There remains, thus, much room for improvement, and notably so in most countries inhabited by a population of Asiatic or African origin, where very high rates still prevail.

The decrease of the death rate has been brought about largely by a saving of infant life and a reduction of epidemic diseases, tuberculosis and intestinal affections. Little progress has been made, on the contrary, in regard to the chronic affections of more

4. LEGITIMATE BIRTHS PER 1,000 MARRIED WOMEN AND ILLEGITIMATE BIRTHS PER 1,000 SINGLE WOMEN AT EACH AGE IN SWEDEN, 1881-1890, 1901-1910 AND 1926-1930 (LOGARITHMIC SCALE).

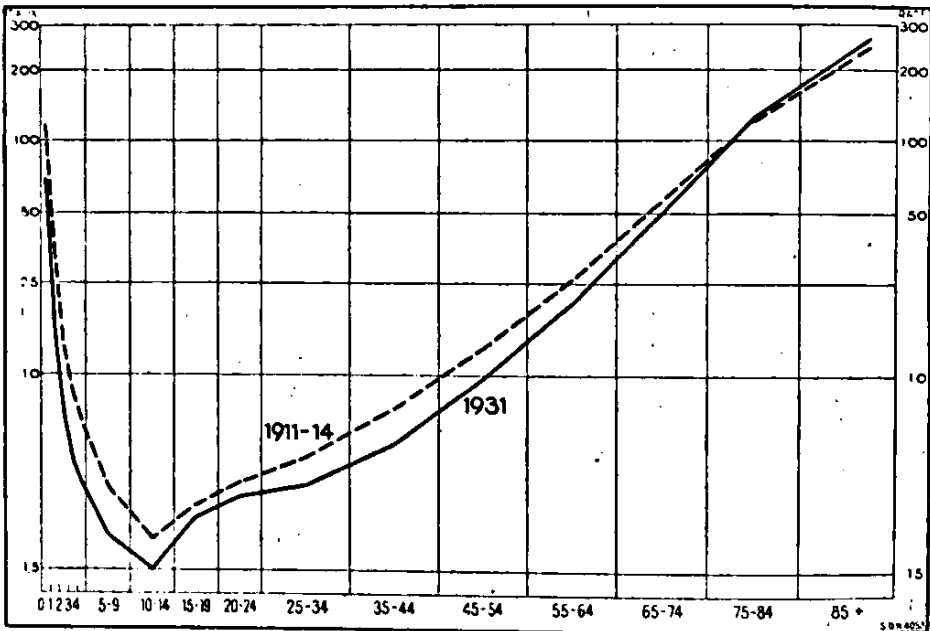


5. LEGITIMATE BIRTHS PER 1,000 MARRIED WOMEN AT EACH AGE IN SWEDEN AND IN PRUSSIA IN 1929 (LOGARITHMIC SCALE).



advanced life (see Diagram 6). Although the mortality in adult life on the whole has diminished less than infant mortality, there can be no doubt that an improved state of health of the parents has contributed to the saving of infants.

6. SPECIFIC DEATH RATES PER 1,000 INHABITANTS AT EACH AGE IN ENGLAND AND WALES, 1911-1914 AND 1931 (LOGARITHMIC SCALE).



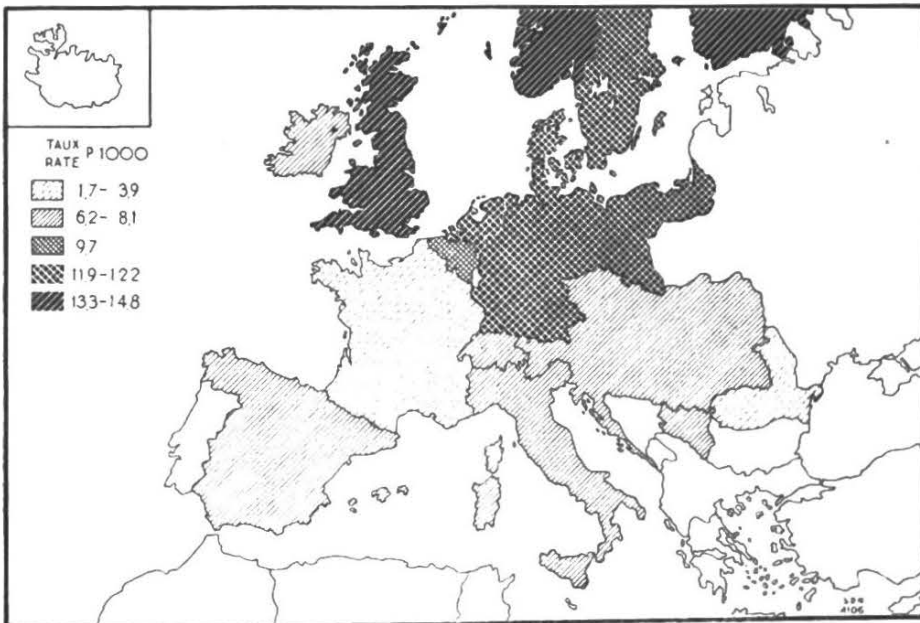
It may be added that the massive reduction of mortality is not confined to infancy, but extends with almost equal relative force to the early part of childhood. Although the percentage reduction of mortality is practically of the same order between the ages of 1 and 5 years as under 1 year, its absolute importance is much smaller there, since the death rates have always decreased rapidly after the first year of life. This fact proves, however, that the reduction of infant mortality is not an isolated phenomenon, but a link of a vast improvement in the conditions of child life, which may be counted as the foremost title to credit of a period which has failed in so many other fields.

3. NATURAL INCREASE OF THE POPULATION.

The great demographic change is thus caused, first of all, by an alteration of the conditions surrounding the entry in life of the new generation : fall of the birth rate, decrease of infant and child mortality.

The natural increase of the population, which is at least one very important element in determining the population pressure, depends on the difference between the birth rate and the death rate. In a period when both are moving rapidly and not at the same rate, a considerable instability is likely to result ; hence the danger of generalising on racial characteristics where, in reality, only problems of changing relativity are involved.

7. NATURAL INCREASE OF THE POPULATION PER 1,000 INHABITANTS IN EUROPEAN COUNTRIES, 1871-1880.

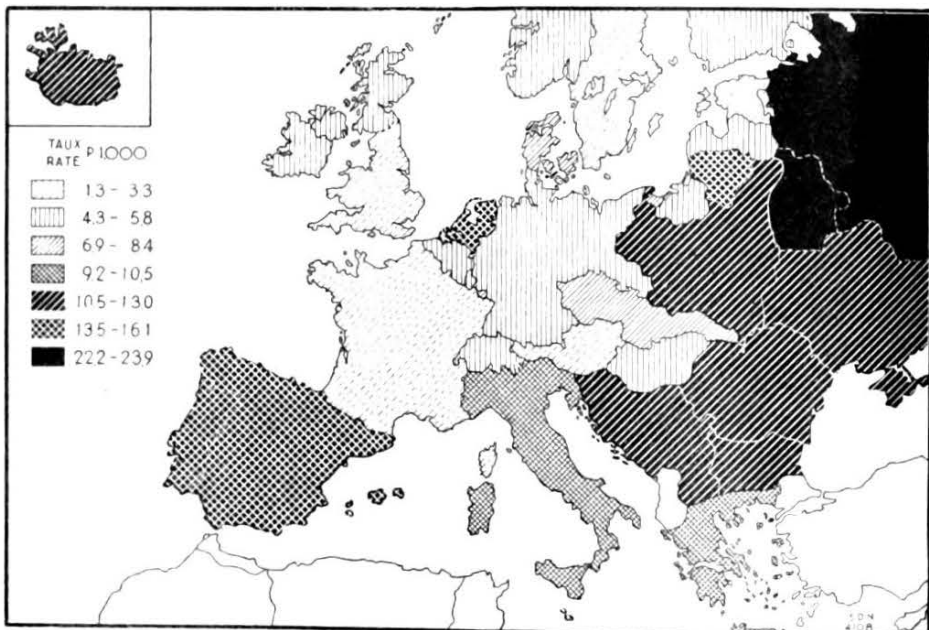


In the 'seventies of the nineteenth century, before the movements of birth and death rates had begun to show any definite tendency, the map of the natural increase of the population in European countries was very different from what it is to-day (see Map 7). The rates of increase were nowhere as high as in the Union of Soviet Socialist Republics of to-day. The highest rates were met with in

Scandinavia, the United Kingdom, Germany and the Netherlands. The increase was only moderate in Southern Europe, on account of the prevailing high death rates, and in Eastern Europe, for the same reason, probably still lower. In France, the population increased only slightly.

At the time of the outbreak of the war, the rate of natural increase had already declined markedly in Sweden, Norway and the British Isles, but was still fairly high. On the other hand, it had further

8. NATURAL INCREASE OF THE POPULATION PER 1,000 INHABITANTS IN EUROPEAN COUNTRIES IN 1932.



Note : The data for the Ukraine refer to 1929, those for the remainder of the U.S.S.R. to 1928.

augmented in the Netherlands, Denmark and Germany and, even more so, in Southern and Eastern Europe, where the decrease of the death rate had outstripped the fall of the birth rate.

The present distribution shows a complete change from the pre-war time. The population now increases only slowly in nearly all of Western, Northern and Central Europe. In this area, only the Netherlands and Iceland have maintained a high rate of increase. The increase is fairly fast, on the other hand, in Southern Europe and very rapid in Eastern Europe (see Map 8).

It is interesting to note that the variation of the rates of natural increase from country to country has become greater. The same observation holds true in regard to the birth rate and the infant mortality. In general, as far as demographic factors are concerned, Europe has thus not been moving towards greater uniformity, but, on the contrary, away from it. This fact, however, must not be interpreted as an accentuation of existing national individuality, an interpretation which is refuted by the complete reversion of the areas of high and low pressure. The correct interpretation is undoubtedly that the elements of organic renewal of the population were in a state of natural equilibrium up to the 'seventies or 'eighties of the nineteenth century. The new factors which broke this equilibrium acted as stones thrown into water, provoking gradually spreading concentric circles around the first points of attack. The subsequent images of the population map are cross-sections of these concentrically travelling circles, and, while, therefore, showing greater diversity, reflect no stable situation. The very dispersion of the demographic measurements now prevailing prove that we are not as yet approaching a new stabilisation.

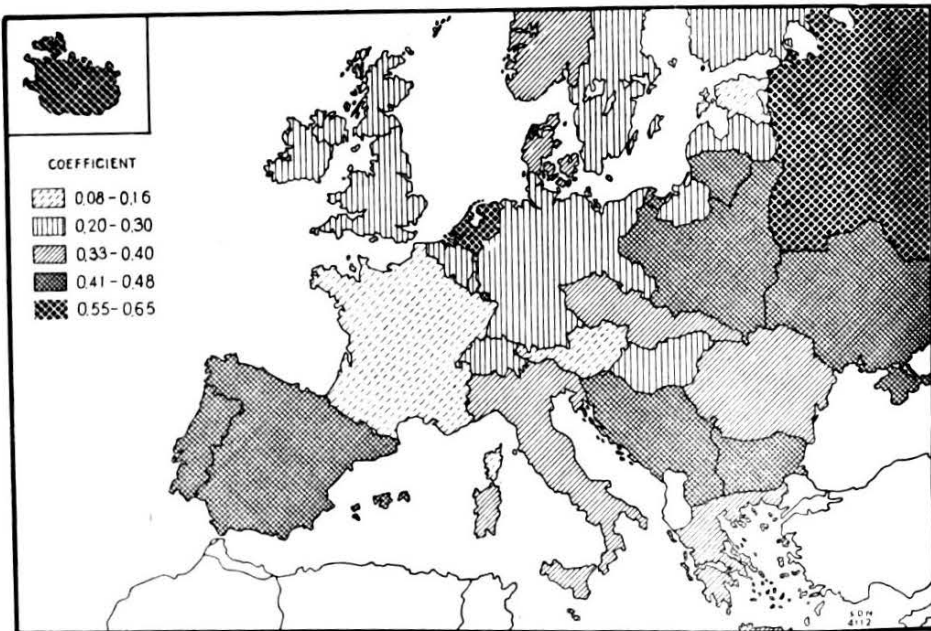
The population increase in countries outside of Europe inhabited by races of European origin still remains fairly high, but is, however, abating almost everywhere, and notably so in the United States and Australia, where a rapid decline of the birth rate is taking place. Chile alone, amongst the countries for which statistics are available, shows an increase, owing to a fall in the very high death rate.

Egypt, with its very high birth rate, in spite of a death rate which is also high, is the only country showing a population increase approaching that of the Union of Soviet Socialist Republics. In Japan, with its fairly constant birth rate, the rate of increase remains rather high—about the same as in the Balkans. A similar increase of population is now met with in Ceylon, where the birth rate has increased and death rate decreased. The population increase is only moderate in India, approaching the present rates of Denmark and Italy.

It is useful, on account of the rapid changes in demographic factors, to establish a measure for the effort spent by a given population in order to increase and spread. A simple measure of this sort can be had by establishing the ratio between the natural

increase of the population and the birth rate. We will call this measure the coefficient of demographic efficiency. When this coefficient is zero, the population is stationary ; when it is negative, the population is decreasing ; when positive, it is increasing. A coefficient of 0.33 means, for example, that one-third of the births is left to increase the population, while the remainder has gone to make up losses by death. It should be remembered that this coefficient is affected, not merely by the rates of fertility and mortality, but also by the age distribution of the population.

9. COEFFICIENT OF DEMOGRAPHIC EFFICIENCY (RATIO OF NATURAL INCREASE TO LIVE BIRTHS) IN EUROPEAN COUNTRIES IN 1932.



Note : The data for the Ukraine refer to 1929, those for the remainder of the U.S.S.R. to 1928.

In Europe (see Map 9), the coefficient of demographic efficiency is lowest in Austria, France and Estonia. The rate is now low also in most of Central Europe and in Sweden. It is highest in the Union of Soviet Socialist Republics, the Netherlands, Iceland and the Faroe Islands (0.65), where from one-half to two-thirds of the births effectively increase the population.

Equally high coefficients are met with only among the white population of South Africa (0.64), in Australia (0.57), and in New

Zealand (0.54). In 1930, the coefficient of Japan was 0.41, that of the United States 0.40, while that of India was only 0.25, or about the same as that of Belgium.

Having briefly sketched the framework of the great demographic change now in progress, we shall proceed to analyse the elements of the infant mortality, the reduction of which is the surest road to demographic efficiency.

II. SAVING OF INFANT LIFE.

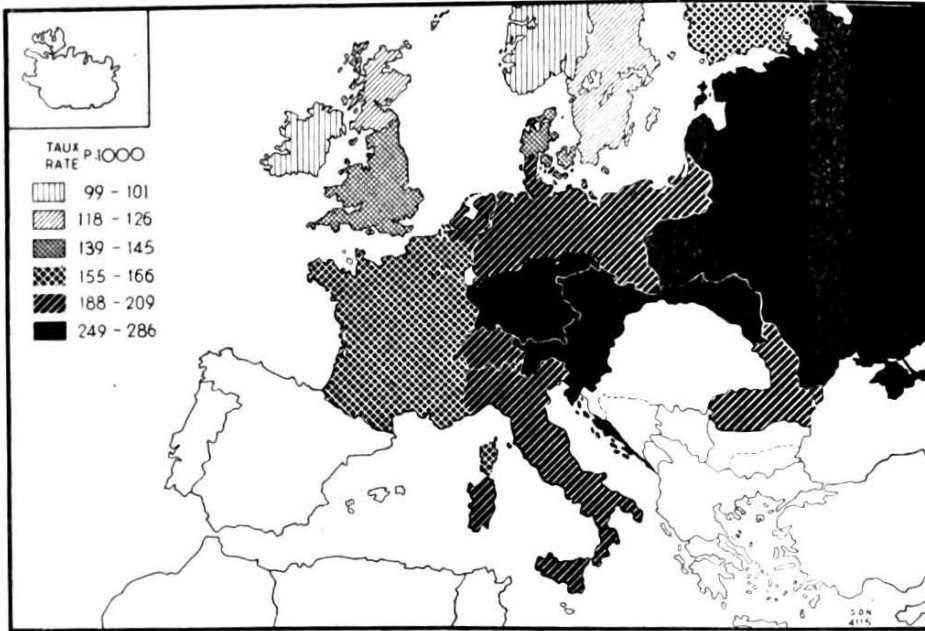
1. INFANT MORTALITY IN THE NINETEENTH CENTURY AND NOW.

In the 'seventies of last century, when the birth rate was at its height, the distribution of infant mortality in Europe was very different from what it is to-day. The rates varied from 100 per 1,000 live births in Ireland and Norway to nearly 300 in Southern Germany ; while, at present, rates as low as 45 or 50 are found in Northern Europe, and no rate, except for a few small localities, exceeds 200 (see Map 10 on the following page).

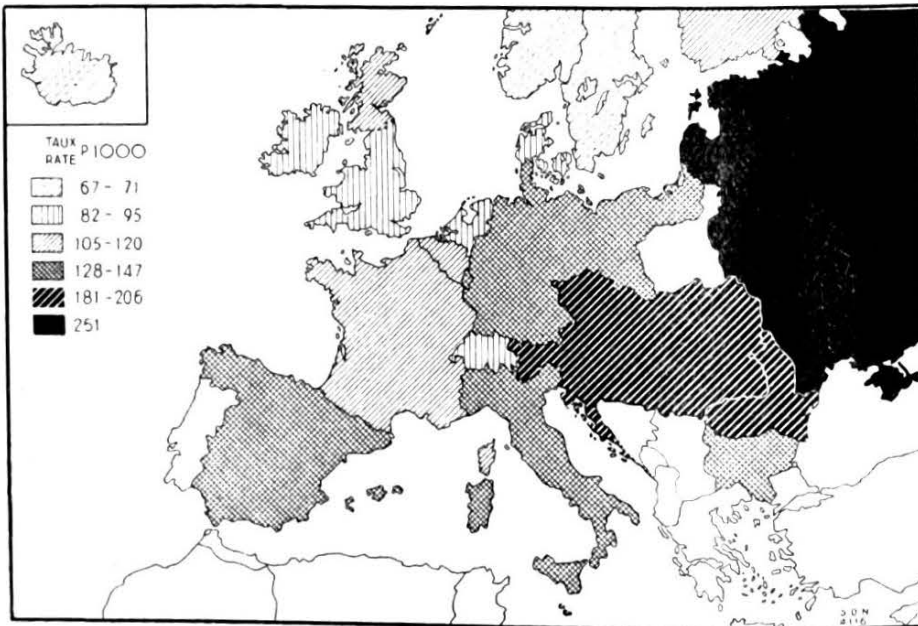
During the period 1876-1880, which is fairly typical for the type of community prevailing after the middle of the nineteenth century, infant mortality rates below 150 were met with in the three Scandinavian countries and in the British Isles, but nowhere else. The infant mortality was highest in Central and Eastern Europe, the difference between the latter two areas being negligible. Southern Germany showed the highest rates (Wurtemberg, 302 ; Bavaria, 298 ; Saxony, 295).

We choose for comparison 1912, a normal year as far as mortality conditions are concerned, because the great war marks the end of the nineteenth century social and economic conditions (see Map 11). Rates well below 100 were, during that year, met with in the three Scandinavian countries, England, the Netherlands and Switzerland. It is interesting to note that these two Central European countries, where formerly very high rates prevailed, had joined the area of very low infant mortality, where they have remained ever since. Central, Southern and Western Europe showed a very marked improvement, the ratio being everywhere below 150. Higher rates were found only in the Dual Monarchy (Austria-Hungary), the

10. INFANT MORTALITY PER 1,000 LIVE BIRTHS IN EUROPEAN COUNTRIES, 1876-1880.



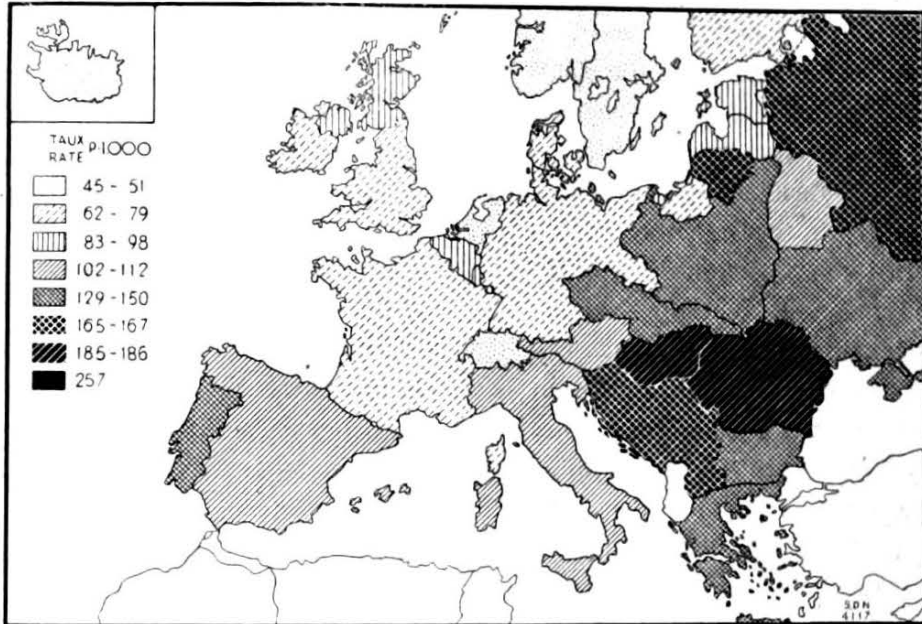
11. INFANT MORTALITY PER 1,000 LIVE BIRTHS IN EUROPEAN COUNTRIES IN 1912.



Note : The data for Russia refer to 1909.

Balkans and probably in Eastern Europe. It would thus seem that the influences since long at work in the northern countries had spread to the entire western half of Europe.

12. INFANT MORTALITY PER 1,000 LIVE BIRTHS IN EUROPEAN COUNTRIES IN 1932.



Note : The data for the Ukraine refer to 1929, those for the remainder of the U.S.S.R. to 1928.

The last ten or fifteen years have witnessed an acceleration of the fall in the infant mortality in nearly all European countries (see Map 12). Rates of 50 per 1,000 live births, or less, are now encountered in Norway, Sweden, Iceland, the Netherlands and Switzerland. The rates are well below 100 in all of Central and Western Europe, except in the countries formerly belonging to the Dual Monarchy, and a marked improvement has taken place also in these, apart from Hungary. The rates for Eastern Europe and the Balkans are mostly between 150 and 200 per 1,000. A rate exceeding 200 is met with only in Malta.

While the fall of the infant mortality has brought about considerable changes in the areas of high and low rates, it is noteworthy that no levelling-up of the differences has taken place; they have, on the contrary, been accentuated. During the quinquennial period 1876-1880, the coefficient of variation of the infant mortality rate

for fifteen European countries was 0.266. No significant change had taken place up to the period 1896-1900, when the corresponding coefficient for the same fifteen countries was 0.253. In 1912, however, the coefficient of variation for the same countries had increased to 0.313, and in 1932 to 0.422. Neither of the two latter years was affected by any unusual epidemic prevalence, but were entirely representative of their time. The explanation of this increasing variation of the infant mortality, in spite of the similarity of the methods of control employed in the different countries, is undoubtedly that the fall of the rate has begun at different periods in the various countries and is progressing with different rapidity. Contrary to the nineteenth century, which was still a relatively stationary period, 1912 and 1932 give us samples of conditions in a continent where rapid changes are in progress. There is no scientific reason to believe that the stabilisation, when it finally approaches, should maintain the extreme national individualism now shown by the infant mortality and other demographic factors.

Changes in areas of high and low infant mortality have also taken place in several cases inside a given country. In Germany, for example, the rates were highest, throughout the nineteenth century, as far as records go back, in Southern Germany and Saxony. In 1903, there had been no noteworthy change of the relative position. The rate was 250 per 1,000 live births in Bavaria, 222 in Wurtemberg, 207 in Baden, and 247 in Saxony. The rates were relatively low—from 139 to 173—in a belt stretching from Schleswig-Holstein in the north to Hesse and the Palatinate in the south. The rates were high also in Eastern Germany—from 207 to 236 in Pomerania, Brandenburg, the province of Saxony, Silesia, Posnanian, East and West Prussia.

In 1930, the rates had everywhere decreased enormously. Bavaria and Eastern Germany had still the highest rates with from 86 to 122 deaths below 1 year per 1,000 live births. The area of very low infant mortality in Hesse remains (55 to 59 per 1,000), but these low rates are immediately followed by those of Baden, Wurtemberg and Saxony (70 to 72), which were formerly high.

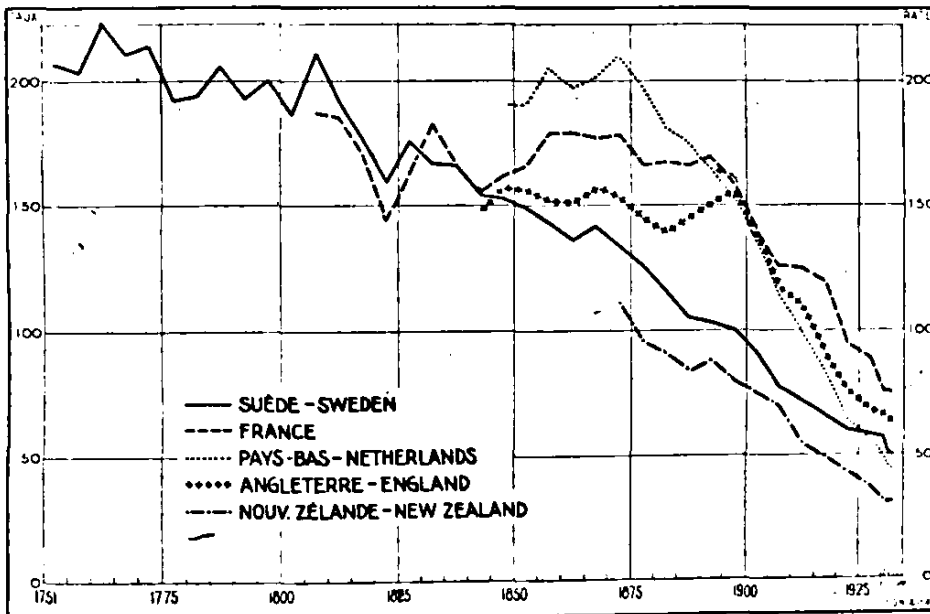
In Italy, rates below 100 are now prevailing in all of Central Italy, where the infant mortality was particularly high in the nineteenth century. In Tuscany, the rate was only 69 in 1931 (in the province of Pisa even 58), or but a trifle higher than in

England. In the 'seventies of last century, the Tuscan rates were, on the contrary, well above 200, and about equal to those prevailing in Sicily, where the rate was still 141 in 1931.

Other features of the internal geographical distribution of infant mortality remain constant, on the other hand, such as the excess of infant mortality in Northern England as compared with the South or the Midlands.

The fall of the infant mortality has, on the whole, been far greater in towns than in rural districts, but the important problem of urban and rural mortality will be dealt with in a special chapter.

13. INFANT MORTALITY PER 1,000 LIVE BIRTHS IN CERTAIN EUROPEAN COUNTRIES AND IN NEW ZEALAND, 1751-1933.



Note : The rates are shown for quinquennial periods up to 1930.

Although the greater part of the fall of the infant mortality has occurred in the twentieth century, its beginning dates, in certain countries, much further back (see Diagram 13). This is the case notably in Sweden, where the rates were well above 200 from 1751 to 1775, while they were mostly below that figure during the subsequent years. After 1810, a lasting improvement took place, the rates for quinquennial periods being 211 in 1806-1810, 192 in 1811-1815, 176 in 1816-1820, and 159 in 1821-1825. The latter quinquennium was exceptionally favourable also in France, where the

rate was 144, as against 171 during the preceding and 163 during the following five years.

The infant mortality of Sweden rose again to 176 during the five years 1826-1830 ; but, after that time, there has been a fairly steady decrease, which has never suffered any serious setback. In France, a similar increase occurred after the low rate for 1821-1825.

In Norway, a rate as low as 118 was met with as early as 1841-1845. Ten years later, the rate was 105, since when the improvement was very slow up to the beginning of the twentieth century. The same was the case also in Denmark, where the rates remained around 135 or 140 from the beginning of the records in 1836 up to the end of the century.

Only a few other countries have statistics of infant mortality dating back farther than to the middle of the nineteenth century, but none of those show signs of an earlier decrease. A marked increase took place, on the contrary, in Bavaria from the 'forties to the 'sixties, an increase of which we find trace also in France, Belgium, the Netherlands, Saxony and Austria.

On the whole, the 'sixties and 'seventies were not favourable as far as infant mortality is concerned ; but, after that period, a marked decrease began in certain countries. This was the case notably in Finland, the Netherlands, Southern Germany, Switzerland and Italy, where the rates continued to fall steadily up to and after the end of the century. Little improvement took place until the beginning of the twentieth century in the British Isles, France, Belgium and Northern Germany. It is evident that we are thus confronted, in the nineteenth century, with regional movements and not with influences extending to all of Europe.

Immediately after the beginning of the twentieth century, a steady reduction of infant mortality extended to the British Isles, Norway, Denmark, France and Belgium. Northern Germany follows suit in the second quinquennium, and the improvement then becomes general in nearly all of Europe, apart from the south-eastern countries.

The decrease of infant mortality has augmented in vigour since the war, and there is now hardly any country which cannot show important achievements in this field. Only a very few countries still seem to be marking time, such as Lithuania, Hungary, Roumania and Bulgaria.

Figures for the Union of Soviet Socialist Republics are not available for recent years, but the rates for 1928 (167 in European Russia proper and 137 in the Ukraine) were much below the pre-war level for Russia.

It is gratifying to note that there is no sign of any slackening in the decrease of the European infant mortality. The fall continues even in countries where the rates are lowest. A comparison of the three years 1930-1932 with the three preceding years shows, in spite of the less favourable economic conditions, a decrease of the infant mortality in every one of the European countries except Greece and Yugoslavia, where an apparent increase may be wholly or partly due to an amelioration of the registration. The rate of the Irish Free State has been stationary during these years, but a new improvement is recorded in 1933. The decrease of the infant mortality rate from 1927-1929 to 1930-1932 has been of 10 to 15 points in nearly all of Central Europe, France, Italy and Spain, and of 4 to 6 points in the United Kingdom and Scandinavia.

The evolution of the infant mortality rate in North America, Australia and South Africa has been much the same as in Europe. Rates for the United States birth registration area are available from 1915, since when there has been a steady improvement. The rate for the three years 1915-1917 averaged 99, that for 1929-1931 65 per 1,000, which is roughly a reduction of one-third in fourteen years. A marked improvement has taken place also in Canada, where the rate was 82 in 1930-1932 as against 102 in 1921-1923. The fall of the North American rates has not been arrested by the crisis, the 1932 rates being particularly low. Favourable infant mortality rates are recorded also among the white population of South Africa, where the rate was 66 in 1930-1932, as against 91 in 1909-1913.

The lowest infant mortality rates in the world are, however, those reported in Australia and in New Zealand. The fall of the infant mortality in these countries began in the 'eighties of last century, when the rates were comparable to those of Norway, and became greatly accentuated in the twentieth century. In 1932, the rate was 41 in Australia and only 31 in New Zealand. It is noteworthy that this fall does not seem to have come to an end, but has, on the contrary, been accelerated in 1931 and 1932. A rate of only 24 infant deaths per 1,000 live births was recorded in 1932 in the town of Dunedin in New Zealand. Rates from 23 to 25 obtained

in the provincial districts of Hawke's Bay in the north and Otago and the Southland in the south of New Zealand, showing the extremely low level to which infant mortality can be reduced.

The infant mortality of Japan, which has always been low in comparison with other Asiatic countries, has decreased only during the last ten years. The rate averaged 133 per 1,000 for the years 1929-1931, as against 139, 154 and 167 during the three preceding triennial periods.

A noteworthy decrease of the infant mortality has taken place since the war also in other Asiatic countries. The rate for India, which averaged 206 in 1911-1913, was 177 in 1928-1930 ; that of Ceylon decreased from 200 in 1910-1913 to 165 in 1930-1932.

2. INFANT MORTALITY AND THE BIRTH RATE.

The coincidence of the striking decrease of the infant mortality with the equally spectacular decrease of the birth rate has induced certain writers to assume that the former may be chiefly due to the latter. The problem is important and demands to be elucidated, because this theory raises the question of the utility of the immense effort of the last thirty years aiming at the improvement of health conditions throughout the world.

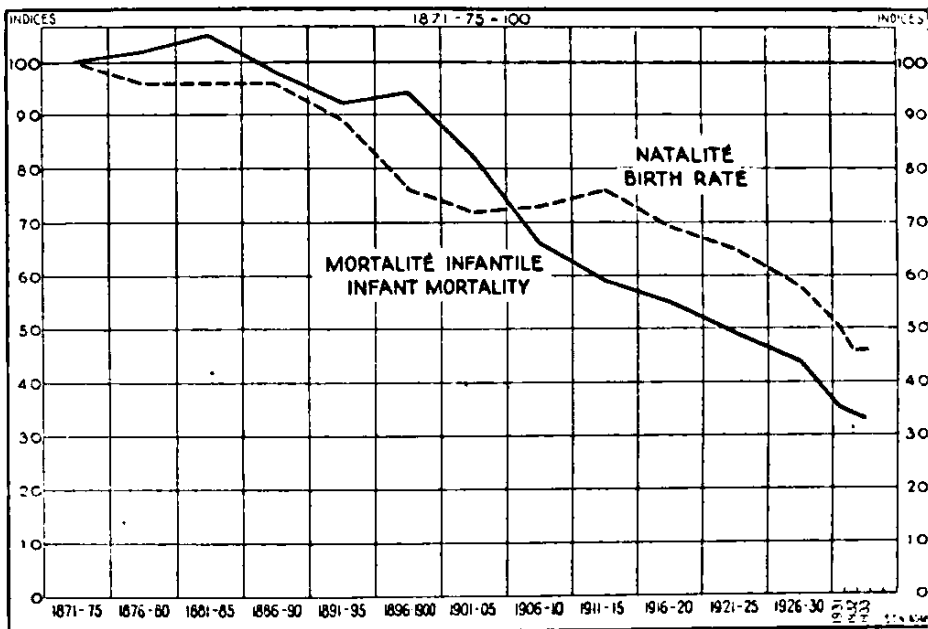
It is not unlikely that the social development of this period may have had an important influence both upon the birth rate and the infant mortality, but it is somewhat rash therefrom to conclude that there is a causal relationship between these two demographic factors overshadowing all other elements. Although it is likely that an only baby of a family may frequently be particularly well looked after, it is hard to understand why improved housing and water supply, proper care and feeding, attention of visiting nurses, etc., should not have the same effect in a large family as in a small one.

The demographer knows that every one of the general rates that he computes is the result of a great many factors—social, economic, climatic, sanitary, hereditary, etc. He is wary, therefore, in attributing their movements to a single one of these causes before having eliminated, as far as possible, the influence of the others. It is rather curious, and not altogether to the credit of scientific thought, that it should minimise the effect of human will and effort just in the twentieth century, when the rapid movements of all

indices vividly demonstrate the influence of the activity of man, while it held the contrary view in the nineteenth century, when conditions were almost stationary and gave little evidence of his intervention.

As far as the alleged dependency of the decrease of the infant mortality upon the decrease of the birth rate is concerned, the fact that the birth rate fell steadily for long years in several countries without producing any change in the infant mortality should induce us to caution.

14. INDEX OF LIVE-BIRTH RATE AND OF INFANT MORTALITY RATE (1871-1875 = 100) IN AUSTRALIA, 1871-1933.



Take England and Wales, for example. The birth rate fell gradually from 35.5 in 1871-1875 to 29.3 in 1896-1900, while the infant mortality, during the same period, rose slightly from 153 to 156 per 1,000 live births. In France, the birth rate fell from 27.4 in 1841-1850 to 22.2 in 1891-1900, while the infant mortality, at the same time, increased from 159 to 164. Examples exist, on the other hand, of very considerable decreases of the infant mortality in periods when the birth rate was constant. In New Zealand, the infant mortality decreased from 89 in 1892 to 61 in 1909, while the birth rate remained constant at about 27. In Australia, the birth rate was slightly higher in 1917 than in 1903, but the infant mortality fell at the same time from 111 to 56 (see Diagram 14).

It may be argued that these are not the spectacular decreases of the birth rate to which we have become accustomed in recent years. Let us then pose the problem differently.

If the fall of the birth rate is the principal cause of the fall of the infant mortality, then there should obviously be everywhere, apart from climatic and such-like influences, a fairly close relation between the two. We find, on the contrary, that the two European countries, apart from Eastern and Southern Europe, having the highest birth rate in 1932 — the Netherlands with 22.0 and Iceland with 24.3 — have the lowest infant mortality rate, 46 and 45 per 1,000, respectively. The Faroe Islands have similarly an infant mortality of 46, with a birth rate of 24.7. Austria, on the other hand, with a birth rate of only 15.2, has an infant mortality rate of 106, exceeded only by those of the Eastern and Southern European countries.

A more general measure for the relationship between the birth rate and the infant mortality rate can be had by establishing the coefficient of correlation between them. It may be useful to explain for readers who are not statisticians that a coefficient of 1.0 denotes a perfect direct correlation between the two series of figures examined, a coefficient of -1.0 a perfect inverse correlation. The values in between these extremes show the degree of relationship. No degree of correlation, however perfect it may be, proves that a causal relationship exists, as the coinciding movements may be due to the presence of a third factor influencing both series of figures. Absence of a significant correlation, on the contrary, proves the absence of a causal relationship. A coefficient of correlation is usually deemed significant only when it is at least five or six times greater than its probable error.

The coefficient of correlation between the birth rate and the infant mortality in fifteen European countries for which reliable statistics are available and which have not been subject to territorial changes capable of seriously modifying the rates was, in 1890, 0.477 ± 0.135 . The coefficient of correlation was thus only 3.53 times the probable error.

The corresponding coefficient of correlation for the same countries was, in 1910, 0.561 ± 0.119 , or 4.71 times the probable error. In 1931, it was 0.460 ± 0.137 , or 3.36 times the probable error.

Although there is evidently a certain degree of coincidence between low birth rates and low infant mortality rates, we are nevertheless

in a position to affirm that the height of the birth rate never was, and is particularly not now, the principal factor determining the level of infant mortality in European countries.

Still more conclusive results are obtained when establishing the coefficient of correlation between the percentage decrease of the birth rate and that of the infant mortality rate in the same fifteen countries from 1912 to 1932. This coefficient is found to be 0.274 ± 0.161 , or only 1.70 times the probable error.

The latter result enables us to state that the varying degree of success met with by the different countries in the reduction of their infant mortality is not due to the different intensity of the fall of the birth rate. It is clearly impossible to maintain, after having established these facts, that the fall of the infant mortality rate should be chiefly due to the fall of the birth rate.

This general conclusion is not invalidated by the fact that a significant correlation between the infant mortality and the birth rate may be found inside the frontiers of a given country. Here, the influence of sanitary and child welfare work is practically eliminated, because the work may be assumed to have been carried on, apart from certain particularly progressive towns, with almost the same intensity and according to similar principles throughout the country. The differences must therefore largely be due to social and economic conditions the influence of which upon both rates cannot be denied. We find thus, for the principal German States and Prussian provinces in 1930, a correlation between the birth rate and the infant mortality rate of 0.680 ± 0.081 , or 8.40 times the probable error. This coefficient is significant, but does not in any way prove that the infant mortality rate is low *because* the birth rate is also low in the same localities.

A very different result is obtained when the percentage decrease of the birth rate and that of the infant mortality rate in German States and provinces is considered. A correlation coefficient of 0.114 ± 0.157 is found for the decrease from 1903 to 1929, which means that there is absolutely no evidence of any relationship between the fall of the infant mortality and that of the birth rate. In short, the correlation found for a given year disappears altogether when long-time changes are considered permitting the effect of sanitary and other progress which affects the infant mortality but not the birth rate to intervene.

There is no reason to suspect any inaccuracy in the figures upon which these calculations are based, as they show a remarkable degree of similarity in adjacent provinces of similar character. The decrease of the birth rate from 1903 to 1929 varied only from 41 to 44 per cent in the whole area comprising Pomerania, Brandenburg, the province of Saxony, Schleswig-Holstein and Hanover ; while it was only 35 per cent in East Prussia, but from 51 to 53 per cent in the industrial areas of Rhineland, Westphalia and the ancient Kingdom of Saxony. The infant mortality decreased between 62 and 67 per cent in Baden, Wurtemberg and Saxony, rates which were followed closely by those for Hesse, Hesse-Nassau, the Palatinate and Bavaria ; while the Rhineland, Hanover, the province of Saxony and Silesia gave percentages of decrease of 47 or 48.

It seems obvious, therefore, that the attribution of the fall in the infant mortality chiefly to the decreasing birth rate is untenable. The causes of the reduction of the infant mortality must decidedly be looked for elsewhere, and can be elucidated only by an analysis of the various factors influencing mortality during this early part of life.

3. INFANT MORTALITY AND SIZE OF THE FAMILY.

The number of children per family depends naturally to some extent upon the height of the birth rate ; but there is no reason to assume that a given birth rate should always correspond to a given distribution of families according to number of children. Two areas may have the same birth rate but be composed of quite different social and racial elements, which are reflected in the composition of the families. One area may have a wide dispersion around the mean, another a small dispersion, and the mean may nevertheless be the same.

It should further be remembered that the size of families is related, not merely to the birth rate at the time of the census, but depends also upon the birth rate during each of the previous fifteen years or more. In order to reach an eighth child in a family, for example, we have to deal with seven preceding children born in the course of half-a-score of years or more, during which period the birth rate may have fallen more rapidly in one area than in the other.

Very good examples of wide variations of the distribution according to families in spite of similarity of the birth rates are furnished by the French statistics.

The French census of 1926 classifies the families according to number of surviving children for each department. Statistics including the children who died before the taking of the census would have given a somewhat different result ; but, in so far as a comparison between areas with approximately the same infant and child mortality is concerned, these differences would not sensibly modify the result.

Brittany, comprising the departments of Finistère, Côtes-du-Nord and Morbihan, had, in 1926, a birth rate of 22.7. The three northern departments taken together—Pas-de-Calais, Nord and Somme—had also a birth rate of 22.7. In Brittany, there were 404,531 families with children, of which 14,727, or 36.4 per 1,000, had eight children or more. In the three northern departments, 20,839 families, or 23.9 per 1,000, out of a total of 873,649 families with children, had eight children or more. The excess of proportion of families having eight surviving children or more in Brittany over the corresponding proportion in the northern departments was thus 52 per cent. The infant mortality in the North was slightly higher than in Brittany—101 as against 87—but addition of the dead children would not change the relative result very materially, the more so as the mortality in childhood was higher in Brittany than in the northern departments.

It should further be remembered that, in each family of eight children, there has been a first, second, third, fourth, fifth, sixth, and seventh child. When considering children born, according to their order in the family, instead of families according to the number of children, the differences are thereby increased. We thus find 6.1 per 1,000 children born as eighth child or more in Brittany, as against 3.7 per 1,000 in the northern departments. The excess of Brittany is accordingly increased to 65 per cent.

This comparison does not even represent extreme differences. The department of Lozère in the Auvergne had, for example, 52 families with eight surviving children or more per 1,000 families with children, as compared with only 14 per 1,000 in the department of Seine-et-Marne in the north-east, although the birth rates of the two departments were almost equal (18.1 in Lozère and 17.9 in

Seine-et-Marne). Thus, even a threefold difference bearing no relation whatever to the birth rate can exist inside a single country.

It is more than doubtful, therefore, whether the distribution of families according to size in the United States of America would apply to English counties having similar birth rates. Since this has been assumed by Dr. Peter McKINLAY and the assumption taken as a basis for his investigation of infant mortality in relation to order of birth of infant in four English counties, 1927-1928,¹ the value of his rates is open to criticism. This, of course, does not necessarily invalidate certain general conclusions warranted already by his crude data, particularly as far as certain medical characteristics of mortality amongst the first-born or for the last births in large families are concerned.

The French example is quite relevant in this connection, because a rapidly growing American population nourished by immigration is likely to be related, in regards to size of family, to the English counties in question in much the same way as the northern departments of France are to Brittany. There is therefore every reason to believe that the enormous increase of the infant death rate with position in the family found by the English investigators is very much exaggerated.

The infant mortality rates according to position of the child in the family obtained by the English investigation were as follows: first child, 94 per 1,000 first children born alive; second child, 57; third child, 78; fourth and fifth child, 114; sixth and seventh child, 155; eighth child and over, 299. The average is 101 per 1,000 live births.

The eighth child should thus have a more than five times greater risk of dying than the second child, which seems incredible. As a matter of fact, no other investigation confirms this extraordinary result. Other investigations do show a certain handicapping of the first-born and an increase of mortality from the third or fourth child and on, but of a much more moderate nature.

¹ Ministry of Health, Reports on Public Health and Medical Subjects, No. 55, "Infant Mortality". Report by Dame Janet CAMPBELL and P. L. McKINLAY, London, 1929.

First of all, illegitimate births should be eliminated from such comparison, because their high mortality will affect almost entirely the first-born children. The next condition is to establish the exact distribution of the births according to their order in the family. Further, the influence of the age of the mother and of social conditions should, as far as possible, be eliminated. Finally, it should be stated whether the investigation deals with finished families or births occurring in a given year.

These conditions are fulfilled by an investigation by WOODBURY of live births in selected normal years in eight towns of the United States of America.¹ The results obtained by this investigation are shown in the table below :

Infant Mortality in Eight Towns of the United States according to Order of Birth (WOODBURY'S Investigation of 22,967 Live Births).

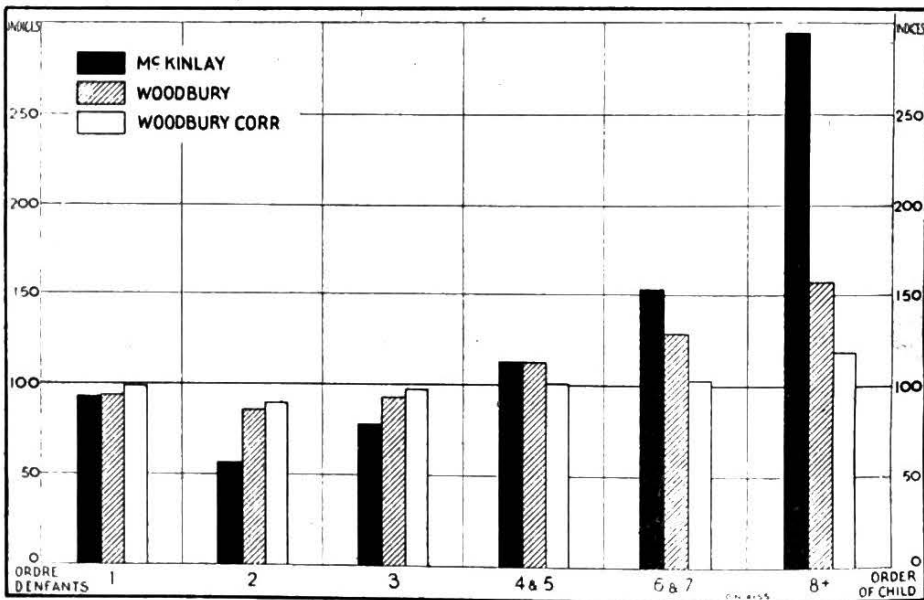
| Order of birth | Infant mortality | Index of infant mortality | Ratio of actual to expected deaths after elimination of influence of | |
|--------------------|------------------|---------------------------|--|---|
| | | | Age of mother | Age of mother, earnings of father and multiple births |
| First | 105 | 94 | 93 | 99 |
| Second | 96 | 86 | 88 | 90 |
| Third | 105 | 94 | 98 | 98 |
| Fourth | 109 | 98 | 101 | 100 |
| Fifth | 119 | 107 | 109 | 104 |
| Sixth | 123 | 110 | 110 | 96 |
| Seventh | 137 | 123 | 118 | 113 |
| Eighth | 136 | 122 | 115 | 105 |
| Ninth | 147 | 132 | 120 | 112 |
| Tenth and later .. | 182 | 163 | 142 | 131 |
| Total | 111 | 100 | 100 | 100 |

¹ Robert M. WOODBURY : " Infant Mortality and its Causes". The Williams & Wilkins Company, Baltimore, 1926.

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The conclusion, after eliminating foreign influences, is that the infant mortality of the first-born is some 10 per cent higher than that of the second-born children. The infant mortality increases after the second child with the size of the family, but the increase is not very great in middle-sized families. It is only in the very large families that the increase reaches 30 or 40 per cent, once the influence of social conditions, and notably of the increasing age of the mother, is eliminated.

15. INDEX OF INFANT MORTALITY RATE BY ORDER OF CHILD IN FAMILY (AVERAGE FOR EACH SERIES = 100) ACCORDING TO THE INVESTIGATIONS OF WOODBURY (SELECTED TOWNS OF THE U.S.A.) AND MCKINLAY (SELECTED ENGLISH COUNTIES).



Note : The white columns indicate WOODBURY's results after elimination of the influence of age of mother, earnings of father and multiple births.

The results of the investigations of WOODBURY and of MCKINLAY are compared below (see also Diagram 15). The rates have been reduced to index figures in order to facilitate the comparison, and WOODBURY's results have been recalculated in order to give averages for the fourth and fifth, sixth and seventh, eighth and later child.

*Indices of Infant Mortality according to Order of Child
in the Family resulting from the Investigations
of WOODBURY and MCKINLAY.*

| Order of birth | Woodbury | Woodbury corrected ¹ | McKinlay |
|-------------------------|----------|---------------------------------|----------|
| First | 94 | 99 | 93 |
| Second | 86 | 90 | 56 |
| Third | 94 | 98 | 78 |
| Fourth and fifth | 113 | 101 | 113 |
| Sixth and seventh | 129 | 103 | 154 |
| Eighth and later | 158 | 118 | 296 |
| Total | 100 | 100 | 100 |

Such tables, however, give only a cross-section at a given moment of families in various states of development from the beginning to the end of reproductive life. They tell us nothing about the mortality of the first- and second-born in a family which subsequently becomes large in comparison with those in families who stop there. It is more than probable that the encouragement of very large families is as uneconomic as it has proved ineffective in promoting an increase of the population ; but these fragile eighth and later babies are certainly too rare to exercise a decisive effect upon the general incidence of infant mortality. The decrease of the infant mortality is due to quite different causes.

Apart from causes of death relating to the pregnancy and the delivery which, in the case of *primiparæ*, undoubtedly become more difficult with the increasing age of the mother, a general observation regarding the excess of infant mortality in large families may be of interest. One is too easily hypnotised by the date and year on the calendar repeated everywhere on books, newspapers, documents, etc. It may be justifiable to write 1934 in the League of Nations' Secretariat, but that does not prevent many parts of Europe from still living in nineteenth or even in eighteenth century conditions and mentality. Such nineteenth-century people are scattered about, even in the most advanced countries. High birth rates and high infant mortality rates were current in the nineteenth century, and there is no reason why they should not be

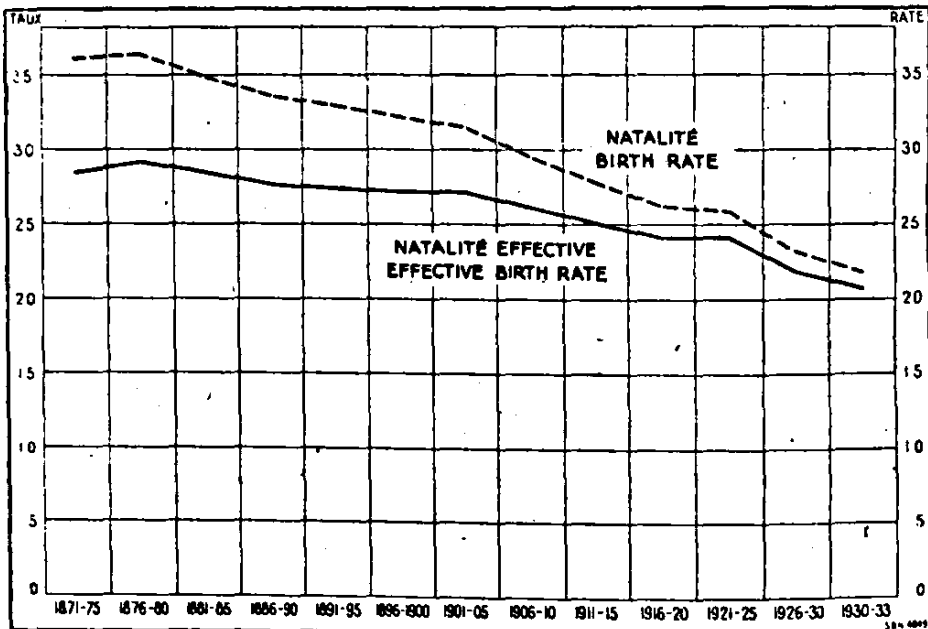
¹ After elimination of influence of age of mother, earnings of father and multiple births.

so to a certain extent also amongst the nineteenth-century people of to-day. The statistics furnish, therefore, no clue as to the probable infant mortality in a large twentieth-century family which, in regard to living conditions and mentality, belongs to our own time.

4. THE EFFECTIVE BIRTH RATE.

No decrease of the infant mortality, however important it may be, will suffice to counterbalance the drastic fall of the birth rate in the twentieth century ; but it may serve as a parachute, and, as such, mitigate the demographic disturbances caused by too abrupt changes in the birth rate.

16. BIRTH RATE AND EFFECTIVE BIRTH RATE (LIVE BIRTHS LESS INFANT DEATHS) PER 1,000 INHABITANTS IN THE NETHERLANDS, 1871-1933.



In the Netherlands, for example, the birth rate decreased by 14.4 points, from 36.1 in 1871-1875 to 21.7 in 1931-1933. The effective birth rate—the birth rate after deduction of the infant deaths—decreased during the same period from 28.5 to 20.7, or only by 7.8 points. Nearly half of the fall in the birth rate was thus made good by the saving of infants (see Diagram 16).

Similarly, the birth-rate map of Europe does not undergo a complete change by replacing it with a map of the effective birth rate, but some interesting changes are nevertheless observed. The effective birth rate of Hungary (18.7) is much lower, for example, than that of the Netherlands (22.0), although the Hungarian birth rate is a whole point higher than the Dutch rate. The effective birth rate of Austria is lower than that of Sweden. The effective birth rate of Iceland (23.2) is almost equal to that of Malta (24.1), which has a birth rate of 32.5, as against 24.3 for Iceland.

The stabilising effect of a low infant mortality in a difficult period of transition like ours should therefore not be lost sight of.

III. AGE DISTRIBUTION OF INFANT MORTALITY.

1. THE SELECTIVE EFFECT OF INFANT MORTALITY.

If infant mortality is the fee paid on entering life, the question arises as to the nature of the forces which take this toll. Are the infants exposed chiefly to a selective weeding out of the unfit, or are they submitted to a brutal taxation of blind destructive forces having their origin in the imperfect control by mankind of his surroundings ?

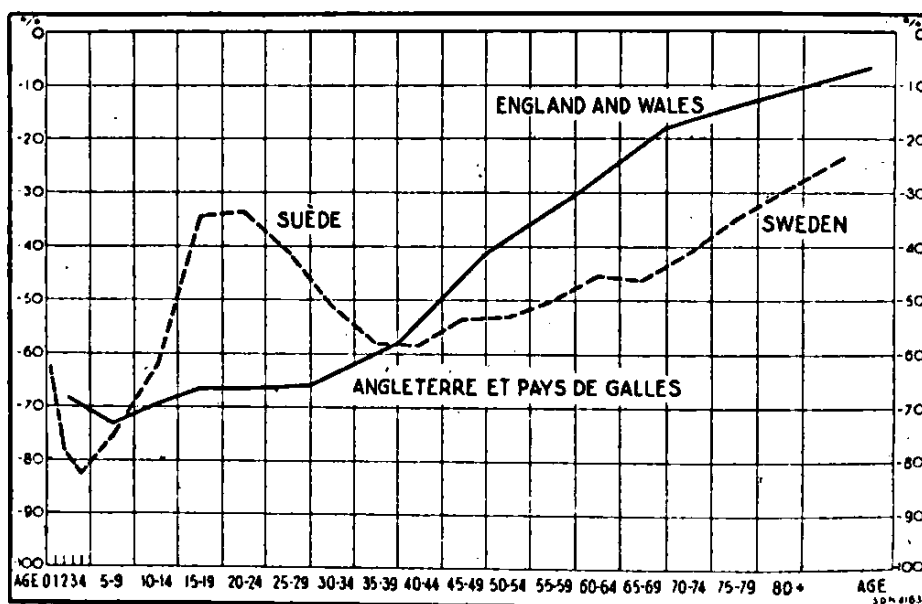
It is evident that the causes of infant mortality may be divided into two distinct categories : (*a*) those depending upon the fitness of the infant to live at all, and (*b*) those arising from the unfitness of the surroundings to support infant life. Mortality due to the first category of causes is evidently selective ; those consequential to the second category of causes may be selective so long as the surroundings remain unchanged, but they are by no means necessarily so. They may, on the contrary, quite well weaken the resistance of the organism against subsequent dangers.

Before analysing our direct knowledge of infant mortality in this respect, it will be useful to examine the nature of the general reduction of mortality which has been going on during the last half-century or more.

When comparing the general mortality rates by age over a long period of years, we find, in all countries where infant mortality has been materially reduced, an important decrease of mortality also

at other ages. This decrease is frequently greater than in infancy. Diagram 17 shows the percentage decrease of mortality by age in England and Wales and in Sweden from 1841-1850 to 1926-1930. The reduction of the infant mortality during these eighty years amounted in Sweden to 62.4 per cent and in England and Wales to 55.6 per cent. Still higher percentages of reduction were found in Sweden up to the age of 9 : in England, even up to the age of 40

17. PERCENTAGE DECREASE AT EACH AGE OF THE SPECIFIC DEATH RATES IN SWEDEN AND IN ENGLAND AND WALES FROM 1841-1850 TO 1926-1930.



Note : The age groups shown are for Sweden : under 1 year, 1-2 years, 3-4 years, quinquennial age groups from 5 years and on to 80 years, 80 years and over ; for England and Wales : quinquennial age groups up to 24 years completed, decennial groups from 25 to 84, 85 years and over. Note that the percentages of decrease are shown measured from the top down ; the lower the line the greater the decrease.

or 44. We shall not attempt here to discuss the reasons for this difference between Sweden and England, which is probably mostly due to the degree of urbanisation and the spread and trend of tuberculosis. In both countries, it is evident, in spite of these important differences, that the reduction of mortality in infancy and childhood has not been followed by an increased mortality later in life. We must therefore conclude that the massive reduction of infant mortality has not in the least impaired any selective effect

which it might have had. It must be that the surroundings have become less hostile so as not to demand a large fee of entry possessing no biological utility.

The decrease of mortality falls off very markedly after the middle of life toward old age in both countries. This slackening of the decrease, however, cannot be interpreted as a compensatory effect of the fall of mortality in infancy and childhood, because this fall had hardly begun when the persons of advanced age now dying were children.

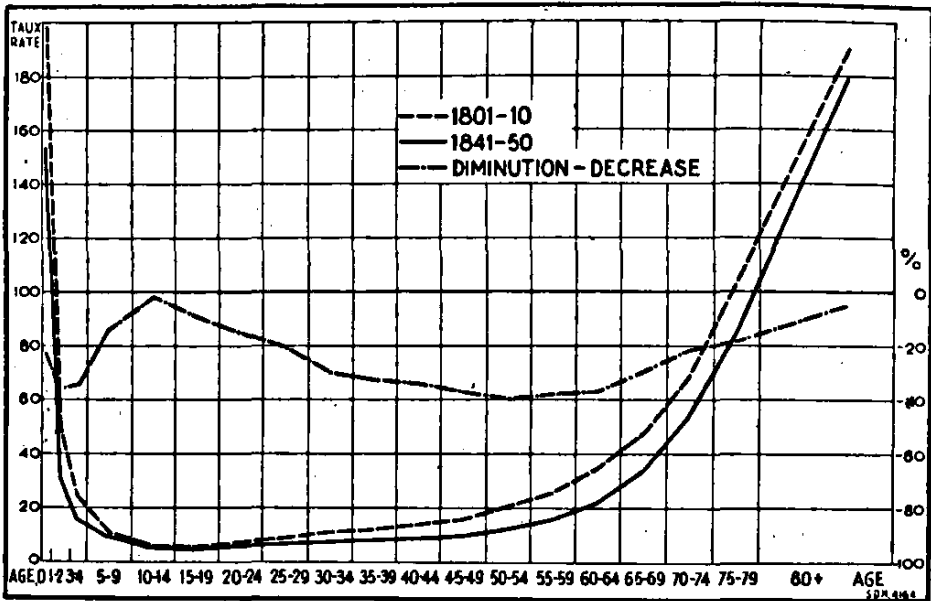
It is possible to follow the mortality rates by age of several generations throughout life in one country only—namely, in Sweden. Even there, it is necessary to reconstruct the years of birth from the years of deaths combined with the age, and the result can be only approximate. It seems reasonably certain, however, that no significant error can arise from this procedure.

A considerable decrease of mortality in infancy and early childhood occurred in Sweden between 1801-1810 and 1841-1850. This decrease of the mortality of persons born in 1841-1850, as compared with those born in 1801-1810, was much less pronounced in later childhood, probably owing to epidemic prevalence in the 'fifties. A very marked decrease of mortality occurred, on the other hand, from the years of youth and onward, reaching a maximum at the ages from 45 to 64. The curves of the percentage decrease by age are so regular that they dispel any doubts as to the value of the data. We may thus conclude that a very marked fall of mortality in adult life corresponded to an equally marked fall of infant and early childhood mortality (see Diagram 18).

Diagram 19 shows the percentage decrease of the specific death rates in England and Wales of persons born in given years in comparison with the corresponding rates prevailing when these persons were born. This diagram may thus be taken to illustrate the gradually improved chances of life of each new generation. The form of the curves suggests that this improvement, which is becoming more and more marked, may gradually come to extend up to an advanced age.

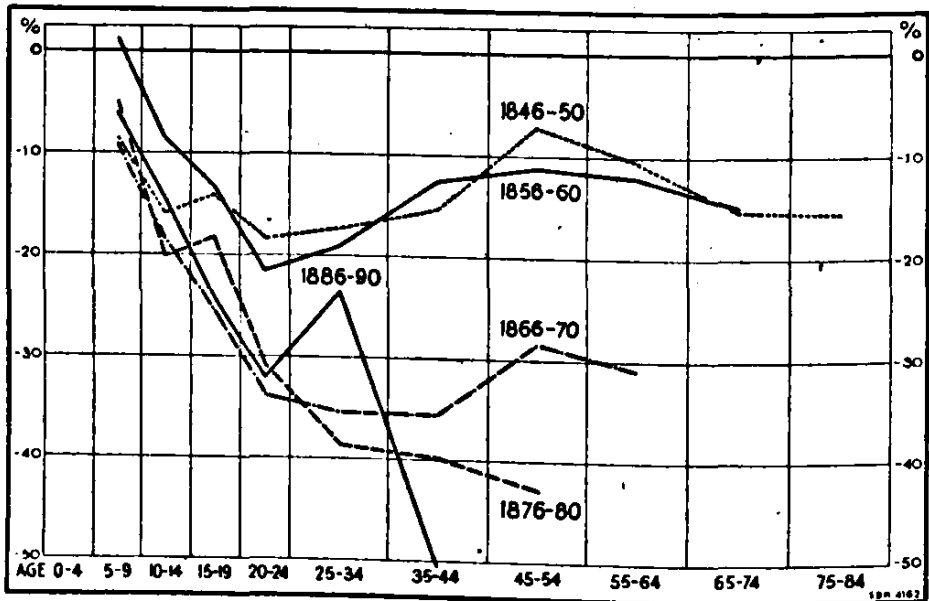
It is not possible to determine what effect the great decrease of infant and child mortality in the twentieth century may have upon the mortality in adult and advanced age, because the persons born during these years have not yet reached that stage of life. Up to

18. SPECIFIC DEATH RATES BY AGE IN SWEDEN OF PERSONS BORN APPROXIMATELY 1801-1810 AND 1841-1850, AND PERCENTAGE DECREASE OF THESE RATES AT EACH AGE FROM THE FIRST TO THE SECOND OF THESE GROUPS.



Note : These age curves follow two different generations throughout life. The decennium of birth is approximate, having been calculated from the year of death and the age at death, which is given only in quinquennial age groups. Note that the percentages of decrease are shown from the 100 line downward ; the lower the line the greater the decrease.

19. PERCENTAGE DECREASE AT EACH AGE OF THE SPECIFIC DEATH RATES IN ENGLAND AND WALES OF PERSONS BORN APPROXIMATELY DURING THE YEARS INDICATED FROM THE CORRESPONDING SPECIFIC DEATH RATES PREVAILING AT THE TIME OF THEIR BIRTH.

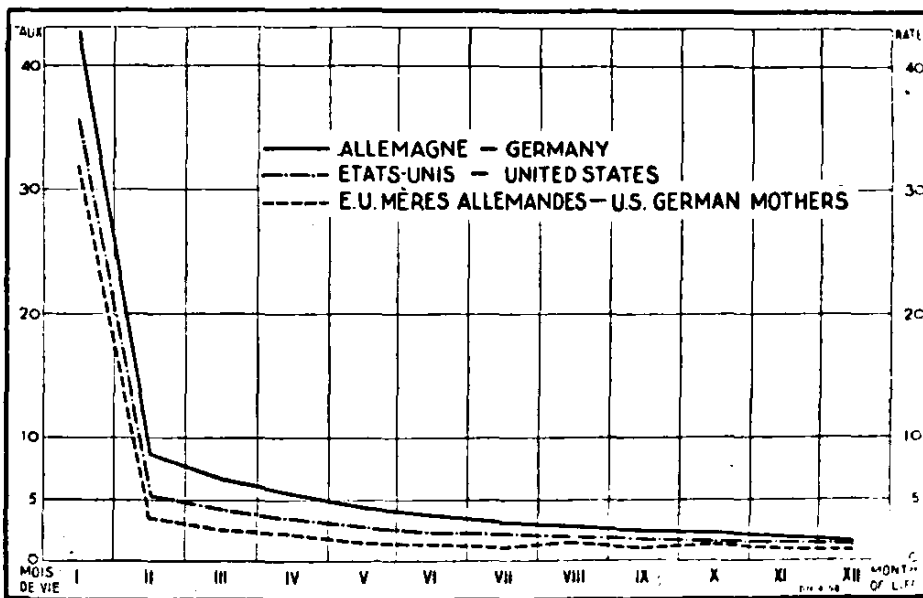


Note : Same observations as for the previous diagram. The relatively low decrease at the ages 25-34 of persons born 1886-1890 is due to war mortality ; without this incident, the trend of the curve would not have been disturbed.

the present, the persons born under the star of the falling infant mortality have also benefited by a lowered mortality in childhood and youth, but the regularity of the curves is much disturbed by the influence of the war and the great influenza epidemic of 1918-19.

The general impression gained from the available material is that the easier a generation passes through infancy and childhood, the better are its chances of survival later on. This conclusion tallies with what we know—that a high mortality in early life corresponds to a large amount of infectious disease of various kinds which may leave the organism permanently impaired and therefore less resistant later on in life.

20. INFANT MORTALITY BY MONTHS OF LIFE PER 1,000 LIVE BIRTHS IN GERMANY, IN THE UNITED STATES AND FOR INFANTS OF GERMAN MOTHERS IN THE LATTER COUNTRY IN 1930.



A very low infant mortality, on the contrary, is selective, because it eliminates, in the first place, the infants unfit to live at all. Hence, an additional argument in favour of a massive reduction of the infant mortality.

2. NEO-NATAL AND LATER INFANT MORTALITY.

It is natural that the mortality should be highest immediately after birth, and it is obvious that neo-natal deaths must comprise a large proportion of the infants unfit to live at all. Diagram 20,

which gives the infant mortality by months of age in the United States of America and in Germany, shows how the mortality during the first month of life stands out distinctly from that of the subsequent months. The infant mortality falls regularly from the second month of life and on, but the curve tends to flatten out from about the ninth month.

A detailed analysis of the mortality during the first month of life shows a similar distribution. By far the greater part of these deaths occur during the first week of life, and their number decreases regularly from the second to the fourth week. The mortality on the first day of life is frequently as high or higher than that of the remainder of the first week.

Infant Mortality during Various Parts of the First Month of Life in England and Wales in 1931, and in the United States Birth Registration Area in 1930.
(Rates per 1,000 live births.)

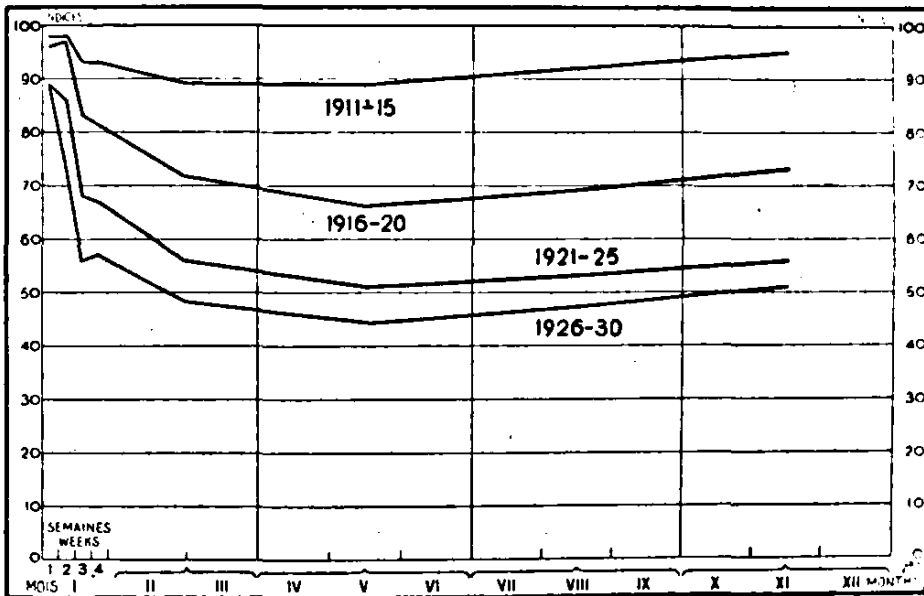
| Age | England and Wales | | | The United States of America | | |
|------------------------|-------------------|--------|---------|------------------------------|--------|---------|
| | Male | Female | Persons | Male | Female | Persons |
| Under 1 day | 11.6 | 9.1 | 10.4 | 16.8 | 13.1 | 15.0 |
| 1 day | 3.9 | 3.1 | 3.5 | 4.7 | 3.6 | 4.2 |
| 2 days | 3.8 | 2.4 | 3.1 | 3.4 | 2.4 | 2.9 |
| 3 days | 2.6 | 1.8 | 2.2 | 5.8 | 4.4 | 5.1 |
| 4 days | 1.3 | 1.1 | 1.2 | | | |
| 5 days | 1.0 | 0.8 | 0.9 | | | |
| 6 days | 0.8 | 0.7 | 0.8 | | | |
| Total under 1 week .. | 25.1 | 19.0 | 22.1 | 30.7 | 23.5 | 27.2 |
| 1 week | 4.4 | 3.6 | 4.0 | 4.2 | 3.5 | 3.9 |
| 2 weeks | 3.6 | 2.6 | 3.1 | 2.7 | 2.3 | 2.5 |
| 3 weeks | 2.7 | 2.0 | 2.4 | 2.3 | 1.9 | 2.1 |
| Total under 4 weeks .. | 35.8 | 27.2 | 31.6 | 39.9 | 31.3 | 35.7 |

It appears from the above figures that the mortality is heaviest at the time of birth and shortly after, and that it subsequently decreases rapidly. The mortality on the first day of life amounts, in the United States of America, to more than half, in England and Wales to nearly half, of the first week's mortality. The

first week's mortality accounts in the United States for three-fourths, and in England for over two-thirds, of the whole mortality during the first month of life. The mortality during the first month is, in England, nearly equal to, and exceeds in the United States, the total of mortality during the subsequent eleven months.

This decrease of mortality continues right up to the age of puberty. The interpretation of this fact must be that, once most of the quite unfit are eliminated, the surviving infants or children gain rapidly and more and more completely a foothold in life.

21. INDEX FIGURES OF THE INFANT MORTALITY BY AGE (THE RATES AT EACH AGE FOR 1906-1910 TAKEN AS 100) IN ENGLAND AND WALES IN QUINQUENNIAL PERIODS FROM 1911 TO 1930.



Note : The curves do not show the rates of mortality, but the relative amelioration at each age.

It now remains to be seen in what part of infant life the reduction of mortality has been the most active. Unfortunately, we do not possess much detailed information over a long period of years as to the age distribution of infant mortality. Such information is available for England and Wales for twenty-six years, during which period the infant mortality has been reduced by about one-half. Diagram 21, in which the mortality rate of each age-group in 1906-1910 has been taken as 100, shows the various stages of the decrease. It appears from this diagram that there has been very little reduction

of the mortality rates during the first week of life. The percentage reduction of mortality on the first day of life is about the same—10 per cent—as during the six subsequent days. After the first week, the reduction is gradually becoming greater and reaches a maximum between the third and the sixth months. The steepness of the infant mortality curve by age (diagram 20) is thus becoming more and more accentuated, its highest part remaining nearly constant while the slope is being hollowed out and the flatter part worn away.

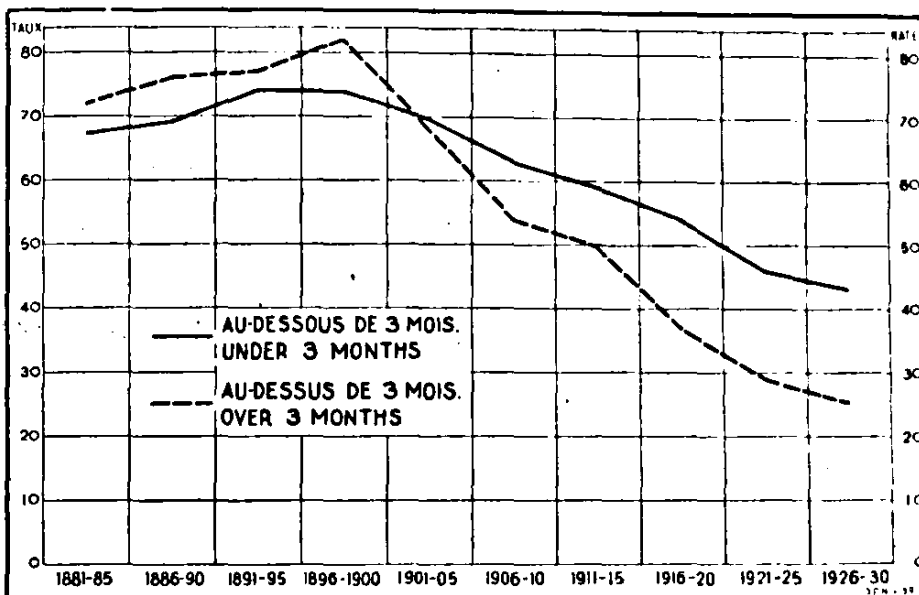
The earlier reduction of infant mortality has probably followed similar lines. Diagram 22 shows that, in England and Wales, the mortality of infants over 3 months has always been subject to greater fluctuations than that of early infancy. Diagram 23, which shows the course of infant mortality under and over 1 month in New Zealand, is still more conclusive. The decrease of mortality over 1 month began already towards the end of the nineteenth century. The total reduction since then now amounts to over five-sixths, although the rate, as early as in the 'eighties of last century, was much lower than those prevailing at the time in European countries. The decrease of the mortality under 1 month, on the contrary, began only after the war and has, so far, not exceeded one-fourth. The latter rates have shown a remarkable degree of stability, the fluctuations never having reached 10 per cent over a period of more than forty years, although the infant mortality over 1 month decreased by two-thirds during these years.

We may conclude, therefore, that infant welfare work and other forces active in the reduction of infant mortality, during long years, has benefited the infant only after the first shock of birth has been passed. The statistics of several countries in recent years show a beginning decline also of the neo-natal mortality, which can be explained only by assuming that new forces are active. It is probably too early to venture a definite opinion as to the nature of these forces; the reduced average age of the mothers may have some influence, and so may pre-natal care or still other factors.

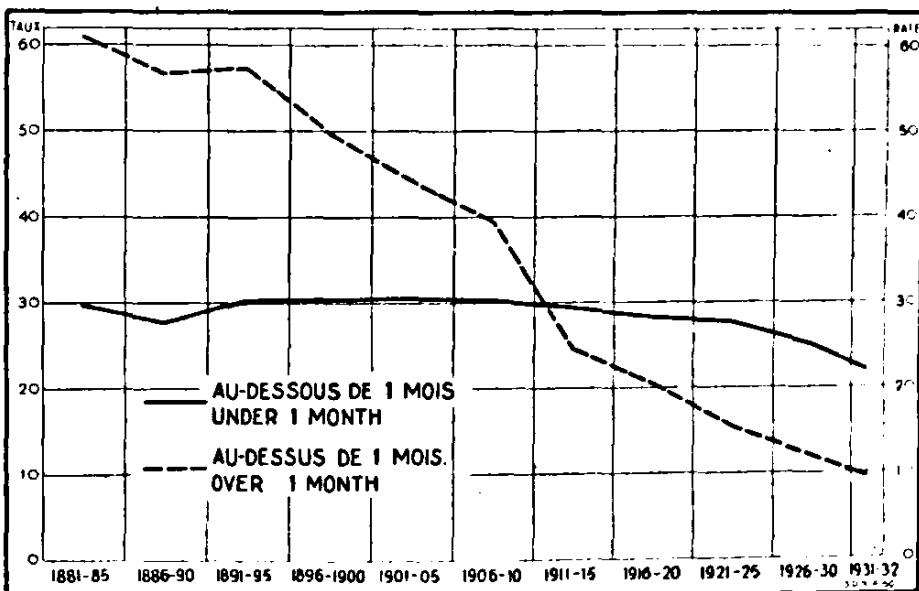
3. GEOGRAPHICAL DISTRIBUTION OF EARLY AND LATER INFANT MORTALITY.

Given the fundamental differences in regard to the height, causes and decrease of early and later infant mortality, it is useful to

22. INFANT MORTALITY UNDER AND OVER 3 MONTHS OF AGE PER 1,000 LIVE BIRTHS IN ENGLAND AND WALES, 1881-1930.

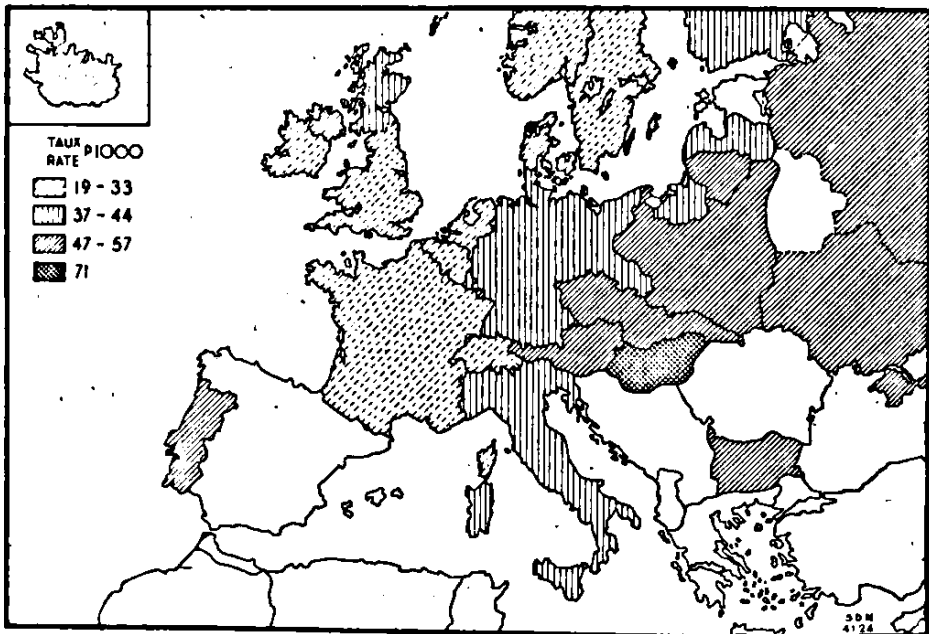


23. INFANT MORTALITY UNDER AND OVER 1 MONTH OF AGE PER 1,000 LIVE BIRTHS IN NEW ZEALAND, 1881-1932.



establish the geographical distribution of each. A serious difficulty intervenes, however, in the form of the different rules of registration in use in the various countries. In certain countries, such as France, Belgium and Spain, infants dying during the first days of life, before being registered, are counted as still-births. The effect of this is to swell the still-birth rate at the expense of the early infant mortality rate. It is difficult to estimate the exact effect of this procedure, but it is probable that it may result in a fictitious diminution of the first month's mortality of about one-fourth. It is possible that

24. INFANT MORTALITY UNDER 1 MONTH OF AGE PER 1,000 LIVE BIRTHS
IN EUROPEAN COUNTRIES IN 1929.



Note : The data for the Ukraine are for 1929, those for European Russia proper for 1928.

the registration of infant deaths may be defective also in certain other countries; such deficiency will naturally be most pronounced among infants dying shortly after birth. An international comparison of early infant mortality is therefore more subject to caution than the rates for the remainder of infant life.

In order to remedy to some extent this defect, two maps referring to neo-natal mortality have been prepared—one showing the mortality under 1 month (Map 24) and another (Map 25) where the still-birth rate has been added to these rates in such countries

where the registration of still-births seems to be reasonably complete. Even the last measure, however, is not wholly satisfactory, because the definition of still-births is not the same in all countries. A comparison of the two maps may nevertheless be useful. The second map brings out, for example, that France and Belgium should not be in the lowest but in the second group of countries for early infant mortality.

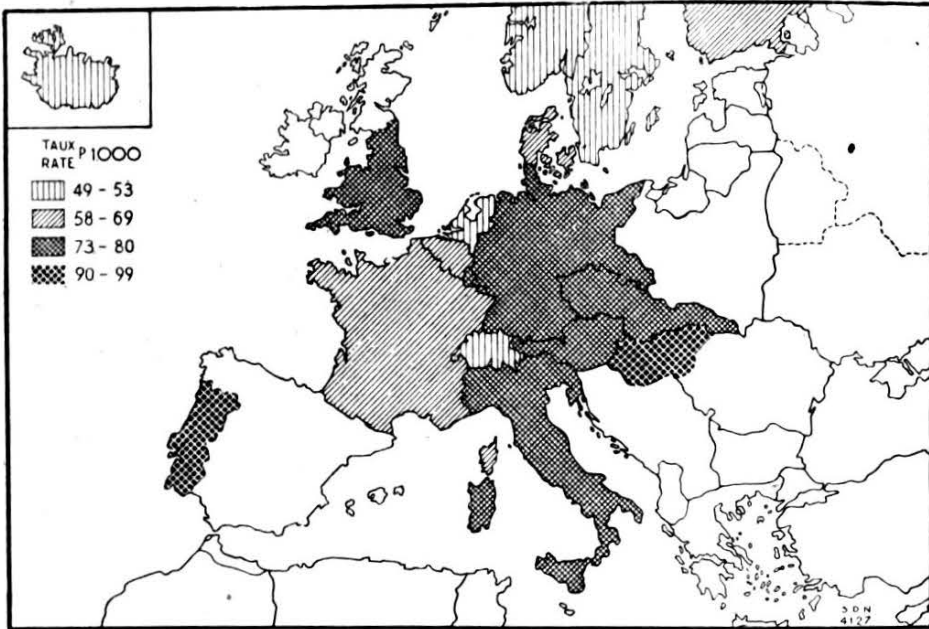
Map 25 should thus, in theory, show the mortality from about three months before to one month after birth. The uniformity of these rates, in spite of all imperfections of the data, is rather remarkable. Apart from Portugal and Hungary, where early infant mortality is very high, the rates varied only from 49 to 80 per 1,000 births. Infant mortality rates over 1 month varied in European countries, on the other hand, from 23 to 155, or by more than six times the lowest rate. This agrees with the observations made in the previous sub-chapter concerning the smaller decrease of early infant mortality in comparison with later infant mortality. The mortality rates shown on Map 25 result largely from causes relating to lack of vitality, those on Map 26 (over 1 month) mostly from causes resulting from surroundings, and surroundings are more subject to change than is vitality.

We find, on Map 25 (still-births and infant mortality under 1 month), the lowest group constituted by the Netherlands, Iceland, Norway, Sweden and Switzerland, which are also the countries having the lowest infant mortality over 1 month. The rates for these countries, which vary from 49 to 53, are about equal to those of New Zealand (50 in 1929, 46 in 1932), and may thus be considered as typical for countries having a healthy population living under reasonably good social conditions and enjoying sufficient medical and sanitary attention. New Zealand has succeeded, however, in reducing her infant mortality over 1 month to 10 per 1,000 live births, while the above-mentioned five most favourable European countries showed rates between 23 (Switzerland) and 35 (the Netherlands).

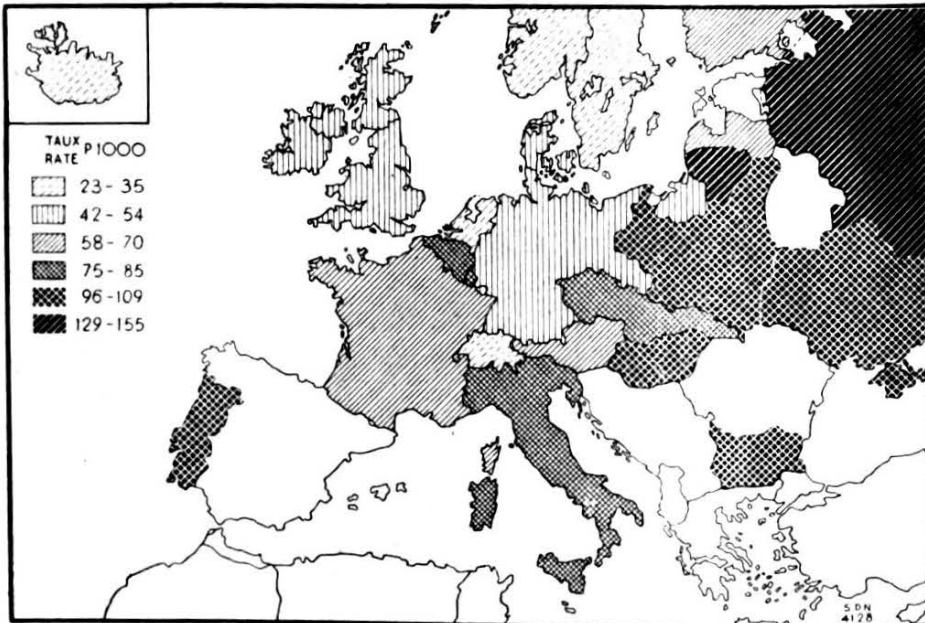
Infant mortality has frequently been stated to be the best measure of the sanitary state of a country. There is no such measure expressed by a single rate ; but, if the infant mortality rate is employed for this purpose, it should clearly be only the part of it relating to infants over 1 month. Nevertheless, it is obvious

INFANT MORTALITY

25. STILL-BIRTHS AND DEATHS UNDER 1 MONTH OF AGE PER 1,000 BIRTHS IN EUROPEAN COUNTRIES IN 1929.



26. INFANT MORTALITY OVER 1 MONTH OF AGE PER 1,000 LIVE BIRTHS IN EUROPEAN COUNTRIES IN 1929.



Note : The data for the Ukraine are for 1929, those for European Russia proper for 1928.

that a difference in this rate—as, for example, from 25 in Norway to 81 in Italy—corresponds, not merely to differences in sanitation, but also, and probably still more, to climatic and social differences quite beyond the control of the sanitarian.

Central Europe furnishes a good example of this contention. The combined rate of still-births and deaths under 1 month ranges only from 75 to 79 per 1,000 births in an area comprising Germany, Austria, Czechoslovakia, Luxemburg and the Saar Territory. The extraordinary similarity of these rates furnishes striking evidence of the uniformity of the human element over this area as far as the fundamental factors concerning their potential vitality are concerned. The infant mortality over 1 month varies, on the contrary, in these countries, from 52 to 85 per 1,000 live births, without taking into consideration the administrative subdivisions which undoubtedly show still greater variations. The latter rates are obviously greatly affected by the state of sanitation, which seems to have no effect upon the natural selection.

It would be rash, however, to attribute to racial differences the variations shown by this total rate of still-births and infant deaths under 1 month which we may name *birth mortality*. It should, further, be remembered that race bears absolutely no relation to nationality, several races being represented in every one of the European countries.

This is brought out by the fact that the mortality under 1 month in the United States by country of birth of the mother shows no correlation whatever to the corresponding rates prevailing in these European countries. The still-birth statistics are not published according to country of birth of the mother, but it is less necessary to consider them than in Europe, as we are here dealing exclusively with registration law and practice in force in the United States.

Social differences undoubtedly unite with those of nationality in forming the rates recorded in the United States ; but the old emigration, represented notably by the United Kingdom, Ireland, Germany and Scandinavia, is undoubtedly fairly homogeneous in this respect.

The following table shows that the infant mortality rates over 1 month are always lower in the United States than in the home country of the mother, but this is not always the case with the early infant mortality. It is further seen that public health work

has generally penetrated more deeply amongst the old immigration (from the United Kingdom, Germany and Scandinavia) than amongst the more recent arrivals (Italy and Poland). This fact notwithstanding, the Italians benefit from a lower mortality under 1 month than the older immigration.

*Infant Mortality according to Country of Birth
of the Mother in the United States Birth Registration
Area, in 1930, compared with the Rates prevailing
in the Corresponding European Countries.*

| Country of birth of mother | The United States | | European countries | |
|----------------------------|-------------------|-----------------|--------------------|-----------------|
| | Under 1 month | Over 1 month | Under 1 month | Over 1 month |
| Italy | 28.8 | 30.4 | 43 | 81 |
| United Kingdom | 31.4 | 17.5 | 35 | 45 |
| Germany | 31.8 | 18.4 | 44 | 52 |
| Scandinavia | 32.9 | 17.4 | 28 | 35 |
| Ireland | 33.4 | 25.9 | 25 | 45 |
| Poland | 37.5 | 35.3 | 52 | 100 |
| All foreign | 32.2 | 30.5 | — | — |
| The United States : | | | | |
| White | 34.1 | 25.5 | — | — |
| Negro | 47.6 | 51.9 | — | — |

If the viability of the new being—the vitality of the population so to speak—exercises a predominant influence upon what we have styled the “birth mortality”, and if general sanitation and infant welfare work, on the other hand, has been most effective on the mortality over 1 month, the relation between the latter and the birth mortality may prove of some interest. The ratio of the latter to the former may furnish some indication of what has been done with the infant material in hand. Allowing that the result of any such comparison must be received with caution due to the imperfection of the data and to the multiple and often intangible causes at work, certain facts seem to stand out quite clearly. The ratio is lowest—indicating surroundings favourable to the infant—in Switzerland, Iceland, Norway, England and Wales, and Sweden. It ranges between 0.43 and 0.60 in these countries.

It is high—between 0.95 and 1.15—in France, Belgium, Luxembourg, Italy, Hungary and Portugal. It is of medium height in Central Europe (0.67 to 0.82). A certain influence of climate seems to make itself felt in the geographical distribution of this ratio.

That there is still much room for improvement is shown by the figures for New Zealand, where the ratio between the infant mortality over 1 month and the "birth mortality" was as low as 0.20 in 1932. We may take it that this is a striking example of a country where infant mortality has become truly selective and has ceased to be destructive.

4. ANTE-NATAL MORTALITY.

The lack of international comparability of still-birth statistics has been referred to in the previous chapter. It arises from differences in definition of both the upper (distinction between live and dead births) and the lower limits (duration of gestation before an abortion is considered a still-birth) defining the term "still-birth".

It seems wisest, therefore, to refrain from a direct comparison of the still-birth rates in the various countries. All that it is possible to say with a reasonable degree of certainty is that, in countries where the statistics seem to be of a fair quality and where a white population lives under normal climatic and social conditions, the frequency of still-births ranges between 24 and 45 per 1,000 births. The range may, of course, be wider for local areas. The rate seems to be lowest (from 24 to 26 per 1,000) in the four Scandinavian countries (Denmark, Norway, Sweden, Finland), the Netherlands and Switzerland. The rates for these countries are so similar that this cannot be ascribed to chance. There is a similar uniformity of the rates in Germany, Austria and Hungary (28 to 30 per 1,000). The incidence (40 per 1,000) seems to be higher in England, but this may be due partly to differences in definition.

It is noteworthy that the model country for infant welfare work, New Zealand, has not an exceptionally low still-birth rate (29 in 1932).

This tallies with what a study of other parts of the world brings out—namely, that the still-birth rate is usually not closely related to the infant mortality over 1 month. In the six European countries mentioned above as enjoying a uniformly low still-birth rate, we thus find the infant mortality over 1 month ranging from 23 per 1,000 in Switzerland to 58 in Finland. In Central Europe, we find equally important variations from 52 in Germany to 109 in Hungary.

A certain degree of relationship may exist between the still-birth rate and the neo-natal mortality. This relationship is, however, frequently obscured by the differing definitions of still-birth, which affect both of these rates, but in opposite sense. It would be dangerous therefore to try to establish coefficients of correlation between these two elements of the "birth mortality".

It is natural that some sort of relationship should exist, because the still-birth rate must be considered as the prolongation of the mortality curve back beyond the moment of birth. The justification of this conception is borne out by the sex distribution of mortality before and after birth, which will be referred to later. It is further justified by another fact which has not received sufficient attention—namely, that the movements of the still-birth rate show a certain degree of similarity to those of the neo-natal mortality.

We have seen that the great decrease of the infant mortality over 1 month which occurred during the first quarter of this century was not accompanied by any pronounced decrease of the neo-natal mortality. The still-birth rate also remained practically constant during this period. In recent years, however, a downward trend of the still-birth rate is noted in several countries.

In Switzerland, for example, the still-birth rate fell regularly from 28.6 per 1,000 births in 1922 to 23.7 in 1930. In Italy, there was a fairly steady fall from 41.6 in 1925 to 31.4 in 1932. In Germany, the rate decreased from 32.7 in 1926 to 30.2 in 1931. In New Zealand, where the decrease of mortality under 1 week began in 1929, the still-birth rate also showed a small decrease from 31.5 in that year to 29.1 in 1932. The decrease, where not due to changes in registration procedure, is everywhere of quite recent date. In a great many countries, it has not yet made its appearance.

It is probable that the lowered average age of the mother is one of the causes of this recent decrease of the still-birth rate. It is certain, at any rate, that, once the age of the twenties is passed, the frequency of still-births increases rapidly with the age of the mother.

Statistics of the United States Birth Registration Area for 1930 give a very regular curve of the incidence of still-birth according to age of the mother, with a minimum between 25 and 29. The rates, for ages of mother, of still-births per 1,000 live births were : 15-19, 44 ; 20-24, 34 ; 25-29, 32 ; 30-34, 38 ; 35-39, 49 ; 40-44, 65 ;

45-49, 86. - The regularity of this curve is conclusive as to the reality of the fact.

New Zealand statistics show the corresponding ratio for legitimate still-births in 1928-1932 : Under 20, 23.0 ; 20-24, 22.5 ; 25-29, 27.0 ; 30-34, 30.7 ; 35-39, 42.7 ; 40 and over, 64.9.

The close relationship between the still-birth rate and the neonatal mortality is further shown by their geographical distribution in England and Wales, where it may be assumed that the quality and procedure of registration are the same for all parts of the country.

The table below, in which the rates for each age-group for the whole of England and Wales have been taken as 100, show the order of the geographical divisions according to height of rate to be almost identical for still-births and for mortality during the first week of life. The still-birth rate shows somewhat greater range than the death rate for the first week of life, which may be explained from the fact that the latter covers certain more or less accidental risks which are probably about the same everywhere.

With the advancing age of the infant, this original order disappears. The nature of the risks to which the infant is exposed is evidently no longer the same.

Indices of Still-birth Rate, Infant Mortality Rate at Various Stages of Infant Life and Mortality of Early Childhood (the Rate for England and Wales at Each Age = 100) in Geographical Districts of England and Wales in 1931.

| Districts | Still-births | Under 1 week | 1-4 weeks | 1-3 months | 3-6 months | 6-12 months | 1-2 years | 2-5 years |
|---------------------------------|--------------|--------------|-----------|------------|------------|-------------|-----------|-----------|
| Greater London. | 80 | 83 | 77 | 95 | 109 | 88 | 73 | 76 |
| South-east ¹ | 82 | 82 | 78 | 64 | 57 | 51 | 53 | 63 |
| East | 96 | 95 | 101 | 87 | 69 | 65 | 57 | 65 |
| South-west | 97 | 94 | 94 | 80 | 60 | 61 | 65 | 69 |
| Midland II | 99 | 109 | 109 | 90 | 95 | 95 | 86 | 87 |
| Midland I | 101 | 104 | 99 | 94 | 95 | 102 | 104 | 102 |
| North II | 101 | 112 | 105 | 118 | 100 | 127 | 150 | 133 |
| North I | 104 | 113 | 136 | 129 | 149 | 158 | 190 | 167 |
| North III | 112 | 114 | 114 | 108 | 110 | 109 | 114 | 129 |
| North IV | 115 | 111 | 111 | 127 | 127 | 135 | 136 | 123 |
| Wales II | 131 | 116 | 107 | 105 | 96 | 78 | 69 | 90 |
| Wales I | 141 | 116 | 122 | 116 | 99 | 118 | 125 | 125 |
| England and Wales | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |

¹ Without Greater London.

The still-birth rate is always much higher for illegitimate than for legitimate birth. This question will be dealt with later on.

Racial influences are important in the United States of America. The still-birth rate was, in 1930, 79 per 1,000 live births amongst negroes, as against 34 for the white population.

5. THE HANDICAPPING OF THE MALE INFANT.

The male infant dies more easily than the female infant. This has always been so, although no sufficient explanation of this phenomenon has ever been established. The excess of male mortality is certainly not due to accidents at birth, as some have suggested, because it persists almost throughout life, and is very marked also in old age, when conditions of life of man and woman have again become fairly identical.

A question of vitality is undoubtedly involved, because the excess of male mortality is very marked already in intra-uterine life. One might be tempted to say that nature has endowed the female organism with greater vitality than the male organism, because it is meant to bring forth, in due time, the next generation. If so, this surplus of vitality dates back to intra-uterine life and does not disappear even after the end of the reproductive period, possibly because it is not entirely consumed in child-bearing, which now rarely goes on to its potential limit.

The excess of male mortality forms a regular curve, rising from intra-uterine life to a maximum at about two or three months after birth and falling slowly to a minimum at the age of puberty. After puberty, the regularity of the curve disappears owing to the differing conditions of life of man and woman (work and child-bearing).

The English statistics are instructive in this respect. The male mortality expressed in percentage of the female mortality of the same age-group was, in 1931 : still-births, 118 ; under 4 weeks, 132 ; 4 weeks to 3 months, 140 ; 3-6 months, 137 ; 6-9 months, 126 ; 9-12 months, 121 ; 1-2 years, 118 ; 2-5 years, 110 ; 5-10 years, 115 ; 10-15 years, 99.

The corresponding figures for Germany in 1930 were : still-births, 118 ; under 1 month, 125 ; 1-3 months, 134 ; 3-6 months, 130 ; 6-9 months, 121 ; 9-12 months, 109.

The curves are not so regular in all countries when only a single year is considered, but they all show the same trend. It is this peculiar distribution which determines the degree of excess of male infant mortality. The proportion of early deaths increases, and with that automatically the excess of male mortality, when the infant death rate falls. Hence, a higher male excess of infant mortality in recent years than formerly, a higher male excess in countries with a low infant mortality than in those where high rates are prevailing. These changes are slow, but quite perceptible. An increase of the male excess may thus be taken as a sign that the selective forces are gaining on the destructive forces causing infant mortality.

6. AGE OF THE MOTHER AND INTERVAL BETWEEN CONSECUTIVE BIRTHS.

It is unfortunate that no national infant mortality statistics are classified according to age of the mother. We have seen above that (1) the average age of women in child-bed decreases markedly when the birth rate declines, and (2) the incidence of still-births, once the factor of illegitimacy is eliminated, increases with the age of mothers from 25 or 30 years and on, to become two or three times as high toward the end of the reproductive period as amongst young women.

It is probable, therefore, that (1) infant mortality also increases when the age of the mother passes a certain limit ; (2) this increase would be most marked for the neo-natal mortality ; and (3) this might influence the general trend of infant, and especially of neo-natal, mortality.

WOODBURY has examined this question, but has, unfortunately, made no distinction between neo-natal and later infant mortality. His principal table referring to this subject is reproduced below,¹ but some of the rates must be accepted with a certain reserve, owing to an insufficient number of observations in these groups (notably for the fifth child at ages 20-24). The decimals have been omitted as being without any real significance.

¹ *Opus cit.*, page 73.

*Infant Mortality Rates by Age of Mother and Order of Births
in Eight Selected Towns of the United States.*

(WOODBURY'S investigation.)

| Order of birth | Total | Age of mother | | | | | |
|-----------------------|-------|---------------|-------|-------|-------|-------|-------------|
| | | Under 20 | 20-24 | 25-29 | 30-34 | 35-39 | 40 and over |
| Total | 111 | 136 | 109 | 101 | 105 | 127 | 137 |
| First | 105 | 126 | 101 | 90 | 103 | 132 | — |
| Second | 96 | 167 | 106 | 74 | 77 | 113 | — |
| Third | 105 | — | 125 | 104 | 82 | 73 | — |
| Fourth | 109 | — | 155 | 100 | 107 | 82 | — |
| Fifth | 119 | — | 98 | 136 | 97 | 128 | — |
| Sixth | 123 | — | — | 150 | 102 | 129 | — |
| Seventh | 137 | — | — | 196 | 122 | 131 | 109 |
| Eighth | 136 | — | — | — | 137 | 121 | — |
| Ninth | 147 | — | — | — | 175 | 134 | — |
| Tenth and later | 182 | — | — | — | 228 | 194 | 160 |

Very early child-bearing seems to be particularly harmful to the infant. WOODBURY obtained the rates of 160 for mothers under 18, and of 129 for mothers of 18 or 19 years of age.

The above table calls for a little more comment than that offered by WOODBURY. At first sight, the indications of these rates are contradictory. The infant mortality increases with the age of the mother for a first or second child once she has passed the age of 30, but this is rarely the case as far as the later children are concerned. Moreover, there is no handicapping of the first-born when the mother is under 25. It is therefore evident that still another factor, not hitherto mentioned, is active.

The nature of this factor can be surmised from the fact that certain rates are much higher than should be expected, notably those for the second child of mothers under 20 ; for the third and fourth children of mothers from 20 to 24 ; for the fifth, sixth and seventh children of mothers from 25 to 29. For still later children, the infant mortality decreases regularly with the increasing age of the mother.

This peculiar distribution can be explained only by attributing the excess of these rates to the too short intervals between births, which have prevented the mother from recuperating strength.

As a matter of fact, it is not possible to have two children before the age of 20, four before the age of 25, or six or seven before the age of 30, unless the interval between births is very short. It is reasonable to conclude from the above table, therefore, that too short intervals between the births are an important cause of an increase in the infant mortality. It is not unlikely that this may even be one of the principal causes of the excess of infant mortality in large families.

It is certainly suggestive of this explanation that mothers from 35 to 39 years of age should experience the lowest infant mortality for their third and fourth children and not for their second child, as is normal. A second child of that age means in most cases that child-bearing has begun at an abnormally late age. When a woman reaches her fourth child at that age, it generally means, on the contrary, that she has had ample time to gather strength between births.

WOODBURY has obtained a certain amount of information regarding this question only for Baltimore;¹ but his material seems nevertheless conclusive, although it has not been possible to bring out the relationship to the other factors influencing the infant mortality. The rates found by WOODBURY are shown below. They seem to indicate that it is preferable to leave the mother two years for recuperating before a new pregnancy. No benefit seems to be derived, on the other hand, by extending the interval beyond three years.

*Infant Mortality Rates by Interval since preceding Birth²
in Baltimore (WOODBURY).*

| | Rate per 1,000 births |
|-----------------------------------|--------------------------|
| First births | 95 |
| All second and later births | 107 |
| Interval : | |
| One year | 147 |
| Two years | 99 |
| Three years | 87 |
| Four years and over | 85 |

¹ *Opus cit.*, page 46.

² As measured by the difference in even years between the mother's age at the time of birth and her age at the time of the preceding birth.

It appears, furthermore, that a subsequent pregnancy of the mother while the child is still an infant seems also to be very injurious to its health. Such cases were not numerous in Baltimore, and the rates therefore not quite conclusive. WOODBURY found that such infants experienced a mortality from two to three times as high as the normal.

It seems unwise, therefore, to encourage large families without at the same time attracting the attention of the parents to this fact.

McKINLAY has also dealt with the question of the age of the mother in relation to infant mortality.¹ He has estimated his births by age of mother, however, by assuming that their distribution was the same in the selected English counties as that found by KNIBBS in Australia some twenty-five years earlier. This assumption is hardly justified, as the distribution of births by age of mother varies greatly in time and from one county to another (see page 538). It would also have been preferable to show infants of mothers under 20 separately, as they may be expected to be subject to a higher mortality than those of mothers from 20 to 25.

The results of McKINLAY are as follows :

Infant Mortality and Still-Births per 1,000 Births by Age of Mother in Selected English Counties.

| Age of mother | Still-births and deaths in first day of life | Infant mortality less first day of life | Infant mortality and still-births |
|------------------|--|---|-----------------------------------|
| 15-24 | 44.3 | 49.3 | 93.6 |
| 25-29 | 49.2 | 51.2 | 100.4 |
| 30-34 | 41.3 | 41.7 | 83.0 |
| 35-39 | 60.5 | 56.7 | 117.2 |
| 40 and over | 81.3 | 57.8 | 139.1 |
| Total | 50.6 | 49.8 | 100.4 |

The course of the rates is irregular, and the result therefore inconclusive. It is clear, nevertheless, that the combined incidence of still-births and deaths during the first day of life shows a greater excess for infants of mothers over 40 than does the infant mortality properly speaking after deduction of deaths during the first day of life. It is not possible to say on the basis of these data, however, how far this excess is due directly to the age of the mother and

¹ *Opus cit.*, pages 43 to 49.

what part of it may be due to shorter intervals between the births, to the size of the family, to social conditions and the like factors.

It is a great pity that reliable statistics of infant mortality in relation to the size of the family, the age of the mother and notably to the interval between consecutive births are so rare. It is suggested that these questions be made the subject of future investigation.

IV. URBAN AND RURAL INFANT MORTALITY.

1. THE URBAN "MALAXATOR".

More than by the periodical changes of international frontiers have Europe and other industrialised parts of the world been affected by the progressive concentration of its population in towns. An always rising current of young men and women has been flowing from the green countryside toward the arid canyons of the towns for nearly a century, and thereby radically changed the mode of life of the bulk of the population. Migration of a European country lad to an American farm probably changes his mode of life less than his moving some ten or twenty miles from the field to the factory, tenement house and town life in general. The urban "malaxator" breaks up the old rocks of local backwood particularities and goes on steadily blending the new mortar of which the future will be built. But, before the cement is ready, much hard grinding takes place between the disparate elements thrown together under conditions for which their past has not prepared them.

The force of this movement of internal migration is shown by the fact that, in an old industrial country like England, the proportion of urban population increased from 50.2 per cent in 1851 to 80.3 per cent in 1931. Even though the urban growth may now be slackening, owing to the lessened demand of labour in industry—which will probably be permanent on account of technical progress—this human current toward the towns will not altogether cease for some time to come. This is so because of the rapid fall of the birth rate in most large towns, which has gone so far that, in 1933, the birth rate was lower than the death rate in thirty-seven European towns of over 100,000 inhabitants, while, in a great many others, the natural increase was insignificant.

The large towns showing a natural decrease of population—which is made up by immigration—are far from being confined to a narrow area. It suffices to mention them, in order to prove this point : Oslo, Stockholm, Tallinn, Riga, Bournemouth, Brighton, Southend-on-Sea, Blackburn, Blackpool, Bolton, Bradford, Huddersfield, Oldham, Stockport, Paris, Lille, Bordeaux, Geneva, Frankfort-on-Main, Wiesbaden, Solingen, Wuppertal, Hanover, Brunswick, Altona, Hamburg, Berlin, Magdeburg, Leipzig, Dresden, Munich, Prague, Pilsen, Vienna (birth rate, 7.6 ; death rate, 13.6), Budapest, Florence and Bologna. Their number increases from year to year.

It is also noteworthy that the towns attract more young women than young men. Many of these live as domestic servants under unfavourable conditions and often return to their homes in the country with their health permanently impaired. The importance of the health of this class of the population is evident ; they become subsequently the mothers of a large part of the next generation.

It is only natural that infant mortality, which is the most sensitive part of the mortality curve, should be affected by a movement of such profound social consequences. The early part of the affluence to the towns was, as might have been expected, a disaster as far as infant mortality was concerned.

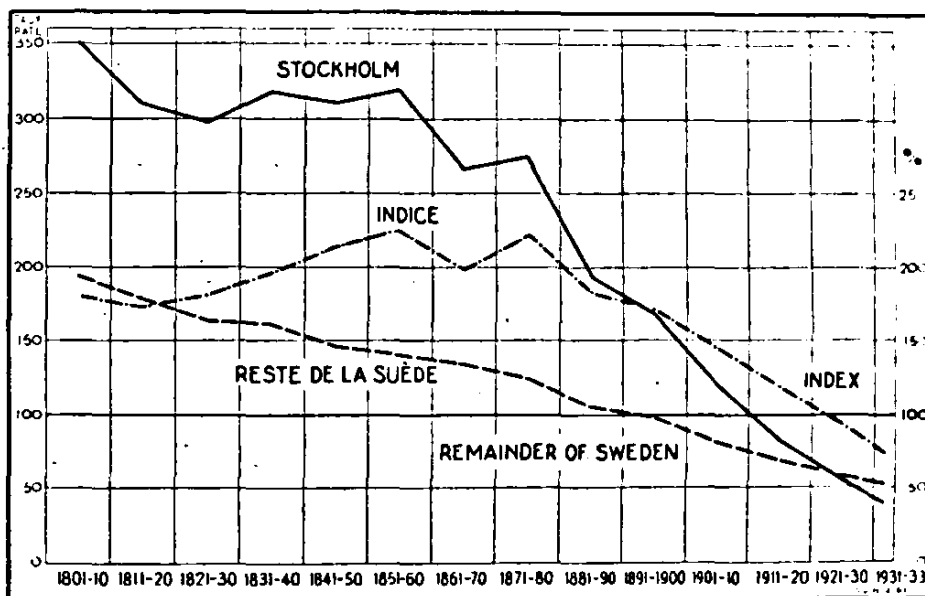
The vital statistics of Stockholm, which are available from 1720, furnish a good example of the destructive effect of urban development in a time when the nature of infectious disease was unknown and adequate sanitary measures inexistent. The population of Stockholm grew from 45,000 in 1720 to 110,000 in 1860. During this period, the birth rate varied between 32 and 41 per 1,000, the general death rate between 38 and 61. From 1726 to 1860, every quinquennium showed, in spite of the high birth rate, a natural decrease of the population which, in 1806-1810 reached 28 per 1,000 inhabitants. Only after 1860 was a precarious natural increase of the population maintained.

Information concerning the infant mortality is available from 1801. The rate was as high as 351 per 1,000 live births during the first ten years of the nineteenth century and remained almost constantly above 300 during the following fifty years. While there was no improvement in Stockholm up to 1860, the infant mortality decreased steadily, at the same time, in the remainder of Sweden. We may add in this connection that Sweden has now enjoyed a

period of 120 years of unbroken peace, and even the first half of the nineteenth century was therefore a period of steady, economic progress. It is not surprising, therefore, that rural Sweden, in spite of the absence of adequate sanitation, should show a decreasing infant mortality with exceptionally low rates in comparison with those prevailing elsewhere at the time.

It is consequently suggestive of very powerful influences being at work that Stockholm, as far as infant mortality is concerned,

27. INFANT MORTALITY PER 1,000 LIVE BIRTHS AT STOCKHOLM AND IN THE REMAINDER OF SWEDEN, 1801-1933, AND INDEX FOR STOCKHOLM, TAKING THE RATE OF THE REMAINDER OF SWEDEN FOR EACH DECENNIAL PERIOD AS 100.



did not benefit in the least by these favourable circumstances. The excess of infant mortality at Stockholm over that of the remainder of Sweden increased, on the contrary, from 74 per cent in 1801-1810 to 126 per cent in 1851-1860, and was still 122 per cent in 1871-1880. This increasing excess of the Stockholm mortality gives striking evidence of the destructive effect of the urban "malaxator" in those early days of its activity. The population of Stockholm increased from 98,000 in 1855 to 216,000 in 1885, absorbing during these thirty years a number of country people about equal to its original population. The tremendous demographic impulse which an addition of such an amount of new and healthy blood should have given was thus entirely absorbed by the effort of existing at all under the new conditions of life (see Diagram 27).

An amelioration began to make itself felt after 1880, and gained momentum in the twentieth century. The excess of the Stockholm infant mortality was reduced to 46 per cent in 1901-1910, and further to 19 per cent in 1911-1920. During the following decennium, the infant mortality of Stockholm was 7 per cent *lower* than that of the remainder of Sweden. This favourable position of the capital was further improved, so that the rate reached a level of 26 per cent below that of the rest of the country during the three years 1931-1933. The urban "malaxator", provided with adequate safeguards, had finally been brought to work smoothly and without unnecessary waste.

A similar evolution is going on in most other large towns, some of which have got as far as Stockholm, while others are still in earlier stages of their development.

Space does not allow of dealing with the historical development of infant mortality in the various towns separately. Some towns had a lower infant mortality than Stockholm in the early part of the nineteenth century; but others, and they are more numerous, had a still higher rate. Berlin had, for example, an infant mortality rate of 379 per 1,000 live births as late as 1871-1875, a rate which is greatly in excess of those now prevailing in the primitive towns of the Nile Valley or in the large towns of India.

Paris figures cannot be used for early years because of the prevailing custom of sending the tiny babies away to the country for nursing. The influence of this practice is so great that BERTILLON has not wished to publish these rates at all. It seems that conditions were less bad than in Berlin, but the extension which this very custom had taken proves how generally it was realised in all social classes that urban life was not fit for the infant.

The English statistics of the nineteenth century do not contain a clear division between urban and rural areas. They gave, however, a comparison between selected counties which were chiefly urban and others which were chiefly rural. The infant mortality of the urban counties was, during the last thirty years of the nineteenth century, constantly from 27 to 32 per cent higher than the rate of the rural counties. It is probable, however, that the real urban excess was greater than indicated by these figures, which each cover both urban and rural areas.

England shows even to-day an excess of infant mortality in towns. The rates for 1931 were 77.0 for county boroughs, 64.8 for other urban areas, and 57.8 for rural districts. The infant mortality rate of Greater London for the same year was 59.0 as against 45.5 for the remainder of the south-eastern division.

The infant mortality is now lower in towns than in rural districts in most of Central Europe. This is particularly marked in the Netherlands, Belgium, Bavaria and Switzerland. In Prussia, there is little difference between urban and rural rates. The same is now the case in Italy and Spain. In the Netherlands, where urban and rural rates were equal during the period 1895-1904, the rural infant mortality has shown an excess of about one-third over the urban rates during the last ten years. The rates decrease regularly with the size of the towns, which is exactly the opposite of what occurred in the nineteenth century. The rates for 1933 were : 32 in towns of over 100,000 inhabitants ; 42 in towns between 50,000 and 100,000 ; 44 in towns between 20,000 and 50,000 ; 48 in communes of less than 20,000 inhabitants.

A similar evolution has occurred in the United States of America. In 1917, the infant mortality was 99.4 in the towns of the birth registration area as against 87.8 in the rural districts. In 1930, this relation was reversed, the urban rate being 61.9 as compared with a rural rate of 64.7. A rural excess was noted for the first time in 1929. The infant mortality of the coloured population is, however, still in excess in the towns (urban, 111 ; rural, 98, in 1930).

The abolition of the urban excess mortality now accomplished or in progress in most countries means the final repeal of FARR's terrible law. The reader will recall that FARR found on the basis of English statistics that the mortality was a function of the density of the population. His formula of 1843 showed the mortality to vary with the sixth root of the density. In the 'sixties he found that the relation was expressed approximately by the eighth root of the density. It has now been abundantly proved that mortality need not increase at all with the density of the population, so long as other influences are not active at the same time. This is notably true as far as infant mortality is concerned, and it may be said that, in most advanced countries, the infants have now little to suffer from the struggle for adaptation to an urban mode of life.

I am inclined to believe that this effective control of the urban "malaxator", although much less spectacular than the invention of the automobile, the aeroplane, the cinema and wireless broadcasting, is the greatest and most lasting achievement of the first third of the twentieth century. It is true that modesty is the mother of all virtues, but sanitarians should remember that one may abuse a good thing. Too little has certainly been said of this great change in the life and welfare of mankind.

2. URBAN INFANT MORTALITY IN 1933.

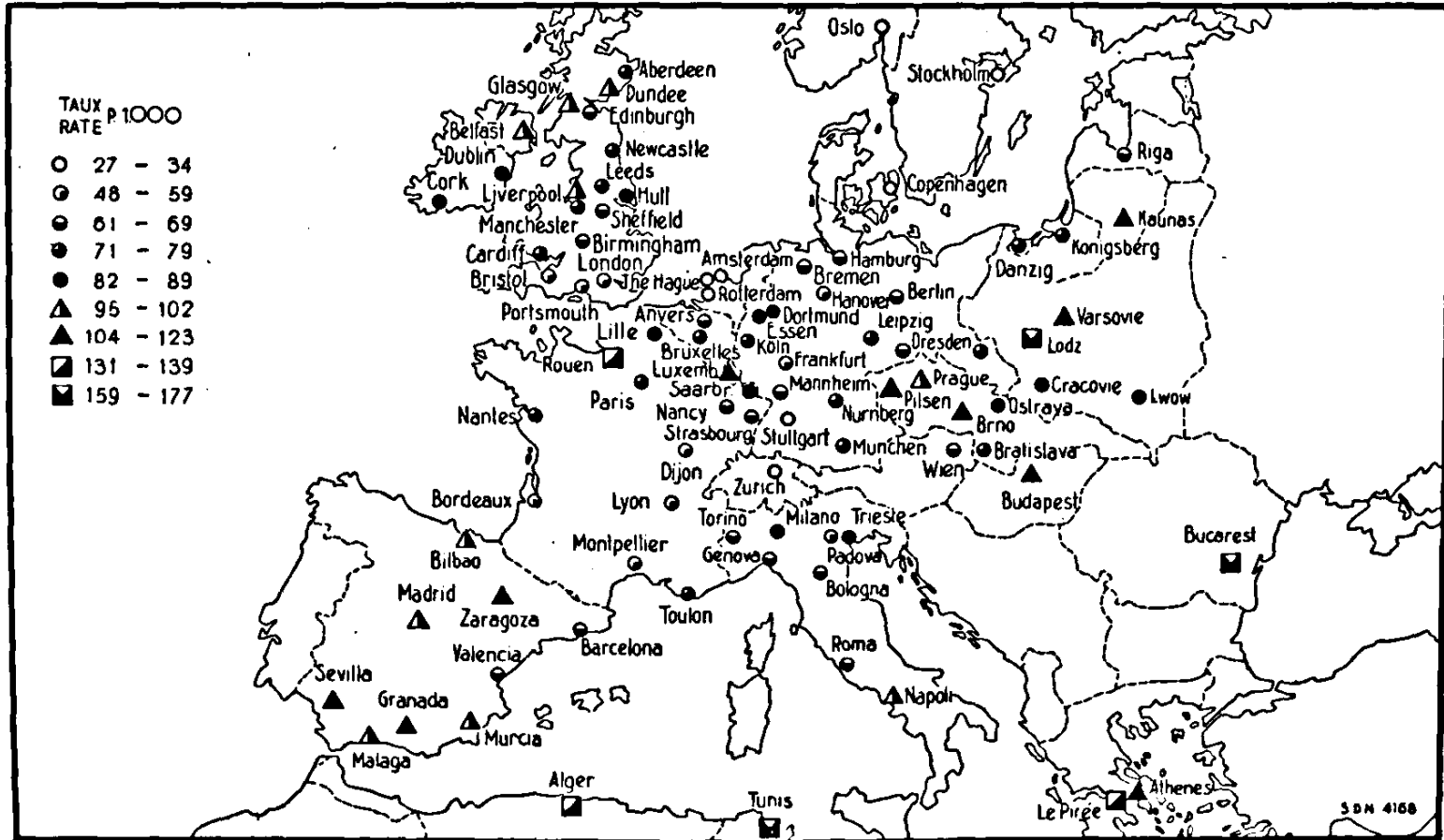
The exceptionally low infant mortality now prevailing in a great many towns can be in large measure attributed to infant welfare work, general sanitation, nursing improvements, amelioration of social conditions and such-like activities, which oftentimes are due to the initiative of more or less autonomous local governments. It is not surprising, therefore, that a map of the infant mortality in towns should differ considerably from those shown earlier in this report for countries as a whole.

Map 28 brings out the fact that over one-half of the large European towns had an infant mortality below 80 in 1933. It is natural that most of the towns so favoured should be situated in countries having an equally low infant death rate. These countries are those of the two lowest groups on Map 12. It is much to the credit of several towns in Southern Europe, however, to have attained equally low infant mortality rates : Pisa, 42 ; Padua, 48 ; Bologna, 61 ; Turin, 64 ; Rome and Genoa, 69 ; Barcelona, 63 ; Valencia, 64. The achievements of these towns prove that a Mediterranean climate is not incompatible with a low infant mortality.

Infant mortality rates much below the average for the country in which they are situated are also found at Vienna (61), Riga (64), Cracow (83), Lwow (88) and Bratislava (79). It seems that the large Eastern and Southern European towns have, on the whole, lower rates than the surrounding country.

Irish and Scotch towns (apart from Edinburgh) have, on the other hand, a high infant mortality. Belfast, for example, had a rate of 102, which is about equal to that of the Castilian and Andalusian towns. Still worse anomalies occur : Rouen has thus

28. INFANT MORTALITY PER 1,000 LIVE BIRTHS IN LARGE EUROPEAN TOWNS IN 1933.



nearly the same infant death rate (136) as Algiers (139). Very low rates obtained, on the contrary, in several towns of Southern France, such as Montpellier (52), Bordeaux (58) and Lyons (59).

The lowest infant mortality rate in any large town throughout the world was registered at Oslo, where, in 1933, only 27 infants died out of every 1,000 live births. This exceedingly low rate is closely followed by those of Amsterdam (31), Rotterdam (32), The Hague (33), Stockholm (34) and Zurich (34).

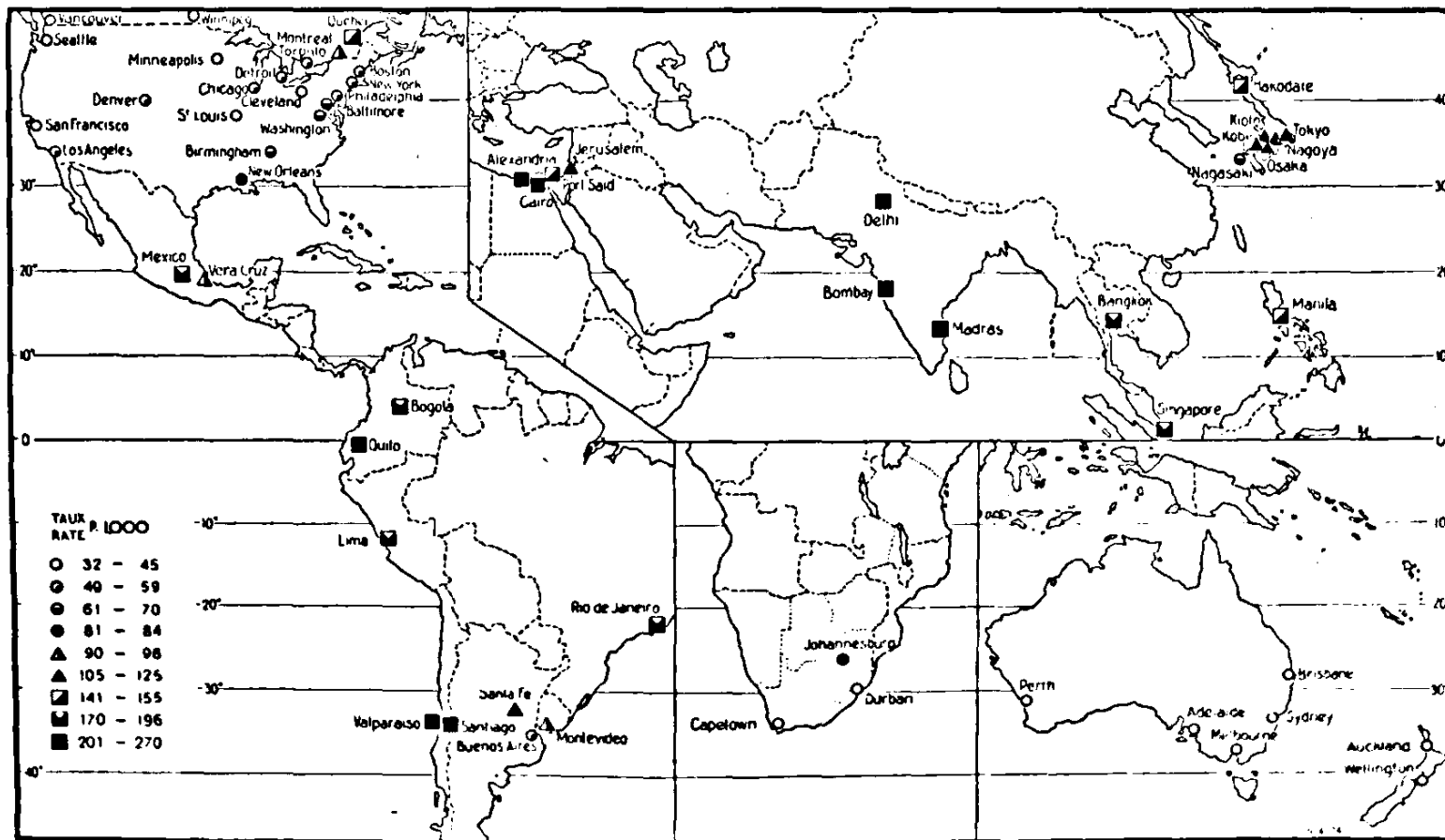
As far as other parts of the world are concerned (see Map 29), it is naturally the New Zealand and Australian towns which have the lowest infant mortality, ranging from 32 in Adelaide to 43 in Brisbane. Equally low rates are recorded at Vancouver (33) and at Seattle (34). Other towns of the United States of America show mostly rates varying between 40 (San Francisco) and 61 (Baltimore). Noteworthy exceptions are Washington (D.C.) and Buffalo (69), Birmingham (Ala.) (70) and New Orleans (84). The negro element contributes to the higher rates in the southern towns. Canadian towns have also low infant mortality rates, except Ottawa (81), Montreal (96) and Quebec (141). The infant mortality is equally low at Capetown and Durban (40 and 45 respectively). Elsewhere in the world, very few large towns have a low infant death rate. We note, however, Buenos Aires (52) as an important exception.

An intermediate infant death rate between 60 and 90, to which category the majority of European towns belong, is hardly ever met with outside of Europe. Either the rates are very low, as in the countries mentioned above, or they are much higher than those usually prevailing in European towns. Nearest to an intermediate position, although somewhat higher, comes Montevideo (98), Jerusalem (108) and the Japanese towns, where the rates mostly vary between 105 and 125. It is noteworthy that the highest infant mortality rate in a large Japanese town should be recorded at Hakodate (155) in the north. A cold climate seems here to have the opposite effect to that observed in Europe.

The infant mortality of the large Latin-American towns is relatively high, apart from Buenos Aires, Montevideo, Santa Fé and Vera Cruz.

In the Near East, the rates for Cairo and Alexandria are higher than those for Suez and Port Said, which are, again, higher than that of Jerusalem. The rate of Port Said is intermediate between

29. INFANT MORTALITY PER 1,000 LIVE BIRTHS IN LARGE TOWNS OUTSIDE EUROPE IN 1933.



INFANT MORTALITY

those of Tunis and Algiers, while that of Jerusalem is equal to the average Castilian and Andalusian rates.

In tropical Asia we find a considerably higher infant mortality in Indian towns than in Singapore and Bangkok. The rate for Delhi was 201 in 1932, which is lower than that of the great ports. It is highly creditable to the health service of the municipality of Singapore that, in a hot and moist climate, and with an immigrated oriental population, an infant death rate (176) should have been obtained, which is approximately equal to that of Rio de Janeiro or Bucharest.

No reliable infant mortality rates can be computed for Chinese towns, owing to a deficient birth registration. At Hong-Kong and Shanghai, more than one-third of all deaths are infant deaths, and there is consequently no doubt that the infant mortality must be very high.

The two maps of infant mortality in towns show conclusively the enormous progress made in urban sanitation. Even large tropical towns no longer suffer such a terrific loss of infant life as did European towns fifty years ago. Modern sanitation has largely concentrated its efforts upon the towns, but the improvement gradually radiates from these to the surrounding country. The remarkable achievements attained in many large towns are therefore indicative of conditions which may soon obtain in the whole country in which they are situated.

3. THE AGE FACTOR IN URBAN AND RURAL INFANT MORTALITY.

How do urban and rural surroundings affect infants in the various stages of their life? In order to answer this question, it is necessary to examine the distribution of mortality in typical countries.

It has been shown in the previous parts of this chapter that the urban infant mortality in England and Wales is consistently higher than the rural rates. The following table shows the distribution of this excess by age.

*Mortality in Infancy and Early Childhood
in Urban and Rural Districts of England and Wales, 1931.*

| Age | County boroughs ¹ | Other urban districts | Rural districts | Percentage excess of county boroughs over rural districts |
|-----------------------|------------------------------|-----------------------|-----------------|---|
| Under 1 week . . . | 23.3 | 22.9 | 22.9 | 1.7 |
| 1- 4 weeks | 10.4 | 10.1 | 9.2 | 13.0 |
| 1- 3 months | 12.7 | 10.4 | 8.8 | 44.3 |
| 3- 6 months | 11.7 | 8.0 | 6.3 | 85.7 |
| 6- 9 months | 9.9 | 7.0 | 5.7 | 73.7 |
| 9-12 months | 9.0 | 6.4 | 4.8 | 87.5 |
| 1- 2 years | 21.4 | 14.9 | 11.3 | 89.4 |
| 2- 5 years | 6.1 | 5.1 | 3.7 | 65.0 |

This table shows that urban and rural English babies are born equal, at any rate so far as their immediate risk of death is concerned, but that the equality is of short duration. As a matter of fact, there is no significant difference between urban and rural mortality during the first week of life, from which we may conclude that the vitality of the new-born city infants is not inferior to that of the country infants. The couple of generations which may separate the women of the towns from the green fields of their ancestors have not sufficed to impair their life-giving capacity.

During the following three weeks, a small excess of mortality appears in the county boroughs as compared with the rural districts. The position of the other urban districts, which chiefly consist of smaller towns and suburban localities, is intermediate between the two and remains so throughout infancy and early childhood. The excess of the county boroughs increases to 44 per cent during the second and third months and, further, to 86 per cent from the fourth to the sixth month of life. It remains practically at this level throughout the second half-year and the whole of the second year of life, after which it diminishes somewhat.

English statistics are not available further back than 1911 for the same classification of urban and rural districts. The incidence of infant deaths was, however, still sufficiently high during the decennium 1911-1920 to show a marked contrast with the conditions now prevailing. The reduction of the infant mortality from 1911-1920 to 1931 was about the same in town and country : 32 per cent for

¹ Excluding Greater London.

county boroughs, 33 per cent for other urban districts, and 31 per cent for rural districts. Analysed by age, certain differences nevertheless appear which are shown in the table below.

*Mortality in Infancy and Early Childhood
in Urban and Rural Districts of England and Wales, 1911-1920.*

| Age | County boroughs ¹ | Other urban districts | Rural districts | Percentage excess of county boroughs over rural districts |
|----------------------|------------------------------|-----------------------|-----------------|---|
| Under 1 week . . . | 24.8 | 23.7 | 24.2 | 2.5 |
| 1- 4 weeks | 15.8 | 14.2 | 12.9 | 22.5 |
| 1- 3 months . . . | 21.1 | 17.8 | 14.8 | 42.6 |
| 3- 6 months . . . | 20.1 | 16.3 | 12.7 | 58.3 |
| 6- 9 months . . . | 16.8 | 13.3 | 10.3 | 63.1 |
| 9-12 months . . . | 15.0 | 11.9 | 8.7 | 72.4 |
| 1- 2 years | 41.5 | 29.8 | 20.4 | 103.4 |
| 2- 5 years | 12.5 | 9.2 | 6.3 | 98.4 |

A comparison with the first table shows a very marked reduction of infant and early childhood mortality since 1911-920, except for the first week of life, both in urban and rural districts. Then, as now, the neo natal mortality was the same in towns as in the country. In 1911-1920, the urban excess of mortality rose gradually from birth up to the second year of life, when it was highest. From the fourth to the twelfth month, the relative decrease of mortality has been greater in the rural districts than in the towns. The table below shows the decrease in each age-group in the various areas.

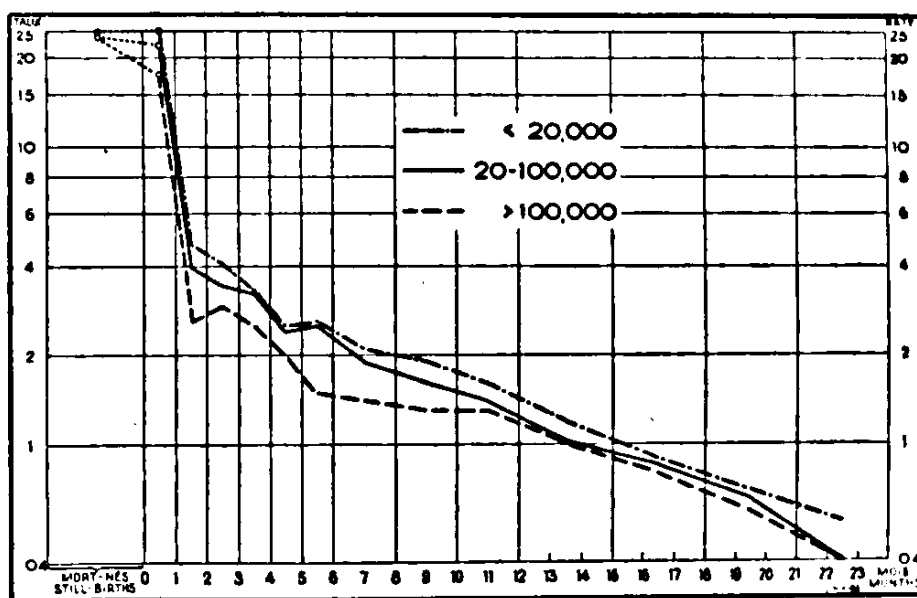
*Mortality in Infancy and Childhood in Urban and Rural
Districts of England and Wales in 1931 in Percentage
of the Corresponding Rates for 1911-1920.*

| Age | County boroughs ¹ | Other urban districts | Rural districts |
|------------------------|------------------------------|-----------------------|-----------------|
| Under 1 week | 94 | 97 | 95 |
| 1- 4 weeks | 66 | 71 | 71 |
| 1- 3 months | 60 | 58 | 59 |
| 3- 6 months | 58 | 49 | 50 |
| 6- 9 months | 59 | 53 | 55 |
| 9-12 months | 60 | 54 | 55 |
| 1- 2 years | 52 | 50 | 55 |
| 2- 5 years | 49 | 55 | 59 |

¹ Excluding Greater London.

Crossing the Channel to the Netherlands, we find a very different distribution of mortality between town and country. Dutch statistics are published in five groups according to size of communes. In the table on page 598, towns from 20,000 to 50,000 have been combined with those of 50,000 to 100,000, as there is little difference

30. STILL-BIRTH RATE AND SPECIFIC DEATH RATE FOR EACH MONTH DURING THE FIRST TWO YEARS OF LIFE, ACCORDING TO SIZE OF COMMUNES, IN THE NETHERLANDS, 1930-1932 (LOGARITHMIC SCALE).



between the rates of the two groups. For the same reason, small towns under 20,000 have been combined with rural districts. The still-birth rates are based on total births, the mortality rates under 1 year on live births for the same year, and deaths during the second year of life upon live births during the previous year after deduction of infant deaths (see also Diagram 30, where monthly rates are shown).

*Specific Death Rates per 1,000 under 2 Years of Age,
according to Size of Communes, in the Netherlands, 1930-1932.*

| Age in completed months | 100,000 and over | 20,000 to 100,000 | Under 20,000 |
|---------------------------|---------------------|----------------------|-----------------|
| Still-births | 24.65 | 24.68 | 25.11 |
| Under 1 month | 17.72 | 22.05 | 25.23 |
| 1 month | 2.61 | 3.94 | 4.72 |
| 2 months | 2.91 | 3.37 | 4.11 |
| 3 months | 2.49 | 3.15 | 3.27 |
| 4 months | 2.02 | 2.42 | 2.53 |
| 5 months | 1.54 | 2.46 | 2.55 |
| 6-7 months | 2.87 | 3.77 | 4.19 |
| 8-9 months | 2.65 | 3.26 | 3.89 |
| 10-11 months | 2.55 | 2.86 | 3.23 |
| Under 1 year | 37.35 | 47.29 | 53.74 |
| 12-14 months | 3.08 | 3.28 | 3.70 |
| 15-17 months | 2.37 | 2.55 | 2.78 |
| 18-20 months | 1.89 | 1.98 | 2.11 |
| 21-23 months | 1.31 | 1.25 | 1.65 |
| 1-2 years | 8.64 | 9.05 | 10.23 |

It is seen that the still-birth rate is practically the same in large towns, small towns and rural districts. Unfortunately, deaths during the first week of life are not given separately. The rate for the first month of life, however, is 42 per cent higher in the communes under 20,000 inhabitants than in those over 100,000. This rural excess is maintained with little change during the first year of life. The percentage of rural excess (shown by larger age-groups in order to eliminate the effect of irregularities in the statement of age on the death certificate) is as follows : under 3 months, 47 ; 3-6 months, 38 ; 6-12 months, 40 ; 12-24 months, 18 per cent. The rates for the middle-sized towns are intermediate between these two groups throughout the first two years of life.

We are evidently here confronted with a distribution of infant mortality resulting from a most intensive public health work in its widest sense. Not only have the bad influences of urbanisation been vanquished, but the mortality at all periods of infant life has been driven far below the general level of the surrounding country. This astonishing result invites, nevertheless, the reflection that the rural infant death rates, if similar attention was given to the country districts, could undoubtedly be brought down to an equally low or even lower level. The rural infant death rate in the Netherlands

compares still very favourably with that of most other European countries, in many of which the countryside has been neglected in favour of the towns. This might have been justifiable in the days when the towns constituted the one great danger spot, but the time seems to have come to remedy this omission.

A comparison by age of English and Dutch urban and rural infant death rates brings out certain interesting facts. In the table below, the rates for county boroughs have been compared with Dutch towns of over 100,000 inhabitants, English rural rates with those for communes of under 20,000 inhabitants in the Netherlands. The classification is thus not exactly the same but sufficiently similar to warrant a comparison.

Urban and Rural Infant Mortality by Age in the Netherlands, 1930-1932, and in England and Wales, 1931.

| Age | Dutch towns over 100,000 | County boroughs | Percentage of excess | Dutch communes under 20,000 | English rural districts | Percentage of excess |
|------------------|--------------------------|-----------------|----------------------|-----------------------------|-------------------------|----------------------|
| Under 1 month . | 17.7 | 33.7 | 90 | 25.2 | 32.1 | 27 |
| 1- 3 months ... | 5.5 | 12.7 | 131 | 8.8 | 18.0 | 105 |
| 3- 6 months ... | 6.0 | 11.7 | 95 | 8.3 | 6.3 | — 24 |
| 6-12 months ... | 8.1 | 18.9 | 133 | 11.3 | 10.5 | — 7 |
| 1- 2 years | 8.6 | 21.4 | 149 | 10.2 | 11.3 | 11 |

The above table shows that the death rate during the first two years of life is consistently twice as high or higher in English county boroughs as in large Dutch towns. As far as rural districts are concerned, an equally large excess of the English rates is found only during the second and third months of life. The English rural death rates are lower, on the contrary, than the corresponding Dutch rates during the last nine months of infant life.

The very low urban death rate during the second and third months of life in comparison with the rural rate is not peculiar to the Netherlands. This feature is even more pronounced in Denmark. In the table on page 600, the rates for still-births and deaths during the first two years of life have been calculated for the capital (Copenhagen and Frederiksberg) and for the remainder of the country. It has been thought advisable to combine the provincial towns with the rural districts, because an abnormally high still-birth rate and infant death rate for the first month of life in the provincial towns gives reason to believe that some of the still-births and neo-natal deaths occurring in institutions located in these towns have not been

charged back to the district of residence of the mother as the regulations require. The rural character of the total is not materially changed, because no provincial town exceeds 86,000, and only nine towns have more than 20,000 inhabitants. The rates are calculated according to the same rules as those for the Netherlands.

Specific Death Rates per 1,000 under Two Years of Age in the Capital and in the Remainder of Denmark, 1931-1933.

| Age | The capital | Remainder of the country | Percentage of rural excess |
|---------------------|-------------|--------------------------|----------------------------|
| Still-births | 22.0 | 24.9 | 13.2 |
| Under 1 month | 25.5 | 29.5 | 15.7 |
| 2- 3 months | 7.1 | 15.1 | 112.7 |
| 4-12 months | 25.3 | 32.5 | 28.5 |
| Under 1 year | 57.8 | 77.0 | 33.2 |
| 1-2 years | 9.8 | 7.9 | — 19.4 |

Copenhagen is a town of 750,000 inhabitants. Conditions of life are therefore essentially different from those obtaining in the remainder of the country. Public health and social welfare work has undoubtedly been pursued more vigorously there than elsewhere in the provinces. It may be added that it is not customary in Denmark to send the babies to the countryside for nursing, and the rates may therefore be considered as exact. We may, therefore, rely on the above figures, which show that the rates of still-births and of deaths during the first month of life are only slightly (13 to 16 per cent) higher in the remainder of the country than in the capital. During the second and third months of life, however, less than half as many infants die in the capital for each 1,000 born as in the remainder of the country. This large rural excess of mortality gradually wears off during the rest of the first year of life. During the second year of life, the death rate of the capital becomes some 24 per cent higher than that of the remainder of the country.

A comparison of Danish and Dutch rates turns out in the favour of the Netherlands, and notably so in respect of those of rural districts during the second and third months of life. The death rate for the second year of life constitutes an exception, being lower in Danish than in Dutch rural districts.

It results from the preceding that the death rate during the second and third months of life is particularly sensitive. It seems to be at this point of infant life that the greatest achievements have been realised by the more active health services of the large towns.

It follows that the health services of rural districts, as well as of large towns which are still somewhat behind in this respect, would do well in directing their attention toward the problems connected with infant life during these critical months.

The United States of America affords an example of a country where an urban excess of infant mortality is just changing into a rural excess. The table below gives a comparison of the infant mortality by age for the years 1924 and 1930, which were both years of low mortality in comparison with the preceding period.

Urban and Rural Infant Mortality by Age per 1,000 Live Births in the United States Birth Registration Area in 1924 and 1930.

| Age in completed months | Towns | | | Rural districts | | | Urban excess | |
|-------------------------|-------|------|---------------------|-----------------|------|---------------------|--------------|--------|
| | 1924 | 1930 | Percentage decrease | 1924 | 1930 | Percentage decrease | 1924 | 1930 |
| Under 1 month | 39.2 | 35.4 | 9.7 | 38.1 | 35.4 | 7.1 | 2.9 | 0.0 |
| 1 month | 5.6 | 4.7 | 16.0 | 6.1 | 5.6 | 8.2 | - 8.2 | - 16.1 |
| 2 months | 4.3 | 3.8 | 11.6 | 4.5 | 4.4 | 2.2 | - 4.4 | - 13.6 |
| 3- 5 months | 9.8 | 8.0 | 18.4 | 9.1 | 8.9 | 2.2 | 7.7 | - 10.1 |
| 6- 8 months | 7.4 | 5.8 | 21.6 | 6.1 | 6.0 | 1.6 | 21.3 | - 3.3 |
| 9-11 months | 6.2 | 4.2 | 32.3 | 4.9 | 4.4 | 10.2 | 26.5 | - 4.5 |
| Under 1 year | 72.6 | 61.9 | 14.7 | 68.9 | 64.7 | 6.1 | 5.4 | - 4.3 |

It is seen that the infant mortality is decreasing both in towns and rural districts, but more rapidly in the former than in the latter. The decrease is greatest during the latter part of infant life. On the other hand, the infant mortality rate during the first month of life is the same in town and country. The rural rates had, in 1930, become higher than the urban rates throughout the remainder of the first year of life. This rural excess was greatest during the second and third months of life. It should be noted that the rural excess during these two months of life dates back even farther than to 1924. We thus find, also on the other side of the Atlantic, these two months to be of crucial importance in the lagging behind of the countryside in the general reduction of infant mortality.

V. OTHER DEMOGRAPHIC ELEMENTS.

1. THE "ILLEGITIMATE" INFANT.

Most important amongst the social factors in infant mortality ranks unquestionably the legitimacy of the infant. Under penalty

of paying a greatly increased fee of entry, the infant must present itself upon the threshold of life with two parents duly united in wedlock. This has been so ever since vital statistics have been kept, and was certainly so long before such records were thought of. When we propose, nevertheless, to examine afresh this question, it is because the excess of the illegitimate infant mortality varies widely from one country to another.

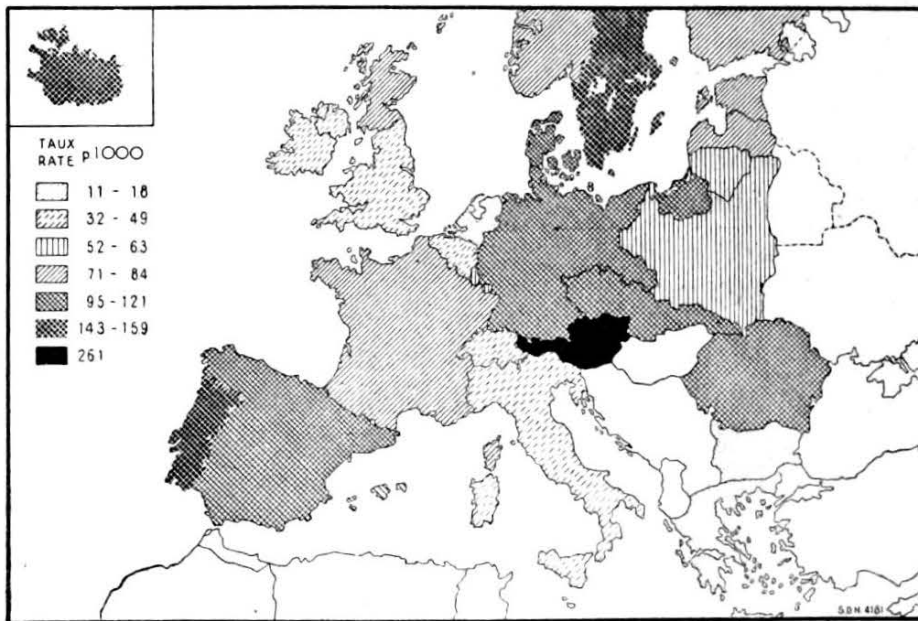
Apart from very special cases, the illegitimate infant will probably always be subject to a somewhat higher mortality than the legitimate infant, owing to the improvidence of its mother, which is frequently the very cause of its conception. Furthermore, and partly for the same reason, illegitimate births are most frequent in the layer of the population which has been unsuccessful in reaching a normal working-class standard of life. A considerable proportion of the illegitimate infants will therefore be exposed to unsatisfactory social and sanitary conditions typical of the most unfortunate class of society.

A reduction of the excess mortality of illegitimate infants depends, therefore, to a large extent upon the readiness of society to remedy this lack of foresight. The unmarried mothers possess neither wealth nor political influence; the fate of their infants is therefore more dependent upon a quality of which too little is said in our days—namely, the heart culture of the people—than upon the general state of its wealth and sanitation. It is worth adding, however, that the scarcity of births from which so many countries are now suffering should induce society to recuperate in its own interest the illegitimate infants to a far greater extent than has hitherto been the case. This recuperation has undoubtedly been taken in hand in several countries where a reduction of the excess mortality of illegitimate infants is now in evidence.

The practical importance of the illegitimate excess mortality varies, naturally, with the frequency of illegitimate births. It is thus relatively unimportant in the Netherlands, where less than 2 per cent of the live births are illegitimate, but extremely important in Austria and in Saxony, where the corresponding proportion amounts to 26 and 21 per cent respectively.

The frequency of illegitimate births in relation to all live births in European countries is shown on Map 31. Conclusions from this map as to morality should be strictly avoided, because the legislation concerning illegitimate children, and notably their legitimising, varies greatly from country to country. The Nordic and Germanic countries show, on the whole, a high frequency of illegitimate births; while they are fairly rare in Great Britain and Ireland, the Netherlands,

31. NUMBER OF ILLEGITIMATE BIRTHS PER 1,000 LIVE BIRTHS IN EUROPEAN COUNTRIES IN 1929.



Belgium, Switzerland, Italy and the Balkans. The general impression is that psychological factors outweigh racial and social influences in determining the incidence of illegitimacy. The influence of religion is much less in evidence than has generally been believed. Catholic Austria heads the list with the highest illegitimacy rate, followed by Protestant Sweden; while the Netherlands, in majority Protestant, ranks last on the list, just after Catholic Belgium.

The frequency of illegitimate births is low in the United States of America, Canada, Australia, New Zealand and South Africa.

It is very low in Mohammedan countries (including Java), where the institution of marriage, however, differs somewhat from that of Christian countries. It is fairly low (6.7) also in Japan. Extremely high rates predominate, on the contrary, in Latin America and the West Indies.

Very marked racial differences exist in the United States. The proportion of illegitimate live births in the birth registration area was 1.8 per cent for the white as compared with 13.8 per cent for the coloured population.

No well-established relation can be demonstrated between the frequency of illegitimacy and the excess mortality of illegitimate infants. It is true that some countries having a high proportion of illegitimate children, such as Austria, Sweden and Portugal, have a low excess of illegitimate infant mortality; while this excess is high in Ireland and Switzerland, where the incidence of illegitimate births is low. It may be that the social opprobrium resting upon the unmarried mother weighs heavier in the latter countries than in the former, which would account for the low rate of illegitimacy, but, in its turn, react unfavourably upon the fate of the infant. This explanation does not hold good for Italy and Bulgaria, however, where the excess mortality of illegitimate infants is relatively low in spite of the low frequency of illegitimacy. It seems clear, therefore, that there are ways to protect the illegitimate infant without, at the same time, encouraging illegitimacy.

The distribution of the excess mortality of illegitimate infants is shown on Map 32. It is seen that the position of the illegitimate infant is most unfavourable in the Irish Free State, where its mortality is, year after year, about five times as high as that of the legitimate infant.

Only one country in the world can so far boast of having altogether abolished the excess mortality of illegitimate infants. That country is Iceland. Nowhere in Europe is the general infant mortality lower than in Iceland, and this low rate is obtaining for illegitimate as well as for legitimate infants. In 1921-1925, the illegitimate excess mortality was still 24.4 per cent; in 1928-29, the illegitimate infant death rate had become 2.5 per cent lower than the legitimate rate. In other countries, the excess ranges from 25 per cent (in Sweden) to 109 per cent (in Northern Ireland). The percentage for Switzerland is more than twice as high as that of the surrounding

countries—Italy, Austria and Bavaria. It seems that the excess is generally lowest in Southern Europe and highest in Western Europe. The whole of North Central Europe forms a block showing an excess of average height.

A study of the distribution of the excess of illegitimate infant mortality in Germany is of considerable interest (see Map 33). The lowest percentage is recorded in Catholic Bavaria (37), which compares very favourably with the percentages for Protestant Wurttemberg (64) and Prussia (71). An area extending from Schleswig-Holstein in the north to Hesse-Nassau in the south shows particularly high percentages (from 82 to 106). This area extends across the frontier to the Saar Territory, Luxemburg and, somewhat attenuated, to the Netherlands and France. Brandenburg, with Berlin, has also a high excess, while the situation of the Baltic littoral is more favourable.

The illegitimate infant death rate is known for only a few countries outside of Europe. Its excess over the legitimate infant death rate was 48.7 per cent in Japan in 1929. The corresponding percentages for Australia and New Zealand in 1932 were 45 and 40 respectively. These three countries thus compare favourably with most European countries.

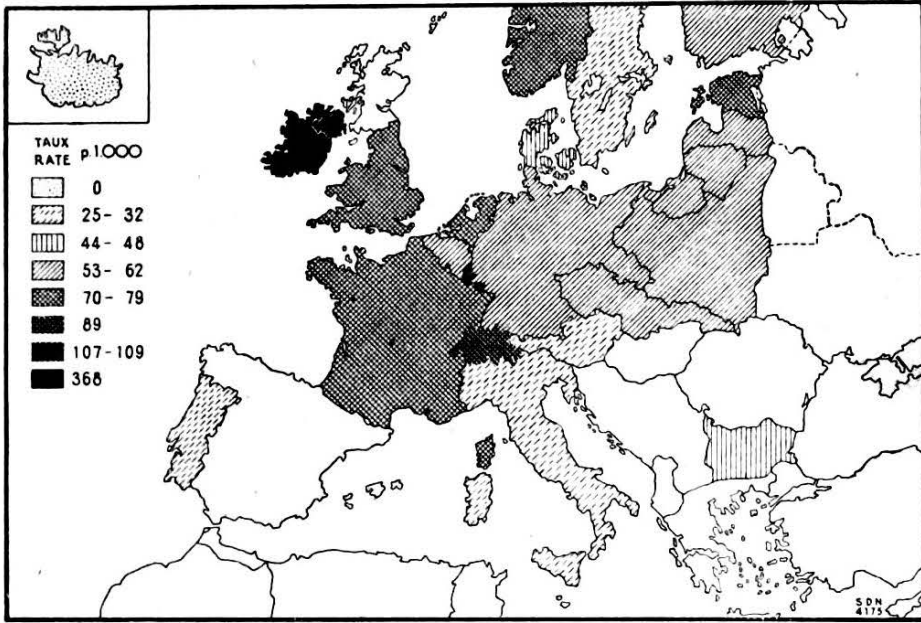
A diminution of the excess of the illegitimate infant mortality has taken place in certain countries, but not in all. The amelioration has been only slight in some. The excess was greater in 1929 in Switzerland (89 per cent) and in the Netherlands (70 per cent) than in 1896-1905 (67 and 62 per cent respectively). In France, the percentage of excess has remained practically unchanged since the end of the nineteenth century, and the diminution has been inconsiderable in Germany (70 per cent in 1901-1905, 61 per cent in 1928-1930).

There has been a very marked improvement, on the other hand, in Denmark and in Sweden. In Denmark, the excess was high (as it still is in the neighbouring Schleswig-Holstein and North-West Germany) up to the time of the war. In 1895-1905, it was 105 per cent. It had diminished to 40 per cent in 1932.

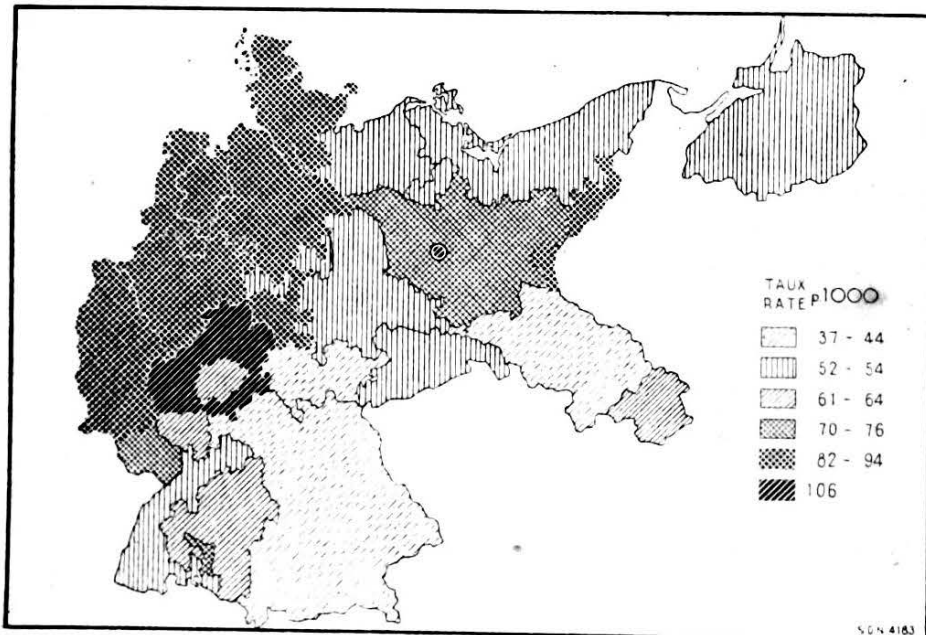
In Sweden, the excess of the illegitimate infant mortality exceeded 100 per cent during the first twenty years of the nineteenth century. During the remainder of the nineteenth and the first decennium of the twentieth century, it was about 70 per cent. Since then,

INFANT MORTALITY

32. PERCENTAGE OF EXCESS OF THE ILLEGITIMATE OVER THE LEGITIMATE INFANT MORTALITY IN EUROPEAN COUNTRIES IN 1929.

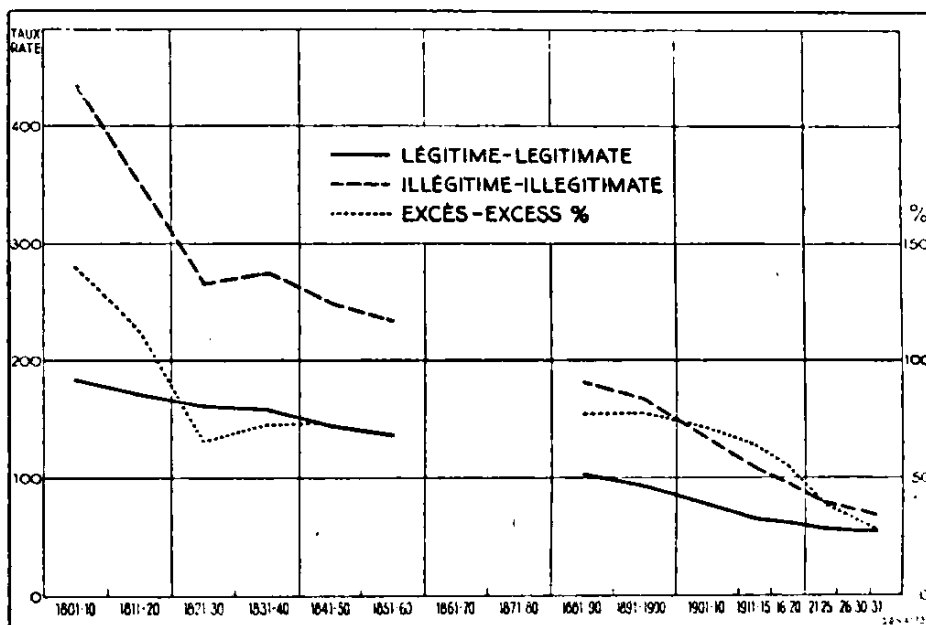


33. PERCENTAGE OF EXCESS OF THE ILLEGITIMATE OVER THE LEGITIMATE INFANT MORTALITY IN GERMAN STATES AND PRUSSIAN PROVINCES, 1928-1930.



it has diminished regularly and was only 26 per cent in 1931 (see Diagram 34).

34. ILLEGITIMATE AND LEGITIMATE INFANT MORTALITY, AND PERCENTAGE EXCESS OF THE FORMER OVER THE LATTER IN SWEDEN, 1801-1931.



Note. No information is available for the period 1861-1880.

The excess of mortality of illegitimate infants is generally greatest during the early part of infancy. This is well brought out by the table on page 608.

This table shows that the excess mortality of illegitimate infants was greatest during the first twenty-four hours of life and fell markedly after the end of the third month. The differences between the excess of male and female infants are hardly significant.

INFANT MORTALITY

*Mortality of Legitimate and Illegitimate Infants by Sex
and Age in Denmark, 1926-1930.*
(Rates per 1,000 live births.)

| Age | Legitimate | | Illegitimate | | Percentage excess of illegitimate mortality | |
|----------------------------|------------|--------|--------------|--------|---|--------|
| | Male | Female | Male | Female | Male | Female |
| Under 24 hours | 11.6 | 8.9 | 25.2 | 19.5 | 117 | 119 |
| 24 hours-1 month | 21.8 | 17.2 | 33.5 | 25.7 | 54 | 49 |
| 1- 2 months | 8.7 | 6.7 | 12.9 | 9.6 | 48 | 43 |
| 2- 3 months | 8.2 | 6.4 | 12.4 | 9.0 | 51 | 41 |
| 3- 6 months | 17.7 | 12.8 | 22.0 | 16.8 | 24 | 31 |
| 6- 9 months | 12.2 | 10.2 | 12.4 | 11.7 | 2 | 15 |
| 9-12 months | 7.5 | 6.5 | 7.8 | 8.5 | 4 | 31 |
| Under 1 year | 87.7 | 68.7 | 126.2 | 100.8 | 44 | 47 |

Somewhat similar results are obtained from English statistics :

*Mortality of Legitimate and Illegitimate Infants by Age
in England and Wales, 1931.*
(Rates per 1,000 live births.)

| Age | Legitimate | Illegitimate | Percentage excess of illegitimate mortality |
|----------------------------|------------|--------------|---|
| Less than 1 day | 9.8 | 23.5 | 140 |
| 1 day-4 weeks | 20.7 | 31.3 | 51 |
| 4 weeks-3 months | 10.4 | 19.9 | 91 |
| 3- 6 months | 9.0 | 16.7 | 86 |
| 6- 9 months | 7.6 | 10.7 | 41 |
| 9-12 months | 6.7 | 8.7 | 30 |
| Under 1 year | 64.3 | 110.7 | 72 |

In England, as in Denmark, it is during the first day of life that the illegitimate infant is most seriously handicapped. Its excess mortality falls there, as it does in Denmark, to some 50 per cent during the remainder of the first month of life. In England, however, the percentage of excess rises again during the critical second and third months of life, after the end of which it gradually decreases as the infant grows. It is only 30 per cent during the last three months of infancy, an excess which may partly be attributed to ordinary social influences inherent to the least fortunate part of the population where illegitimate births are most frequent.

The foregoing tables seem to be fairly typical for the distribution of the illegitimate surplus mortality by age of the infant. The table below shows similar features for five typical European countries, although the information available is less detailed. The first three months of life are evidently everywhere very critical for the illegitimate infant. France and Switzerland show a particularly heavy surplus mortality for illegitimate infants during the second and third months of life.

Percentage Excess of Illegitimate over Legitimate Infant Mortality by Age in Typical European Countries in 1929.

| Country | Under 1 month | 1-3 months | 3-12 months |
|---------------------|---------------|------------|-------------|
| France (1928) | 65 | 141 | 66 |
| Switzerland | 108 | 154 | 25 |
| Italy | 62 | 66 | 2 |
| Bavaria | 47 | 61 | 23 |
| Prussia | 84 | 96 | 42 |

The surplus mortality of the illegitimate infants is to a very high extent due to lack of care and even to violence of some form or another. Where the lack of will to keep the child alive, not to speak of the will to suppress it, is so clearly involved, it is natural that the still-birth rate should also be higher for illegitimate than for legitimate infants. It is the more necessary to consider the still-birth rate in this connection, since several countries, such as France, Belgium and Spain, register as still-births a certain number of infants who die during the first days of life. It should be kept in mind that the differences in the definition of still-births in regard to their lower limit (length of gestation) may, to some extent, impair the value of the comparison. The range of the surplus percentages is, nevertheless, sufficiently great to warrant conclusions.

In Europe, we find a well-defined group of countries with a quite low excess of the illegitimate over the legitimate still-birth rate ranging from 20 to 30 per cent—Sweden, Norway, Denmark, the Netherlands, Bavaria, Austria and Italy. Slightly higher percentages (36 to 37 per cent) are met with in England and Hungary. An intermediate position (51 to 55 per cent) is occupied by Prussia, France, Belgium and Portugal. The percentage of surplus is 67 in Czechoslovakia. A high excess is met with (76 to 78 per cent) in Switzerland, Spain and Roumania. The registration of still-

births in various other countries is not sufficiently complete to warrant conclusions.

It may be added that a surplus percentage of 66 is obtaining in Canada. The excess of the frequency of illegitimate still-births is particularly high in Japan, where it exceeds that of legitimate still-births by 210 per cent.

Great care must always be taken to avoid foreign influences in a detailed comparison of the mortality of legitimate and illegitimate infants, and particularly so as far as the causes of death are concerned. Illegitimate births are usually more frequent in towns than in rural districts, more common in the poorest classes of society than among people of higher social levels. It is inevitable, therefore, that the constitution of the illegitimate infant death rate by age, cause, etc., should be influenced by the distribution of mortality peculiar to these environments. It should also be remembered that the majority of the illegitimate infants are the first-born progeny, and partake of the peculiar mortality conditions of such infants. This warning is the more necessary as the mortality of the illegitimate infant, in spite of the improvement noted in recent years in certain countries, or rather because these countries are still relatively rare, constitutes a very necessary field for future research and action.

2. GENERAL REMARKS.

Modern society is a cauldron in ebullition. All its elements are in rapid movement and overlapping each other. Co-ordinates hitherto considered stable points of departure are themselves undergoing changes. All measures become problems of relativity, questions of relation between several factors, all of which are moving with different velocities. The town penetrates the countryside by means of the extraordinary development of communications. Rural life, in its turn, penetrates the town in the form of garden cities. Social classes change their relative position. Fertility changes, and so does the age constitution of the population. The epidemic background is completely modified. In short, the old stratified sedimentary rocks of human existence are being folded as were the mountains in early geological ages.

It is not surprising that the demographer has some difficulty in finding a firm foothold where no stability exists. It is true that statistical methods have been improved, but imperfections of the data frequently render useless the employment of such analysis. A comprehensive knowledge of the general movements going on, combined with an intuitive sense of figures, is therefore indispensable.

The preceding chapters do not pretend to be an exhaustive analysis of infant mortality. It has been the sole intention of the author to give an image of its *demographic* setting, and to show that this setting is not one of stones fixed in hard metal, but a play of moving lights and shadows reflecting multiple and often unknown forces. This tentative may be taken as a modest fragment of what Auguste Comte very fittingly termed social dynamics.

The medical causes of infant mortality have been left strictly alone, even where it might have been easy to give some indications in this respect. It is not worth while and is inducive of serious errors to touch on this subject without pushing the analysis to its end. This is also why the change of the seasonal curve of infant mortality in countries where infant life is well protected has not been dealt with. The cause of this change is purely medical and due to the amputation of the summer peak of intestinal diseases, while the winter mortality of respiratory diseases, having proved more resistant, stands out as a new peak.

Social influences have necessarily been touched upon in several places because they constantly overlap with demographic factors. It has been thought preferable, however, in this report not to deal with the strictly social elements influencing infant mortality. It is obvious that poverty and wealth constitute backgrounds for the welfare of the infant as different as night and day; but the distribution of wealth is now undergoing such rapid changes that a superficial analysis will prove of little avail. Moreover, modern infant welfare work and sanitary improvement in general have introduced a new element working against the effect that poverty would otherwise have had. We are thus here again confronted with an interplay of multiple forces reaching beyond the scope of this enquiry.

The outstanding fact brought out by this bird's-eye survey is that the gateway to life has been rendered less perilous, that the world has been rendered less hostile to young human life. This has been brought about without impairing any selective effect

which infant mortality may possess. It is also clear that this amelioration is still in progress, is even being accelerated. Where we thought ten years ago to have exhausted all possibilities of improvement, we have seen, on the contrary, the fall of the infant death rate become more rapid.

We cannot sufficiently emphasise the lesson of encouragement contained in these undeniable facts at a time when discouragement and uncertainty as to the future prevail. Here is an achievement of everlasting importance to all humanity, poor and rich alike, largely brought about by a class of workers who never appeal to passion, but who patiently pursue the sole aim of making the world safe for humanity.

It is true that part of the amelioration—it is hardly possible to say how much—is due to other than sanitary influences. How still more rejoicing! It must then be that the crisis through which we are passing, far from being an agony, is one of adaptation, the first favourable effects of which can already be discerned.

Generation follows generation and they do not resemble each other, either by their mode of life or by their mentality. They form, nevertheless, an unbroken chain the ends of which are lost from view in the dark past and in the unknown future. It is the task of the demographer to test the links of this chain and discern its trend. Demography is, however, a relatively new science—being only an infant in comparison with physics and astronomy—and we cannot yet reasonably demand of it the solution of all riddles of the struggle for life.

**A FIFTH ANALYTICAL REVIEW
OF REPORTS FROM PASTEUR INSTITUTES
ON THE RESULTS
OF ANTI-RABIES TREATMENT¹**

by

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I. GENERAL.

The statistics dealt with in this review relate mainly to the year 1932. A few reports relating to earlier years, received since the publication of the fourth review, are included. Schedules which reached Geneva later than May 31st, 1934, will be dealt with in the next review, together with the bulk of the statistics for 1933.

For various reasons, the statistics submitted from the U.S.S.R. will be separately dealt with.

The present analysis deals with a total of 115,959 persons treated (U.S.S.R. institutes excluded), as compared with 119,433 in the fourth review, 69,541 in the third, 69,707 in the second, and 31,656 in the first. This response in the submission of schedules is gratifying, and the reviewer takes this opportunity of expressing his thanks to the directors of the various institutes for their willing co-operation.

The general characteristics of each schedule are given in the following table.

¹ For previous reviews, see document C.H. 844, and *Quarterly Bulletin*, I, pages 110 and 725, II, page 553.

METHODS USED AND RESULTS OBTAINED.

| Institute | Year | Vaccine | Days of treatment | Number treated | Deaths | Mortality (per cent) | Paralytic accidents |
|---|------|-------------------------|-------------------|----------------|--------|----------------------|---------------------|
| (1) <i>Dried or glycerinated cords.</i> | | | | | | | |
| 1. Bari | 1932 | Dried 2-6 days. | 15-26 | 177 | 0 | 0 | 0 |
| 2. Berne | 1932 | Dried 3-10 days : glyc. | 18-21 | 3 | 0 | 0 | 0 |
| 3. Bologna | 1932 | Dried 2-8 days | 15-20 | 135 | 0 | 0 | 0 |
| 4. Brussels | 1930 | Dried 2-9 days : glyc. | 18-23 | 22 | 0 | 0 | 0 |
| 5. Brussels | 1931 | Dried 2-9 days : glyc. | 18-23 | 18 | 0 | 0 | 0 |
| 6. Brussels | 1932 | Dried 2-9 days : glyc. | 18-23 | 27 | 0 | 0 | 0 |
| 7. Buenos Aires | 1932 | Dried 1-8 days | 16-21 | 1,612 | 3 | 0.18 | 3 (all recovered) |
| 8. Dakar (Europeans) | 1932 | Dried 2-4 days : glyc. | 8-16 | 21 | 0 | 0 | 0 |
| 9. Dakar (non-Europeans) | 1932 | Dried 2-4 days : glyc. | 8-16 | 22 | 1 | 4.5 | 0 |
| 10. Lille | 1932 | Dried 2-4 days : glyc. | 14-24 | 75 | 0 | 0 | 0 |
| 11. Lyons | 1932 | Dried : glyc. | 15-25 | 200 | 0 | 0 | 0 |
| 12. Montevideo | 1932 | Dried 2-10 days | 16-21 | 645 | 1 | 0.15 | 0 |
| 13. Montpellier | 1932 | Dried 2-5 days : glyc. | 13-24 | 248 | 0 | 0 | 0 |
| 14. Palermo | 1932 | Dried 2-8 days | 27-39 | 392 | 0 | 0 | 0 |
| 15. Paris | 1932 | Dried 2-5 days : glyc. | 15-25 | 561 | 0 | 0 | 0 |
| 16. Bordeaux | 1932 | Dried 2-5 days : glyc. | 14-21 | 194 | 0 | 0 | 0 |
| 17. Marseilles | 1932 | Dried : glyc. | 15-21 | 447 | 0 | 0 | 0 |
| 18. Tartu (Estonia) | 1931 | Dried 2-4 days | 21 | 40 | 0 | 0 | 0 |
| 19. Tartu (Estonia) | 1932 | Dried 2-4 days | 21 | 115 | 0 | 0 | 0 |
| 20. Tokio | 1932 | Dried 1-5 days | 18 | 49 | 0 | 0 | 0 |
| 21. Ceará (Brazil) | 1932 | Dried 2-9 days : glyc. | ? | 248 | 1 | 0.40 | 0 |
| 22. Bangkok | 1932 | Dried | 18-25 | 373 | 3 | 0.80 | 0 |
| 23. Keijo (Chosen) | 1932 | Dried 1-5 days : glyc. | 18 | 1,619 | 9 | 0.55 | 0 |
| 24. Hanoi | 1932 | Dried 0-6 days : glyc. | 15-20 | 1,121 | 4 | 0.35 | 0 |
| 25. Vilno | 1932 | Dried 2-8 days : glyc. | 14-20 | 28 | 0 | 0 | 0 |
| 26. Tunis | 1932 | Dried 1-4 days : glyc. | 16-23 | 1,788 | 6 | 0.34 | 0 |
| 27. Antananarivo | 1931 | Dried 1-5 days : glyc. | 12-20 | 158 | 1 | 0.63 | 0 |
| 28. Antananarivo | 1932 | Dried 1-5 days : glyc. | 12-20 | 147 | 2 | 1.36 | 0 |
| 29. Rabat | 1932 | Dried : glyc. | 15-25 | 754 | 0 | 0 | 0 |
| 30. Algiers | 1932 | Dried 2-5 days : glyc. | 15-25 | 2,336 | 5 | 0.21 | 0 |
| | | | | 13,574 | 36 | 0.27 | 3 |

(2) *Modified dilution methods.*

| | | | | | | | |
|-------------------------------------|------|--------------------------------|-------|-------|----|------|-------------|
| 1. Barcelona | 1932 | Högyes modified 1/100-1/5000 | 20 | 890 | 1 | 0.11 | 0 |
| 2. Certain Bulgarian institutes . . | 1932 | Boecker's vaccine : 0.090 gr. | 20 | 2,671 | 12 | 0.45 | 0 |
| 3. Cernauti (Roumania) | 1932 | Högyes modified : 1/100-1/2000 | 15-23 | 1,097 | 2 | 0.19 | 3 (2 fatal) |
| 4. Beirut (Liban) | 1932 | Högyes modified | 8-15 | 208 | 1 | 0.48 | 0 |
| 5. Helsinki (Finland) | 1931 | Dried 1 day | 12-21 | 1 | 0 | 0 | 0 |
| 6. Riga (at institute) | 1932 | Dried 1 day : glyc. | 14-21 | 33 | 0 | 0 | 0 |
| 7. Riga (outside) | 1932 | Dried 1 day : glyc. phenol | 14-21 | 248 | 1 | 0.40 | 0 |
| | | | | 5,148 | 17 | 0.33 | 3 |

(3) *Killed phenol vaccines.*

| | | | | | | | |
|--------------------------------------|------|-----------------------|-------|-------|----|------|---------------|
| 1. Kasauli (at institute : Europ.) | 1932 | 1400-3500 mg. Semple | 7-14 | 88 | 0 | 0 | 0 |
| 2. Kasauli (at institute : non-Eur.) | 1932 | 1400-3500 mg. Semple | 7-14 | 6,780 | 51 | 0.75 | 0 |
| 3. Kasauli (outside : European) . . | 1932 | 1400-3500 mg. Semple | 7-14 | 1,046 | 0 | 0 | 0 |
| 4. Kasauli (outside : non-Europ.) | 1932 | 1400-3500 mg. Semple | 7-14 | 4,887 | 22 | 0.45 | 0 |
| 5. Lisbon (at institute) | 1932 | 2500-10000 mg. Semple | 10-40 | 369 | 0 | 0 | 0 |
| 6. Lisbon (outside) | 1932 | 2500-10000 mg. Semple | 10-40 | 39 | 0 | 0 | 0 |
| 7. Cracow | 1932 | " Semple | 20 | 37 | 1 | 2.70 | 0 |
| 8. Cairo (European) | 1932 | 700-1050 mg. Semple | 14-21 | 64 | 0 | 0 | 0 |
| 9. Cairo (non-European) | 1932 | 700-1050 mg. Semple | 14-21 | 2,198 | 12 | 0.54 | 1 (recovered) |
| 10. Bangkok (at institute) | 1932 | Carbolised | 14 | 757 | 8 | 1.05 | 0 |
| 11. Bangkok (outside) | 1932 | Carbolised | 14 | 494 | 1 | 0.20 | 0 |
| 12. Baghdad (European) | 1932 | 700-3500 mg. Semple | 14-20 | 14 | 0 | 0 | 0 |
| 13. Baghdad (non-European) | 1932 | 700-3500 mg. Semple | 14-20 | 230 | 2 | 0.87 | 0 |
| 14. Shanghai (European) | 1932 | " Semple | 15-18 | 136 | 2 | 1.48 | 0 |
| 15. Shanghai (non-European) | 1932 | " Semple | 15-18 | 176 | 2 | 1.14 | 0 |
| 16. Santiago (Chile) | 1932 | 4000 mg. Semple | 20 | 75 | 0 | 0 | 0 |
| 17. Rangoon (European) | 1932 | 700-3500 mg. Semple | 7-14 | 137 | 0 | 0 | 1 (recovered) |
| 18. Rangoon (non-European) | 1932 | 700-3500 mg. Semple | 7-14 | 1,140 | 6 | 0.52 | 0 |
| 19. New York | 1931 | " Semple | 14-21 | 1,146 | 0 | 0 | 1 (recovered) |
| 20. New York | 1932 | " Semple | 14-21 | 1,308 | 0 | 0 | 0 |
| 21. Milan | 1932 | 4500-7500 mg. Semple | 15-25 | 62 | 0 | 0 | 0 |
| 22. Lwow | 1932 | Mulford's vaccine | 20 | 712 | 0 | 0 | 0 |

| Institute | Year | Vaccine | Days of treatment | Number treated | Deaths | Mortality (per cent) | Paralytic accidents |
|--|------|---------------------|-------------------|----------------|--------|----------------------|---------------------|
| 23. Coonoor (European) | 1932 | 700-3500 Semple | 14 | 405 | 1 | 0.24 | 0 |
| 24. Coonoor (non-European) | 1932 | 700-3500 Semple | 14 | 8,613 | 37 | 0.43 | 0 |
| 25. Bombay (European) | 1932 | 700-3500 Semple | 7-14 | 292 | 0 | 0 | 0 |
| 26. Bombay (non-European) | 1932 | 700-3500 Semple | 7-14 | 7,191 | 63 | 0.87 | 0 |
| 27. Shillong | 1932 | 1400 mg. Semple | 14 | 1,269 | 11 | 0.87 | 0 |
| 28. Calcutta | 1932 | 350-700 mg. Semple | 7-14 | 7,250 | 48 | 0.66 | 1 (recovered) |
| 29. Nairobi and out-stations | 1932 | 500-3500 mg. Semple | 14 | 21 | 0 | 0 | 0 |
| 30. Kuala Lumpur | 1932 | 700-1050 mg. Semple | 14-21 | 103 | 2 | 1.94 | 0 |
| 31. Hong-Kong | 1932 | 1400 mg. Semple | 14 | 148 | 0 | 0 | 0 |
| 32. Colombo | 1932 | 700-1000 mg. Semple | 14-20 | 1,041 | 6 | 0.58 | 0 |
| 33. Jerusalem | 1932 | 700 mg. Semple | 14 | 1,690 | 3 | 0.17 | 3 (2 fatal) |
| 34. Warsaw (at institute) | 1932 | 800 mg. Semple | 20 | 277 | 1 | 0.36 | 0 |
| 35. Warsaw (outside) | 1932 | 800 mg. Semple | 20 | 1,476 | 4 | 0.27 | 0 |
| | | | | 51,671 | 283 | 0.55 | 7 |

(4) *Live phenol vaccines.*

| | | | | | | | |
|----------------------|------|------------------|-------|-----|---|------|---|
| 1. Ancona | 1932 | Puntoni's method | 16-20 | 26 | 1 | 3.84 | 0 |
| 2. Catania | 1932 | Puntoni's method | 15-25 | 71 | 0 | 0 | 0 |
| 3. Rome | 1932 | Puntoni's method | 15-25 | 202 | 0 | 0 | 0 |
| 4. Pisa | 1930 | Puntoni's method | 15-25 | 12 | 0 | 0 | 0 |
| 5. Pisa | 1931 | Puntoni's method | 15-25 | 16 | 0 | 0 | 0 |
| 6. Pisa | 1932 | Puntoni's method | 15-25 | 5 | 0 | 0 | 0 |
| 7. Torino | 1932 | Puntoni's method | 15-25 | 69 | 0 | 0 | 0 |
| | | | | 401 | 1 | 0.25 | 0 |

(5) *Fermi's vaccine.*

| | | | | | | | |
|--------------------------------------|------|-------------|-------|-------|---|------|---|
| 1. Genoa | 1932 | 375-625 mg. | 15-25 | 4 | 0 | 0 | 0 |
| 2. Brazzaville | 1932 | | 15 | 6 | 0 | 0 | 0 |
| 3. Kosice (Czechoslovakia) | 1929 | | 14-21 | 681 | 3 | 0.44 | 0 |
| 4. Kosice (Czechoslovakia) | 1930 | | 14-21 | 409 | 0 | 0 | 0 |
| 5. Kosice (Czechoslovakia) | 1931 | | 14-21 | 306 | 3 | 0.98 | 0 |
| 6. Kosice (Czechoslovakia) | 1932 | | 14-21 | 356 | 0 | 0 | 0 |
| | | | | 1,762 | 6 | 0.34 | 0 |

(6) *Fermi's sero-vaccine.*

| | | | | | | | |
|------------------|------|----------------------|---|-----|---|---|---|
| 1. Sassari | 1932 | Fermi's sero-vaccine | ? | 178 | 0 | 0 | 0 |
|------------------|------|----------------------|---|-----|---|---|---|

(7) *Heated vaccines.*

| | | | | | | | |
|--------------------------|------|------------------------------------|-------|--------|----|------|--------------------|
| 1. Bucharest | 1932 | Dried 0-6 days + heated 50°-65° C. | 10-24 | 7,288 | 13 | 0.18 | 0 |
| 2. Jassy | 1931 | One per cent heated 45°-65° C. | 15-23 | 2,649 | 0 | 0 | 2 (both recovered) |
| 3. Jassy | 1932 | One per cent heated 45°-65° C. | 15-23 | 3,865 | 2 | 0.05 | 0 |
| 4. Cluj (Roumania) | 1929 | Dried 0-4 days + heated 68°-75° C. | 10-25 | 2,524 | 17 | 0.67 | 0 |
| 5. Cluj (Roumania) | 1930 | Dried 0-4 days + heated 68°-75° C. | 8-25 | 3,006 | 12 | 0.39 | 0 |
| 6. Cluj (Roumania) | 1931 | Dried 0-4 days + heated 68°-75° C. | 8-25 | 3,556 | 11 | 0.30 | 0 |
| 7. Cluj (Roumania) | 1932 | Dried 0-4 days + heated 68°-75° C. | 8-25 | 4,189 | 10 | 0.23 | 0 |
| | | | | 27,077 | 65 | 0.24 | 2 |

(8) *Killed ether vaccines.*

| | | | | | | | |
|------------------------------|------|---------------------------|-----|-------|----|------|---|
| 1. Yugoslav institutes | 1932 | Standard vaccine of Hempt | 1-6 | 7,265 | 20 | 0.28 | 0 |
|------------------------------|------|---------------------------|-----|-------|----|------|---|

(9) *Mixed treatment.*

| | | | | | | | |
|------------------------------------|------|--|-------|-------|---|------|-------------------|
| 1. Athens | 1931 | Slight cases : cords dried 2-5 days | 18-? | 1,630 | 2 | 0.12 | 3 (all recovered) |
| 2. Athens | 1932 | | | | | | |
| 3. Certain Bulgarian institutes .. | 1932 | Severe cases : same + Alivisatos' ether vaccine | 18-? | 1,667 | 0 | 0 | 1 (recovered) |
| 4. Madrid | 1932 | | | | | | |
| 5. Vienna | 1932 | Slight cases : Högyes Severe cases : same + Alivisatos' ether vaccine | 13-21 | 2,499 | 5 | 0.20 | 2 (one fatal) |
| | | | | | | | |
| | | | 17-20 | 1,398 | 1 | 0.07 | 0 |
| | | | 13-21 | 244 | 0 | 0 | 0 |
| | | | | 7,438 | 8 | 0.11 | 6 |

(10) *Yalren vaccine.*

| | | | | | | | |
|------------------------------------|------|-------------|-------|-------|---|------|---------------|
| 1. Certain Bulgarian institutes .. | 1932 | 410-570 mg. | 15-18 | 1,345 | 3 | 0.22 | 1 (recovered) |
|------------------------------------|------|-------------|-------|-------|---|------|---------------|

II. METHODS OF TREATMENT.

The method of treatment employed at each institute, the duration of treatment, and, where available, its dosage are given in the table on pages 614 to 617.

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

1. *Dried or glycerinated cords.*—At the majority of institutes in this group, the method of Calmette is employed. At Bangkok, Bari, Bologna, Buenos Aires, Montevideo, Palermo, Tartu (Estonia) and Rabat, the original method of Pasteur has been used.

2. *Modified dilution methods.*—Boecker's method is now included in this group (*vide* fourth review). At Riga and Helsinki, cords are dried for twenty-four hours and then diluted with glycerine. It has been assumed, as formerly, that drying for so short a period of time is insufficient to justify inclusion in group 1 above.

3. *Killed phenol vaccines.*—Mulford's vaccine is used at Lwow. At the rest, Semple's modification of Fermi's original method (*i.e.*, the phenol vaccine is incubated at 37° C. for twenty-four hours) is employed.

4. *Live phenol vaccines.*—The method of Puntoni—*i.e.*, of phenol vaccines of graduated virulence—is employed at the Italian institutes comprised within this group.

5. *Fermi's vaccine.*—Phenol vaccines (not incubated) are used at Genoa and Brazzaville.

6. *Fermi's sero-vaccine* is employed at Sassari.

7. *Heated vaccines* are used at Jassy, and in combination with dried cords at Bucharest and Cluj (Roumania).

8. *Killed ether vaccines*, phenolised according to the method of Hempt, are employed at the Yugoslav institutes.

9. *Mixed treatment.*—This term has been adopted to indicate the procedures in which the slightly bitten are treated either by dilutions or by dried cords, with the addition of ether vaccine (prepared according to the method of Alivisatos) in severely bitten cases. The first alternative is employed at Madrid and Vienna, the second at Athens.

10. *Yatren vaccine* is employed at certain Bulgarian institutes. In analysing the statistics the reviewer has, in certain instances, made use of a shorter classification—viz. :

1. Killed vaccines : comprising 3 and 8 above ;
2. Live vaccines : comprising 1, 2, 4 and 9 above ;
3. Heated vaccines : group 7 above ;
4. Other : comprising 5, 6 and 10 above.

III. NUMBERS OF PERSONS TREATED.

The total number of persons treated regarding whom information has been submitted was 115,859. The number of annual returns—that is to say, the number of returns relating to patients, whatever their race type, and whether treated at the institutes or at its subsidiary centres—was eighty-six.

The returns from all Yugoslav institutes were submitted in a single schedule, and those from Bulgarian institutes were summarised in three schedules, one relating to treatment by “mixed” methods, a second by *Yatren vaccine*, and a third by *Boecker’s dilution method*.

The adjoining table gives the distribution of patients according to method of treatment, the number of institutes at which they were treated, the number of annual returns received, and the average number of patients per annual return :

| | Patients | Institutes | Annual returns | Average per annual return |
|-------------------------------|----------|------------|----------------|---------------------------|
| 1. Cords | 13,574 | 25 | 29 | 468 |
| 2. Dilutions | 5,148 | — | — | — |
| 3. Killed phenol | 51,671 | 22 | 23 | 2,247 |
| 4. Live phenol | 401 | 5 | 7 | 57 |
| 5. Fermi’s vaccine | 1,762 | 3 | 6 | 297 |
| 6. Fermi’s sero-vaccine | 178 | 1 | 1 | 178 |
| 7. Heated | 27,077 | 3 | 7 | 3,868 |
| 8. Killed ether | 7,265 | — | — | — |
| 9. Mixed | 7,438 | — | — | — |
| 10. <i>Yatren</i> | 1,345 | — | — | — |
| Total | 115,859 | | | |

The detail where no entry is made will be found in the table on pages 614 to 617.

IV. MORTALITIES FOR ALL PATIENTS.

Of the total of 115,859 persons treated, 439 died of rabies. The percentage mortality is thus 0.38, as compared with 0.49 in the

first review, 0.48 in the second, 0.23 in the third, 0.48 in the fourth, and 0.41 over the whole period covered by the five reviews.

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

| | Fifth review | | | All five reviews | | | |
|------------------------------|----------------|------------|-------------|------------------|--------------|-------------------------|-------------|
| | Number treated | Deaths | Mortality % | Number treated | Deaths | | Mortality % |
| | | | | | Observed | Calculated ¹ | |
| 1. Cords | 13,574 | 36 | 0.27 | 63,653 | 242 | 261 | 0.38 |
| 2. Dilutions ... | 5,148 | 17 | 0.33 | 27,040 | 48 | 111 | 0.18 |
| 3. Killed phenol. | 51,671 | 283 | 0.55 | 173,684 | 1,156 | 713 | 0.67 |
| 4. Live phenol . | 401 | 1 | 0.25 | 1,967 | 4 | 8 | 0.20 |
| 5. Fermi's vacc. | 1,762 | 6 | 0.34 | 4,773 | 12 | 2 | 0.27 |
| 6. Fermi's sero-vaccine | 178 | 0 | 0 | 255 | 0 | 1 | 0 |
| 7. Heated | 27,077 | 65 | 0.24 | 55,044 | 97 | 226 | 0.18 |
| 8. Killed ether.. | 7,265 | 20 | 0.28 | 38,299 | 52 | 157 | 0.14 |
| 9. Mixed | 7,438 | 8 | 0.11 | 36,097 | 44 | 148 | 0.12 |
| 10. Yatren | 1,345 | 3 | 0.22 | 5,384 | 13 | 22 | 0.24 |
| Total | 115,859 | 439 | 0.38 | 406,196 | 1,668 | 1,666 | 0.41 |

P < 1 in a million.

According to the shorter method of classification the figures are :

| | Fifth review | | | All five reviews | | | |
|--------------------|----------------|------------|-------------|------------------|--------------|--------------|-------------|
| | Number treated | Deaths | Mortality % | Number treated | Deaths | | Mortality % |
| | | | | | Observed | Calculated | |
| 1. Killed | 58,936 | 303 | 0.51 | 211,983 | 1,208 | 870 | 0.57 |
| 2. Live | 26,561 | 62 | 0.23 | 128,757 | 338 | 529 | 0.26 |
| 3. Heated | 27,077 | 65 | 0.24 | 55,044 | 97 | 226 | 0.18 |
| 4. Other | 3,285 | 9 | 0.27 | 10,412 | 25 | 43 | 0.24 |
| Total | 115,859 | 439 | 0.34 | 406,196 | 1,668 | 1,668 | 0.41 |

P < 1 in a million,

The mortalities in the successive reviews and in the whole set were:

| | First | Second | Third | Fourth | Fifth | All five |
|-------------------|-------------|-------------|-------------|-------------|-------------|-------------|
| 1. Killed | 0.65 | 0.80 | 0.28 | 0.66 | 0.51 | 0.57 |
| 2. Live | 0.27 | 0.26 | 0.21 | 0.26 | 0.23 | 0.26 |
| 3. Heated | — | 0.15 | 0.08 | 0.04 | 0.24 | 0.18 |
| 4. Other | — | — | — | 0.22 | 0.27 | 0.24 |
| Total..... | 0.49 | 0.48 | 0.23 | 0.48 | 0.34 | 0.41 |

A higher mortality occurs in this review amongst those treated by heated vaccines. From Bucharest, in 1932, a rate of 0.18 is

¹ "Calculated" from the mortality of the total of the ten groups (i.e., from 0.41 : for example—261 = 0.41 × 63,653 ÷ 100).

reported as compared with 0.019 in 1931, and statistics have for the first time been received from Cluj (Roumania) relating to the years 1929, 1930, 1931 and 1932, in which the rates were 0.67, 0.39, 0.30 and 0.23 respectively. The same tests of significance of differences as were employed and described in previous reviews have been used, and will not be recapitulated here. 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 conventionally be taken as being defined by $P = 0.05$, any lesser value indicating a real discrepancy.

V. RACIAL STATISTICS.

Information is wanting regarding 1,690 persons treated by killed vaccines, of whom 3 died of rabies. These were treated at Jerusalem, where a strict classification according to race type appears to be difficult to determine. Of the remaining 114,169, 66,133 were Europeans (57.9 per cent) and 48,036 were of non-European birth (42.1 per cent).

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

| | First | Second | Third | Fourth | Fifth | All five |
|---------------------------------------|-------------|-------------|-------------|-------------|-------------|-------------|
| 1. Cords | 57.6 | 52.7 | 50.2 | 62.5 | 56.1 | 52.2 |
| 2. Dilutions . . . | 100 | 100 | 100 | 94.8 | 96.6 | 98.0 |
| 3. Killed phenol. | 19.7 | 11.9 | 62.1 | 10.3 | 15.6 | 15.7 |
| 4. Live phenol . | — | 100 | 100 | 100 | 100 | 100 |
| 5. Fermi's vacc. | — | — | — | 100 | 90 | 100 |
| 6. Fermi's sero- vaccine | — | — | — | 100 | 100 | 100 |
| 7. Heated | — | 100 | 100 | 100 | 100 | 100 |
| 8. Killed ether.. | 99.7 | — | 100 | 100 | 100 | 100 |
| 9. Mixed | 100 | 100 | 100 | 100 | 100 | 100 |
| 10. Yatren | — | — | — | 100 | 100 | 100 |
| Total | 52.4 | 53.5 | 81.1 | 48.9 | 58.0 | 57.8 |

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

| | Fifth review | | | | All five reviews | | | |
|-------------------------------|----------------|------------|--------------|-------------|------------------|--------------|--------------|-------------|
| | Number treated | Deaths | | Mortality % | Number treated | Deaths | | Mortality % |
| | | Observed | Calculated | | | Observed | Calculated | |
| <i>Europeans.</i> | | | | | | | | |
| 1. Cords | 7,613 | 9 | 16 | 0.12 | 33,213 | 56 | 50 | 0.17 |
| 2. Dilutions | 4,974 | 16 | 10 | 0.32 | 26,488 | 38 | 40 | 0.14 |
| 3. Killed phenol. | 8,081 | 9 | 17 | 0.11 | 27,277 | 31 | 41 | 0.11 |
| 4. Live phenol .. | 401 | 1 | 0.8 | 0.25 | 1,967 | 4 | 3 | 0.20 |
| 5. Fermi's vacc.. | 1,761 | 6 | 4 | 0.34 | 4,772 | 12 | 7 | 0.20 |
| 6. Fermi's sero-vaccine | 178 | 0 | 0.4 | 0 | 255 | 0 | 0.4 | 0 |
| 7. Heated | 27,077 | 65 | 56 | 0.24 | 55,044 | 97 | 83 | 0.18 |
| 8. Killed ether .. | 7,265 | 20 | 15 | 0.28 | 38,299 | 52 | 58 | 0.14 |
| 9. Mixed | 7,438 | 8 | 15 | 0.11 | 36,097 | 44 | 55 | 0.12 |
| 10. Yatren | 1,345 | 3 | 3 | 0.22 | 5,384 | 13 | 8 | 0.24 |
| Total | 66,133 | 137 | 137.2 | 0.21 | 228,796 | 347 | 346.4 | 0.15 |
| | | P = 0.08 | | | | P = 0.07 | | |
| <i>Non-Europeans.</i> | | | | | | | | |
| 1. Cords | 5,960 | 27 | 37 | 0.45 | 26,477 | 177 | 206 | 0.67 |
| 2. Dilutions | 174 | 1 | 1 | 0.57 | 552 | 10 | 4 | 1.81 |
| 3. Killed phenol . | 41,901 | 271 | 261 | 0.65 | 140,064 | 1,114 | 1,091 | 0.80 |
| Total | 48,035 | 299 | 299 | 0.62 | 167,093 | 1,301 | 1,301 | 0.78 |
| | | P = 0.20 | | | | P = 0.0014. | | |

These may also be classified as under :

| | Fifth review | | | | All five reviews | | | |
|----------------------|----------------|------------|------------|-------------|------------------|--------------|--------------|-------------|
| | Number treated | Deaths | | Mortality % | Number treated | Deaths | | Mortality % |
| | | Observed | Calculated | | | Observed | Calculated | |
| <i>Europeans.</i> | | | | | | | | |
| 1. Killed | 15,346 | 29 | 32 | 0.19 | 65,576 | 83 | 99 | 0.13 |
| 2. Live | 20,426 | 34 | 42 | 0.17 | 97,765 | 142 | 148 | 0.15 |
| 3. Heated | 27,077 | 65 | 56 | 0.24 | 55,044 | 97 | 83 | 0.18 |
| 4. Other | 3,284 | 9 | 7 | 0.27 | 10,411 | 25 | 16 | 0.24 |
| Total | 66,133 | 137 | 137 | 0.21 | 228,796 | 347 | 346 | 0.15 |
| | | P = 0.09 | | | | P = 0.019 | | |
| <i>Non-European.</i> | | | | | | | | |
| 1. Killed | 41,901 | 271 | 261 | 0.65 | 140,064 | 1,114 | 1,091 | 0.80 |
| 2. Live | 6,134 | 28 | 38 | 0.46 | 27,029 | 187 | 210 | 0.69 |
| Total | 48,035 | 299 | 299 | 0.62 | 167,093 | 1,301 | 1,301 | 0.78 |
| | | P = 0.08 | | | | P = 0.08 | | |

The mortalities as compared with previous reviews are as under :

| <i>Europeans.</i> | First | Second | Third | Fourth | Fifth | All five |
|------------------------|-------|--------|-------|--------|-------|----------|
| 1. Killed | 0.10 | 0.14 | 0.10 | 0.12 | 0.19 | 0.13 |
| 2. Live | 0.20 | 0.11 | 0.13 | 0.15 | 0.17 | 0.15 |
| 3. Heated | — | 0.15 | 0.08 | 0.04 | 0.24 | 0.18 |
| 4. Other | — | — | — | 0.19 | 0.27 | 0.24 |
| Total | 0.17 | 0.13 | 0.10 | 0.14 | 0.21 | 0.15 |
| <i>Non-Europeans :</i> | | | | | | |
| 1. Killed | 0.83 | 0.89 | 0.93 | 0.85 | 0.65 | 0.80 |
| 2. Live | 1.02 | 0.82 | 0.71 | 0.74 | 0.46 | 0.69 |
| Total | 0.84 | 0.88 | 0.78 | 0.83 | 0.62 | 0.78 |

It will be noticed that only two of the *P* values indicate significant differences—namely, (a) $P = 0.0014$ for non-Europeans according to the first system of classification, and (b) $P = 0.019$ for Europeans according to the second system. In the case of the former, (a), it is obvious that the heterogeneity is carried forward from previous years, as is shown by the fact that the value of *P* for the corresponding table relating to the fifth review only is 0.20. The main source of disturbance is obviously in the dilution group, and it was pointed out in the fourth review that it occurred under very exceptional circumstances at a single institute. If the dilution group be excluded, and the sets of statistics relating to those treated by cords and by killed phenol vaccines are treated separately, it appears that $P = 0.032$ —that is to say, there is some evidence of heterogeneity but not of a very conclusive character, and this is in favour of treatment by cords. The fact that, in the corresponding European figures, the order of efficiency is reversed, though the difference in the mortalities is not actually significant ($P = 0.09$), indicates the need for caution in accepting the above result. With regard to (b), the heterogeneity is due mainly to the group of persons treated by Yatren vaccine, in which the mortality is above the average.

Finally, it appears from the combined figures that the mortality amongst non-Europeans is 5.2 times as great as that amongst Europeans. This difference is highly significant and will be further examined in succeeding sections.

VI. SPECIES OF BITING ANIMAL.

The percentages of persons bitten by the different species of animals are as detailed below.

| | Dog | Cat | Wolf | Jackal | Solipeds | Ruminants | Other | Human |
|-------------------------------|------|------|------|--------|----------|-----------|-------|-------|
| 1. Cords | 85.7 | 10.8 | 0.01 | 0.05 | 1.2 | 0.4 | 1.4 | 0.3 |
| 2. Dilutions | 83.2 | 9.3 | 0.2 | 0.04 | 0.3 | 4.8 | 0.8 | 1.3 |
| 3. Killed phenol | 88.3 | 1.8 | 0.1 | 6.1 | 0.5 | 0.9 | 1.5 | 0.8 |
| 4. Live phenol | 75.3 | 18.4 | — | — | — | 2.0 | 4.2 | — |
| 5. Fermi's vaccine | 93.0 | 4.8 | — | — | 0.1 | — | 1.5 | 0.6 |
| 6. Fermi's sero-vaccine | 98.9 | 1.1 | — | — | — | — | — | — |
| 7. Heated | 86.8 | 6.5 | 0.1 | 0.3 | 3.8 | 1.5 | 1.1 | — |
| 8. Killed ether | 86.2 | 6.8 | 0.8 | — | 0.8 | 2.0 | 0.8 | 2.5 |
| 9. Mixed | 87.7 | 8.4 | 0.01 | 0.1 | 1.0 | 1.6 | 0.7 | 0.4 |
| 10. Yatren | 87.9 | 6.7 | 1.0 | — | 0.1 | 3.6 | 0.4 | 0.2 |
| Total | 87.3 | 5.2 | 0.2 | 2.8 | 1.4 | 1.3 | 1.2 | 0.6 |

The figures relating to mortality are as follows :

| | (a) Dog | | | (b) Cat | | |
|-------------------------------|----------------|--------|-------------|----------------|--------|-------------|
| | Number treated | Deaths | Mortality % | Number treated | Deaths | Mortality % |
| 1. Cords | 11,634 | 36 | 0.31 | 1,472 | 0 | 0 |
| 2. Dilutions | 4,269 | 14 | 0.33 | 477 | 0 | 0 |
| 3. Killed phenol | 45,610 | 228 | 0.50 | 941 | 0 | 0 |
| 4. Live phenol | 302 | 1 | 0.33 | 74 | 0 | 0 |
| 5. Fermi's vaccine | 1,638 | 6 | 0.37 | 85 | 0 | 0 |
| 6. Fermi's sero-vaccine | 176 | 0 | 0 | 2 | 0 | 0 |
| 7. Heated | 23,491 | 59 | 0.25 | 1,764 | 2 | 0.11 |
| 8. Killed ether | 6,260 | 16 | 0.26 | 497 | 0 | 0 |
| 9. Mixed | 6,524 | 7 | 0.11 | 623 | 0 | 0 |
| 10. Yatren..... | 1,183 | 3 | 0.25 | 90 | 0 | 0 |
| Total | 101,087 | 370 | 0.36' | 6,025 | 2 | 0.03 |

| | (c) Wolf | | | All five reviews | | | |
|------------------------|----------------|--------|-------------|------------------|----------|------------|-------------|
| | Fifth review | | | Number treated | Deaths | | Mortality % |
| | Number treated | Deaths | Mortality % | | Observed | Calculated | |
| 1. Cords | 2 | 0 | 0 | 23 | 4 | 2.0 | 17.4 |
| 2. Dilutions | 10 | 3 | 30.0 | 21 | 4 | 1.9 | 19.0 |
| 3. Killed phenol | 58 | 6 | 10.3 | 209 | 26 | 18.4 | 12.4 |
| 7. Heated | 33 | 4 | 12.1 | 47 | 4 | 4.1 | 8.5 |
| 8. Killed ether | 59 | 4 | 6.8 | 172 | 6 | 15.1 | 3.5 |
| 9. Mixed | 1 | 1 | 100.0 | 60 | 5 | 5.3 | 8.3 |
| 10. Yatren | 13 | 0 | 0 | 23 | 0 | 2.0 | 0 |
| Total | 176 | 18 | 10.2 | 556 | 49 | 48.8 | 8.8 |

P = 0.02

(d) *Jackal*

| | Fifth review | | | All five reviews | | |
|-----------------------|----------------|-----------|-------------|------------------|------------|-------------|
| | Number treated | Deaths | Mortality % | Number treated | Deaths | Mortality % |
| 1. Cords..... | 7 | 0 | 0 | 43 | 0 | 0 |
| 2. Dilutions | 2 | 0 | 0 | 2 | 0 | 0 |
| 3. Killed phenol..... | 3,162 | 48 | 1.52 | 12,731 | 227 | 1.78 |
| 7. Heated | 70 | 0 | 0 | 70 | 0 | 0 |
| 9. Mixed | 11 | 0 | 0 | 25 | 1 | 0 |
| Total..... | 3,252 | 48 | 1.48 | 12,871 | 228 | 1.77 |

(e) *Solipeds, Ruminants, Human and Other*

| | Solipeds | Ruminants | Other | Human |
|-------------------------------|--------------|--------------|---------------|------------|
| 1. Cords | 166 | 60 | 188 | 45 |
| 2. Dilutions | 17 | 248 | 40 | 65 |
| 3. Killed phenol | 273 | 471 | 763 (1 death) | 393 |
| 4. Live phenol | 2 | 8 | 17 | — |
| 5. Fermi's vaccine | 2 | — | 26 | 11 |
| 6. Fermi's sero-vaccine | — | — | — | — |
| 7. Heated | 1,031 | 395 | 293 | — |
| 8. Killed ether | 57 | 146 | 61 | 185 |
| 9. Mixed | 78 | 121 | 52 | 28 |
| 10. Yatren | 2 | 48 | 6 | 3 |
| Total | 1,626 | 1,497 | 1,446 | 730 |

Information regarding the biting animal was lacking in the case of twenty persons. The single death amongst those bitten by "other" animals refers to a bite from an unknown animal.

As was pointed out in the previous review, the subdivision into "human" and "other" is not precise. The human group is probably largely composed of persons who have come in contact with human saliva.

From the combined figures for the five reviews, it appears that, of 9,004 persons bitten by solipeds and ruminants, none has developed rabies. Of 2,185 persons who had been in contact with a case of human rabies, none developed the disease ; whilst, of 5,586 bitten by "other animals", one bitten by a hyena and another bitten by an "unknown animal" developed rabies.

VII. EVIDENCE OF RABIES IN THE BITING ANIMAL.

The percentages of treated persons belonging to the different categories are as follows :

| | A | B | C | D |
|-------------------------------|------|------|------|------|
| 1. Cords | 11.2 | 19.3 | 60.4 | 9.1 |
| 2. Dilutions | 6.6 | 35.3 | 46.2 | 11.8 |
| 3. Killed phenol | 6.7 | 7.9 | 82.5 | 2.8 |
| 4. Live phenol | 14.9 | 19.8 | 63.6 | 1.6 |
| 5. Fermi's vaccine | 3.2 | 49.0 | 47.7 | 0 |
| 6. Fermi's sero-vaccine | — | — | — | — |
| 7. Heated | 15.6 | 22.3 | 60.9 | 1.3 |
| 8. Killed ether | 24.2 | 11.9 | 63.9 | 0 |
| 9. Mixed | 25.8 | 41.4 | 25.4 | 7.4 |
| 10. Yatren | 5.9 | 43.9 | 27.9 | 22.1 |
| Total | 11.7 | 17.5 | 66.9 | 3.9 |

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

Category A.

| | Fifth review | | | All five reviews | | |
|-------------------------------|----------------|--------|-------------|------------------|--------|-------------|
| | Number treated | Deaths | Mortality % | Number treated | Deaths | Mortality % |
| 1. Cords | 1,492 | 7 | 0.47 | 3,337 | 24 | 0.72 |
| 2. Dilutions | 340 | 3 | 0.88 | 1,328 | 5 | 0.38 |
| 3. Killed phenol | 3,336 | 28 | 0.84 | 6,823 | 47 | 0.69 |
| 4. Live phenol | 55 | 0 | 0 | 132 | 0 | 0 |
| 5. Fermi's vaccine | 57 | 1 | 1.79 | 60 | 1 | 1.67 |
| 6. Fermi's sero-vaccine | — | — | — | 5 | 0 | 0 |
| 7. Heated | 4,150 | 15 | 0.36 | 4,348 | 16 | 0.37 |
| 8. Killed ether | 1,762 | 9 | 0.51 | 3,009 | 11 | 0.37 |
| 9. Mixed | 1,923 | 2 | 0.10 | 3,902 | 5 | 0.13 |
| 10. Yatren | 80 | 0 | 0 | 298 | 0 | 0 |
| Total | 13,195 | 65 | 0.49 | 23,242 | 109 | 0.47 |

Category B.

| | | | | | | |
|-------------------------------|--------|----|------|--------|-----|------|
| 1. Cords | 2,578 | 19 | 0.73 | 11,438 | 75 | 0.66 |
| 2. Dilutions | 1,809 | 8 | 0.44 | 5,885 | 17 | 0.29 |
| 3. Killed phenol | 3,918 | 11 | 0.28 | 10,764 | 43 | 0.40 |
| 4. Live phenol | 73 | 0 | 0 | 428 | 1 | 0.23 |
| 5. Fermi's vaccine | 860 | 2 | 0.23 | 860 | 2 | 0.23 |
| 6. Fermi's sero-vaccine | — | — | — | 23 | 0 | 0 |
| 7. Heated | 5,934 | 8 | 0.13 | 12,103 | 21 | 0.17 |
| 8. Killed ether | 864 | 3 | 0.35 | 3,653 | 6 | 0.16 |
| 9. Mixed | 3,077 | 4 | 0.13 | 14,544 | 24 | 0.17 |
| 10. Yatren | 591 | 1 | 0.17 | 2,644 | 9 | 0.34 |
| Total | 19,704 | 56 | 0.28 | 62,342 | 198 | 0.32 |

Category C.

| | Fifth review | | | All five reviews | | |
|-------------------------|----------------|------------|-------------|------------------|--------------|-------------|
| | Number treated | Deaths | Mortality % | Number treated | Deaths | Mortality % |
| 1. Cords | 8,050 | 10 | 0.12 | 37,537 | 115 | 0.31 |
| 2. Dilutions | 2,365 | 2 | 0.08 | 14,181 | 19 | 0.13 |
| 3. Killed phenol | 40,886 | 242 | 0.59 | 137,986 | 1,030 | 0.75 |
| 4. Live phenol | 234 | 1 | 0.43 | 952 | 2 | 0.21 |
| 5. Fermi's vaccine ... | 839 | 3 | 0.36 | 854 | 3 | 0.35 |
| 6. Fermi's sero-vaccine | — | — | — | 5 | 0 | 0 |
| 7. Heated | 16,228 | 42 | 0.26 | 35,178 | 57 | 0.16 |
| 8. Killed ether | 4,639 | 8 | 0.17 | 15,917 | 28 | 0.18 |
| 9. Mixed | 1,890 | 0 | 0 | 9,511 | 8 | 0.08 |
| 10. Yatren | 376 | 2 | 0.53 | 1,486 | 4 | 0.27 |
| Total | 75,507 | 310 | 0.41 | 253,607 | 1,266 | 0.50 |

Category D.

| | | | | | | |
|-------------------------|--------------|----------|-------------|---------------|-----------|-------------|
| 1. Cords | 1,217 | 0 | 0 | 4,348 | 3 | 0.07 |
| 2. Dilutions | 608 | 4 | 0.66 | 3,342 | 4 | 0.12 |
| 3. Killed phenol | 1,394 | 0 | 0 | 6,317 | 6 | 0.09 |
| 4. Live phenol | 6 | 0 | 0 | 79 | 0 | 0 |
| 5. Fermi's vaccine ... | 0 | — | — | 11 | 0 | 0 |
| 6. Fermi's sero-vaccine | — | — | — | — | — | — |
| 7. Heated | 342 | 0 | 0 | 1,972 | 0 | 0 |
| 8. Killed ether | 0 | — | — | 12,722 | 0 | 0 |
| 9. Mixed | 548 | 2 | 0.37 | 4,576 | 2 | 0.04 |
| 10. Yatren | 298 | 0 | 0 | 956 | 0 | 0 |
| Total | 4,413 | 6 | 0.14 | 34,333 | 15 | 0.04 |

Details regarding 3,040 persons, of whom two died of rabies, are lacking.

It will be observed that six deaths occurred in the D category. These all emanated from Bulgarian institutes. There seems to be some dubiety as to the definitions of the various categories. The system adopted at the Paris International Rabies Conference should be strictly adhered to—namely :

- A = proved rabid by experiment ;
- B = certified rabid by medical or veterinary physician ;
- C = suspected to be rabid ;
- D = not suspected to be rabid.

In this and in subsequent sections the statistics of the two race types will, as far as is possible, be treated separately, as the degree of heterogeneity introduced when the two race types are considered together is so great as to mask other effects. This procedure has been rendered possible by the fact that the majority of directors

of institutes have acceded to the request that the figures relating to the two race types should be submitted on separate schedules. A few directors have not done so, and their attention is again drawn to the importance of this procedure. For this reason, the whole of the returns are not available for analysis.

In the following table, the statistics for categories A and B combined—that is, the statistics regarding those bitten by animals proved or certified to be rabid—and those for category C are given for the fifth review and for the total of the five reviews.

Categories A and B (combined).

| | Fifth review | | | Number treated | All five reviews Deaths | | Mortality % |
|---------------------------------------|----------------|--------|-------------|----------------|----------------------------|------------|-------------|
| | Number treated | Deaths | Mortality % | | Observed | Calculated | |
| <i>Europeans :</i> | | | | | | | |
| 1. Cords | 1,928 | 2 | 0.10 | 5,925 | 12 | 12.3 | 0.20 |
| 2. Dilutions . . . | 2,116 | 11 | 0.52 | 9,409 | 24 | 19.6 | 0.26 |
| 3. Killed phenol | 2,745 | 6 | 0.22 | 8,299 | 12 | 17.3 | 0.14 |
| 4. Live phenol. | 128 | 0 | 0 | 866 | 2 | 1.8 | 0.23 |
| 5. Fermi's vacc. | 917 | 3 | 0.33 | 920 | 3 | 1.9 | 0.33 |
| 6. Fermi's sero- vaccine | — | — | — | 28 | 0 | 0.06 | 0 |
| 7. Heated | 10,084 | 23 | 0.23 | 17,461 | 40 | 36.4 | 0.23 |
| 8. Killed ether . | 2,626 | 12 | 0.46 | 9,660 | 24 | 20.1 | 0.25 |
| 9. Mixed | 5,000 | 6 | 0.12 | 20,774 | 33 | 43.3 | 0.16 |
| 10. Yatren | 671 | 1 | 0.15 | 2,942 | 9 | 6.1 | 0.31 |
| Total | 26,215 | 64 | 0.24 | 76,284 | 159 | 158.8 | 0.21 |
| | | | | | P = 0.24 | | |
| <i>Non-Europeans :</i> | | | | | | | |
| 1. Cords | 897 | 10 | 1.11 | 999 | 11 | 7.2 | 1.10 |
| 3. Killed phenol. | 3,000 | 18 | 0.60 | 5,769 | 38 | 41.8 | 0.66 |
| Total | 3,897 | 28 | 0.72 | 6,768 | 49 | 49.0 | 0.72 |
| | | | | | P = 0.15 | | |

Category C.

| | | | | Number treated | | | Mortality % |
|---------------------------------------|----------------|--------|-------------|----------------|----------|------------|-------------|
| | Number treated | Deaths | Mortality % | | Observed | Calculated | |
| <i>Europeans :</i> | | | | | | | |
| 1. Cords | 2,644 | 2 | 0.08 | 7,474 | 10 | 10.5 | 0.13 |
| 2. Dilutions . . . | 2,216 | 1 | 0.05 | 13,654 | 10 | 19.2 | 0.07 |
| 3. Killed phenol | 4,381 | 3 | 0.07 | 11,871 | 14 | 16.7 | 0.12 |
| 4. Live phenol. | 234 | 1 | 0.43 | 952 | 2 | 1.3 | 0.21 |
| 5. Fermi's vacc. | 839 | 3 | 0.36 | 854 | 3 | 1.2 | 0.35 |
| 6. Fermi's sero- vaccine | — | — | — | 5 | 0 | 0 | 0 |
| 7. Heated | 16,228 | 42 | 0.26 | 35,178 | 57 | 49.4 | 0.16 |
| 8. Killed ether . | 4,639 | 8 | 0.17 | 15,917 | 28 | 22.3 | 0.18 |
| 9. Mixed | 1,890 | 0 | 0 | 9,511 | 8 | 13.3 | 0.08 |
| 10. Yatren | 376 | 2 | 0.53 | 1,486 | 4 | 2.1 | 0.27 |
| Total | 33,447 | 62 | 0.19 | 96,902 | 136 | 136.0 | 0.14 |
| | | | | | P = 0.07 | | |

| | Number treated | Fifth review | | Number treated | All five reviews Deaths | | Mortality % |
|------------------------|----------------|--------------|-------------|----------------|-------------------------|------------|-------------|
| | | Deaths | Mortality % | | Observed | Calculated | |
| <i>Non-Europeans</i> : | | | | | | | |
| 1. Cords | 1,343 | 4 | 0.30 | 2,693 | 17 | 21.0 | 0.63 |
| 3. Killed phenol. | 27,345 | 184 | 0.67 | 63,653 | 502 | 497.9 | 0.79 |
| Total | 28,688 | 188 | 0.66 | 66,346 | 519 | 518.9 | 0.78 |

P = 0.37

The values of P for the figures referring to all five reviews indicate that, when the two race types are considered separately—that is, when the heterogeneity due to race type is excluded—there is no evidence of heterogeneity in either the A and B categories or the C category arising from differences in the methods of treatment employed.

It also appears that, in the A and B categories, the mortality amongst non-Europeans is 3.4 times as great as amongst Europeans ; whilst, in the C category, the ratio is 5.6 (the P values in each case being less than one in a million).

Again, in the case of Europeans, the mortality in the A and B categories is 1.5 times as great as that in the C category (P = 0.0006); whilst, in the case of non-Europeans, the mortality in the A and B categories is 0.92 of that in the C category (P = 0.57). The first P value indicates a significant difference, the second does not. Thus again the fact is brought out that, in the case of non-Europeans, those in the C category are practically at as high a degree of risk as those in the A and B categories—presumably because non-Europeans rarely present themselves for treatment unless the animal which bit them is certainly rabid.

VIII. SEVERITY OF BITING.

The percentage proportions in the several groups are as follows :

| | Deep | Superficial | No visible lesion |
|-----------------------------------|------|-------------|-------------------|
| 1. Cords | 20.5 | 65.1 | 14.4 |
| 2. Dilutions | 14.5 | 62.8 | 22.7 |
| 3. Killed phenol | 51.5 | 39.8 | 8.7 |
| 4. Live phenol | 32.2 | 57.6 | 10.2 |
| 5. Fermi's vaccine | 29.9 | 68.1 | 2.0 |
| 6. Fermi's sero-vaccine | 2.2 | 84.3 | 13.5 |
| 7. Heated | 20.5 | 67.4 | 12.1 |
| 8. Killed ether | 19.7 | 63.4 | 17.0 |
| 9. Mixed | 35.4 | 47.6 | 17.0 |
| 10. Yatren | 2.5 | 65.4 | 32.0 |
| Total | 34.7 | 53.3 | 12.0 |

The figures relating to mortality are as follows :

| | (a) Deep | | | (b) Superficial | | | No visible lesion | |
|-------------------------------|----------------|--------|-----------|-----------------|--------|-----------|-------------------|--------|
| | Number treated | Deaths | Mortality | Number treated | Deaths | Mortality | Number treated | Deaths |
| 1. Cords | 2,768 | 27 | 0.98 | 8,808 | 8 | 0.09 | 1,950 | 0 |
| 2. Dilutions | 747 | 11 | 1.47 | 3,234 | 5 | 0.15 | 1,166 | 1 |
| 3. Killed phenol .. | 25,767 | 247 | 0.96 | 19,938 | 36 | 0.18 | 4,334 | 0 |
| 4. Live phenol | 129 | 1 | 0.78 | 231 | 0 | 0 | 41 | 0 |
| 5. Fermi's vaccine. | 526 | 6 | 1.14 | 1,200 | 0 | 0 | 36 | 0 |
| 6. Fermi's sero-vaccine | 4 | 0 | 0 | 150 | 0 | 0 | 24 | 0 |
| 7. Heated | 5,549 | 24 | 0.43 | 18,249 | 39 | 0.21 | 3,279 | 2 |
| 8. Killed ether | 1,429 | 13 | 0.91 | 4,603 | 7 | 0.15 | 1,233 | 0 |
| 9. Mixed | 2,634 | 5 | 0.19 | 3,541 | 3 | 0.08 | 1,263 | 0 |
| 10. Yatren | 34 | 1 | 29.41 | 880 | 2 | 0.23 | 431 | 0 |
| Total | 39,587 | 335 | 0.85 | 60,834 | 100 | 0.16 | 13,757 | 3 |

Information regarding the depth of wound was lacking in the case of 1,681 persons, none of whom developed rabies.

Three deaths are recorded amongst those with "no visible lesion". One of these is reported from Cernauti and two from Cluj, both in Roumania.

In the following table, the statistics for the period covered by the five reviews are, as before, subdivided according to race type.

All five reviews.

| | (a) Deep | | | | (b) Superficial | | | |
|-------------------------------|----------------|--------------------|------------|-------------|-----------------|-----------|------------|-------------|
| | Number treated | Deaths | | Mortality % | Number treated | Deaths | | Mortality % |
| | | Observed | Calculated | | | Observed | Calculated | |
| <i>Europeans.</i> | | | | | | | | |
| 1. Cords | 3,415 | 20 | 15.5 | 0.58 | 11,928 | 6 | 11.1 | 0.05 |
| 2. Dilutions | 4,892 | 31 | 22.3 | 0.63 | 12,863 | 11 | 11.9 | 0.09 |
| 3. Killed phenol. | 2,395 | 19 | 10.9 | 0.79 | 13,282 | 9 | 12.3 | 0.07 |
| 4. Live phenol .. | 557 | 1 | 2.5 | 0.18 | 1,131 | 3 | 1.0 | 0.27 |
| 5. Fermi's vacc. . | 528 | 6 | 2.4 | 1.14 | 1,222 | 0 | 1.1 | 0 |
| 6. Fermi's sero-vaccine | 8 | 0 | 0 | 0 | 218 | 0 | 0.2 | 0 |
| 7. Heated | 10,057 | 40 | 45.8 | 0.40 | 41,050 | 55 | 38.0 | 0.13 |
| 8. Killed ether .. | 8,546 | 37 | 38.9 | 0.43 | 24,662 | 15 | 22.9 | 0.06 |
| 9. Mixed | 11,366 | 30 | 50.7 | 0.26 | 18,732 | 14 | 17.4 | 0.07 |
| 10. Yatren | 187 | 7 | 0.9 | 3.74 | 3,334 | 6 | 3.1 | 0.18 |
| Total | 41,951 | 191 | 189.9 | 0.46 | 128,422 | 119 | 119 | 0.093 |
| | | P < 1 in a million | | | | P = 0.008 | | |
| <i>Non-Europeans.</i> | | | | | | | | |
| 1. Cords | 668 | 17 | 7.7 | 2.54 | 2,824 | 10 | 7.4 | 0.36 |
| 3. Killed phenol . | 40,997 | 465 | 474.3 | 1.13 | 30,546 | 78 | 80.6 | 0.26 |
| Total | 41,665 | 482 | 482 | 1.16 | 33,370 | 88 | 88.0 | 0.26 |
| | | P = 0.0009 | | | | P = 0.32 | | |

The values of P are somewhat different from those recorded last year, when the values were 0.029 and 0.01 for deep bites, and 0.53 and 0.40 for superficial bites in Europeans and non-Europeans respectively. Thus the evidence of heterogeneity amongst the deeply bitten is greater than was recorded in the last review, and also heterogeneity is now indicated amongst superficially bitten Europeans. This is mainly due to excessive mortalities amongst those treated by heated vaccines at Cluj (Roumania). It would appear that there is considerable variation in the interpretation of the phrase "deeply bitten" at the various institutes. It appears that, for those deeply bitten, the mortality amongst non-Europeans is 2.3 times as great as amongst Europeans, whilst, in the case of those bitten superficially, the ratio is 2.8. Comparing these ratios with the ratio 5.2 found in Section V for all degrees of severity of biting, it is clear that severity of bite is one of the factors, but not the sole factor, which determine the difference in mortality between the two race types. This is in conformity with the fact that, amongst Europeans, the percentage of those deeply bitten is 24.6, whereas amongst non-Europeans it is 55.5.

Finally, amongst Europeans, the mortality from deep bites is 4.9 times as great as from superficial, whilst amongst non-Europeans it is 4.4 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 | 69.9 | 30.1 |
| 2. Dilutions | 69.1 | 30.9 |
| 3. Killed phenol | 80.5 | 19.5 |
| 4. Live phenol | 64.3 | 35.7 |
| 5. Fermi's vaccine | 60.4 | 39.6 |
| 6. Fermi's sero-vaccine | 38.8 | 61.2 |
| 7. Heated | 63.6 | 36.4 |
| 8. Killed ether | 49.8 | 50.2 |
| 9. Mixed | 68.5 | 31.5 |
| 10. Yatren | 66.7 | 33.2 |
| Total | 71.7 | 28.3 |

The figures relating to mortality are :

| | (a) On bare skin | | | (b) Through clothing | | |
|-----------------------------------|------------------|------------|-------------|----------------------|-----------|-------------|
| | Number treated | Deaths | Mortality % | Number treated | Deaths | Mortality % |
| 1. Cords | 8,071 | 25 | 0.31 | 3,473 | 5 | 0.14 |
| 2. Dilutions ... | 3,554 | 16 | 0.45 | 1,594 | 1 | 0.06 |
| 3. Killed phenol | 40,761 | 270 | 0.66 | 9,899 | 13 | 0.13 |
| 4. Live phenol . | 258 | 1 | 0.39 | 143 | 0 | 0 |
| 5. Fermi's vacc. | 1,061 | 5 | 0.47 | 695 | 1 | 0.14 |
| 6. Fermi's sero- vaccine | 69 | 0 | 0 | 109 | 0 | 0 |
| 7. Heated | 17,220 | 59 | 0.34 | 9,857 | 6 | 0.06 |
| 8. Killed ether.. | 3,002 | 20 | 0.67 | 3,030 | 0 | 0 |
| 9. Mixed | 5,094 | 5 | 0.98 | 2,344 | 3 | 0.13 |
| 10. Yatren | 898 | 2 | 0.22 | 447 | 1 | 0.22 |
| Total | 79,988 | 403 | 0.50 | 31,591 | 30 | 0.09 |

Information regarding 4,280 persons, of whom six developed rabies, was lacking.

The corresponding statistics for the set of five reviews subdivided according to race type are as follows :

| | (a) On bare skin | | | | (b) Through clothing | | | |
|-----------------------------------|------------------|------------|-------------------|-------------|----------------------|-----------|------------------|--------------|
| | Number treated | Deaths | | Mortality % | Number treated | Deaths | | Mortality % |
| | | Observed | Calculated | | | Observed | Calculated | |
| <i>Europeans :</i> | | | | | | | | |
| 1. Cords | 11,359 | 25 | 27.2 | 0.22 | 5,087 | 1 | 1.5 | 0.020 |
| 2. Dilutions ... | 15,847 | 42 | 37.9 | 0.27 | 6,790 | 1 | 2.0 | 0.015 |
| 3. Killed phenol. | 16,705 | 26 | 39.9 | 0.16 | 5,033 | 1 | 1.5 | 0.020 |
| 4. Live phenol .. | 1,259 | 3 | 3.0 | 0.24 | 671 | 1 | 0.2 | 0.149 |
| 5. Fermi's vacc.. | 1,084 | 5 | 2.6 | 0.46 | 701 | 1 | 0.2 | 0.143 |
| 6. Fermi's sero- vaccine | 98 | 0 | 0.2 | 0 | 157 | 0 | 0.05 | 0 |
| 7. Heated | 34,692 | 89 | 82.9 | 0.26 | 20,352 | 8 | 6.1 | 0.039 |
| 8. Killed ether .. | 13,193 | 50 | 31.5 | 0.38 | 17,157 | 1 | 5.2 | 0.006 |
| 9. Mixed | 23,290 | 39 | 55.7 | 0.17 | 12,359 | 5 | 3.7 | 0.040 |
| 10. Yatren | 3,767 | 11 | 9.0 | 0.29 | 1,617 | 2 | 0.5 | 0.124 |
| Total | 121,294 | 290 | 289.8 | 0.24 | 69,924 | 21 | 20.95 | 0.030 |
| | | | P = 0.0008 | | | | P = 0.015 | |
| <i>Non-Europeans :</i> | | | | | | | | |
| 1. Cords | 2,218 | 23 | 19.7 | 1.04 | 1,541 | 5 | 3.3 | 0.32 |
| 3. Killed phenol . | 57,834 | 511 | 514.3 | 0.88 | 15,856 | 32 | 33.7 | 0.20 |
| Total | 60,052 | 534 | 534.0 | 0.89 | 17,397 | 37 | 37.0 | 0.21 |
| | | | P = 0.45 | | | | P = 0.32 | |

There is no evidence of heterogeneity in the non-European statistics. Amongst Europeans, however, there is evidence of

heterogeneity in both sets of statistics. The evidence in the case of those bitten on the bare skin is due mainly to excessive mortality amongst those treated by killed ether vaccines at the Yugoslav institutes. In the case of those bitten through clothing, it is due mainly to mortalities higher than the average in groups 4, 5 and 10.

The mortality amongst those bitten on the bare skin is, in the case of Europeans, 8 times, and, in the case of non-Europeans, 4.2 times as great as that observed amongst those bitten through clothing. The probable reason for this difference is that the European bitten on the bare skin is usually bitten on the head or hands, whereas this is not so generally the case amongst non-Europeans.

The mortality amongst non-Europeans in the case of those bitten on the bare skin is 3.7 times, and, in the case of those bitten through clothing, is 7 times as great as amongst Europeans. These ratios are less than that found in Section V, where intervention of clothing is disregarded, and the reduction is in agreement with the view that intervention of clothing is one of the factors which bring about the different mortalities in the two race types. The higher ratio for those bitten through clothing would seem to indicate that the clothing of the European is a greater safeguard than is that of the non-European.

X. POSITION OF BITE.

The percentage figures for those bitten on the different localities are as follows :

| | Head | Arm | Trunk | Leg |
|-------------------------------|------------|-------------|------------|-------------|
| 1. Cords | 5.7 | 48.3 | 4.1 | 41.9 |
| 2. Dilutions | 5.3 | 56.5 | 7.5 | 30.8 |
| 3. Killed phenol | 5.7 | 34.5 | 3.5 | 56.3 |
| 4. Live phenol | 5.7 | 50.1 | 5.7 | 38.4 |
| 5. Fermi's vaccine | 5.0 | 47.6 | 4.7 | 42.6 |
| 6. Fermi's sero-vaccine | 2.8 | 72.4 | 1.7 | 23.0 |
| 7. Heated | 5.2 | 51.4 | 4.8 | 38.4 |
| 8. Killed ether | 6.1 | 37.4 | 4.2 | 52.3 |
| 9. Mixed | 4.3 | 56.3 | 2.8 | 36.7 |
| 10. Yatren | 1.8 | 62.1 | 2.2 | 33.9 |
| Total | 5.4 | 43.2 | 4.0 | 47.3 |

The figures relating to mortality are :

| | (a) Head | | | (b) Arm | | |
|-------------------------------|----------------|--------|-------------|----------------|--------|-------------|
| | Number treated | Deaths | Mortality % | Number treated | Deaths | Mortality % |
| 1. Cords | 722 | 16 | 2.21 | 6,154 | 11 | 0.18 |
| 2. Dilutions | 271 | 9 | 3.32 | 2,906 | 6 | 0.21 |
| 3. Killed phenol | 2,857 | 91 | 3.19 | 17,188 | 78 | 0.45 |
| 4. Live phenol | 23 | 1 | 4.35 | 201 | 0 | 0 |
| 5. Fermi's vaccine | 87 | 4 | 4.60 | 822 | 1 | 0.12 |
| 6. Fermi's sero-vaccine | 5 | 0 | 0 | 129 | 0 | 0 |
| 7. Heated | 1,234 | 29 | 2.35 | 12,258 | 31 | 0.25 |
| 8. Killed ether | 369 | 15 | 4.07 | 2,255 | 5 | 0.22 |
| 9. Mixed | 319 | 3 | 0.94 | 4,187 | 2 | 0.05 |
| 10. Yatren | 24 | 0 | 0 | 836 | 2 | 0.24 |
| Total | 5,911 | 168 | 2.84 | 46,936 | 136 | 0.29 |

| | (c) Trunk | | | (d) Leg | | |
|-------------------------------|----------------|--------|-------------|----------------|--------|-------------|
| | Number treated | Deaths | Mortality % | Number treated | Deaths | Mortality % |
| 1. Cords | 524 | 1 | 0.19 | 5,345 | 8 | 0.15 |
| 2. Dilutions | 384 | 0 | 0 | 1,587 | 2 | 0.13 |
| 3. Killed phenol | 1,735 | 3 | 0.17 | 28,076 | 89 | 0.32 |
| 4. Live phenol | 23 | 0 | 0 | 154 | 0 | 0 |
| 5. Fermi's vaccine | 82 | 0 | 0 | 736 | 1 | 0.14 |
| 6. Fermi's sero-vaccine | 3 | 0 | 0 | 41 | 0 | 0 |
| 7. Heated | 1,153 | 0 | 0 | 9,158 | 3 | 0.03 |
| 8. Killed ether | 253 | 0 | 0 | 3,155 | 0 | 0 |
| 9. Mixed | 205 | 1 | 0.49 | 2,727 | 2 | 0.07 |
| 10. Yatren | 29 | 0 | 0 | 456 | 1 | 0.22 |
| Total | 4,391 | 5 | 0.11 | 51,435 | 106 | 0.21 |

Information regarding the position of the bite was wanting in the case of 5,781 persons, none of whom died. A further reduction of 1,405, of whom 22 died of rabies, has had to be made. These are such cases from British India (treated by killed phenol vaccines) as are classified' as "multiple". This term indicates that the individual was bitten on two or more of the localities—arm, trunk, and leg. The omission of these figures is unavoidable, and is regrettable, as it vitiates the statistics relating to killed phenol vaccines in (b), (c) and (d) above. The Indian group "multiple face", which indicates that the person is bitten on two or more positions, one of which is the head, is included in (a) above.

The statistics for all five reviews subdivided into race type are as follows :

| | (a) Head | | | | (b) Arm | | | |
|-------------------------------|----------------|------------|--------------|------------------|----------------|------------|--------------|------------------|
| | Number treated | Deaths | | Mortality % | Number treated | Deaths | | Mortality % |
| | | Observed | Calculated | | | Observed | Calculated | |
| <i>Europeans.</i> | | | | | | | | |
| 1. Cords | 1,068 | 9 | 13.7 | 0.84 | 10,001 | 14 | 13.5 | 0.14 |
| 2. Dilutions | 2,041 | 26 | 26.1 | 1.27 | 15,708 | 16 | 21.1 | 0.10 |
| 3. Killed phenol. | 1,490 | 15 | 19.1 | 1.01 | 14,220 | 10 | 19.1 | 0.07 |
| 4. Live phenol .. | 133 | 1 | 1.7 | 0.75 | 1,023 | 2 | 1.4 | 0.20 |
| 5. Fermi's vacc.. | 165 | 7 | 2.1 | 4.24 | 1,792 | 1 | 2.4 | 0.06 |
| 6. Fermi's sero-vaccine | 10 | 0 | 0.1 | 0 | 160 | 0 | 0.2 | 0 |
| 7. Heated | 2,640 | 42 | 33.7 | 1.59 | 17,294 | 39 | 23.3 | 0.23 |
| 8. Killed ether .. | 2,069 | 31 | 26.5 | 1.50 | 11,482 | 21 | 15.5 | 0.18 |
| 9. Mixed | 2,091 | 15 | 26.7 | 0.72 | 18,551 | 18 | 25.0 | 0.10 |
| 10. Yatren | 180 | 6 | 2.3 | 3.33 | 3,393 | 5 | 4.6 | 0.15 |
| Total | 11,887 | 152 | 152.0 | 1.28 | 93,624 | 126 | 126.1 | 0.13 |
| | | | | P = 0.003 | | | | P = 0.010 |
| <i>Non-Europeans.</i> | | | | | | | | |
| 1. Cords | 204 | 12 | 9.6 | 5.88 | 1,097 | 5 | 7.4 | 0.46 |
| 3. Killed phenol . | 3,647 | 169 | 171.4 | 4.63 | 21,087 | 144 | 141.6 | 0.68 |
| Total | 3,851 | 181 | 181.0 | 4.70 | 22,184 | 149 | 149.0 | 0.67 |
| | | | | P = 0.34 | | | | P = 0.37 |
| | (c) Trunk | | | | (d) Leg | | | |
| | Number treated | Deaths | | Mortality % | Number treated | Deaths | | Mortality % |
| | | Observed | Calculated | | | Observed | Calculated | |
| <i>Europeans.</i> | | | | | | | | |
| 1. Cords | 424 | 0 | — | 0 | 5,619 | 5 | 2.2 | 0.19 |
| 2. Dilutions | 610 | 0 | — | 0 | 8,214 | 5 | 3.2 | 0.06 |
| 3. Killed phenol. | 640 | 0 | — | 0 | 6,806 | 2 | 2.7 | 0.03 |
| 4. Live phenol .. | 89 | 0 | — | 0 | 685 | 1 | 0.3 | 0.15 |
| 5. Fermi's vacc. . | 138 | 0 | — | 0 | 1,758 | 1 | 0.7 | 0.06 |
| 6. Fermi's sero-vaccine | 6 | 0 | — | 0 | 76 | 0 | 0.03 | 0 |
| 7. Heated | 3,101 | 0 | — | 0 | 14,527 | 3 | 5.7 | 0.02 |
| 8. Killed ether .. | 1,669 | 0 | — | 0 | 18,152 | 0 | 7.1 | 0. |
| 9. Mixed | 1,323 | 2 | — | 0.15 | 13,684 | 9 | 5.4 | 0.07 |
| 10. Yatren | 112 | 0 | — | 0 | 1,699 | 2 | 0.7 | 0.12 |
| Total | 8,112 | 2 | — | 0.025 | 71,220 | 28 | 28.0 | 0.039 |
| | | | | | | | | P = 0.014 |
| <i>Non-Europeans.</i> | | | | | | | | |
| 1. Cords | 265 | 1 | 0.7 | 0.38 | 2,235 | 10 | 8.7 | 0.45 |
| 3. Killed phenol . | 2,571 | 6 | 6.3 | 0.23 | 43,691 | 168 | 169.3 | 0.38 |
| Total | 2,836 | 7 | 7.0 | 0.24 | 45,926 | 178 | 178.0 | 0.39 |
| | | | | P = 0.89 | | | | P = 0.65 |

As in the fourth review, the values of P indicate no evidence of heterogeneity amongst non-Europeans. There is, however, evidence of heterogeneity in the European statistics. In the case of those bitten on the head, evidence of heterogeneity almost disappears ($P = 0.04$) when the Yatren and Fermi's vaccine groups from Bulgaria and Czechoslovakia respectively are excluded—in fact, when the cords and killed phenol statistics alone are compared, the difference in mortality is entirely insignificant ($P = 0.68$). In the case of those bitten on the arm, the evidence of heterogeneity depends mainly on those treated by heated vaccines, the observed mortality being much in excess at Bucharest and Cluj. In the case of those bitten on the leg, the chief disturbing factor is amongst those treated in Yugoslavia by killed ether vaccines, the observed number of deaths being zero, instead of 7.1 as calculated from the average mortality. This is a curious result. In fact, persons bitten on the leg in Yugoslavia show a persistent absence of deaths. From the summary of four reviews published last year, no deaths, instead of an expected 4.8, were recorded amongst 14,997 treated persons.

Summarising these results, it appears that, in the positions head and arm, the sources of disturbance do not seem to be related in any direct way to the method of treatment, but rather to the geographical situation of the institutes concerned—namely, Bulgaria, Czechoslovakia, and Roumania.

The mortalities amongst those bitten on the various positions for the two race types are as follows :

| | Europeans | Non-Europeans | Ratio | <u>Non-Europeans</u> Europeans |
|-------------|-----------|---------------|-------|-----------------------------------|
| Head | 1.28 | 4.70 | | 3.7 |
| Arm | 0.13 | 0.67 | | 5.0 |
| Trunk | 0.025 | 0.24 | | 9.9 |
| Leg | 0.039 | 0.39 | | 9.9 |

Each of these ratios indicates a significant difference. That the legs of the Europeans are more usually clothed than those of non-Europeans probably accounts for the high ratio for those bitten on the leg.

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 | 75.7 | 23.6 | 13.6 | 5.0 |
| 2. Dilutions | 49.1 | 27.3 | 17.3 | 6.5 |
| 3. Killed phenol | 59.6 | 19.4 | 14.0 | 7.0 |
| 4. Live phenol | 54.9 | 20.0 | 16.7 | 8.5 |
| 5. Fermi's vaccine | 72.6 | 18.5 | 6.0 | 2.9 |
| 6. Fermi's sero-vaccine | 53.4 | 21.9 | 23.0 | 1.7 |
| 7. Heated | 54.6 | 30.5 | 11.5 | 3.4 |
| 8. Killed ether | 71.2 | 13.8 | 9.5 | 5.5 |
| 9. Mixed | 47.8 | 25.0 | 19.1 | 8.1 |
| 10. Yatren | 36.3 | 27.6 | 23.9 | 12.0 |
| Total | 58.0 | 22.0 | 13.8 | 6.2 |

The figures relating to mortality in the several groups are :

| | (a) 0 to 4 days | | | (b) 5 to 7 days | | |
|-------------------------------|-----------------|------------|-------------|-----------------|-----------|-------------|
| | Number treated | Deaths | Mortality % | Number treated | Deaths | Mortality % |
| 1. Cords | 7,721 | 22 | 0.31 | 3,160 | 8 | 0.25 |
| 2. Dilutions | 2,525 | 10 | 0.40 | 1,406 | 6 | 0.43 |
| 3. Killed phenol | 30,655 | 164 | 0.46 | 9,981 | 45 | 0.45 |
| 4. Live phenol | 220 | 1 | 0.45 | 80 | 0 | 0 |
| 5. Fermi's vaccine | 1,280 | 6 | 0.47 | 326 | 0 | 0 |
| 6. Fermi's sero-vaccine | 95 | 0 | 0 | 39 | 0 | 0 |
| 7. Heated | 7,543 | 12 | 0.17 | 4,204 | 2 | 0.05 |
| 8. Killed ether | 5,172 | 16 | 0.31 | 1,002 | 3 | 0.30 |
| 9. Mixed | 3,555 | 5 | 0.14 | 1,860 | 3 | 0.16 |
| 10. Yatren | 489 | 1 | 0.20 | 372 | 2 | 0.54 |
| Total | 59,255 | 237 | 0.40 | 22,430 | 69 | 0.31 |

| | (c) 8 to 14 days | | | (d) More than 14 days | | |
|-------------------------------|------------------|-----------|-------------|-----------------------|-----------|-------------|
| | Number treated | Deaths | Mortality % | Number treated | Deaths | Mortality % |
| 1. Cords | 1,820 | 4 | 0.22 | 673 | 2 | 0.30 |
| 2. Dilutions | 888 | 0 | 0 | 333 | 1 | 0.30 |
| 3. Killed phenol | 7,192 | 44 | 0.61 | 3,586 | 30 | 0.84 |
| 4. Live phenol | 67 | 0 | 0 | 34 | 0 | 0 |
| 5. Fermi's vaccine | 105 | 0 | 0 | 51 | 0 | 0 |
| 6. Fermi's sero-vaccine | 41 | 0 | 0 | 3 | 0 | 0 |
| 7. Heated | 1,585 | 1 | 0.06 | 470 | 0 | 0 |
| 8. Killed ether | 693 | 1 | 0.14 | 398 | 0 | 0 |
| 9. Mixed | 1,421 | 0 | 0 | 602 | 0 | 0 |
| 10. Yatren | 322 | 0 | 0 | 162 | 0 | 0 |
| Total | 14,134 | 50 | 0.35 | 6,312 | 33 | 0.52 |

Information was lacking in the case of 13,728 persons, of whom fifty died of rabies. These refer mainly to statistics regarding persons treated at Cluj (Roumania), which were submitted in a form differing somewhat from the usual classification.

The figures for the whole set of five reviews, subdivided according to race type, are as follows :

| | (a) 0 to 4 days | | | | (b) 5 to 7 days | | | |
|-------------------------------|------------------|----------|------------|-------------|-----------------------|----------|------------|-------------|
| | Number treated | Deaths | | Mortality % | Number treated | Deaths | | Mortality % |
| | | Observed | Calculated | | | Observed | Calculated | |
| <i>Europeans :</i> | | | | | | | | |
| 1. Cords | 9,213 | 16 | 14.8 | 0.17 | 3,206 | 6 | 3.9 | 0.19 |
| 2. Dilutions | 16,596 | 33 | 26.6 | 0.20 | 5,308 | 10 | 6.4 | 0.19 |
| 3. Killed phenol | 14,324 | 21 | 23.0 | 0.15 | 4,619 | 3 | 5.6 | 0.06 |
| 4. Live phenol .. | 1,022 | 3 | 1.6 | 0.29 | 404 | 1 | 0.5 | 0.25 |
| 5. Fermi's vacc. . | 1,697 | 6 | 2.7 | 0.35 | 664 | 1 | 0.8 | 0.15 |
| 6. Fermi's sero-vaccine | 150 | 0 | 0.2 | 0 | 54 | 0 | 0.06 | 0 |
| 7. Heated | 26,143 | 35 | 41.9 | 0.13 | 10,542 | 8 | 12.7 | 0.08 |
| 8. Killed ether .. | 28,256 | 44 | 45.3 | 0.16 | 5,437 | 4 | 6.5 | 0.07 |
| 9. Mixed | 19,652 | 25 | 31.5 | 0.13 | 8,132 | 11 | 9.8 | 0.14 |
| 10. Yatren | 2,080 | 8 | 3.3 | 0.38 | 1,500 | 4 | 1.8 | 0.27 |
| Total | 119,133 | 191 | 190.9 | 0.16 | 39,866 | 48 | 48.06 | 0.12 |
| | | P = 0.11 | | | | P = 0.18 | | |
| <i>Non-Europeans.</i> | | | | | | | | |
| 1. Cords | 1,966 | 15 | 14.2 | 0.76 | 965 | 4 | 6.0 | 0.41 |
| 3. Killed phenol .. | 44,815 | 324 | 324.7 | 0.72 | 14,602 | 93 | 91.0 | 0.64 |
| Total | 46,781 | 339 | 338.9 | 0.72 | 15,567 | 97 | 97.0 | 0.62 |
| | | P = 0.83 | | | | P = 0.40 | | |
| | (c) 8 to 14 days | | | | (d) More than 14 days | | | |
| | Number treated | Deaths | | Mortality % | Number treated | Deaths | | Mortality % |
| | | Observed | Calculated | | | Observed | Calculated | |
| <i>Europeans. .</i> | | | | | | | | |
| 1. Cords | 3,357 | 3 | 2.6 | 0.09 | 964 | 1 | 1.0 | 0.10 |
| 2. Dilutions | 3,305 | 1 | 2.6 | 0.03 | 1,581 | 3 | 1.6 | 0.19 |
| 3. Killed phenol .. | 3,230 | 3 | 2.5 | 0.09 | 1,237 | 1 | 1.2 | 0.08 |
| 4. Live phenol... | 320 | 0 | 0.3 | 0 | 184 | 0 | 0.2 | 0 |
| 5. Fermi's vacc. . | 398 | 0 | 0.3 | 0 | 137 | 0 | 0.1 | 0 |
| 6. Fermi's sero-vaccine | 46 | 0 | 0.04 | 0 | 5 | 0 | 0 | 0 |
| 7. Heated | 3,920 | 3 | 3.1 | 0.07 | 1,164 | 1 | 1.2 | 0.09 |
| 8. Killed ether... | 2,891 | 4 | 2.3 | 0.14 | 1,715 | 0 | 1.7 | 0 |
| 9. Mixed..... | 5,503 | 5 | 4.3 | 0.09 | 2,362 | 3 | 2.4 | 0.13 |
| 10. Yatren | 1,189 | 0 | 0.9 | 0 | 615 | 1 | 0.6 | 0.16 |
| Total | 24,159 | 19 | 18.9 | 0.079 | 9,964 | 10 | 10.0 | 0.10 |
| | | P = 0.68 | | | | P = 0.70 | | |
| <i>Non-Europeans.</i> | | | | | | | | |
| 1. Cords | 518 | 3 | 3.6 | 0.58 | 261 | 6 | 3.2 | 2.30 |
| 3. Killed phenol .. | 9,595 | 68 | 67.3 | 0.71 | 4,928 | 58 | 60.8 | 1.18 |
| Total | 10,113 | 71 | 70.9 | 0.70 | 5,189 | 64 | 64.0 | 1.23 |
| | | P = 0.75 | | | | P = 0.11 | | |

In none of the groups do the values of P indicate significant differences ; consequently, the effects of heterogeneity due to method of treatment may be neglected, and the figures may be summed as under.

| | Number treated | Deaths | | Mortality % |
|-------------------------|----------------|------------|--------------|-------------|
| | | Observed | Calculated | |
| <i>Europeans.</i> | | | | |
| 0 to 4 days | 119,133 | 191 | 165.3 | 0.16 |
| 5 to 7 days | 39,866 | 48 | 55.3 | 0.12 |
| 8 to 14 days | 24,159 | 19 | 33.5 | 0.08 |
| More than 14 days | 9,964 | 10 | 13.8 | 0.10 |
| Total | 193,122 | 268 | 267.9 | 0.14 |
| $P = 0.007$ | | | | |
| <i>Non-Europeans.</i> | | | | |
| 0 to 4 days | 46,781 | 339 | 344.0 | 0.72 |
| 5 to 7 days | 15,567 | 97 | 114.5 | 0.62 |
| 8 to 14 days | 10,113 | 71 | 74.4 | 0.70 |
| More than 14 days | 5,189 | 64 | 38.1 | 1.23 |
| Total | 77,650 | 571 | 571.0 | 0.73 |
| $P = 0.00015$ | | | | |

In this table, the values of P for both race types are significant. It may be noted that, in the non-European group, the mortalities for the three periods less than 14 days are of the same order, whilst the mortality for late arrivals—more than 14 days late—is much higher. In the European group, on the other hand, there is a general tendency for the mortalities to fall, the disturbances leading to heterogeneity occurring in the 0 to 4 group, where it is above the average, and in the 8 to 14 group, where it is less than the average.

If the statistics be divided into the two groups, less than 14 days and more than 14 days, the figures are as follows :

| | Number treated | Deaths | | Mortality % |
|-------------------------|----------------|------------|--------------|-------------|
| | | Observed | Calculated | |
| <i>Europeans.</i> | | | | |
| Less than 14 days | 183,158 | 258 | 254.2 | 0.14 |
| More than 14 days | 9,964 | 10 | 13.8 | 0.11 |
| | 193,122 | 268 | 268.0 | 0.14 |
| $P = 0.29$ | | | | |
| <i>Non-Europeans :</i> | | | | |
| Less than 14 days | 72,461 | 507 | 532.8 | 0.70 |
| More than 14 days | 5,189 | 64 | 38.2 | 1.23 |
| | 77,650 | 571 | 571.0 | 0.73 |
| $P = 0.000015$ | | | | |

Thus the fact which was drawn attention to in the previous review is emphasised—namely, that, for some reason which does not appear, the handicap of late arrival, though pronounced in the non-European statistics, is not evident in the European statistics.

It is of interest to note that, in the several successive periods, the ratios of non-European to European mortalities are 4.5, 5.1, 9.0 and 12.3. Thus the relative mortality increases progressively with lateness of arrival.

XII. PARALYTIC ACCIDENTS.

The figures relating to the occurrence of post-vaccinal paralysis in the fifth review are as follows :

| | Number treated | Accidents | Proportion | Percentage | |
|-----------------------------------|----------------|-----------|-------------------|--------------|----------------|
| 1. Cords | 13,574 | 3 | 1 in 4,524 | 0.022 | 0 fatal |
| 2. Dilutions | 5,148 | 3 | 1 in 1,716 | 0.058 | 2 fatal |
| 3. Killed phenol . . | 51,671 | 7 | 1 in 7,381 | 0.014 | 2 fatal |
| 4. Live phenol | 401 | 0 | — | 0 | |
| 5. Fermi's vaccine . | 1,762 | 0 | — | 0 | |
| 6. Fermi's sero-vaccine | 178 | 0 | — | 0 | |
| 7. Heated | 27,077 | 2 | 1 in 13,539 | 0.007 | 0 fatal |
| 8. Killed ether | 7,265 | 0 | — | 0 | |
| 9. Mixed | 7,438 | 6 | 1 in 1,240 | 0.081 | 1 fatal |
| 10. Yatren | 1,345 | 1 | 1 in 1,345 | 0.074 | 0 fatal |
| Total | 115,859 | 22 | 1 in 5,266 | 0.019 | 5 fatal |

The figures relating to accidents over the period covered by the five reviews are :

| | Number treated | Accidents | Proportion | Percentage | |
|-----------------------------------|----------------|-----------|-------------------|--------------|-----------------|
| 1. Cords | 63,653 | 24 | 1 in 2,893 | 0.035 | 3 fatal |
| 2. Dilutions | 27,040 | 12 | 1 in 2,253 | 0.044 | 7 fatal |
| 3. Killed phenol . . | 173,684 | 17 | 1 in 10,217 | 0.0098 | 4 fatal |
| 4. Live phenol | 1,967 | 0 | — | 0 | — |
| 5. Fermi's vaccine . | 4,773 | 2 | 1 in 2,387 | 0.057 | 1 fatal |
| 6. Fermi's sero-vaccine | 255 | 0 | — | 0 | — |
| 7. Heated | 55,044 | 2 | 1 in 27,522 | 0.0036 | 0 fatal |
| 8. Killed ether | 38,299 | 4 | 1 in 9,574 | 0.010 | 2 fatal |
| 9. Mixed | 36,097 | 16 | 1 in 2,256 | 0.044 | 2 fatal |
| 10. Yatren | 5,384 | 3 | 1 in 1,795 | 0.056 | 0 fatal |
| Total | 406,196 | 80 | 1 in 5,078 | 0.020 | 19 fatal |

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

| | Number treated | Deaths | | Proportion | Percentage |
|--------------------|----------------|-----------|-------------|-------------------|---------------|
| | | Observed | Calculated | | |
| 1. Killed | 211,983 | 21 | 41.7 | 1 in 10,094 | 0.0099 |
| 2. Live | 128,757 | 52 | 25.3 | 1 in 2,476 | 0.0405 |
| 3. Heated | 55,044 | 2 | 10.8 | 1 in 27,522 | 0.0036 |
| 4. Other | 10,412 | 5 | 2.1 | 1 in 2,084 | 0.0480 |
| Total | 406,196 | 80 | 79.9 | 1 in 5,078 | 0.0197 |

P < 1 in a million.

It appears that the liability to accident after treatment by live vaccines is four times as great as after treatment by killed vaccines, and eleven times as great as after treatment by heated vaccines.

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 |
|---------------------------|--------------|---------------|--------------|---------------|--------------|
| All patients | 0.49 | 0.48 | 0.23 | 0.48 | 0.38 |
| (a) Live vaccines | 0.27 | 0.26 | 0.21 | 0.26 | 0.23 |
| (b) Killed vaccines | 0.65 | 0.80 | 0.28 | 0.66 | 0.51 |
| Europeans | 0.17 | 0.13 | 0.10 | 0.14 | 0.21 |
| (a) Live vaccines | 0.20 | 0.11 | 0.13 | 0.15 | 0.17 |
| (b) Killed vaccines | 0.10 | 0.14 | 0.10 | 0.12 | 0.19 |
| Non-Europeans | 0.84 | 0.88 | 0.78 | 0.83 | 0.62 |
| (a) Live vaccines | 1.02 | 0.82 | 0.71 | 0.74 | 0.46 |
| (b) Killed vaccines | 0.83 | 0.89 | 0.93 | 0.85 | 0.65 |
| Biting animal : | | | | | |
| Dog | 0.42 | 0.44 | 0.24 | 0.47 | 0.36 |
| Cat | 0 | 0.07 | 0.04 | 0.06 | 0.03 |
| Wolf | 18.31 | 0 | 5.52 | 7.3 | 10.2 |
| Jackal | 1.58 | 1.64 | 5.56 | 2.2 | 1.48 |
| Category : | | | | | |
| A | 0.29 | 0.34 | 0.47 | 0.44 | 0.49 |
| B | 0.18 | 0.38 | 0.31 | 0.34 | 0.28 |
| C | 0.60 | 0.57 | 0.25 | 0.62 | 0.41 |
| D | 0.10 | 0.05 | 0.02 | 0.01 | 0.14 |
| Deep bites | 1.18 | 1.06 | 0.74 | 1.10 | 0.85 |
| Superficial bites | 0.12 | 0.24 | 0.09 | 0.18 | 0.16 |
| On bare skin | 0.66 | 0.62 | 0.38 | 0.66 | 0.50 |
| Through clothing | 0.10 | 0.13 | 0.04 | 0.12 | 0.09 |

STATISTICS ON RABIES

| Locality : | First review | Second review | Third review | Fourth review | Fifth review |
|---------------------------------|--------------|---------------|--------------|---------------|--------------|
| Head | 2.85 | 2.42 | 1.24 | 3.17 | 2.84 |
| Arm | 0.40 | 0.49 | 0.25 | 0.35 | 0.29 |
| Trunk | 0.42 | 0.11 | 0.10 | 0.31 | 0.11 |
| Leg | 0.30 | 0.40 | 0.11 | 0.30 | 0.21 |
| Delay in commencing treatment : | | | | | |
| 0 to 4 days | 0.35 | 0.46 | 0.18 | 0.53 | 0.40 |
| 5 to 7 days | 0.59 | 0.46 | 0.16 | 0.38 | 0.31 |
| 8 to 14 days | 0.64 | 0.49 | 0.28 | 0.40 | 0.35 |
| More than 14 days | 1.04 | 0.69 | 0.33 | 0.73 | 0.52 |
| Post vaccinal paralyses ... | 0.025 | 0.009 | 0.027 | 0.021 | 0.019 |
| (a) Cords | 0.22 | 0.019 | 0.048 | 0.025 | 0.022 |
| (b) Dilutions | 0.03 | 0.03 | 0 | 0.105 | 0.058 |
| (c) Killed phenol | 0.006 | 0.003 | 0.026 | 0.008 | 0.014 |

The statistics in which the two race types—European and non-European—are separable have increased considerably in bulk. It is hoped that, in the near future, when the request that they be submitted on separate schedules is acceded to more universally, the numbers will be sufficiently large for definite conclusions to be deduced from them. In the preceding pages, separated tables have been drawn up for the set of five reviews relating to the different categories : depth of bite ; intervention of clothing ; locality of bite ; and delay in the commencement of treatment.

A. With regard to *non-Europeans*, the only evidences of heterogeneity when different methods of treatment are compared are found in (a) the non-European group in Section V, where it is pointed out that the main source of disturbance occurred under exceptional circumstances at a single institute during the period covered by the fourth review ; and (b) in the deeply bitten group, on account of mortalities higher than the average occurring amongst those treated by dried cords. It is suggested that there is probably considerable variation in the interpretation of the phrase "deeply bitten" from institute to institute.

B. With regard to *Europeans*, there is evidence of heterogeneity in seven out of a total of fourteen groups—namely, the deeply bitten, superficially bitten, bitten on bare skin, bitten through clothing, bitten on head, on arm, and on leg. When each of these groups is separately examined, it appears that, in most cases, the disturbance is related more to geographical position than to method of treatment. The main sources of heterogeneity are excessive

mortalities reported from institutes situated in the Balkan peninsula or in its neighbourhood. For example, in the case of the deeply bitten, the heterogeneity arises mainly from Bulgarian statistics relating to treatment by Yatren vaccine. For those bitten superficially, it occurs in the statistics from Cluj (Roumania), where heated vaccines are used. For those bitten through clothing, Bulgarian statistics from institutes using Yatren vaccine are again responsible for the heterogeneity. For those bitten on the arm, the disturbance is due to excessive mortalities at Bucharest and Cluj. The remarkable absence of mortality amongst persons bitten on the leg and treated by killed ether vaccines in Yugoslavia has been referred to in Section X. Thus the figures suggest that, as regards degree of risk, the Balkan group takes an intermediate position between the European and the non-European. Further statistics will no doubt clear up this point.

It would thus appear that, from the statistics so far available, it has not been found possible to detect any clear indication of differences in the efficiencies of the various methods of treatment employed, or, more generally, of a difference between the results of treatment by live and by dead vaccines.

With regard to the degree of the difference between the mortalities of the two race types—European and non-European—and its cause, the conclusions to be drawn from the combined statistics of the five reviews are very similar to those arrived at in the previous review. The mortality amongst non-Europeans is 5.2 times as great as that amongst Europeans.

The racial difference is *reduced* in the case of those belonging to the categories A and B (that is to say, in the case of those bitten by animals proved or certified to be rabid); amongst the deeply bitten; amongst those bitten on the bare skin; and amongst those bitten on the head. Thus, in general, the racial difference is reduced in the case of those at a high degree of risk.

It is *increased* in the case of those in the C category (presumably because the non-European is better acquainted with the symptoms of rabies in animals than is the European); in the case of those bitten through clothing (presumably because the clothing of the European affords a better protection than does that of the non-European); in the case of those bitten on the leg (presumably because the legs of the European are more usually clothed than

are those of the non-European), and in the case of those who arrive late for treatment (possibly because the better educated European, if at risk, recognises more fully the advantage of early arrival, and usually commands more rapid transport facilities).

It would appear that no single one of the factors which reduce the racial difference in mortality is in itself sufficient to account for the racial difference, but that they all participate in it.

Evidence of the advantage of early arrival appears to emerge with definiteness from the non-European statistics, but not from the statistics relating to the Europeans. It was pointed out in the previous review that the influences which come into play in determining the time of arrival are very complex. If the time of arrival were entirely random—that is to say, if it were uncorrelated with the degree of risk—then the variation of mortality would no doubt be an indication of the benefit of early treatment. This is far from being the case. Many factors, psychological as well as material, come into play, and these may differ greatly in different localities and amongst different races.

From figures relating to 406,196 persons treated by the various methods, it appears that the liability to post-vaccinal paralysis amongst those treated by live vaccines is four times as great as amongst those treated by killed vaccines, and eleven times as great as amongst those treated by heated vaccines.

Anti-rabies Treatment in the Union of Soviet Socialist Republics, 1927-1932.

The following schedules relate to persons treated during the years 1931 and 1932. It will be seen that the statistics relating to all persons treated have been subdivided according to the various methods of treatment, but that in dealing with the characteristics of the case histories—namely : biting animal, category, nature of bite, intervention of clothing, and delay in arrival for treatment—no such subdivision has been made. Consequently, the detailed system of analysis employed in these reviews cannot be followed and the effects of the different methods of treatment can only be estimated from the figures relating to all types of case.

| | 1931 Treatment | | | Deaths | |
|--------------------------|-------------------|----------------|------------|--------|---------------------------|
| | Total treated | Persons bitten | Percentage | Total | Per 100 persons bitten |
| Number treated | 59,580 | 38,961 | 66.4 | 53 | 0.14 |
| Methods : | | | | | |
| Pasteur | 5,384 | 4,372 | 11.2 | 5 | 0.11 |
| Ferml | 13,527 | 8,472 | 21.7 | 16 | 0.19 |
| Högyes-Philipps | 38,823 | 24,649 | 63.3 | 32 | 0.13 |
| Remlinger | 498 | 498 | 1.3 | 0 | 0 |
| Fermi and Philipps | 1,348 | 970 | 2.5 | 0 | 0 |
| Biting animal : | | | | | |
| Dog | 44,266 | 31,290 | 85.0 | 41 | 0.13 |
| Cat | 4,095 | 2,925 | 7.9 | 0 | 0 |
| Wolf | 135 | 126 | 0.3 | 6 | 4.76 |
| Horse | 619 | 448 | 1.2 | 0 | 0 |
| Cow | 1,817 | 737 | 2.0 | 0 | 0 |
| Pig | 431 | 321 | 0.9 | 0 | 0 |
| Rat | 634 | 617 | 1.7 | 0 | 0 |
| Rabbit | 15 | 12 | 0.03 | 0 | 0 |
| Fox | 1 | 1 | 0.003 | 0 | 0 |
| Goat | 102 | 47 | 0.13 | 0 | 0 |
| Sheep | 51 | 28 | 0.08 | 0 | 0 |
| Other animals | 223 | 102 | 0.3 | 0 | 0 |
| Man | 644 | 171 | 0.5 | 0 | 0 |
| Not specified | 6,547 | 2,136 | — | 6 | 0.28 |
| Category : | | | | | |
| A | 5,962 | 3,640 | 10.5 | 7 | 0.19 |
| B | 10,654 | 5,978 | 17.2 | 4 | 0.07 |
| C | 31,469 | 25,069 | 72.2 | 31 | 0.14 |
| Not specified | 11,495 | 4,274 | — | 8 | 0.19 |
| Bites : | | | | | |
| Single | — | 16,030 | 54.4 | 8 | 0.05 |
| Multiple | — | 13,411 | 45.5 | 34 | 0.25 |
| Not specified | — | 9,520 | — | 11 | 0.12 |

| | 1931 | | | Deaths | |
|-----------------------------------|---------------|----------------|------------|--------|------------------------|
| | Total treated | Persons bitten | Percentage | Total | Per 100 persons bitten |
| Intervention of clothing : | | | | | |
| On bare skin | — | 17,842 | 54.4 | 42 | 0.23 |
| Through clothing | — | 14,960 | 45.6 | 1 | 0.007 |
| Not specified | — | 6,159 | — | 10 | 0.16 |
| Position : | | | | | |
| Head | — | 2,842 | 7.7 | 28 | 0.98 |
| Hands | — | 10,607 | 28.9 | 9 | 0.08 |
| Arm and shoulder | — | 6,226 | 17.0 | 4 | 0.06 |
| Trunk | — | 1,614 | 4.4 | 0 | 0 |
| Leg | — | 15,415 | 42.0 | 5 | 0.03 |
| Not specified | — | 2,257 | — | 7 | 0.31 |
| Delay in arrival : | | | | | |
| 0- 4 days | — | 19,988 | 58.1 | 28 | 0.14 |
| 5- 7 days | — | 9,391 | 27.3 | 5 | 0.05 |
| 8-14 days | — | 3,582 | 10.4 | 2 | 0.06 |
| More than 14 days | — | 1,457 | 4.5 | 1 | 0.07 |
| Not specified | — | 4,543 | — | 17 | 0.37 |
| <hr/> | | | | | |
| 1932 | | | | | |
| Number treated | 41,720 | 27,647 | 66.3 | 36 | 0.13 |
| Methods : | | | | | |
| Pasteur | 4,517 | 3,650 | 13.2 | 6 | 0.16 |
| Fermi | 9,516 | 5,734 | 20.7 | 8 | 0.14 |
| Högyes-Philipps | 25,614 | 16,761 | 60.6 | 19 | 0.11 |
| Remlinger | 595 | 595 | 2.2 | 2 | 0.33 |
| Fermi and Philipps | 1,478 | 907 | 3.3 | 1 | 0.11 |
| Biting animal : | | | | | |
| Dog | 30,752 | 22,880 | 84.4 | 23 | 0.10 |
| Cat | 2,461 | 2,000 | 7.4 | 0 | 0 |
| Wolf | 73 | 66 | 0.2 | 7 | 10.61 |
| Horse | 354 | 243 | 0.9 | 0 | 0 |
| Cow | 949 | 464 | 1.7 | 0 | 0 |

| | | | | | |
|---|--------|--------|-------|----|------|
| Pig | 249 | 193 | 0.7 | 0 | 0 |
| Rat | 831 | 812 | 3.0 | 0 | 0 |
| Rabbit | 9 | 6 | 0.02 | 0 | 0 |
| Fox | 2 | 1 | 0.004 | 0 | 0 |
| Goat | 52 | 20 | 0.07 | 0 | 0 |
| Sheep | 12 | 9 | 0.03 | 0 | 0 |
| Other animals | 414 | 325 | 1.2 | 0 | 0 |
| Man | 345 | 85 | 0.3 | 0 | 0 |
| Not specified | 5,217 | 543 | — | 6 | 1.10 |
| Category : | | | | | |
| A | 3,617 | 2,147 | 8.6 | 4 | 0.19 |
| B | 6,663 | 3,853 | 15.5 | 6 | 0.16 |
| C | 23,230 | 18,895 | 75.9 | 20 | 0.11 |
| Not specified | 8,210 | 2,752 | — | 6 | 0.22 |
| Bites :¹ | | | | | |
| Single | — | 9,347 | 57.5 | 2 | 0.02 |
| Multiple | — | 6,908 | 42.5 | 20 | 0.28 |
| Not specified | — | 7,302 | — | 6 | |
| Intervention of clothing :¹ | | | | | |
| On bare skin | — | 11,192 | 56.5 | 21 | 0.18 |
| Through clothing | — | 8,617 | 43.5 | 1 | 0.01 |
| Not specified | — | 3,748 | — | 6 | |
| Position :¹ | | | | | |
| Head | — | 1,669 | 7.7 | 13 | 0.78 |
| Hands | — | 5,374 | 24.9 | 5 | 0.09 |
| Arm and shoulder | — | 4,140 | 19.2 | 4 | 0.09 |
| Trunk | — | 861 | 3.9 | 0 | 0 |
| Leg | — | 9,554 | 44.3 | 0 | 0 |
| Not specified | — | 1,959 | — | 6 | |
| Delay in arrival : | | | | | |
| 0- 4 days | — | 14,187 | 58.8 | 24 | 0.17 |
| 5- 7 days | — | 6,568 | 27.2 | 3 | 0.05 |
| 8-14 days | — | 2,437 | 10.1 | 2 | 0.08 |
| More than 14 days | — | 940 | 3.9 | 0 | 0 |
| Not specified | — | 3,515 | — | 7 | 0.20 |

¹ The statistics under these headings are incomplete, and refer only to a section of the total.

The numbers of institutes employing the various methods of treatment from which returns were received were as follows :

| | Pasteur | Fermi | Högyes- Philipps | Remlinger | Pasteur + Fermi | Philipps + Fermi | Total |
|------------|---------|-------|---------------------|-----------|--------------------|---------------------|-------|
| 1927 | 27 | 14 | 29 | 1 | 1 | — | 72 |
| 1928 | 27 | 7 | 24 | 1 | 1 | — | 60 |
| 1929 | 15 | 9 | 27 | 1 | — | 1 | 53 |
| 1930 | 10 | 8 | 33 | 1 | — | 3 | 55 |
| 1931 | 7 | 9 | 33 | 1 | — | 2 | 52 |
| 1932 | 6 | 10 | 32 | 1 | — | 1 | 50 |

In the above table, outstations are included in the parent institute. The designations of the various methods of treatment are as given in the schedules. The original method of Pasteur and Calmette's modification of it are grouped together. The method of Fermi is described as follows : " 4 to 5 per cent emulsion of cord in half to one per cent phenol, administered in doses of 2 to 5 cc." Under the heading Högyes-Philipps are combined numerous modifications of the original dilution method, including that of Boecker (*vide* Fourth Review, page 559). Remlinger's method is employed at Irkutsk, and is defined as follows : " Cords are dried over caustic potash for two days, after which they are administered at the rate of 80 mg. in 6, 4 or 3 days, according to the severity of the bite". " In very grave cases certain institutes (Poltava, Odessa, etc.) employ a combined treatment—*e.g.*, Fermi and Philipps, Pasteur and Fermi, etc."

For convenience of reference, the statistics subdivided according to methods of treatment for the successive years 1927 to 1932 have been brought together in the following table (page 649). The last set gives the combined figures for the six years.

It will be noted that there are considerable decreases both in the numbers of institutes from which schedules were received and in the numbers of persons to which these schedules refer. In a memorandum submitted with the schedules for 1931 and 1932 it is stated that, " since there are as many as 70 institutes in the Union of Soviet Socialist Republics with more than 300 stations attached to them, the particulars furnished should be regarded as referring to a part of the total number treated. In spite of the lack of exhaustive details, it is possible, by comparing the details of the institutes

Recapitulatory Table, 1927-1932

| | 1927 | | | 1928 | | | 1929 | | | 1930 | | |
|---------------------|---------------|------------|-------------|---------------|------------|-------------|----------------|------------|--------------|---------------|-----------|-------------|
| | Number bitten | Deaths | Mortality | Number bitten | Deaths | Mortality | Number bitten | Deaths | Mortality | Number bitten | Deaths | Mortality |
| Pasteur | 28,241 | 85 | 0.30 | 21,932 | 53 | 0.24 | 11,108 | 16 | 0.14 | 7,032 | 11 | 0.16 |
| Fermi | 12,232 | 29 | 0.24 | 6,029 | 9 | 0.15 | 6,386 | 13 | 0.20 | 4,604 | 6 | 0.13 |
| Högyes-Philipps ... | 32,435 | 53 | 0.16 | 36,778 | 60 | 0.16 | 32,918 | 41 | 0.12 | 33,085 | 32 | 0.09 |
| Remlinger | 481 | 4 | 0.83 | 584 | 2 | 0.34 | 531 | 3 | 0.56 | 470 | 1 | 0.21 |
| Pasteur + Fermi .. | 1,041 | 5 | 0.48 | 831 | 6 | 0.72 | — | — | — | — | — | — |
| Philipps + Fermi .. | — | — | — | — | — | — | 2,575 | 6 | 0.23 | 4,208 | 4 | 0.10 |
| | <u>74,430</u> | <u>176</u> | <u>0.23</u> | <u>66,154</u> | <u>130</u> | <u>0.20</u> | <u>53,518</u> | <u>79</u> | <u>0.15</u> | <u>49,399</u> | <u>54</u> | <u>0.11</u> |
| | | | | | | | 1927-1932 | | | | | |
| | 1931 | | | 1932 | | | Number bitten | Deaths | | Mortality | | |
| | | | | | | | | Observed | Calculated | | | |
| Pasteur | 4,372 | 5 | 0.11 | 3,650 | 6 | 0.16 | 76,335 | 176 | 129 | 0.23 | | |
| Fermi | 8,472 | 16 | 0.19 | 5,734 | 8 | 0.14 | 43,457 | 81 | 74 | 0.19 | | |
| Högyes-Philipps ... | 24,649 | 32 | 0.13 | 16,761 | 19 | 0.11 | 176,626 | 237 | 301 | 0.13 | | |
| Remlinger | 498 | 0 | 0 | 595 | 2 | 0.33 | 3,159 | 12 | 5.4 | 0.38 | | |
| Pasteur + Fermi .. | — | — | — | — | — | — | 1,872 | 11 | 3.2 | 0.59 | | |
| Philipps + Fermi .. | 970 | 0 | 0 | 907 | 1 | 0.11 | 8,660 | 11 | 15 | 0.13 | | |
| | <u>38,961</u> | <u>53</u> | <u>0.14</u> | <u>27,647</u> | <u>36</u> | <u>0.13</u> | <u>310,109</u> | <u>528</u> | <u>527.6</u> | <u>0.17</u> | | |

furnishing annual information regarding their work, to observe a general regular decrease in the number of persons applying for inoculation." This view is supported by the following figures extracted from the foregoing tables :

| | Number of institutes | Number of persons bitten and treated | Average number of patients 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 |
| | <hr/> 342 | <hr/> 310,109 | <hr/> 907 |

The mortality rates for all methods of treatment during the successive years were 0.23, 0.20, 0.15, 0.11, 0.14 and 0.13—that is to say, the rate fell rapidly from 1927 to 1929, and thereafter remained approximately constant.

It is evident—as was stated in the previous review—that a profound change has occurred during the period of years under examination, and that a comparison of the efficacies of the various methods of treatment based upon the combined figures for the six-year period would lead to a spurious result. In fact, both when the statistics are combined according to years but subdivided according to method, and also when they are combined according to method but subdivided according to years, evidence of a marked degree of heterogeneity is found.

Further light regarding the effects of the various methods of treatment may, however, be obtained by examining the figures for the various methods in the successive years. The table in the former review giving the values of P for the various pairs of methods is here extended to include the years 1931 and 1932.

| | | | | |
|--------------------|---------|-------|--------------------|-----------|
| 1927 : | Pasteur | Fermi | Högyes Philipps | Remlinger |
| Pasteur | 1 | 0.26 | 0.0004 | 0.038 |
| Fermi | | 1 | 0.105 | 0.011 |
| Högyes-Philipps .. | | | 1 | 0.0004 |
| Remlinger | | | | 1 |
| 1928 : | Pasteur | Fermi | Högyes Philipps | Remlinger |
| Pasteur | 1 | 0.17 | 0.036 | 0.62 |
| Fermi | | 1 | 0.81 | 0.27 |
| Högyes-Philipps .. | | | 1 | 0.29 |
| Remlinger | | | | 1 |

STATISTICS ON RABIES

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| | Pasteur | Fermi | Högyes Philipps | Remlinger |
|--------------------|---------|-------|--------------------|-----------|
| 1929 : | | | | |
| Pasteur | 1 | 0.35 | 0.62 | 0.019 |
| Fermi | | 1 | 0.12 | 0.6 |
| Högyes-Philipps .. | | | 1 | 0.006 |
| Remlinger | | | | 1 |
| 1930 : | | | | |
| Pasteur | 1 | 0.72 | 0.17 | 0.76 |
| Fermi | | 1 | 0.50 | 0.65 |
| Högyes-Philipps .. | | | 1 | 0.43 |
| Remlinger | | | | 1 |
| 1931 : | | | | |
| Pasteur | 1 | 0.33 | 0.77 | — |
| Fermi | | 1 | 0.22 | — |
| Högyes-Philipps .. | | | 1 | — |
| Remlinger | | | | 1 |
| 1932 : | | | | |
| Pasteur | 1 | 0.74 | 0.43 | 0.36 |
| Fermi | | 1 | 0.38 | 0.25 |
| Högyes-Philipps .. | | | 1 | 0.11 |
| Remlinger | | | | 1 |

The figures show that the evidences of heterogeneity which existed in the year 1927 have become less during the succeeding years and have not been detectable since 1930. The reason for this alteration cannot be determined from the facts submitted in the schedules.

It seems advisable at this stage to examine the statistics for evidence of any changes in the constitution of the populations which might account for the general fall in mortality.

(a) The proportions of persons who were treated but were not bitten show no significant change. The percentages during the successive years were 33, 31, 30, 30, 33 and 33.

(b) The numbers of persons bitten by wolves were 406, 153, 82, 104, 126 and 66, and the corresponding percentage incidences were 0.6, 0.3, 0.2, 0.2, 0.3 and 0.2. Deaths from wolf-bites numbered 35, 20, 3, 6, 6 and 7, and the corresponding mortality rates were 8.6, 13.1, 3.7, 5.8, 4.8 and 10.6. There is thus evidence of a significant decline in the number and proportion of persons bitten by wolves, and this would lead to a fall in the general mortality. The mortality rates amongst those bitten by dogs were successively 0.21, 0.21, 0.17, 0.10, 0.13 and 0.1, and examination of the figures from which these rates were calculated shows that the variation is highly

significant (P approximately 0.00001). It would thus appear that the marked decrease in the number and proportion of those bitten by wolves is not in itself sufficient to account for the whole of the drop in the general mortality.

(c) The proportion of cases belonging to the different categories shows no significant change. The percentages of the combined A and B categories were 27, 24, 27, 28, 28 and 24.

(d) The percentages of persons with multiple bites do not differ significantly. They were 44, 39, 45, 45, 46 and 43.¹

(e) The percentages of those bitten on the bare skin do not vary significantly. They were 51, 58, 64, 58, 54 and 57.¹

(f) The same is true for those bitten on the head. The percentages were 6.7, 8, 6.7, 7.5, 7.7, and 7.7.¹

(g) In the percentages of late arrivals, there is evidence of a steady decline. Thus for those arriving more than a week late, they were 26, 22, 20, 18, 15 and 14.

It would thus appear that the only significant changes in the constitution of the treated populations are a decrease in the number and proportion of those bitten by wolves, and a decrease in the proportion of those who arrive late for treatment. These have without doubt participated in bringing about the fall in the general mortality rate, though they are not, in themselves, probably sufficient to account for its magnitude.

Only one case of paralytic accident is reported as having occurred within the period 1931-32. It was of the Landry type, and the method of treatment upon which the symptoms supervened is not stated. The numbers of accidents reported during the successive years were 20 in 1927, 17 in 1928, 12 in 1929, 5 in 1930, and 1 in the period 1931-32. The corresponding percentage rates were 0.018, 0.015, 0.016, 0.007 and 0.001. For the classification of these according to the method of treatment employed, reference may be made to the table in the previous review.

(1) Although the schedules submitted relate only to fractions of the total number of persons treated in the Union of Soviet

¹ Calculated from incomplete figures. See footnote to schedule for the year 1932.

Socialist Republics, there is evidence of a decline in the number of those presenting themselves for treatment, and further the proportion of those bitten by wolves has fallen. These changes might be accounted for by assuming that a reduction has occurred in the chance of being bitten—*e.g.*, by a reduction in the number of rabid animals, or by a redistribution of the human population in those parts of Russia from which the patients were drawn. With respect to the latter alternative, it is to be noted that the large majority of the institutes concerned are in European Russia.

(2) At the same time, the mortality amongst the treated has declined, the percentage mortalities for the successive years being 0.23, 0.2, 0.15, 0.11, 0.14 and 0.13. This fall is partly accounted for by a decrease in the number and proportion of those bitten by wolves, and by a reduction in the proportion of those arriving late for treatment. No other significant changes in the characteristics of the class of case dealt with have been detected.

(3) The comparative results of the different methods of treatment have been analysed. It appears that, since 1930, no significant differences between the various pairs of methods can be detected. In 1927, the results obtained by the Pasteur method were significantly inferior to those obtained by the Högyes-Philipps method, but, although the arrangement in order of superiority—(1) Högyes-Philipps, (2) Fermi, (3) Pasteur and (4) Remlinger—is, in general, maintained, it seems that the differences are no longer significant. It may be that some factor associated in the earlier years with the Pasteur method has been eliminated. Such an elimination would clearly result in a reduction of the general mortality rate.

A BRIEF GUIDE TO THE VARIETIES OF "ANOPHELES MACULIPENNIS".

BEING THE REPORT OF THE MEETING OF EXPERTS
CONVENED IN ROME (AUGUST 20-22 1934) BY THE
MALARIA COMMISSION OF THE LEAGUE OF NATIONS.

The report is the outcome of the discussion of a preliminary report by Dr. L. W. HACKETT and Professor A. MISSIROLI, which will appear in English in the *Rivista di Malariologia* and in French in the *Medicina de los Paises Cálidos*.

In this report have been incorporated data submitted for the purpose by :

BARBER and HACKETT for the U.S.S.R.
DE BUEN and GIL COLLADO for Spain.
SERGENT, Et., and TRENZS for France and Algeria.
SHANNON for Greece.
SHUTE for England.
SWELLENGREBEL for Holland.
ZOTTA for Yugoslavia.

It is now clear that *Anopheles maculipennis* is not a homogeneous species, but consists of a number of recognised varieties.

Up to the present, the following varieties are considered valid :¹

| | | |
|----|---------------------|-----------------------------------|
| A. | <i>maculipennis</i> | Meigen (type). ² |
| A. | " | var. <i>atroparvus</i> van Thiel. |
| A. | " | var. <i>messeæ</i> Falleroni. |
| A. | " | var. <i>labranchiæ</i> Falleroni. |
| A. | " | var. <i>melanoon</i> Hackett. |

¹ No consideration has here been given to the American forms.

² The name "basilei" was suggested for the type by FALLERONI in 1933, but appears to be unnecessary.

In addition, there is a closely allied species—or a further variety—occurring in the old world :

A. elutus Edwards.

IDENTIFICATION.

So far as present knowledge goes, the following is a provisional key,¹ giving the differential characters of these forms :

I. Apex of wing dark. Spotting of wing often inconspicuous. Thorax uniformly coloured. Sides of scutum no darker than median part. Floats of egg often absent or at most only a little wider than fringe. No more than a fifth of egg length. **Upper surface frosty gray without definite black patches.**

(Hair No. 1 on second abdominal segment of larva sometimes palmate. Antepalmate hair on fourth and fifth segments with nine to ten branches.

Outer spine of harpago sharp or blunt.)

A. elutus.

II. Fringe at apex of wing usually with a pale spot. Spotting of wing distinct. Thorax with sides of scutum darker than median part.

Floats of egg usually distinctly wider than fringe, never less than a fifth of egg length. **Upper surface always with some dark areas.**

1. Upper surface of egg black or with two dark transverse bars at the level of the ends of the floats.

¹ *Notes on the Use of the Key.*

Heavy type indicates important definite characters. Entries in parentheses give additional information which may be useful in certain circumstances.

The number of branches to the antepalmate hairs on the fourth and fifth abdominal segments are calculated as the average of the two hairs on the same side of the segments.

Dark areas are portions of the surface where the columellæ are much shorter and the general tone darker than elsewhere. This does not refer to the dark spaces between the columellæ which are always present.

The appearance of a single egg may often be ambiguous, but, as the whole batch of eggs laid by the female should, whenever possible, be examined, no difficulty arises.

The intercostal membrane is the membranous part of the float between the ribs.

(a) **Dark bars distinct.** Upper surface of egg, except for dark bars, all pale or with only one or two dark spots between the bars. Pale areas rather frosty. Intercostal membrane of float with fine transverse lines or reticulations extending on to upper surface.

(Hair No. 1 on second segment forming imperfectly developed palmate hairs [flattened leaflets not more than four to five]. Antepalmate hairs on fourth and fifth segments with about seven branches.

External spine of harpago always blunt and short, frequently single.)

Maculipennis (type).

(b) **Dark bars distinct.** Upper surface of egg, in addition to dark bars, with numerous dark areas, the pale portions dullish. Intercostal membrane with thick cross bars or coarse reticulations extending on to upper surface.

(Hair No. 1 on second segment most commonly branched only, but often showing more or less well-developed palmate hair. Antepalmate hair about eight branches.

External spine of harpago often blunt and often single.)

Var. *messeæ*.

(c) **Dark bars almost or entirely obscured by black.** Intercostal membrane usually without cross bars or reticulations.

(Hair No. 1 on second segment and antepalmate hairs on fourth and fifth segments as in *messeæ*.)

External spine of harpago as in *messeæ*.)

Var. *melanoon*.

2. Upper surface of egg not black and without two dark bars, at level of end of floats.

(a) **Oblique dark cuneiform spots springing from the sides and tapering toward median line** sometimes by fusion extending across egg to form bands irregularly placed, but in this case oblique and without reference to

floats. Pale areas not having frosted appearance. **Upper aspect of columellæ stellate with black dot in centre.** Intercostal membrane smooth (especially the upper surface), with a few cross-lines toward the extremities.

(Hair No. 1 on second segment often well developed, never hairlike. Antepalmate hair on fourth and fifth segments usually four to six branches and always less than nine.

External spine of harpago always sharp-pointed. Very seldom single.)

Var. atroparvus.

(b) **Cuneiform dark spots few and short. Pale areas frosted as in elutus. Upper aspect of columellæ irregular in size and shape without any dot or at most a faint dark spot in the centre.** Intercostal membrane always with dense network of fine lines.

(Hair No. 1 on second segment almost always well developed, never hairlike. Antepalmate hair on fourth and fifth segments usually four to six branches and always less than nine.

External spine of harpago always sharp-pointed, single or double.)

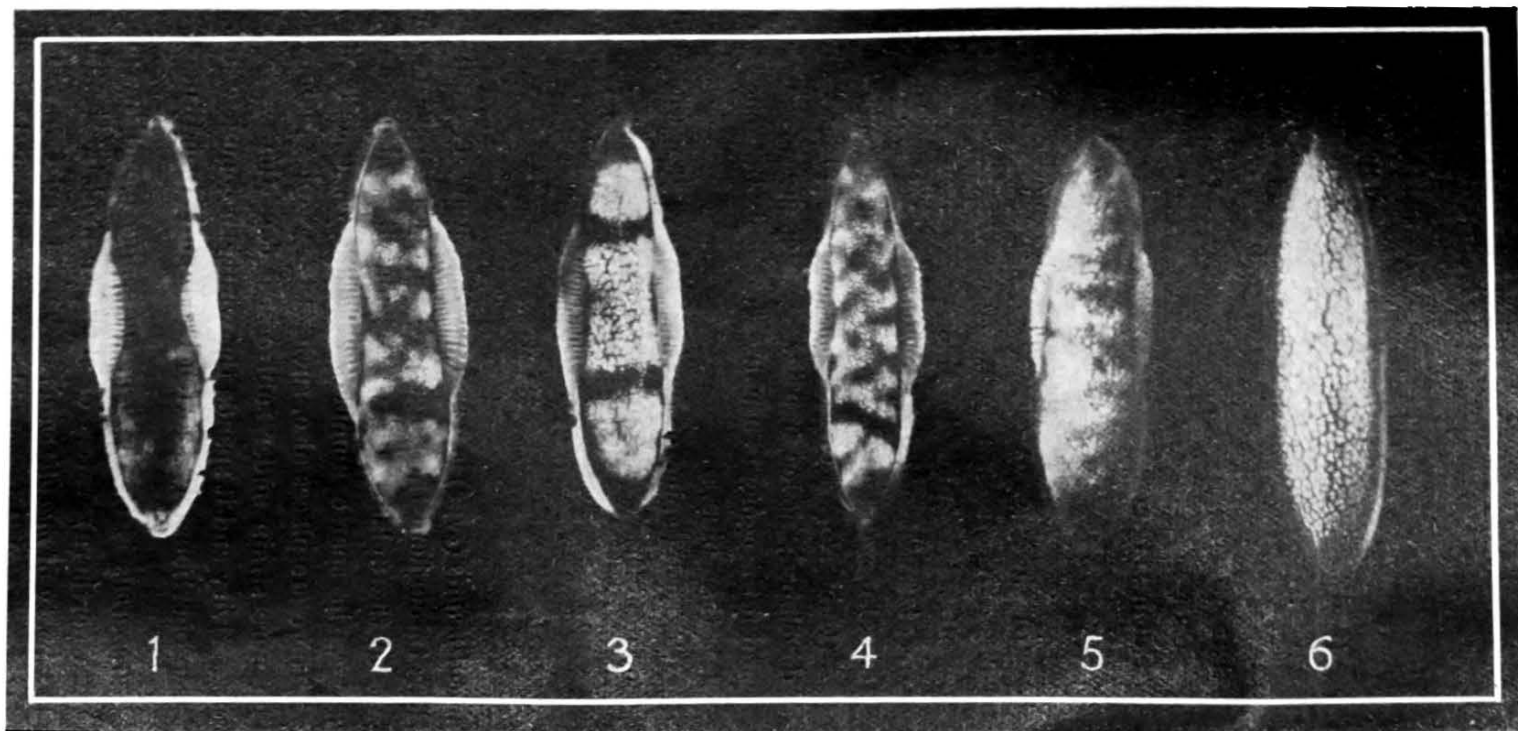
Var. labbranchiæ.

HABITS.

A. maculipennis (type) is found breeding under two quite separate conditions throughout the range of the species. It is the characteristic race of the upland cold waters, but it is also found mingled with *messeæ* in sparse numbers at sea-level, usually in running water. There are places also, such as the Naples plain, where it is found in pure strain under subtropical conditions. It refuses to mate in captivity and it spends the winter in complete hibernation, which is proportionately shortened in southern latitudes.

Var. atroparvus is the only *maculipennis* found breeding in the cool (more northern) waters of slight to moderate salinity. It is the only variety of *maculipennis* in which copulation will take place in small cages, and it is possible that in nature the males do not

THE SIX KNOWN VARIETIES OF *A. maculipennis*.



1. Var. *melanoon*

2. Var. *messeæ*

3. Type

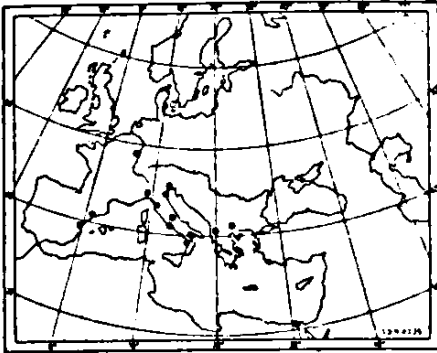
4. Var. *atroparvus*

5. Var. *labranchie*

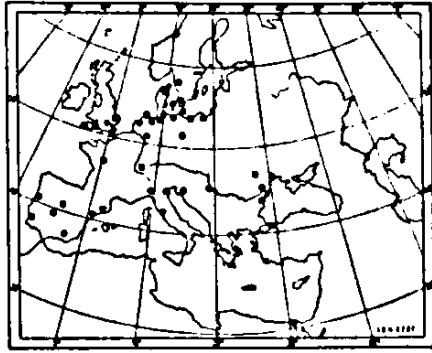
6. *A. elutus*

GEOGRAPHICAL DISTRIBUTION OF THE VARIETIES OF *A. maculipennis*.

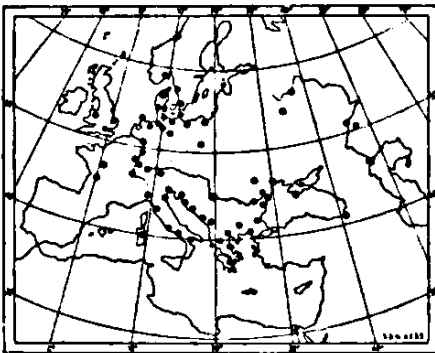
1. *A. melanoon.*



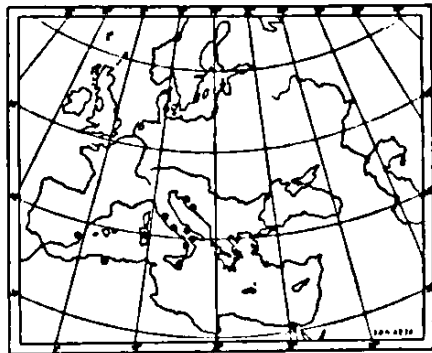
4. *A. atroparvus*



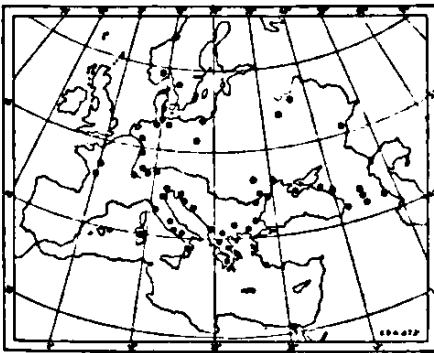
2. *A. messeæ.*



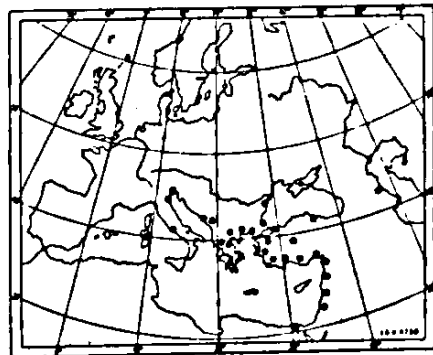
5. *A. labranchiæ.*



3. *A. maculipennis* (type)



6 *A. elutus*



swarm in the open. It chooses warm rather than cold places for its semi-hibernation and takes occasional blood meals throughout the winter, ovarian activity being suspended. Under certain conditions, it is also capable of hibernating completely. The ovarian inertia (beginning in September in Holland and in November in Italy) can be overcome under artificial conditions of warmth and nourishment, but with greater difficulty in the north than in the south.

Var. *messeæ* is the predominant variety of continental areas, especially in North Europe, since it prefers cool waters as well as fresh. It is more often found in standing than running water and yields to some other varieties in southern areas in the period of highest summer temperature. It will not mate in confinement, and swarming of the males has been frequently observed. It always hibernates completely in cold shelters and does not take blood during the period when its sexual functions are suspended, but lives on its fat throughout the cold period of the year.

Var. *labranchiæ* is a saline water breeder, like *atroparvus*, but in a different climatic range. It also breeds in fresh water when relieved of the competition of other races. It will not mate in confinement and, although its annual cycle is characterised by a winter pause, this is easily interrupted, both in the laboratory and in nature, by a rise in temperature.

Var. *melanoon*. As far as known, its habits are very similar to those of *messeæ*. In Spain and Northern Italy, it is often found associated with rice culture.

GEOGRAPHICAL DISTRIBUTION.

The distribution of these varieties, so far as known, is shown in the maps on page 659.

RELATION TO MALARIA.

A. maculipennis (type), var. *messeæ* and probably var. *melanoon* are fairly likely to be deviated by stabulated cattle, but capable of transmitting malaria where suitable conditions bring them into close contact with man. In general, they are not varieties of great significance in relation to malaria diffusion.

Var. *atroparvus* is also a form likely to be deviated by stabulated cattle and capable of transmitting malaria where suitable conditions bring it into close contact with man. However, owing to its partial hibernation, it is liable to be an important autumnal or winter transmitter of malaria in some of the coastal areas of Northern Europe.

Var. *labranchiæ* and *A. elutus* are always associated with an intense malaria. They share many of the same physiological characters and, wherever we find them, they persistently try to enter bedrooms, even in the presence of an abundance of animal blood.

The facts set forth in this report may well have a practical application in anti-malarial work. An intensive study of the larval habitat of the different varieties is recommended to those engaged in anti-malaria work in regions where *A. maculipennis* is a vector.

The Experts recommend that the present report should be published by the Health Organisation of the League of Nations, together with the distribution maps, and a plate showing the typical features of eggs of the six forms, which will be kindly supplied by the Stazione Sperimentale per la Lotta Antimalarica, Rome.

(Signed) R. CHRISTOPHERS.
L. W. HACKETT.
S. P. JAMES.
A. MISSIROLI.
G. PITTALUGA.
Edmond SERGENT.
N. H. SWELLENGREBEL.

MILK HYGIENE IN THE DEPARTMENT OF MEURTHE-ET-MOSELLE

by

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of Hygiene of Nancy.

PHYSICO-CHEMICAL AND CYTO-BACTERIOLOGICAL STUDY OF MILK,
AS PRODUCED AND AS CONSUMED. CONCLUSIONS TO BE DRAWN
REGARDING PREVENTION.

CHAPTER I.—THE PRODUCTION AND CONSUMPTION OF MILK IN THE DEPARTMENT.

1. MILK PRODUCTION IN MEURTHE-ET-MOSELLE.

A. *The Natural Agricultural Areas.*

In 1931, the Department of Meurthe-et-Moselle, which covers rather more than 523,000 hectares, had a population of 592,632. It consists of 3 *arrondissements* (Nancy, Lunéville, Briey), 29 cantons and 600 communes, and, although its geological formation belongs to the secondary epoch, it presents very varied features. The successive outcrops of different strata delimit the five natural areas in the Department, which, going from east to west, are as follows :

- (1) *La Montagne* (36,000 hectares, 7 per cent of the total area), 20 per cent of natural meadow, grass and pasture land ;

(2) *La Plaine*, still known as the Plateau of Lorraine (244,000 hectares, 46.5 per cent of the total area), 28 per cent of natural meadow and pasture land. This is a stock-breeding district, where 60 per cent of the cattle in the Department are to be found. The road system traversing this district, mainly on level ground, converges more or less on Nancy, and the greater part of the milk produced in the district is sent to that town ; railways are few and the number of long-distance consignments by rail is very small ;

(3) *Les Plateaux* (177,000 hectares, 34 per cent of the total area), a district which is both industrial and agricultural ; 12.5 per cent of natural meadow and pasture land ;

(4) *La Woivre* (50,000 hectares, 9.5 per cent of the total area), 18.5 per cent of meadow and grass land on which the grass and hay is almost too coarse for cattle, so that neither stock-breeding nor milk production can be carried on there on any extensive scale ;

(5) *Les Côtes de Meuse* (17,000 hectares, 3 per cent of the total area), a district of small landholders ; the milk production is very small.

Most of the milk produced in the Department comes from *La Plaine*.

B. Cattle.

In 1933, the number of cows kept chiefly for milk production was 55,453. The fact that the Department of Meurthe-et-Moselle does not produce milk on a large scale is clearly shown by the comparatively small number of cattle in proportion to the area. Whereas the usual proportion in France is 1 horse to every 20 hectares and 5 cattle to 1 horse, in Meurthe-et-Moselle it is 1 horse to every 11 hectares, but barely 2 cattle to 1 horse ; hence there are in the Department about twice as many horses, but only half as many cattle, as in the rest of the country (A. GAY).

Consequently, the number of cattle in Meurthe-et-Moselle falls below the general average in France ; however, from the point of view of milk production, *breed* is no less important than numbers.

There is no native breed in Lorraine, where any number of different breeds are represented, further varieties having been introduced

by the delivery of cattle from Germany by way of Reparations. Generally speaking, the regions can be classified as follows :

(1) The northern region, where the Dutch black-and-white breed predominates ; at the present time, this breed is spreading southwards. Although the meat of the Dutch black-and-white cows is of poor quality, they yield a large quantity of milk, which, however, is somewhat deficient in fatty substances. This explains the rather low average proportion of fats (32 grammes per thousand according to Dr. HOUDINIÈRE) in the milk consumed in Nancy.

(2) The southern region, where the breed is mixed, the cows having been bred from the Swiss mottled cattle or the breeds in the East of France ; these are the Eastern speckled cows : speckled red-and-white and Fribourg (black-and-white). They yield a smaller quantity of milk than the Dutch cows, but are more rustic and hardy ; they possess the twofold advantage of supplying a better quality of milk and excellent butcher's meat.

Generally speaking, the conditions under which the Lorraine cows are kept are unhygienic. Except in places rebuilt after the war, the byres are low, dark and badly ventilated. The litter is not often renewed. With a few very rare exceptions, the animals are never rubbed down or combed and the dung and urine are not removed. In Lorraine, less care is taken over the *feeding* of cattle than of horses. The ration of hay and oat or wheat straw is supplemented by chopped-up beetroot and husks from the neighbouring breweries, of which there are a large number in the district ; the use of oil-cakes is still comparatively rare.

Thanks to the supervision of the departmental veterinary services, *epizootic diseases* are not very common among cattle. " Owing to its mild nature and the small area of infection " (R. PATRIAT), *foot-and-mouth disease* has never given much trouble, although it exists in an endemic state and there have been a few outbreaks each year, notably in 1929, 1932 and 1933 ; *anthrax* is rare (1 case in 1933).

From the point of view of milk production, *bovine tuberculosis* is of greater importance. An approximate idea of its prevalence can be obtained by the number of carcasses seized after tuberculous

lesions had been discovered in the slaughter-houses of the Department. The total number of carcasses seized, which in 1923 was 455 (157 from Meurthe-et-Moselle), after rising slightly, appeared to remain stationary ; from 562 in 1927 and 723 in 1928, it fell to 472 in 1931 (213 animals from Meurthe-et-Moselle) and in 1932 was 630 (194 animals from the Department). However, as these figures relate solely to slaughtered animals, they cannot furnish a precise indication of tuberculosis infection among Lorraine cattle. For this purpose, it is necessary to ascertain :

(1) The number of infected farms or sheds placed under sanitary supervision by the veterinary services : the number of farms declared to be infected during the year was 75 in 1926, 55 in 1927, 62 in 1928, 60 in 1929, 48 in 1930, 34 in 1931, 29 in 1932. Since the promulgation of the Law of July 7th, 1933, and the Ministerial Circular of July 29th, 1933, measures for the prevention of bovine tuberculosis have ceased to be compulsory and, therefore, no later figures are available. Nevertheless, the above-mentioned figures show that, since 1928, there has been a steady decline in the number of infected farms.

(2) The number of animals with a positive tuberculin reaction ; the tuberculin tests carried out by the veterinary services from 1922 to 1933 were subsidised by the Departmental Agricultural Office, so that every facility was given to the cattle-breeding syndicates for that purpose.

The tuberculin tests were carried out in regard to byres in which the presence of tuberculosis has been revealed by the seizure of an infected carcass in the slaughter-house. The number steadily increased from 1926 (842) up to 1929 (1,638), a slight decrease being noted in 1930 (1,184) and 1931 (774). The proportion of positive reactions as compared with the total number of animals tested is comparatively low : from 1926 to 1932, the proportion was for each successive year 5, 6.2, 7, 6.66, 5.48, 8.78 and 4.42 per cent, making an average of 6.2 per cent. On the other hand, if the figures are confined to sheds in which animals with a positive reaction were found, the proportion is higher : 16.75 per cent in 1930 ; 17.48 in 1931 ; 16.73 in 1932.

Actually, the tuberculosis infection among the cattle of Meurthe-et-Moselle is very light compared to that of other French Departments. This position may be improved still further by the immunisation of calves with BCG vaccine, which was introduced into Meurthe-et-Moselle in 1926, the number of calves immunised during that year being 857.

On the other hand, the cattle are threatened by a new danger—namely, bovine *brucella melitensis* infection. While infectious abortion due to Bang's bacillus (now known as *brucella abortus bovis*) was hitherto the only form met with in the Department, the work of the Regional Institute of Hygiene of Meurthe-et-Moselle (Professor Jacques PARISOT and Dr. ROBERT LÉVY) has shown the existence, since 1932, of bovine *brucella melitensis* infection, due to the contact of cattle with infected sheep. This bovine *brucella melitensis* infection, which spreads much more quickly than bovine *brucella abortus*, constitutes a serious danger to the cattle and the population of the Department. Three proofs of this may be cited :

(1) Identification of 8 strains of *brucella melitensis* as against 6 strains of *brucella abortus bovis* isolated from 1932 to 1934 by the Montpellier Research Centre for Undulant Fever after 41 samples of cows' milk with a positive *brucella* lacto-diagnosis had been injected into guinea-pigs ;

(2) The large number of positive sero-diagnoses for *brucellæ* among cows which had had abortions; 18 out of 36—*i.e.*, 50 per cent ;

(3) The rapid increase in bovine cases in places infected with *brucella melitensis* and the appearance of cases of human *brucella* infection.

C. Farming.

Rural property in Meurthe-et-Moselle is divided up into numerous small holdings. For a long time the large number of small plots of land scattered throughout every commune made the rational cultivation of the soil impossible. Although the practice of the "reconstitution" of property has improved the situation in a certain number of communes since the application of the Chauveau Law (November 27th, 1918) and the Law of March 4th, 1919, which applies exclusively to the devastated areas, in Meurthe-et-Moselle

the land is still divided up among *smallholders*. There are few really large estates, and not a great many average-sized properties ; on the other hand, there are a large number of small and medium-sized holdings.

Hygiene is bound to suffer under this division of property. Although some large farms in La Plaine and Les Plateaux are well equipped, on the small Lorraine farm, except in the devastated areas where the old type has given place to new constructions, men and animals live at close quarters. Drinking-water is often lacking ; the peasant prefers well-water, even when a water system exists. In the rural communes of less than 1,000 inhabitants, which are for the most part engaged in milk production, a proper water system is still too rare. It is lacking in 65 out of 95 communes (*i.e.*, 68.5 per cent) in the Briey *arrondissement* ; in 90 out of 162 (*i.e.*, 55.5 per cent) in the Lunéville *arrondissement*, and in 113 out of 269 (*i.e.*, 42 per cent) in the Nancy *arrondissement*. If to this lack of a water supply is added the fact that IMBEAUX in 1875 counted in Meurthe-et-Moselle more than 39,000 communal, public or private wells—in which the water is usually highly polluted—it is not surprising that the hygienic conditions on the farms are unsatisfactory.

D. *Milk Production.*

The quantity of milk produced each year in the Department is about 1 million hectolitres, of which one-half is consumed by the population, the remainder being sent to the neighbouring Departments, particularly Moselle, or used for the manufacture of butter and cheese, which are prepared in the 27 dairies, butter or cheese making establishments of the Department.

The dividing up of property in Meurthe-et-Moselle and the predominance of medium-size and small holdings lead one to suppose *a priori* that milk production must be divided up in the same way. This is, indeed, the case ; there are no important centres where milk is produced on a large scale. The Lorraine milk producer is a *small producer* coming under one of the three following heads :

- (1) The " feeding " dairyman living near a large town, who buys newly calved cows and feeds them—whence his name—during the lactation period, after which he sells them again ;

(2) The farmer who (a) sells his own milk to the town or (b) delivers it to a collector, who sells it for his own account or (c) delivers it to the collectors of a dairy company, who make a large round. These companies collect milk from all parts of the Department, chiefly from the district round La Plaine (Xaintois, Vermois, Pays de Seille in particular), but also from Les Plateaux (Pays de Haye). The cows are kept for three or four years by the farmer, who sells them again when their yield of milk begins to fall off ;

(3) The farmer who does not sell his milk as such, but converts it into butter and cheese.

The first of these three categories of producers is gradually disappearing, as the profit on feeding is very small ; on the other hand, the second category is gradually increasing at the expense of the last. The lack of agricultural labour and the offers of the collectors who are sent round by the dairy companies are inducing the small farmer to seek a definite daily return which he obtains without any trouble and without additional expense. That is why to-day, more than formerly, a large number, or we might almost say all peasants, " make milk ".

From the point of view of milk production, therefore, the features are the same as for the agricultural production of the Department in general. We find small farms, small properties and a small milk production, sometimes consisting of only a few litres (the average for the 7,500 dairy farms which supply 46,000 litres of milk a day to Nancy is about 6 litres per farm) (Dr. HOUDINIÈRE).

II. SALE AND CONSUMPTION OF MILK IN MEURTHE-ET-MOSELLE.

While the production of milk is governed by agricultural conditions, its consumption is necessarily based on demographic conditions.

The 529,632 inhabitants of the Department are distributed as follows : the chief town of the Department, Nancy (120,578 inhabitants in 1932), is surrounded by suburban communes which are densely populated and bring up the total for the Nancy district

to nearly 165,000 inhabitants. There is only 1 town with more than 20,000 inhabitants, Lunéville (24,668) ; there are 4 towns with more than 10,000 ; 13 towns with a population between 5,000 and 10,000, and 61 villages with between 1,000 and 5,000 inhabitants ; the rest of the population is scattered among 520 villages with less than 1,000 inhabitants.

The Department has therefore an urban population of some 197,000 inhabitants (Nancy and its suburbs, Lunéville), an industrial population (Briey *arrondissement*) and a rural population. This somewhat rough-and-ready classification will enable us to study the consumption and sale of milk in Meurthe-et-Moselle.

A. *Rural Consumption.*

In rural districts, milk is usually consumed in the place where it is produced ; each village supplies its own milk. This is usually consumed raw, although the use of boiled milk is gradually becoming more general. As a rule, the price of the milk depends on the price charged for it in the town.

B. *Urban Consumption.*

A typical example of urban consumption is afforded by the town of Nancy, which has recently been studied by the Veterinary Surgeon HOUDINIÈRE (*Le Lait*, July, August, September, October 1933). Nancy consumes 46,000 litres of milk per day, making an average per head per day of 0.27 litre for Nancy and its outskirts and 0.38 litre for Nancy town. This figure is rather low compared with that of New York (0.85 litre), Vienna (0.48 litre), Copenhagen (0.45 litre) ; it is higher than that for Berlin (0.22 litre).

The milk reaches the consumer in two forms : raw milk and treated milk :

(a) The *raw milk* supplied by itinerant dairymen (120 for the town of Nancy) is produced by the dairyman himself or collected from farmers by a collector ; however, only a small number of farmers deliver their milk to collectors, and the milk is therefore not mixed to any great extent. 24,000 litres of this milk are consumed at Nancy per day. It is sold in the three forms provided for in the Decree

of March 25th, 1924 : *whole milk* (red label) ; *semi-skimmed milk* (green label) ; *skimmed milk* (blue label). Dr. HOUDINIÈRE gives the following figures for the consumption in each category : whole milk, 6,800 litres ; semi-skimmed milk, 17,500 litres ; skimmed milk, 100 litres. Consequently, the population of Nancy shows a marked preference for semi-skimmed milk, in which form the greater part (71.7 per cent) of the raw milk is consumed.

In the summer of 1934 the price of these different grades of milk was 1.20 francs per litre for whole milk and 1 franc for semi-skimmed milk. The price of skimmed milk is difficult to ascertain, as there is practically no sale for it.

Raw milk is sold in two different ways :

(1) *Direct sale* by the dairyman himself, who delivers the milk from house to house each morning. The milk is poured into a metal container holding 5, 10 or even 20 litres ; it is usually delivered by horse-carts, and more rarely by motor-vans.

(2) *Sale by middlemen*.—The dairyman deposits a certain quantity of milk with a grocery and milk shop and this is then sold retail ; this method of selling is less usual than the previous one.

(b) *Industrially Treated Milk*.—For Nancy there are four establishments situated in the town itself or on its outskirts. The collection of the milk is organised by the dairy companies, who send round motor-vans covering a large distance. This is " anonymous " milk obtained from many different farms. It is filtered, pasteurised and chilled and then poured into cans or bottles.

21,000 litres of this milk are sold each day at Nancy, in two forms only : whole milk and semi-skimmed milk. In this category, also, the consumption of semi-skimmed milk is much larger than that of whole milk—17,600 litres as against 4,000 litres ; it represents 81.4 per cent of the total consumption of industrially treated milk (HOUDINIÈRE).

This milk is sold in glass bottles containing 0.90 litre and bearing the company's trade-mark. The bottles are covered with a tin cap in the regulation colours bearing in relief letters the grade of the milk and the day of the week on which it must be sold (the day

after its manufacture). The milk is distributed early in the morning. Industrial milk is also sold to retailers in cans.

The present price is 1.15 francs per bottle containing 0.90 litre—*i.e.*, 1.26 francs per litre—for pasteurised whole milk, and 1.05 francs per 90 centilitres sold by measure (1.16 francs per litre). The price of semi-skimmed milk is 0.90 franc per bottle containing 0.90 litre or 90 centilitres sold by measure—*i.e.*, 1 franc per litre.

Industrial milk is sold in the same manner as the previous category : (1) *direct sale*, delivery of the milk in bottles from house to house by the company's vans ; (2) *indirect sale*, which is more usual, through the milk depots kept by grocers and milk-shops, who sell the milk either in bottles or by measure out of the cans.

III. SUPERVISION OF THE QUALITY OF THE MILK.

Up to the present, only one form of supervision has been instituted by French law : supervision of its commercial quality. Under the Decree of March 25th, 1924, the adulteration of milk is defined in the same way as that of other foodstuffs covered by the Law of August 1st, 1905.

In the Department this supervision is exercised by the Departmental service for the suppression of fraud at Nancy and the veterinary inspector responsible for the inspection of foodstuffs of the city. The object is to detect milk that has been watered or skimmed and milk that is unfit for consumption. Up to recent years, analyses were carried out by the analytical laboratory of the Agricultural Centre of Nancy. The average number of analyses made in the Department from 1926 to 1929 was 110 and the number of milk samples condemned was 42, making a percentage of 38 per cent of condemned milk. As no definite figures are available for the last few years, we can only say that, according to the information furnished by the Departmental director of the service for the suppression of fraud, the percentage of condemned milk varies at the present time from 20 to 25 per cent.

CHAPTER II.—TECHNICAL METHODS USUALLY EMPLOYED FOR EXAMINATION.

I. GENERAL METHODS.

These include physical examination, chemical examination and the various biological and cyto-bacteriological tests.

1. *Physical examination.*—Two factors were selected : *density* as determined by the densimeter, and *cleanliness* as determined by the cotton-wool lactofilter. This apparatus consists of a bottle without any bottom which is placed neck downwards on a stand. The lower opening is covered with wire netting which holds in position a fairly thin pad of cotton-wool 30 millimetres in diameter. A litre of the milk to be examined is poured through the upper opening ; the pad of cotton-wool retains all the impurities on its upper surface. The cleanliness of the milk is determined directly, according to whether the cotton-wool, after it has been dried, is more or less dark in colour.

2. *Chemical examination.*—Two tests were applied : the measurement of *acidity* expressed in Dornic degrees, by the recognised method ; the *content in fatty substances* (GERBER'S method).

3. *Biological examination.*—Only one test was employed—namely, the *reductase* test by Orla JENSEN'S method : to 40 cc. of milk is added 1 cc. of a solution of methylene blue in dilute alcohol (5 cc. of alcoholic solution saturated with the blue to 195 cc. of distilled water) ; this is placed in the incubator and the time at which discoloration occurs is noted. Any discoloration occurring in less than 20 minutes shows that the milk is of bad quality ; in from 20 minutes to 2 hours, that it is of indifferent quality ; in from 2 to 6 hours, that it is of medium quality ; and after, 6 hours, that it is of good quality.

4. *Cytological examination.*—This examination is carried out on slides, on which the residue obtained by the centrifugalisation of 40 cc. of milk for 20 minutes at 3,000 revolutions is smeared. It furnishes additional data visible to the naked eye as to the cleanliness of the milk, according to its volume and the colour of the residue. Its chief merit is, however, that it enables the cellular

elements of the milk to be studied after the residue has merely been stained.

5. *Bacteriological examination.*—This includes two kinds of tests :

(a) *Quantitative : Bacterial count per cc.* Direct counting methods (BREED, FROST) were used for preference; the number of colonies being counted after the seeding of appropriate dilutions in Petri dishes. Although many scientists dispute the value of this process, chiefly on the ground of the variability of the results obtained, we nevertheless consider it the most satisfactory from the bacteriological standpoint and sufficiently accurate. After making various comparative tests, we decided to adopt seeding on haricot-bean agar (Maggi laboratories' formula), a medium which can be easily and cheaply prepared and gives very good results. It is prepared as follows : boil 250 grammes of dried white haricots in a litre of water over a gentle heat until they swell : filter through cotton and reduce the filtrate to 1 litre ; add 10 grammes of peptone, 1 gramme of Liebig's extract and 20 grammes of agar ; adjust alkalinity with litmus ; bind together with a whole egg ; autoclave for 15 minutes at 125° ; filter through Chardin paper ; place in tubes and sterilise for 15 minutes at 115°. 1 cc. of two appropriate dilutions is then seeded in Petri dishes by the method used for water analysis. After they have been kept in the incubator at 37° for 48 hours, the colonies in each dish are counted ; the number per cc. can easily be computed according to the coefficient of dilution. The number of colonies per cc. is obtained by taking the average of the two counts.

(b) *Qualitative :* The qualitative test consists of two stages. The first furnishes a general indication (number and relative proportion of the different aspects of the bacterial flora). This is obtained by gram-staining the residue left after centrifugalisation, which is smeared on a slide. The second stage is more definite : the detection of pathogenic bacteria—*i.e.*, streptococcus, bacilli of the coli-aerogenes group and the tubercle bacillus.

Streptococci are found by seeding on solid media, when the examination of the residue has shown that they are present in abundance.

With regard to the bacilli of the coli-aerogenes group, after making a large number of comparative tests between the various methods recommended for their detection [neutral red media (Professor ROCHAIX) ; neutral red sweetened media (BESSON) ; taurocholate of soda lactose media (Irene LIPSKA) ; lactose media stained with fuchsin or malachite green with bromo-thymol blue as indicator (ZAVAGLI)], we decided to adopt the method of PIEN, BACHIMONT and FILHIOL (*Le Lait*, July-August 1933, No. 127), which is a simple one, the usual media being employed. These authors seeded increasing dilutions of milk in peptonised water containing 20 grammes of peptone per thousand, poured into tubes at the rate of 10 cc. per tube. After they have been kept in the incubator at 41° C. for 24 hours, they are tested for indol. Tubes giving a negative reaction are eliminated. The tubes corresponding to the two weakest dilutions which have given a positive reaction are re-seeded in a 1 : 1,000 dilution of *carbolised* peptone water and placed in the incubator at a temperature of 41° C.. After 24 hours they are again tested for indol, and then re-seeded in a 1 : 1,600 solution of *carbolised* peptone water. At the end of 24 hours, a further test is made for indol. If the reaction is positive, bacilli of the coli-aerogenes group are present and the number of *B. coli* per litre is deduced from the initial dilution. If the reaction is negative, those bacilli are not present. The bacilli thus obtained can be identified by their morphological and biological characteristics (VOSGES-PROSKAUER test ; methyl-red test ; seeding on citrated agar by JIMMONS KOSER's method). The position of these bacilli in the coli-aerogenes group will thus be determined—*i.e.*, whether they are fecal *B. coli* or belong to the lacti-aerogenes group. Lastly, isolated strains were injected into guinea-pigs to enable us to study their pathogenic properties.

The tubercle bacillus was detected by direct examination (staining by ZIEHL-NEELSEN's method of the residue from centrifugalisation smeared on a slide) in the case of all samples ; 1 cc. of the mixture obtained by triturating the residue resulting from the centrifugalisation of 40 cc. of milk with the cream floating on top was also injected into animals (guinea-pigs) ; lastly, some of these mixtures were seeded on PETRAGNANI's medium.

6. *Serological examination.*—The spread of *brucella* infection in Lorraine induced us to test the milk of Meurthe-et-Moselle for

brucellæ by lacto-agglutination according to the method of SERGENT, GILLOT and LEMAIRE. One drop of milk heated for half an hour at 56° C. after centrifugalisation is added in turn to two tubes containing 9 and 19 drops of sterilised distilled water ; 10 drops of antigen (antigen from the Montpellier Research Centre for Undulant Fever) are then added to each tube. These are placed in the incubator for 6 hours and the temperature is then reduced to that of the laboratory ; the reading is made at the end of 24 hours. If the agglutination is positive, the limit of agglutination is ascertained by means of a further series of dilutions.

II. METHODS OF APPLICATION.

The application of these methods in the course of researches dealing alike with untreated milk and milk industrially treated and with samples taken at different times of the year necessarily involved modifications of detail, particularly as regards the bacteriological examination, which is specially affected by climatic conditions.

(a) *Cold season* (November to April) : average temperature of the milk 12° C. to 15°. For the bacterial count, 1 cc. of a 1 : 1,000 dilution and 1 cc. of a 1 : 10,000 dilution are seeded. For taking *B. coli* counts, 2 cc. and 1 cc. of pure milk are seeded and also 1 cc. of each of the following dilutions : 1 : 10 and 1 : 100 ; this gives a range of between 300 and 100,000 *B. coli* per litre.

(b) *Warm season* (May to September) : average temperature of the milk : 20° to 23° C.. For the bacterial count, 1 cc. of each of the following dilutions is seeded : 1 : 10,000, 1 : 100,000. For taking *B. coli* counts, 1 cc. of pure milk is seeded and also 1 cc. of the following dilutions : 1 : 10, 1 : 100 and 1 : 1,000 ; this gives a scale of between 1,000 and 1,000,000 *B. coli* per litre.

II. As regards the origin of the milk, a similar difference, varying, however, in extent, is found between the cold and hot seasons. For instance, in the cold season, industrial milk will require the additional seeding of 4 cc. of pure milk ; similarly, in the case of milk taken from the udder, in winter as in summer, 4 cc. of pure milk

should also be seeded and the seeding limited to dilutions of 1 in 10. It is essential to obtain for every sample of milk, according to its origin or previous treatment, a sufficiently wide scale of dilutions to enable its impurities to be detected and determined.

III. METHODS EMPLOYED.

It remains to be seen whether, after employing all these methods, we shall be in a position to determine with a sufficient degree of accuracy the commercial and hygienic value of the milk.

1. *Commercial value.*—This can be adequately determined by the density, acidity and fat content, which, taken together, show whether the milk is in a good state of preservation and whether the two common frauds, watering and skimming, have been committed.

2. *Hygienic value.*—This can be roughly ascertained by the degree of cleanliness on filtration, which can be rapidly confirmed by the reductase test. It can subsequently be determined more accurately by the bacterial count, and after this by testing the milk for pathogenic bacilli, particularly *B. coli*, the streptococcus and the tubercle bacillus. Consequently, these methods taken as a whole furnish sufficient data ; the latter must, however, be defined more clearly if the milk is to be graded according to its hygienic value.

What criteria should be adopted ? The example of a large number of foreign countries will help us to fix the limits which should be adopted for each test, the object being to determine whether the milk is hygienically acceptable.

Foreign regulations for the hygienic control of milk are lacking in both simplicity and uniformity. The variations are readily comprehensible, as it is difficult to apply a single bacteriological standard to different countries and at all times of the year. Taking milk control in the United States of America and in England alone, it will be seen that the figures adopted are very variable.

In the United States, although the Public Health Service of the Federal Government has recommended the adoption of the Milk Ordinance by all towns, the regulations vary from one municipality

to another. Under the Milk Ordinance, eight grades of milk are permitted ; these are defined as follows :

- (1) Certified milk : less than 10,000 bacteria per cc. ; no B. coli.
- (2) Grade A, raw : 50,000 bacteria per cc. ; reductase : 8 hours.
- (3) Grade B, raw : less than 200,000 bacteria per cc. ; reductase : 6 hours.
- (4) Grade C, raw : 1,000,000 bacteria per cc. ; reductase : $3\frac{1}{2}$ hours.
- (5) Grade D, raw : more than 1,000,000 bacteria.
- (6) Grade A, pasteurised : 50,000 bacteria per cc.
- (7) Grade B, pasteurised : 50,000 bacteria per cc.
- (8) Grade C, pasteurised : more than 50,000 bacteria per cc.

In England there are only five grades :

- (1) Certified milk : 30,000 bacteria per cc. ; less than 10,000 B. coli per litre.
- (2) Grade A T T (tuberculin-tested cows) : 200,000 bacteria per cc. ; less than 100,000 B. coli per litre.
- (3) Grade A : 200,000 bacteria per cc. ; less than 100,000 B. coli per litre.
- (4) Grade A, pasteurised : 30,000 bacteria per cc. ; less than 10,000 B. coli per litre.
- (5) Pasteurised milk : 100,000 bacteria per cc.

In his thesis on hygienic milk control methods (1930), A. Névor proposed a simplified grading for France, consisting of only two standard types : (1) raw certified milk : reductase, 8 hours ; 30,000 bacteria per cc. ; no B. coli ; (2) pasteurised certified milk : reductase, 5 hours ; no B. coli ; no figure for the bacterial count per cc.

The bacteriological criterion for approved milk which we have adopted is as follows : *reductase in* : more than 6 hours ; *bacterial count per cc.* : less than 200,000 ; *number of B. coli per litre* : less than 10,000.

Reductase in over 6 hours is the standard adopted for grade 1 by Orla JENSEN. The number of colonies per cc. is that of grade A of the English classification and of grade B raw of the American scale.

As regards the *B. coli* content per litre, we have adopted the figure 10,000, which, according to our tests, appeared to correspond more closely to the bacterial content of the milk than the figure of 100,000 adopted under the English and American grading ; moreover, it seems to us that the milk can hardly be regarded as hygienically pure when it contains such a large number of *B. coli*, the pathogenic action of which we have often demonstrated by experiment. On the other hand, it hardly seemed possible to require a complete absence of *B. coli*.

We did not consider it advisable to adopt a special bacteriological standard for pasteurised milk. The results set forth in the course of this report lead us to believe that this standard, which may appear to be rather too lax in the case of milk treated industrially, is, *at any rate at the present time*, adequate for all grades, and we should be glad indeed if all the milk sold in Meurthe-et-Moselle complied with these modest requirements.

These are the general methods employed in the examination of 600 samples of milk—125 samples of milk as delivered to the consumer and 475 samples of milk on production.

CHAPTER III.—MILK AS DELIVERED TO THE CONSUMER.

The study of milk for immediate consumption involves the examination of the milk as it reaches the consumer—*i.e.*, in the condition in which it is to be consumed. There is, therefore, no special method of taking samples other than by buying them from milkmen.

The form in which the milk is sold varies according to its origin. The dairyman who produces or collects the milk sells it himself or deposits it with retailers ; in either case, the milk is sold from a "measure"—a metal container holding a quarter or half a litre, which is dipped into the milkcan each time. The dairy companies sell their milk, which has been treated, either in capped bottles stamped with the date on which the milk is to be sold or in cans holding from 10 to 20 litres, known as "brochons" (cans). In the latter case, the milk is sold direct from the vans which go from house to house, or through agents who sell the milk retail (in bottles or by measure).

Two kinds of milk are therefore supplied to the consumer :

(1) *Milk for immediate consumption*, which has not undergone any previous treatment and comes from only one farm, on which it is produced, or from a few farms, from which it is collected by dairyman collectors ;

(2) *Industrial milk* treated prior to sale by industrial methods and collected from a large number of different farms (mixed milk).

The foregoing classification shows the difference between the two categories. We examined 125 samples of milk for immediate consumption, including 95 samples of milk supplied direct to the consumer and 30 industrial samples.

I. WINTER MILK : 53 SAMPLES.

A. *Milk for Immediate Consumption* : 39 Samples.

Thirty-nine samples were purchased from retail dairymen in the town and collected in glass bottles, which had merely been carefully washed and not sterilised, so that the samples might be collected under normal conditions. They were then placed in the refrigerator until they could be examined.

From the *physical* standpoint, while the density of all the samples was satisfactory, their cleanliness in many cases left much to be desired. In the case of every litre there was always a coloured sediment, which in some cases was dark brown. The examination of the sediment, slightly magnified, revealed the presence of a large quantity of vegetable debris, mineral particles, cotton threads, fluff, etc.

The only interesting point revealed by the *chemical* examination was the variation in acidity : minimum 15° Dornic, maximum 23°. The average is 18° Dornic, which is a fair commercial average. Only one of the samples subjected to this test was of poor commercial quality, exceeding the standard limits of 15° to 22°. The average fat content is 32 grammes per litre—a figure which corresponds to the average fat content of the milk of Nancy (HOUDINIÈRE).

However, the results of the *biological* and *cyto-bacteriological* examinations were very different.

The fairly homogeneous nature of the group as revealed by the foregoing tests was confirmed by the *reductase* test. None of the samples reduced methylene blue in less than 20 minutes. Only 1 became discoloured in less than 2 hours ; 13 in less than 6 hours ; 25 in more than 6 hours.

In the case of nearly every smear, the *cytological* examination revealed the presence of polynuclear cells ; but only in 15 per cent of the samples was the residue found to contain a very large number of these cells ; mononuclear cells were present fairly often, though in smaller numbers. The smears also revealed a large and varied bacterial flora, Gram-positive diplococci predominating ; however, in many cases Gram-positive bacilli, chains of Gram-positive cocci, Gram-negative bacilli (sometimes ingested by phagocytes) and anthracomorphic bacilli were present.

These many and varied aspects of the bacterial flora were confirmed by *bacteriological* examination.

(a) *Number of colonies per cc.*—17 samples contained less than 200,000 bacteria ; 15 more than 200,000 ; 7 more than 1 million.

(b) *B. coli counts.*—13 samples contained less than 1,000 *B. coli* per litre ; 4 from 1,000 to 10,000 ; 17 samples less than 10,000 ; 22 contained a larger number. It may therefore be inferred that no milk is without *B. coli*.

(c) *Pathogenic bacilli.*—No streptococcus was isolated ; no milk contained acid-fast bacilli.

The *serological* examination of these samples of mixed milk from a small number of farms showed three positive agglutinations for *Brucella* (*i.e.*, 7.6 per cent) in the proportion of 1/30 to 1/40. This rather low proportion is explained by the fact that the milk was mixed.

If we compare the grading of these samples by means of the various bacteriological tests, we shall see from the graphs on page 701 that, when the rule laid down in the previous chapter is applied—reductase in more than 6 hours ; less than 200,000 bacteria per cc. ; less than 10,000 *B. coli* per litre—the grading by means of the reductase test is much less strict than grading by the other tests. Whereas in the former case 25 out of 39 samples (64 per cent) exceeded the required standard, this number was reduced to 17 (*i.e.*, 43 per cent) as a result of the bacterial count, and, in particular, the *B. coli* count.

Although the total number of tests was not very large, the diversity of the samples and their varied origin led us to conclude that, in winter, the commercial quality of the untreated milk at Nancy is satisfactory, but that, on the other hand, its hygienic quality leaves much to be desired—out of 39 samples, only 17 (43 per cent) came up to the required standard in every respect.

B. *Industrially Treated Milk : 14 Samples.*

As we have already seen, this milk is collected from a large number of different farms ; it is mixed milk treated by various processes included under the general name of pasteurisation. Fourteen samples were purchased either in capped bottles or by measure ; they were of various brands ; 10 came from establishments in Nancy and 4 from the depots of dairy companies whose headquarters are situated elsewhere.

The commercial quality revealed by the *physical* and *chemical* examinations was satisfactory, although in 4 cases a dark deposit was left after straining, which is difficult to explain in the case of milk treated correctly, which has passed through the successive stages of straining, pasteurisation and refrigeration. The acidity varied from 16 to 19° Dornic (average, 17.2). The fat content was 32 grammes (5 per thousand).

Reductase test : 10 samples, 6 hours ; 3, more than 2 hours ; 1, less than 2 hours.

After *centrifugalisation*, the residue of 2 samples presented a pus-like appearance ; this was confirmed by the smears, which revealed dense masses of polynuclear cells. The presence of polynuclear cells is not a rare occurrence ; 10 out of 14 samples contained a very large number of those cells. This cytological test is important, as it shows that milk collected from a large number of farms sometimes contains milk which could not be sold untreated, the large number of polynuclear cells in the residue affording definite proof of its contamination.

From the *bacteriological* standpoint, 10 samples contained less than 200,000 bacteria per cc. ; 2, from 200,000 to 1 million ; 2, more than 1 million ; 9 samples contained less than 10,000 *B. coli* per litre, of which 7 contained less than 1,000, while 5 contained more than 10,000. No tubercle bacilli were found when the residue was

examined, as the milk in question was mixed to such a degree that the consequent dilution of agglutinin precluded the possibility of obtaining significant results. In other cases, the milk had been previously heated to temperatures which varied but which would interfere seriously with serological reactions.

The result of the various tests carried out on treated milk shows that the differences are less considerable than in the case of untreated milk. This is only logical, as the milk has been treated by a process designed to bring it up to a hygienically acceptable standard. However, this result is not always achieved, for a recent investigation made by the Zagreb School of Hygiene revealed the fact that, in that town, pasteurised milk was inferior, from the commercial and hygienic standpoint, to untreated milk as sold by the producers. The number of samples which came up to the required standard was as follows : reductase, 10 ; bacterial count, 10 ; B. coli count, 9 ; the percentage thus being 71, 71, 64. These percentages are encouraging, although they should be higher. They show that, at the present time, treated milk, even in winter, does not always furnish the guarantees which the consumer has the right to expect.

The results of the examination of winter milk as supplied to the consumer are summarised in Table I and the graph on page 701.

Table I.—Classification of Untreated Winter Milk according to the Various Bacteriological Tests.

| | Winter | | | | | | | |
|--------------------------|-----------------------------|----------------------|-----------------------|-----------------------|------------------------------|----------------------|-----------------------|-----------------------|
| | Untreated Milk : 39 samples | | | | Industrial Milk : 14 samples | | | |
| | 6 hours | 2 to 6 hours | 20 minutes to 2 hours | Less than 20 minutes | 6 hours | 2 to 6 hours | 20 minutes to 2 hours | Less than 20 minutes |
| Reductase | 25 (64%) | 13 | 1 | 0 | 10 (71%) | 3 | 1 | 0 |
| Bacteria per cc. | 0 to 200,000 | 200,000 to 1 million | 1 to 100 million | More than 100 million | 0 to 200,000 | 200,000 to 1 million | 1 to 100 million | More than 100 million |
| | 17 (43%) | 15 | 7 | 0 | 10 (71%) | 2 | 1 | 1 |
| B. coli per litre | 0 to 10,000 | 10,000 to 100,000 | 100,000 to 1 million | More than 1 million | 0 to 10,000 | 10,000 to 100,000 | 100,000 to 1 million | More than 1 million |
| | 17 (43%) | 22 | 0 | 0 | 9 (64%) | 5 | 0 | 0 |

II. SUMMER MILK : 72 SAMPLES.

A. *Untreated Milk* : 56 Samples.

The average temperature of this milk, the samples of which were taken during the hot season, was approximately 25° (minimum temperature, 19° ; maximum, 28°). It might be thought *a priori* that, under the predisposing influence of the temperature, this milk would be dirtier than winter milk. In addition to the influence of the temperature, there are a number of secondary factors, such as the greater number of dry days, the larger amount of dust, etc. The results we obtained confirmed this assumption.

Fifty-six samples were examined. Their *physical* properties were fairly satisfactory ; density about 1,030 ; cleanliness somewhat unequal. The *chemical* examination showed an acidity in Dornic degrees varying from 13 (minimum) to 30 (maximum) ; average, 17.6, which is slightly below that of winter milk. This may appear paradoxical, but is probably due to artificial improvement. The average fat content was 33 grammes without any marked variations.

Reductase test : Only 5 samples in more than 6 hours ; 21 in 2 to 6 hours ; 14 in 20 minutes to 2 hours ; 16 in less than 20 minutes.

The *cytological* examination showed that, after centrifugalisation, the residue from 22 out of 56 samples (39 per cent) contained a very large number of polynuclear cells, the proportion being much higher than in winter.

The *bacteriological* results were as follows : Bacterial count (colonies on agar) : only 1 sample contained less than 200,000 bacteria per cc. ; 1 less than 1 million ; 31 less than 100 million ; 19 more than 100 million ; 4 more than 1 milliard.

B. coli count : Only 1 sample contained less than 1,000 *B. coli* per litre ; 7 from 1,000 to 10,000 ; 7 from 10,000 to 100,000 ; on the other hand, 11 contained more than 100,000 and 30 more than 1 million.

The serological test was not made in the summer. On the other hand, 7 guinea-pigs were inoculated with a view to detecting,

pathogenic bacilli ; 6 with the residue and cream from 40 cc. of milk, 1 with 1 cc. of the total residue from 1 litre of milk. The 7 guinea-pigs all died within periods varying from 2 to 38 days (2 in 2 days, 1 in 7 days, 1 in 15 days, 2 in 26 days, 1 in 38 days) after rapid and considerable loss of weight (120 grammes in 2 days). The lesions varied considerably; local lesions appeared first, with large abscesses in 3 cases. The distant lesions (fibrino-purulent peritonitis and pericarditis : 3 cases) were, however, more serious. The seeding of the heart blood and bile of the 7 dead guinea-pigs enabled us to isolate a bacillus in 5 cases : 1 enterococcus, 1 non-hæmolytic streptococcus and in 3 cases a colibacillus, all these germs being identified by their recognised reactions. It should be noted that the 3 guinea-pigs which gave positive colibacillus blood cultures died in 2 days and in 7 days ; the milk with which they were inoculated contained more than 1 million *B. coli* per litre.

Confining ourselves to this last criterion—namely, inoculation—we can therefore assert that untreated summer milk is dangerous, as it contains highly pathogenic germs which, in the vast majority of cases, kill the guinea-pig. However, if we compare, as above, the results of the different tests, we shall find that the bacteriological tests alone afforded sufficient indication of the deplorable quality of this milk.

Only four samples passed the reductase test—*i.e.*, 8.9 per cent ; the bacterial count must be less than 200,000 bacteria per cc., and only 1.7 per cent of the samples passed this test ; lastly, *B. coli* counts showed that only 8 (14.2 per cent) contained less than 10,000 *B. coli* per litre. We would mention in passing that the corresponding percentages for winter milk were : 64, 43, 43.

B. *Industrial Milk* : 16 Samples.

The 16 samples analysed in summer were obtained from the same source as those analysed in winter.

We need not go into the *physical* and *chemical* properties of this milk, the density and fat content of which were normal. We would merely point out that the average acidity in Dornic degrees was 17 (maximum, 18 ; minimum, 15) and that the result of straining through cotton-wool revealed the same inequality from the point

of view of cleanliness as in winter milk. It is true that the deposit on the filtre pads was smaller than in the case of untreated milk ; but, though the result of the filtration of certain brands was impeccable, in too many cases particles remained in suspension, showing that the process used was defective or had been carelessly applied.

The foregoing findings regarding winter milk were confirmed by the *cytological* test, which showed that 12 out of 16 residues contained a very large number of polinuclear cells (75 per cent of the samples).

The biological and bacteriological tests also revealed marked inequalities. While under the reductase test 13 samples reduced in more than 6 hours and 3 samples in 2 to 6 hours, when the bacterial count was made, only 4 samples were found to contain less than 200,000 bacteria per cc. ; 1 sample contained less than 1 million bacteria, 10 from 1 to 100 million and 1 more than 1 milliard. According to the *B. coli* count, the 16 samples were classified as follows : 7 with less than 10,000 *B. coli*, of which 6 contained less than 1,000 ; 4 from 10,000 to 100,000 ; 1 from 100,000 to 1 million.

No tubercle bacilli were found in 15 residues from centrifugalisation. Only one contained acid and alcohol fast bacilli. One inoculated guinea-pig died in 24 hours without apparent lesions ; the heart blood and bile remained sterile after seeding.

Two guinea-pigs were inoculated with 2 samples containing 12 million bacteria per cc. and 10,000 *B. coli* per litre ; 8 million bacteria per cc. and less than 1,000 *B. coli*, respectively ; the animals were still alive after 40 days without loss of weight.

On summarising the foregoing results, we find that 81 per cent of the samples passed the reductase test ; 25 and 43.7 per cent respectively were acceptable according to the bacterial count and *B. coli* count, as compared with the following winter percentages : 71, 71, 64. These figures show that there is a serious deterioration in the quality of industrial milk in summer.

Table II.—Classification of Untreated Summer Milk according to the Results of the Various Bacteriological Tests.

| | Summer | | | | | | | |
|-------------------|-----------------------------|----------------------|-----------------------|----------------------|------------------------------|----------------------|-----------------------|----------------------|
| | Untreated Milk : 56 samples | | | | Industrial Milk : 16 samples | | | |
| | 6 hours | 2 to 6 hours | 20 minutes to 2 hours | Less than 20 minutes | 6 hours | 2 to 6 hours | 20 minutes to 2 hours | Less than 20 minutes |
| Reductase | 5 (8.9%) | 21 | 14 | 16 | 13 (81%) | 3 | 0 | 0 |
| Bacteria per cc. | 0 to 200,000 | 200,000 to 1 million | 1 to 100 million | Over 100 million | 0 to 200,000 | 200,000 to 1 million | 1 to 100 million | Over 100 million |
| | 1 (1.7%) | 1 | 31 | 23 | 4 (25%) | 1 | 10 | 1 |
| B. coli per litre | 0 to 10,000 | 10,000 to 100,000 | 100,000 to 1 million | Over 1 million | 0 to 10,000 | 10,000 to 100,000 | 100,000 to 1 million | Over 1 million |
| | 8 (14.2%) | 7 | 11 | 30 | 7 (43.7%) | 4 | 1 | 4 |

III. CONCLUSIONS.

The examination at Nancy of 125 samples of milk as delivered to the consumer (53 samples of winter milk and 72 of summer milk) showed that, while their commercial quality was satisfactory, their hygienic quality was inferior.

1. In the case of untreated milk (95 samples), the hygienic quality, which was already very mediocre in winter (64 acceptable samples out of 100 when they were examined by the reductase test; 43 out of 100 by the other more severe tests), became deplorable in summer, when only 8.9 per cent of samples passed the reductase test, and when the other tests were applied, in the one case nearly all the samples (98.3 per cent) were rejected and in the other rather more than four-fifths (85.8 per cent).

2. In the case of samples of industrially treated milk (30), although the quality was less poor, it did not come up to expectation. Some were good on the whole, but this cannot be said of the majority. When the bacteriological tests were applied, about two-thirds of the

winter samples were found to be of good hygienic quality (from 64 to 71 per cent) ; in summer, however, the proportion of satisfactory samples, which was high under the reductase test (81 per cent), fell to 25 per cent after the bacterial count and to 43.7 per cent after the B. coli count had been taken.

The beneficial effect of industrial treatment is shown in Table III. This has been definitely proved, and it can only be regretted that it is not as effective in summer as it is in winter.

Table III.—Percentage of Acceptable Samples of Untreated Milk.

| Season | Untreated Milk : 95 samples | | | Industrial Milk : 30 samples | | |
|----------------|-----------------------------|-----------------|---------------|------------------------------|-----------------|---------------|
| | Reductase | Bacterial count | B. coli count | Reductase | Bacterial count | B. coli count |
| Winter | 64% | 43% | 43% | 71% | 71% | 64% |
| Summer | 8.9% | 1.7% | 14.2% | 81% | 25% | 43.7% |

CHAPTER IV.—MILK ON PRODUCTION.

Since the hygienic quality of the untreated milk is very inferior, the question necessarily arises, At what moment does the milk which reaches the consumer in a dirty state become contaminated? If this happens at the time of production, efforts must be made to improve the hygienic quality of the milk at that initial stage. We therefore examined 475 samples of milk collected, not only from the udder, but at the various stages from production to consumption through which it passes. These 475 samples were obtained as follows :

| | |
|--|--|
| 1. Milk taken from the udder. . . . | { by hand milking 116 by mechanical milking. 9 |
| 2. Milk taken from the byre { immediately after | |
| 3. Milk collected under the usual conditions | 341 |
| | 475 |

The comparative study of these various samples appeared to us to be of the greatest interest, since they form a continuous chain

covering the intermediate stages which, we believe, are rarely investigated, although the milk in its initial and final stages—*i.e.*, milk taken from the udder and milk as offered for consumption—has been examined time after time.

All these samples were collected in sterilised bottles, which were placed in the refrigerator for 4 or 5 hours after milking and examined at the end of a varying period, which in no case exceeded 4 hours. We will now deal with each category in the same way as in the previous chapter, dividing the milk into winter and summer milk.

1. WINTER MILK : 249 SAMPLES.

A. *Samples taken from the Udder* : 84.

The samples taken from the udder were obtained either by hand-milking or by mechanical milking.

1. *Hand-milking* : 83 samples.—This method of milking is used by all the small farmers, who, as we have seen, supply the greater part of the milk in Meurthe-et-Moselle. Hand-milking is usually carried out in the byre at 5 a.m. and 4 p.m. by the farm hand, the "marcaire", or by a milkmaid, under very unhygienic conditions. The udder is rarely washed and the hands of the milker more rarely still. The milk is collected in open pails, which in most cases are simply rinsed out with water from the nearest well. In view of the conditions of hand-milking in Lorraine, the examination of milk taken from the udder was obviously important from a local standpoint.

Eighty-three samples were taken from the udders of apparently healthy cows belonging to different farms, under the usual milking conditions ; the cow was, however, milked straight into the sterilised bottle. Only biological and cyto-bacteriological examinations were carried out on these samples.

Under *reductase* test, none of these 83 samples reduced in less than 8 hours and in some cases even 11 hours. The *cytological* analysis was of much greater value than in the case of mixed milk, since the milk had been obtained from a specific teat of a specific animal. The question of the cytological elements of milk has been discussed at length and we need not refer to it again. It can hardly be disputed, however, that, while the presence of lipophage mono-

nuclear cells does not denote a pathological condition and is merely a sign of the retention of milk, the presence of a large number of polynuclear cells in the mammary secretion, as elsewhere, is a sign of *infection*. This is amply proved by the frequent presence in milk taken from the udder of signs of phagocytosis. Out of 83 samples taken from the udder, 15 contained a very large number of polynuclear cells (30 to 40 per visual field, 2 fixed objects 1/12), 17 contained a few polynuclear cells (2 to 3 per field); the others contained only a few cellular elements, mainly mononuclear. The proportion of infected teats is therefore about 18 per cent—that is to say, 1 in 5 is infected. It is not surprising, therefore, that, in the case of mixed milk from a small number of cows (1 to 6), the cell-content of that milk is very frequently abnormal, and also that, in the case of mixed milk as delivered to the consumer, which comes from a larger number of cows, the proportion containing polynuclear cells is smaller.

The *bacteriological* examinations proper gave the following results :

Bacterial-count per cc. : 1 sample remained sterile ; 36 samples contained less than 1,000 bacteria per cc. (minimum 100 ; maximum 900) ; 36 less than 10,000 ; 8 less than 100,000 ; 2 less than 200,000 and more than 100,000. *B. coli* count : the number of *B. coli* per litre was under 250 in 68 cases and under 500 in 15 cases.

No sero-diagnostic test for *brucellæ* gave positive results. It should be noted that the byres from which the samples were taken belonged to farms on which no cases of epizootic abortion had occurred and were situated in places where there had been no signs of human or animal *brucella* infection. It is interesting to compare this absence of any positive results under these conditions with the frequency of positive lacto-agglutination in *brucella*-infected places. In communes where human cases of *brucella* infection have occurred, Dr. Robert LÉVY obtained in the laboratory of the Regional Institute of Hygiene of Nancy 28 *brucella*-positive lacto-diagnoses out of 96—*i.e.*, 29 per cent ; approximately the same proportion was found in Meuse : 23 out of 71—*i.e.*, 30 per cent. In communes with no human cases of *brucella* infection, there were 13 positive results out of 21—*i.e.*, 61 per cent.

These results show that, in spite of the unsatisfactory hygienic conditions, the milk taken from the udder by hand-milking was

comparatively clean, and, in particular, that all the samples contained less than 500 *B. coli* per litre; some of them may not have contained as many, as the volume of milk seeded in no case exceeded 4 cc. and the limit of the *B. coli* count is then 200 *B. coli* (5 cc. seeded in 2 tubes).

As the result of all these tests, the proportion of acceptable samples was found to be 100 per cent. Consequently, the milk obtained by hand-milking retained its full hygienic value when it left the udder. This is not a new finding, but it is worthy of note, in view of the conditions under which milking is done in Meurthe-et-Moselle.

Like many others before us, we endeavoured to ascertain the differences from the bacteriological standpoint between the various milking stages:

(a) *Start of milking*.—27 samples obtained at the start of milking were examined separately; only 3 of those samples contained fewer bacteria than the subsequent samples; in 90 per cent of cases, the first portion of the milk was more contaminated than the following portions. This coincides with the findings of SCHULTZ, FREUDENREICH, GORINI, GORRIERI and many other investigators.

(b) *Middle stage*.—The milk from the middle stage of milking was more satisfactory; some samples contained only from 100 to 200 bacteria per cc.

(c) *End of milking*.—Milk obtained during the last stage of milking was of the same quality as that obtained during the middle stage in most of the samples examined (13 out of 16). In 3 cases, the residue from centrifugalisation was found to contain a very much larger number of polynuclear cells than the first portions, thus proving the existence of an inflammatory lesion irritated by somewhat prolonged milking.

These supplementary data enable us to conclude that the number of bacteria in milk taken from the udder is very small and that *B. coli* is rarely present. As GORRIERI stated, *B. coli* is not a germ proper to milk. Its subsequent presence in the milk is due to contamination; it has nothing to do with the animal from which the milk is taken. We shall endeavour to prove this later. In Meurthe-et-Moselle, as elsewhere, the milk as it leaves the cow's udder is therefore of good quality from the bacteriological standpoint.

2. *Mechanical milking : 1 sample.*—In view of the results of hand-milking, still more satisfactory results might be expected from mechanical milking. This operation is performed on several farms in Meurthe-et Moselle by machines mainly of foreign make, but the mechanical milking is always completed by hand-milking. The only sample of winter milk taken gave the following results : reductase, more than 8 hours ; 980,000 bacteria per cc., less than 500 *B. coli* per litre ; quality of milk inferior to that of the milk obtained by hand-milking.

B. Milk taken from Byres after Milking : 4 Samples.

Four samples were collected *as soon as the milking was completed*. Of these, three were of good quality, reductase in 8 hours ; 2 contained 11,200 bacteria per cc. and less than 250 *B. coli* per litre ; 1 contained 142,000 bacteria per cc. and less than 500 *B. coli* per litre. The fourth, which was a mixed sample of milk obtained by mechanical milking, contained 980,000 bacteria per cc., less than 500 *B. coli* per litre ; reductase : 8 hours ; it might be regarded as just passable, although it was inferior to the others.

C. Milk collected from a Number of Farms : 161 Samples.

These were samples of the milk which is collected each morning by the dairy companies on their rounds (mixed milk from a large number of farms) or which is delivered to itinerant milkmen to be distributed in the town (mixed milk from a small number of farms). All this milk is therefore at least 12 hours old (reckoned from the evening milking), in the case of skimmed and semi-skimmed milk (a mixture of skimmed milk from the evening milking and of whole milk from the morning milking), and about 6 hours old in the case of whole milk. The bacteriological analysis of this milk is obviously of very great importance, as it is on its way to the consumer and has already undergone various processes, has been subjected to temperatures varying from that of the byre to the outdoor temperature and has been mixed (semi-skimmed milk), and its initial quality has thus been modified.

1. *Physical.*—The density varied between 1,029.7 and 1,038.5 ; the average density was between 1,030 and 1,033. The physical

purity varied greatly ; the samples sometimes contained extraordinary objects which could be seen with the naked eye. When the cans in which the milk is collected are emptied at the factory, the most varied articles are sometimes found : common objects, textile and vegetable debris, straw, hay, insects, flies, etc. The cleanliness of the milk on filtration was very unequal. There appears to be a constant of uncleanness proper to each farm.

2. *Chemical*.—The acidity in Dornic degrees was between 14° and 29°, but those figures were rarely attained : the average—17° Dornic—was satisfactory. The fat content, the extreme figures of which were 21 grammes per thousand and 57 grammes per thousand, was 35.3 grammes per thousand on an average, which is higher than the usual average for Nancy milk (32 grammes per thousand according to HOUDINIÈRE).

3. *Biological*.—As a result of the reductase test, the samples were divided into four very unequal groups : 106 samples in more than 6 hours (65.8 per cent) ; 39 in more than 2 hours ; 14 in less than 2 hours ; 2 in less than 20 minutes.

4. *Cytological*.—Out of the total number of samples collected, 40—*i.e.*, 24.8 per cent—were found to contain a very large number of polynuclear cells when subjected to cytological analysis ; in 3 cases the residue from centrifugalisation was hæmatic.

5. *Serological*.—7 out of 161 samples agglutinated brucellæ, the proportion being 4.3 per cent.

6. *Bacteriological*.—Count of colonies on agar : the 161 samples were divided up as follows according to the number of colonies : 90 contained less than 200,000 per cc. (55.9 per cent) ; 42 between 200,000 and 1,000,000 ; 29 exceeded 1,000,000 ; maximum : 9,220,000 B. coli count : 127 samples (78 per cent) contained less than 10,000 B. coli per litre, of which 83 contained less than 1,000 ; 34 contained more than 10,000 ; no guinea-pigs were inoculated.

The hygienic value of collected milk is therefore inferior to that of milk obtained by hand-milking. This deterioration is shown in the following table and in the graph on page 701, the comparison being confined to milk taken from the udder by hand-milking and to collected milk.

Table IV.—Classification of Winter Milk on Production according to the Results of the Different Bacteriological Tests.

| | | Winter | | | | | | | |
|-------------------|--------------|--|-----------------------|----------------------|---------------|------------------------------|-----------------------|----------------------|---|
| | | Milk taken from the udder : 83 samples | | | | Collected milk : 161 samples | | | |
| Reductase | 6 hours | 2 to 6 hours | 20 minutes to 2 hours | Less than 20 minutes | 6 hours | 2 to 6 hours | 20 minutes to 2 hours | Less than 20 minutes | |
| | | 83 (100%) | 0 | 0 | 0 | 106 (65.8%) | 39 | 14 | 2 |
| Bacteria per cc. | 0 to 200,000 | 200,000 to 1 million | 1 to 100 million | Over 100 million | 0 to 200,000 | 200,000 to 1 million | 1 to 100 million | Over 100 million | |
| | 83 (100%) | 0 | 0 | 0 | 90 (55.9%) | 42 | 29 | 0 | |
| B. coli per litre | 0 to 10,000 | 10,000 to 100,000 | 100,000 to 1 million | Over 1 million | 0 to 10,000 | 10,000 to 100,000 | 100,000 to 1 million | Over 1 million | |
| | 83 (100%) | 0 | 0 | 0 | 127 (78%) | 34 | 0 | 0 | |

II. SUMMER MILK : 226 SAMPLES.

A. Taken from the Udder : 41 Samples.

As in the foregoing cases, we shall distinguish between hand and mechanical milking.

(1) *Hand-milking* : 33 samples.—In view of the constancy of the results obtained with winter samples and the first summer samples, we confined our examination to 33 samples.

Both in summer and in winter, the results were completely concordant. Cytological examination showed that 7 samples contained a very large number of polynuclear cells (21.2 per cent), methylene blue was discoloured in more than 8 hours ; all the samples contained less than 50,000 bacteria per cc. (minimum 100, maximum 42,000). A more detailed subdivision of the samples gives a better idea of the bacterial content ; it was found that, out of 33 samples, 29 contained less than 10,000 bacilli per cc. ; one sample only contained 1,000 B. coli to the litre, the others less than 250 B. coli.

We also verified, in the summer, the data concerning the beginning, middle and end of the milking process. At the beginning, the milk almost always contained more bacteria ; at the end, it generally contained more cellular debris, the cellular content being above all noticeable in milk rich in polynuclear cells from the first spurt.

We have therefore nothing to add to or retract from the previous conclusions. Both in winter and summer, the milk as it comes from the cow's udder is, under present milking conditions in Lorraine, of very good quality from a hygienic standpoint.

(2) *Mechanical milking : 8 samples.*—Eight samples were taken in several dairies where milking is done by machinery. The results of the tests place them in a lower category than the samples of milk obtained by hand-milking. No sample survives the reductase test : all become discoloured in from 20 minutes to 2 hours ; the count gives figures well over 1,000,000, in one case over 1,000,000,000 per cc. *B. coli* are present in all : 100,000 per litre in three samples, over 1,000,000 in the other five.

Taken under ordinary working conditions, therefore, milk obtained by mechanical milking is of a definitely inferior quality. The reasons for this will be given in the following chapter.

B. *Samples of Milk taken in the Byre after Milking : 5 Samples.*

These samples were taken in the byre from the receptacle containing a mixture of milk from several cows of the same farm immediately after milking. The milk was all obtained by hand-milking.

Here again we had proof of the quality of milk obtained by hand-milking. The 5 byre samples met the required conditions : reductase in more than 6 hours ; less than 200,000 colonies per cc. ; less than 500 *B. coli* to the litre.

C. *Samples taken from Milk collected from Various Sources : 180 Samples.*

Both as regards origin and destination, the samples were exactly the same as those taken in the winter. They showed the following characteristics :

1. *Physical.*—Their average density was normal ; 1,030.5 (the extreme limits being 1,025.9 and 1,034.9 respectively). Their

cleanliness always varied considerably, but fairly often uncleanness was noticeable in both winter and summer samples taken on the same farm.

2. *Chemical*.—Acidity varied more than in winter (12 to 64° Dornic). These wide variations seem to indicate that the almost normal average (17.6) is not a natural one, but is the result of artificial alkalisation in many cases. The amount of fatty substance was 34.7 grammes on an average (the extremes being 24 grammes and 51 grammes respectively), or slightly less than the winter average.

3. *Biological*.—Only 53 samples (29.4 per cent) could be placed in the first category (over 6 hours) in the light of the reductase test ; 61 in the second ; 34 in the third ; 32 in the fourth.

4. *Cytological*.—The bacterial content of the residue was excessive, but the vast majority of the samples were also very rich in polynuclear cells : 53, or 29.4 per cent.

5. *Serological*.—No lacto-agglutination tests were carried out in the summer.

6. *Bacteriological*.—The classical tests gave the following results : 3 samples (1.6 per cent) with less than 200,000 bacteria per cc. ; 9 less than 1,000,000 ; 13 over 1,000,000,000 (extreme figures 80,000 and 4,700,000,000).

Thirty samples contained less than 10,000 *B. coli* to the litre (11 per cent) ; 34 from 10,000 to 100,000 ; 51 from 100,000 to 1,000,000 ; 65 over 1,000,000.

In the matter of pathogenic bacteria, tests for the tubercle bacillus were invariably negative ; streptococcus was isolated on two occasions (non-hæmolytic streptococcus, with many long phagocyte chains in the centrifuge residue). Twenty-one guinea-pigs were inoculated. Before examining the details of these inoculations we propose, as above, to compare, in the light of the bacteriological tests, the samples taken at the udder (hand-milked) and of collected summer milk.

Table V.—Classification of Samples of Milk (Summer) in the Light of Various Bacteriological Tests.

| | Summer | | | | | | | |
|-------------------|---|----------------------|-----------------------|-----------------------|---------------------------------|----------------------|-----------------------|-----------------------|
| | Samples of milk taken at the udder : 33 | | | | Samples of collected milk : 180 | | | |
| | 6 hours | 2 to 6 hours | 20 minutes to 2 hours | Less than 20 minutes | 6 hours | 2 to 6 hours | 20 minutes to 2 hours | Less than 20 minutes |
| Reductase | 33 (100%) | 0 | 0 | 0 | 53 (29.4%) | 61 | 34 | 32 |
| Bacteria per cc. | 0 to 200,000 | 200,000 to 1 million | 1 to 100 million | More than 100 million | 0 to 200,000 | 200,000 to 1 million | 1 to 100 million | More than 100 million |
| | 33 (100%) | 0 | 0 | 0 | 2 (1.6%) | 10 | 109 | 59 |
| B. coli per litre | 0 to 10,000 | 10,000 to 100,000 | 100,000 to 1 million | More than 1 million | 0 to 10,000 | 10,000 to 100,000 | 100,000 to 1 million | More than 1 million |
| | 33 (100%) | 0 | 0 | 0 | 30 (11%) | 34 | 51 | 65 |

Table V and the graph on page 701, when compared, show how appreciable the difference is between milk taken at the udder and milk collected from various sources. The results of inoculating guinea-pigs with 21 samples of "collected" milk will demonstrate the pathogenic character of its bacterial flora.

Of the 21 guinea-pigs inoculated, 20 died within from 2 to 40 days ; only 1 survived. On seeding blood from the heart, we were able to isolate the following bacteria : enterococcus, twice ; streptococcus, once ; paratyphoid *B. bacillus*, once ; *B. coli*, three times. The 13 other seedings were negative ; twice, however, seedings of vesicular bile gave a *B. coli* pathogenic to guinea-pigs ; 1 cc. of bouillon culture killed the guinea-pig in 36 hours with positive blood and bile cultures ; *B. coli* present.

The lesions observed were of very different kinds.

(a) In a first group of 12 guinea-pigs (tardy death and negative blood cultures), autopsy revealed no appreciable lesions. Emaciation was pronounced, the animals losing 200 grammes in one month. Only in one case (a pregnant female) were miliary mesenteric and hepatic granulations noted after 20 days, together with a lumbar

lymph gland the size of a grain of wheat. There were no germs or tubercle bacilli in these lesions. Löwenstein's blood culture was negative. The appearance of the lesions was such, however, as to suggest that they might be tuberculous.

(b) In one case the only lesion was a large local abscess at the point of inoculation ; the pus revealed numerous deteriorated polynuclear cells and a monomicrobial flora : hæmolytic streptococcus (died in 19 days). The milk used for inoculation changed the blue in $7\frac{1}{2}$ hours ; 216 million germs per cc. ; over 100,000 B. coli to the litre. The centrifuge residue contained cocci in numerous small chains (milk 427).

(c) There remained the group of 7 positive blood cultures. These we will classify and examine according to the germ isolated.

1. *Hæmolytic Streptococcus*.—Inoculated with milk 509 (reductase $3\frac{1}{2}$ hours ; 186,800,000 bacteria per cc. ; over one million B. coli per litre), the guinea-pig died in 18 days, after losing 177 grammes in weight. It had a large abscess on the right thigh (B. coli and streptococcus) ; a subcutaneous B. coli abscess in the sternal region and a B. coli abscess in the left lung. Blood culture gave a hæmolytic streptococcus.

2. *Enterococcus*.—First guinea-pig : inoculated with milk 394 : 135,000 bacteria per cc. and less than 1,000 B. coli to the litre. Died in 30 days, losing 100 grammes in weight. Hæmorrhagic congestion of the lungs. Second guinea-pig : inoculated with milk 408 : 15,560,000 bacteria to the cc. ; over 100,000 B. coli to the litre ; died in 27 days after losing 220 grammes in weight ; some pulmonary lesions ; both blood cultures gave enterococcus.

Paratyphoid B. Bacillus.—Inoculated with milk 407 (reductase in 10 minutes ; 329,600,000 bacteria to the cc. ; over 100,000 B. coli to the litre), the guinea-pig died in 21 days, after losing 170 grammes in weight. Peritoneal fluid coloured ; liver infected ; swollen spleen ; bile and blood from heart gave, in 24 hours, a classical paratyphoid B. bacillus, agglutinable in a 1 : 3,200 dilution by anti B. serum. Was this germ of human or animal origin ? There was no reported case in the commune of origin ; moreover, J. FRICKER and J. WARTER have recently proved (*Société de Pathologie Comparée*, July 10th, 1934) the possibility of the bovine species becoming infected by salmonellosis in the Bas-Rhin. Among 100 samples

of milk, they found positive agglutination in a 1 : 100 dilution for paratyphoid B. bacillus and 2 positives in a 1 : 50 dilution for Aertrycke's bacillus. It was not possible to establish the source of the contamination of this milk.

4. *B. coli*.—In the three cases in which blood culture revealed the presence of *B. coli*, the guinea-pigs' death was premature ; 2 days, 4 and 5 days. This agrees with the results obtained by inoculating with samples of milk as delivered to the consumer. In one case only was there a lesion at the point of inoculation : a large abscess on the right thigh. It coincided, in this case, with the visceral lesions observed in the other guinea-pigs : fibrinopurulent peritonitis and fibrinopurulent pericarditis, forming in one case a thick coating around the heart ; streaky discoloration of the kidneys ; infected liver. The animals lost flesh very rapidly, 100 grammes in 2 days ; 110 grammes in 4 days ; 160 grammes in 5 days. Seedings of blood from the heart, of the peritoneal fluid, of the pericardial fluid and of the bile all gave a typical and strongly indol producing *B. coli*. Of the samples of milk used for inoculation, the first two (487 and 490) came from the same locality. The characteristics were : reductase in 50 minutes and 5 minutes ; 80 million and 600 million germs to the cc. ; over 1 million *B. coli* per litre. As regards the third sample (512), reductase occurred in $6\frac{1}{2}$ hours and there were 324 million bacteria to the cc. and 10,000 *B. coli* to the litre.

The *B. coli* strain isolated from the blood of guinea-pig 487 was inoculated into a fresh guinea-pig ; 1 cc. of a dilution in physiological saline of an agar culture (diluted to about 7 thousand million per cc.), administered by subcutaneous injection, killed this guinea-pig in 36 hours, with visceral congestion and hæmorrhagic peritoneal effusion : *B. coli* was isolated from the heart blood, from the bile and from a hæmorrhagic lymph gland in the inoculated region. Two other *B. coli* strains were shown to be equally pathogenic.

The results of these inoculations call for several remarks :

(a) The bacteria encountered are not—with the exception of the streptococcus which is almost certainly of mammary origin—some of the ordinary bacterial flora of the milk ; they come from outside.

(b) These germs have been isolated in guinea-pigs inoculated with milk which ordinary bacteriological examination had shown to be very bad, except the two which either reductase (milk 512)

or the bacterial count or the *B. coli* count had shown to be passable (milk 394).

(c) All the germs isolated (except the streptococcus) are ordinarily present in the intestinal tract. But are they of human origin? That is a difficult question to answer. One thing is certain: they do not come from the intestine of the guinea-pig. It might have been thought that the presence of *B. coli*, particularly in the guinea-pig's heart blood, might be due to the passage of this bacillus from its intestine into its circulation, as a result of the general disorder caused by inoculation. Two arguments militate against this theory. The first is a common-sense one: all the guinea-pigs that died should then have had *B. coli* in their blood. But we have 13 negative blood cultures. The second argument is a point of fact: the presence of the same *B. coli* in the local abscess, in the concomitant lymph gland and in the distant lesions (fibrinopurulent pericarditis) indicating the path followed by the bacillus in its passage from the local lesion into the general circulation. There is even a third argument: the inoculation into the guinea-pig of *B. coli* strains isolated from milk; 4 different strains caused the death of one of the guinea-pigs in 36 hours.

Two last facts should be mentioned with regard to these inoculations:

(1) The absence of tubercular lesions. True, in one case out of thirty we believed that there were tubercular lesions, but could not prove it. Moreover, in only one case did we find acid-fast bacilli in the centrifuge residue. This fact is certainly astonishing when compared with the results obtained by Mme. BOVIN in 1923, which she describes in a monograph on the presence of tubercle bacilli in Meurthe-et-Moselle milk. Her figures give 50 to 77 per cent positive results. We propose to re-examine this aspect of the question later, on the basis of tests other than the present ones, which led to the rapid death of the animals without there being time for the tuberculosis infection to develop.

(2) The positive results obtained at the Montpellier Undulating Fever Research Centre by inoculating guinea-pigs with brucellosis-contaminated milk samples from Meuse and Meurthe-et-Moselle: 12 strains of *Brucella melitensis* and 4 of *Brucella abortus bovis* were thus isolated.

III. CONCLUSIONS.

The examination of 475 samples of milk from Nancy (125 samples taken at the udder or in the byre ; 9 samples of milk obtained by mechanical milking, and 340 samples of " collected " milk) shows a satisfactory commercial quality, but very varying qualities from a health point of view.

1. The samples of milk taken at the udder are in all cases bacteriologically excellent after hand-milking and very doubtful after mechanical milking. There is no appreciable seasonal difference ; both in winter and summer, the proportion of acceptable milk is 100 per cent.

2. The samples of " collected " milk—the quality of which is already doubtful in winter as compared with milk taken at the udder—show appalling and dangerous defects in summer. The reality of the danger is proved, not only by ordinary tests (reductase : 29.4 per cent ; bacterial count : 1.6 per cent ; B. coli count : 11 per cent), but above all by the inoculation tests which reveal the presence of pathogenic germs, mainly of intestinal origin—a further indirect, if not conclusive, proof of their human origin. Two main categories of commercial milk (milk taken at the udder and " collected " milk) are compared in the following table.

Table VI.—Percentage of Acceptable Commercial Milk.

| Season | Milk taken at the udder : 116 (hand milking) | | | "Collected" milk : 341 | | |
|----------------|---|--------------------|------------------|------------------------|--------------------|------------------|
| | Reductase | Bacterial count | B. coli count | Reductase | Bacterial count | B. coli count |
| Winter | 100% | 100% | 100% | 65.8% | 55.9% | 78% |
| Summer . . . | 100% | 100% | 100% | 29.4% | 1.6% | 11% |

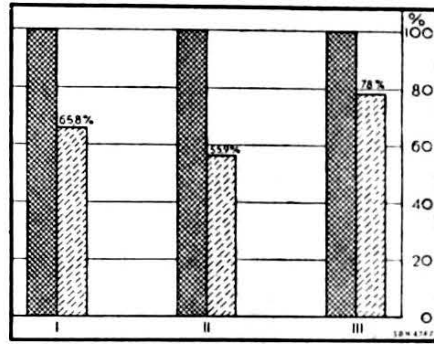
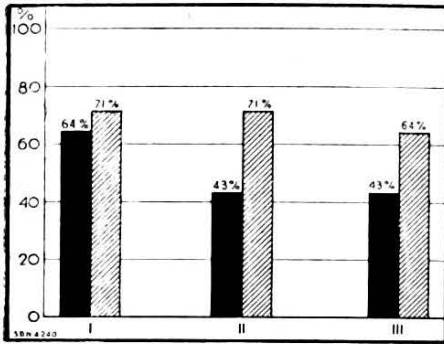
PERCENTAGES OF MILK THAT HAVE SATISFIED THE VARIOUS BACTERIOLOGICAL TESTS.

MILK AS CONSUMED.

MILK AS PRODUCED.

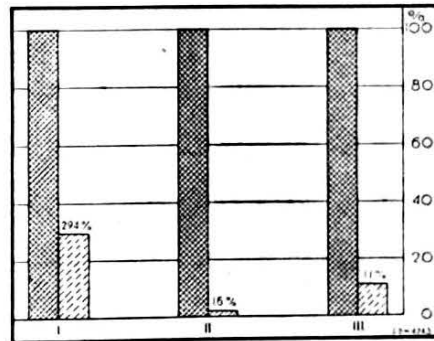
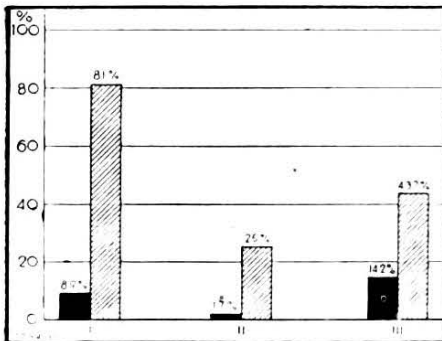
1. *Winter Milk.*

3. *Winter Milk.*



2. *Summer Milk.*

4. *Summer Milk.*



■ Untreated milk.
 □ Treated milk.

▨ Milk taken at the udder.
 ▤ "Collected" milk.

I. Reductase, over 6 hours. II. Less than 200,000 bacteria per cc.
 III. Less than 10,000 B. coli to the litre.

CHAPTER V.—THE MAIN SOURCES OF MILK CONTAMINATION.

In the two previous chapters we have shown that milk is generally of very good quality when fresh from the cow, but becomes increasingly suspect and poor as it approaches the consumer. The latter, it is true, rarely worries about its hygienic value, particularly because, as we have already pointed out, the milk itself always looks pure and white. Nevertheless, this apparently innocent liquid, which is the child's almost exclusive article of diet, contains, when it reaches him, much cellular debris, various bacteria, several of which are pathogenic, and soluble substances of microbial origin that can certainly do him no good. If the campaign against such contamination is to be effectively organised, we must examine each stage of milk production and endeavour to ascertain where contamination begins or increases. Only then can we develop our prophylactic work with a reasonable hope of improving the production and healthiness of milk in the future. We will, therefore, trace the progress of milk from the cow to the consumer.

I. MILKING.

Milk may be contaminated in different ways at the milking, according to whether the hands or machinery are used.

A. *Milking by Hand.*

In hand-milking the milk may be contaminated from three main sources : the animal, man or the atmosphere.

(a) *The Animal.*—Pathogenic—namely, disease-producing—germs may pass out with the milk itself.

The tubercle bacillus would seem to be rare in Meurthe-et-Moselle milk. Although the various samples of milk examined by Mme. BOUIN in 1923 at Nancy showed a proportion of 57.8 to 77.8 per cent tubercle bacillus in the case of " collected " milk and 27.8

to 28.4 per cent in the case of individual samples, we ourselves have only once discovered acid-fast bacilli in industrially treated milk and only once—out of 30 inoculations—were possible tuberculosis lesions detected.

Streptococcus comes mostly from the animal itself. In Meurthe-et-Moselle, instances of its passing from infected teats would seem to be rare. It has only been isolated twice, and then in a non-hæmolytic state. The phagocytosis traces visible in the residue from these milks prove the animal origin of this germ. The presence of *Brucella* in sero-diagnostically positive milk has been noted by the Montpellier Fever Research Centre, to which samples have been sent by the Regional Health Institute for the isolation of strains. Thus, in certain contaminated establishments in Meurthe-et-Moselle, after 41 lacto-diagnoses with positive results, 8 strains of *Brucella melitensis* and 6 of *Brucella abortus bovis* were isolated from the milk. In other Meurthe-et-Moselle dairies, after 23 lacto-diagnoses with positive results, 7 strains of *Brucella melitensis* and 3 of *Brucella abortus bovis* were obtained. The example of the village of Allain-aux-Bœufs, where Professors Jacques PARISOT, VIDAL and R. LÉVY conclusively proved for the first time in 1932 that *Brucella melitensis* had passed out with the milk of cows that had come into contact with infected sheep, demonstrates the danger of milk contamination. This danger is increased by the fact, demonstrated by TAYLOR, VIDAL and ROMAN before the Biological Society in 1934, that such elimination may be chronic, continuing for years and sometimes even infecting other cows in the same byre which had previously been healthy.

Foot and mouth virus, owing to the veterinary measures taken, has not given rise to any epidemiological observations.

Can *B. coli* be regarded as a pathogenic germ of bovine origin? The exceptional number of samples taken at the udder that contained *B. coli*, and the pathogenic character of the strains isolated, warrant the opinion that, generally speaking, *B. coli* is not derived from the animal; and yet milk must frequently be contaminated by animal excrements. Are not these excrements and cow-dung a source of *B. coli*? BAUMANN's experiments at Liebfeld in 1932, under the direction of Professor BURRI, have established a number of rather unexpected facts in this connection. BAUMANN has shown that "the addition of fresh cow-dung to clean milk does not

increase the milk's bacterial flora. In fact, the procedure even has the additional advantage of giving to the milk "that cowey taste" which the consumer so highly appreciates. In any case we think that *B. coli* in milk may be of animal origin, but that the pathogenic bacillus has probably a human origin, as will be seen below.

(b) *The Atmosphere*.—Germs from the litter, soil and air are numerous at milking-time, particularly if that is also the feeding-time of the animals. These are saprophytic and non-pathogenic germs of the type of *B. lactis aerogenes* which we have several times been able to isolate from "collected" milk, but they have much more effect on the commercial quality of the milk than on its hygienic purity.

(c) *Man*.—Man is still the main source of pathogenic germs when milking is done by hand. Anyone who has seen a milker at work can feel no surprise that the milk, pure as it spurts from the teat, is immediately contaminated by germs during its passage into the pail. First the milker's hands: they are rarely washed, sometimes dipped in the previous pail of milk, sometimes moistened with spittle, constantly damp, and the drops fall from them into the pail beneath the cow's udder. Furthermore, hands are mainly contaminated with matter of faecal origin. This is the greatest danger of hand-milking. The high proportion of intestinal bacteria isolated after guinea-pig inoculation—7 *B. coli*, 3 enterococcus, 1 paratyphoid *B. bacillus* (*i.e.*, 11 intestinal bacteria out of 12 isolated)—proves how great the danger is. The rhinopharyngeal system would certainly seem to be less dangerous, although it is usual to blame it.

The main danger therefore lies in the contamination of the milker's hands, particularly as regards intestinal germs. We can without exaggeration say that, in the matter of *B. coli*, hand-milked milk, though often contaminated by the milker's hands, is (as we shall see later) far more often infected by uncleanly handling in which dirty hands play an essential part.

B. *Mechanical Milking.*

In theory, mechanical milking would seem to be the ideal, in that a closed circuit protected from the air is established from the

“ milker ” to the covered receptacle to which the milk is adducted. Germs from the atmosphere and from the hands of man are entirely eliminated. The only source therefore from which germs can derive is the animal organism, the teat itself. But what happens in practice? In the first place, the milking has to be finished off by hand; the risk, diminished because the time is shorter, is there all the same. But, in fact, mechanical milking introduces a new source of contamination: the apparatus itself. The results of several experiments illustrate this danger. In a dairy which otherwise left nothing to be desired, the milk obtained by mechanical milking from several cows contained, in winter, 980,000 germs per cc. and more than 250 *B. coli* to the litre; whereas five cows on the same farm milked by hand gave milk with a bacterial content per cc. varying from 900 (minimum) to 82,000 (maximum); a mixture of the five milks gave 11,000 bacteria per cc. One single sample contained over 250 *B. coli* to the litre; but the mixture contained less than 250 to the litre. This superiority of hand-milking, under average healthy conditions, to mechanical milking is far greater than is at present recognised. Professor PANISSET (*Recueil de Médecine Vétérinaire*, No. 6, June 1932) points out that, according to the comparative statistics published, it cannot be hoped that mechanical milking will give milk of a bacterial content *distinctly less* than that obtained by hand-milking *under good hygienic conditions*. Furthermore, he adds, the bacteria which pass into the milk during its journey through the tubes are mainly *saprophytic*. The considerable difference noted between our two samples proves that the milk becomes contaminated during its passage through the apparatus and, above all, that it does not collect only *saprophytes* therein.

The following experiments prove this. Two litres of physiologically sterile water were drawn by suction through the mechanical-milking apparatus, ready to be used for the evening milking (it had already been used for milking in the morning), and were collected into a sterilised receptacle. The highly opalescent liquid obtained was then seeded in the usual manner. The results—for the warm months—were as follows:

The bacterial content was enormous: 14,600,000; 22,600,000; 54,400,000 and 90,000,000 germs per cc.; *B. coli* content per litre was over 10,000 for the first wash and more than 1,000,000 for the three others. Finally, operating a mechanical-milking apparatus

that had not been rinsed, we obtained milk containing 18,200,000 bacteria per cc. and 1,000,000 *B. coli* per litre.

The presence of *B. coli* raises the question of its origin. It is more than probable that the original contamination is caused by the water used for washing the apparatus. This water is often drawn from any source nearest to the byres, or is polluted by unclean manipulation. The germ, having been introduced into the apparatus by the water, then finds in the residual liquid limited aerobiotic conditions which are favourable to multiplication. This explains the enormous numbers found in the rinsing water and the first milk that passes through the apparatus.

Obviously, therefore, inadequately supervised mechanical milking is dangerous. Under the cloak of a hygienic operation it still, as the above results abundantly prove, involves considerable risks.

II. TREATMENT OF MILK AFTER MILKING.

The Receptacles.

The milk is collected into receptacles—open in the case of hand-milking, closed in the case of mechanical milking. The state of these receptacles can readily be imagined. Generally left standing in the byre between the morning and evening milkings, rarely washed before or after use, they are more often than not just hurriedly rinsed before use with water which has to be economised in the summer, since in several parts of the Meurthe-et-Moselle it is none too plentiful. The fresh milk is poured into these receptacles, and from them it passes into the milk-cans, direct in the case of whole milk, otherwise only after skimming. The milk thus stored is very seldom protected from flies, dust and even domestic animals. We ourselves have seen cats come and drink this milk quite freely.

We have endeavoured to ascertain the extent to which receptacles may contaminate milk, by seeding the liquid obtained from washing two milk-cans and a bucket in a small producer's farm. These receptacles had been rinsed with pure spring-water. The washing waters proved to be only very slightly polluted : Milk-can No. 1 : 388 colonies on agar per cubic cc. ; 20 colonies per cc. on gelatine in 10 days; less than 10 *B. coli* to the litre. Milk-can No. 2 : 871

colonies per cc. on agar ; 1,415 on gelatine ; less than 10 B. coli to the litre. Bucket : 73 colonies per cc. on agar ; 515 on gelatine ; less than 10 B. coli to the litre.

Under average good hygienic conditions, therefore, when liberally rinsed with pure water, the receptacles do not seem to play any considerable part in contaminating the milk. This is, however, not always the case. A. NÉVOT, in his thesis (Paris, 1930), mentions the high bacterial percentages found on seeding the water used for washing dairy-cans : 420,000 colonies per cc. to 4,500,000.

The quality of the water used for cleaning receptacles does undoubtedly affect the bacteriological quality of the milk stored in them ; but it is very difficult in practice to make a study of the water used, because it is impossible to obtain from producers any definite and reliable information on the subject.

III. HANDLING AND PRESERVATION OF MILK.

The milk remains at the farm in the milk-cans until the collector comes round or the producer leaves for town. Twelve hours elapse between the evening milking and the following morning, by which time the cream has risen and is collected with ladles. This skimmed milk is mixed with the morning's milkings to make up that semi-skimmed milk which Nancy consumers prefer (three-fourths of the consumption according to Dr. HOUDINIÈRE). We will now consider the straining of the milk, its preservation, skimming, mixture and the addition of water.

A. *Straining.*

The milk is strained through muslin to free it from gross dirt. This muslin is simply rinsed, and only rarely washed in hot water, between each operation. It is then put out to dry in the open, near the house, exposed to dust, flies and farmyard poultry.

B. *Preservation.*

In Meurthe-et-Moselle there are scarcely any central milk depots for the sorting and handling of "collected" milk before this is

sent to the factories for treatment. The collectors on their rounds simply collect the milk in the milk-cans and it is from these same milk-cans that the retail milkman distributes his milk in town.

How is this milk preserved? It may be said that in Meurthe-et-Moselle it is quite exceptional for any special precautions to be taken to maintain the milk at a temperature suitable for its preservation. We are still far from the careful Nordic standard or American industrial methods. The milk-can is very seldom placed in water; it is mostly kept in a shed or even in the byre winter and summer.

MIQUEL's tables proved long ago the combined influence of time and temperature on the growth of the bacterial flora in milk. Italian experiments have also demonstrated that *B. coli*, though not an initial contamination, is a barometer of the particular conditions under which the milk has been kept. In milk taken at the udder and kept *below* 6° to 7°, *B. coli* does not increase. Above this temperature, however, the colonies of *B. coli* multiply considerably in proportion to the increase in temperature.

We have tested this point with six samples of milk kept at various temperatures. The results are as follows:

| | Reductase | Bacteria per cc. | <i>B. coli</i> per litre |
|--|----------------|------------------|--------------------------|
| Sample 276 on arrival | More than 8 h. | 54,000 | Less than 250 |
| After { 18 h. at 8° | 6 hours | 73,000 | Less than 500 |
| { 18 h. at 37° | 4 hours | 1,220,000 | More than 500 |
| Sample 278 on arrival | More than 8 h. | 142,000 | Less than 500 |
| After { 18 h. at 8° | 6 hours | 162,000 | More than 500 |
| { 18 h. at 37° | 4 hours | 7,880,000 | More than 1,000 |
| Sample 311 on arrival | More than 8 h. | 11,200 | Less than 250 |
| After 48 h. at + 1° | More than 6 h. | 138,000 | Less than 250 |
| Sample 337 on arrival (taken at the udder) | More than 6 h. | 400 | Less than 250 |
| After 4 days at 0° | More than 6 h. | 500 | Less than 250 |
| Sample 339 on arrival (taken at the udder) | More than 6 h. | 38,600 | Less than 250 |
| After 4 days at 0° | More than 6 h. | 34,000 | Less than 250 |

A temperature of 1° (which can be controlled in a refrigerator), even if it does not prevent the proliferation of certain germs, does prevent that of *B. coli*.

C. *Skimming.*

Skimming by the dairyman in the morning is a further source of contamination. The ladle used to collect the floating cream is rarely washed and is often laid upon the ground. Moreover, in collecting the cream, full of microbes brought to the surface with the rising fatty globules, the ladle seeds not only the receptacle into which it is dipped but subsequent receptacles. But, even in the case of milk already so contaminated, it is difficult to prove that there is a difference between whole and semi-skimmed milk.

D. *Mixture.*

The mixture of milk from various sources causes no fresh contamination, but favours the proliferation of microbes, in that the medium is renewed by the addition of fresh nutritive elements.

E. *Watering.*

Fortunately, this cause is not frequent. When done at the farm, it is far more dangerous than that secret matutinal operation of which the public fountains themselves are sometimes the only witnesses. At any rate, the water from the public fountains is fairly pure, whereas the farm water, polluted in many cases, rich in *B. coli* and in bacteria of the intestinal tract, is a certain source of bacterial contamination.

IV. DISTRIBUTION AND SALE OF MILK.

A. *Transport.*

The milk is mostly transported in small motor-vans, less frequently in horse-drawn floats. The jolting on the roads sometimes loosens the fastenings of the cans so that their contents are exposed to the dust of road and town. The milk thus arrives in the town, where it will be dealt with by the dairies (at which juncture, in theory, its contamination should end) or be deposited with a retailer or be sold direct retail.

B. Retail Sale.

Milk is sold either in the street or in the shop.

(a) *In the open street.*—This is the method followed by retail milkmen. The milkman trundles his cans from door to door, passes the liquid from one receptacle to another and finally delivers with his "measure" the amount of milk the housewife requires. The measure, hooked on to the inside of the can, is hardly protected at all. It is being constantly used by the milkman and remains more or less wet with milk, so that drops fall from it between each delivery into the receptacle, carrying with them all the dirt of the milkman's hands, which have been abundantly polluted from the time he has risen from his bed and has completed his summary toilet, by repeated contact with horse, cart, motor-car, etc.

(b) *In the shop.*—Certain retailers, particularly in summer, keep the milk in an ice-box either in bottles or cans. But others simply keep the milk at the temperature of the room. Often, the milk from the cans is drawn off into an open, unprotected basin in order to facilitate the operation of sale. Thus, the progressive collection of germs goes on until the time when the housewife puts the milk on the fire.

Is the bacteriological career of milk terminated at that moment? Unfortunately not, for, though prolonged boiling destroys most of the germs, the boiled milk must be kept either in an ice-box or at a low temperature and protected from flies, dust and other impurities. The latter condition is essential. We found in milk boiled and kept at a temperature of 15° under good conditions of protection the following bacteriological characteristics : before boiling : 11,200 colonies to the cc., less than 250 B. coli to the litre, reductase over 8 hours ; 6 hours after boiling : 200 colonies to the cc., less than 500 B. coli to the litre, reductase over 6 hours.

V. CONCLUSIONS.

As many writers on the subject have already observed, and as GORRIERI and ZAVAGLI have recently made abundantly clear, it is impossible to obtain, on a large scale, milk free from germs, parti-

cularly those of the coli-aerogenes group, at any rate 24 hours after milking. Milk is contaminated in so many ways on its journey from the udder to the consumer that it is not surprising that, in a modern Italian installation specially supervised for the production of milk to be consumed unboiled, 25 samples of milk out of 30 contained *B. coli* in 1 cc. In one hygienic dairy in Italy, ZAVAGLI found that 81 per cent of the samples contained 1,000 bacilli of the coli-aerogenes group per litre.

The sources of contamination are : (1) the hands of the milker and the mechanical milking apparatus ; (2) above all, contaminated receptacles ; (3) unclean handling. Contamination is greatly augmented when these operations are carried out at a favourable temperature.

We may therefore conclude, like Professor PANISSET and the Swiss writers on the subject, that the large number of germs and resultant defective preservation of milk are rather the result of its contact with dirty milking and transport utensils and insufficient cooling than uncleanliness in the milking itself. This important conclusion should be valuable in Meurthe-et-Moselle, as elsewhere, as a guide in the matter of preventive measures, since, on the whole, it corresponds with our own observations.

CHAPTER VI.—HOW TO PROTECT MILK FROM CONTAMINATION.

In spite of all assertions to the contrary, it is not an impossibility to supply consumers in France with hygienic milk. Even if most of the results of our analyses are rather discouraging, some of them do at least prove that hygienic milk is not a myth in Meurthe-et-Moselle. In summer, 11 samples of "collected" milk, and even one sample of milk from a retailer, contained less than 1,000 *B. coli* to the litre. Obviously, the number of these exemplary purveyors is too small, but the fact that hygienic milk does exist proves the possibility of obtaining it on a large scale. Moreover, the commercial milk supplied by certain firms maintains a sufficiently high hygienic standard to justify the conclusion that hygienic milk could be secured from both sources of supply. Why should what is possible in one place be impossible in another ?

We have seen in the previous chapter the various influences which help to deteriorate milk. We will now study the means of combating them. These means may be grouped under two familiar heads : preventive measures and palliative measures.

I. PREVENTIVE MEASURES.

This means, of course, preventive measures from the udder to the consumer.

A. *At the Origin.*

The policy should be to eliminate from milk production all cows suffering from or suspect of any disease transmissible to man through milk. For this, the veterinary authorities must be responsible. Highly efficient veterinary supervision is exercised in Meurthe-et-Moselle, so that there is complete security on this score.

B. *At the Milking.*

1. *Hand-milking*, as practised in Lorraine, in spite of its imperfections, gives good-quality milk. But better results could be obtained by improving milking conditions. In the first place, the milker : he should be free of all pathogenic germs. No person suffering or recovering from an infectious disease should be allowed to milk. In short, cows should not be milked by any germ-carrier, particularly an intestinal-germ carrier. The actual operation of milking could be improved by the observance of a few simple hygienic rules. Educational propaganda should be conducted throughout the countryside, emphasis being laid on the benefits which the farmers themselves would secure by observing such rules. Without hoping to achieve the luxury of American installations—particularly the Walker-Gordon establishments at New York, where the cows are brought up one by one on a turntable, are douched, dried by a ventilator, wiped and then milked—or the degree of hygiene of certain model farms of the Dutch or Danish type, the cleanliness of the animals' hind-quarters, the immobilisation of the tail during milking, the washing of the udders, the washing of the milker's

hands, the discarding of the first portions of milk and the avoidance of foddering during milking, are measures which can easily be understood and accepted by the producer. At a small farm we succeeded, by giving certain pieces of advice which were effectively followed, in improving the quality of milk obtained by hand in a very appreciable manner. (Number of bacteria per cc. reduced from 280,000 to 11,200 ; number of *B. coli* per litre reduced from over 1,000 to less than 250.)

The introduction of milking competitions with bacteriological inspection, organised through the producers' unions, might be of great value from this point of view in dairy-farming regions. By the prizes offered for the best milk, such a measure would give an economic stimulus that would be much appreciated by the rural populations, which are more responsive to an appeal of this kind than to that of hygienic principles.

2. *Mechanical milking* is comparatively common in the average-sized farms, and is appreciated by producers owing to its higher yield. But, as we have seen above, it constitutes a real danger. The complicated mechanism of the apparatus necessitates constant watching and renders its cleaning very difficult. Much too little emphasis is, moreover, laid on such cleaning in the instructions delivered with the apparatus. Some merely recommend daily rinsing in cold water, and only prescribe disinfection once a week.

We have seen above, from the results of seeding the water used for washing the apparatus, what a harmful practice this is, because it only cleans partially, and particularly because the water used, which is often of very doubtful quality, contributes to a proliferation of the bacterial flora.

The owners of the apparatus must be reminded that careful cleaning after each milking operation is absolutely essential. A recent study by PARFITT (*Indiana Station Bull.*, 348, 1931) recommends : (1) rinsing with cold water immediately after milking ; (2) a second rinsing with hot water at 165° F. at the rate of about 7 litres per apparatus ; (3) the filling of the milking goblets and milk tubes, placed over a drainer, with a disinfectant solution. The drawing by suction of cold water through the apparatus is sufficient to remove the remaining traces of disinfectant before further milking. Sodium hypochlorite and chloramine may be used as disinfectants, but these two substances leave a troublesome

precipitate in the milk tubes ; an ordinary lye solution diluted at 0.3 to 0.5 per cent would be as effective. VAN OYEN recommends washing in cold water, then the immersion of the goblets and rubber tubes for an hour or two in a specially prepared solution of a commercial preparation of calcium hypochlorite known as " Caporit ". The excess of this product is eliminated with hot water. By means of these precautions, but by these precautions only, mechanical milking will give milk of excellent bacteriological quality.

C. After Milking.

It is in the course of the subsequent operations that preventive prophylaxis must be exercised to a maximum degree. It is no good perfecting a milking process providing milk which is already of good quality if the milk is subsequently going to lose this initial quality. It therefore appears to us a matter of still greater urgency to take measures in the subsequent stages.

Attention must first of all be given to the *receptacles* and their washing. Nearly always, receptacles are simply rinsed with cold water before and after milking. To be effective, this rinsing must be prolonged ; it therefore necessitates *abundant* water, but it is also imperative that the water should be *pure* and that its use should not introduce a new source of contamination.

These two conditions are not fulfilled in Meurthe-et-Moselle in the milk-producing regions :

(a) *Water is not always abundant.*—Owing to the nature of its soil, the Department is not well provided with drinking-water. This is often available only in limited quantities in summer, and very little is allowed for dairy operations which would require an ample supply.

(b) *Water is not always pure.*—Although, particularly since 1920, piped water-supply systems have been introduced in the Department (in 326 communes out of 600, or 52.2 per cent), so that about five-sixths of the total population now benefit thereby, some efforts must still be made for the benefit of the rural districts, as one of us has demonstrated in a recent study on typhoid fever in Meurthe-et-Moselle (*Revue d'Hygiène*, No. 7, July 1934). While the percentage of the population supplied with drinking-water is 93 in communes of over 1,000 inhabitants, it is only 55 in communes

of under 1,000 inhabitants. It is mainly the agricultural communes, however, which are producers of milk, and, even in the case of those communes which have an entirely satisfactory water supply, the farmer usually employs the water found close to his farm, in most cases from his well or a pond, and sometimes river water, all of which we know to be polluted to an enormous extent.

The danger presented by this polluted water would, indeed, be comparatively small if, after washing, brushing and rinsing with cold water, the receptacles were washed with boiling water to which sodium carbonate was added ; this washing should be followed by rinsing with boiling water and by draining. The receptacles should further be disinfected once or twice a week with a solution of sodium hypochlorite, the remaining traces being removed by rinsing. A receptacle treated in this way would offer all the necessary guarantees for obtaining clean milk in a clean way. But can one advise the producer to employ such measures, to be repeated morning and evening, with the slightest hope of their being adopted ? We do not think so.

Hence, the problem of drinking-water in the rural districts, supplied in a liberal manner to each farm, is an urgent matter from the point of view of dairy hygiene. By improving the hygienic conditions of dwellings, and especially of byres, a pure and abundant water supply will certainly already exercise a beneficial influence on the hygienic production of milk ; but it is particularly by ensuring an adequate cleaning of receptacles that it will delay the contamination of milk, and by prolonging its existence will enable it to retain its full value.

It is not sufficient to have drinking-water available for all ; it must be used. Here, again, it is only by means of educational propaganda, which might begin at school, that this idea of the essential character of water as the source of all hygiene can be inculcated into the masses. In Meurthe-et-Moselle a very interesting piece of educational propaganda has been carried out by the distribution of 50,000 tracts on dairy hygiene among the milk producers supplying the town of Nancy. These tracts, published by the Departmental Veterinary Service, set out in simple and convincing form the principles of the hygiene of the stable, the milch cow, the milker, milking, receptacles and the handling of milk.

D. *During the Handling of the Milk.*

Given an abundant supply of drinking-water, of which he is expected to make proper use, the dairyman who has received his milk in clean containers must keep it fresh for sale next morning (evening milking). For all the subsequent operations, preventive measures are essential ; we shall deal with these in the same order as in the previous chapter.

1. *Straining.*—The cloth used for straining must be washed each time after it is used and dried in a place where no dust, flies, etc., can reach it.

2. *Preservation.*—The milk obtained in a clean state can only be kept in good condition at a *low temperature*. This is a classical rule observed in foreign countries and on a few large farms near Paris. But, in a region of small farms, how can this essential requirement be reconciled with economic conditions ? As we have seen, the temperature should not exceed + 6° C. in order to prevent the proliferation of germs, and particularly *B. coli*. This low temperature can only be obtained by means of expensive plant, which the producer cannot afford to instal. The temperature of an ordinary refrigerator is too low, and, besides, it would have to be a very large one. The cost of a cold-storage chamber is prohibitive, and, moreover, in the villages, ice is a luxury within the reach of very few.

This material impossibility of keeping the milk at a low temperature can only be remedied by palliatives. We know from MIQUEL's tables that milk kept at 15° C. will contain 120 times fewer germs than milk kept at 25°. The pathogenic strains will, however, increase considerably and to such an extent as to make the milk dangerous. Given present conditions, it does not seem possible to improve this state of affairs in Meurthe-et-Moselle. The only practical recommendation we can make is that the milk should be kept in covered containers ; in summer, standing in running water, the temperature of which is some degrees lower than the outdoor temperature and will thus check the proliferation of bacteria ; in winter, in a place protected from frost but with a temperature approaching zero. It is only in a region producing milk on a large

scale (which is not the case in Meurthe-et-Moselle) and where there are large farms, that the big producers' syndicates are in a position to chill the milk without making the cost of production too high.

3. *Skimming*.—The degree of contamination due to skimming is small compared with that caused by the improper preservation of the milk. Provided it is carried out with utensils rinsed before they are used and protected from dirt, skimming may, on the contrary, improve the milk. It is a well-known fact that, when the cream rises to the top, it brings with it not only the fatty globules but germs as well, which, of course, is so much the worse for those who consume fresh cream.

4. *Mixed Milk from Successive Milkings*.—The marked preference of the Nancy consumer for semi-skimmed milk makes this mixing compulsory in Meurthe-et-Moselle. The amount of contamination due to the skimmed milk can hardly affect the quality of the whole milk which is added to it in the morning, if this is reduced by the foregoing measures. Nevertheless, this mixing is regrettable, but it is unfortunately a habit which is difficult to change.

5. *Watering*.—This fraudulent operation does not constitute a very grave danger in Meurthe-et-Moselle ; it is kept in check by the proceedings taken by the service for the prevention of fraud. Moreover, the results of the chemical analyses of milk as produced and as consumed have shown that its commercial quality is satisfactory, although, owing to local conditions, the average is rather lower than that of French milk in general. Watering, which is always a fraudulent operation, is not necessarily unhygienic, provided the water used is of good quality from a bacteriological standpoint.

E. *During the Distribution and Sale of the Milk.*

An improvement in *transport* conditions can easily be effected and supervised. This supervision might be exercised in the same way as that of foodstuffs, when the milk enters the urban area where the municipal decrees can be enforced.

As regards the distribution and sale of the milk, this also takes place in the urban area. It should therefore be a very easy matter

to regulate it by municipal decree—in the street, by forbidding milkmen to pour the milk from one can to another, either in the van or in the open air ; in the shops, by strictly regulating the method of sale of the milk.

It is true that a few retailers, who have more knowledge of hygiene and are more anxious to keep their customers, place the milk in a refrigerator, but the usual method of keeping the milk is less satisfactory. The can, or even the open pan into which the milk is poured, is kept at the shop temperature and often comes into contact with flies, dust and dirty human hands.

The method of sale of the milk might also be improved. When it is taken out of the can or pan, into which the measure is dipped, there is a risk of seeding each time, as the measure is put down anywhere between two successive sales—on the counter, for instance. It would be better to draw the milk from a tap at the bottom of a container which is always kept closed. In that case, however, the customer, who is always concerned about the commercial quality of what he buys, will consider that he has been unfairly treated, because, when the milk is not stirred up, the cream rises to the top. Those who are first served will thus receive milk with a very low fat content, while the last-comers will obtain a much richer quality. A closed can has been invented in which the milk is stirred up mechanically before each sale, and is drawn from a tap at the bottom of the can. There are also automatic distributors similar to those used for petrol pumps, but they are difficult to keep clean.

In any case, the sale of milk from open pans should be strictly prohibited, and it should be made compulsory for the milk to be kept chilled in the shops—which can easily be done in an urban area—by municipal decree.

The method of sale of industrially treated milk is fairly satisfactory. The bottles are usually kept in the refrigerator ; only the method of covering is open to criticism. It should be possible to require the bottles to be covered with metal caps. Cardboard discs are used by certain firms, but these are difficult to extract and the neck of the bottle is necessarily soiled by the fingers. The sale of pasteurised milk delivered in cans and sold by measure should be prohibited, as this is a heresy from the point of view of hygiene. The guarantee afforded by the sale of milk which is pasteurised only in name is altogether illusory.

For all this preventive prophylaxis the following measures are essential :

(1) Administrative measures : municipal decrees the effect of which is confined to the urban area.

(2) Measures of general rural hygiene, an improved standard of living in rural districts, more hygienic dwellings, better-kept byres and a campaign against flies ; lastly, and most important of all, a drinking-water supply. The combined effect of all these factors is bound to make milk production more hygienic.

(3) In accordance with the conclusion reached by the Tenth Milk Congress at Milan (April-May 1934), educational propaganda with a view to instructing the producer how to make possible improvements is even more essential. How can we induce him to adopt measures such as the cleansing and disinfection of containers, the installation of refrigerating systems, or even more elementary precautions, such as cleanliness in handling and the use of clean water, when the eternal objection—*i.e.*, the economic objection—will at once arise ? It is the duty of propagandists to reply to this objection by pointing out that the expenditure involved is not enormous, and particularly that, like all sums devoted to purposes of health, that expenditure is productive, since it enables the rural producer to keep and even to increase his clientele. The directors of the dairy producers' syndicates should undertake these improvements and should follow the excellent example given by the town of Milan. In accordance with very definite regulations, the central factory, which has the monopoly of pasteurised milk in that town, pays for the milk supplied by the producer at different prices according to the results of the chemical and bacteriological examination which is carried out.

This economic stimulus is not one of the least important arguments which can be advanced by propagandists to make the producer realise the necessity for the proposed measures. Nevertheless, other methods of propaganda, such as lectures, pamphlets, newspaper articles and tracts, should not be neglected. The tracts might be presented in the simple and practical form, described

above, in which they have been drawn up by the Departmental Veterinary Services of Meurthe-et-Moselle.

II. PALLIATIVE PROPHYLAXIS.

Owing to the difficulty of applying the foregoing measures in districts which are not yet sufficiently advanced to realise the necessity for them and the possibility of one or other of those measures being imperfectly applied or omitted, the introduction of preventive prophylaxis is likely to be a slow process. It is firmly established in certain foreign countries where it has made it possible to sell certified raw milk ; but this preventive method cannot be introduced straight away among the small producers of Meurthe-et-Moselle, although it can be applied on the large farms where the economic factor is less acute.

In view of the contamination of untreated milk, which is all too common, it is important to exercise *palliative prophylaxis* forthwith, pending the general introduction of preventive prophylaxis, which is already applied by certain producers who supply clean milk.

Palliative prophylaxis can be applied :

(1) Either immediately before consumption—*i.e.*, *household prophylaxis* : careful and prolonged boiling of the milk, which should be kept in covered containers in the refrigerator ; this is within everyone's reach ;

(2) Or between production and consumption—*i.e.*, *industrial prophylaxis* ; in a word : pasteurisation. Whatever method is adopted (" high-temperature " pasteurisation, " low-temperature " pasteurisation, stassanisation, biorisation), pasteurisation, by destroying the pathogenic flora and reducing the harmless flora, diminishes the contamination of various kinds which the milk has suffered during its various stages. Provided this process is duly followed by chilling and placing in clean containers, which are then kept in a cool place, it constitutes at the present time, if carefully applied, the best method of obtaining milk which is consistently satisfactory.

However, it requires considerable capital which only the industrial companies or corporative groups possess, and its use by small producers is therefore almost impossible. If it were made compulsory by law, the small retail producers would be ruined. The draft law of Bam and Klotz introduced for this purpose as long ago as 1912 has never been passed ; it advocated the effective pasteurisation of milk intended to be consumed raw. A unanimous outcry was raised against it in the Agricultural Commission on behalf of the small producers. And yet compulsory pasteurisation will have to come if no efforts are made to ensure the hygienic production of milk by preventive and educational methods.

However, if compulsory pasteurisation is ever introduced into France, as Professor PANISSET, in his report to the Conseil supérieur d'Hygiène publique de France (1934), thinks it ultimately must be, compulsory, effective and frequent supervision will be essential. Professor PANISSET considers that milk obtained from various sources and intended for current consumption should be pasteurised by means of apparatus approved by the Conseil supérieur d'Hygiène publique, in authorised establishments which should be kept under supervision.

This necessity for strict supervision and control is proved by the results of our analyses of industrial milk. There is a striking inequality between the samples. While some milk is uniformly of good quality, other milk is, to put it mildly, from time to time or consistently of poor quality. In some milk factories the control exercised by the manufacturer is therefore too often defective, and in many cases it is non-existent. A high standard of pasteurisation must thus be ensured and maintained by means of official control by the laboratories authorised in the same way as they are for water analysis (institutes of hygiene, regional laboratories, approved laboratories) to carry out the bacteriological analysis of milk. Compulsory pasteurisation must not, however, delay the preventive measures to ensure that the milk will reach the factory in a cleaner state, thus lightening the task of pasteurisation, which will, however, remain as a final and definite guarantee.

CHAPTER VII.—GENERAL CONCLUSIONS AND DEDUCTIONS.

I. THE POSITION OF THE DEPARTMENT OF MEURTHE-ET-MOSELLE FROM THE POINT OF VIEW OF MILK HYGIENE.

While the quantity of milk produced in Meurthe-et-Moselle is satisfactory, since the output of the Department is sufficient for its needs, the quality is, on the whole, inferior.

1. *Commercial Quality.*

This is slightly below the normal for France as a whole owing to the increasing predominance among Lorraine cattle of the Dutch breed, which yields milk with a rather low fat content, this being the traditional test of the commercial value of milk. Moreover, the number of milk samples condemned by the service for the suppression of fraud shows that milk of poor commercial quality is still offered for sale.

2. *Hygienic Quality.*

Taken as a whole, the bacteriological analyses of untreated milk clearly show that the hygienic quality is very inferior.

(a) *Milk supplied direct to the Consumer.*—This is produced by small farmers possessing only a few head of cattle and is sold direct to the consumer without any previous treatment. The *degree* of contamination is very great. While the proportion of acceptable milk varies from 43 per cent to 64 per cent in winter, it falls in summer to the appallingly low figure of from 1.7 per cent to 14.2 per cent, according to the test applied.

In this connection we may mention, for purposes of comparison, the fact that, among 60 samples of Parisian *winter* milk, R. A. NEVOT found 21 unfit for consumption—*i.e.*, 65 per cent of acceptable milk. The *nature* of the contamination is an excessive bacterial flora consisting mainly of saprophytic germs, but including some pathogenic bacteria the presence of which was revealed by the

inoculation of guinea-pigs. *B. coli*, in particular, of which they contained sometimes enormous quantities, would seem to be a by no means negligible danger in Meurthe-et-Moselle milk also. The *sources* of contamination are many. In fact, contamination is unavoidable under local conditions of milk production : dirty live-stock, badly arranged byres, badly kept receptacles, dirty handling, antiquated traditional methods. The danger of badly supervised mechanical milking apparatus in medium-sized or large dairy-farms should also be borne in mind. After the milk has been contaminated from all these sources, it is further contaminated when being sold retail.

(b) *Industrially Treated Milk*.—Produced in Nancy by four well-equipped factories using various pasteurisation methods, industrially treated milk has proved to be of indisputably higher quality. The proportion of acceptable milk, which varies from 64 to 71 per cent in winter, is, in summer, from 25 to 81 per cent according to tests. Although, therefore, this milk is *less frequently* contaminated than that previously described, the frequency is still too great to justify the use of the term “pasteurised”. The *nature* of the contamination is the same as in the case of other milk, but its pathogenic flora is less rich and generally of only one kind—*B. coli*. In theory, the *origin* of the contamination ought to be subsequent to the industrial treatment ; in practice, it may be due to insufficient pasteurisation plus poor preservation and defective retail selling conditions.

II. SUGGESTED PREVENTIVE MEASURES.

The situation described is not peculiar to the Department of Meurthe-et-Moselle, but it is in some danger of becoming stabilised in Lorraine owing to economic conditions, and steps should be taken to improve it. This might be done in various ways according to the category of milk dealt with.

A. *Industrially Treated Milk*.

Here immediate results could be obtained. Pasteurisation by apparatus of a type approved by the Supreme Council of Public

Health, in authorised establishments, would make it possible to institute official supervision forthwith. Some establishments do not at present invariably supply the consumer with really pure milk ; that is because they themselves do not adequately supervise their pasteurisation and retail selling conditions. These defects should be remedied by official supervision. Simultaneously, municipal decrees should be promulgated laying down obligatory hygienic rules for the sale of milk.

B. *Milk supplied direct to the Consumer.*

Here progress will necessarily be slower, because the task is a vast and complicated one. In fact, farmers will have to be induced to change their methods and adopt a more hygienic procedure.

(1) The first requisite is to *provide drinking-water systems*. The bad quality of the drinking-water in rural districts is a cause of defective sanitation. Though 50 per cent of the total number of communes of less than 1,000 inhabitants are supplied with drinking-water, the proportion is much lower in certain dairy-farming cantons. In the Xaintois region, the cantons of Haroué (10 water-supply systems in a total of 30 communes) and Vezelise (22 water-supply systems in a total of 33 communes) show a rate of 66 per cent of communes without a proper supply of drinking-water.

(2) Simultaneously, *the education in health matters* of the country population and, in particular, dairy farmers should be undertaken without delay. The pamphlet on milk hygiene issued in 1934 by the departmental veterinary services is an excellent example of such a propaganda, because the procedure it advocates can be understood by all and does not involve, for the farmers, a disproportionate expenditure. The results of this propaganda, however, will probably not be noticeable for several years to come.

(3) Finally, *the conditions under which milk is sold can be subjected to supervision* immediately by municipal decrees that could easily be passed and enforced.

Will these measures suffice ? In some cases, greater difficulty will be encountered than in others, and the period within which these measures can be put into effect must therefore vary, and will depend largely on the familiarisation of farmers with the rules of hygiene. As the danger is bound to continue for some time yet, one step

should certainly be taken as a measure of prudence : *the pasteurisation of all milk intended for human consumption*. *Compulsory and supervised* pasteurisation is, in fact, the only way in which the quality of milk in Meurthe-et-Moselle can be rapidly and definitively improved. This system has already been adopted with success at Strasburg, Milan and in numerous American towns.

Compulsory pasteurisation will affect the legitimate interests of small producers, the sale of milk to large dairies being less remunerative than sale to town customers. Private and public interests are not always easy to reconcile, but can there be any hesitation as to the choice when public health is at stake ?

III. HEALTH SUPERVISION OF MILK.

Supervision connotes control which, if it is to be effective, should be official. In France, we have only at present physico-chemical control. This is not enough ; *hygienic control* as it exists in many other countries should be organised in France.

This control should be bacteriological and should include the tests we have made during this enquiry : reductase, bacterial count, B. coli count. In the United States, the standard method is the count ; other countries have adopted reductase or, less frequently, tests to detect the presence of B. coli. These latter tests would seem to be necessary, however, because, both as regards milk and water, its presence almost invariably connotes—at any rate in Meurthe-et-Moselle—through the reactions of the isolated strains, a pollution of fæcal origin. We think it would be too hazardous to rely on a single form of test. Reductase alone is not sufficiently conclusive, because, as W. DORNER points out, it merely “ indicates the worst milks, without revealing the best ”. Consequently, its results sometimes conflict with those of other tests. The counting of colonies on agar has been so strongly criticised that it could not be adopted as the sole test. B. coli count is, we think, the only method which could be employed alone. We ourselves have found it to be the most accurate criterion of purity.

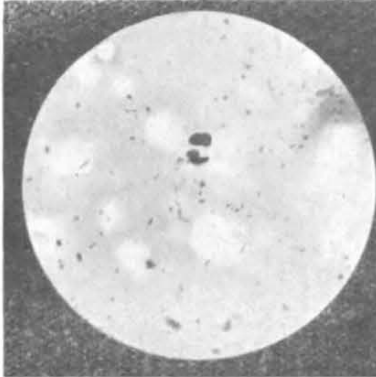
It would be much better to employ all three methods. Reductase eliminates the very bad milks ; the two other bacteriological methods supplement and define the reductase results. These three simple

tests should always, we think, be carried out conjointly, the following results being necessary to indicate good-quality milk : reductase in more than 6 hours ; less than 200,000 colonies to the cc. ; less than 10,000 *B. coli* per litre. These figures should be considerably less if compulsory pasteurisation is adopted.

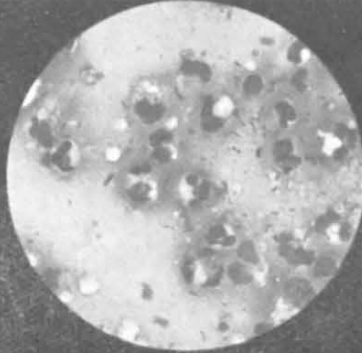
Bacteriological control should therefore be inaugurated forthwith on these lines. Applied to pasteurised milks, it will guarantee their value. Applied to milks for direct consumption, it will enable us, as physico-medical control does at present, to reject all milk that does not come up to the required standard. The consumption of such milk could be prohibited and legal proceedings could, if necessary, be instituted. In the case of pasteurised and other milks, the progress of the hygienic production of milk for consumption could be followed. If carried out by laboratories officially authorised to conduct the bacteriological analysis of milk, like the bacteriological analysis of water (regional institutes of hygiene, for instance), such supervision, keeping in touch with progress and insisting on its maintenance, would in future provide both consumers and producers with every guarantee of safety.

A FEW MICROSCOPICAL ASPECTS OF THE CENTRIFUGATION DEPOSIT OF 40 C.C. OF MILK.

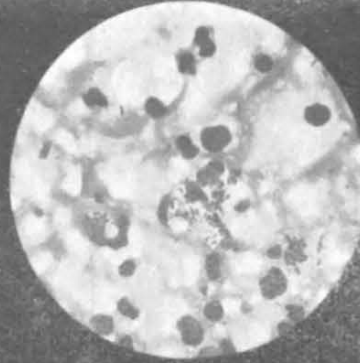
39.
Rare polynuclear cells.
A few cocci.



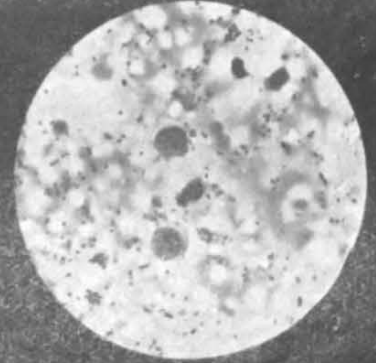
372.
Numerous poly., mono., pyo-
cytes. Abundant and poly-
morphous flora.



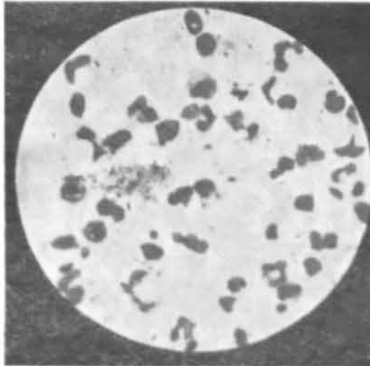
373.
Numerous poly., mono., pyo-
cytes. Phagocytoses.



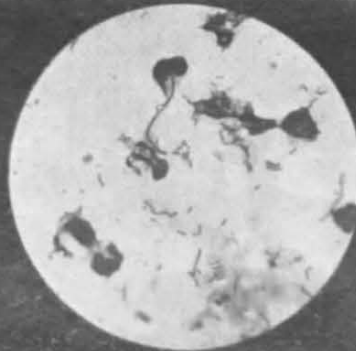
390.
A few poly. and mononuclears.
Mass of microbes.



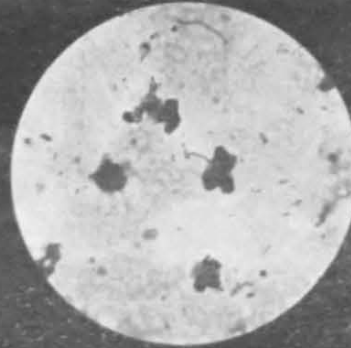
512.
Very numerous altered polynu-
clears. Numerous cocci and
bacilli.



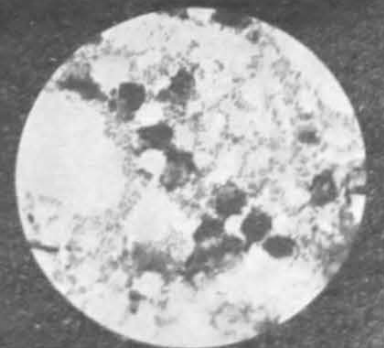
550.
Very numerous altered poly-
nuclears. Cocci, bacilli and
chains.



551.
Chain phagocytoses.



569.
Very numerous altered poly-
nuclears. Mass of microbes.



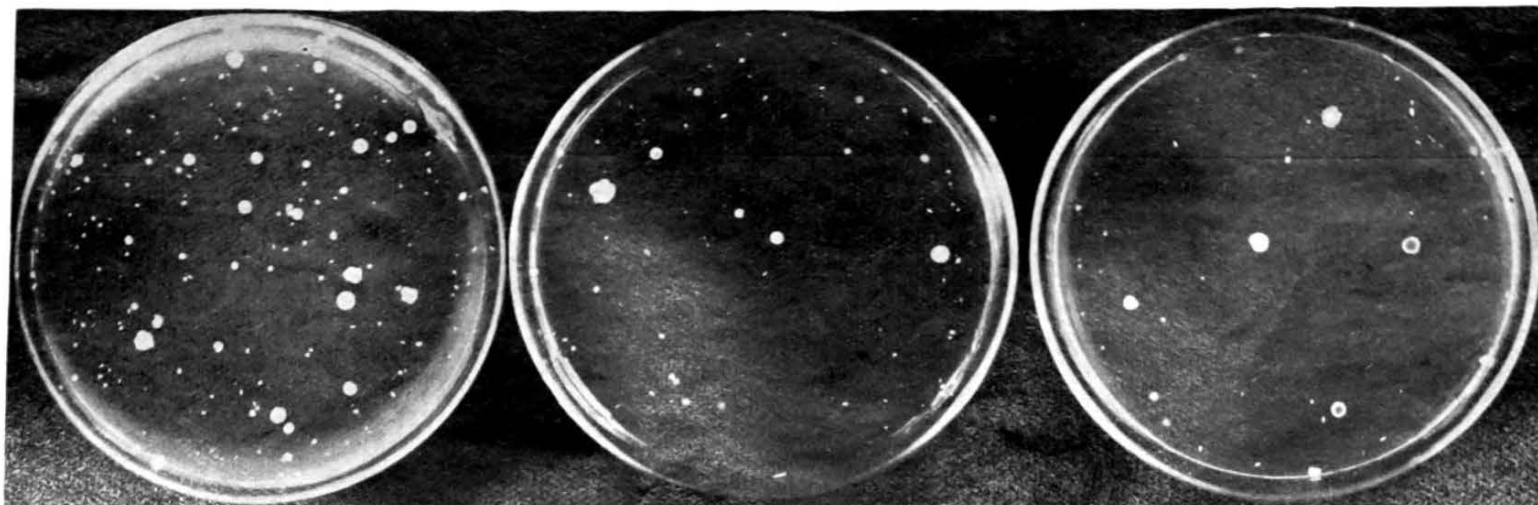
SEEDING OF MILK SAMPLE TAKEN FROM THE UDDER.

48-hour agar culture.

Beginning of milking : 1,960 germs per c.c.

Middle of milking : 1,102 germs per c.c.

End of milking : 530 germs per c.c.

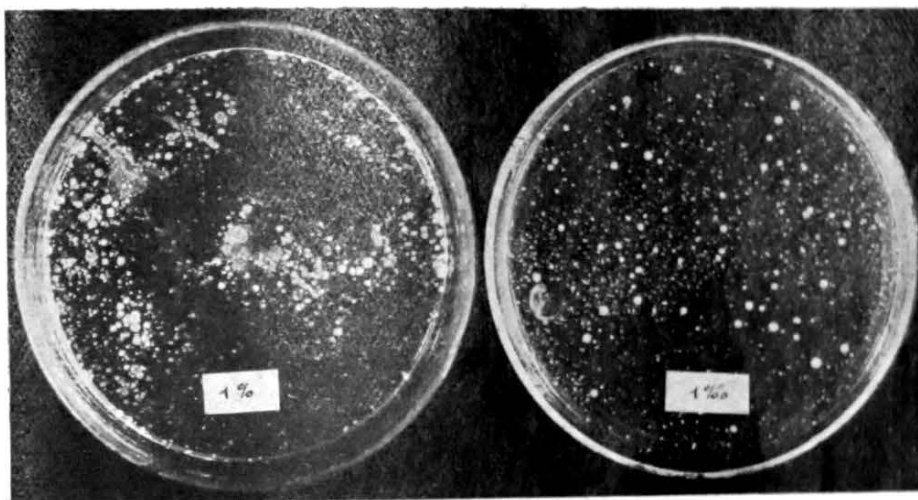


MECHANICAL MILKING.

Its hygienic valuelessness if the apparatus is not thoroughly cleaned and disinfected after each milking.

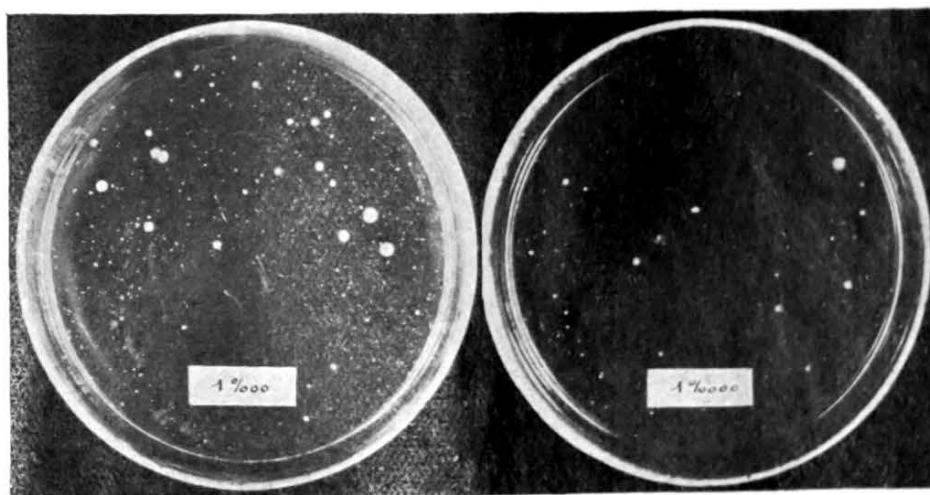
Cultures obtained by seeding ordinary agar dishes with sterile distilled water which has been simply sucked through the apparatus immediately after milking.

Result : 90,000,000 germs per c.c. .



1 c.c. of rinsing water
diluted to 1 : 100.

1 c.c. of rinsing water
diluted to 1 : 1,000.



1 c.c. of rinsing water
diluted to 1 : 10,000.

1 c.c. of rinsing water
diluted to 1 : 100,000.

CURRENT NOTES ON THE WORK OF THE HEALTH ORGANISATION.

DEATH OF PROFESSOR CARLOS CHAGAS.

This year is, for the Health Organisation, a year of deep bereavement : after suffering the loss of Professors Léon BERNARD and J. CANTACUZÈNE, it now has to record the premature death of Professor Carlos CHAGAS.

The name of Carlos CHAGAS will ever be remembered in the annals of science : the Chagas disease, which he discovered, studied in detail, and completely elucidated by identifying the parasite, the virus reservoir, the transmitting agent and the clinical and epidemiological aspects of the disease, forms one of the most absorbing chapters of parasitology.

It was above all as a hygienist that Professor CHAGAS played so brilliant a part in the work of the Health Organisation. A pupil of Oswaldo Cruz, he assumed his master's mantle both as Director of the famous Manguinhos Institute and as an apostle of hygiene in Brazil. For eight years he was Director of the Federal Service of Public Health, where he proved to be, not only a man of ideas, but also a successful organiser. In the Health Committee of the League of Nations, as a member of the Malaria Committee, he was one of the first to study the connection between malaria and housing. He often reverted to a question he had very much at heart : the value of terminal disinfection. The main effects of his work, however, are to be seen in leprosy prophylaxis. He it was who in 1925 asked that the problem of leprosy should be included in the Health Committee's programme. He was appointed Chairman of the Committee on Leprosy. At Rio de Janeiro he founded an International Centre for the Study of Leprosy under the auspices of the League of Nations. He conquered or overcame all obstacles due to unforeseen circumstances : the Centre was officially inaugurated in April 1934.

Thanks to Professor CHAGAS, Brazil will still further increase her valuable contribution to international health work ; the American Continent possesses a Leprosy Institute as well equipped as those in the Far East, and the Health Organisation is endowed with a new instrument of study and exchange in the field of epidemiology and social hygiene.

By his originality, intuition and independence of thought, by his hardy initiative and the world reputation he had acquired as a man of science and of action, Professor CHAGAS enjoyed in his own country an undisputed authority which was of the greatest value for the development of his Centre. He had established not merely a programme of research work, but also the plan for the necessary installations : the laboratories at the Oswaldo Cruz Institute and new premises.

Can there be any doubt that the study of leprosy, which is now, like yellow fever, a Brazilian question, will always be held in high esteem at the Oswaldo Cruz Institute, where, according to a tradition confirmed in the practice of Professor CHAGAS himself, research work once begun, however distant the goal may seem, will be continued until that goal is reached ?

Erratum to No. 3 (September 1934).

Page 437. Note 4, letter (b). Replace in both cases the sign + by —.

LEAGUE OF NATIONS

QUARTERLY
BULLETIN
of the
HEALTH
ORGANISATION

Volume IV, 1935

GENEVA

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LEAGUE OF NATIONS
QUARTERLY BULLETIN
OF THE HEALTH ORGANISATION

Special Number

January 1935

**A. REPORT OF THE PERMANENT COMMISSION
ON BIOLOGICAL STANDARDISATION**

*Session held at Copenhagen from
August 28th to 30th, 1934¹*

I. GAS GANGRENE ANTITOXINS.

(a) GAS GANGRENE ANTITOXIN (*Vibrio septique*).

At its session in June 1931, the Commission had recommended that an attempt should be made to obtain international agreement

¹ The following members were present :

Dr. Th. MADSEN, Director of the Statens Serum Institut, Copenhagen,
President ;
Sir Henry DALE, Director of the National Institute for Medical Research,
London.
Professor Louis MARTIN, Director of the Pasteur Institute, Paris ;
Dr. G. W. MCCOY, Director of the National Institute of Health,
Washington ;

The following also attended as experts :

Dr. D. T. FRASER, Associate Director of the Connaught Laboratories, Toronto ;
Dr. P. HARTLEY, Director of Biological Standards, National Institute for
Medical Research, London ;
Dr. Claus JENSEN, Statens Serum Institut, Copenhagen ;
Dr. C. REYMANN, Statens Serum Institut, Copenhagen ;
Dr. S. SCHMIDT, Statens Serum Institut, Copenhagen ;
Dr. L. WALBUM, Statens Serum Institut, Copenhagen ;
Professor M. WEINBERG, Chef de laboratoire, Pasteur Institute, Paris.

on the adoption of a standard preparation and a unit for gas gangrene antitoxin (*vibrio septique*). ●

Acting upon this recommendation, the National Institute for Medical Research in London prepared, from a quantity of antitoxin generously placed at its disposal by Professor M. Weinberg, of the Pasteur Institute, Paris, a dry stable standard for gas gangrene antitoxin (*vibrio septique*), with a view to its adoption for international use.

The proposed international standard, together with a provisional standard prepared at Washington, a gas gangrene antitoxin (*vibrio septique*) of unstated potency and a dry test toxin (*vibrio septique*) were distributed by the National Institute for Medical Research, London, to the following institutes :

| | |
|-----------------|--|
| Germany : | Staatliches Institut für experimentelle Therapie, Frankfort-on-Main ; |
| Denmark : | Statens Serum Institut, Copenhagen ; |
| United States : | National Institute of Health, Washington ; |
| France : | Pasteur Institute, Paris ; |
| Great Britain : | { Wellcome Physiological Research Laboratories, Beckenham ; Lister Institute for Preventive Medicine, Elstree. |

These institutes were requested to compare the potency of the proposed international and provisional American standards and to assay the antitoxin of unstated potency in terms of the provisional unit proposed for the purposes of the international enquiry.

These assays, the details of which will be found in Annex 1, demonstrated that the solutions of the American provisional standard and of the proposed standard preparation were equivalent and that the potency of gas gangrene antitoxin (*vibrio septique*) can be determined with a high degree of accuracy.

In these circumstances, the Commission recommends :

That the dry stable preparation of gas gangrene antitoxin (vibrio septique) prepared at the National Institute for Medical Research, London, from material supplied by Dr. Weinberg, of the Pasteur Institute, Paris, be accepted as the International Standard for

*this antitoxin and that the specific antitoxic activity contained in 0.2377 mgrm. of the dry standard preparation be defined as one international unit.*¹

(b) GAS GANGRENE ANTITOXIN (*Ædematiens*).

In accordance with a recommendation adopted by the Commission in 1932, the Statens Serum Institut, Copenhagen, prepared a dry stable standard for gas gangrene antitoxin (*ædematiens*) and proposed a unit defined in terms thereof, with a view to acceptance for international use.

The proposed international standard, together with a gas gangrene antitoxin (*ædematiens*) of unstated potency and a dry test toxin were distributed by the Statens Serum Institute to the following institutes :

United States : National Institute of Health, Washington ;
Germany : Reichsgesundheitsamt, Berlin ;
Great Britain : { National Institute for Medical Research, London ;
Lister Institute of Preventive Medicine, Elstree.
Wellcome Physiological Research Laboratories,
Beckenham.

These institutes were requested to assay the gas gangrene antitoxin (*ædematiens*) of unstated potency in terms of the proposed international unit, using the test toxin supplied, and local laboratory toxins, for the purposes of the comparative tests.

The results of these comparative tests, the details of which will be found in Annex 2, fully confirmed those obtained at the Statens Serum Institut, and demonstrated that the potency of gas gangrene antitoxin (*ædematiens*) can be determined with a high degree of accuracy. The Commission accordingly recommends :

That the dry stable standard for gas gangrene antitoxin (ædematiens) prepared at the Statens Serum Institut, Copenhagen,

¹ At the request of Professor Martin, the information is added that this unit neutralised about 24 lethal doses for the mouse of the particular test toxin which was used in the experimental work incidental to the preparation of the standard.

be accepted as the International Standard for this antitoxin and that the specific antitoxic activity contained in 0.2681 mgrm. of the dry standard preparation be defined as one international unit.¹

II. ANTIPNEUMOCOCCUS SERA.

As long ago as 1921, the Commission considered the question of the standardisation of antipneumococcus serum ; in 1931, however, it was still unable to make any recommendations with regard to the adoption of an international standard.

In view, however, of the ever-increasing use which is being made of antipneumococcus sera, types I and II, in certain countries, and of the practice which has developed there of titrating such sera against the bi-valent serum No. F.146 prepared by Dr. D. L. FELTON, of the Harvard University School of Medicine, the question of the adoption of international standards for antipneumococcus sera, types I and II, appeared to be ripe for further consideration by the Commission.

Serum F.146 was supplied in liquid form and the existing stock had been nearly exhausted. It appeared desirable to provide, for international use, dry stable standard preparations and to determine the weights of the respective standards equivalent to the type I and type II specific antibody contained in 1/200 c.c. of the serum F.146—the units originally proposed by Felton.

(a) ANTIPNEUMOCOCCUS SERUM, TYPE I.

By agreement with the National Institute of Health, Washington, the National Institute for Medical Research, London, undertook to prepare a dry stable standard for antipneumococcus serum, type I. Comparative tests carried out at the latter institute showed that the specific activity contained in 0.0886 mgrm. of the proposed standard preparation was equivalent to one unit of antipneumococcus serum, type I, as originally proposed by Felton and contained in 1/200 c.c. of serum F.146.

¹ At the request of Professor Martin, the information is added that this unit neutralised about 1,400 lethal doses (for the mouse) of the particular test toxin which was used in the experimental work incidental to the preparation of the standard.

The National Institute for Medical Research thereupon sent the dry standard preparation and the serum F.146 to Dr. Felton and to the following institutes :

| | | |
|-----------------|--|---|
| Canada : | Connaught Laboratories, Toronto. | |
| United States : | { Division of Laboratories and Research, Department of Health, New York State, Albany ; Lederle Laboratories, New York ; Parke Davis Laboratories, Detroit ; | |
| | | { Lister Institute of Preventive Medicine, Elstree ; Wellcome Physiological Research Laboratories, Beckenham ; |
| | | |

requesting them to determine the relative potencies of the dry standard preparation and the type I component of the serum F.146.

These comparative tests, details of which will be found in Annex 3, fully confirmed the results obtained by the National Institute for Medical Research. They showed, further, that the presence of glycerol in the solvent had no adverse effect upon the tests ; the standard can thus be supplied in the form of a glycerol solution, a circumstance which will make for economy in the use of the dry standard preparation.

The Commission accordingly recommends :

That the dry stable standard for antipneumococcus serum, type I, prepared at the National Institute for Medical Research, London, be accepted for international use and that the specific activity contained in 0.0886 mgrm. of the dry standard preparation be defined as one international unit.

(b) ANTIPNEUMOCOCCUS SERUM, TYPE II.

The National Institute for Medical Research, London, prepared a dry stable standard for type II antipneumococcus serum, and determined its potency in relation to the type II component of serum F.146. These titrations showed that the specific activity

contained in 0.0894 mgrm. of the dry standard preparation was equivalent to one unit of antipneumococcus serum type II as originally proposed by Felton, and contained in 1/200 c.c. of serum F.146.

Though it was not possible, for the reasons explained in Annex 4, for similar comparative tests to be carried out by other laboratories, the Commission nevertheless recommends :

That the dry stable standard for antipneumococcus serum, type II, prepared at the National Institute for Medical Research, London, be accepted for international use and that the specific activity contained in 0.0894 mgrm. of the standard preparation be defined as one international unit.

III. STAPHYLOCOCCUS ANTITOXIN.

Staphylococcus antitoxin and toxoid are now frequently used in treatment. It appears desirable, therefore, that an international standard and unit for staphylococcus antitoxin should be adopted. Accordingly, the National Institute for Medical Research, London, took the initiative by submitting to the Commission a dry standard antitoxin and proposed a unit expressed in terms of it for adoption for international use.

The Institute distributed for the purposes of an international investigation a dry sample of the proposed standard preparation, a solution of that preparation in glycerol saline, two antitoxins of unstated potency and an explanatory memorandum (Appendix, page 111) to the following institutes :

| | |
|-------------|--|
| Germany : | } Staatliches Institut für experimentelle Therapie, Frankfort-on-Main ; Institut für experimentelle Therapie "Emil von Behring", Marburg ; |
| Australia : | |
| Belgium : | Laboratoire Central de l'Administration d'Hygiène, Brussels ; |
| Canada : | Connaught Laboratories, Toronto ; |
| Denmark : | Statens Serum Institut, Copenhagen ; |

United States of America : National Institute of Health, Washington ;

France : Pasteur Institute, Paris ;

Great Britain : { Wellcome Physiological Research Laboratories,
Beckenham ;
Lister Institute of Preventive Medicine, Elstree.

For the reasons given in Annex 5, it appeared preferable not to supply these institutes with test toxin, but to request each institute to assay the antitoxins of unstated potency by means of test toxins in use in the different institutes. The proposed unit was defined as the specific neutralising activity for staphylococcus toxin contained in 0.5 mgrm. of the dry standard preparation.

The reports of the institutes which took part in these researches are given in Annex 5. The titrations carried out by one or several methods (hæmolysis method, method of intradermal injection into guinea-pigs or rabbits ; method of intravenous or intraperitoneal injection into mice) showed that the potency of a staphylococcus antitoxin can be determined with a high degree of accuracy and that the various methods of titration used gave concordant results.

Since, moreover, the unit appeared to be suitable, the Commission recommends :

*That the dry stable preparation of staphylococcus antitoxin prepared at the National Institute for Medical Research, London, be accepted as the International Standard for this antitoxin and that the specific antitoxic activity contained in 0.5 mgrm. of the dry standard preparation be defined as one international unit.*¹

IV. ANTI-TETANUS SERUM.

The Commission decided to ask the Statens Serum Institut, Copenhagen, to draw up a fresh scheme of comparative research

¹ At the request of Professor Martin, Director of the Pasteur Institute, Paris, the information is added that this unit neutralised 10 to 200 minimum hæmolytic doses, 20 to 100 minimum skin-necrosing doses (for the guinea-pig), and 140 to 1,500 minimum skin-necrosing doses (for the rabbit) of the particular test toxins which were used in the experimental work incidental to the preparation of the standard. The unit neutralised 10 to 13 lethal doses (for the mouse), of those toxins which were used in tests based on the lethal effect on mice.

work. This scheme should, as far as possible, eliminate variable factors from the experiments ; to that end—

- (1) The purity of the strains used for the production of the toxin should be verified ;
- (2) One and the same toxin should be used by all the institutes taking part in the comparative titrations ;
- (3) The manner in which the toxin is preserved should be stated ;
- (4) The toxin should be diluted in glycerol ;
- (5) The p_H of the mixtures of toxin and antitoxin should be that of the toxin ;
- (6) The period between the preparation of the mixtures of toxin and antitoxin and their injection, and the temperature at which the mixtures are maintained during this period, should be fixed ;
- (7) Guinea-pigs and mice should be used simultaneously for the comparative tests.

V. ANTI-DYSENTERY SERUM (SHIGA).

In view of the suggested discrepancies between the different standards for anti-dysentery serum (Shiga) kept in certain of the National Control Institutes, the Commission recommends that the statisticians of the institutes concerned should re-examine the documentary material collected.¹

VI. STREPTOCOCCUS ANTITOXIN (ANTISCARLATINA SERUM).

The possibility was considered of accepting a standard for this serum, and a unit defined in terms thereof, by international agree-

¹ Since the meeting of the Commission, an exchange of views has taken place between statisticians of the institutes concerned, and it was agreed that the potency of a solution containing 100 mgrm. of the German anti-dysentery (Shiga) standard serum in 4.3 c.c. of physiological saline is indistinguishable from that of a solution of the international standard containing 200 international units per c.c. In view of this agreement, *the international unit for anti-dysentery serum remains unchanged.*

ment. A provisional dry standard had been prepared at the request of the Commission in 1927 at the National Institute for Medical Research, London. This was circulated, with a dry toxin, for international trial.

Reports were received from Professor Hirszfeld (Warsaw), Dr. O'Brien (Beckenham, England), Drs. James, Joe and Swyer (London), and Dr. Wadsworth (Albany, U.S.A.), and were presented to a meeting of the Commission in Frankfort in 1928. At that meeting the Commission was informed that Dr. McCoy had found it necessary, for official reasons, to prepare a standard and define a unit for use in determining the strength of this serum in the U.S.A. The Commission had accordingly communicated with Dr. McCoy by cable. In reply, he expressed his willingness to supply sufficient of this American standard for use in further exploratory work. The Commission had thereupon adopted the following resolution :

“Without expressing an opinion on the ætiology of scarlet fever or on the methods of testing sera prepared with the products of cultures of hæmolytic streptococci isolated from cases of scarlet fever, it would be useful to render future researches along this line more readily comparable. To this end, the standard serum adopted by the Federal Government of the United States may be selected as a basis for study ; the Hygienic Laboratory has agreed to place at the disposal of the Health Organisation of the League of Nations a sufficient quantity of the standard serum ” (Frankfort—1928).

The Commission, in reviewing the position, recognised that no effective action towards the creation and adoption of an international standard for this serum had been taken since that date. In a discussion of the causes of the arrest of activity in this matter, the Commission recognised that further action had been hindered by the fact that patents covering the preparation of this serum, and the toxin used in producing and testing it, existed in the United States of America and in several other countries, including Canada and Great Britain. By the terms of licences granted by the patentees, Drs. George and Gladys Dick, of Chicago, for the manufacture of the serum, the producers are bound to submit a sample from every batch of such serum to the patentees, for a determination

of its value in terms of a unit, defined as the quantity required to neutralise 5 human skin-test doses of streptococcal toxin. It was reported to the Commission that, even in countries such as the United States, where a legal standard serum and unit in terms thereof had been defined by official authority, the manufacturers were bound, by the terms of their licences, to submit samples from each batch of serum to the patentees, for an independent and possibly discordant indication of its value, in units defined by them as above indicated.

In these circumstances, the Commission decided that it was useless for it to proceed with work preparatory to an agreement on a standard and unit for international use, the application of which in some countries might conflict with the authority exercised by the patentees. It recommended that this decision, and the circumstances in which it had felt itself obliged to take it, should be reported to the Health Committee of the League of Nations.

VII. STAPHYLOCOCCUS TOXOID.

The Commission heard a statement by Dr. D. T. Fraser, who stressed the desirability, now that an international standard is available for staphylococcus antitoxin, of securing agreement as to the properties which staphylococcus toxoid should possess. The clinical use of this substance has now passed the experimental stage.

Dr. Fraser outlined the method hitherto employed at the Connaught Laboratories, Toronto, for demonstrating adequate antigenic potency of samples of staphylococcus toxoid—viz., two spaced injections of the toxoid administered intravenously into rabbits and measurement of the antitoxin content of the serum at a fixed interval after the second injection.

The discussion on Dr. Fraser's statement which ensued showed the need for determining the part played by various factors, such as the choice of animal species, the number of injections given, the route of administration of the toxoid, the dose to be injected, and the interval between injections.

Acknowledging the importance of the question raised by Dr. Fraser, the Commission considers :

That it is desirable to arrive, at the earliest possible moment, at an international agreement as to the antigenic potency of staphylococcus toxoid required for practical use and recommends that the investigations carried out by Dr. Fraser should be taken as a basis for further international studies.

VIII. B. COLI ANTITOXIN.

Professor Weinberg explained to the Commission the advantages to be derived from the administration of B. coli antitoxin at the same time as gas gangrene antitoxin, in cases of perforating appendicitis and peritonitis. The Commission accordingly decided to place the question of the standardisation of an anti-B. coli serum on the agenda of its next session. In the meantime, samples of serum and toxin will be placed at the disposal of interested laboratories by Professor Weinberg.

IX. ANTI-TYPHOID SERUM.

The Commission decided to place on the agenda of its next session the question of anti-typhoid serum.

X. INTERNATIONAL BUREAU OF MICROBIAL SPECIES.

Professor Weinberg submitted to the Commission a proposal for the institution, under the auspices of the League of Nations Health Organisation, of an International Bureau of Microbial Species. It would be the function of this Bureau to verify and endorse the description of newly described species ; it should also create a museum of all known microbial species, both aerobes and anaerobes.

The Commission felt that it could not take up such a proposal before it had fuller particulars as to the expenditure involved. It

asked Professor Weinberg and the Secretary of the Commission to submit a detailed report at its next session.

XI. VITAMINS.

After examining the report of the Second International Conference on Vitamin Standards, held in London from July 12th to 14th, 1934, the Commission proposes to the Health Committee that the report be adopted.

**1. A PROPOSED INTERNATIONAL STANDARD
FOR GAS GANGRENE ANTITOXIN
(VIBRION SEPTIQUE)**

By

PERCIVAL HARTLEY and P. BRUCE WHITE

(from the National Institute for Medical Research, Hampstead, London).

The Permanent Commission on Biological Standardisation, at its meeting in London in June 1931, recommended " that the possibility be explored of obtaining international agreement on the adoption of a standard preparation and unit for gas gangrene (*vibrion septique*) antitoxin, the work to be performed on lines similar to those followed for *perfringens* antitoxin " (document C.H.1056(1)1931).

The work of preparing the necessary reagents for the enquiry, and the organisation of the preliminary investigations, on an international basis, was undertaken by the National Institute for Medical Research, Hampstead, London. Through the courtesy and generosity of Dr. Weinberg, of the Pasteur Institute, Paris, an adequate quantity (about 150 grm.) of a dry *vibrion septique* antitoxin was provided for the investigation ; a sample of dried *vibrion septique* antitoxin prepared at the National Institute of Health, Washington, as a provisional standard for use in the United States of America, was kindly supplied by Dr. G. W. McCoy ; several dry, stable preparations of *vibrion septique* toxin were prepared and their properties investigated, and the methods of assay critically

examined at the National Institute for Medical Research, Hampstead.

For the purpose of the international enquiry, and with a view to the eventual decision by the Permanent Commission on Biological Standardisation regarding the unit to be recommended for adoption for international use, it was decided to assay the dry preparation supplied by Dr. Weinberg in terms of the Provisional American Standard. Eventually, from these two dry *vibrion septique* antitoxins two standard solutions (in glycerol-saline) were prepared, and participating experts were invited to investigate the claim—based on the results obtained at Hampstead—that the two solutions were of identical potency (*i.e.*, that each solution contained 100 provisional units per c.c.). As a second part of the international enquiry, a preparation of *vibrion septique* antitoxin of unstated potency was distributed and experts were invited to determine the potency of this preparation in terms of the provisional unit suggested. To facilitate the work, a preparation of dry stable *vibrion septique* toxin was supplied to all participators. A short memorandum (see Appendix, page 33), supplied with the reagents, indicated the purpose of the investigation, outlined methods of assay which, in this Institute, had given consistent results, and made suggestions relating to the experiments to be performed. The experts participating were especially asked to employ other methods and other toxins for comparing the potency of the two standard solutions and for assaying the antitoxin of unstated potency.

The reagents and memorandum were sent to the following experts in the five countries named :

Denmark : Dr. Th. Madsen, State Serum Institute, Copenhagen ;

France : Dr. M. Weinberg, Pasteur Institute, Paris ;

Germany : Geh. Professor Dr. W. Kolle, State Institute for Experimental Therapy, Frankfort-on-Main ;

Great Britain : (1) Dr. R. A. O'Brien, Wellcome Physiological Research Laboratories, Beckenham, Kent ; (2) Dr. G. F. Petrie, The Lister Institute, Elstree, Herts ;

United States of America : Dr. G. W. McCoy, National Institute of Health, Washington.

The experts participating in the investigation have completed their experiments and submitted reports. These are set out below. For convenience of reference and correlation of the results, the phrases "Provisional American (Standard or solution)" and "Proposed International (Standard or solution)" have been used for the products supplied by Dr. McCoy and Dr. Weinberg respectively; and, in some cases, the data and results have been slightly rearranged so as to secure as great a uniformity of presentation as possible.

1. REPORT RECEIVED FROM DR. TH. MADSEN, COPENHAGEN.

A. Comparison of the Provisional American Standard and the Proposed International Standard.

(1) By the mouse intravenous method.

| Toxin dose (V.S.10) (mgrm.) | Proportion of mice surviving | |
|-----------------------------------|--|--|
| | Provisional American solution 0.2 c.c. = 1 P. unit. | Proposed International solution 0.2 c.c. = 1 P. unit. |
| 4.7 | 0/6 | 0/6 |
| 4.4 | 3/6 | 4/6 |
| 4.1 | 6/6 | 6/6 |
| 3.8 | 6/6 | 6/6 |

| Toxin dose (V.S.10) (mgrm.) | Provisional American solution | | Proposed International solution | |
|-----------------------------------|-------------------------------|---------------------------------|---------------------------------|---------------------------------|
| | Antitoxin P. units | Proportion of mice surviving | Antitoxin P. units | Proportion of mice surviving |
| 4.4 | 0.9 | 0/6 | 0.9 | 0/6 |
| | 1.0 | 3/6 | 1.0 | 0/6 |
| | 1.1 | 5/6 | 1.1 | 6/6 |
| 4.3 | 0.9 | 0/6 | 0.9 | 0/6 |
| | 1.0 | 2/6 | 1.0 | 1/6 |
| | 1.1 | 6/6 | 1.1 | 6/6 |

(2) *By the guinea-pig intracutaneous method.*

| Antitoxin solution | Mixture injected in 0.2 c.c. | | Result : 48 hours |
|------------------------------|------------------------------|-------------|-------------------|
| | Toxin V.S.10 mgrm. | Antitoxin | |
| Provisional American | 3.0 | 0.5 P. unit | Large reaction. |
| | 2.7 | | Large reaction. |
| | 2.4 | | Small reaction. |
| | 2.1 | | No reaction. |
| | 1.8 | | No reaction. |
| Proposed International | 3.0 | 0.5 P. unit | Large reaction. |
| | 2.7 | | Large reaction. |
| | 2.4 | | Small reaction. |
| | 2.1 | | No reaction. |
| | 1.8 | | No reaction. |

These experiments show a complete uniformity of the two standards.

B. *Assay of the Antitoxin of Unstated Potency.*(1) *By the mouse intravenous method.*

| Toxin dose (V.S.10) (mgrm.) | Proposed International solution | | Antitoxin of unstated potency | |
|-----------------------------|---------------------------------|------------------------------|-------------------------------|------------------------------|
| | P. units | Proportion of mice surviving | c.c. | Proportion of mice surviving |
| 4.3 (16.I.34) | 0.9 | 0/6 | 0.0075 | 6/6 |
| | 1.0 | 3/6 | 0.0070 | 6/6 |
| | 1.1 | 6/6 | 0.0065 | 5/6 |
| | | | 0.0060 | 1/6 |
| 4.3 (19.I.34) | 0.9 | 0/6 | 0.007 | 6/6 |
| | 1.0 | 3/6 | 0.0065 | 4/6 |
| | 1.1 | 6/6 | 0.006 | 4/6 |
| | | | 0.0055 | 0/6 |

(2) *By the guinea-pig intracutaneous method.*

| Antitoxin solution | Mixture injected in 0.2 c.c. | | Result : 48 hours | |
|--------------------------------|------------------------------|-------------|-------------------|-----------------|
| | Toxin (V.S.10) mgrm. | Antitoxin | Guinea-pig 5866 | Guinea-pig 7578 |
| Proposed International | 2.7 | 0.5 P. unit | Large reaction | Large reaction. |
| | 2.4 | | Small reaction | Small reaction. |
| | 2.1 | | No reaction | No reaction. |
| Anti-toxin of unstated potency | 2.4 | 0.0035 c.c. | No reaction | No reaction. |
| | | 0.0032 c.c. | Small reaction | Small reaction. |
| | | 0.0030 c.c. | Large reaction | Large reaction. |
| | | 0.0027 c.c. | Large reaction | Large reaction. |

The guinea-pig method shows that the antitoxin contains 154 provisional units per c.c. ; the mouse method shows that the antitoxin contains between 154 and 167 provisional units per c.c.

2. REPORT RECEIVED FROM DR. M. WEINBERG, PARIS.

A. Comparison of the Provisional American Standard and the Proposed International Standard.

(1) By the mouse intravenous method.

| Toxin dose (V.S.10) (mgrm.) | Proportion of mice surviving | |
|-----------------------------|---|---|
| | Provisional American solution 0.2 c.c. = 1 P. unit | Proposed International solution 0.2 c.c. = 1 P. unit |
| 4.7 | 0 / 6 | 0 / 6 |
| 4.4 | 0 / 6 | 0 / 6 |
| 4.1 | 3 / 6 | 3 / 6 |
| 3.8 | 6 / 6 | 6 / 6 |

| Toxin dose (V.S.10) (mgrm.) | Provisional American solution | | Proposed International solution | |
|-----------------------------|-------------------------------|------------------------------|---------------------------------|------------------------------|
| | Antitoxin P. units | Proportion of mice surviving | Antitoxin P. units | Proportion of mice surviving |
| 4.2 | 0.9 | 0 / 6 | 0.9 | 0 / 6 |
| | 1.0 | 3 / 6 | 1.0 | 3 / 6 |
| | 1.1 | 6 / 6 | 1.1 | 6 / 6 |
| 4.1 | 0.9 | 0 / 6 | 0.9 | 0 / 6 |
| | 1.0 | 3 / 6 | 1.0 | 5 / 6 |
| | 1.1 | 6 / 6 | 1.1 | 6 / 6 |

(2) By the guinea-pig intracutaneous method.

In all these experiments, toxin V.S.11 was used ; each guinea-pig received five injections, three on the left and two on the right flank.

| Antitoxin solution | Mixture injected in 0.2 c.c. | | Result | No. of guinea-pig |
|-------------------------|------------------------------|-------------|----------------------------|-------------------|
| | Toxin mgrm. | Antitoxin | | |
| Provisional American... | 2.7 | 0.5 P. unit | Marked reaction : necrosis | Not stated. |
| | 2.4 | | Marked reaction : necrosis | |
| | 2.1 | | Marked reaction : necrosis | |
| | 1.8 | | No reaction | |
| | 1.5 | | No reaction | |
| Proposed International | 2.7 | 0.5 P. unit | Marked reaction : necrosis | Not stated. |
| | 2.4 | | Marked reaction : necrosis | |
| | 2.1 | | Marked reaction : necrosis | |
| | 1.8 | | No reaction | |
| | 1.5 | | No reaction | |

| Antitoxin solution | Mixture injected in 0.2 c.c. | | Result | No. of guinea-pig |
|-------------------------|------------------------------|-------------|----------------------------|-------------------|
| | Toxin | Antitoxin | | |
| Provisional American... | 2.7 | 0.5 P. unit | Reaction : necrosis | A. 14 |
| | 2.4 | | Reaction : necrosis | |
| | 2.1 | | No reaction | |
| | 1.8 | | No reaction | |
| | 1.5 | | No reaction | |
| Provisional American... | 2.7 | 0.5 P. unit | Reaction : necrosis | D. 84 |
| | 2.4 | | Reaction : necrosis | |
| | 2.1 | | No reaction | |
| | 1.8 | | No reaction | |
| | 1.5 | | No reaction | |
| Proposed International | 2.7 | 0.5 P. unit | Marked reaction : necrosis | D. 74 |
| | 2.4 | | Marked reaction : necrosis | |
| | 2.1 | | Marked reaction : necrosis | |
| | 1.8 | | No reaction | |
| | 1.5 | | No reaction | |
| Proposed International | 2.7 | 0.5 P. unit | Marked reaction : necrosis | D. 82 |
| | 2.4 | | Marked reaction : necrosis | |
| | 2.1 | | No reaction | |
| | 1.8 | | No reaction | |
| | 1.5 | | No reaction | |

B. Assay of the Antitoxin of Unstated Potency.

The mouse intravenous method was used. In the first experiment, toxin V.S.10 was used at a test dose of 4.1 mgrm.; in the second experiment, toxin V.S.11 was used at a test dose of 3.6 mgrm.

| Toxin dose (mgrm.) | Antitoxin of unstated potency | |
|--------------------|-------------------------------|------------------------------|
| | c.c. | Proportion of mice surviving |
| 4.1 (V.S.10)..... | 1/200 | 0/6 |
| | 1/180 | 4/6 |
| | 1/160 | 6/6 |
| | 1/140 | 6/6 |
| | 1/120 | 6/6 |
| | 1/100 | 6/6 |
| 3.6 (V.S.11)..... | 1/200 | 0/5 |
| | 1/190 | 0/5 |
| | 1/180 | 0/5 |
| | 1/170 | 1/5 |
| | 1/160 | 5/5 |

It is considered that the antitoxin of unstated potency contains 170 provisional units per c.c.

Conclusion.—The mouse intravenous method should be used when the exact titre of an antitoxin is to be determined. However,

the guinea-pig intracutaneous method is of great service when a sufficient number of mice is not available, or when an approximate estimate of antitoxic potency only is required.

3. REPORT RECEIVED FROM PROFESSOR DR. W. KOLLE,
FRANKFORT-ON-MAIN.

A. *Comparison of the Provisional American
and the Proposed International Standards.*

The mouse intravenous method was used.

| Toxin dose (mgrm.) | Provisional American solution | | Proposed International solution | |
|-----------------------|-------------------------------|---------------------------------|---------------------------------|---------------------------------|
| | Antitoxin P. units | Proportion of mice surviving | Antitoxin P. units | Proportion of mice surviving |
| 4.1 (V.S.10).. | 0.9 | 0/6 | 0.9 | 3/6 |
| | 1.0 | 6/6 | 1.0 | 5/6 |
| | 1.1 | 6/6 | 1.1 | 6/6 |
| 1.9 (Vsg 93).. | 0.9 | 0/12 | 0.9 | 0/12 |
| | 1.0 | 3/12 | 1.0 | 7/12 |
| | 1.1 | 11/12 | 1.1 | 12/12 |

B. *Assay of the Antitoxin of Unstated Potency.*

The mouse intravenous method was used ; the potency of the antitoxin was determined by means of toxin V.S.10 and toxin Vsg 93 (a toxin prepared at Frankfort).

| Toxin dose (mgrm.) | Provisional American solution | | Antitoxin of unstated potency | |
|---|-------------------------------|---------------------------------|-------------------------------|---------------------------------|
| | P. units | Proportion of mice surviving | c.c. | Proportion of mice surviving |
| 4.1 (V.S.10).. | 1.1 | 6/6 | 1/100 | 6/6 |
| | 1.0 | 6/6 | 1/125 | 6/6 |
| | 0.9 | 0/6 | 1/156 | 6/6 |
| | | | 1/200 | 0/6 |
| Titre of antitoxin under test : 156-200 P. units per c.c. | | | | |
| 4.1 (V.S.10).. | 1.1 | 6/6 | 1/156 | 6/6 |
| | 1.0 | 6/6 | 1/179 | 1/6 |
| | 0.9 | 0/6 | 1/200 | 0/6 |
| Titre of antitoxin under test : 156-179 P. units per c.c. | | | | |
| 1.9 (Vsg 93).. | 1.1 | 11/12 | 1/145 | 6/6 |
| | 1.0 | 3/12 | 1/155 | 4/6 |
| | | | 1/160 | 0/6 |
| | | | 1/170 | 0/6 |
| | | | 1/178 | 0/6 |
| 0.9 | 0/12 | 1/189 | 0/6 | |
| Titre of antitoxin under test : ca. 160 P. units per c.c. | | | | |

*C. Additional Tests carried out at Frankfort
on the Provisional American, the Proposed International
and the German Standard Vibron Septique Antitoxins.*

(1) Using the solution of the Provisional American Standard supplied from Hampstead, the test dose of toxin V.S.10 and Vsg 93 was found to be 4.1 mgrm. and 1.9 mgrm. respectively.

(2) Using the Frankfort toxin Vsg 93 at a dose of 1.9 mgrm., the following series of comparative tests of the three antitoxins were carried out :

(a) *Assay of the German Dry Standard in terms of the Provisional American Standard, the solution used being that supplied from Hampstead.*

| Toxin dose (Vsg 93) (mgrm.) | Provisional American solution | | The German Dry Standard | |
|-----------------------------------|-------------------------------|---------------------------------|-------------------------|---------------------------------|
| | Antitoxin P. units | Proportion of mice surviving | Dose (mgrm.) | Proportion of mice surviving |
| 1.9 | 1.1 | 11 /12 | 0.264 | 6 /6 |
| | 1.0 | 3 /12 | 0.242 | 5 /12 |
| | 0.9 | 0 /12 | 0.220 | 0 /12 |
| | | | 0.198 | 0 /6 |

Result : 0.242 mgrm. of the German Dry Standard = 1 P. unit.

(b) *Assay of the German Dry Standard in terms of the Provisional American Standard.*

In this test, two solutions of the Provisional American Standard were used ; the first was the solution supplied from Hampstead, and the second was prepared at Frankfort by dissolving the dry Provisional American Standard so as to make a solution of which 1 c.c. contained 15.6 mgrm. Also two solutions of the German Dry Standard were made, from ampoules 2 and 3 respectively.

Comparative tests of the four solutions, using toxin Vsg 93 at a test dose of 1.9 mgrm., gave the following results :

| Toxin dose (Vsg 93) (mgrm.) | Provisional American Standard | | | | German Dry Standard | | | |
|-----------------------------|-------------------------------|------------------------------|--------------------|------------------------------|---------------------|------------------------------|--------------|------------------------------|
| | Hampstead solution | | Frankfort solution | | Ampoule 2 | | Ampoule 3 | |
| | Antitoxin P. units | Proportion of mice surviving | Dose (mgrm.) | Proportion of mice surviving | Dose (mgrm.) | Proportion of mice surviving | Dose (mgrm.) | Proportion of mice surviving |
| 1.9 | 1.1 | 6/6 | 0.172 | 6/6 | 0.266 | 6/6 | 0.266 | 6/6 |
| | 1.0 | 4/6 | 0.156 | 6/6 | 0.242 | 4/6 | 0.242 | 5/6 |
| | 0.9 | 0/6 | 0.140 | 0/6 | 0.218 | 0/6 | 0.218 | 1/6 |

Result : 0.242 mgrm. of the German Dry Standard = 1 P. unit.

Note.—According to the determinations made at Hampstead (see Appendix, page 35), 1 P. unit is contained in 0.156 mgrm. of the Dry Provisional American Standard. This result is confirmed by the above experiment carried out at Frankfort on another ampoule of the Provisional American Standard, and by the use of another dry *vibrion septique* toxin in the comparative tests.

(c) *Assay of the German Standard in terms of the Proposed International Standard.*

In this experiment, two solutions of the Proposed International Standard were used ; the first was the solution supplied from Hampstead, and the second was prepared at Frankfort by dissolving the Proposed International Standard so as to make a solution of which 1 c.c. contained 23.77 mgrm. Also, two solutions of the German Dry Standard were made, from ampoules 2 and 4 respectively. Comparative tests of the four solutions, using toxin Vsg 93 at a test dose of 1.9 mgrm., gave the following results :

| Toxin dose (Vsg 93) (mgrm.) | Proposed International Standard | | | | German Dry Standard | | | |
|-----------------------------------|---------------------------------|------------------------------|--------------------|------------------------------|---------------------|------------------------------|--------------|------------------------------|
| | Hampstead solution | | Frankfort solution | | Ampoule 2 | | Ampoule 4 | |
| | Antitoxin P. units | Proportion of mice surviving | Dose (mgrm.) | Proportion of mice surviving | Dose (mgrm.) | Proportion of mice surviving | Dose (mgrm.) | Proportion of mice surviving |
| 1.9 | 1.1 | 6/6 | 0.2615 | 6/6 | 0.266 | 6/6 | 0.266 | 6/6 |
| | 1.0 | 4/6 | 0.2377 | 1/6 | 0.242 | 4/6 | 0.242 | 5/6 |
| | 0.9 | 0/6 | 0.2139 | 0/6 | 0.218 | 0/6 | 0.218 | 0/6 |

Result : 0.2377 mgrm. of the Proposed International Standard = 0.242 mgrm. of the German Dry Standard = 1 P. unit.

Note.—According to the determinations made at Hampstead (see Appendix, page 35), 1 P. unit is contained in 0.2377 mgrm. of the Proposed International Standard preparation. This result is confirmed in the above experiment carried out at Frankfort on another ampoule of the Proposed International Standard and by the use of another dry *vibrion septique* toxin in the comparative tests.

4. REPORT RECEIVED FROM DR. R. A. O'BRIEN, BECKENHAM, ENGLAND.

A. Comparison of the Provisional American Standard and the Proposed International Standard.

(1) By the mouse intravenous method.

| Toxin dose (V.S.10) (mgrm.) | Proportion of mice surviving | | | | | | | | | |
|-----------------------------------|--|------|------|------|--------|--|------|------|------|--------|
| | Provisional American solution, 0.2 c.c. = 1 P. unit | | | | | Proposed International solution, 0.2 c.c. = 1 P. unit | | | | |
| | 11/1 | 17/1 | 22/1 | 25/1 | Summed | 11/1 | 17/1 | 22/1 | 25/1 | Summed |
| 4.8 | — | 0/3 | 0/3 | 1/3 | 1/9 | — | 0/3 | 0/3 | 1/3 | 1/9 |
| 4.5 | 0/3 | 0/3 | 1/3 | 2/3 | 3/12 | 0/3 | 2/3 | 0/3 | 0/3 | 2/12 |
| 4.2 | 1/3 | 3/3 | 3/3 | 2/3 | 9/12 | 1/3 | 3/3 | 3/3 | 2/3 | 9/12 |
| 3.9 | 3/3 | 3/3 | — | — | 6/6 | 2/3 | 3/3 | — | — | 5/6 |

(2) *By the guinea-pig intracutaneous method.*

The mixtures injected (0.2 c.c.) contained 0.5 P. unit + the quantities of toxin shown.

| Toxin dose (V.S.10) (mgrm.) | Provisional American solution | | | | Proposed International solution | | | |
|-----------------------------------|-------------------------------|---|---------------------|---|---------------------------------|-----|---------------------|----|
| | 11 /1 | | 17 /1 | | 22 /1 | | 25 /1 | |
| | guinea- pig 1 | 2 | guinea- pig 3 | 4 | guinea- pig 5 | 6 | guinea- pig 7 | 8 |
| 2.7 | | | + | + | | | | |
| 2.55 | + | + | + | + | + | + | ± | ± |
| 2.4 | (+) | + | + | ± | ?— | (S) | S | ?S |
| 2.25 | — | — | S | — | — | — | ?S | — |
| 2.1 | — | — | — | — | — | — | — | — |

- + = Definite necrotic reaction.
- ± = Definite necrotic reaction of reduced size.
- S = A trace of necrosis only.
- = No reaction.

A reaction given in parenthesis indicates some form of reaction without necrosis (ghost reaction).

The Proposed International Standard appears slightly stronger than the Provisional American according to the guinea-pig intracutaneous tests, but not according to the mouse tests.

B. *Assay of the Antitoxin of Unstated Potency.*

Toxin V.S.10 was used at the test dose of 4.2 mgrm.

| Units tested for | Mouse intravenous method | | | | | Guinea-pig intracutaneous method | | | | | | |
|---------------------|---------------------------------|-------|-------|-------|--------|-------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| | Proportion of mice surviving | | | | | Guinea-pig A | Guinea-pig B | Guinea-pig C | Guinea-pig D | Guinea-pig E | Guinea-pig F | Guinea-pig G |
| | 11 /1 | 17 /1 | 22 /1 | 25 /1 | Summed | 11 /1 | 17 /1 | 22 /1 | 25 /1 | | | |
| 120 | 3 /3 | — | — | — | 3 /3 | — | — | | | | | |
| 150 | 3 /3 | 3 /3 | 3 /3 | 3 /3 | 12 /12 | ?S | — | | | | | |
| 165 | — | 0 /3 | 3 /3 | 2 /3 | 5 /9 | | | — | — | — | ?— | |
| 180 | — | 0 /3 | 0 /3 | 2 /3 | 2 /9 | ± | — | ± | S | S | S | |
| 200 | 0 /3 | — | — | — | 0 /3 | | | + | + | + | + | |

The intravenous test dose of 4.2 mgrm. appears slightly low according to our results, but was chosen because it had been used in the Hampstead experiments.

The unit value, for the mouse intravenous tests, which we should allot to the antitoxin of unstated potency is 160.

In order to conserve the toxin, the same mixtures were used for the skin tests, although 15 per cent more toxin per unit of antitoxin should be used to give border-line reactions. Therefore, by calculation, these results again give a value to the antitoxin of unstated potency of 160 (or slightly less).

The test dose of a toxin (E) prepared at the Wellcome Laboratories was found using the Provisional American and Proposed International Standard and the value of the antitoxin of unstated potency subsequently titrated against it. In all the titrations with this toxin, we have found that the intracutaneous results were easily repeatable to 10 per cent, but the intravenous mouse tests were very irregular. By the intracutaneous method, the value of the antitoxin of unstated potency, found with toxin E, was 160 units per c.c. The Proposed International Standard again appears to be slightly stronger than the Provisional American Standard according to the intracutaneous tests with this toxin.

5. REPORT RECEIVED FROM DR. G. F. PETRIE, ELSTREE, ENGLAND.

A. *Comparison of the American Provisional Standard and the Proposed International Standard.*

(1) *By the mouse intravenous method.*

| Toxin dose (V.S.10) (mgrm.) | Proportion of mice surviving | |
|-----------------------------------|--|--|
| | Provisional American solution, 0.2 c.c. = 1 P. unit | Proposed International solution, 0.2 c.c. = 1 P. unit |
| 4.7 | 0 / 6 | 0 / 6 |
| 4.4 | 0 / 6 | 0 / 6 |
| 4.1 | 4 / 12 | 5 / 12 |
| 3.8 | 11 / 12 | 8 / 12 |

(2) *By the guinea-pig intracutaneous method.*

| Antitoxin solution | Mixture injected in 0.2 c.c. | | Result |
|------------------------------|------------------------------|-------------|----------------------------------|
| | Toxin (V.S.11) mgrm. | Antitoxin | |
| Provisional American | 2.70 | 0.5 P. unit | Large reaction : necrosis. |
| | 2.55 | | Large reaction : necrosis. |
| | 2.40 | | Large reaction : trace necrosis. |
| | 2.25 | | Large reaction : trace necrosis. |
| | 2.10 | | Small reaction. |
| | 1.95 | | Trace reaction. |
| Proposed International | 2.70 | 0.5 P. unit | Large reaction : necrosis. |
| | 2.55 | | Large reaction : necrosis. |
| | 2.40 | | Large reaction : trace necrosis. |
| | 2.25 | | Large reaction : trace necrosis. |
| | 2.10 | | Small reaction. |
| | 1.95 | | Trace reaction. |

According to the above tests, the Provisional American and Proposed International Standard solutions are equivalent.

B. *Assay of Antitoxin of Unstated Potency.*

(1) *By the mouse intravenous method.*

| Toxin dose (mgrm.) | Proposed International solution | | Antitoxin of unstated potency | |
|--------------------|---------------------------------|------------------------------|-------------------------------|------------------------------|
| | P. units | Proportion of mice surviving | Dose c.c. | Proportion of mice surviving |
| 4.1 (V.S.10) ... | 1 | 2 / 12 | 0.0083 | 6 / 6 |
| | | | 0.0071 | 11 / 12 |
| | | | 0.0067 | 10 / 12 |
| | | | 0.0063 | 2 / 12 |
| | | | 0.0056 | 0 / 6 |
| 3.5 (V.S.11) ... | 1 | 4 / 6 | 0.0071 | 6 / 6 |
| | | | 0.0067 | 4 / 6 |
| | | | 0.0063 | 1 / 6 |
| | | | 0.0059 | 1 / 6 |

(2) *By the guinea-pig intracutaneous method.*

| Antitoxin solution. | Mixture injected in 0.2 c.c. | | Result : 48 hours |
|-------------------------------------|------------------------------|-------------|------------------------------|
| | Toxin (V.S.11) mgrm. | Antitoxin | |
| Proposed International | 2.2 | 0.5 P. unit | Small reaction. ¹ |
| Antitoxin of un- stated potency. | 2.2 | 0.0028 | Large reaction. |
| | | 0.0029 | Large reaction. |
| | | 0.0031 | Large reaction. |
| | | 0.0033 | Small reaction. ¹ |
| | | 0.0036 | Small reaction. |

According to the above tests, the sample of antitoxin of unstated potency contains 150 to 155 provisional units per c.c.

6. REPORT RECEIVED FROM DR. G. W. MCCOY, WASHINGTON.

A. *Comparison of the Provisional American Standard and the Proposed International Standard.*(1) *By the mouse intravenous method.*

| Toxin dose (mgrm.) | Proportion of mice surviving | |
|--------------------|--|--|
| | Provisional American solution, 0.2 c.c. = 1 P. unit | Proposed International solution, 0.2 c.c. = 1 P. unit |
| (V. S. 10) : | | |
| 4.7 | 0/6 | 0/6 |
| 4.4 | 1/6 | 1/6 |
| 4.1 | 3/6 | 5/6 |
| 3.8 | 6/6 | 6/6 |
| (U. S.) V. S. 1 : | | |
| 5.6 | 0/6 | 0/6 |
| 5.3 | 0/6 | 0/6 |
| 5.0 | 3/6 | 2/6 |
| 4.7 | 6/6 | 4/6 |
| 4.4 | 6/6 | 6/6 |

¹ These reactions were equal.

| Toxin dose (mgrm.) | Provisional American solution | | Proposed International solution | |
|--------------------------|-------------------------------|------------------------------|---------------------------------|------------------------------|
| | Antitoxin P. units | Proportion of mice surviving | Antitoxin P. units | Proportion of mice surviving |
| (V.S.10) 4.1.. | 0.9 | 0/6 | 0.9 | 1/6 |
| | 1.0 | 3/6 | 1.0 | 5/6 |
| | 1.1 | 6/6 | 1.1 | 6/6 |
| (V.S.10) 4.2.. | 0.9 | 0/6 | 0.9 | 0/6 |
| | 1.0 | 2/6 | 1.0 | 4/6 |
| | 1.1 | 6/6 | 1.1 | 5/6 |
| ((U.S.) V.S.1) 5.0 | 0.9 | 0/6 | 0.9 | 0/6 |
| | 1.0 | 1/6 | 1.0 | 1/6 |
| | 1.1 | 4/6 | 1.1 | 5/6 |
| ((U.S.) V.S.1) 2.5 | 0.45 | 3/6 | 0.45 | 1/6 |
| | 0.50 | 4/6 | 0.50 | 3/6 |
| | 0.55 | 6/6 | 0.55 | 6/6 |

(2) *By the guinea-pig intracutaneous method.*

| Antitoxin solution | Mixture injected in 0.2 c.c. | | Result : 48 hours |
|------------------------------|------------------------------|-------------|---|
| | Toxin mgrm. | Antitoxin | |
| Provisional American | (V.S. 11) | 0.5 P. unit | Large reaction : necrosis. Rather large reaction : necrosis. Moderate reaction : small necrosis. Slight or no reaction. No reaction. No reaction. |
| | 2.70 | | |
| | 2.55 | | |
| | 2.40 | | |
| | 2.25 | | |
| | 2.10 | | |
| | 1.95 | | |
| Proposed International | (V.S. 11) | 0.5 P. unit | Large reaction : necrosis. Rather large reaction : necrosis. Moderate reaction : small necrosis. Slight or no reaction. No reaction. No reaction. |
| | 2.70 | | |
| | 2.55 | | |
| | 2.40 | | |
| | 2.25 | | |
| | 2.10 | | |
| | 1.95 | | |
| Provisional American | ((U.S.) V.S.1) | 0.5 P. unit | Marked reaction : necrosis. Marked reaction : necrosis. Moderate reaction : small necrosis. Slight reaction. Negative reaction. Negative reaction. |
| | 2.70 | | |
| | 2.55 | | |
| | 2.40 | | |
| | 2.25 | | |
| 2.10 | | | |
| 1.95 | | | |

| Antitoxin solution | Mixture injected in 0.2 c.c. | | Result : 48 hours |
|------------------------------|--|-------------|-------------------------------------|
| | Toxin mgrm. ((U.S.) V.S.1) | Antitoxin | |
| Proposed International | 2.70 2.55 2.40 2.25 2.10 1.95 | 0.5 P. unit | Marked reaction : necrosis. |
| | | | Marked reaction : necrosis. |
| | | | Moderate reaction : small necrosis. |
| | | | Slight reaction. |
| | | | Negative reaction. |
| | | | Negative reaction. |

A further test, using the U.S. toxin V.S.1 at a constant dose of 2.4 mgrm. and varying the antitoxin doses, gave the following results :

| Antitoxin solution | Mixture injected in 0.2 c.c. | | Result : 48 hours |
|------------------------------|--------------------------------|-----------------------|----------------------------|
| | Toxin (U.S.) V.S.1 mgrm. | Antitoxin P. units | |
| Provisional American | 2.4 | 0.450 | Large reaction : necrosis. |
| | | 0.475 | Large reaction : necrosis. |
| | | 0.500 | Moderate reaction. |
| | | 0.525 | Slight reaction. |
| | | 0.550 | Negative reaction. |
| Proposed International | 2.4 | 0.450 | Large reaction : necrosis. |
| | | 0.475 | Large reaction : necrosis. |
| | | 0.500 | Moderate reaction. |
| | | 0.525 | Slight reaction. |
| | | 0.550 | Negative reaction. |

B. Assay of the Antitoxin of Unstated Potency.

(1) By the mouse intravenous method.

A preliminary test indicated that the preparation contained between 150 and 200 P. units per c.c.

| Number of P. units tested for | Volume of antitoxin of unstated potency injected with 1 test dose of toxin c.c. | Proportion of mice surviving | |
|-------------------------------|--|---------------------------------------|---|
| | | Toxin V.S.10, test dose, 4.2 mgrm. | Toxin (U.S.) V.S.1, test dose, 5.0 mgrm. |
| 200 | 1/200 | 0/6 | 0/6 |
| 190 | 1/190 | 0/6 | 0/6 |
| 180 | 1/180 | 1/6 | 0/6 |
| 170 | 1/170 | 4/6 | 1/6 |
| 160 | 1/160 | 5/6 | 4/6 |
| 150 | 1/150 | 6/6 | 6/6 |

The antitoxin of unstated potency contains 160 to 170 units per c.c.

(2) *By the guinea-pig intracutaneous method.*

| Antitoxin solution | Mixture injected in 0.2 c.c. | | Result : 48 hours |
|------------------------------------|------------------------------|---------------------|----------------------------|
| | Toxin (U.S.) V.S.1 mgrm. | Antitoxin | |
| Provisional American | 2.4 | 0.5 P. unit c.c. | Moderate reaction. |
| Antitoxin of un- stated potency | 2.4 | 0.00278 | Large reaction : necrosis. |
| | | 0.00293 | Large reaction : necrosis. |
| | | 0.00313 | Moderate reaction. |
| | | 0.00338 | Slight reaction. |
| | | 0.00367 | Negative reaction. |

The antitoxin of unstated potency contains 160 to 170 P. units per c.c.

C. Comparative Tests, using the Toxin V.S.10, supplied from Hampstead, and the Toxin (U.S.) V.S.1, to determine the Potency of One Commercial Antitoxin.

(1) *Protocol of test of June 3rd, 1933, on serum 259, showing results of tests made according to method of the National Institute of Health.*

| Antitoxin | Number of units tested for | Volume of antitoxin 259 injected c.c. | Toxin (U.S.) V.S.1 mgrm. | Proportion of mice surviving |
|--------------------------------|----------------------------|--|-----------------------------|------------------------------|
| No. 259 | 90 | 1/360 | 2.5 | 6/6 |
| | 100 | 1/400 | 2.5 | 6/6 |
| | 110 | 1/440 | 2.5 | 2/6 |
| | 120 | 1/480 | 2.5 | 0/6 |
| Provisional American Standard. | 50 | 0.25 c.c. of a 1 in 50 dilution | 2.5 | 4/6 |

(2) *Protocol of test of March 15th, 1934, on serum 259, showing results of tests made according to method outlined in the Memorandum.*

| Antitoxin | Number of units tested for | Volume of antitoxin 259 injected | Toxin V.S.10 mgrm. | Proportion of mice surviving |
|---------------|----------------------------|----------------------------------|-----------------------|------------------------------|
| No. 259 | 180 | 1/180 | 4.2 | 6/6 |
| | 200 | 1/200 | 4.2 | 6/6 |
| | 220 | 1/220 | 4.2 | 2/6 |
| | 240 | 1/240 | 4.2 | 0/6 |

The results are in exact agreement, the serum containing 110 of the American units under consideration and 220 of the proposed P. (international) units (the American units under consideration being twice as large as the proposed international).

Additional Note.—At the request of the National Institute for Medical Research, Hampstead, Dr. McCoy, of the National Institute of Health, Washington, kindly supplied three samples of gas gangrene antitoxin (*vibrion septique*), prepared in two different laboratories in the United States, for the purpose of independent testing. These were “*vibrion septique* antitoxins of unknown potency” and were tested independently in the Washington and Hampstead Institutes. The results obtained in the two institutes are summarised in the following table :

| Vibrion septique antitoxin | Results of potency tests carried out in | | | | | |
|----------------------------------|---|---------------------|----------------------|-------------------------------|--------------------|----------------------|
| | Washington | | | London | | |
| | Method | Toxin used | P. units per c.c. | Method | Toxin used | P. units per c.c. |
| A .. | mouse i.v. | American British | 220 220 | guinea-pig i.c. | British | 210 |
| B... | mouse i.v. | American | 540 to 600 | mouse i.v. guinea-pig i.c. | British British | 590 580 |
| C ¹ .. | mouse i.v. | American | 300 | mouse i.v. guinea-pig i.c. | British British | 310 330 |

SUMMARY.

The international enquiry was planned with a view to obtaining such information and data relating to a dry stable preparation of *vibrion septique* antitoxin which would enable the Permanent Commission on Biological Standardisation to arrive at a decision as to its suitability and practicability for adoption as the international standard for this antitoxin.

In support of the view that the dry standard preparation adequately fulfils the requirements of an international standard, the

¹ An independent test of sample C, carried out in another American laboratory, indicated that the potency of this sample was 300 P. units per c.c.

following points, in regard to the results obtained in the joint enquiry, are submitted for consideration :

1. The claim made that two glycerol solutions of *vibrion septique* antitoxin were of identical potency was confirmed by independent tests carried out in six different laboratories. In a few tests, slight differences in potency appeared to be demonstrated, but they were very small and of no practical significance. The results obtained by six different investigators show, indeed, a remarkable degree of uniformity and agreement.

2. Investigators were invited to determine the potency of a sample of "*vibrion septique* antitoxin of unstated potency". The following values were returned.

| Investigator | P. units per c.c. |
|-----------------------------|-------------------|
| Madsen (Denmark) | 154-167 |
| Weinberg (France) | 170 |
| Kolle (Germany) | 160 |
| O'Brien (England) | 160 |
| Petrie (England) | 150-155 |
| Bruce White (England) | 155 |
| McCoy (U.S.A.) | 160-170 |

In this series of independent tests, also, the results show good agreement and suggest that, in practice, the assay of *vibrion septique* antitoxin with an accuracy of at least ten per cent should present no difficulty.

3. Investigators were especially invited to carry out tests on the *vibrion septique* antitoxins supplied by means of toxins other than V.S.10 (the sample supplied). This was done in three laboratories, and in every case the results obtained confirmed those yielded by similar tests in which toxin V.S.10 was used—*i.e.*, the identity of the two glycerol solutions was established and the same value returned for the antitoxin of unstated potency. Three laboratories were supplied from Hampstead with a second *vibrion septique* toxin (V.S.11) and the results obtained by the use of this toxin confirmed those obtained by the use of toxin V.S.10.

4. Two methods of assay of *vibrion septique* antitoxin were described in the Appendix. Of these, the mouse-intravenous method is the more familiar and possibly the method of choice in most laboratories. It is of interest to record, however, that five of the six investigators also employed the guinea-pig intracutaneous method ; and, although in most of these laboratories the method is

novel and not in regular use, examination of the protocols shows that the claims made for this method in the Memorandum were fully substantiated by four of the five investigators. It is considered that greater experience of the method will lead to its more general employment.¹ It is to be noted that, in all but a very few instances, the same results were obtained by the use of either of the two methods.

5. The results obtained in certain of the additional tests which some of the investigators carried out are of especial importance, as it is considered that they provide additional and independent evidence of the suitability and practicability of the dry stable preparation of *vibrion septique* antitoxin, now available for adoption as the international standard. The Beckenham laboratory standardised a test toxin in terms of the standard preparation and assayed the antitoxin of unknown potency by its use. The Frankfort laboratory similarly standardised test toxins and, by an interesting series of tests, assayed the value of a dry preparation of antitoxin in terms of both the dry standards supplied for this investigation and obtained identical results; incidentally, the Frankfort experiments confirmed the findings of the Hampstead laboratory in regard to the weights of each of the standard preparations corresponding to one provisional unit. The Washington laboratory assayed a commercial sample of *vibrion septique* antitoxin by using two slightly different methods and two separately tested toxins, and obtained identical results. Finally, the Washington and Hampstead laboratories, using different toxins and different methods, and working quite independently, returned identical values for the potency of three samples of *vibrion septique* antitoxin.

CONCLUSIONS.

It is suggested that the following conclusions may be drawn from the results presented above :

1. That gas gangrene antitoxin (*vibrion septique*) can be assayed with a high degree of accuracy.

¹ It may be added that, in order to make the principle of the method as clear as possible, the description given in the Memorandum involved the use of an unnecessarily large amount of toxin ; a simple modification of procedure, without change of principle, would reduce the amount of toxin used.

2. That the methods of intravenous injection into mice or intracutaneous injection into guinea-pigs of toxin-antitoxin mixtures are simple and practicable and yield consistent and comparable results when applied by different investigators.

3. That dry, stable preparations of gas gangrene antitoxin (*vibrion septique*) can be prepared and assayed in terms of an accepted standard preparation, and accurately standardised solutions, suitable for distribution for purposes of biological assay, can be prepared.

RECOMMENDATION.

It is recommended that the Permanent Commission on Biological Standardisation should accept the dry stable preparation of gas gangrene antitoxin (*vibrion septique*), prepared at the National Institute for Medical Research, London, from material supplied by Dr. Weinberg of the Pasteur Institute, Paris, as the international standard for this antitoxin ; and that the Commission should define a unit, in terms of this standard preparation, for adoption for international use.

APPENDIX.

MEMORANDUM CONCERNING A PROPOSED INTERNATIONAL STANDARD FOR GAS GANGRENE ANTITOXIN (VIBRION SEPTIQUE).

By

Percival HARTLEY and P. BRUCE WHITE

(from the National Institute for Medical Research, Hampstead, London.)

At a meeting of the Permanent Commission on Biological Standardisation, held in London in June 1931, the National Institute for Medical Research, London, was requested to undertake the preparation of a standard for gas gangrene antitoxin (*vibrion septique*) and to arrange for preliminary laboratory investigations with a view to international agreement on a standard preparation and the definition of a unit in terms of it. It was suggested that the work should be organised on lines similar to those adopted in the case of gas gangrene antitoxin (*perfringens*). The steps taken to comply with this request are described below.

THE STANDARD FOR GAS GANGRENE ANTITOXIN (*vibrion septique*)
PROPOSED FOR INTERNATIONAL ADOPTION.

Through the courtesy and generosity of Dr. Weinberg, of the Pasteur Institute, Paris, the Permanent Commission on Biological Standardisation has been presented with an adequate supply of a dry *vibrion septique* antitoxin. The material, which was received in a number of large sealed tubes, was pooled and distributed into ampoules, each ampoule containing approximately 1 grm. The filled ampoules were exposed to further dehydration over phosphorus pentoxide, *in vacuo*, until the product was absolutely dry, as shown by the attainment of constant weight by selected ampoules. The ampoules were then filled with pure, dry nitrogen gas and sealed. The dry standard preparation is stored continuously in the dark, at -4° C. The total number of sealed ampoules, each containing approximately 1 grm. of the dry standard preparation, is 150.

THE UNIT.

Shortly after the work was begun in this Institute, we received, through the courtesy of Dr. G. W. McCoy, of the National Institute of Health, Washington, U.S.A., a sample of dried gas gangrene antitoxin (*vibrion septique*) prepared in his Institute for use as a provisional standard, together with an indication of the unit recommended for provisional adoption in the United States of America. This unit was about twice that which we had been using up to that time at the National Institute for Medical Research, London. In October 1932, a paper appeared in the *Annales de l'Institut Pasteur* (Vol. XLIX, page 387) by WEINBERG, DAVESNE and PRÉVOT, in which a unit is proposed which is about half of that to which we had been working, and about a quarter of that recommended for provisional use in America by Dr. McCoy.

It is suggested that the question of the dimensions of the unit to be adopted for international use shall be left for decision to the Permanent Commission on Biological Standardisation. For the purpose of these preliminary investigations, we have adopted a *Provisional International Unit* which is exactly half of the unit proposed by Dr. McCoy, and about twice the unit proposed by Weinberg, Davesne and Prévot. Throughout this Memorandum, therefore, the unit referred to is to be understood as a *provisional international unit* and, for brevity and convenience, is referred to as the *P. unit*.

MATERIALS SUPPLIED.

1. A solution of gas gangrene antitoxin (*vibrion septique*) prepared from the dry preparation made as a provisional standard at the National Institute of Health, Washington, U.S.A. (label marked 1).

In accordance with instructions received from Dr. McCoy, the contents of 1 ampoule were dissolved in 125 c.c. of a glycerol-saline solution (glycerol, 2 parts : physiological salt solution, 1 part). Of this solution :

1 cubic centimetre contains 100 *P. units*.

According to our determinations of the weight of dry substance contained in each of three ampoules supplied by Dr. McCoy, 1 P. unit is contained in 0.156 mgrm. of the American Provisional Standard preparation.

2. A solution of gas gangrene antitoxin (*vibrion septique*) prepared by dissolving an accurately weighed quantity of the Proposed International Standard preparation in glycerol (2 parts)—saline (1 part) (*label marked 2*). According to our determinations, 1 P. unit is contained in 0.2377 grm. of the Proposed International Standard preparation. The volume of the solution was finally adjusted so that 1 c.c. contains 23.77 mgrm. of the dry standard preparation—*i.e.*, in this case also :

1 cubic centimetre contains 100 P. units.

3. A dry preparation of gas gangrene toxin (*vibrion septique*) (*label marked 3*). This has been prepared by precipitating the germ-free filtrate from a three-day growth of the organism with ammonium sulphate, removing the precipitate and drying it over phosphorus pentoxide.

The sealed ampoule contains rather more than 2 grm. of dry toxin. It is recommended that, after the ampoule has been opened, it should be preserved in a small desiccator over phosphorus pentoxide.

4. Two sealed ampoules, each containing about 2.5 c.c. of a gas gangrene antitoxin (*vibrion septique*) of unstated potency, for the purpose of trial assay (*label marked 4*).

METHODS.

The assay of the dry standard preparation of gas gangrene antitoxin (*vibrion septique*) proposed for international adoption, in comparison with the American preparation, has been carried out by two methods :

- A : By the intravenous injection of mixtures of toxin and antitoxin into the tail veins of mice weighing from 17 to 20 grm., and
- B : By the intracutaneous injection of mixtures of toxin and antitoxin into the shaven, or depilated, flanks of white or light-coloured guinea-pigs weighing from 300 to 400 grm.

A. *The mouse intravenous method.*

By adopting the following procedures, the "test dose" of the toxin supplied and the relative potencies of the glycerol solutions of the two preparations of gas gangrene antitoxin (*vibrion septique*) may be determined in one and the same experiment :

- (1) 1 c.c. of the solution of the Provisional American Standard antitoxin is diluted to 20 c.c. ;
- (2) 1 c.c. of the solution of the Proposed International Standard is diluted to 20 c.c. ;
- (3) A quantity of the dry toxin V.S.10 is quickly and accurately weighed out and dissolved in physiological salt solution, the final volume being adjusted so that 1 c.c. of the toxin solution contains 20 mgrm. ;

- (4) Mixtures of each of the antitoxin dilutions are made so that 0.5 c.c. of each mixture (the quantity injected intravenously into a mouse) contains 0.2 c.c. of the diluted antitoxin (1 P. unit) + varying quantities of the toxin solution. Suitable quantities of the toxin for purposes of the test will probably be found to be between 3.5 and 4.5 mgrm. (see Table I).

The mixtures are allowed to stand at room temperature for 1 hour and then 0.5 c.c. quantities are injected intravenously into groups of mice. The mice used should be drawn from a uniform stock and should be as nearly equal in weight as practicable (17 to 20 gm.). For the final comparison of the two solutions of antitoxin, we have used groups of six or more mice for each mixture of toxin and antitoxin tested. The mice are kept under observation for three days: the majority of the animals which succumb to the injection die during the first forty-eight hours, but deaths occurring within seventy-two hours of the injection are regarded as significant.

The protocol of an experiment carried out as described above is given in Table I.

Table I.

| Toxin dose (mgrm.) | + 0.2 c.c. = 1 P. unit (American solution) | | | | + 0.2 c.c. = 1 P. unit (Proposed International Standard solution) | | | |
|-----------------------|---|-------------------------|-----------------------------|-------------------------|---|-------------------------|-----------------------------|-------------------------|
| | Number of mice used | Number of mice dying | Number of mice surviving | Proportion surviving | Number of mice used | Number of mice dying | Number of mice surviving | Proportion surviving |
| 4.7 | 6 | 6 | 0 | 0/6 | 6 | 6 | 0 | 0/6 |
| 4.4 | 6 | 6 | 0 | 0/6 | 6 | 5 | 1 | 1/6 |
| 4.1 | 6 | 4 | 2 | 2/6 | 6 | 3 | 3 | 3/6 |
| 3.8 | 6 | 0 | 6 | 6/6 | 6 | 0 | 6 | 6/6 |

From the results of several experiments, it is concluded that the "test dose" of toxin V.S. 10 (*i.e.*, the dose which, when mixed with 1 P. unit of antitoxin and injected intravenously into groups of mice kills some, but not all, of the mice injected) is about 4.1 mgrm. The average lethal dose of the toxin is about 0.17 mgrm. The "test dose", therefore, contains about twenty-four average lethal doses.

The potencies of the two glycerol solutions of antitoxin were also compared in two experiments in which the toxin dose was kept constant for each particular test and the doses of the antitoxins varied. The results are collected in Table II.

B. The guinea-pig intracutaneous method.

TZEKHOVITZER and KAROUTH (1930 : *Comptes rendus de la Société de Biologie*, Vol. 103, page 1094) and GLENNY, LLEWELLYN JONES and MASON (1931 :

Table II.

| Toxin dose (mgrm.) | Solution of American Provisional Standard | | | | | Solution of Proposed International Standard | | | | |
|--------------------|---|----------------|-------|-----------|----------------------|---|----------------|-------|-----------|----------------------|
| | Antitoxin P. units | Number of mice | | | | Antitoxin P. units | Number of mice | | | |
| | | Injected | Dying | Surviving | Proportion surviving | | Injected | Dying | Surviving | Proportion surviving |
| 4.1 | 0.9 | 6 | 4 | 2 | 2/6 | 0.9 | 6 | 4 | 2 | 2/6 |
| | 1.0 | 6 | 1 | 5 | 5/6 | 1.0 | 6 | 2 | 4 | 4/6 |
| | 1.1 | 6 | 0 | 6 | 6/6 | 1.1 | 6 | 0 | 6 | 6/6 |
| 4.2 | 0.9 | 12 | 11 | 1 | 1/12 | 0.9 | 12 | 12 | 0 | 0/12 |
| | 1.0 | 12 | 4 | 8 | 8/12 | 1.0 | 12 | 5 | 7 | 7/12 |
| | 1.1 | 13 | 1 | 12 | 12/13 | 1.1 | 12 | 0 | 12 | 12/12 |

Journal of Pathology and Bacteriology, Vol. 34, page 201) have shown that *vibron septique* toxin and antitoxin may be assayed by the intracutaneous method of testing in guinea-pigs. We have found that this method is simple, convenient and economical, and yields results comparable in accuracy with those obtained by the mouse-intravenous method.

It is recommended that the character of the lesion produced in the skin of guinea-pigs by the toxin of *vibron septique* should first be studied. With the toxin supplied (V.S.10) it will be found that 0.5 mgrm. injected in a volume of 0.2 c.c. usually produces a large necrotic lesion, while 0.05 mgrm. produces a very small reaction and 0.025 mgrm. fails to produce a reaction. Doses intermediate between 0.5 mgrm. and 0.025 mgrm. should therefore be injected so that the individual observer may decide for himself the end-point to which he prefers to work; experience will also be gained as to the best sites and spacing for the injections. White or light-coloured guinea-pigs weighing from 300 to 400 gm. are suitable, and not more than five, or at most six, injections should be made on each flank of the animal. Reactions may be read twenty-four hours after injection, the final reading being made forty-eight hours after injection.

As in the case of the mouse-intravenous method, the "test-dose" of the toxin supplied (V.S.10) and the relative potencies of the glycerol solutions of the two preparations of gas gangrene antitoxin (*vibron septique*) may be determined in one and the same experiment. The antitoxin dilutions are the same as for the mouse intravenous method (*i.e.*, 1 c.c. of each solution diluted to 20 c.c., so that 1 c.c. of each antitoxin dilution contains 5 P. units); it is convenient to make the toxin solution of such a strength that 1 c.c. contains 30 mgrm. of toxin V.S.10. A series of mixtures of toxin and each antitoxin are made in which, in a total volume of 2 c.c., 5 P. units of antitoxin are mixed with varying quantities of toxin. The mixtures are allowed to stand at room temperature for one hour, and then 0.2 c.c. quantities are injected intracutaneously; each

actual dose injected, therefore, contains 0.5 P. unit of antitoxin + one-tenth of the total amount of toxin in the full 2 c.c. of mixture. Thus the $\frac{Lr}{2}$ dose of the toxin is determined—*i.e.*, the quantity of toxin which, when mixed with 0.5 P. unit of antitoxin and injected intracutaneously, produces a small but characteristic reaction in the skin of the guinea-pig. The mixtures of toxin and the solution of the American Provisional Standard antitoxin are injected on one flank of the guinea-pig, and the mixtures of toxin and the solution of the Proposed International Standard antitoxin are injected at corresponding sites on the other flank of the animal.

The protocol of an actual test, carried out with the reagents supplied, is given in Table III.

Table III.

| Antitoxin solution | Mixtures prepared : volume = 2 c.c. | | Dose of mixture injected | Result : 48 hours | |
|------------------------------|-------------------------------------|-----------|--------------------------|-------------------|--|
| | Toxin | Antitoxin | | | |
| | c.c. | mgram. | | | |
| American . . | 1.0 | 30 | 1 c.c. = 5 P. units | 0.2 c.c. | Large reaction : ventral œdema. Large reaction. Small reaction. No reaction. No reaction. |
| | 0.9 | 27 | | | |
| | 0.8 | 24 | | | |
| | 0.7 | 21 | | | |
| | 0.6 | 18 | | | |
| Proposed International . . . | 1.0 | 30 | 1 c.c. = 5 P. units | 0.2 c.c. | Large reaction : ventral œdema. Large reaction. Very small reaction. No reaction. No reaction. |
| | 0.9 | 27 | | | |
| | 0.8 | 24 | | | |
| | 0.7 | 21 | | | |
| | 0.6 | 18 | | | |

The potencies of the two glycerol solutions of antitoxin were also compared in an experiment in which the toxin dose was kept constant and the doses of the antitoxins varied. The results are given in Table IV.

INVESTIGATIONS SUGGESTED.

1. Investigators in different countries are invited to verify the relationship between the solutions of the Proposed International Standard and the American Provisional Standard of gas gangrene antitoxin (*vibrio septique*).

This may be done by either, or both, of the methods outlined above and by the use of the toxin supplied. A comparison by other methods which individual workers may have in use, and especially by the use of *vibrio septique* toxins other than the one supplied, would be of special interest.

2. It is suggested that the sample of gas gangrene antitoxin (*vibrio septique*) supplied (label marked 4) be standardised in terms of the P. unit indicated.

For this purpose either, or both, of the methods indicated above and the toxin supplied may be used ; or other methods and other reagents which

individual workers have in use may be applied. The sample supplied is to be regarded as a gas gangrene antitoxin (*vibrion septique*) of unknown potency ; but, in order to economise time and animals, it may be stated that the value, according to our determinations, lies between 100 and 200 P. units per c.c.

Table IV.

| Antitoxin solution | Mixtures prepared : volume = 2 c.c. | | Volume of mixture injected | Result : 48 hours | |
|------------------------|--|-----------|----------------------------|-------------------|---|
| | Toxin | Antitoxin | | | |
| American ... | 25 mgrm. | c.c. | P. units | 0.2 c.c. | Large reaction ; necrosis ; ventral œdema. Large reaction ; necrosis ; ventral œdema. Doubtful reaction, or nil. No reaction. No reaction. |
| | | 0.90 | 4.50 | | |
| | | 0.95 | 4.75 | | |
| | | 1.00 | 5.00 | | |
| | | 1.05 | 5.25 | | |
| | | 1.10 | 5.50 | | |
| Proposed International | 25 mgrm. | 0.90 | 4.50 | | Large reaction ; necrosis ; ventral œdema. Moderate reaction ; necrosis ; slight œdema. Doubtful reaction, or nil. No reaction. No reaction. |
| | | 0.95 | 4.75 | | |
| | | 1.00 | 5.00 | | |
| | | 1.05 | 5.25 | | |
| | | 1.10 | 5.50 | | |

Note.—In order to avoid unduly large reactions in testing antitoxins of unknown potency, preliminary tests should be carried out using the $\frac{Lr}{5}$ or $\frac{Lr}{10}$ doses of toxin.

ADDENDUM.

The quantity of *vibrion septique* toxin V.S. 10 having been exhausted, another toxin, V.S. 11, has been prepared and the *approximate* test dose determined. Protocols of the tests are given below.

A. By the mouse intravenous method.

| Toxin dose V.S.11 mgrm. | Antitoxin : Provisional Standard | Number of mice used | Number dying | Number surviving | Proportion surviving |
|----------------------------|--|---------------------------|-----------------|---------------------|-------------------------|
| 4.0 | 1 P. unit | 4 | 4 | 0 | 0/4 |
| 3.6 | | 4 | 2 | 2 | 2/4 |
| 3.2 | | 4 | 0 | 4 | 4/4 |
| 2.8 | | 4 | 0 | 4 | 4/4 |

B. *By the guinea-pig intracutaneous method.*

The procedure followed is exactly as described on page 36. The $\frac{Lr}{2}$ dose of the toxin has been determined as before (for toxin V.S. 11, this value is between 2.25 and 2.4 mgrm.), and in the same experiment a comparative test of the potencies of the American and Provisional International Standard solutions was carried out; this test showed that the two solutions are of identical potency.

The solution of toxin used in the test was of such a strength that 1 c.c. contained 30 mgrm. of the dry toxin V.S. 11.

| Antitoxin solution | Mixtures prepared : vol. = 2 c.c. | | Dose of mixture injected | Result : 48 hours | |
|-------------------------|-----------------------------------|---------------------|--------------------------|--|--|
| | Toxin V.S.11 | Antitoxin | | | |
| American ... | c.c. mgrm. | 1 c.c. = 5 P. units | 0.2 c.c. | Large reaction ; necrosis ; ventral œdema. Large reaction ; necrosis ; ventral œdema. Moderate reaction ; small necrosis. Doubtful reaction or nil. No reaction. No reaction. | |
| | 0.9 = 27 | | | | |
| | 0.85 = 25.5 | | | | |
| | 0.8 = 24 | | | | |
| | 0.75 = 22.5 | | | | |
| | 0.7 = 21 | | | | |
| 0.65 = 19.5 | | | | | |
| Proposed International. | 0.9 = 27 | 1 c.c. = 5 P. units | | 0.2 c.c. | Large reaction ; necrosis ; ventral œdema. Large reaction ; necrosis ; ventral œdema. Moderate reaction ; small necrosis. Doubtful reaction or nil. No reaction. No reaction. |
| | 0.85 = 25.5 | | | | |
| | 0.8 = 24 | | | | |
| | 0.75 = 22.5 | | | | |
| | 0.7 = 21 | | | | |
| | 0.65 = 19.5 | | | | |

Requests for further details as to the assay of gas gangrene antitoxins (*vibrio septique*) of unknown potency, in terms of the P. unit, by the intracutaneous method of testing having been received, an illustrative protocol is given below. (Preliminary tests had indicated that the sample contained between 250 and 400 P. units per c.c.)

| Mixtures prepared | | | | Volume of mixture injected intracutaneously | Actual quantities injected | | Result : forty-eight hours |
|-------------------|--------------------------|-------------------------------|--------------------------|---|----------------------------|-------------------|---|
| No. | Toxin | Antitoxin 1/50 dilution | Salt solution c.c. | | Toxin | Antitoxin c.c. | |
| 1 | 24 mgrm. in 1 c.c. | 1.0 | — | 0.2 c.c. | 2.4 mgrm. | 0.002 | No reaction. |
| 2 | | 0.9 | 0.1 | | | 0.0018 | No reaction. |
| 3 | | 0.8 | 0.2 | | | 0.0016 | Moderate reaction : slight necrosis. |
| 4 | | 0.7 | 0.3 | | | 0.0014 | Large reaction : necrosis. |
| 5 | | 0.6 | 0.4 | | | 0.0012 | Large reaction : necrosis, oedema. |
| Control | 24 mgrm. in 1 c.c. | 5 P. units in 1 c.c. | — | 0.2 c.c. | 2.4 mgrm. | 0.5 P. unit | Small reaction : no necrosis |

The sample of gas gangrene antitoxin (*vibrion septique*) contains more than 280 P. units per c.c. and slightly less than 310 P. units per c.c.

2. A PROPOSED INTERNATIONAL STANDARD FOR GAS GANGRENE ANTITOXIN (*ŒDEMATIENS*)

By

L. E. WALBUM and C. REYMANN
(State Serum Institute, Copenhagen).

At a meeting held by the Permanent Commission on Biological Standardisation at Copenhagen, in November 1932, it was decided that the State Serum Institute of Copenhagen should prepare a standard for gas gangrene antitoxin (*œdematiens*), following the plan of work which had been adopted earlier, when the international unit for gas gangrene antitoxin (*perfringens*) was established.

Research was accordingly begun without delay, and we now report below on the work so far accomplished in this connection.

THE UNIT.

Two gas-gangrene antitoxin units (*œdematiens*) were available—namely, a *French* unit (Dr. WEINBERG) and a *German* unit (Professor H. SCHMIDT, Marburg).

Careful measurement carried out at our Institute (see tables appended) revealed the fact that the ratio of these two units is the following :

1 *French unit* = 5 *German units*.

For practical reasons, it will, however, prove more suitable to create an international unit somewhat larger than either of the above, and we consequently propose that *a unit exactly ten times*

the French unit be chosen as the international provisional standard, so that :

1 international provisional unit = 10 French = 50 German units.

The unit referred to in the present report is accordingly the international provisional unit as just defined (abridged to *P. unit*).

COMPARISON BETWEEN THE FRENCH UNIT (DR. WEINBERG), THE GERMAN UNIT (PROFESSOR H. SCHMIDT), AND THE PROPOSED INTERNATIONAL PROVISIONAL STANDARD OF GAS GANGRENE ANTITOXIN (*Œdematiens*).

(“Test dose” of toxin 1.34 = 3.9 mgrm.)

French Standard Antitoxin.

| Unit | Toxin mgrm. | Proportion of mice surviving |
|------|-------------|------------------------------|
| 0.22 | 3.9 | 7/7 |
| 0.20 | 3.9 | 2/7 |
| 0.18 | 3.9 | 0/7 |

German Standard Antitoxin.

| Unit | Toxin mgrm. | Proportion of mice surviving |
|------|-------------|------------------------------|
| 1.1 | 3.9 | 7/7 |
| 1.0 | 3.9 | 5/7 |
| 0.9 | 3.9 | 0/7 |

International Provisional Standard Antitoxin.

| Unit | Toxin mgrm. | Proportion of mice surviving |
|-------|-------------|------------------------------|
| 0.022 | 3.9 | 7/7 |
| 0.020 | 3.9 | 2/7 |
| 0.018 | 3.9 | 0/7 |

According to these and a number of other corresponding experiments :

1 FRENCH unit = 5 GERMAN units = 0.1 international provisional units, or 1 international provisional unit = 10 French = 50 German.

PREPARATION OF THE GAS GANGRENE ANTITOXIN (*Œdematiens*)
TO BE USED AS A STANDARD.

The *antitoxin utilised* was a serum (without the addition of any preservative) taken from the blood of a horse (No. 1024, bleeding 5/4 33) immunised against gas gangrene toxin (*œdematiens*), and prepared at our Institute.

By means of an accurately working distributing apparatus, 5 c.c. serum were delivered into each of a number of dry, sterile ampoules.

The ampoules were then placed into vacuum-desiccators containing calcium chloride at the ordinary room temperature until the contents of the ampoules present the outward appearance of dryness. This stage was reached after three to four days ; it was, however, necessary to change the calcium chloride contained in the vacuum-desiccators several times.

The drying was subsequently continued in another set of vacuum-desiccators over phosphorus pentoxide until complete dryness was attained, the process taking about two months. By way of check, a couple of ampoules were removed from each desiccator and weighed.

The ampoules were then filled with dry nitrogen and sealed.

These ampoules were kept at -4° C.

The weight of the dry substance contained in eight ampoules was ascertained to be as follows :

| Grm. | Grm. |
|-----------|-----------|
| 1. 0.4291 | 5. 0.4289 |
| 2. 0.4290 | 6. 0.4297 |
| 3. 0.4285 | 7. 0.4294 |
| 4. 0.4286 | 8. 0.4290 |

Mean : 0.429 gm.

Largest deviation from the mean : 0.16 per cent.

The dry substance enclosed in each ampoule (0.429 gm.) represents, according to our measurements, 1,600 P. units; in other words, 1 P. unit = 0.2681 mgrm.

The contents of two ampoules are dissolved in sterile physiological saline, and glycerin is added until it represents 66 per cent of the solution, which is thereby brought up to a total volume of 160 c.c.

1 c.c. of this solution = 20 P. units.

THE PREPARATION OF THE *Œdematiens* TEST TOXIN.

The culture medium used is the "meat medium" with liquid paraffin. Ordinary veal broth is taken, and 1.5 per cent Riedel peptone and 0.5 per cent sodium chloride are added. After inoculation with a fresh culture from a toxic strain of *B. Œdematiens*, the culture is kept in the thermostat at 37° C. for five to six days. Following the removal from the thermostat, each flask (about 1 litre of medium) is examined bacteriologically, and the toxicity of the unfiltered culture is determined by means of intramuscular injections in mice. Any flasks which show an impure culture or prove atoxic or subtoxic should be eliminated. The contents of the remainder are mixed and filtered through a Seitz filter. The filtrate is precipitated as soon as possible by saturation with ammonium sulphate (about 750 grammes to 1 litre toxin). There is evidence to show that the toxin is often considerably weakened by this process and that this is probably due to the combined action of the ammonium sulphate and the oxygen in the air. It can be entirely avoided, however, if the precipitation is carried out in an atmosphere of nitrogen. The toxin thus precipitated is collected in porcelain dishes, subjected to moderate pressure for five to ten minutes, and thereupon placed into large vacuum-desiccators containing calcium chloride. At the end of about two days, the toxin is removed from the desiccators, ground in a mortar and then passed through a fine sieve. After this powder has been mixed as thoroughly as possible, it is distributed into ampoules containing 2 grm. each, and the toxin is then dried *in vacuo*, over phosphorus pentoxide, until constancy of weight is reached (from one to one and a-half months). The ampoules are filled with dried nitrogen and sealed.

DETERMINATION OF THE "TEST DOSE" OF THE TOXIN
BY MEANS OF INTRAMUSCULAR INJECTIONS IN MICE.

The "test dose" of the toxin is defined as the quantity which, mixed with 0.02 P. unit, kills some, but not all (about half), of the mice into which it was injected.

In order to determine the "test dose", the following solutions are prepared :

- (a) Of the standard antitoxin solution, 1 c.c. is diluted to 100 c.c., so that 1 c.c. of the solution contains 0.2 P. unit ;

(b) A suitable quantity of the dry test toxin is weighed accurately in a dry weighing-glass and diluted in physiological saline until 1 c.c. of the solution contains 50 mgrm. toxin.

One gramme toxin 1.34 displaces 0.64 c.c. water.

It is recommended to keep the opened ampoule in a small desiccator containing CaCl_2 *in vacuo*.

The mixtures of standard antitoxin solution and toxin solution are prepared in such a manner that 0.2 c.c. (the quantity to be injected in mice) contains 0.1 c.c. of the antitoxin solution (= 0.02 P. unit) + varying quantities of the toxin solution.

These mixtures are kept at the ordinary room temperature for one hour, after which they are injected intramuscularly in mice (0.2 c.c.). The animals are under observation for three days after the injection.

The following table illustrates how the "test dose" of *ædematiens* test toxin 1.34 was determined :

| P. unit | Toxin 1.34 mgrm. | Proportion of mice surviving |
|---------|---------------------|---------------------------------|
| 0.02 | 4.2 | 0/7 |
| 0.02 | 3.9 | 3/7 |
| 0.02 | 3.6 | 7/7 |

The various experiments carried out point to the conclusion that the "test dose" of toxin 1.34 (*i.e.*, the dose which, mixed with 0.02 provisional antitoxin unit and injected intramuscularly in a batch of mice, kills some, but not all, of them) is about 3.9 mgrm.

The minimum lethal dose of the toxin is about 0.14 mgrm. The "test dose" contains therefore about twenty-eight lethal doses of the toxin.

With this "test dose" of the toxin we made several titrations of various solutions of the standard antitoxin, and it was always found that the results agreed satisfactorily (example in the following table).

| P. unit | Toxin 1.34 mgrm. | Proportion of mice surviving |
|---------|---------------------|---------------------------------|
| 0.022 | 3.9 | 7/7 |
| 0.02 | 3.9 | 3/7 |
| 0.018 | 3.9 | 0/7 |

The laboratories of the various countries are requested to verify the above neutralisation ratio as between the provisional standard for gas gangrene antitoxin (*œdematiens*) and the toxin preparation 1.34 ; as well as to determine the antitoxin titre (expressed in P. units) of the sample of gas gangrene antitoxin (*œdematiens*) accompanying the present report.

It will be particularly interesting to test not only against toxin 1.34, but also against one or several other test toxins.

The sample referred to above is marked "Gas gangrene antitoxin (*œdematiens*) of unknown strength". In order, however, to economise both time and animals, we have indicated that, according to our own observations, the value is between 300 and 400 P. units per c.c.

Addendum.

The serum of unknown potency has been assayed in six different laboratories with the following results:

| | Toxin used | Number of units per c.c. | Method |
|---|--------------|--------------------------|---------------------------------|
| National Institute for Medical Research, London | I 34 | 324 | Intramuscularly in mice |
| | No. 5 | 323 | |
| | I 34 | 320 | Intracutaneously in guinea-pigs |
| | I 34 | 308 | |
| | No. 5 | 304 | |
| Lister Institute, Elstree. | No. 5 | 320 | Intramuscularly in mice |
| | | 300-325 | |
| National Institute of Health, Washington.. | | 320-350 | |
| Wellcome Physiological Research Laboratories, Beckenham | I 34 | 320 | |
| | NN 30 T | 320 | |
| Reichsgesundheitsamt, Berlin | I 34 | 325-330 | |
| | German toxin | 325-330 | |
| Statens Serum Institut, Copenhagen | | 330 | |

3. A PROPOSED INTERNATIONAL STANDARD FOR ANTIPNEUMOCOCCUS SERUM (TYPE I)

By

PERCIVAL HARTLEY and WILSON SMITH

(from the National Institute for Medical Research, Hampstead, London).

The provision of dry stable standards, and the definition of units in terms thereof, for Antipneumococcus Serum Type I and Type II became a matter of urgent practical importance in Great Britain some years ago.

In the opinion of British workers, the proper use of antipneumococcus sera in the treatment of pneumonia, the study of the methods of preparation and purification of specific antisera and, most especially, the elucidation of the problems associated with the standardisation of antipneumococcus sera depend, to a considerable extent, for their further progress and orderly advance upon the establishment of dry stable standards of reference and their adoption, by common agreement, by all investigators in this field. In the absence of such standards of reference, the results of clinical and laboratory studies obtained in different countries, by the use of products either unstandardised or standardised by reference to different standards and units, cannot be compared and lose much of their value.

An event of outstanding importance in the study of the standardisation of antipneumococcus sera was the provision in 1930, by Dr. D. Lloyd FELTON, of the Harvard University Medical School, of a bivalent antipneumococcus serum, F.146, for use as a standard serum in the assay of Antipneumococcus Sera Type I and Type II, and workers in this field throughout the world are indebted to Dr. Felton for making this serum available for the purposes of their work. In Great Britain, in particular, the value and importance of

the antiserum F.146 was immediately recognised, as it provided a means whereby the clinical and laboratory investigations then being intensively pursued in America and Great Britain could be evaluated and compared.

Investigators in Great Britain took the view, however, that, since the serum F.146 was a liquid and therefore could not be expected to retain its potency indefinitely, and, further, since the total supply available for distribution was not large (actually, the stocks of F.146 are now exhausted), steps should be taken to give greater permanence and stability to the standards and units proposed by Felton for these antibodies and, as far as practicable and desirable, ensure the continuity of present practice in their standardisation and assay. To this end, dry stable standard preparations of Antipneumococcus Serum Type I and Type II have been prepared (each standard being prepared from a monovalent serum of high potency) at the National Institute for Medical Research, London, and each standard has been assayed, as accurately as the methods at present available allow, in terms of the Type I and Type II components respectively of the liquid serum F.146. It has been established by these comparative tests that 0.0886 mgrm. of the dry stable standard preparation of Antipneumococcus Serum Type I and 0.0894 mgrm. of the dry stable standard preparation of Antipneumococcus Serum Type II are equivalent, respectively, to the units for the Type I and Type II antibodies proposed by Dr. Felton.

It is emphasised that, while the main purpose of our work has been to provide stable standard preparations for the use of all investigators in this field, it is not proposed that units of activity different from those proposed by Felton should be adopted. In the United States of America, Canada and Great Britain—countries in which antipneumococcus sera have been widely used clinically, and in which problems relating to the production, purification and assay of these antisera have been widely studied—physicians and laboratory workers have become accustomed to the system of unitage introduced by Felton and it is considered desirable that as little change as possible, in regard to the dimensions of the units of activity, should be introduced. It is considered that the adoption of stable standards, assayed in terms of the units proposed by Felton, is a necessary and progressive development towards greater uniformity of procedure ; moreover, a situation which was uncertain because

of the fluid nature and limited amounts available of the serum F.146 is thereby rendered more stable and, where continuity of present practice is considered desirable, such continuity is ensured.

The National Institute for Medical Research, London, in preparing these stable standards, has had in view, not only the immediate and future needs of Great Britain, but the possible adoption by the Permanent Commission on Biological Standardisation of the dry stable standards either as international standards or as the basis of such standards as the Commission may recommend for adoption.

The dry stable standards for Antipneumococcus Serum Type I and Type II are placed, therefore, by the National Institute for Medical Research, London, at the disposal of the Permanent Commission on Biological Standardisation of the Health Organisation of the League of Nations, and it is suggested that they be accepted for adoption as the international standards for these antibodies. It is further suggested that the units proposed for Antipneumococcus Serum Type I (0.0886 mgrm. of the standard preparation) and for Antipneumococcus Serum Type II (0.0894 mgrm. of the standard preparation) be adopted for international use.

The quantities of each of the standard preparations available for distribution (about 200 ampoules of the Type I standard and about 160 ampoules of the Type II standard) are adequate to meet the needs of world requirements for many years.

THE PERMANENT COMMISSION ON BIOLOGICAL STANDARDISATION AND THE STANDARDISATION OF ANTIPNEUMOCOCCUS SERA.

The question of the standardisation of antipneumococcus serum was discussed at the first International Serological Conference, held in London in 1921. At this Conference the view was expressed that tests for the agglutinative power of antipneumococcus serum were of no value as an indication of its therapeutic efficiency, and that the best method of titrating the serum is the measurement of the bactericidal power in animals, preferably mice. It was arranged that the methods of standardisation should be further investigated.

The results of these investigations were communicated at the second International Serological Conference, held in Paris in 1922, reports having special reference to standardisation being received from COTONI (Paris), NEUFELD (Berlin) and WADSWORTH (Albany, U.S.A.). An important resolution was passed to the effect that, without expressing an opinion in regard to the therapeutic value of the serum in the treatment of pneumonia, it was considered that the titration test in the mouse, when controlled by a standard serum, provides a basis for the standardisation of the serum. It was emphasised that for every titration a standard serum must be used.

The different methods by which the mouse protection test may be applied were discussed, and it may be said generally that, in many of the investigations on the standardisation of antipneumococcus serum which have been reported since 1922, the principles outlined at that time have formed the basis of much of this later work. It is of interest to record that the important fact of the variability in the reaction of the mouse, and the consequent need for the use of large numbers of animals in the test, was recognised by investigators in 1922, and has been fully confirmed in more recent work. Further, the hope expressed in 1922 that an *in vitro* method of testing which would eliminate the variable factor of individual resistance, and incidentally reduce the cost of standardisation, would be discovered has been realised to the extent that such methods have been described [FRIEDLANDER, SOBOTKA and BANZHAF (1928) ; ZOZAYA, BOYER and CLARK (1930) ; HEIDELBERGER, SIA and KENDAL (1930) ; FELTON (1931) ; WILSON SMITH (1932) ; BROWN (1933)] and their value for the assay of antipneumococcus serum, in comparison with methods based on mouse protection tests, investigated.

The Permanent Standards Commission, at its meeting in Geneva in 1926, stated that the problem of the standardisation of antipneumococcus serum has not yet reached a stage which permits the adoption of recommendations from the international point of view.

The Permanent Commission on Biological Standardisation, at its meeting in London in 1931, stated that at present the Commission could take no effective action towards improving the standardisation of antipneumococcus serum.

One of us (P. H.) discussed the question of providing dry stable standards for the pneumococcus antibodies with Dr. McCoy in 1930. It was suggested that the National Institute of Health, Washington, should prepare a dry stable standard preparation for Antipneumococcus Serum Type I, and define a unit in terms of it. It was also suggested that Great Britain should also prepare a dry stable preparation and assay it in terms of the unit proposed by Washington. The object of the proposed procedure was to replace the fluid serum F.146 by stable preparations and to fix the value of the unit ; stability and uniformity would thus be introduced and more effective co-operation secured between the investigators of at least two countries particularly interested in these questions at that time. In view of the interest shown and the work done in problems relating to pneumonia in the United States of America since the war, it was considered in Great Britain that it was proper, and in accordance with the general policy of the Permanent Commission on Biological Standardisation, that the United States should provide dry stable standard preparations for the pneumococcus antibodies, and define units in terms of these, with a view to their adoption, ultimately, by the Permanent Commission on Biological Standardisation for international use. Dr. McCoy, for various reasons, was unable to proceed with the work on the lines discussed ; he was, however, sympathetic towards the alternative scheme whereby dry stable standards should be prepared in Great Britain.

THE NEED FOR STABLE STANDARD PREPARATIONS FOR THE ASSAY OF ANTIPNEUMOCOCCUS SERA.

Since 1922, when the standardisation of antipneumococcus serum was last discussed by the Commission, the pneumococcus group has probably been the subject of more numerous and more varied investigations than any other group of visible micro-organisms. In addition to the striking advance in our knowledge of the bacteriology of the group, marked progress in the preparation and large-scale production of antipneumococcus serum, and in the methods for the purification and concentration of the specific antibodies, has been made. The necessity for methods by which the specific antibodies could be estimated became increasingly evident to

laboratory workers and manufacturers, and the need was emphasised when antipneumococcus sera began to be used clinically for the treatment of pneumonia. Following the encouraging clinical results reported from America, the preparation of antipneumococcus serum and its use clinically were stimulated in other countries. In Great Britain, for example, two extensive clinical trials have been carried out on behalf of the Medical Research Council and the British Red Cross Society respectively. At the present time, very diverse views are held regarding the therapeutic value of the antipneumococcus serum preparations at present available for the treatment of pneumonia, and it would appear that a final judgment will not be possible until further information, gained from carefully controlled clinical investigations, is available.

As mentioned above, the Permanent Standards Commission in 1922 emphasised the importance of including a standard in the assay of antipneumococcus serum. In 1909, NEUFELD, in reporting on the methods of standardisation, also stressed the importance of a standard serum. In the United States of America, a standard serum has been employed in New York State since 1918 and, shortly afterwards, a standard serum was made available by the Hygienic Laboratory (now the National Institute of Health, Washington) for Federal use. These standards were used in order to set a minimum standard of potency for sera intended for therapeutic use. They were liquid sera, renewed from time to time, and at each renewal a serum with a slightly higher potency was chosen as the standard. There is no doubt that these standard sera serve a useful purpose. It is not claimed that, by their use, a quantitative determination of antibody is effected; they do ensure, however, that sera intended for clinical use exhibit, in comparative tests, protective properties not less than those of the standard, or control, serum.

FELTON, while recognising the practical usefulness of such standard or control sera, pointed out their limitations in so far as they fail to measure the actual amount of antibody in a preparation. For the purpose of his work, it was necessary to measure, with a greater precision than had hitherto been attempted, the antibody content of sera and other solutions. He therefore defined as the unit of protective antibody "that dilution of the antibody, or serum, which will protect against a million minimum lethal doses of virulent

pneumococci". PARK and COOPER (1928), in a paper dealing with the administration and dosage of antipneumococcus serum, stress the urgent necessity for using standardised preparations and remark that, "before one can speak intelligently of dosage, a unit of antibody must be agreed upon"; their definition of a unit is practically identical with the one put forward by Felton. In a later paper (1930; *Journal of Immunology*, Vol. 19, page 485) dealing with standardisation, Felton states:

"The important issue is the judicious use of a control serum and a well-standardised culture. Results, consistent with the many variables, can be obtained if lethal doses of organisms not greater than 5 millions nor less than 0.1 million are employed. . . . The problem of a standard serum has been met temporarily by the distribution of serum F.146 to many different laboratories. This is a polyvalent Type I and Type II serum containing about the same number of protective units against both types of organism. We are setting this serum value at 500 units of protection against both Type I and Type II cultures. It is comparatively simple to test another sample of fresh serum with this one, so that a permanent standard of this, or approximately this, value can be maintained. . . ."

It is considered that, in emphasising the importance of a standard serum and defining a unit in terms of it, Felton proceeded on sound and well-established principles. Further, since it is customary, and legitimate, to fix the size of a unit, *in the first instance*, in some such arbitrary way as by defining the quantity of the standard preparation which will neutralise the specific biological activity of an arbitrarily chosen quantity of antigen, no objection, on principle, can be taken to the unit originally defined by Felton—viz., as the protective activity contained in $\frac{1}{500}$ c.c. of his standard serum F.146. But, once this arbitrarily chosen unit has been decided upon and defined, it is in the highest degree essential that it should be adhered to. The size of the unit proposed, in terms of the chosen standard serum F.146, has, however, been changed more than once, with the result that bewilderment and confusion have been introduced into this field of biological assay, resulting in a situation which was becoming progressively more difficult and

involved. British workers were unanimous and emphatic in their view, first, that *stable* standards must be provided and, second, that the unit must also be *fixed* and *stable*, and defined, as in the case of other units, as the specific biological activity contained in a definite weight of the respective standard preparations. From the beginning it has been the desire and object of British investigators to work in the closest possible co-operation with American investigators ; but it is quite impossible to secure either co-operation or reasonable and intelligent discussion in problems relating to biological standardisation when the very basis of such work—the unit—is constantly changing in size. It was therefore necessary to be certain that one value, and one only, should be ascribed to the dimensions of the units for the Type I and Type II pneumococcus antibodies and that this value, once decided upon, should be adhered to. It was ascertained, by correspondence, that, by arrangement with the American manufacturers, $\frac{1}{200}$ c.c. of serum F.145 is to be taken as the unit for the Type I, and $\frac{1}{200}$ c.c. of serum F.146 is to be taken as the unit for the Type II pneumococcus antibodies. The same values for the units for the Type I and Type II antibodies are given in the *Journal of the American Medical Association*, December 16th, 1933, page 1968, where it is stated :

“ While the unit originally was intended to be the amount of antibody that will protect against one million fatal doses of culture, it has lately been taken to be $\frac{1}{200}$ c.c. of the control serum (F.146) distributed by Dr. Felton.”

As this statement is published by the Council on Pharmacy and Chemistry of the American Medical Association, it is assumed that a final decision has now been reached in America as to the units for Antipneumococcus Serum Type I and Type II.

We understand that the supply of serum F.146 is now exhausted, but, as we have explained above, each of the dry standards we have prepared has been assayed in terms of the serum F.146, and the value of the unit, both for the Type I and Type II antibody as adopted in the United States of America, can now be expressed in terms of the respective dry stable standard preparations.

THE ASSAY OF THE DRY STABLE STANDARDS
FOR ANTIPNEUMOCOCCUS SERUM TYPE I AND TYPE II,
IN TERMS OF THE LIQUID SERUM F.146.

Since the serum F.146 had been extensively used as a standard in the assay of Antipneumococcus Sera Type I and Type II, it was clearly of importance that the dry stable standards for the Type I and Type II antibodies prepared at Hampstead should be assayed as exactly as possible in terms of the serum F.146. Before the results of the comparative tests are given, attention is drawn to two factors which have to be taken into account in assessing the results of these tests :

1. The amount of the serum F.146 available in Great Britain for the comparative tests was small. The quantities held in three British laboratories were pooled and samples of the pool were used in the comparative tests carried out in England, and a sample of the pool was also sent to Dr. Felton, who used it in a comparative test with the Type I standard. The dry standard was sent to six other laboratories with a request that its potency should be determined *in comparison with the actual sample of F.146 held in those laboratories*. Three laboratories held small stocks of F.146 and were able to carry out comparative tests of the dry standard and their laboratory specimens of F.146. Another laboratory carried out comparative tests of the dry standard and of another Antipneumococcus Serum Type I which, in other tests, had been shown to be identical in potency with F.146. No reports have been received from the remaining two laboratories. Now the serum F.146 was made available for standardisation purposes in 1930. It is unfortunate that all the comparative tests could not be conducted with the same sample of F.146, since we have no knowledge of the conditions under which the different samples of the preparation were stored in the various laboratories, and it is possible that the variation in the results may be due, in part, to the fact that the decline in potency of F.146 has been greater in some laboratories than in others. It is extremely difficult, if not impossible, to determine whether an antiserum has declined in potency, and, if so, to what extent, in the absence of a dry stable preparation with

which the sample can be compared. MORGAN and PETRIE (1933) have, however, carried out one series of observations in which the serum F.146 was titrated, on several occasions between March and November 1933, against the dry standard for the Type I antibody, and these tests showed that the serum F.146 had certainly declined in potency, to the extent of about 30 per cent, during this period. We were informed in June 1932 by Dr. Felton that, "in his experience and that of two commercial houses, F.146 has deteriorated in the neighbourhood of 50 per cent from its original value".

2. The methods of assay of antipneumococcus serum are not very precise. TREVAN (1930), whose paper should be consulted for details, in a statistical analysis of data obtained by PARISH (1930), showed that, even when large numbers of mice—20 or 40 per serum dose—are used, the error of the test is considerable; *e.g.*, even if 40 mice are used in each group, one serum may be estimated as equal in potency to another when the latter really has a potency as low as 70 per cent or as high as 140 per cent of the former. MORGAN and PETRIE (1933) have shown that, using 40 mice per serum group, differences in doses of serum of 25 per cent, or even 12.5 per cent, can be detected. In the comparative tests carried out in England, on the serum F.146 and the dry standard for Antipneumococcus Serum Type I, 40 mice, or more, per serum dose were used; in the reports received from the other laboratories, the number of mice used is either not stated or is less than the numbers used in England. The error of the test is, of course, increased when the number of mice used per serum dose is reduced.

THE RESULTS OF THE COMPARATIVE TESTS OF THE SERUM F.146 AND THE DRY STANDARD FOR ANTIPNEUMOCOCCUS SERUM TYPE I.

Samples of the dry standard Antipneumococcus Serum Type I have been sent to a number of laboratories. Investigators were instructed to add 5 c.c. of distilled water to the ampoule and asked to compare the potency of the solution so obtained with that of the serum F.146. The investigators in three English laboratories, as well as Dr. FELTON, were supplied with a small quantity of the pooled F.146, prepared from the stocks of this preparation available in England, for the purposes of their comparative tests. Workers

in other laboratories were asked to compare the potency of the reconstructed dry standard with their own laboratory specimen of F.146.

The results of these comparative tests are summarised below.

1. *Results obtained at the Lister Institute, Elstree.*

Methods : Prophylactic tests in mice and curative tests in mice.

Number of mice per serum dose : 20 to 40.

Result : Prophylactic tests—reconstructed standard = $5 \times$ F.146 ;
curative tests—reconstructed standard = $5 \times$ F.146.

2. *Results obtained at the National Institute for Medical Research, London.*

Methods : Precipitation tests and mouse protection tests.

Number of mice per serum dose : 40.

Result : Precipitation tests—reconstructed standard = $5 \times$ F.146 ;
mouse protection tests—reconstructed standard = $3.5 \times$ F.146 (*a*),
 $4.25 \times$ F.146 (*b*). [(*a*) and (*b*) are separate determinations.]

3. *Results obtained at the Wellcome Physiological Research Laboratories, Beckenham.*

Method : Protection test in mice.

Number of mice per serum dose : 40.

Result : Reconstructed standard = $3.2 \times$ F.146 (six-day) (*a*) ;
reconstructed standard = $4.5 \times$ F.146 (two-day) (*b*). [(*a*) and (*b*)
are the mean values from two experiments and based on “ six-day ”
and “ two-day ” observations respectively.]

4. *Results obtained at the Lederle Laboratories, Pearl River, New York, U.S.A.*

Method : Mouse protection tests.

Number of mice per serum dose : 20.

Result : Reconstructed standard = $3.5 \times$ F.146.

5. *Results obtained at the Parke Davis Laboratories, Detroit, U.S.A.*

Method : Not stated.

Number of mice per serum dose : Not stated.

Result : Reconstructed standard = $10 \times$ F.146.

6. *Results obtained at the Connaught Laboratories, Toronto, Canada.*

Method : Mouse protection tests.

Number of mice per serum dose : Not stated.

Result :

“Our findings showed the . . . standard when reconstructed to be equal to $5 \times$ the F.146 which we have had on hand.”

7. *Results obtained at the Division of Laboratories and Research, Department of Health, New York State, Albany, U.S.A.*

No details received, but Dr. Kirkbride writes as follows :

“The dried sample, when reconstructed according to your directions, appeared to be approximately five times as potent as our serum No. 495, which previous tests had shown to correspond with the Felton standard serum F.146. Our results therefore correspond quite closely to yours.”

8. *Results obtained by Dr. Felton, Harvard University Medical School, Boston, U.S.A.*

Method : Mouse protection tests.

Number of mice per serum dose : 10.

Result :

“I have run your dried material against the sample of F.146 you returned and a fresh sample (of F.146) that I had in the ice-box. . . . The results, as judged from the protocol, would indicate that F.146 had deteriorated little if at all, and that the dried material is at least four times more potent than F.146. Of course you understand that this is a preliminary titration and cannot be taken as absolute value, especially when only ten mice were used in a dilution.”

In view of the acknowledged limitations of the mouse protection tests, and since the investigators in different laboratories used varying numbers of animals in their tests, and especially in view of the fact that the dry standard was compared with different samples of the serum F.146, which has been in currency since 1930, it is considered that the results of these comparative tests show as good an agree-

ment as can reasonably be expected. Three laboratories returned the potency of the reconstructed standard as being 5 times the potency of F.146, and one laboratory obtained this value by an *in vitro* test ; four laboratories returned the potency of the reconstructed standard as 3.2 to 4.5 times the potency of F.146. One laboratory assigned a higher potency to the reconstructed dry standard in comparison with F.146 ; in the absence of details as to the method by which the test was applied, it is not possible to say whether the error to be expected in this test was unduly large, or whether, as is possible, the potency of the sample of F.146 used was actually lower than that of the samples of F.146 used by other investigators.

In all, twelve estimates of the value of the reconstructed dry standard, in terms of five different samples of the serum F.146 (and one serum of equal potency to F.146), have been returned from eight laboratories. The average value of the twelve estimates is *reconstructed dry standard* = $5 \times F.146$. If the high figure of $10 \times F.146$ received from one laboratory is excluded, the average of the remaining eleven estimates (one at 3.2, two at 3.5, one at greater than 4, one at 4.25, one at 4.5, five at 5) is *reconstructed dry standard* = $4.4 \times F.146$.

In arriving at the value of the unit in terms of the dry standard for antipneumococcus serum, we have taken the value of the reconstructed dry standard as being five times the potency of the serum F.146. Since F.146 is held to contain 200 units per c.c., each ampoule contains 5,000 units of Type I antibody ; and, since each ampoule contains 0.4429 grm. of dry standard, 1 unit is contained in 0.0886 mgrm. of the dry standard preparation. It is proposed that this value for the unit of Antipneumococcus Serum Type I be adopted for international use.

TESTS IN WHICH A GLYCEROL SOLUTION OF THE STANDARD WAS USED.

In order to economise the standard preparation for Antipneumococcus Serum Type I, and at the same time produce it for use in a convenient yet stable form, a solution of the standard in 66 per cent glycerol saline was prepared. Twenty-five c.c. of the glycerol

saline were used for the dissolving of the contents of one ampoule, so that the strength of this glycerol solution should be one-fifth that of the solution obtained by dissolving the contents of one ampoule in 5 c.c. distilled water. Laboratories were supplied with the glycerol solution of the standard and asked to verify the relationship.

The following is a brief summary of the results of these comparative tests :

1. *Results obtained at the Lister Institute, Elstree.*

Method : Prophylactic test in mice.

Number of mice per serum dose : 100.

Result : The reconstructed standard (in 5 c.c. distilled water) possesses five times the protective value of the glycerol solution.

2. *Results obtained from the National Institute for Medical Research, London.*

Method : Precipitation tests and mouse protection tests.

Number of mice per serum dose : 40.

Result :

“The glycerol solution of antibody had exactly one-fifth the protective power of the standard serum (reconstructed by the addition of 5 c.c. distilled water), so that the presence of 66 per cent glycerol could have had no deleterious action upon the protective antibodies measurable by the mouse test.

“The results of the precipitation tests were also in complete agreement with the known volumetric ratio of the two preparations, the antigen-antibody ratio of the reconstructed standard serum being just five times greater than that of the glycerol solution.”

3. *Results obtained at the Wellcome Physiological Research Laboratories, Beckenham.*

Method : Mouse protection tests.

Number of mice per serum dose : 25.

Result :

“The potency ratio of the reconstructed serum to the glycerol solution is identical with the dilution ratio (six-day

observation), but if two-day results are taken the potency ratio is 4.2 : 1."

4. *Results obtained at the Lederle Laboratories, Pearl River, New York, U.S.A.*

Method : Mouse protection tests.

Number of mice per serum dose : 20.

(*Note.*—In this laboratory the glycerol solution of the dry standard was compared with the laboratory sample of F.146.)

Result : In one series of tests the "glycerinated standard was somewhat lower than our sample of F.146". In another series of tests, "the two standards more nearly matched". A third series of tests, in which a glycerol solution of the standard made according to instructions supplied, and in an exactly similar way to the solution previously supplied, was used, "showed this freshly prepared glycerinated solution to be practically identical with our sample of F.146".

5. *Results obtained at the Parke Davis Laboratories, Detroit, U.S.A.*

Method : Not stated.

Number of mice per serum dose : Not stated.

(*Note.*—In this laboratory the glycerol solution of the dry standard was compared with the laboratory sample of the serum F.146.)

Result : F.146 = 200 units per c.c. ; Glycerol solution of dry standard = 300 units per c.c.

6. *Results obtained at the Division of Laboratories and Research, Department of Health, New York State, Albany, U.S.A.*

No details received, but Dr. Kirkbride writes :

"The results were less uniform with the glycerolated serum, but we should not wish to draw any conclusions without making further tests on it. . . ."

The results of these comparative tests exhibit several features of interest. The glycerol solution of the standard was prepared and

distributed in order to see whether, in the event of the dry standard being accepted for international use, an economy might be effected by supplying it in the familiar form of a standard solution in glycerol. The results show clearly that the glycerol interferes in no way with the performance either of the animal or the precipitation tests. Further, the comparative testing of the glycerol solution of the standard with the dry standard reconstructed by the addition of distilled water provided an opportunity for further applications of the mouse protection and precipitation tests ; in the tests conducted in the three English laboratories, the potency relationship between the two solutions was known and in all three laboratories this relationship was exactly confirmed both by animal and precipitation tests. In two American laboratories, the glycerol solution was compared with the laboratory sample of the serum F.146. According to determinations made in England, these two solutions should have approximately the same potency and, within the limit of accuracy with which the test can be applied, this was found to be the case in one of the laboratories. In the other laboratory, a higher value was assigned to the glycerol solution of the standard, in comparison with this laboratory's sample of the serum F.146, and it is interesting to note that this was the laboratory which also returned the unusually high figure for the value of the reconstructed standard in terms of its own sample of F.146.

It is considered that, in the event of the dry standard preparation for Antipneumococcus Serum Type I being accepted for international use, its issue in the form of a standard solution in glycerol saline presents no difficulty and would serve to economise the standard preparation.

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4. A PROPOSED INTERNATIONAL STANDARD FOR ANTIPNEUMOCOCCUS SERUM (TYPE II)

By

PERCIVAL HARTLEY and WILSON SMITH.

(From the National Institute for Medical Research, Hampstead, London.)

The circumstances and considerations which led to the preparation, at the National Institute for Medical Research, London, of a dry stable standard for Antipneumococcus Serum Type I have been described in the previous paper presented for the consideration of the Commission, and, *mutatis mutandis*, the position in regard to Antipneumococcus Serum Type II is substantially the same. Little further need therefore be added.

The preparation of the dry stable standard for Antipneumococcus Serum Type II, the study of its properties and its comparative assay in terms of a sample of the serum F.146 (kindly furnished for this purpose by Dr. FELTON) have been carried out by Wilson SMITH, Werner FISCHER and M. LLEWELLYN SMITH, and the results of their work are described in a paper entitled "A Provisional Stable Standard for Antipneumococcus Serum Type II and its Practical Application" (*Lancet*, 1934, ii, 155).

As in the case of the standard prepared for Antipneumococcus Serum Type I, the assay of the standard for the Type II antibody in terms of the Type II component of the serum F.146 has been regarded as a matter of first importance, and it is considered that the value of the unit for Antipneumococcus Serum Type II (now accepted in the United States of America as being the quantity of Type II antibody contained in $\frac{1}{200}$ c.c. of the serum F.146) has been determined, in terms of the dry stable standard prepared in this institute, as accurately as the methods at present available allow.

For some reasons it was not possible, and for other reasons it appeared unnecessary, to distribute the dry stable standard for the Type II antibody and the serum F.146 to a number of different laboratories for comparative testing. As explained elsewhere, the supplies of the serum F.146 are now exhausted, and we ourselves were obliged to make still another appeal to Dr. Felton for a further quantity of his serum on July 27th, 1933. Dr. Felton very kindly sent us two ampoules of the serum F.146 from the very limited supply remaining in September 1933. Dr. Felton informed us that the sample had not been tested for approximately one year, and he was unable to state whether the sample had deteriorated in potency. Further, preliminary work had suggested that the assay of the Type II antibody is less precise than that of the Type I antibody, larger numbers of mice per serum dose and a wider range of serum doses being necessary to obtain the same degree of accuracy—factors which add greatly to the cost of standardisation. In all the circumstances, therefore, it was decided to assay the dry standard for Antipneumococcus Serum Type II in this institute as accurately as possible in terms of the Type II component of the actual sample of the serum F.146 available.

Four comparative tests were carried out, 20 to 40 mice per serum dose being used for each serum in each test. The results of these tests are given in the paper referred to above, and, taken together with the values obtained by the application of the precipitation test (SMITH, 1932), they show that the potency of the solution obtained when the contents of one ampoule of the dry standard are dissolved in 5 c.c. of distilled water is five times the potency of the serum F.146, and we consider that the potency relationship has been established with as great an accuracy as is possible under present conditions of testing.

According to these determinations, 0.0894 mgrm. of the dry stable standard preparation of Antipneumococcus Serum Type II is equivalent to the unit for the Type II antibody—*i.e.*, equivalent to the quantity of Type II antibody contained in $\frac{1}{200}$ c.c. of the serum F.146.

The dry stable standard for Antipneumococcus Serum Type II is placed, therefore, at the disposal of the Permanent Commission on Biological Standardisation, and it is suggested that it be accepted for adoption as the international standard preparation. It is

further suggested that the unit proposed—viz., 0.0894 mgrm. of the standard preparation—be adopted for international use.

About 160 ampoules of the dry standard preparation are available and, since experiments have shown that a standard solution in glycerol may be prepared which would prove satisfactory for use in comparative tests, the quantity of the standard preparation is adequate to meet the needs of world requirements for many years.

5. A PROPOSED INTERNATIONAL STANDARD FOR STAPHYLOCOCCUS ANTITOXIN

By

PERCIVAL HARTLEY and MARGARET LLEWELLYN SMITH

(from the National Institute for Medical Research, Hampstead, London).

INTRODUCTION.

The study of the properties of filtrates obtained from the growth of certain strains of staphylococci began towards the close of last century. Prior to 1928, however, few attempts were made to assay the potency of either staphylococcus toxin or antitoxin ; accordingly, no review of the somewhat extensive earlier literature will be given here.

In 1928, the death of twelve children at Bundaberg, Australia, following the injection of diphtheria toxin-antitoxin mixture contaminated by a pyogenic staphylococcus, aroused a new interest and gave a new direction to the investigation of the many and varied problems raised. In particular, the methods of preparation of staphylococcus toxin and the study of its properties, the immunisation of animals and the study of the specific antitoxin, the conversion of toxin to toxoid, and the use of staphylococcus antitoxin and toxoid in the treatment of staphylococcus infections have been the subject of many investigations since 1928. Observations have also been made regarding the antitoxin content of the serum of human beings suffering from, undergoing treatment for, or recovered from staphylococcus infections. (The references to recent

publications dealing with these different aspects of the subject are given on pages 109 and 110.)

It was shown by BURNET that the hæmolytic, necrotic and lethal properties of staphylococcus toxin are neutralised in a quantitative and parallel manner by specific antitoxin, and he and later workers have shown that simple and accurate methods of assay, similar in principle to those which have been successfully applied to other antitoxins, are available for the standardisation of staphylococcus toxin and antitoxin.

STANDARDS AND UNITS HITHERTO EMPLOYED OR SUGGESTED.

In the absence of a common standard of reference accepted for international use, the individual laboratory worker must, perforce, adopt a standard for himself, in order that the results of his own work may be compared and correlated. But, since the laboratory standards and units adopted are different, no comparison of the results obtained in different laboratories is at present possible. An example of the consequent confusion which may arise through the adoption of a multiplicity of standards and units is provided by recent publications on staphylococcus toxin and antitoxin. BURNET (1931) adopted a particular staphylococcus antitoxin as a standard, 1 c.c. of which neutralised 8,000 minimum hæmolytic doses of an arbitrarily chosen toxin ; he adopted as his unit the quantity of this serum which neutralised one minimum hæmolytic dose of that toxin—*i.e.*, 1/8000 c.c. PARISH and CLARK (1932) adopted a particular staphylococcus antitoxin as a laboratory standard and expressed the value of other antitoxins in terms of it without employing a unit notation. GROSS (1933) also adopted a definite volume of a particular antitoxin as the unit for staphylococcus antitoxin. Other investigators have attempted the estimation of the potency of staphylococcus antitoxins by determining the quantity of the preparation which will neutralise one hæmolytic, or one skin-necrosing, dose of an arbitrarily chosen laboratory toxin ; since "toxins" contain widely varying quantities of toxoid and the definition and determination of the minimum hæmolytic, or minimum skin-necrosing, dose varies in different laboratories, and since the test

dose of the toxin used contains so little toxin, potency values determined on such a basis lack both accuracy and significance. The adoption of such a method is a return to the conditions which had brought the assay of diphtheria antitoxin into such confusion before Ehrlich's classical investigations on which the present methods for the measurement of that antitoxin are based.

THE NEED FOR A COMMON STANDARD AND UNIT FOR STAPHYLOCOCCUS ANTITOXIN.

Staphylococcus antitoxins of high potency are already being prepared, and it is probable that even more potent preparations will be produced in the near future. There is, as yet, little information as to the clinical value of antitoxin in the treatment of staphylococcus infections ; nevertheless, if the effect of antitoxin treatment is to be correctly evaluated, the maximum of information to be obtained from clinical trials, and the results obtained in different countries to be rendered comparable one with another, it is essential that all antitoxins used clinically should be tested in relation to a common standard and their potency expressed in terms of a common unit. Staphylococcus toxoid, on the other hand, has already been widely used in the treatment of staphylococcus infections and with encouraging results. It has been emphasised that potent antigens should be employed. Practical tests for the immunising value of the preparations used clinically will involve, in all probability, the determination of the combining power of the toxoid (or of the toxin from which it is prepared) and of the degree of immunity produced by the preparation in injected animals ; for the purposes of all such tests, it is clearly of importance that the measurements should be made in terms of the same standard and unit. Further, in the treatment of cases of staphylococcus infection by toxoid, it is customary and desirable to follow the effect of treatment by determinations of the antitoxin content of the patient's serum, and if such determinations, made in different countries, are to be correctly interpreted and compared, the antitoxin content, as in the case of similar clinical studies in diphtheria, must be expressed in terms of a common unit.

THE DRY STABLE PREPARATION OF STAPHYLOCOCCUS ANTITOXIN
PROPOSED FOR INTERNATIONAL ADOPTION.

Since no stable standard for staphylococcus antitoxin, and no unit defined in terms thereof, has yet been adopted for international use, the National Institute for Medical Research, London, has prepared a dry stable standard and has defined a provisional unit in terms of it, with a view to its possible adoption by the Permanent Commission on Biological Standardisation of the Health Organisation of the League of Nations.

The relevant data concerning the preparation, properties and mode of application of the standard, a short description of the methods of assay, and a statement of the factors taken into consideration in arriving at the definition of the provisional unit are set out in a special Memorandum (see Appendix, page 111). This Memorandum, together with samples of the standard preparation and samples of two staphylococcus antitoxins of unstated potency, has been sent to the following experts in the countries named :

Australia :

Dr. F. M. BURNET, The Walter and Eliza Hall Institute of Research in Pathology and Medicine, Melbourne.

Belgium :

Dr. P. NÉLIS, Laboratoire Central de l'Administration de l'Hygiène, Brussels.

Canada :

Dr. C. E. DOLMAN, The Connaught Laboratories, The University, Toronto.

Denmark :

Dr. Th. MADSEN, Statens Serum Institute, Copenhagen.

France :

Professor G. RAMON, Institut Pasteur, Garches, Paris.

Germany :

(1) Geheimrat Professor Dr. W. KOLLE, Staatliches Institut für experimentelle Therapie, Frankfurt.

(2) Dr. H. SCHMIDT, Institut für experimentelle Therapie, "Emil von Behring", Marburg.

Great Britain :

- (1) Dr. R. A. O'BRIEN, The Wellcome Physiological Research Laboratories, Beckenham, Kent.
- (2) Dr. G. F. PETRIE, The Lister Institute, Elstree.

United States of America :

- Dr. G. W. McCoy, The National Institute of Health, Washington.

The following materials were sent to each of the above during the period February 23rd, 1934, to March 21st, 1934 :

- (1) A sample of the dry standard preparation of staphylococcus antitoxin ;
- (2) A glycerol solution of the standard preparation of which 1 c.c. contained twenty provisional units ;
- (3) Samples of two staphylococcus antitoxins of unstated potency, labelled " S " and " T " respectively.

It was suggested that the co-operating experts should determine the test dose of their own staphylococcus toxins by means of the standard supplied, and that the potency of the two staphylococcus antitoxins, S and T, should then be determined and expressed in provisional units.

Reports have been received from seven of the ten experts mentioned above, and are reproduced below. Most of the reports are given in the form in which they were received, but, in a few cases, the data and results have been slightly rearranged in order to secure as great a uniformity of presentation as possible. The phrase " P. unit " is used throughout to indicate the " provisional unit " as defined in the Appendix, page 112.

Before giving the results obtained by the different investigators, it should be explained that the antitoxins of unstated potency, S and T, provided for the international enquiry, were prepared at the National Institute for Medical Research, London, from samples of staphylococcus antitoxins kindly supplied by some of our friends.

Antitoxin S is a pool of three concentrated staphylococcus antitoxins of high potency prepared at the Wellcome Physiological Research Laboratories, Beckenham ; equal volumes of the three antitoxins were mixed and 2.5 volumes of normal horse serum

(containing 0.5 per cent phenol) were added to 1 volume of the mixture of the three antitoxins.

Antitoxin T is a mixture consisting of 20 c.c. of an antitoxin of moderate potency, 20 c.c. of another antitoxin of lower potency and 60 c.c. of normal horse serum (containing 0.5 per cent phenol). These two antitoxins were prepared at the Connaught Laboratories, Toronto.

1. THE RESULTS OBTAINED AT THE NATIONAL INSTITUTE FOR MEDICAL RESEARCH, LONDON.

The "test dose" of a number of staphylococcus toxins, some prepared in this Institute and others sent to us from other laboratories, has been determined. The antitoxins S and T have also been assayed by means of a number of these toxins and by different methods. The purpose of these extensive tests was to provide as much data as possible for the consideration of the Commission and to see whether staphylococcus toxins and antitoxins prepared in different laboratories and different countries exhibited qualitative differences. The results are summarised in the two following tables :

(a) *The "test dose" of a number of staphylococcus toxins.*

| Toxin No. | Source of toxin | Test dose, c.c. | | | | |
|----------------------|---|-----------------|------------|--------|--------------------|-------------------------|
| | | LH | Lr/10 | | I. + | |
| | | Rabbit cells | Guinea-pig | Rabbit | Mouse, intravenous | Mouse, intra-peritoneal |
| | | mgram. | mgram. | | | |
| 1b | National Institute for Medical Research, London | 0.15 | 0.025 | 0.014 | 0.21 | 0.21 |
| 2 | | 0.25 | 0.045 | — | — | — |
| VIII | | 0.20 | 0.033 | 0.020 | 0.25 | 0.25 |
| IV | | 0.25 | 0.04 | — | 0.33 | — |
| 20 | | 0.048 | 0.0083 | 0.005 | 0.07 | — |
| 10d | | 0.4 | 0.076 | — | — | — |
| 4 | Elstree | 0.4 | 0.075 | — | — | — |
| A pooled toxin | Beckenham | 0.16 | 0.028 | — | 0.22 | 0.22 |
| B. 8750 | | 0.12 | 0.02 | — | — | — |
| S. 300 | | 0.10 | 0.018 | — | 0.14 | — |
| 53 | Brussels | 0.2 | 0.04 | — | — | — |
| A dry toxin . | Toronto | 0.72 | 0.12 | — | — | — |

(b) *Determination of the potency of staphylococcus antitoxins, S and T, by means of different test toxins and by different methods.*

| Staphylo- coccus antitoxin | Toxin used in test | P. units per c.c. | | | | |
|----------------------------------|-------------------------------|---------------------|--------------------------|--------|------------------|---------------------------|
| | | Hæmolytic method | Intracutaneous method | | Mouse method | |
| | | | Guinea-pig | Rabbit | Intra- venous | Intra- peri- toneal |
| S ... | 1b | — | 200 | | 200 | 200 |
| | 2 | 200 ; 200 | | | | |
| | VIII | 200 ; 220 | 200 ; 190 | | | |
| | 4 (Elstree) | 200 | 200 | 200 | | |
| | 53 (Brussels) ... | 220 | 200 | | | |
| | Dry (Toronto) .. | 200 | 200 | | | |
| T ... | 1b | — | 120 ; 120 | | 140 | ca.140 |
| | 2 | 150 ; ca. 140 ; 140 | — | | | |
| | VIII | 130-140 ; 130 | 120-130 ; 125 | | | |
| | 4 (Elstree) | 150 | ca. 120 | | | |
| | 53 (Brussels) ... | 140 | 130 | 130 | | |
| | Dry (Toronto) .. | 140 | 140 | | | |
| | B.8750 (Becken- ham) | | ca. 130 | | | |

Summary of Results.

The potency of antitoxin S was determined by means of six different toxins and by five different methods, sixteen separate determinations in all being made. In thirteen of these tests, the value obtained was 200 P. units per c.c. In one test, the value 190, and in two tests, the value 220, was obtained.

The potency of antitoxin T was determined by means of seven different toxins and by five different methods. The arithmetic mean of twenty separate determinations is 133 P. units per c.c., the range for the determinations being between 120 and 150 P. units per c.c.

2. REPORT RECEIVED FROM DR. F. M. BURNET, WALTER AND ELIZA HALL INSTITUTE, MELBOURNE.

The activities of the antisera supplied were tested against a stock toxin made according to the soft agar method previously described

and stored in the cold with a little gentian violet as bacteriostatic agent. This toxin had been prepared about two months previously and when first tested showed a hæmolytic activity corresponding to 2,000 of the units originally used in this laboratory.

A rough test showed that it contained 15 (\pm 2) p. B units per c.c.

In the subsequent experiments, this toxin was diluted 1 : 15 in normal saline and 0.5 c.c. distributed to all tubes. The sera S and T were diluted 1 : 10 in 50 per cent glycerol saline and the standard used either as the glycerinated solution supplied or as a solution of the dry material diluted to 45.9 c.c. with 50 per cent glycerol saline. From these solutions, the amounts shown were delivered to the toxin-containing tubes by the use of a standardised Trevan micro-syringe.

After thorough mixing, the tubes were placed in the 37° C. incubator for twenty minutes and the contents tested by adding two drops (0.05 c.c.) of a 10 per cent suspension of washed rabbit red cells. Readings of the degree of hæmolysis were made at one hour, when the trays were removed from the incubator and after standing in the refrigerator overnight.

In the first experiment, each mixture was injected intradermally (0.1 c.c.) in duplicate rabbits and then red blood cells added to the remainder of the mixture to give an absolute comparison between the rabbit skin-necrotic and hæmolytic effects.

In this experiment, therefore, the contact between toxin and antitoxin was half to three-quarters of an hour longer (at room temperature) than in experiment 2.

The results in experiment 2 indicate clearly that the sera S and T show a less distinct end-point than the standard serum—*i.e.*, they are of lower avidity—and it seems more reasonable to take the 50 per cent hæmolysis level as the end-point than complete absence of hæmolysis. This difference of avidity may perhaps be due to the fact that they passed through the tropics in the liquid state while the standard was in dry condition.

Detailed protocols are appended.

Summary.

The values of the two sera S and T were estimated against a local toxin, in comparison with the provisional British standard serum

by hæmolytic and rabbit skin-necrosis methods. The results obtained were :

| Antitoxin | P. units per c.c. | |
|-----------|-------------------|---------------|
| | Hæmolytic | Skin necrotic |
| S | 196 (5 %) | 200 (10 %) |
| T | 139 (5 %) | 138 (10 %) |

Experiment 1 :

Toxin "Eg." 1 : 15 ; 0.5 c.c. to all tubes.

Standard serum : original glycerol solution.

| Volume of serum | Hæmolysis | | Skin necrosis | |
|-------------------------|-----------|------|---------------|----------|
| | 1 hr. | O.N. | Rabbit A | Rabbit B |
| Standard 20 U : | | | | |
| 0.020 | c- | c | + | ++ |
| 0.0225 | tr. | c- | — | tr. |
| 0.025 | 0 | 0 | — | — |
| 0.0275 | 0 | 0 | — | — |
| 0.03 | 0 | 0 | — | — |
| 0.033 | 0 | 0 | — | — |
| Serum S 1 : 10 : | | | | |
| 0.020 | c- | c | + | ++ |
| 0.0225 | tr. | c- | — | tr. |
| 0.025 | 0 | 0 | — | — |
| 0.0275 | 0 | 0 | — | — |
| 0.03 | 0 | 0 | — | — |
| 0.033 | 0 | 0 | — | — |
| Serum T 1 : 10 : | | | | |
| 0.0275 | c- | c | + | + |
| 0.03 | + | c- | — | — |
| 0.033 | 0 | 5 % | — | — |
| 0.036 | 0 | 0 | — | — |
| 0.04 | 0 | 0 | — | — |
| 0.044 | 0 | 0 | — | — |

++ and + = definite necrotic lesions, tr. = erythema.

Taking as hæmolytic end-point no trace hæmolysis, and as skin end-point no real necrosis :

S = 200 (hæmolytic), 200 (skin) ;

T = 138 (hæmolytic), 150 (skin).

Experiment 2 :

Toxin "Eg" diluted 1 : 15 ; 0.5 c.c. to all tubes.

Standard serum made up from dried material.

| Volume of serum | Hæmolysis | | |
|-------------------------|-----------|------|-------------------------------|
| | 1 hr. | O.N. | |
| Standard 20 U : | | | |
| 0.0212 | 90 | c | LH ₅₀ = 1.025 c.c. |
| 0.0224 | 15 | 90 | |
| 0.0232 | 0 | 50 | LH _{50%} = 1.078 |
| 0.0242 | 0 | tr- | |
| 0.0252 | 0 | 0 | |
| 0.0266 | 0 | 0 | |
| 0.0282 | 0 | 0 | |
| 0.0300 | 0 | 0 | |
| Serum S 1 : 10 : | | | |
| 0.0212 | 90 | c- | Serum titre |
| 0.0224 | 20 | 80 | H ₀ level 183 u |
| 0.0232 | tr- | 65 | |
| 0.0242 | 0 | 40 | H _{50%} level 196 u |
| 0.0252 | 0 | 10 | |
| 0.0266 | 0 | 0 | |
| 0.0282 | 0 | 0 | |
| Serum T 1 : 10 : | | | |
| 0.0282 | c- | c | Serum titre |
| 0.03 | 90 | c- | H ₀ level 129 u |
| 0.0316 | 25 | 95 | |
| 0.0328 | tr- | 70 | H _{50%} level 139 u |
| 0.034 | 0 | 25 | |
| 0.0356 | 0 | 10 | |
| 0.0378 | 0 | 0 | |
| 0.04 | 0 | 0 | |

Percentage hæmolysis shown.

3. REPORT RECEIVED FROM DR. P. NÉLIS (CENTRAL LABORATORY OF THE HEALTH DEPARTMENT, BRUSSELS).

A. *Hæmolytic Method.*

I. *Determination of the Hæmolytic Test Dose of Toxins.*

The assay of toxins for hæmolytic potency is carried out as follows :

Doses of 1 unit of standard antitoxin are delivered into a series of test tubes together with increasing quantities of toxin, and the

total volume in each tube adjusted to 2 c.c. One drop of a 1 in 3 dilution of thrice-washed rabbit's red blood corpuscles is then added (1 drop = 0.05 c.c.). The tubes are shaken to distribute the red blood corpuscles evenly throughout the fluid, they are heated to 37° C. and left in the incubator for sixty minutes (being usually shaken after thirty minutes). They are then taken out of the incubator and left at room temperature for from one to two hours. The reading of the hæmolytic test is then taken.

A fair quantity (10 c.c.) of rabbit's blood should be taken so that a solution containing a constant concentration of corpuscles may be available.

1. *Determination of the hæmolytic test dose of toxin No. 53 :*

1st Test.¹

| | | | | | | |
|----------------------------------|------|-----|-----|------|------|------|
| Standard antitoxin (units) | 1 | 1 | 1 | 1 | 1 | 1 |
| Toxin 53 (c.c.) | 0.05 | 0.1 | 0.2 | 0.3 | 0.4 | 0.5 |
| Hæmolytic test | — | — | +++ | ++++ | ++++ | ++++ |

2nd Test.

| | | | | | | | |
|--------------------------------|------|------|------|------|------|------|------|
| Standard anti-toxin (units) .. | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Toxin 53 (c.c.) .. | 0.15 | 0.16 | 0.17 | 0.18 | 0.19 | 0.2 | 0.21 |
| Hæmolytic test | — | — | — | ++ | +++ | ++++ | ++++ |

3rd Test.

| | | | | | | |
|----------------------------------|------|------|------|------|------|------|
| Standard antitoxin (units) | 1 | 1 | 1 | 1 | 1 | 1 |
| Toxin 53 (c.c.) | 0.16 | 0.17 | 0.18 | 0.19 | 0.2 | 0.21 |
| Hæmolytic test | — | — | ++ | ++++ | ++++ | ++++ |

¹ Meaning of signs :

- no hæmolytic test
- + traces of hæmolytic test
- ++ slight hæmolytic test
- +++ sub-total hæmolytic test
- ++++ total hæmolytic test

Six weeks after these first trials, the test toxin was re-assayed, with the following results :

4th Test.

| | | | | | | |
|----------------------------------|------|------|------|------|------|------|
| Standard antitoxin (units) | 1 | 1 | 1 | 1 | 1 | 1 |
| Toxin 55 (c.c.) | 0.17 | 0.18 | 0.19 | 0.2 | 0.21 | 0.22 |
| Hæmolysis | — | — | +++ | ++++ | ++++ | ++++ |

When the standard antitoxin solution was prepared from dry antitoxin, further control tests of the test toxin were made, which gave 0.19 as the test dose.

These first experiments show that the test dose of the staphylococcus toxin can be very accurately determined.

If the toxin is kept cool (+ 4° C.) and in the dark, it retains its toxic potency intact for a long period ; but it is advisable to make a control test every two or three months, as is done with diphtheria toxin.

The hæmolytic test dose of toxin No. 53 was accordingly fixed at 0.19.

The figures yielded by the various tests were as follows :

0.18-0.19 ; 0.19 ; 0.19 ; 0.19 ; 0.20,

so that the hæmolytic test dose of toxin 53 = 0.19.

2. Determination of the hæmolytic test dose of toxin No. 55 A :

1st Test.

| | | | | | |
|----------------------------------|------|------|------|------|------|
| Standard antitoxin (units) | 1 | 1 | 1 | 1 | 1 |
| Toxin 55 A (c.c.) | 0.22 | 0.24 | 0.26 | 0.28 | 0.3 |
| Hæmolysis | — | — | — | — | ++++ |

2nd Test.

| | | | | |
|----------------------------------|------|------|------|------|
| Standard antitoxin (units) | 1 | 1 | 1 | 1 |
| Toxin 53 A (c.c.) | 0.28 | 0.29 | 0.3 | 0.31 |
| Hæmolysis | — | — | ++++ | ++++ |

Test dose : 0.30.

3. *Determination of the hæmolytic test dose of toxin 55 B :*

Test dose : 0.26.

Comparatively weak toxins were also tested ; the test dose came out as high as 0.6 and 0.7. It was felt, however, that, at so high a level, the determination becomes less accurate. It is therefore advisable to use for the hæmolytic test dose toxins which are very potent but have been stabilised—*i.e.*, kept in the ice-chest for some weeks or even months ; under these conditions, the assay is extremely accurate.

II. *Determination of the Antitoxic Potency of Antitoxins S and T by the Hæmolytic Method.*1. *Toxin used : No. 53 = test dose : 0.19 :**1st Test (preliminary).*

| | | | | | |
|---------------------------|-------|-------|-------|-------|-------|
| Toxin 53 (c.c.) | 0.19 | 0.19 | 0.19 | 0.19 | 0.19 |
| Antitoxin S. (c.c.) . . . | 1/100 | 1/150 | 1/200 | 1/250 | 1/300 |
| Hæmolysis | — | — | — | ++++ | ++++ |
| Toxin 53 (c.c.) | 0.19 | 0.19 | 0.19 | 0.19 | 0.19 |
| Antitoxin T. (c.c.) . . . | 1/100 | 1/150 | 1/200 | 1/250 | 1/300 |
| Hæmolysis | — | ++++ | ++++ | ++++ | ++++ |

2nd Test.

| | | | | | | | | | |
|-------------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Toxin 53 (c.c.) . . . | 0.19 | 0.19 | 0.19 | 0.19 | 0.19 | 0.19 | 0.19 | | |
| Antitoxin S. (c.c.) . . | 1/200 | 1/205 | 1/210 | 1/215 | 1/220 | 1/225 | 1/230 | | |
| Hæmolysis | — | — | +++ | ++++ | ++++ | ++++ | ++++ | | |
| Toxin 53 (c.c.) . . . | 0.19 | 0.19 | 0.19 | 0.19 | 0.19 | 0.19 | 0.19 | 0.19 | 0.19 |
| Antitoxin T. (c.c.) . . | 1/100 | 1/115 | 1/120 | 1/125 | 1/130 | 1/135 | 1/140 | 1/145 | 1/150 |
| Hæmolysis | — | — | — | — | + | +++ | ++++ | ++++ | ++++ |

3rd Test.

| | | | | | | |
|---------------------------|-------|-------|-------|-------|-------|-------|
| Toxin 53 (c.c.) | 0.19 | 0.19 | 0.19 | 0.19 | 0.19 | 0.19 |
| Antitoxin S. (c.c.) . . . | 1/200 | 1/205 | 1/210 | 1/215 | 1/220 | 1/225 |
| Hæmolysis | — | ++ | +++ | ++++ | ++++ | ++++ |
| Toxin 53 (c.c.) | 0.19 | 0.19 | 0.19 | 0.19 | 0.19 | 0.19 |
| Antitoxin T. (c.c.) . . . | 1/125 | 1/130 | 1/135 | 1/140 | 1/145 | 1/150 |
| Hæmolysis | — | — | + | +++ | ++++ | ++++ |

The following are the antitoxin titres obtained with test toxin 53 :

For antitoxin S : 210, 210, 215, 220. Mean value : 215.

For antitoxin T : 135, 140, 145. Mean value : 140.

2. *Determination of the antitoxin titres of S and T sera with toxin No. 55 A :*

1st Test.

| | | | | | |
|---------------------------|-------|-------|-------|-------|-------|
| Toxin 55 (c.c.) | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 |
| Antitoxin S. (c.c.) . . . | 1/200 | 1/205 | 1/210 | 1/215 | 1/220 |
| Hæmolysis | — | — | — | — | ++ |
| Toxin 55 (c.c.) | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 |
| Antitoxin T. (c.c.) . . . | 1/300 | 1/135 | 1/140 | 1/145 | 1/150 |
| Hæmolysis | — | — | — | ++++ | ++++ |

Antitoxin S = 220-225 units per c.c.

Antitoxin T = 145 units per c.c.

These experiments show, for serum S, a titre varying between 210 and 220 units per c.c. and, for serum T, a titre varying between 140 and 145. This degree of accuracy in the titration of a serum is thought to be entirely adequate, and comparable, if not superior, to the accuracy achieved in the assay of other sera.

The assay by the hæmolytic method has been discussed at some length because it is extremely easy, quick, accurate and inexpensive ; assuming that the results *in vivo* correspond to the titration *in vitro*, the hæmolytic method of titration will appear preferable because of these various advantages.

B. *Intradermal Method.*

I. *Determination of the Skin Test Dose.*

The first question that arises is whether the hæmolytic dose bears any constant relation to the skin dose of a toxin. If it does, then, the ratio $\frac{\text{hæmolytic test dose}}{\text{skin test dose}}$ will enable the skin test dose of another toxin to be calculated when only the hæmolytic test dose is known —*e.g.* :

$$\frac{\text{Hæmolytic test dose toxin 1 } b}{\text{skin test dose toxin 1 } b} = \frac{\text{Hæmolytic test dose toxin 53}}{\text{skin test dose toxin 53}}, \text{ or } \frac{15}{25} = \frac{19}{X}, \text{ whence } X = 32$$

The skin test dose, therefore, is 0.032.

Does this ratio exist in fact ?

1. *Determination of the skin test dose of toxin No. 53 :**Test.*

| | | | | | | |
|-------------------------------------|-------|------|-------|-------|-------|-------|
| Standard antitoxin (c.c.) | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| Toxin (No. 53 c.c.) . . . | 0.027 | 0.03 | 0.033 | 0.036 | 0.039 | 0.042 |
| Reaction | — | — | — | necr. | necr. | necr. |

Hence the test dose is 0.036, or very slightly higher than that theoretical quantity.

2. *Determination of the skin test dose of toxin No. 55 B :*A. *By Theoretical Calculation.*

Hæmolytic test dose of toxin 55 B. = 0.26.

$$\text{If } \frac{15}{25} = \frac{26}{X}, \text{ then } X = 43.$$

The skin test dose, therefore, is 0.043.

B. *By Animal Experiments.*

| | | | | | | | | |
|--|-------|-------|-------|--------|-------|-------|-------|-------|
| Standard anti-toxin (units) . . . | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| Toxin 55 B (c.c.) . . . (0.2 c.c. injected into the guinea-pig) | 0.035 | 0.038 | 0.040 | 0.0415 | 0.043 | 0.045 | 0.048 | 0.051 |
| Reaction | — | — | — | — | — | necr. | necr. | necr. |

The skin test dose is 0.45, and is thus slightly higher than the test dose as calculated theoretically.

II. *Determination of the Antitoxic Potency of Antitoxins S and T by the Intradermal Method.*

Toxin 53 was used. Test dose : 0.036.

1st Test.

| | | | | | | |
|----------------------------|-------|-------|-------|-------|-------|-------|
| Toxin 53 (c.c.) | 0.036 | 0.036 | 0.036 | 0.036 | 0.036 | 0.036 |
| Antitoxin S (c.c.) | 1/190 | 1/200 | 1/210 | 1/220 | 1/230 | 1/240 |
| Reaction | — | — | — | necr. | necr. | necr. |
| Toxin 53 (c.c.) | 0.036 | 0.036 | 0.036 | 0.036 | 0.036 | 0.036 |
| Antitoxin T (c.c.) | 1/110 | 1/120 | 1/130 | 1/140 | 1/150 | 1/160 |
| Reaction | — | — | necr. | necr. | necr. | necr. |

2nd Test.

| | | | | | |
|---|-------|-------|-------|-------|-------|
| Toxin 53 (c.c.) | 0.036 | 0.036 | 0.036 | 0.036 | 0.036 |
| Antitoxin S (c.c.) (mean value 1/215) .. | 1/205 | 1/210 | 1/215 | 1/220 | 1/225 |
| Reaction | — | necr. | ± ? | necr. | necr. |
| Toxin 53 (c.c.) | 0.036 | 0.036 | 0.036 | 0.036 | 0.036 |
| Antitoxin T (c.c.) (mean value 1/130) .. | 1/120 | 1/125 | 1/130 | 1/135 | 1/140 |
| Reaction | — | necr. | ? | necr. | necr. |

The antitoxin titre, as determined by the intradermal method, is thus seen to be from 215 to 220 units for antitoxin S and 130 units for antitoxin T.

C. *Method by Inoculation of the Mouse (Intraperitoneal Injection).*

Temporary difficulties in obtaining mice set limits to these experiments, which extended only to the determination of :

- (a) The intraperitoneal test dose of toxin No. 53 for the mouse ;
- (b) The titre of antitoxin S by means of this same method.

I. *Determination of the Test Dose (Intraperitoneal Injection into the Mouse).*

Determination of the test dose for toxin 53.

| Standard antitoxin | Toxin 53 (c.c.) | Number of mice dead after three days |
|-------------------------|-----------------|--------------------------------------|
| 1 unit in 0.5 c.c. | 0.24 | 1/4 |
| | 0.26 | 4/4 |
| | 0.28 | 3/4 |
| | 0.30 | 4/4 |
| | 0.32 | 4/4 |

The volume of the injection per mouse is thus 0.7 c.c.
The test dose may be put at about 0.25.

II. *Determination of the Potency of Antitoxin S by the Intraperitoneal Method.*

| | Antitoxin 53 (c.c.) | Number of mice dead after three days | |
|------------|---------------------|--------------------------------------|-------|
| 0.25 | + { | 1 / 190 | 1 / 5 |
| | | 1 / 200 | 1 / 3 |
| | | 1 / 210 | 2 / 5 |
| | | 1 / 220 | 1 / 5 |
| | | 1 / 230 | 0 / 5 |
| | | 1 / 240 | 3 / 5 |

This experiment is of no great value, as the intraperitoneal test dose was not established on a sufficient number of mice. The antitoxin titre of serum S may, however, be put at about 240 units per c.c.

General Remarks.

These few experiments seem to show that the hæmolytic, intradermal and intraperitoneal methods of determining the antitoxin titre of the anti-staphylococcus serum yield the same results in practice. If it should prove that these methods are always equivalent, which implies that the toxin is always one and the same, then the hæmolytic method would seem to be preferable because, being simpler, more accurate, quicker and cheaper, it presents all the advantages of a method *in vitro* as compared with methods *in vivo*.

Still greater accuracy can be achieved in the hæmolytic method by using *calibrated* pipettes for the dilutions and *micrometric* pipettes (0.1 c.c. divided into hundredths) to deliver the toxin.

If kept cool and in the dark, the toxin retains its toxic potency unimpaired. It is advisable to verify the test dose every three months. It may be added that, if the standard antitoxin is adopted, it would be desirable for the various laboratories working on the question to receive a few c.c. of standard antitoxin once or twice a year, so that they can readjust their toxins. We are sure that the adoption of a staphylococcus antitoxin standard will facilitate the study of staphylococcus toxins and antitoxins by making it possible to compare the results obtained in different laboratories and so stimulating research in this field.

4. REPORT RECEIVED FROM DR. C. E. DOLMAN, THE CONNAUGHT LABORATORIES, TORONTO, CANADA.

Abridged protocol showing :

(a) Determination of "test dose" of staphylococcus toxin, No. 24 m, and

(b) Assay of staphylococcus antitoxins S and T, by :

- (i) Hæmolytic method (rabbits' red blood corpuscles) ;
- (ii) Intracutaneous method (guinea-pig) ;
- (iii) Intraperitoneal method (mouse).

Intravenous method (mouse) and intracutaneous method (rabbit) not completed.

I. *The Hæmolytic Method.*

(a) *Determination of test dose of toxin 24 m.*

| | | | | | | |
|--------------------------------|------|------|------|------|------|---|
| Standard A.T. (P. units) | 1 | 1 | 1 | 1 | 1 | 1 |
| Toxin 24 m (c.c.) | 0.01 | 0.02 | 0.03 | 0.04 | 0.05 | 0 |
| Hæmolysis | 0 | 0 | C- | C | C | 0 |

Test dose, (LH), taken as 0.03 c.c.

(b) *Assay of staphylococcus antitoxins S and T.*

| Amount (c.c.) of antitoxin S | Amount of toxin in each mixture = 1 test dose (0.03 c.c.) | | | | | | | 1 P.U. |
|-----------------------------------|---|-------|-------|-------|-------|-------|------|--------|
| | 0.004 | 0.005 | 0.006 | 0.007 | 0.008 | 0.009 | 0.01 | |
| Hæmolysis | C | C | P | 0 | 0 | 0 | 0 | C- |
| Amount (c.c.) of antitoxin T ... | 0.004 | 0.005 | 0.006 | 0.007 | 0.008 | 0.009 | 0.01 | 1 P.U. |
| Hæmolysis | C | C | C | C | C- | 0 | 0 | C- |

Strength of antitoxin S = 1/0.006 P.U. per c.c. = 166 ± 11.

A later estimate, using smaller increments of antitoxin, gave 1/0.0063 as a closer approximation—*i.e.* 159 ± 7.

Strength of antitoxin T = 1/0.0085 P.U. per c.c. = 117 ± 6.

A later estimate, using smaller increments of antitoxin, gave 1/0.0088 as a closer approximation—*i.e.* 114 ± 4.

II. Intracutaneous Method (Guinea-pig).

(a) Determination of test dose of toxin 24 m. against 0.5 P. unit.

| | | | | | | | |
|------------------------------|-------|-------|-------|-------|-------|-----|-------|
| Standard A.T. (P.U.)... | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 00 |
| Toxin 24 m (c.c.) | 0.032 | 0.028 | 0.024 | 0.020 | 0.016 | 000 | 0.016 |
| Reaction | + | + | + | 0 | 0 | 0 | + |
| Hemolysis ¹ | C | C | C | C | C- | 0 | C |

0.2 c.c. of mixtures injected.

Test dose (Lr) taken as 0.047 c.c.

(b) Assay of antitoxins S and T.

| Toxin 24 m (c.c.) | Dilution of antitoxin S | Guinea-pig skin necrosis | Dilution of antitoxin T | Guinea-pig skin necrosis |
|-------------------|-------------------------|--------------------------|-------------------------|--------------------------|
| 0.047 | 1/120 | 0 | 1/100 | 0 |
| | 1/130 | 0 | 1/110 | ± |
| | 1/140 | 0 | 1/115 | + tr- |
| | 1/150 | ± | 1/120 | + |
| | 1/160 | + | 1/125 | + |
| | 1/170 | + | 1 test dose | + |
| | 1 test dose | + | | |

Serum S contains 150 (+ 7) P.U. per c.c.

Serum T contains 115 (— 2) P.U. per c.c.

III. Intraperitoneal Method (Mouse).

(a) Determination of test dose of toxin 24 m.

| Standard antitoxin | Toxin 24 m (c.c.) | Proportion of mice dead within three days |
|--------------------|-------------------|---|
| 1 P. unit | 0.033 | 1/6 |
| | 0.040 | 2/6 |
| | 0.046 | 3/6 |
| | 0.053 | 3/6 |
| | 0.060 | 5/6 — 13/17 (sum of 3 determinations) |
| | 0.066 | 6/6 |
| 0000 | 0.000 | 0/3 |
| | 0.066 | 6/6 |

Test dose taken as 0.06 c.c.

¹ Rabbit red blood cells added to remainder of mixtures (LH = 0.032).

(b) Assay of *staphylococcus antitoxins S and T.*

| Toxin 24 m | Antitoxin S (c.c.) | Proportion of mice dead within three days | Antitoxin T (c.c.) | Proportion of mice dead within three days |
|----------------|--------------------|---|--------------------|---|
| 0.06 c.c. | 1/110 | 0/6 | 1/90 | 2/9 |
| | 1/120 | 2/11 | 1/100 | 1/6 |
| | 1/135 | 3/12 | 1/110 | 2/6 |
| | 1/150 | 5/14 | 1/115 | 6/8 |
| | 1/170 | 7/11 | 1/120 | 4/6 |
| | 1/200 | 5/6 | 1/130 | 6/6 |

Estimated potency of antitoxin S = 150 (+) P. units.

Estimated potency of antitoxin T = 110 (+) P. units.

*Determination of Intracutaneous Test Dose (Rabbit)
against 0.5 P.U.*

| 0.5 P.U. in each mixture. Total volume of mixtures 2 c.c., 0.2 c.c. of each injected. | | | | | | | |
|--|------|-------|-------|-------|-------|-------|-------|
| Toxin 24 m (c.c.) | 0.01 | 0.012 | 0.014 | 0.016 | 0.018 | 0.020 | 0.022 |
| Reaction | 0 | 0 | 0 | + | + | + | + |
| Hæmolysis ¹ | 0 | 0 | 0 | tr | C | C | C |

Intracutaneous test dose (rabbit) = 0.032 c.c.

Summary of Results.

| Method | Test dose | Antitoxin S | Antitoxin T |
|--|-------------------------|----------------------|----------------------|
| Hæmolytic | 0.03 c.c. | 159 (± 7) P.U. | 111 (± 1) P.U. |
| Intracutaneous (guinea-pig) | 0.047 c.c. | 150 (+7) P.U. | 115 (-2) P.U. |
| Intraperitoneal (mouse). Intracutaneous (rabbit). | 0.06 c.c. 0.032 c.c. | 150 + P.U. — | 110 + P.U. — |

Probable potency of antitoxin S = 151-162 P.U.

Probable potency of antitoxin T = 110-115 P.U.

¹ On addition of rabbit erythrocytes to mixtures subsequently.

5. REPORT RECEIVED FROM DR. TH. MADSEN
RECORDING THE INVESTIGATIONS OF DR. CLAUD JENSEN
AT THE STATE SERUM INSTITUTE, COPENHAGEN.

The investigations reported below will be confined to the study of the possibility of standardisation of staphylococcus toxin and antitoxin by the intracutaneous method in rabbits on the basis of the provisional antitoxin unit mentioned above ; they should only be considered as preliminary. More thorough investigations on the problem will be taken up at this institute and will be reported later.

The present experiments have been conducted in accordance with the main principles used for the intracutaneous testing of diphtheria toxin and antitoxin in rabbits, and all details as to the rabbits used, treatment, pipetting and technique of injection will be found in the monograph¹ published from this institute in 1933.

The materials used.—The toxin employed in the present study, staphylococcus toxin S 300, was kindly supplied by the National Institute for Medical Research, London. At that Institute, the following values for the toxin had been determined :

| | |
|---|-------------------------|
| Minimum hemolytic dose (rabbit cells) | = 0.0012 c.c. (± 100 %) |
| L.II (see Appendix) | = 0.10 c.c. (± 10 %) |
| M.R.D. (guinea-pigs) | = 0.0025 c.c. (± 100 %) |
| $\frac{L.F}{10}$ (i.c. guinea-pig ; see Appendix) | = 0.018 c.c. (± 15 %) |
| L+ (l.v. mice ; see Appendix) | = 0.14 c.c. (± 15 %) |

Some of these values have also been determined at this institute and will be found below.

The antitoxins used were : (a) the dry provisional standard for staphylococcus antitoxin ; (b) a glycerol solution of the provisional standard for staphylococcus antitoxin, 1 c.c. = 20 P. units ; (c) staphylococcus antitoxins S and T of unknown potency.

The lesion produced in the rabbit's skin by the injection of staphylococcus toxin.—The effect of staphylococcus toxin when injected intracutaneously in rabbits is essentially a necrotic one. It may be preceded or accompanied by some redness and induration. The redness is generally transitory and does not seem to be specific, as in most cases it is not neutralised by staphylococcus antitoxin.

¹ CLAUD JENSEN : *Die intracutane Kaninchenmethode zur Auswertung von Diphtherie-Toxin und -Antitoxin.* Levin & Munksgaard, Publishers, Copenhagen, 1933.

On the other hand, the necrosis is completely prohibited by a sufficient amount of antitoxin.

Reading.—When a not too small amount of toxin or fairly under-neutralised mixtures of toxin or antitoxin are injected, the evidence of free toxin can be clearly seen as an ischamic area of the skin at the site of injection one or two hours later. Necrosis will be well developed twenty-four hours after injection. At this time, a reading can easily be made and in most cases agrees with the forty-eight-hours reading. In some instances, however, a dubious twenty-four-hours necrosis may have developed into a definite necrosis. For this reason, *the final reading should take place on the second day after injection.* The reading is conveniently recorded by the following abbreviations :

- n? = dubious necrosis ;
 n = superficial but definite necrosis ;
 N = pronounced necrosis ;

the size of the reactions given in millimetres as the arithmetical mean of the smallest and biggest diameter.

Determination of the M.R.D. (rabbits).—The method employed for preparing the dilution of the toxin S 300 for this determination is given in the abridged Protocol I, which shows the reactions produced by the same series of dilutions in three different rabbits.

Protocol I (abridged).

| Toxin S 300 diluted 1 : 80 | Phosphate buffer- solution, isotonic. pg 7.38 | Amount of toxin present in the 0.10 c.c. injected | Reaction (second-day reading) | | | |
|----------------------------------|---|---|-------------------------------|--------------------|--------------------|---------------------------|
| | | | Rabbit No. 4500 | Rabbit No. 4498 | Rabbit No. 4499 | Rabbit No. 4499 (a) |
| c.c. | c.c. | c.c. | | | | |
| 0.050 | 0.95 | 0.000063 | 0 | 0 | 0 | 0 |
| 0.063 | 0.94 | 0.000080 | 0 | 0 | 0 | 0 |
| 0.080 | 0.92 | 0.00010 | 0 | 5n | 0 | 0 |
| 0.10 | 0.90 | 0.000125 | 5n | 8N | 6n | 8n |
| 0.125 | 0.87 | 0.00016 | 8n | 10N | 8n | 10n |
| 0.16 | 0.84 | 0.00020 | 10n | 10N | 10n | 10n |
| 0.20 | 0.80 | 0.00025 | 10N | 10N | 10N | 10N |

Result : M.R.D. (in c.c.) = 0.000125 0.00010 0.000125 0.000125

Minimal reacting dose, M.R.D., taken as 0.000125 c.c.

As the protocol shows, the value for the M.R.D. varies only very little for the three rabbits here tested and can be taken as 0.000125 c.c.

The stability of toxin S 300 in dilutions.—Only one experiment has been made (see Protocol I, last column, rabbit No. 4499 (a); the identical dilutions, that were used for the M.R.D. determination, were placed at 37° C. for four hours. No deterioration could be established, the M.R.D. being again 0.000125 c.c.

Sensitiveness of rabbit's skin as compared to guinea-pig's skin to staphylococcus toxin.—As mentioned above, the M.R.D. of toxin S 300 for guinea-pigs was found by HARTLEY and LEWELLYN SMITH to be 0.0025 c.c. In rabbits, the M.R.D. was twenty times less—viz., 0.000125 c.c.—showing that the rabbit's skin is much more susceptible than that of guinea-pigs.

Determination of the LR/30 test dose¹ of toxin S 300.—Protocol II shows the manner of making the mixtures for the determination of this test dose, the reactions produced and values obtained in three different rabbits.

Protocol II (abridged).

| Toxin S 300 diluted 1 : 9 | Phosphate buffer- solution, isotonic, pH 7.38 | Standard A.T. diluted 1 : 20 (0.1 c.c. = 0.1 P.U.) | Amount of toxin present in the 0.10 c.c. injected | Reaction (second-day reading) | | |
|--------------------------------------|---|--|---|-------------------------------|--------------------|--------------------|
| | | | | Rabbit No. 4500 | Rabbit No. 4499 | Rabbit No. 4509 |
| c.c. | c.c. | c.c. | c.c. | | | |
| 0.071 | 0.13 | 0.10 | 0.0025 | 0 | 0 | 0 |
| 0.080 | 0.12 | 0.10 | 0.0030 | 0 | 0 | 0 |
| 0.090 | 0.11 | 0.10 | 0.0033 | 0 | 0 | 0 |
| 0.10 | 0.10 | 0.10 | 0.0037 | 8N | 5n | 5n |
| 0.11 | 0.09 | 0.10 | 0.0041 | 10N | 8N | 12N |
| 0.125 | 0.07 | 0.10 | 0.0046 | 16N | 10N | 14N |
| 0.14 | 0.06 | 0.10 | 0.0052 | 18N | 12N | 20N |
| LR/30-dose of toxin S 300 (in c.c.)= | | | | 0.0037 | 0.0037 | 0.0037 |

Test dose, LR/30, taken as 0.0037 c.c.

¹ The test dose, LR/30, is the quantity of toxin which, when mixed with 1/30 provisional unit of antitoxin and injected intracutaneously in a volume of 0.10 c.c., causes a small but characteristic necrotic lesion in the skin of the rabbit, corresponding in size and character to that provoked by 1 M.R.D.

The end point taken for determining the test dose of the toxin is the quantity which just permits the development of a small (5-8 mean diameter) but definite area of necrosis ($n \rightarrow N$).

Law of multiple proportions.—A few experiments have been made to find out if the law of multiple proportions holds good. The results are given in Protocol III.

Protocol III : Law of Multiple Proportions.

| Rabbit No. 4500 | | | |
|-----------------|-----------------|----------------------------------|------------------------------|
| Test dose | Observed value | Calc. value after multiple prop. | Number of M.R.D in test dose |
| | c.c. | c.c. | ca. |
| LR /3 | 0.037 (0 %) | 0.037 | 300 |
| LR /10 | 0.011 (0 %) | 0.011 | 85 |
| LR /30 | 0.0037 (0 %) | 0.0037 | 30 |
| LR /100 | 0.0013 (15 % +) | 0.0011 | 10 |
| LR /300 | 0.0006 (38 % +) | 0.00037 | 5 |

These show that the law of multiple proportions is valid for the test doses LR /3, LR /10 and LR /30, each of these test doses containing respectively 300, 85 and 30 M.R.D.s. The LR /100 test dose contains only 10 M.R.D.s and the amount of toxin is 15 per cent higher than expected. The LR /300 test dose is 38 per cent higher than expected and contains 5 M.R.D.s. For a first preliminary titration of a staphylococcus antitoxin of unknown potency, the LR /100 or LR /30 test dose will be more suitable. A fairly big rabbit (2,500 to 3,000 grm.) may easily take sixty injections of the former test dose and forty of the latter.

For the final narrower titrations, the LR /3 dose should be employed. Each animal may take about thirty injections. When squaring up the skin for the injections, the squares are increased in size corresponding to the mixtures containing less antitoxin, the tendency to the development of large reactions in this way being less troublesome.

Control series.—On each rabbit used for titration a series of mixtures of the provisional standard antitoxin and the constant test dose of the toxin employed is always injected, the mixtures being prepared in such a way that the series contains over-neutralised as well as under-neutralised mixtures. *In this way, the indi-*

vidual variations in the rabbits are eliminated. (For details see Claus JENSEN, 1933, *loc. cit.*, pages 166 to 174.)

Assay of the Two Staphylococcus Antitoxins S and T of Unknown Potency :

(a) Titration at the *LR/30 level*.—A titration of the two antitoxins S and T has been made in nine different rabbits in the manner indicated above. The way of preparing the mixtures, the reactions and the results obtained are given in detail in Protocol IV.

The results obtained are fairly encouraging as to the use of rabbits for the intracutaneous testing of staphylococcus antitoxin. Owing to the correction determined by the control series, the values obtained for the two antitoxins in the different rabbits vary only a little. According to Protocol IV, *the estimated potency of the antitoxins S and T (arithmetic mean) is 199 and 137 P. units respectively.*

(b) Titration at the *LR/3 level*.—A titration of the two antitoxins was also made by using the *LR/3* test dose of toxin S 300 in two rabbits. The results are given in Protocol V. As indicated by this protocol, the reactions are very clearcut. No doubt a titration at narrower limits could be made at this level of testing if desired. The results are practically the same in the two rabbits and correspond fairly well to the values obtained in the experiments given in Protocol IV. *The antitoxins S and T are here found to contain 190 and 141 P. units per c.c.*

Protocol IV (abridged).

| Control-series | Standard antitoxin diluted 1:20 (0.10 c.c. = 0.10 P.U.) | Phosphate buffer-sol. (pH 7.5), isotonic | Toxin S 300 diluted 1:10 | Correction | 4514 | 4530 | (Second-day reading) Rabbit No. | | | | | | |
|---|---|--|--------------------------|--------------------------|-------------|-------------|------------------------------------|--------------|-------------|-------------|--------------|-------------|-------------|
| | | | | | | | 4548 | 4549 | 4550 | 4553 | 4554 | 4555 | 4558 |
| | c.c. | c.c. | c.c. | | | | | | | | | | |
| Test-toxin S 300 diluted 1:9 Test dose 3 LR/30 = 0.10 c.c. | 0.125 | 0.07 | 0.10 | 1.25 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 0.11 | 0.09 | 0.10 | 1.1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 0.10 | 0.10 | 0.10 | 1.0 | 0 | 3n | 8N | 10N | 8n | 3n | 0 | 5N | 3N |
| | 0.09 | 0.11 | 0.10 | 0.9 | 5n | 12N | 12N | 14N | 14N | 8N | 10N | 10N | 10N |
| | 0.08 | 0.12 | 0.10 | 0.8 | 12N | 16N | 14N | 16N | 18N | 12N | 12N | 12N | 10N |
| | | | Correction: | | 0.9 | 1.0 | 1.0 | 1.05 | 1.0 | 1.0 | 0.95 | 1.0 | 1.0 |
| Antitoxin S.. | Antitoxin S diluted 1:200 | | | Tested for P.U. per c.c. | | | | | | | | | |
| | c.c. | | | | | | | | | | | | |
| | 0.14 | 0.06 | 0.10 | 140 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 0.125 | 0.07 | 0.10 | 160 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 0.11 | 0.09 | 0.10 | 180 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 0.10 | 0.10 | 0.10 | 200 | 0 | 8N | 5N | 14N | 14N | 8N | n? | 8N | 8N |
| 0.09 | 0.11 | 0.10 | 220 | 10N | 10N | 12N | 16N | 20N | 12N | 10 | 12N | 10N | |
| | | | Result: | | 198 | 200 | 200 | 200 | 190 | 200 | 200 | 200 | 200 |
| | | | | | (0.9 × 210) | (1.0 × 200) | (1.0 × 200) | (1.05 × 190) | (1.0 × 190) | (1.0 × 200) | (0.95 × 210) | (1.0 × 200) | (1.0 × 200) |
| Antitoxin T.. | Antitoxin T diluted 1:200 | | | | | | | | | | | | |
| | c.c. | | | | | | | | | | | | |
| | 0.18 | 0.02 | 0.10 | 110 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 0.16 | 0.04 | 0.10 | 125 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 0.14 | 0.06 | 0.10 | 140 | 0 | 12N | 3N | 14N | 11N | 10N | 5N | 8N | 10N |
| | 0.125 | 0.07 | 0.10 | 160 | 8N | 14N | 12N | 20N | 18N | 14N | 10N | 10N | 10N |
| 0.11 | 0.09 | 0.10 | 180 | 10N | 16N | 14N | 20N | 22N | 18N | 12N | 12N | 12N | |
| | | | Result: | | 144 | 133 | 140 | 140 | 133 | 133 | 133 | 140 | 133 |
| | | | | | (0.9 × 160) | (1.0 × 133) | (1.0 × 140) | (1.05 × 133) | (1.0 × 133) | (1.0 × 133) | (0.95 × 140) | (1.0 × 140) | (1.0 × 133) |

STAPHYLOCOCCUS ANTITOXIN

Estimated potency of antitoxin S (arithmetic mean) : 199 P. units.
 Estimated potency of antitoxin T (arithmetic mean) : 137 P. units.

Protocol V.

| Control-series | Standard antitoxin P.U. in mixture | Rabbit No. 4518 (second-day reading) | | Rabbit No. 4517 (second-day reading) | |
|--|------------------------------------|--------------------------------------|--------------------|--------------------------------------|--------------------------------|
| • Test-toxin S 300 undiluted Test dose 3 × LR/3 = 0.11 c.c. | 1.4 | 0 | } No correction | 0 | } Correction 0.95 |
| | 1.25 | 0 | | 0 | |
| | 1.1 | 0 | | 0 | |
| | 1.0 | 5n | | 0 | |
| | 0.90 | 18N | | 14N | |
| | 0.80 | 20N | | 22N | |
| | 0.71 | 25N | | 30N | |
| | Tested for P.U. per c.c. | | | | |
| Antitoxin S | 140 | 0 | } Result : 190 | 0 | } Result : 190 (200 × 0.95) |
| | 160 | 0 | | 0 | |
| | 180 | 0 | | 0 | |
| | 200 | 12N | | 8N | |
| | 220 | 16N | | 14N | |
| | 250 | 20N | | 18N | |
| | 280 | 25N | | 22N | |
| Antitoxin T | 100 | 0 | } Result : 140 | 0 | } Result : 142 (150 × 0.95) |
| | 110 | 0 | | 0 | |
| | 125 | 0 | | 0 | |
| | 140 | 8N | | 0 | |
| | 160 | 14N | | 22N | |
| | 180 | 18N | | 24N | |
| | 200 | 22N | | 28N | |

Antitoxin S : 190 P. units per c.c.

Antitoxin T : 141 P. units per c.c.

Addendum.

A few experiments have been made to study the method of testing the two antitoxins S and T by the *hæmolytic* method.

The technique employed is practically the same as that used at the National Institute for Medical Research, London, and indicated in the Memorandum : " A Provisional Stable Standard for Staphylococcus Antitoxin ", on pages 5 and 8. The only modifications consist in the use of citrated blood (a 10 per cent solution of Na-citrate mixed with the blood in the proportion 1 : 20). The rabbit

Protocol VI (abridged).

(a) Determination of test dose of toxin S 300.

| | | | | | | | | | | |
|--------------------------------|-------|---------|---------|--------|--------|----------|-------|-------|---|---|
| Standard A.T. (P. units) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Toxin S 300 (c.c.) | 0.16 | 0.14 | 0.13 | 0.12 | 0.11 | 0.10 | 0.09 | 0.08 | 0 | 0 |
| Hæmolysis | 100 % | ≤ 100 % | ≤ 100 % | > 50 % | > 50 % | ca. 50 % | trace | trace | 0 | 0 |

Test dose, LH, taken as 0.10 c.c.

(b) Assay of staphylococcus antitoxin S.

| | | | | | | | | | | |
|-------------------------|---------|---------|---------|---------|--------|----------|-------|-------|-------|-------|
| Toxin S 300 (c.c.) | 0.10 | 0.10 | 0.10 | 0.10 | 0.10 | 0.10 | 0.10 | 0.10 | 0.10 | 0 |
| Antitoxin S (c.c.) | 1/360 | 1/320 | 1/280 | 1/250 | 1/220 | 1/200 | 1/180 | 1/160 | 1/140 | 1/140 |
| Hæmolysis | ≤ 100 % | ≤ 100 % | ≤ 100 % | ≤ 100 % | > 50 % | ca. 25 % | 0 | 0 | 0 | 0 |

Estimated potency of antitoxin S : 200 P. units.

(c) Assay of staphylococcus antitoxin T.

| | | | | | | | | | | |
|-------------------------|-------|---------|---------|---------|---------|--------|--------|--------|-------|-------|
| Toxin S 300 (c.c.) | 0.10 | 0.10 | 0.10 | 0.10 | 0.10 | 0.10 | 0.10 | 0.10 | 0.10 | 0 |
| Antitoxin T (c.c.) | 1/280 | 1/250 | 1/220 | 1/200 | 1/180 | 1/165 | 1/155 | 1/143 | 1/133 | 1/133 |
| Hæmolysis | 100 % | ≤ 100 % | ≤ 100 % | ≤ 100 % | ≤ 100 % | > 50 % | > 50 % | < 50 % | trace | 0 |
| | | | | | | | | > 25 % | | |

Estimated potency of antitoxin T : 143 P. units.

red cells are washed twice with the phosphate buffer solution¹ p_H 7.38, which, at this institute, is used throughout for dilutions of toxins and antitoxins and for the preparation of toxin-antitoxin mixtures, in place of the commonly employed 0.85 per cent NaCl-solution.

A series of mixtures containing 1 P. unit of A.T. in 1 c.c. is prepared, falling quantities of toxin are added and the volume of each mixture brought to 2 c.c. by addition of the phosphate buffer solution. The mixtures are allowed to stand on the bench for about fifteen minutes ; 0.5 c.c. of a 2 per cent emulsion of the washed rabbit red cells is added, and the tubes are placed in a bath at 37° C. for one hour. They are then put on the bench for an hour, and all the mixtures except those with complete hæmolysis are then centrifuged for two minutes ; the reading is then very easily done. To estimate the degree of hæmolysis, the mixture contained in two tubes with complete hæmolysis is diluted corresponding to 50 and 25 per cent hæmolysis respectively. In this way, the test dose, LII, of the toxin is determined as the quantity of toxin which is nearly, but not quite, neutralised by 1 P. unit of antitoxin (the tube showing a partial hæmolysis of approximately 25 per cent).

The results obtained by this method are given in Protocol VI, on facing page.

6. REPORT RECEIVED FROM DR. R. A. O'BRIEN,
RECORDING THE INVESTIGATIONS OF MR. A. T. GLENNY
AT THE WELLCOME PHYSIOLOGICAL RESEARCH LABORATORIES,
BECKENHAM, ENGLAND.

Provisional Standard for Staphylococcus Antitoxin.

The following is a summary of the results of our tests on the provisional standard, the two unknown sera (S and T) and our own

¹ This consists of 4 parts of *Sorensen's* phosphate buffer mixture p_H 7.38 + 1 part 2½ per cent solution of NaCl in distilled, CO₂-free water. This mixture is isotonic with the blood.

subsidiary standard (CPR 1895) which is 4.25 times the standard A.14958.

| Results in P. units for | Hæmolytic titrations (with rabbit cells) | | Intracutaneous (in guinea-pigs) | |
|-------------------------|---|------------------------|------------------------------------|------------------------|
| | α Toxin | $\alpha + \beta$ Toxin | α Toxin | $\alpha + \beta$ Toxin |
| Provisional standard | 20 | 20 | 20 | 20 |
| CPR 1895 | 315 | 310 | 300 | 300 |
| S | 200 | 200 | 200 | 180 |
| T | 140 | 140 | 135 | 135 |

The tendency for lower guinea-pig values may be due to titrations at so low a level as LR/10, which, in our opinion, is too low for accuracy. We have always used what is now equivalent to 7LR/10, and so we suggest LR/2 as suitable with the new unit.

7. REPORT RECEIVED FROM DR. G. F. PETRIE,
RECORDING THE INVESTIGATIONS OF DR. D. McCLEAN,
AT THE LISTER INSTITUTE, ELSTREE, ENGLAND.

Preliminary Hæmolytic and Intracutaneous Tests.

Preliminary tests by both the hæmolytic and intracutaneous methods were made in parallel against two freshly prepared toxins :

- (1) A toxin prepared in Bigger's medium and labelled B11.V ; LH dose = 0.15 c.c., Lr/10 dose = 0.035 c.c.
- (2) A toxin kindly supplied by Dr. R. A. O'Brien ; LH dose = 0.10 c.c., Lr/10 dose = 0.020 c.c.

The tests with these toxins gave consistent results and indicated that, by the hæmolytic test, sample S contained 180 P. units per c.c. and sample T contained 130 P. units per c.c., and that, by the intracutaneous test, sample S contained 170-180 P. units per c.c. and sample T contained 120 P. units per c.c.

Final Hæmolytic Tests.

There was, however, some indication that either the test dose of these toxins had not been determined within sufficiently narrow limits or that it had altered slightly during the period these tests were being made. The tests were therefore repeated with other samples of toxin, prepared in Bigger's medium, which had probably become stabilised and the test dose of which had been precisely determined. The results are given below:

*Determination of Test Dose of Toxin B28/V.**1st Test.*

| | | | | | | |
|--|------|------|------|------|------|------|
| Glycerinated standard A.T. (P units) | 1 | 1 | 1 | 1 | 1 | 1 |
| Toxin B28/V (c.c.) | 0.15 | 0.14 | 0.13 | 0.12 | 0.11 | 0.10 |
| Hæmolysis | 4 | 4 | 2 | 1 | 1 | 0 |

Note.—In all the tables 4 = complete hæmolysis ; 3, 2, 1 = degrees of partial hæmolysis ; 0 = no hæmolysis.

2nd Test.

| | | | | | | |
|--|------|------|------|------|------|------|
| Reconstituted dry standard A.T. (P. units) | 1 | 1 | 1 | 1 | 1 | 1 |
| Toxin B 28/V (c.c.) | 0.16 | 0.15 | 0.14 | 0.13 | 0.12 | 0.11 |
| Hæmolysis | 4 | 3 | 2 | 1 | tr | 0 |

The test with the reconstituted dry standard, when repeated, gave the same result.

In the first assay of the antitoxins of unknown potency, the test dose of the toxin was taken as 0.13 c.c. ; in the second assay, the test dose was increased to 0.14 c.c., with the following results :

First assay of antitoxins S and T.

| | | | | | | |
|-------------------------|-------|-------|-------|-------|-------|-------|
| Toxin B 28/V (c.c.)... | 0.13 | 0.13 | 0.13 | 0.13 | 0.13 | 0.13 |
| Antitoxin S (c.c.) | 1/220 | 1/210 | 1/200 | 1/190 | 1/180 | 1/170 |
| Hæmolysis | 4 | 3 | 2 | tr | 0 | 0 |
| Antitoxin T (c.c.) | 1/150 | 1/145 | 1/140 | 1/135 | 1/130 | 1/125 |
| Hæmolysis | 4 | 3 | 2 | 1 | 0 | 0 |

Second assay of antitoxins S and T and assay of another antitoxin, S 17, intended as a laboratory standard.

| | | | | | | | | |
|-----------------------------|-------|-------|-------|-------|-------|-------|-------|-------|
| Toxin B28/V (c.c.) | 0.14 | 0.14 | 0.14 | 0.14 | 0.14 | 0.14 | 0.14 | 0.14 |
| Antitoxin S (c.c.) | 1/220 | 1/200 | 1/200 | 1/190 | 1/180 | 1/170 | 1/160 | 1/150 |
| Hæmolysis | 4 | 3 | 2 | 1 | 1 | 0 | 0 | 0 |
| Antitoxin T (c.c.) | 1/150 | 1/145 | 1/140 | 1/135 | 1/130 | 1/125 | 1/120 | 1/110 |
| Hæmolysis | 4 | 4 | 4 | 3 | 2 | 1 | 1 | 0 |
| Antitoxin S 17 (c.c.) | 1/310 | 1/330 | 1/320 | 1/310 | 1/300 | 1/290 | 1/280 | 1/270 |
| Hæmolysis | 4 | 3 | 3 | 2 | 1 | tr | 0 | 0 |

Estimated potency from the final hæmolytic tests :

Antitoxin S = 200 units per c.c.

Antitoxin T = 130-140 units per c.c.

Antitoxin S 17 = 310 units per c.c.

Final Intracutaneous Tests.

The toxin B2/VI used was prepared in the same medium, and found to have a smaller Lr/10 dose than B28/V.

In all the intracutaneous tests on the guinea-pig, considerable difficulty was experienced, owing to variations in the response of individual animals, both in assessing the correct test dose of the toxin and in deciding on the "end points" of the titrations.

*Determination of Test Dose of Toxin B2/VI.**1st Test (three guinea-pigs).*

| | | | | | |
|--------------------------------|-------|-------|-------------------------------------|-------|-------|
| Standard A.T. (P. units) | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| Toxin B2/VI (c.c.) | 0.045 | 0.040 | 0.0375 | 0.035 | 0.030 |
| Reactions | RN | RN | RN 2 guinea-pigs RN 1 guinea-pig | r | tr |

First Assay of Antitoxins S, T and S 17.

(Test dose taken as 0.0375 c.c.)

| | | | | | | |
|--------------------------|--------|--------|--------|--------|--------|--------|
| Toxin B2/VI (c.c.) .. | 0.0375 | 0.0375 | 0.0375 | 0.0375 | 0.0375 | 0.0375 |
| Antitoxin S (c.c.) | 1/2200 | 1/2100 | 1/2000 | 1/1900 | 1/1800 | 1/1700 |
| Reactions | rN | rN | rN | rN | rn | r |
| Standard A.T. (c.c.) .. | 1/220 | 1/210 | 1/200 | 1/190 | 1/180 | |
| Reactions | rn | rn | ? | r | r | |
| Antitoxin T (c.c.) | 1/1500 | 1/1450 | 1/1400 | 1/1350 | 1/1300 | 1/1250 |
| Reactions | RN | RN | RN | RN | rn | rn |
| Standard A.T. (c.c.) .. | 1/220 | 1/210 | 1/200 | 1/190 | 1/180 | |
| Reactions | R?n | R | R | r | r | |
| Antitoxin S 17 (c.c.) .. | 1/340 | 1/330 | 1/320 | 1/310 | 1/300 | |
| Reactions | RN | RN | RN | RN | rn | |
| Standard A.T. (c.c.) .. | 1/220 | 1/210 | 1/200 | 1/190 | 1/180 | |
| | rn | r?n | r?n | r | tr | |

R = large reaction. N = large area of necrosis.

r = small reaction. n = small area of necrosis.

These animals showed a definite variation in the intensity of the lesions produced by the test dose of toxin when added to doses of standard antitoxin with 5 per cent differences. Moreover, in none of them was the lesion produced by the test dose of toxin when added to 0.1 unit of antitoxin as intense as those obtained in the animals used for the determination of the test dose.

The results indicate that the potency of antitoxin S = 180 units per c.c., the potency of antitoxin T = less than 125 units per c.c., the potency of antitoxin S 17 = less than 300 units per c.c.

Second Assay of Antitoxins S, T and S 17.

The test dose was redetermined in duplicate and the assay of the antitoxins was repeated.

Determination of Test Dose of Toxin B2/V1.

(Test dose taken as 0.045 c.c.)

| | | | | | | | | |
|--|-------|--------|--------|--------|--------|--------|--------|--------|
| Standard A.T. (P. units) . . . | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| Toxin B2/V1 (c.c.) | 0.050 | 0.0475 | 0.045 | 0.0425 | 0.040 | 0.0375 | 0.0350 | 0.0325 |
| Reaction, first guinea-pig . | Rn | Rn | Rn | r | r | r | r | r |
| Reaction, second guinea-pig. | RN | RN | RN | R | R | r | r | r |
| Toxin B2/V1 (c.c.) | | 0.045 | 0.045 | 0.045 | 0.045 | 0.045 | 0.045 | 0.045 |
| Antitoxin S (c.c.) | | 1/2100 | 1/2000 | 1/1900 | 1/1800 | 1/1700 | 1/1600 | 1/1500 |
| Reactions | | RN | RN | RN | RN | rn | r?n | r |
| Control (3 injections of test dose + 0.1 P. unit) . | | r?n | r?n | r | | | | |
| Antitoxin T (c.c.) | | 1/1500 | 1/1450 | 1/1400 | 1/1350 | 1/1300 | 1/1250 | 1/1200 |
| Reactions | | RN | RN | RN | RN | RN | rn | rn |
| Controls (as above) | | r | r | rn | | | | |
| Antitoxin S 17 (c.c.) | | 1/3300 | 1/3200 | 1/3100 | 1/3000 | 1/2900 | 1/2800 | 1/2700 |
| Reactions | | RN | RN | RN | RN | RN | rn | rn |
| Controls (as above) | | r | r | r | | | | |

In these tests, the control was arranged, not by varying the dilutions of standard antitoxin and mixing them with the test dose of toxin as in the previous assay, but by giving to each animal three injections of the same mixture containing 0.1 P. unit mixed with the test dose.

The control reactions were again weaker than those obtained in the animals used for determining the test dose, thus suggesting that the dose of toxin chosen was too small.

The results, however, indicate that the potency of antitoxin S = 160 units per c.c., the potency of antitoxin T = less than 120 units per c.c., the potency of antitoxin S 17 = less than 270 units per c.c.

The above tests were then repeated, using as a test dose 0.05 c.c. of the same toxin.

Third Assay of Antitoxins S, T and S 17.

| Toxin 132 /VI (c.c.) | 0.050 | 0.050 | 0.050 | 0.050 | 0.050 | 0.050 | 0.050 |
|--|---------|---------|---------|---------|---------|---------|---------|
| Antitoxin S (c.c.) | 1 /1900 | 1 /1800 | 1 /1700 | 1 /1600 | 1 /1500 | 1 /1400 | 1 /1300 |
| Reactions | RN | RN | RN | RN | r | r | r |
| Controls (3 injections of test dose + 0.1 P. unit) | RN | r?n | rn | | | | |
| Antitoxin T (c.c.) | 1 /1400 | 1 /1300 | 1 /1250 | 1 /1200 | 1 /1150 | 1 /1100 | 1 /1000 |
| Reactions | RN | RN | RN | RN | rn | rn | r |
| Controls (as above) | rn | r?n | r | | | | |
| Antitoxin S 17 (c.c.) . . . | 1 /3300 | 1 /3000 | 1 /2900 | 1 /2800 | 1 /2700 | 1 /2600 | 1 /2500 |
| Reactions | RN | RN | RN | RN | RN | RN | RN |
| Controls (as above) | RN | RN | RN | | | | |

The reaction with 1/2500 c.c. of S 17, though large, was definitely smaller than any of the three control reactions.

The variation in the control reactions in the three guinea-pigs is again noticeable.

The results indicate that the potency of antitoxin S = 160 units per c.c., the potency of antitoxin T = 110-115 units per c.c., the potency of antitoxin S 17 = 260 units per c.c.

Summary.

The hæmolytic tests have given clear-cut results and the estimated potencies are as follows :

Antitoxin S = 200 units per c.c.

Antitoxin T = 130-140 units per c.c.

Antitoxin S 17 = (proposed laboratory standard)
= 310 units per c.c.

The potency of each of the three antitoxins, as estimated by the combined results of the three intracutaneous tests, is as follows :

Antitoxin S = 160-180 units per c.c.

Antitoxin T = 110-115 units per c.c.

Antitoxin S 17 = 260 units per c.c.

The titres, when estimated by the intracutaneous method, are thus consistently lower than those obtained by the hæmolytic method. Moreover, individual guinea-pigs showed considerable variation in response to intracutaneous injection of the same toxin-antitoxin mixtures.

8. REPORT RECEIVED FROM DR. G. W. MCCOY,
RECORDING THE INVESTIGATIONS OF DR. FLOYD C. TURNER
AT THE NATIONAL INSTITUTE OF HEALTH, WASHINGTON.

A toxin made at Washington was tested against the proposed standard antitoxin. By the hæmolytic method, the following results were obtained :

| | | | | | |
|--|------|------|------|------|------|
| Proposed standard antitoxin (P. units) | 1 | 1 | 1 | 1 | 1 |
| Toxin (C24-10.26.33-frozen) (c.c.) | 0.07 | 0.06 | 0.05 | 0.04 | 0.03 |
| Hæmolysis | C | C | P | 0 | 0 |

The test dose, or LH, was taken to be 0.05 c.c.

The toxin used was made by inoculating strain No. 24 of the Connaught Laboratories, Toronto, Canada, into broth to which had been added 0.5 per cent $MgSO_4$ and sterilised twice by steam at 15 lb. for fifteen minutes and p_H adjusted to 7. Grown six days at 37° C. in 30 per cent CO_2 and then Berkefeld filtered and 10,000 merthiolate added as preservative, this toxin was filtered on October 26th, and kept in a frozen state until used.

Using the "test dose" of toxin so elicited—i.e., 0.05 c.c.—the antitoxins S and T were tested by the hæmolytic method.

| | | | | | | |
|--|-------|-------|-------|-------|-------|-------|
| Toxin (C24-10.26.33-frozen) (c.c.) | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 |
| Antitoxin S. (c.c.) | 1/110 | 1/125 | 1/140 | 1/155 | 1/170 | 1/185 |
| Hæmolysis | 0 | 0 | tr | C | C | C |

Result.—Estimated potency *antitoxin S*, about 140 P. units per c.c.

| | | | | | | |
|--|------|------|------|------|-------|-------|
| Toxin (C24-10.26.33-frozen) (c.c.) | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 |
| Antitoxin T. (c.c.) | 1/50 | 1/65 | 1/80 | 1/95 | 1/110 | 1/125 |
| Hæmolysis | 0 | 0 | 0 | tr | C | C |

Result.—Estimated potency antitoxin T, about 95 P. units per c.c.

Determination of $\frac{I.R}{5}$ Dose of Toxin C24-10.26.33-frozen.

| | | | | | |
|--|------|-------|-------|-------|-------|
| Standard antitoxin (P. units) . . | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 |
| Toxin (C24-10.26.33 - frozen) (c.c.) | 0.02 | 0.018 | 0.016 | 0.014 | 0.012 |
| Results (skin necrosis) | + | + | ± | 0 | 0 |

Toxin 0.012 c.c., without antitoxin, used as control.

Result.—Test dose, $\frac{I.R}{5}$, taken as 0.016 c.c.

Up to the present, no intracutaneous tests have been made with this test dose of toxin to determine the potency of other serums.

Determination of the Test Dose of Toxin C24-10.26.33-frozen by the Method of Intravenous Injection in Mice.

| Provisional standard antitoxin | Toxin C24-10.26.33-frozen (c.c.) | Proportion of mice dead within three days |
|--------------------------------|----------------------------------|---|
| 1 P. unit | 0.03 | 0/10 |
| | 0.04 | 0/10 |
| | 0.05 | 10/10 |
| | 0.06 | 10/10 |
| | 0.07 | 10/10 |

Result.—Test dose taken to be about 0.045 c.c.

*Determination of the Test Dose of the Toxin C24-10.26.33 by
the Method of Intraperitoneal Injection in Mice.*

| Provisional standard antitoxin | Toxin C24-10.26.33-frozen | Proportion of mice dead within three days |
|-----------------------------------|---------------------------|--|
| 1 P. unit | 0.03 | 0 10 |
| | 0.04 | 3 10 |
| | 0.05 | 10 10 |
| | 0.06 | 10 10 |
| | 0.07 | 10 10 |
| | 0.07 | 10 10 |

Result.—Test dose of the toxin taken to be about 0.045 c.c.

Summary.

1. No sample of staphylococcus toxin was distributed with the standard antitoxin for the purpose of the international enquiry. At the time of distribution, our own stocks of suitable test toxins were low, and, until recently, were of low potency. Moreover, it appeared that questions relating to the suitability of the standard, its practical application in assay, and the possible occurrence of toxins and antitoxins differing qualitatively from what may be regarded as the characteristic toxin and antitoxin would be more completely investigated by the use of as many different toxins, made from as many different strains and by as many different methods as possible. By the determination of the test dose of these various toxins by means of the standard antitoxin, and the assay of antitoxins S (a pool of British antitoxins) and T (a pool of Canadian antitoxins) by means of them, information regarding these questions is provided for the consideration of the Commission.

2. The results of all the determinations of the potency of the antitoxins S and T are summarised in the following table.

The results of a large number of potency determinations carried out at Hampstead, in which seven different toxins and five different methods were used, indicate that *antitoxin S contains 200 provisional units per c.c.* and *antitoxin T contains 133 provisional units per c.c.*

The values returned from the Melbourne, Brussels, Copenhagen and Beckenham laboratories are practically identical with those obtained at Hampstead.

Values returned by the Different Investigators for the Potency of Antitoxins S and T.

| Antitoxin | Laboratory | P. units per c.c. | | | | | |
|------------|---------------|--|--|------------------|--------------|------------------|--|
| | | Method of assay | | | | | |
| | | Hemolytic-rabbit cells | Intracutaneous | | Mouse | | |
| Guinea-pig | Rabbit | | Intra-venous | Intra-peritoneal | | | |
| S .. | Hampstead .. | 200 ; 200 ; 200 ; 200 | 200 ; 200 ; 190 ; 200 ; 200 ; 200 ; | 200 | 200 | 200 | |
| | Melbourne .. | 196 | — | 200 | — | — | |
| | Brussels | 210 ; 210 ; 215 ; 220 ; 220-225 | 215-220 | — | — | — | |
| | Toronto | 159 | 150 | — | — | 150 | |
| | Copenhagen .. | 200 | — | 199 ; 190 | — | — | |
| | Beckenham .. | 200 ; 200 | 200 ; 180 | — | — | — | |
| | Elstree | 200 | 180 ; 160 ; 160 | — | — | — | |
| | Washington . | 140 | — | — | — | — | |
| T .. | Hampstead .. | 150 ; ca. 140 ; 140 ; 140 ; 130-140 ; 130 ; 150 ; 140 | 120 ; 120 ; 120-130 ; 125 | — 130 | — 140 | — ca. 140 | |
| | Melbourne .. | 139 | — | 138 | — | — | |
| | Brussels | 135 ; 140 ; 145 ; 145 | 130 | — | — | — | |
| | Toronto | 114 | 115 | — | — | 110 | |
| | Copenhagen .. | 143 | — | 137 | — | — | |
| | Beckenham .. | 140 ; 140 | 135 ; 135 | — | — | — | |
| | Elstree | 130-140 | <125 ; <120 110-115 | — | — | — | |
| | Washington . | 95 | — | — | — | — | |

Some of the values returned from the Elstree laboratory, and all the values returned from the Toronto and the Washington laboratories are lower, and the difference is somewhat greater than is normally to be expected even in an investigation of this kind in which the subject itself is rather new and the practical experience of the participating workers variable. At this stage, it is not possible to attempt a full explanation of these lower values. It should be noted, in any case, that the detection of the discrepancy

is due to the remarkable accuracy and uniformity of the results obtained in the other laboratories. Enquiries so far made suggest that the discrepancy is due, in part, to differences in the way in which the assays are carried out and their results interpreted, and, in part, to the use of toxins, either immediately after preparation or preserved in such a way that the normal maturation is prevented.

CONCLUSIONS.

It is suggested that the following conclusions may be drawn from the results presented above :

(1) That staphylococcus antitoxin can be assayed with a high degree of accuracy ;

(2) That methods of assay in which toxin-antitoxin mixtures are tested for hæmolytic action on rabbits' red blood corpuscles, or by intracutaneous injection into guinea-pigs or rabbits, or by intravenous or intraperitoneal injection into mice, are simple and practicable and yield consistent results when applied by different investigators ;

(3) That dry, stable preparations of staphylococcus antitoxin can be prepared and assayed in terms of an accepted standard preparation ; and that accurately standardised solutions, suitable for distribution for purposes of biological assay, can be prepared.

RECOMMENDATION.

It is recommended that the Permanent Commission on Biological Standardisation of the Health Organisation of the League of Nations should accept the dry stable preparation of staphylococcus antitoxin prepared at the National Institute for Medical Research, London, as the International Standard for this antitoxin.

It is further recommended that the unit accepted for international use shall be defined as the specific neutralising activity for staphylococcus toxin contained in 0.5 mgrm. of the standard preparation.

* * *

REPORT RECEIVED FROM DR. H. SCHMIDT,
 INSTITUTS FÜR EXPERIMENTELLE THERAPIE "EMIL VON BEHRING",
 MARBURG, GERMANY.

(The following results were received from Dr. Schmidt after the report embodying the results of the international enquiry had been prepared.)

My experiments have been very much hampered by not having a sufficiently strong toxin, and all efforts to get a stronger toxin such as required for comparison with the example cited in the Memorandum failed us so far.

I. *Titration of Toxin* (variable amount of toxin + 1 P. unit A.T. ; volume made 2 c.c. in each tube and 1 drop of a 10 % suspension of washed rabbit's red blood cells added).

| | | | | | | | |
|---------------------------|------|-------|------|-------|------|-------|-----|
| Toxin (c.c.) | 0.35 | 0.325 | 0.30 | 0.275 | 0.25 | 0.225 | 0.2 |
| Hæmolysis (after 10 hrs.) | C | C | C | tr-p | 0 | 0 | 0 |
| Hæmolysis (after 20 hrs.) | C | C | C | tr | p | 0 | 0 |

0.265 c.c. toxin taken as test dose.

II. *Preliminary Tests of Antitoxins S and T.*

| | | | | |
|--------------------------|-------|-------|-------|-------|
| Antitoxin S (c.c.) | 1/100 | 1/200 | 1/400 | 1/800 |
| Hæmolysis | 0 | 0 | C | C |
| Antitoxin T (c.c.) | 1/100 | 1/200 | 1/400 | 1/800 |
| Hæmolysis | 0 | C | C | C |

III. *Repeated Tests of Antitoxins S and T.*

| | | | | |
|--------------------------|----------|-------|-------|-------|
| Antitoxin S (c.c.) | 1/200 | 1/250 | 1/300 | 1/350 |
| Hæmolysis | nearly 0 | C | C | C |

Antitoxin S contains "probably 225 units per c.c."

| | | | | |
|--------------------------|-------|-------|----------|-------|
| Antitoxin T (c.c.) | 1/100 | 1/125 | 1/150 | 1/175 |
| Hæmolysis | 0 | 0 | nearly 0 | G |

Antitoxin T contains "probably 160 units per c.c."

(Note.—Dr. Schmidt has not attempted a very accurate assay of the antitoxins S and T, and has used only the hæmolytic method. Nevertheless, his results are interesting, as the values he obtains, by the use of his toxin, are of the same order as those returned by the Hampstead, Melbourne, Brussels, Copenhagen and Beckenham Institutes.)

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APPENDIX.**MEMORANDUM ON A PROVISIONAL STABLE STANDARD FOR
STAPHYLOCOCCUS ANTITOXIN.**

By

Percival HARTLEY and Margaret LLEWELLYN SMITH**(from the National Institute for Medical Research, Hampstead, London).**

A dry, stable, provisional standard for staphylococcus antitoxin has been prepared at the National Institute for Medical Research, London, and can now be supplied to research workers interested in the study of staphylococcus toxin, toxoid and antitoxin.

It seems likely that a common basis of standardisation for such products will soon be required. If the provisional standard above mentioned meets with approval for the purpose indicated, it is at the disposal of the Permanent Commission on Biological Standardisation, either for adoption as the International standard or as the basis of such standard as the Commission may decide to recommend for adoption.

In order that the Permanent Commission may be furnished with the necessary data and information, the standard material is supplied for such experiments as individual workers may wish to carry out. In the paragraphs which follow, investigations are suggested which are likely to provide the kind of information required.

The reaction between staphylococcus toxin and antitoxin resembles other toxin-antitoxin reactions very closely, and suggests that the system of biological standardisation and assay adopted should be based on the same general principles as those upon which the standardisation of diphtheria, tetanus and other antitoxins have been successfully established. Accordingly, a staphylococcus antitoxin, reduced to the absolutely dry condition to ensure its permanence, is proposed for adoption as the standard preparation; it is suggested that the unit should be defined as the specific biological activity contained in a certain weight of the dry, stable standard preparation, that the "test toxins" used for assay purposes should be standardised in terms of the antitoxin standard and unit, and that such standardised test toxins should then be employed for the assay of staphylococcus antitoxins.

THE STAPHYLOCOCCUS TOXINS USED.

These have been prepared by the method described by PARISH and CLARK (1932; *J. Path. Bact.*, Vol. 35, page 251). The strain which, in this Institute, has yielded the most potent toxins is "Wood 86", kindly supplied by Dr. F. M. BURNET. From a study of their properties, the toxins prepared in this Institute

appear to be identical with those described in the recent literature. They are lethal for rabbits, guinea-pigs and mice ; they produce characteristic necrotic lesions when injected into the skin of rabbits and guinea-pigs, and they cause hæmolysis of rabbits' red cells *in vitro*. All these biological properties of the toxin are neutralised by the staphylococcus antitoxin which has been used in this Institute for the preparation of the provisional standard.

THE PROVISIONAL STANDARD STAPHYLOCOCCUS ANTITOXIN.

This has been prepared by the usual method adopted in this Institute, whereby the final product is contained in a series of sealed ampoules, each containing the same quantity of the dry standard. Actually, in the case of the provisional standard for staphylococcus antitoxin, 140 sealed ampoules, each containing 0.4589 ± 0.0016 grm. of the dry standard, are available ; they are preserved under conditions ensuring permanence. Repeated tests have shown that the product is sterile.

THE PROVISIONAL UNIT.

It is suggested that the unit for staphylococcus antitoxin be defined as *the specific neutralising activity for staphylococcus toxin contained in 0.5 mgrm. of the standard preparation.*

In making this proposal as to the dimensions of the provisional unit for staphylococcus antitoxin, consideration has been given to

- (a) The notation used in the labelling of staphylococcus antitoxins intended for clinical use ;
- (b) The use of the standard, and the unit, for the standardisation of "test toxins" ;
- (c) The form of issue of the standard ultimately to be adopted.

(a) It is desirable that the potency of new antitoxic sera proposed for prophylaxis and treatment should, if possible, be expressed in numbers of the same order of magnitude as those with which physicians are familiar in the case of diphtheria, tetanus and other antitoxins.

It is reasonable to expect that the potency of staphylococcus antitoxins prepared in the future will be greater than the potency of antitoxins prepared at present. If the unit now suggested were adopted, the values assigned to good specimens of concentrated antitoxin already being prepared for practical use would vary between 300 and 800 units, while those for natural sera are from 100 to 200 units. The potencies, thus expressed in terms of the provisional unit, may be considered low ; but it may be pointed out that they are of the same order as those for low potency diphtheria and tetanus antitoxins ; and if antitoxins prepared in the future attain even five times the potency of those prepared at present, the figures will still be comparable in magnitude with those in present-day use for diphtheria and tetanus antitoxins.

(b) It is convenient for the "test dose" of toxins used in the biological assay of antitoxins to be determined in terms of 1 unit of antitoxin or a simple fraction

or multiple of the unit. On the basis of the provisional unit suggested, toxins have been obtained, the test dose of which lies between 0.1 c.c. and 1 c.c. ; in the experience of this laboratory, the test dose contains an adequate amount of toxin to give reasonable sharpness to titrations—*i.e.*, it contains a large multiple of the dose of the unmixed toxin producing the desired biological reaction. Moreover, the possibility of more potent toxins being prepared in the future and the determination of the “test dose” against quantities of anti-toxin larger than 1 unit (with consequent increase in the accuracy of titrations) has been borne in mind.

(c) In order to economise the standard preparation and, at the same time, provide it for use in a stable, convenient and familiar form, the possibility of issuing the standard preparation in the form of a glycerol solution has been investigated. A solution in glycerol-saline (glycerol, 2 parts ; normal salt solution, 1 part), of which 1 c.c. contains 10 mgrm. (20 provisional units) of the dry, stable standard preparation, can be prepared without difficulty. Thus, from this standard solution in glycerol-saline, dilutions can readily be made, such that 1 c.c. contains 2, 1, or any desired fraction of the provisional unit.

METHODS OF ASSAY.

It is expected that each worker will employ the method, or methods, of assay with which he is most familiar and in which he has confidence. There is such a large degree of permissible variation in regard to such details as the manner of making the toxin-antitoxin mixtures, the time and temperature during which the mixtures are left before the indicator is added or otherwise applied, the “end-point” adopted, etc., that only the general principles on which a method of assay is based will be indicated in the protocol which follows, and no attempt will be made to describe any particular methods in detail. Following the protocol, a few short notes are added, relating to each of the methods of assay, as employed in this Institute.

Protocol (abridged).

Showing (a) determination of the “test dose” of staphylococcus toxin, No. 1b, and (b) assay of a staphylococcus antitoxin, No. 10, by (1) the hæmolytic method (rabbits’ red blood corpuscles), (2) the intracutaneous method (guinea-pig), (3) the intravenous method (mouse) and (4) the intraperitoneal method (mouse).

1. *The Hæmolytic Method (Rabbits’ Red Blood Corpuscles).*

(a) *Determination of test dose of toxin 1b.*

| | | | | | |
|-------------------------------|------|------|------|------|------|
| Standard A.T. (P. units)..... | 1 | 1 | 1 | 1 | 1 |
| Toxin 1b (c.c.) | 0.17 | 0.16 | 0.15 | 0.14 | 0.13 |
| Hæmolysis | c | c | p | tr | 0 |

Test dose (LH) taken as 0.15 c.c.

STAPHYLOCOCCUS ANTITOXIN

(b) Assay of staphylococcus antitoxin No. 10.

| | | | | | | |
|-----------------------------------|-------|-------|-------|-------|-------|-------|
| Toxin 1b (c.c.) | 0.15 | 0.15 | 0.15 | 0.15 | 0.15 | 0.15 |
| Antitoxin No. 10 (c.c.) | 1/360 | 1/345 | 1/330 | 1/315 | 1/300 | 1/285 |
| Hæmolysis | c | c | p | tr | 0 | 0 |

Estimated potency of A.T. No. 10 = 330 P. units.

c = complete hæmolysis : tr = trace of hæmolysis
p = partial hæmolysis : 0 = no hæmolysis

2. The Intracutaneous Method (Guinea-pig).

(a) Determination of test dose of toxin 1b (v 0.1 P. unit).

| | | | | | |
|------------------------------------|------|-------|-------|-------|-------|
| Standard A.T. (P. units) | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| Toxin 1b (c.c.) | 0.03 | 0.027 | 0.025 | 0.023 | 0.021 |
| Reaction | + | + | tr | 0 | 0 |

Test dose $\frac{Lr}{(10)}$ taken as 0.025 c.c.

(b) Assay of staphylococcus antitoxin No. 10.

| | | | | | |
|-----------------------------------|--------|--------|--------|--------|--------|
| Toxin 1b (c.c.) | 0.025 | 0.025 | 0.025 | 0.025 | 0.025 |
| Antitoxin No. 10 (c.c.) | 1/3600 | 1/3300 | 1/3000 | 1/2750 | 1/2500 |
| Reaction | + | ± | tr | 0 | 0 |

Estimated potency of A.T. No. 10 = 300 (+) P. units.

(c) Determination of test dose of toxin 1b (v 0.2 P. unit).

| | | | | | |
|------------------------------------|-------|-------|-------|-------|-------|
| Standard A.T. (P. units) | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 |
| Toxin 1b (c.c.) | 0.050 | 0.046 | 0.042 | 0.038 | 0.035 |
| Reaction | L+ | S+ | ± | 0 | 0 |

Test dose $\frac{Lr}{(5)}$ taken as 0.042 c.c.

(d) Assay of staphylococcus antitoxin No. 10.

| | | | | | |
|-----------------------------------|--------|--------|--------|--------|--------|
| Toxin 1b (c.c.) | 0.042 | 0.042 | 0.042 | 0.042 | 0.042 |
| Antitoxin No. 10 (c.c.) | 1/1800 | 1/1650 | 1/1500 | 1/1375 | 1/1250 |
| Reaction | + | ± | 0 | 0 | 0 |

Estimated potency of A.T. No. 10 = 330 P. units.

3. *Intravenous Method (Mouse).*(a) *Determination of test dose of toxin 1b (sum of 6 determinations).*

| Standard antitoxin | Toxin 1b (c.c.) | Proportion of mice dead within three days |
|--------------------|-----------------|---|
| 1 P. unit. | 0.19 | 0/8 |
| | 0.20 | 2/11 |
| | 0.21 | 6/11 |
| | 0.22 | 13/15 |
| | 0.23 | 12/12 |

Test dose taken as 0.21 c.c.

(b) *Assay of staphylococcus antitoxin No. 10.*

| Toxin 1b | Antitoxin No. 10 (c.c.) | Proportion of mice dead within three days |
|----------------|-------------------------|---|
| 0.21 c.c. | 1/330 | 3/3 |
| | 1/315 | 3/3 |
| | 1/300 | 2/3 |
| | 1/285 | 0/3 |
| | 1/270 | 0/3 |

Estimated potency of A.T. No. 10 = 300 units.

4. *Intraperitoneal Method (Mouse).*(a) *Determination of test dose of toxin 1b (sum of 5 determinations).*

| Standard antitoxin | Toxin 1b (c.c.) | Proportion of mice dead within three days |
|--------------------|-----------------|---|
| 1 P. unit. | 0.19 | 0/5 |
| | 0.20 | 1/7 |
| | 0.21 | 7/11 |
| | 0.22 | 7/7 |
| | 0.23 | 10/10 |

Test dose taken as 0.21 c.c.

(b) *Assay of staphylococcus antitoxin No. 10.*

| Toxin 1b | Antitoxin No. 10 (c.c.) | Proportion of mice dead within three days |
|----------------|-------------------------|---|
| 0.21 c.c. | 1/360 | 3/3 |
| | 1/330 | 5/6 |
| | 1/300 | 2/6 |
| | 1/275 | 0/3 |
| | 1/250 | 0/3 |

Estimated potency of A.T. No. 10 = 300 (+) P. units.

(1) In this Institute, in the hæmolytic method, the test dose employed (LH) is the quantity of toxin which, when mixed with 1 provisional unit of antitoxin, causes partial hæmolysis of the rabbits' red blood corpuscles added as indicator.

It is emphasised that, in this method, it is essential that well washed rabbits' red blood corpuscles are to be used as indicator ; the use of the red blood corpuscles of other animals is inadmissible.

(2) In the intracutaneous test in this Institute, guinea-pigs are preferred to rabbits, 0.2 c.c. quantities of the toxin-antitoxin mixtures being injected. The test dose $\frac{Lr}{(10)}$ is the quantity of toxin which, when mixed with 0.1 provisional unit of antitoxin, causes a small but characteristic necrotic lesion in the skin of the guinea-pig.

White or light-coloured guinea-pigs weighing from 300 to 400 grm. are suitable, and not more than five injections should be made on each flank of the animal.

Readings are taken twenty-four and forty-eight hours after injection ; when greatly under-neutralised mixtures are injected, the evidence of free toxin can often be clearly seen a few hours after injection.

On every occasion on which the final titration of an antitoxin of unknown potency is being made, injections of mixtures of the test toxin and the standard antitoxin are made on the same animal for comparison.

Greater accuracy in the assay of an antitoxin of unknown potency may be obtained by employing the $\frac{Lr}{(5)}$ dose of toxin in the tests.

(3) In the intravenous method (mouse), the test dose employed is the quantity of toxin which, when mixed with 1 provisional unit of antitoxin, and injected intravenously into the tail veins of groups of mice, causes the death of half the mice injected within three days.

In this test, mixtures are prepared of which 0.5 c.c. quantities contain 1 provisional unit + varying quantities of the toxin under test (for test dose determination) ; or the test dose of the toxin + varying quantities of the antitoxin under test (for the assay of antitoxins of unknown potency) ; and 0.5 c.c. quantities of the mixtures are injected into groups of mice.

(4) In the intraperitoneal method (mouse) the procedure is exactly the same as for the intravenous method (mouse), except that 0.5 c.c. quantities of the prepared mixtures are injected intraperitoneally.

RESULTS OF THE ASSAY OF STAPHYLOCOCCUS ANTITOXINS FROM VARIOUS LABORATORIES.

In the following table, the results of the assay of a number of staphylococcus antitoxins, in terms of the provisional unit, are collected. The antitoxins are arranged, for convenience of reference, in three groups :

(1) *Staphylococcus Antitoxins, A to H.*—These were prepared in an English laboratory, A, any information as to their potency or preparation being designedly withheld until the potency tests carried out in this

Assay of Staphylococcus Antitoxins from Different Laboratories in Terms of the Provisional Unit.

| Anti-toxin | Nature of preparation, etc. | Provisional units of staphylococcus antitoxin per c.c. | | | |
|------------|---|--|-----------|-------------------------------------|-----------|
| | | Hæmolytic method | Tested to | Intra-cutaneous method (guinea-pig) | Tested to |
| | | | % | | % |
| A | Injection of killed staphylococci and toxin | 8-16 | 100 | 16 | 15 |
| B | Injection of toxin alone | 70-120 | — | 100-110 | 10 |
| C | B, concentrated | 240 | 20 | 280 | 15 |
| D | A 1/3.3 dilution of C, Seitz filtered | 60-120 | 100 | 60 | 15 |
| E | Horse E, after first immunisation with toxin | 44-48 | 10 | 50 | 25 |
| F | Horse E, after second immunisation with toxin | 40-44 | 10 | 40 | 25 |
| G | Concentrated antitoxin from bleedings after first to fourth immunisations of horse E. | 320 | 10 | — | — |
| H | Horse E, pool of bleedings after fifth immunisation | 200-240 | 20 | — | — |

| | | Lab. B potency determinations in terms of P. units | | | | |
|----|---------------------------|--|-----|----|-----|----|
| 1 | Natural A.T. | (70) | 70 | 10 | 70 | 10 |
| 2 | Natural A.T. | 155 | 150 | 10 | 145 | 10 |
| 3 | Concentrated A.T. | 385 | 360 | 10 | 380 | 10 |
| 4 | Concentrated A.T. | — | 800 | 10 | — | — |
| 5 | Concentrated A.T. | — | 300 | 15 | — | — |
| 6 | Concentrated A.T. | 770 | 760 | 10 | — | — |
| 7 | Concentrated A.T. | 840 | 760 | 10 | — | — |
| 8 | Concentrated A.T. | 450 | 440 | 10 | — | — |
| 9 | Concentrated A.T. | 250 | 250 | 10 | 220 | 15 |
| 10 | Concentrated A.T. | 350 | 330 | 10 | 300 | 10 |

| | | | | | |
|----|--|-------|----|-------|----|
| 11 | Natural serum | 12 | 20 | 12 | 20 |
| 12 | Pooled plasma from several bleedings | 110 | 5 | 105 | 5 |
| 13 | Concentrated A.T. | 80 | 15 | 80-90 | 10 |
| 14 | Nature of preparation not stated. | 360 | 10 | 330 | 10 |
| 15 | Nature of preparation not stated. | 65 | 10 | 65 | 10 |
| 16 | Nature of preparation not stated. | ca. 5 | 20 | ca. 5 | 10 |

Institute had been completed. Subsequently, a short history of each antitoxin tested was supplied by laboratory A : these histories are summarised in column 2 of the table.

(2) *Staphylococcus Antitoxins, Nos. 1 to 10.*—These were prepared in another English laboratory, B. They had been tested in comparison with a temporary laboratory standard antitoxin (No. 1 in the table) adopted for local use in laboratory B. Since the potency of this temporary laboratory standard could be easily and precisely determined in terms of the provisional unit, it was possible by a simple calculation to restate the potency values obtained in laboratory B for the antitoxins Nos. 1 to 10 in terms of the provisional unit now proposed ; thus, the results of the potency tests carried out in this Institute could be directly compared with those obtained in Laboratory B (see column 2). These two series of results are given in the table.

(3) *Staphylococcus Antitoxins, Nos. 11 to 16.*—The antitoxins in this group were supplied by different laboratories in Europe, Canada and the United States of America.

Little comment on the results given in the preceding table is necessary. No attempt was made to assay the antitoxins to the ultimate limits of accuracy of which the methods of assay are capable. The figures illustrate the order of magnitude which, on the basis of the provisional unit suggested, would be assigned to the potency of staphylococcus antitoxins, natural and concentrated, which are being prepared at the present time—viz., about 100 to 200 provisional units per c.c. for the former and about 300 to 800 provisional units per c.c. for the latter.

The figures given for the group, A to H, are interesting in so far as they exhibit the kind of potency figures one would expect to obtain from serial bleedings of a horse undergoing immunisation and hyperimmunisation, and for concentrated preparations of natural sera, etc.

The figures given for the group Nos. 1 to 10 are interesting, as they show that, by using methods of assay similar in principle to those employed in this Institute but employing locally prepared toxins *other* than those used in this Institute, remarkably good agreement in the estimates of the potency of eight different samples of staphylococcus antitoxin tested in the two laboratories is obtained.

The figures given for the group Nos. 11 to 16, together with the others, show that the potency of staphylococcus antitoxins prepared in different parts of the world at the present time vary considerably in potency ; since different laboratories have reached different stages in the development of the methods and technique of the preparation of toxins, immunisation, etc., this variation is to be expected.

It is considered that the results of the tests of these twenty-four staphylococcus antitoxins, drawn from a variety of sources, emphasise the need for the adoption of a common standard of reference, in terms of which all staphylococcus antitoxins intended for clinical use can be assayed.

MATERIALS SUPPLIED AND SUGGESTIONS FOR PRACTICAL APPLICATION.

(1) A glycerol solution of the standard preparation of which 1 c.c. contains 20 provisional units.

(2) A sealed ampoule containing the total dry solids from 5 c.c. of the original staphylococcus antitoxin (0.4589 ± 0.0016 gm.). It is suggested that the contents of the ampoule be "reconstructed" in the following way: 5 c.c. of sterile distilled water are added to the contents of the ampoule and the whole allowed to stand in the ice-box overnight. The ampoule is rotated gently between the palms of the hands until solution is complete. The dissolved serum is transferred to a sterile graduated 50 c.c. cylinder.

The ampoule is washed out, *either* (a) with successive 3 to 4 c.c. quantities of sterile salt solution, the washings added to the cylinder, and the procedure continued until the volume in the cylinder is 45.9 c.c., or (b) with 5 (or 6), 2 c.c. quantities of sterile salt solution, the washings being added to the cylinder, and the volume made up to 45.9 c.c. by the addition of glycerol.

In either case, the solution so obtained contains

20 provisional units in 1 c.c.

The former preparation (a) is suitable for the determination of the "test dose" of toxins by any of the methods described. Especial care should be taken to guard against bacterial contamination, and the reconstructed (saline) solution should be preserved at ice-box temperature. The glycerol solution of the standard preparation (b) is more stable, but is less convenient for use in the determination of the test dose of toxins by the mouse intravenous or mouse intraperitoneal methods. Precise quantities can, however, be delivered from a Trevan micrometer syringe (*Biochemical Journal*, 1925, Vol. XIX, page 1111).

(3) Samples from two staphylococcus antitoxins of unstated potency, labelled S and T, are also supplied. It is suggested that individual laboratories should assay each of these in terms of the provisional unit proposed, each worker using the method, or methods, he has in regular use, and by means of his own test toxins.

The samples, S and T, supplied are to be regarded as staphylococcus antitoxins of unknown potency; but, in order to economise time and material, it may be stated that the potency, in each case, according to the determinations made in this Institute, lies between 100 and 300 provisional units per c.c.

A small reserve of the staphylococcus antitoxins, S and T, is held at this Institute, and further supplies can be furnished if required. Each ampoule contains 2.5 (+) c.c. In order to economise the materials as far as possible, it is suggested that the primary dilutions of the antitoxins are made by using 0.5 c.c. quantities.

The experience so far gained in this Institute has shown that the results of the assay of staphylococcus antitoxins by the hæmolytic and intracutaneous methods of testing give closely similar results and, in this respect, confirms the experience reported from many other laboratories. The practice in this Institute

is to make the preliminary determination of potency by the hæmolytic method ; the result, by this method, gives the necessary information for the "bracket" for the intracutaneous, or other, animal tests.

(There is some doubt as to whether the hæmolytic and the necrosis-producing properties of staphylococcus toxins are due to the same principle ; but, in the present state of knowledge, and in view of the agreement so frequently obtained by the two methods of testing, the manner of conducting the tests as indicated above may be considered legitimate.)

B. CONFERENCE ON THE STANDARDISATION OF SEX HORMONES

*held at London on July 30th and August 1st, 1932.*¹

PRELIMINARY NOTE

by Sir HENRY H. DALE.

At a meeting of the Permanent Commission on Biological Standardisation, held in London at the beginning of July 1931, Sir Henry Dale was requested to explore the possibility of an international agreement on standards of reference and units of activity for the sex hormones and, in due course, to arrange for a technical conference of experts in this field. The only one of the sex hormones hitherto prepared in a state of chemical purity is the œstrus-producing hormone, originally detected in the fluid from ovarian follicles, but later found to be present in the human placenta, and to be excreted in the urine of pregnant women and mares. From the urine of pregnancy, it has been prepared in pure, crystalline form,

¹ The following members were present :

Sir Henry H. DALE, C.B.E., F.R.S., Director, National Institute for Medical Research, London, President ;

Dr. Adolf BUTENANDT, University of Göttingen ;

Professor E. A. DOISY, Ph.D., Medical School of the University of St. Louis, Missouri ;

Dr. Ernst LAQUEUR, University of Amsterdam ;

Dr. G. F. MARRIAN, D.Sc., University College, London ;

Dr. A. S. PARKES, D.Sc., National Institute for Medical Research, Hampstead, London ;

The following also attended as experts :

Dr. J. H. BURN, London ;

Dr. E. C. DODDS, Middlesex Hospital, London ;

Dr. André GIRARD, Paris ;

Professor Vladimir KORENCHEVSKY, Lister Institute, Elstree.

in sufficient quantities for chemical examination. It has thus been obtained in two principal forms, a keto-hydroxy and a tri-hydroxy form of which the latter can be converted into the former by chemical treatment. The keto-hydroxy form of the hormone is the more active by the ordinary method of testing, for the production of œstrus in small animals subjected to oöphorectomy.

Different investigators have referred to it by various names—follicular hormone, folliculine, œstrin, theelin, progynon, menformon. Both in scientific literature, and in the issue for therapeutic use of preparations containing the hormone, its activity has been indicated in "units" of physiological activity, the "unit" used, in each case, being the quantity required to produce œstrus in a castrated rat or mouse. Such a procedure, however, has resulted in the use of a wide variety of such "units". The quantity needed to produce œstrus in the rat admittedly cannot be assumed to be the same as that required to produce the same effect in a mouse, even when the methods of administration and of appraising the result are identical. It had accordingly become usual to refer to "mouse-units" and "rat-units". Not only, however, have there been differences of practice in different countries with regard to the species employed for the test. Even with one species of test animal, the "unit" will have a wide range of values, owing to differences in the method of administration of the hormone, in watery or in oily solution, in a single dose or in divided doses, or to differences in the stage of œstrus accepted as indicating a "positive" effect, or in the proportion of such "positive" effects, in a series of animals, taken as indicating the effect of one unit.

In preliminary correspondence with the experts who were later members of the Conference, it was agreed that the only basis for international agreement on a common unit of activity for the œstrus-producing hormone would, as in other similar cases, be found in the adoption of a standard substance, in terms of which the unit could be defined, and with reference to which the accepted unit could be measured by methods differing in detail. It was further agreed that the keto-hydroxy form of the hormone, in pure crystalline condition, would be the suitable substance to form such a standard of reference. Opinions differed, however, as to whether an actual standard sample of the pure crystalline hormone would be required to be kept in and distributed from one centre. The

view was held by some that the standard could be sufficiently defined, in terms of chemical and physical characters, to enable it to be prepared as required in any country. Before the Conference met, it had become clear, in the light of further evidence, that even the keto-hydroxy hormone, as prepared in quantities suitable for such practical use, consists of at least two isomeric substances and that these differ in biological activity. It had accordingly become clear that, if this substance was to be adopted as the international standard of reference, the creation of a central sample of it would be necessary. The other point on which opinions differed was the amount of such a standard which should be adopted as defining the activity of one unit. These were the main points to be considered, in personal discussion, at the Conference, which met at the National Institute for Medical Research on July 30th and August 1st, 1932.

RESOLUTIONS OF THE CONFERENCE.

A. ŒSTRUS-PRODUCING HORMONE.

The Conference agreed :

1. On the desirability of finding a substance which can be used as an international standard of the œstrus-producing hormone, and to define a unit in terms of it.
2. That there shall be one material standard preparation preserved as a central standard of reference.
3. That the material standard will consist of the hydroxy ketonic form of the hormone, normally obtained from the urine.
4. That the various countries will be invited to contribute samples which will be combined to form the standard preparation.
5. That the unit will be the specific œstrus-producing activity contained in 0.1 gamma of the standard preparation, this quantity being approximately a third of the original rat unit of activity as defined by Professors Allen and Doisy.
6. That the National Institute for Medical Research will keep the standard and that Dr. Marrian, of the Department of Physiology and Biochemistry of the University College, London, be asked to co-operate in its preparation.

7. That by the term "specific œstrus-producing activity" is to be understood the power of producing, in the adult female animal completely deprived of its ovaries, an accurately recognisable degree of the changes characteristic of normal œstrus. For the present, the only such change regarded by the Conference as providing a suitable basis for quantitative determination of activity in comparison with the standard preparation is the series of changes in the cellular contents of the vaginal secretion of the rat or mouse.

8. That the comparison of an unknown preparation with the standard for such specific activity can only be accurately made if the conditions of administration of both, and of observing the results produced in each case, are completely identical, particularly in the following respects :

(a) The standard and the preparation under test must be administered in identical solvents.

(b) Administration should be by truly subcutaneous and not intramuscular injection.

(c) The standard preparation and the preparation under test should both be administered by a method ensuring slow absorption at identical rates. This can be attained by administering both dissolved in the same oily solvent, in which case single injections may be used, or by preparing both in watery solution, and administering in an equal number of fractions, not less than three, the injections being spaced in an identical manner in both cases, over a total time of not less than nine hours.

(d) The vaginal smears should be taken at the same intervals after the injection from the animals injected with the standard and from those injected with the preparation under test, but should be continued at least once daily until the animals have returned to the diœstrous condition. On the day on which the maximum response is expected, at least two smears should be taken. If the maximum occurs in the animals receiving the standard and in those receiving the preparation under test, at intervals after the injection differing by more than twenty-four hours, the comparison cannot be regarded as valid.

(e) In comparing the activity of a preparation with the standard, the procedure should aim at finding a dose of the unknown preparation producing the chosen limiting reaction in the same proportion of animals as that in which it is produced by a known dose of the standard. A method should be chosen which has been proved, in the hands of the particular investigator, to be capable of determining such equality of activity with an error not greater than plus or minus 20 per cent. According to the experience of the members of the Conference, an accuracy of this degree is not attainable, by any method, with the use of less than 20 animals for each dose.

9. That the preparation be preserved as dry crystals at a temperature of 0° C. or less, and protected from light and from contact with traces of oxygen.

10. That samples of the standard, when its preparation is completed, will be distributed to the different members of this Conference, who will subject it to any tests they consider appropriate, and confirm its suitability for adoption, before it is generally distributed.

11. That, when thus adopted, the standard preparation will be distributed into sealed ampoules filled with dry nitrogen, each containing about 10 milligrammes. A suitable number of these ampoules will be placed at the disposal of each country requiring to use the standard, for local distribution.

12. That, in view of the evidence before them as to the varying ratios between the activity of other forms of the hormone and that of the hydroxyketonic form, as measured by different biological tests, the members of the Conference are unable to recommend the determination of the activity of such other forms in the units here proposed.

13. That it is not possible at present to obtain agreement upon a nomenclature for scientific use.

B. MALE HORMONE.

The Conference agreed :

14. That arrangements be made for a co-operative investigation, in different countries, of the methods of measuring the activity

of the male hormone, with the object of reaching agreement, at a later Conference, concerning a standard preparation of this hormone and a unit defined in terms of that Standard. For these purposes, the following experts should be invited to co-operate :

| | |
|-----------------------------|------------------|
| Professor LAQUEUR, Holland. | |
| Professor BUTENANDT | } Germany. |
| Professor LOEWE | |
| Professor KOCH | } U.S.A. |
| Professor MOORE | |
| Dr. Casimir FUNK, France. | |
| Professor DODDS | } Great Britain. |
| Dr. GREENWOOD | |
| Professor KORENCHEVSKY | |
| Dr. PARKES | |

That preparations of the hormone should be obtained from :

Professor LAQUEUR.
 Professor BUTENANDT.
 Professor KOCH.
 Dr. FUNK.

These should be collected by the National Institute for Medical Research and distributed to the different collaborators. Each of these should be asked to furnish an exact description of the method of standardisation which he will employ, including details of the breeding and feeding of the animals used, and later to furnish a report on the results of his investigations so that these may be made available for comparison.

C. CORPUS LUTEUM HORMONES.

The Conference agreed :

15. That discussion of the *Corpus luteum* hormone(s) would be premature.

D. ANTERIOR PITUITARY HORMONE.

The Conference agreed :

16. That an attempt be made to promote an international and comparative investigation of preparations containing the gonad-stimulating hormone of the anterior pituitary lobe, or of its equivalents in activity as obtained from urine or placenta, with a view to comparing the different methods of measuring this form of activity, and the different units already in use for its quantitative expression. No steps, however, shall be taken in this direction until the views have been obtained, by correspondence, of other workers prominent in this field of investigation, including :

Professor ASCHHEIN.

Professor ZONDEK.

Professor Herbert EVANS.

Professor Philip SMITH.

Professor COLLIP.

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SYPHILIS TREATMENT

Part One.

ENQUIRY IN FIVE COUNTRIES
CARRIED OUT UNDER THE AUSPICES OF THE HEALTH
ORGANISATION OF THE LEAGUE OF NATIONS.

Rapporteur : Professor HANS MARTENSTEIN, Director of the Dermatological Clinic of the Municipal Hospital of Dresden-Friedrichstadt.

1. THE ENQUIRY.

Following a preliminary discussion, which had taken place in Copenhagen on June 6th and 7th, 1928, between Dr. MADSEN, Colonel HARRISON, Professor JADASSOHN and Professor RASCH, the Experts whose names appear below met at Geneva on October 8th to 10th of that year :

Professor J. JADASSOHN, Director of the Dermatological Clinic of the University of Breslau (*Chairman*) ;

Dr. Th. MADSEN, Director of the State Serum-Institute, Copenhagen, *Chairman of the Health Committee of the League of Nations.*

Colonel L. W. HARRISON, of the Ministry of Health, Director of the Venereal Diseases Department of St. Thomas's Hospital, London.

Dr. Louis QUEYRAT, President of the Ligue nationale française contre le péril vénérien, Paris ;

Dr. J. H. STOKES, Professor of Dermatology and Syphilology, School of Medicine, University of Pennsylvania, Philadelphia.

Professor C. RASCH, Director of the Dermatological Clinic of the University, Copenhagen, was unable to attend.

Point 2 of the agenda read as follows :

" Prevention of Syphilis :

" Comparative study of the experience gained by the Public Health agencies concerned in various countries. Proposed plan of enquiry into the effectiveness of the treatment of syphilis in selected clinics and dispensaries of several countries."

In the report on the meeting (document C.H.750), the views of the Experts on this point, as they emerged from the discussion, were recorded as follows :

" The Experts have been struck by the fact that, in the fight against syphilis, the results obtained have not been such as the almost universally recognised progress of syphilis therapy would give reason to expect.

" The explanation which suggested itself, and which has, indeed, been confirmed by various experts, is that new discoveries in the matter of syphilis diagnosis and therapy are not exploited everywhere in the right way and with such promptness as would be desirable, and that a uniform, generally recognised method of treatment does not as yet exist.

" The Experts therefore considered whether a statistical compilation regarding the various methods of treatment in clinics, dispensaries, etc., would not enable a better general idea to be gained of the efficacy of these methods.

" The material available at individual clinics is fairly large, but has usually been treated by one or, at most, a very few methods. An attempt must therefore be made to bring together as much material as possible from different clinics

in different countries, to enable the various methods to be compared on the broadest possible basis.

“ In this connection, it appeared desirable to keep in view the *two purposes* to which every treatment of syphilis should be directed—namely, the *suppression of contagiousness as quickly and as effectively as possible*, and the *protection of the patient from the severe late effects of syphilis*.

“ The Experts recommend that the work be organised on the following lines : The material from the various clinics which are ready to participate would be sent to the Health Section of the League of Nations Secretariat, acting as central bureau of this enquiry, on cards relating to individual patients (‘ individual case record ’) (Annex 1). A *special individual card* has been elaborated for cases of *syphilis in pregnancy* (Annex 2). On the basis of the material thus received, the bureau would then have to work up the various questions which arise in connection with the treatment of syphilis and its results.

“ For this purpose, a large number of cards giving as accurate particulars as possible will be required.

“ Directors of clinics would therefore be requested to work up their cases for a given period of years, to be determined by them, and would include *all cases of syphilis I, II and III* which have been *under observation in their clinics for more than six months* and all the older cases for which adequate medical histories are available. Beyond this, however, no further selection of cases would be made.

“ The manner in which the cards are to be filled in will be plain from the questions themselves and from the *explanatory notes* (see Annex 3).

“ In addition to the cards, which will be filled in under his supervision, the Director of each institute will also be asked to prepare a general statement of the principles which he applies or of the various principles which he has applied at different times. A draft questionnaire with reference to this statement is attached (see Annex 4).”

On the basis of this proposal of the Experts, this retrospective enquiry into syphilis treatment was organised in the following countries : *Denmark, France, Germany, Great Britain* and the *United States of America*. In each of these countries, the derma-

tological and venereal disease clinics were appealed to for their support, and the large majority readily responded.

In view, however, of the fact that not all the clinics of the various countries were asked to contribute records or actually did so, it should be emphasised here that the findings in this report *relate only to the statistical material which has been collected*. Although, for a variety of reasons, the data dealt with in this survey happen to have been analysed country by country, *the results which have emerged cannot be regarded as presenting a complete picture of the practice that is current in these countries*. This is especially the case as they take no account of any change which may have taken place in the principles of treatment applied by the various clinics since 1929.¹

The co-ordination of the work has been ensured in each country as follows :

In Denmark :

Under the direction of Professor C. RASCH (Director of the Dermatological Clinic of the University, Copenhagen) by his assistant, Dr. Esbern LOMHOLT ;

In France :

Under the direction of Professor L. QUEYRAT (President of the Ligue nationale française contre le péril vénérien) by Dr. J. PERONI ;

In Germany :

Under the direction of Professor J. JADASSOHN (Director of the Dermatological Clinic of the University of Breslau) by his assistant, Professor H. MARTENSTEIN ;

In Great Britain :

By Colonel L. W. HARRISON, of the Ministry of Health, London, Director of the Venereal Diseases Department of St. Thomas's Hospital.

In the United States of America :

In turn by Dr. Thomas PARRAN, Jr., Dr. TALIAFERRO CLARK and Dr. John McMULLEN, Assistant Surgeons-General successively in charge of the Division of Venereal Diseases, and Lida J. USILTON, Associate Statistician in the United States Public Health Service ; and by the heads of the University Clinics constituting the Co-operative Clinical Group (H. N. COLE, M.D., Western Reserve University ; J. E. MOORE, M.D., Johns Hopkins University ; P. A. O'LEARY, M.D., Mayo Clinic ; J. H. STOKES, M.D., University of Pennsylvania ; U. J. WILE, M.D., University of Michigan).

In the five countries mentioned, the following clinics generously lent their assistance in the enquiry :

¹ For the principles of treatment applied in the various countries, see bibliography, page 244.

Germany.

| Clinics | Total number of cases | Including | |
|--|-----------------------|-----------|-------|
| | | Men | Women |
| Berlin, Dermatologische Abteilung am Virchow-Krankenhaus | 105 | 79 | 26 |
| Breslau, Dermatologische Abteilung des Allerheiligen-Hospitals | 367 | 140 | 227 |
| Breslau, Universitäts-Hautklinik | 999 | 629 | 370 |
| Dresden, Hautklinik des Krankenhauses Friedrichstadt | 342 | 99 | 243 |
| Erlangen, Universitäts-Hautklinik | 506 | 249 | 257 |
| Frankfort-on-Main, Universitäts-Hautklinik. | 504 | 258 | 246 |
| Freiburg-im-Breisgau, Universitäts-Hautklinik | 217 | 84 | 133 |
| Göttingen, Universitäts-Hautklinik | 199 | 98 | 101 |
| Greifswald, Universitäts-Hautklinik | 85 | 39 | 46 |
| Hamburg, Universitäts-Hautklinik | 100 | 50 | 50 |
| Heidelberg, Universitäts-Hautklinik | 299 | 121 | 178 |
| Jena, Universitäts-Hautklinik | 633 | 260 | 373 |
| Kiel, Universitäts-Hautklinik | 309 | 178 | 131 |
| Cologne, Universitäts-Hautklinik | 130 | 56 | 74 |
| Königsberg, Universitäts-Hautklinik | 597 | 268 | 329 |
| Leipzig, Universitäts-Hautklinik | 290 | 98 | 192 |
| Marburg, Universitäts-Hautklinik | 163 | 66 | 97 |
| Munich, Universitäts-Hautklinik | 459 | 240 | 219 |
| Münster, Universitäts-Hautklinik | 68 | 27 | 41 |
| Tübingen, Universitäts-Hautklinik | 379 | 162 | 217 |
| In all, 20 clinics with | 6,751 | 3,201 | 3,550 |

Denmark.

| Clinics | Total number of cases | Including | |
|--|-----------------------|-----------|-------|
| | | Men | Women |
| Copenhagen. | | | |
| Frederiksberg Hospital | 170 | 57 | 113 |
| Kommunehospitalet | 499 | 265 | 234 |
| Rigshospitalet | 1,611 | 766 | 845 |
| Rudolf Bergh's Hospital | 1,436 | 555 | 881 |
| Dr. FEILBERG | 47 | — | 47 |
| Dr. HASLUND | 18 | 18 | — |
| Dr. HENNINGSEN and Dr. KISSMEYER.... | 88 | 85 | 3 |
| Dr. Svend LOMHOLT..... | 342 | 207 | 135 |
| Dr. MEINCKE and Dr. D. CHRISTENSEN.... | 127 | 95 | 32 |
| Dr. PONTOPPIDAN | 39 | 7 | 32 |
| In all, 10 clinics with | 4,377 | 2,055 | 2,322 |

United States of America.

| Clinics | Total number of cases | Including | |
|---|-----------------------|-----------|-------|
| | | Men | Women |
| Albany, N. Y., Albany Hospital..... | 3 | 3 | — |
| Ann Arbor, University of Michigan | 817 | 457 | 360 |
| Atlanta University School of Medicine | 222 | — | 222 |
| Baltimore, Johns Hopkins University | 2,135 | 909 | 1,226 |
| Binghamton, New York Health Department..... | 319 | 202 | 117 |
| Boston, Massachusetts General Hospital, Department of Dermatology | 89 | 53 | 36 |
| Charlottesville, University of Virginia Hos- pital, Department of Dermatology | 107 | 66 | 41 |
| Cleveland, Western Reserve University Syphilis Clinic | 1,094 | 653 | 441 |
| Des Moines, State University of Iowa, Children's Hospital | 27 | 16 | 11 |
| Detroit, Department of Health | 490 | 248 | 242 |
| Kansas City, Children's Mercy Hospital | 107 | 46 | 61 |
| New York, United States Marine Hospital, United States Public Health Service, Hudson Street | 897 | 897 | — |
| New York, Vanderbilt Clinic | 267 | 116 | 151 |
| Philadelphia, School of Medicine, University of Pennsylvania and University Hospital.. | 502 | 287 | 215 |
| Rochester, Minnesota, Mayo Clinic | 996 | 542 | 454 |
| Rochester, N. Y., Baden Street Dispensary .. | 222 | 170 | 52 |
| Saint Louis, School of Medicine, Washington University | 39 | 18 | 21 |
| In all, 17 clinics with | 8,333 | 4,683 | 3,650 |

France.

| Clinics | Total number of cases | Including | |
|---|-----------------------|-----------|-------|
| | | Men | Women |
| Bordeaux, Dispensaire de prophylaxie anti- vénérienne | 58 | 44 | 14 |
| Limoges, Hôpital | 53 | 28 | 25 |
| Lyons, Hôpital de l'Antiquaille | 34 | 27 | 7 |
| Marseilles, Dispensaire central de prophylaxie Hôtel-Dieu et Hôpital de la Concep- tion | 345 | 241 | 104 |
| Nancy, Clinique dermatologique de Nancy.. | 132 | 53 | 79 |
| Nantes, Hospices civils | 132 | 88 | 44 |
| Paris, Hôpital St. Louis. Professor GOUGEROT | 100 | 49 | 51 |
| Dr. HUDELO | 52 | 26 | 26 |
| Professor JEANSELME | 301 | 215 | 86 |
| Dr. LORTAT-JACOB | 52 | 27 | 25 |
| Dr. MILIAN | 59 | 34 | 25 |
| Dr. RAVAUT | 106 | 85 | 21 |
| <i>Carried forward</i> | 1,424 | 917 | 507 |

France (continued).

| Clinics | Total number of cases | Including | |
|--|-----------------------|-----------|-------|
| | | Men | Women |
| <i>Brought forward</i> | 1,424 | 917 | 507 |
| Paris, Clinique St. Lazare | 195 | 58 | 137 |
| Paris, Hôpital de la Charité, Dr. SÉZARY | 181 | 101 | 80 |
| Rouen, Hôpital général, Service annexe | 193 | 100 | 93 |
| St. Étienne, Hospices civils, Service de prophylaxie | 145 | 75 | 70 |
| Toulon, Dispensaire d'Hygiène sociale | 32 | 23 | 9 |
| In all, 17 clinics with | 2,170 | 1,274 | 896 |

Records for 100 cases, including 70 men and 30 women, were sent in from the Institut prophylactique (Dr. A. VERNES), Paris. These records, though based upon an instructive and interesting method, could unfortunately not be used, since they did not harmonise with the form of case record used in the enquiry.

Great Britain.

| Clinics | Total number of cases | Including | |
|---|-----------------------|-----------|-------|
| | | Men | Women |
| Aberdeen, Royal Infirmary | 49 | 46 | 3 |
| Barnsley, Venereal Disease Dispensary | 68 | 47 | 21 |
| Birmingham, General Hospital, V.D. Department | 73 | 52 | 21 |
| Blackpool, Health Department | 45 | 45 | — |
| Bradford, V.D. Clinic | 230 | 126 | 104 |
| Brighton, Royal Sussex County Hospital, V.D. Clinic | 136 | 76 | 60 |
| British Army, War Office | 186 | 186 | — |
| Dundee, Public Health Institute, V.D. Section | 243 | 193 | 50 |
| Derby, Derbyshire Royal Infirmary | 30 | 22 | 8 |
| Edinburgh, Bruntsfield Women's Hospital.. | | | |
| Edinburgh, Royal Infirmary | 111 | 107 | 4 |
| Glasgow, Bellahouston, V.D. Dispensary ... | 44 | 44 | — |
| Glasgow, Broomielaw, V.D. Dispensary..... | 45 | 45 | — |
| Glasgow, Lock Hospital | 46 | — | 46 |
| Glasgow, Western Infirmary | 37 | 37 | — |
| Grimsby, Queen Street Treatment Centre... | 86 | 46 | 40 |
| Liverpool, Royal Infirmary | 89 | 89 | — |
| London, Guy's Hospital | 300 | 191 | 109 |
| London, Royal Free Hospital | 17 | — | 17 |
| London, Royal Northern Hospital..... | 35 | 35 | — |
| London, St. Paul's Hospital | 49 | 49 | — |
| London, St. Thomas's Hospital | 955 | 675 | 280 |
| Middlesbrough, Grange Road Treatment Centre | 34 | 34 | — |
| Newcastle-on-Tyne, Royal Victoria Infirmary | 247 | 247 | — |
| <i>Carried forward</i> | 3,155 | 2,392 | 763 |

Great Britain (continued).

| Clinics | Total number of cases | Including | |
|--|-----------------------|-----------|-------|
| | | Men | Women |
| <i>Brought forward</i> | 3,155 | 2,392 | 763 |
| Nottingham, North Church Street Treatment Centre | 37 | 37 | — |
| Paisley, Craw Road Centre | 5 | 5 | — |
| Portsmouth, Royal Portsmouth Hospital ... | 134 | 69 | 65 |
| Sheffield, Royal Hospital | 45 | 45 | — |
| Wolverhampton, The Royal Hospital | 195 | 113 | 82 |
| In all, 29 clinics with | 3,571 | 2,661 | 910 |

We are indebted to Professor FRAZIER (Syphilis Clinic of the Peiping Union Medical College, Peiping, China) for particulars of 421 cases (335 men and 86 women) treated in his clinic.

The total material for analysis is therefore as follows :

| | Cases | Including | |
|---|--------|-----------|--------|
| | | Men | Women |
| From Denmark, 10 clinics | 4,377 | 2,055 | 2,322 |
| From France, 17 clinics | 2,170 | 1,274 | 896 |
| From Germany, 20 clinics | 6,751 | 3,201 | 3,550 |
| From Great Britain, 29 clinics | 3,571 | 2,661 | 910 |
| From Peiping, 1 clinic | 421 | 335 | 86 |
| From the United States of America, 17 clinics.. | 8,333 | 4,683 | 3,650 |
| In all, 94 clinics with | 25,623 | 14,209 | 11,414 |

2. THE WORKING-UP OF THE STATISTICAL MATERIAL.

The League of Nations Health Organisation requested me to undertake the examination of the individual cards and the collation of the whole material in close co-operation with Professor JADASSOHN.

Notwithstanding the wide measure of support received from all the agencies interested in these statistics, and the great zeal displayed by my assistants, among whom I may specially mention Dr. Eline EPSTEIN, of Breslau (former assistant at Professor Jadassohn's clinic), the work has unfortunately taken several years to complete. In the process of collecting and working up the individual cards, there arose a number of unforeseen difficulties, the solution of which required extensive correspondence with the various agencies concerned and verbal discussion by the Experts.

The first scrutiny of the material collected led to the elimination of about 3 per cent of the cards (660—i.e., 267 men and 393

women), mainly because the condition of a minimum period of observation of six months had not been satisfied. About 70 per cent of the cards were correctly filled in, a fact which testifies to the interest taken by the co-operating clinics in the enquiry and the care with which they had collected the material. In the remaining cases, it was necessary to obtain supplementary information before the cards could be used.

Altogether, the filling-up of the individual cards in the many clinics and in different countries, the scrutiny of each card, the alteration and the supplementing of the entries took so much time that the completed material was not ready for collation until the beginning of 1932.

The distribution of cases into *stages of syphilis* (see explanations in Annex 3) was as follows :

| | Total | Including | |
|--|--------|-----------|--------|
| | | Men | Women |
| Primary and secondary syphilis (S1, S2, S3 and S4) | 15,333 | 9,528 | 5,805 |
| Latent syphilis (Early latent : S5a, S5b, and late latent : S6h, S6i) | 6,859 | 2,984 | 3,875 |
| Tertiary syphilis (all later manifestations) (S6a, S6b, S6c, S6d, S6e, S6f, S6g) | 1,951 | 1,061 | 890 |
| Congenital syphilis (CS1, CS2, CS3, CS4) | 820 | 369 | 451 |
| Total..... | 24,963 | 13,942 | 11,021 |

Comparison of the share which each country has contributed to the total cases in each stage indicates that only in Germany and the United States has equal attention been given to the collection of material for all stages ; in other countries, the proportion of latent, tertiary and congenital syphilis to primary and secondary cases is much smaller, a tendency specially marked in returns from Great Britain (77 cases as compared with 3,483) (see also Annex 5).

Relatively to the total material, the number of cases of *congenital syphilis* represents only about 3 per cent, and the percentage of the special case records for syphilis *in pregnancy* is still lower, about 2 per cent. These figures appeared too small to yield any significant data by the application of statistical methods. The Experts were therefore asked to decide whether an attempt should be made to expand this material, by seeking the assistance of other clinics, especially those for women, or whether these cases should be excluded from the present survey.

In view of the fact that several extensive statistical compilations have recently been made in this field, more especially in respect of congenital syphilis, the Experts *decided that the material on syphilis in pregnancy and congenital syphilis should not be worked up statistically.*

A further decision also provisionally postponed the analysis of the material relating to *cases of latent and tertiary syphilis.* The reason for this was that the co-operating countries had contributed to the total records of latent and tertiary syphilis in very unequal proportions (see above). A comparative survey of the results of treatment in both these stages on the lines proposed by the Experts would have entailed the collection of supplementary information. Past experience showed, however, that this would result in great loss of time, and it was accordingly suggested that these cases might be presented later in a special report.

The first examination of the records of cases of *primary and secondary* syphilis showed that in a number of instances the particulars supplied were not sufficient to permit of their being classified with certainty in one of the four groups provided for early cases. The result of the serological test at the beginning of treatment is the decisive factor in the subclassification of primary syphilis into sero-negative¹ (S1) or sero-positive (S2), whilst the determination of the duration of infection governs the classification of cases as early secondary (S3, secondary syphilis *within* the first year of the disease), or as late secondary (S4, secondary syphilis *later* than the first year of the disease). It was realised from the outset that the determination of the duration of infection in the prescribed manner would prove impossible in many of the cases of secondary syphilis.

In order that these cards, which had otherwise been correctly filled in, should not be wasted, the subdivision of early syphilis into groups was further elaborated as follows (with the approval of the Experts).

¹ To prevent misunderstanding, it should be pointed out that all cases with primary lesions in which the serological reactions *were negative at the beginning of treatment* have been classified as sero-negative, whether or not the reaction remained constant or showed a transient or permanent change to doubtful or positive in the course of the subsequent serological control.

| Stage | Clinical Diagnosis | <i>Sp. pallida</i> | Serological reaction at the beginning |
|---|--------------------|--|---------------------------------------|
| S1 = sero-negative primary | Primary syphilis | Positive | Negative |
| S1 or S2 = sero-negative or sero-positive primary | Primary syphilis | Positive | Not performed |
| S2 = sero-positive primary ¹ | Primary syphilis | Positive, or negative, or no examination | Positive |
| S3 = secondary syphilis in the first year of infection | Secondary syphilis | Positive, or negative, or no examination | Positive |
| S3 or S4 = secondary syphilis, date of infection unknown | Secondary syphilis | Positive, or negative, or no examination | Positive |
| S4 = secondary syphilis after the first year of infection | Secondary syphilis | Positive, or negative, or no examination | Positive |

Since only cases in which *the diagnosis was certain from the beginning and which were subjected to proper serological control* were to be used, the following special groups had further to be separated from this total material relating to primary and secondary syphilis.

1. *All cases in which the initial diagnosis was doubtful—namely :*

(a) *Clinically diagnosed primary syphilis, in which *Sp. pallida* was not found or looked for at the outset and serological tests were either negative or not performed, but a serological or clinical relapse, or both, occurred in the course of subsequent observation.*

(b) *Clinically diagnosed cases of secondary syphilis, in which *Sp. pallida* was not found and initially serological tests either gave negative results or were not performed, but there was later evidence of a positive serological reaction, or a clinical relapse, or both.*

¹ A positive serological reaction was recognised as sufficient to confirm the diagnosis. It is hardly likely that the results in this group would be affected appreciably by the presence of a few cases of recurrent primary or tertiary syphilis (gumma).

2. *All cases in which the diagnosis of syphilis was altogether doubtful—namely :*

*Clinically diagnosed cases of primary or secondary syphilis, in which *Sp. pallida* was never found or was not looked for, and serological tests either gave negative results throughout (except perhaps for a single doubtful reaction) or were not performed, and no clinical symptom whatever was noted in the course of subsequent observation.*

3. *All cases in which, though the diagnosis was adequately established, there was no subsequent serological control.*

The elimination of these special groups is obviously indicated. The results of treatment in special group No. 1 must necessarily be bad, as classification in this group presupposes a serological or clinical relapse. On the other hand, the results of special group No. 2 must necessarily be good, since a serological or clinical relapse has been *a priori* excluded.

The number of cases in special groups Nos. 1, 2 and 3 was as follows :

| | Total | Including | |
|--------------------------------|--------------|--------------|------------|
| | | Men | Women |
| Denmark | 296 | 174 | 122 |
| France | 221 | 147 | 74 |
| Germany | 458 | 248 | 210 |
| Great Britain | 327 | 284 | 43 |
| Peiping | 7 | 7 | — |
| United States of America | 669 | 459 | 210 |
| | <u>1,978</u> | <u>1,319</u> | <u>659</u> |

Though all these cases have been excluded from the actual statistical analysis, it would appear useful to discuss them briefly, since they enable us to gauge how far the process of diagnosis and of serological observation is conducted in the clinics of the various participating countries in accordance with the principles of present-day practice. There can be no doubt that the swift and effective suppression of contagiousness and the success of treatment are materially influenced by the strictest possible application of these principles.

The above figures will show that the proportion of records thus discarded amounted to *12.9 per cent* (men *13.85* and women *11.35* per cent).

This means that in one case out of every eight in which the clinical diagnosis of recently contracted syphilis is made, the principles generally accepted by present-day science are not applied in verification of the diagnosis and in serological control. Certainly this percentage varies considerably with countries, and particularly with clinics, but an average of nearly 13 per cent of records discarded for this reason is unexpectedly high, especially when it is remembered that the institutes which furnished these statistics are amongst the best managed and equipped in the respective countries. It is extremely probable that the corresponding proportion among patients going for treatment to private practitioners is considerably higher.

It is somewhat surprising to find that the proportion of cases thus eliminated from our statistical material is smaller for women than for men. This applies not only to the material as a whole, but to that from each country (Annex 6).¹

Not only must it be admitted that very many clinics have made extraordinarily little use of serological control, and consequently that an especially high proportion of the records relating to sero-positive primary and to secondary syphilis have had to be discarded, but the percentage of cases of primary syphilis in which the presence of *Sp. pallida* was not proved is surprisingly high. In 375 (19.05 per cent) out of 1,968² cases classified as sero-negative primary syphilis—a diagnosis which can be established with certainty only by the finding of *Sp. pallida*—this essential condition was not fulfilled. In 172 (53.09 per cent) of 324 other cases in which a serological test was not made at the beginning of the treatment, and which would therefore be classified as sero-negative or sero-positive primary syphilis (S1 or S2), there was no evidence that *Sp. pallida* had been demonstrated; in that percentage of cases, therefore, there was neither serological nor microscopical proof of the nature of the disease.

This fact is all the more serious, since the entries on the large majority of these discarded records showed that not only had *Sp. pallida* not been found, but that it had not even been looked

¹ The material furnished by the Peiping Union Medical College is not taken into consideration here and in the following pages, since the figures are much too small. I will therefore merely mention the results of treatment at Peiping when discussing this question.

² The S1 group, less Peiping.

for. Moreover, out of 3,153 cases definitely classified as sero-positive primary syphilis (S2), only 1,836 (58.23 per cent) had been tested for *Sp. pallida*, and its presence had been proved in only 1,377 cases (43.67 per cent).

This circumstance would have entailed the rejection of nearly three-fifths of the cases assigned to this group if the Experts, confronted with these facts, had not agreed (see footnote on page 139) to waive the requirement justified by modern standards of diagnosis that, for classification as sero-positive syphilis, in addition to positive serum reactions, the presence of *Sp. pallida* should have been demonstrated.

The percentage of cases classified as sero-positive primary syphilis that were tested for *Sp. pallida* in the various countries fluctuates within very wide limits; on the other hand, the percentage of the positive results in the cases investigated is approximately the same—namely, about 75 (see Annex 7).

Naturally, the corresponding difficulties are still greater in the case of secondary syphilis; it is only in Germany that tests for *Sp. pallida* are carried out comparatively frequently in secondary cases—that is to say, in about half of all such cases—while the other countries, in particular Denmark and France, would seem, from the records received, to have practically abandoned this method of investigation. In this connection, it must be specially emphasised that the percentage of positive results among cases of secondary syphilis tested for *Sp. pallida* is higher than the corresponding percentage in cases of primary syphilis (see Annex 7).

After elimination of the records which could not be used, the cases examined fell into six groups of primary and secondary syphilis as follows:

Primary Syphilis.

| Country | S1 = sero-negative | | | S1 or S2 | | | S2 = sero-positive | | |
|-----------------------------------|--------------------|--------------|------------|------------|------------|-----------|--------------------|--------------|------------|
| | Total | Men | Women | Total | Men | Women | Total | Men | Women |
| Germany | 349 | 298 | 51 | 9 | 8 | 1 | 529 | 343 | 186 |
| Denmark | 319 | 271 | 48 | 64 | 58 | 6 | 413 | 324 | 89 |
| United States of America | 284 | 271 | 13 | 33 | 28 | 5 | 765 | 630 | 135 |
| France | 118 | 111 | 7 | 26 | 25 | 1 | 362 | 288 | 74 |
| Great Britain | 474 | 448 | 26 | 4 | 3 | 1 | 1,084 | 966 | 118 |
| Total | 1,544 | 1,399 | 145 | 136 | 122 | 14 | 3,153 | 2,551 | 602 |

Secondary Syphilis.

| Country | S3 = during first year of infection | | | S3 or S4 | | | S4 = after first year of infection | | |
|--------------------------------|-------------------------------------|--------------|--------------|--------------|------------|--------------|------------------------------------|------------|------------|
| | Total | Men | Women | Total | Men | Women | Total | Men | Women |
| Germany | 842 | 404 | 438 | 979 | 285 | 694 | 192 | 96 | 96 |
| Denmark | 1,409 | 476 | 933 | 66 | 33 | 33 | 10 | 19 | 21 |
| United States of America | 2,311 | 1,335 | 976 | 161 | 50 | 111 | 215 | 159 | 56 |
| France | 351 | 155 | 196 | 166 | 60 | 106 | 39 | 27 | 12 |
| Great Britain | 821 | 544 | 277 | 731 | 318 | 413 | 42 | 37 | 5 |
| Total | 5,734 | 2,914 | 2,820 | 2,103 | 746 | 1,357 | 528 | 338 | 190 |

Our figures therefore include 4,833 cases (1,072 men and 761 women) of primary syphilis, and 8,365 cases (3,998 men and 4,367 women) of secondary syphilis.

These are divided amongst the various countries as follows :

| | Germany | | | Denmark | | | United States of America | | |
|---------------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------------------|--------------|--------------|
| | Total | Men | Women | Total | Men | Women | Total | Men | Women |
| Primary syphilis .. | 887 | 649 | 238 | 796 | 653 | 143 | 1,082 | 929 | 153 |
| Secondary syphilis. | 2,013 | 785 | 1,228 | 1,515 | 528 | 987 | 2,687 | 1,544 | 1,143 |
| S1—S4 | 2,900 | 1,434 | 1,466 | 2,311 | 1,181 | 1,130 | 3,769 | 2,473 | 1,296 |

| | France | | | Great Britain | | |
|--------------------------|--------------|------------|------------|---------------|--------------|------------|
| | Total | Men | Women | Total | Men | Women |
| Primary syphilis | 506 | 424 | 82 | 1,562 | 1,417 | 145 |
| Secondary syphilis | 556 | 242 | 314 | 1,594 | 899 | 695 |
| S1—S4 | 1,062 | 666 | 396 | 3,156 | 2,316 | 840 |

No reliable deduction can be drawn from the ratios of sero-negative to sero-positive primary syphilis or of females to males in the above tables, because of the different circumstances in which the records were collected in the various countries.

It must therefore be left to those concerned in the countries in question to determine the reasons for the considerable divergencies shown in them.

The working-up of such vast material, in which each case shows peculiarities, presented great difficulties. From the outset, I

considered it inadvisable to use the machines commonly employed for working up large-scale statistics, since this method presupposes a uniformity in the data which is certainly lacking in the present series. An experiment with such machines was made in the United States, but was soon abandoned as useless.

The material was worked up by myself and my assistants on the following principles :

The figures were analysed for each clinic of the country considered. The individual cards of each clinic were classified separately into stages—*i.e.*, in six groups. A top sheet was used for each group (Annex 8) giving, in addition to the name of the country, the clinic and the stage, the following information :

. The total number of cases ;

The age of the patients at the time of first examination in the clinic, or of infection ;

The duration of the infection at the time of first examination in the clinic (figures for men and women being given separately in each case, in addition to the totals) ;

The number of cases in which *Sp. pallida* was looked for or found.

The actual analysis of the figures was effected in the following manner on the basis of the plan set forth in Annex 9 :

Each card was marked in accordance with a *scheme* drawn up for the various groups :

I. Sero-negative primary syphilis = S1 :

A (—) cases—i.e., those which *remained negative* during the entire period of observation.

B cases—i.e., those in which the initially negative serological reactions *changed to doubtful or positive during the first course* (or, in the case of continuous treatment, during the period corresponding thereto), but which were negative during subsequent treatment or observation.¹

¹ As many clinics only rarely made repeated serological tests during the first course, the ultimate combining of these two groups into one seems advisable, for the number of cases of such clinics that fall into group A (—) will necessarily tend to be greater by reason of the fact that the occasional development of a positive reaction will have been overlooked.

- C ? cases—i.e.**, those which were sero-negative during the entire period of observation except for a *doubtful serological reaction on one occasion* during or after the conclusion of treatment. (As the interpretation placed upon such reactions depends to a great extent on the technique or the standards of the serologist concerned, it would hardly seem justifiable to include these cases among the undoubted serological relapses. At the same time, they could not be included in the A (–) group without qualification and have accordingly been put into a separate group.)
- C cases—i.e.**, those in which a *serological relapse* took place during or after the treatment following the first course.
- D cases—i.e.**, those in which an undoubted *clinical relapse* was observed during or after treatment.

II. Sero-negative or sero-positive primary syphilis = S1 or S2 :

A (–) cases (see S1).

A (+) cases—i.e., those in which the *serological reaction remained positive* throughout the period of observation.

B cases—i.e., those in which the *serological reaction became and remained negative*.

C ? cases
 C cases
 D cases

} (see S1).

III. Sero-positive primary syphilis = S2 :

A (+) cases
 B cases
 C ? cases
 C cases
 D cases

} (see S1 or S2).

IV. Secondary syphilis (early and late secondary) = S3, S3 or S4 and S4 :

The same arrangement as in S2, except that, as regards *clinical relapses*, certain cases grouped under the heading D1

were kept separate ; these were cases found to be in a state of clinical relapse when first examined at the clinic after previous treatment elsewhere.

This D1 group was subdivided according to the stage of the disease at which treatment elsewhere had been started, viz. :

D1 a : *Primary syphilis ;*

D1 b : *Secondary syphilis ;*

D1 c : *Clinical signs of syphilis without indication of the stage.*

The subsequent progress in these cases after the beginning of treatment in the clinic is recorded in accordance with the scheme for the groups from S2 to S4.

Each one of the sub-groups A to D is further subdivided in order to show as exactly as possible the characteristics of each case, or to carry the differentiation of groups of like cases through to the smallest units. As it does not appear practicable to reproduce the scheme with all its subdivisions here without overburdening the report, reference is made to Annex 10.

PROFESSOR WESTERGAARD, of Copenhagen, to whom I am greatly indebted for his valuable advice, encouraged me to build up the statistics from as small subdivisions as possible as the most appropriate statistical method. This makes it possible to combine the small units into a number of more elaborate statistical structures planned according to the objective in view.

For each of these smallest units, the relevant data were collected on the form shown in Annex 9—namely :

Nature of the preparation used in the treatment (arsenical, mercury, bismuth, or the possible combinations of these) ;

Evaluation of the total dose in the first course and during the whole period of treatment as compared with an arbitrary scheme of treatment devised as a norm of comparison (see explanation below) ;

Observation period after the termination of treatment (0, $\frac{1}{2}$, 1, 2, 5, 10, 15 years) ;

Result of treatment, clinical and serological ; exact history of any clinical relapse to be rendered on a special form.

The following were also noted on a special form :

Re-infections, with an accurate statement of available data ;

Complications classified separately as jaundice, exanthem, dermatitis and death, as well as other (slighter) complications such as nitritoid crisis, stomatitis, and subsidiary effects of the preparations employed such as bismuth discoloration of the gums and so on (Cf. explanations regarding individual cards) ;

Lumbar puncture : date of operation and result.

Proceeding from the scheme of classification shown in Annex 10, larger and larger sub-groups were built up on uniform principles, until finally the general result for each stage in each country was obtained.

It should be noted, however, that the data for each stage have been divided into four parallel groups (three in the case of primary syphilis)—namely :

- I. Cases treated *intermittently* ;
- II. Cases treated *continuously* ;
- III. Cases treated *intermittently at one time and continuously at another* ;
- IV. Cases found to be in a *state of clinical relapse when first appearing for treatment in the clinic* (not included in I to III). (This last group (group IV) was again subdivided on the basis of I, II and III above, according to the way in which the relapse was treated. Needless to say, it comprises only cases of secondary syphilis.)

As it was impossible at the outset to foresee whether the work of statistical compilation would disclose great differences between the results obtained in different countries with different methods

of treatment, this division into very small groups appeared to be justified, even although it does make the task of examining the results exceedingly difficult for one not familiar with this system. Now that the results are before us, it may appear that perhaps much of this work was not absolutely essential. There can be no doubt, however, that the arrangement of so large a mass of material in this way will later on facilitate the statistical working out of any special problems falling outside the scope of the present enquiry which it may be desired to study.

To allow of comparison of the results of the various methods of treatment, I have selected a *basic treatment* which may, I think, be regarded as of average intensity. This is, of course, a somewhat arbitrary procedure, but I think that the treatment selected as a constant is eminently suitable for the purpose, because the average minimum treatment specified therein, though not so drastic as that urged in some quarters, can nevertheless hardly be described as mild. Judging by the principles of treatment applied by the participating clinics, as described in their answers to the general questionnaire, the plan I have selected corresponds in the main to the treatment adopted by a large number of these. Even the somewhat higher dosage of the arsenical preparations employed by some of these clinics does not invalidate the use of this plan, because the consequent statistical work will itself show whether or not the use of higher arsenical doses has any particular value.

The suggested plan for intermittent treatment was approved by the Experts. That for continuous treatment was laid down at their Copenhagen session, at which the general procedure for alternating continuous treatment employed by the Co-operative Clinical Group in the United States of America was recognised as of decisive importance, because the continuous treatment of syphilis is practised on a large scale in that country.

PLAN FOR INTERMITTENT TREATMENT.

(Statement of the *minimum doses* required.)

Sero-negative primary syphilis :

Ehrlich 914¹ (neo-salvarsan, neo-arsphenamine, novarsenobenzol, etc.) :

Two courses of treatment, each of 4 grammes, for men,

Two courses of treatment, each of 3.5 grammes, for women,

spread over a period of thirty weeks.

In courses of treatment in which appreciably more than 4 grammes of 914 are administered, the thirty-week period of treatment can be prolonged at the rate of one week per 0.5 gramme of 914, a longer period of treatment being required for the larger number of injections. For instance, for two courses of treatment, each involving the administration of 6 grammes, the period would be thirty plus eight weeks (thirty-eight weeks), for a total of 12 (instead of 8) grammes of 914.

Mercury :

| | | |
|---|---|--------------------------|
| Insoluble preparations 0.4 to 0.7 gramme Hg | } | Per course of treatment. |
| Soluble preparations 0.2 gramme | | |
| Inunctions : 30 applications of 3 grammes | | |
| Ungt. Hydrargyri cinereum (= 1 gramme metallic Hg) each | | |

Bismuth :²

0.8 gramme metallic bismuth per course of treatment.

Sero-positive primary and secondary syphilis :

914 :

Five courses of treatment, each of 4 grammes, for men,

Five courses of treatment, each of 3.5 grammes, for women,

spread over a period of twenty-one months.

¹ Hereinafter referred to as "914". Ehrlich 606 (salvarsan, arsphenamine, arsenobenzol, etc.) will similarly be referred to as "606".

² It is a simple matter to bring treatment by various bismuth and mercury preparations into accord with this plan by expressing the dose in terms of metallic mercury or bismuth content of the preparation employed. It is, however, much more difficult to estimate the comparative value of the various arsenical preparations used in various countries. I should add that, in reply to my necessarily numerous enquiries, I have received a great deal of assistance from every quarter.

Mercury and Bismuth :

Each course of treatment according to the indications given under the heading of sero-negative primary syphilis.

Treatment must be continued in any case for twelve months after the last positive clinical or serological findings. In some cases more than five treatment courses may therefore be necessary.

PLAN FOR CONTINUOUS TREATMENT.

914 :

12 grammes over a period of sixty-five weeks (fifteen months) for both men and women.

Mercury :

| | |
|---|--------------------------------------|
| Insoluble preparations : 1.5 gramme Hg | } Over a period of sixty-five weeks. |
| as grey oil or calomel ; up to 2.8 grammes | |
| Hg as salicylate of mercury | |
| Soluble preparations : 0.7 gramme Hg..... | |
| Inunctions : 100 applications of 3 grammes each | |

Bismuth :

4 grammes metallic bismuth over a period of sixty-five weeks.

In this hypothetical scheme, treatment is regarded as *continuous*, provided *no lapse exceeding four weeks* has occurred between injections or courses and provided further that lapses of such length are *quite exceptional*.

All cases which have at times undergone continuous treatment, though broken by lengthy periods of non-treatment, or in which continuous treatment has been preceded or followed by intermittent treatment, have been grouped into a separate statistical category as *partly continuous, partly intermittent* treatment.

Before considering the results of treatment as disclosed by the method I have applied, I may perhaps refer to a few data which have emerged in the course of this work. Although these do not

come within the scope of the particular statistical problem before us, I think they are of universal interest. One of them is the *relative incidence of syphilitic infection recorded in different age-groups.*

AGE OF PATIENTS AT THE TIME OF THE FIRST CLINICAL EXAMINATION
(Approximating to age at time of injection).

| Age groups (years) | Absolute figures for | | | | | | Percentages | | |
|-----------------------|----------------------|--------------|-------------------------------------|--------|------------------------|--------|-------------|-------|------------|
| | Ger- many | Den- mark | United States of Ame- rica | France | Great Brit- tain | Total | Total | Men | Wo- men |
| 5 | 16 | 6 | 6 | 1 | 2 | 31 | 0.26 | 0.21 | 0.33 |
| 6-10 | 10 | 2 | 10 | 1 | 5 | 28 | 0.21 | 0.11 | 0.37 |
| 11-15 | 37 | 10 | 76 | 17 | 16 | 156 | 1.18 | 0.55 | 2.20 |
| 16-20 | 721 | 584 | 714 | 139 | 356 | 2,514 | 18.91 | 12.71 | 28.80 |
| 21-25 | 990 | 858 | 1,169 | 347 | 987 | 4,351 | 32.95 | 33.68 | 31.79 |
| 26-30 | 489 | 444 | 832 | 210 | 758 | 2,733 | 20.74 | 22.85 | 17.37 |
| 31-35 | 258 | 193 | 436 | 111 | 458 | 1,456 | 11.05 | 12.70 | 8.45 |
| 36-40 | 133 | 102 | 246 | 68 | 263 | 812 | 6.22 | 7.30 | 4.51 |
| 41-45 | 85 | 52 | 127 | 44 | 143 | 451 | 3.44 | 4.24 | 2.16 |
| 46-50 | 55 | 28 | 67 | 33 | 70 | 253 | 1.92 | 2.14 | 1.55 |
| 51-55 | 37 | 8 | 33 | 10 | 30 | 118 | 0.91 | 1.04 | 0.66 |
| 56-60 | 14 | 11 | 14 | 7 | 17 | 63 | 0.48 | 0.60 | 0.29 |
| 61-65 | 13 | 10 | 8 | 4 | 12 | 47 | 0.35 | 0.45 | 0.19 |
| 66-70 | 1 | — | 3 | — | 5 | 9 | 0.07 | 0.07 | 0.07 |
| 71-75 | 4 | — | — | — | 1 | 5 | 0.04 | 0.06 | — |
| not stated | 37 | 3 | 28 | 70 | 33 | 171 | 1.31 | 1.33 | 1.28 |
| | 2,910 | 2,311 | 3,769 | 1,062 | 3,156 | 13,198 | | | |

This tabulation of over 13,000 cases of early syphilis shows that in about *one-third* infection was contracted *between 21 and 25 years* of age ; this applies to *both men and women.* Whereas among women the incidence during the five-year period from 16 to 20 seems to be almost as high, the proportion of infections among males of the same age group is less than one-half of this. On the other hand, in age groups above 25, the percentage of men infected is considerably greater than that of women. Although the figures vary considerably from country to country I do not, for the reasons already stated, propose to discuss them in further detail.

It has not been possible, even in cases of primary syphilis (in which the patient's history can to some extent be checked) to utilise the information recorded as to the time that had elapsed between infection and date of first examination. Evidence of the unrelia-

bility of patients' memories is afforded by the percentage (32.7) of cases of sero-positive primary syphilis in which they stated that they had received treatment in a clinic within the first four weeks after infection.

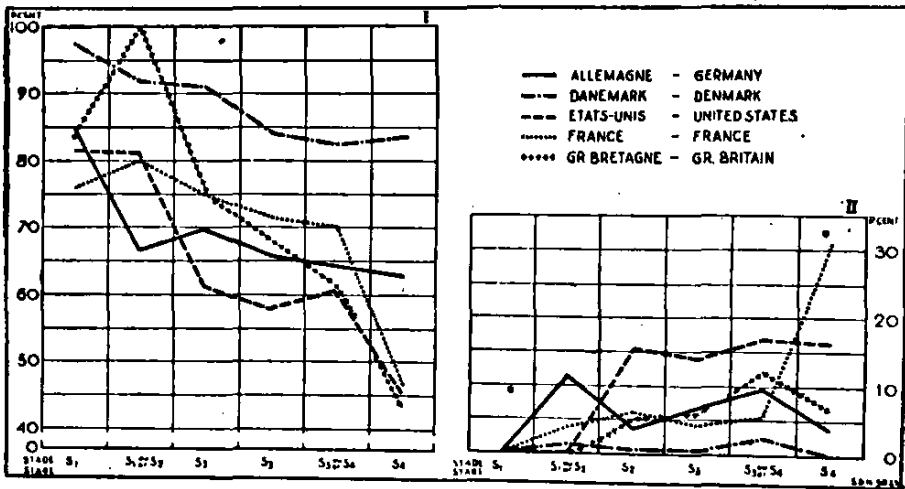
In order to permit of better comparison, the figures relating to *continuously treated* cases have also been set out by stages of the disease, though the smallness of the absolute numbers involved (save for the United States cards) militates against such a tabulation.

3. THE RESULTS OF TREATMENT.

INTERMITTENT TREATMENT.

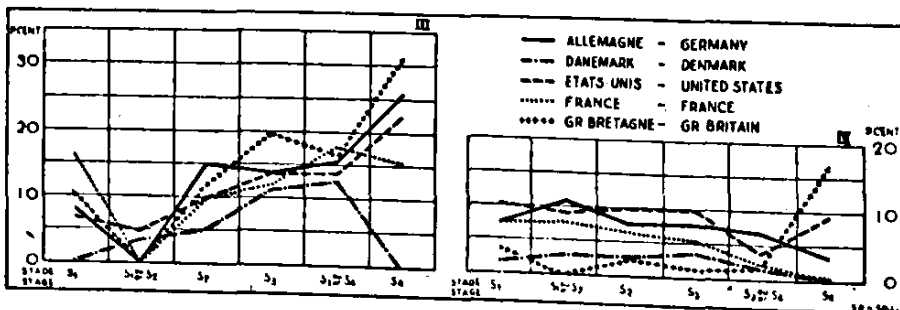
Cases remaining or becoming sero-negative.

Cases remaining sero-positive.



Serological relapses.

Clinical relapses.



Percentage¹ of the Total Cases, treated as described, which remained or became Sero-negative.

| | Stage | | | | | |
|------------------------------------|-------------|------------|-------------|---------------|-------------|------------|
| | S1 | S1 or S2 | S2 | S3 | S3 or S4 | S4 |
| I. Treated intermittently : | | | | | | |
| Germany..... | 82.52 (288) | 66.66 (6) | 70.12 (352) | 65.68 (444) | 64.30 (544) | 62.96 (17) |
| Denmark | 97.49 (311) | 92.18 (59) | 91.06 (376) | 84.17 (1,175) | 82.54 (53) | 83.33 (5) |
| United States of America | 81.37 (131) | 80.95 (17) | 61.70 (298) | 57.80 (763) | 61.21 (71) | 45.21 (33) |
| France | 76.70 (79) | 80.00 (20) | 75.23 (243) | 71.67 (215) | 69.77 (90) | 46.15 (6) |
| Great Britain | 83.37 (386) | 100.00 (4) | 75.24 (708) | 68.11 (519) | 61.55 (429) | 43.75 (7) |
| II. Treated continuously : | | | | | | |
| Germany | — (—) | — (—) | 83.33 (15) | 81.25 (26) | 72.73 (32) | 25.0 (1) |
| United States of America | 90.36 (75) | 100.5 (5) | 81.54 (106) | 78.77 (319) | 70.59 (12) | 100.0 (9) |
| France | 83.33 (5) | — (—) | 100.0 (7) | 66.67 (4) | 100.0 (8) | — (—) |
| Great Britain | 66.67 (4) | — (—) | 84.51 (60) | 100.0 (1) | 100.0 (1) | 100.0 (2) |

| | Cases | | | | | |
|--|--------------------------|-------|-------|--|---------------|---------------|
| | Treated (Actual figures) | | | Remaining or becoming sero-negative after treatment (Percentages) ¹ | | |
| | Total | Men | Women | Total | Men | Women |
| I. Treated intermittently : | | | | | | |
| Germany | 2,409 | 1,196 | 1,213 | 68.53 (1,651) | 70.23 (840) | 66.86 (811) |
| Denmark | 2,262 | 1,154 | 1,108 | 87.49 (1,979) | 92.72 (1,070) | 82.04 (909) |
| United States of America | 2,174 | 1,396 | 778 | 60.40 (1,313) | 61.75 (862) | 57.97 (451) |
| France | 893 | 566 | 327 | 73.12 (653) | 72.09 (408) | 74.92 (245) |
| Great Britain | 2,883 | 2,087 | 796 | 71.21 (2,053) | 72.78 (1,519) | 67.09 (534) |
| S1-S4 | 10,621 | 6,399 | 4,222 | 72.02 (7,649) | 73.43 (4,699) | 69.87 (2,950) |
| II. Treated continuously : | | | | | | |
| Germany | 98 | 41 | 57 | 75.51 (74) | 68.29 (28) | 80.70 (46) |
| Denmark | — | — | — | — | — | — |
| United States of America | 649 | 436 | 213 | 81.05 (526) | 82.11 (358) | 78.40 (168) |
| France | 27 | 18 | 9 | 88.89 (24) | 83.33 (15) | 100.00 (9) |
| Great Britain | 81 | 78 | 3 | 83.95 (68) | 83.33 (65) | 100.00 (3) |
| S1-S4 | 855 | 573 | 282 | 80.94 (692) | 81.33 (466) | 80.14 (226) |
| III. Treated in part continuously, in part intermittently : | | | | | | |
| Germany | 52 | 17 | 35 | 30.79 (16) | 29.41 (5) | 31.43 (11) |
| Denmark | — | — | — | — | — | — |
| United States of America | 643 | 389 | 254 | 55.68 (358) | 53.47 (208) | 59.06 (150) |
| France | 77 | 44 | 33 | 51.95 (40) | 56.82 (25) | 45.45 (15) |
| Great Britain | 121 | 93 | 28 | 64.46 (78) | 66.67 (62) | 57.14 (16) |
| S1-S4 | 893 | 543 | 350 | 55.10 (492) | 55.25 (300) | 54.86 (192) |
| IV. D1 cases (first came under clinical treatment in a state of clinical relapse) (S3-S4, all five countries) : | | | | | | |
| 1. Treated intermittently | 726 | 482 | 244 | 60.47 (439) | 60.79 (293) | 59.84 (146) |
| 2. Treated continuously | 60 | 41 | 19 | 61.67 (37) | 58.54 (24) | 69.42 (13) |
| 3. Treated in part continuously, in part intermittently. | 43 | 31 | 12 | 53.49 (23) | 54.84 (17) | 50.00 (6) |

¹ Absolute figures in parentheses.

Percentage¹ of the Total Cases, treated as described, which remained sero-positive.

| | Stage | | | | | |
|------------------------------------|-------|-----------|------------|-------------|------------|------------|
| | S1 | S1 or S2 | S2 | S3 | S3 or S4 | S4 |
| I. Treated intermittently : | | | | | | |
| Germany | — (—) | 11.11 (1) | 3.39 (17) | 7.10 (48) | 7.45 (63) | 3.70 (1) |
| Denmark | — (—) | 1.56 (1) | 0.73 (3) | 0.57 (8) | 3.17 (2) | — (—) |
| United States of America | — (—) | — (—) | 15.32 (74) | 14.24 (188) | 17.24 (20) | 16.44 (12) |
| France | — (—) | 4.00 (1) | 5.88 (19) | 4.33 (13) | 5.43 (7) | 30.77 (4) |
| Great Britain | — (—) | — (—) | 5.21 (49) | 6.17 (47) | 11.62 (81) | 6.25 (2) |
| II. Treated continuously : | | | | | | |
| Germany | — (—) | — (—) | 5.56 (1) | — (—) | 9.09 (4) | 50.00 (2) |
| United States of America | — (—) | — (—) | 4.62 (6) | 5.43 (22) | 11.76 (2) | — (—) |
| France | — (—) | — (—) | — (—) | — (—) | — (—) | — (—) |
| Great Britain | — (—) | — (—) | 1.41 (1) | — (—) | — (—) | — (—) |

| | Cases | | | | | |
|--|-----------------------------|--------------|--------------|--|-------------------|-------------------|
| | Treated (Actual figures) | | | Remained sero-positive (Percentages) ¹ | | |
| | Total | Men | Women | Total | Men | Women |
| I. Treated intermittently : | | | | | | |
| Germany | 2,409 | 1,196 | 1,213 | 5.40 (130) | 4.52 (54) | 6.27 (76) |
| Denmark | 2,262 | 1,154 | 1,108 | 0.62 (14) | 0.69 (8) | 0.54 (6) |
| United States of America | 2,174 | 1,396 | 778 | 13.52 (294) | 12.68 (177) | 15.04 (117) |
| France | 893 | 566 | 327 | 4.93 (44) | 5.12 (29) | 4.59 (15) |
| Great Britain | 2,883 | 2,087 | 796 | 6.18 (178) | 5.51 (115) | 7.91 (63) |
| S1-S4 | 10,621 | 6,399 | 4,222 | 6.21 (660) | 5.99 (383) | 6.56 (277) |
| II. Treated continuously : | | | | | | |
| Germany | 98 | 41 | 57 | 7.14 (7) | 7.32 (3) | 7.02 (4) |
| Denmark | — | — | — | — | — | — |
| United States of America | 649 | 436 | 213 | 4.62 (30) | 3.44 (15) | 7.04 (15) |
| France | 27 | 18 | 9 | — (—) | — (—) | — (—) |
| Great Britain | 81 | 78 | 3 | 1.23 (1) | 1.28 (1) | — (—) |
| S1-S4 | 855 | 573 | 282 | 4.44 (38) | 3.32 (19) | 6.74 (19) |
| III. Treated in part continuously, in part intermittently : | | | | | | |
| Germany | 52 | 17 | 35 | 7.69 (4) | 11.76 (2) | 5.71 (2) |
| Denmark | — | — | — | — | — | — |
| United States of America | 643 | 389 | 254 | 5.44 (35) | 6.17 (24) | 4.33 (11) |
| France | 77 | 44 | 33 | — (—) | — (—) | — (—) |
| Great Britain | 121 | 93 | 28 | 9.92 (12) | 9.68 (9) | 10.71 (3) |
| S1-S4 | 893 | 543 | 350 | 5.71 (51) | 6.45 (35) | 4.57 (16) |
| IV. D1 cases (first came under clinical treatment in a state of clinical relapse) (S3-S4, all five countries) : | | | | | | |
| 1. Treated intermittently | 726 | 482 | 244 | 12.67 (92) | 12.66 (61) | 12.70 (31) |
| 2. Treated continuously | 60 | 41 | 19 | 13.33 (8) | 12.20 (5) | 15.79 (3) |
| 3. In part continuously, in part intermittently | 43 | 31 | 12 | 6.98 (3) | 6.45 (2) | 8.33 (1) |

¹ Absolute figures in parentheses.

Percentage¹ of the Total Cases, treated as described, which relapsed serologically.

| | Stage | | | | | |
|------------------------------------|------------|----------|-------------|-------------|-------------|------------|
| | S1 | S1 or S2 | S2 | S3 | S3 or S4 | S4 |
| I. Treated intermittently : | | | | | | |
| Germany | 7.73 (27) | — (—) | 15.35 (77) | 13.61 (92) | 15.84 (134) | 25.92 (7) |
| Denmark | 0.31 (1) | 3.13 (2) | 5.08 (21) | 11.18 (156) | 12.70 (8) | — (—) |
| United States of America | 6.83 (11) | 4.76 (1) | 9.94 (48) | 13.71 (181) | 13.79 (16) | 21.92 (16) |
| France | 13.59 (14) | — (—) | 9.60 (31) | 12.33 (37) | 17.83 (23) | 15.38 (2) |
| Great Britain | 9.29 (43) | — (—) | 11.69 (110) | 19.42 (148) | 16.79 (117) | 31.25 (5) |
| II. Treated continuously : | | | | | | |
| Germany | — (—) | — (—) | 11.11 (2) | 18.75 (8) | 13.64 (6) | 25.00 (1) |
| United States of America | 3.61 (3) | — (—) | 10.00 (13) | 6.91 (28) | 5.88 (1) | — (—) |
| France | 16.67 (1) | — (—) | — (—) | 16.67 (1) | — (—) | — (—) |
| Great Britain | 33.33 (2) | — (—) | 8.45 (6) | — (—) | — (—) | — (—) |

| | Cases | | | | | |
|--|--------------------------|-------|-------|---|-------------|-------------|
| | Treated (Actual figures) | | | Relapsed serologically (Percentages) ¹ | | |
| | Total | Men | Women | Total | Men | Women |
| I. Treated intermittently : | | | | | | |
| Germany | 2,409 | 1,196 | 1,213 | 13.99 (337) | 12.46 (149) | 15.50 (188) |
| Denmark | 2,262 | 1,154 | 1,108 | 8.31 (188) | 3.99 (46) | 12.82 (142) |
| United States of America | 2,174 | 1,396 | 778 | 12.56 (273) | 11.89 (166) | 13.75 (107) |
| France | 893 | 566 | 327 | 11.98 (107) | 12.01 (68) | 11.93 (39) |
| Great Britain | 2,883 | 2,087 | 796 | 14.67 (423) | 13.85 (289) | 16.83 (134) |
| S1-S4 | 10,621 | 6,399 | 4,222 | 12.50 (1,328) | 11.22 (718) | 14.45 (610) |
| II. Treated continuously : | | | | | | |
| Germany | 98 | 41 | 57 | 15.31 (15) | 21.95 (9) | 10.53 (6) |
| Denmark | — | — | — | — | — | — |
| United States of America | 649 | 436 | 213 | 6.93 (45) | 7.57 (33) | 5.63 (12) |
| France | 27 | 18 | 9 | 7.41 (2) | 11.11 (2) | — (—) |
| Great Britain | 81 | 78 | 3 | 9.88 (8) | 10.26 (8) | — (—) |
| S1-S4 | 855 | 573 | 282 | 8.19 (70) | 9.07 (52) | 6.38 (18) |
| III. Treated in part continuously, in part intermittently : | | | | | | |
| Germany | 52 | 17 | 35 | 55.77 (29) | 52.94 (9) | 57.14 (20) |
| Denmark | — | — | — | — | — | — |
| United States of America | 643 | 389 | 254 | 21.00 (135) | 21.59 (84) | 20.08 (51) |
| France | 77 | 44 | 33 | 40.26 (31) | 34.09 (15) | 48.48 (16) |
| Great Britain | 121 | 93 | 28 | 18.18 (22) | 17.20 (16) | 21.43 (6) |
| S1-S4 | 893 | 543 | 350 | 24.30 (217) | 22.84 (124) | 26.57 (93) |
| IV. D1 cases (first came under clinical treatment in a state of clinical relapse) (S3-S4, all five countries) : | | | | | | |
| 1. Treated intermittently | 726 | 482 | 244 | 14.05 (102) | 13.69 (66) | 14.75 (36) |
| 2. Treated continuously | 60 | 41 | 19 | 11.67 (7) | 14.63 (6) | 5.26 (1) |
| 3. In part continuously, in part intermittently | 43 | 31 | 12 | 23.26 (10) | 16.13 (5) | 41.87 (5) |

¹ Absolute figures in parentheses.

Percentage¹ of the Total Cases, treated as described, which relapsed clinically.

| | Stage | | | | | |
|-----------------------------------|------------|-----------|------------|-------------|-----------|-----------|
| | S1 | S1 or S2 | S2 | S3 | S3 or S4 | S4 |
| I. Treated intermittently: | | | | | | |
| Germany | 8.02 (28) | 11.11 (1) | 8.35 (42) | 8.28 (56) | 7.21 (61) | 3.70 (1) |
| Denmark | 1.88 (6) | 3.13 (2) | 3.15 (13) | 3.80 (53) | 1.59 (1) | 16.67 (1) |
| United States of America | 10.56 (17) | 9.53 (2) | 10.14 (49) | 10.08 (133) | 3.45 (4) | 9.59 (7) |
| France | 7.77 (8) | 8.00 (2) | 6.81 (22) | 6.00 (18) | 1.55 (2) | — (—) |
| Great Britain | 3.89 (18) | — (—) | 2.87 (27) | 1.84 (14) | 1.86 (13) | — (—) |
| II. Treated continuously: | | | | | | |
| Germany | — (—) | — (—) | — (—) | — (—) | 4.54 (2) | — (—) |
| United States of America | 3.81 (3) | — (—) | 1.54 (2) | — (—) | — (—) | — (—) |
| France | — (—) | — (—) | — (—) | — (—) | — (—) | — (—) |
| Great Britain | — (—) | — (—) | — (—) | — (—) | — (—) | — (—) |

| | Cases | | | | | |
|---|--------------------------|-------|-------|--|------------|------------|
| | Treated (Actual figures) | | | Relapsed clinically (Percentages) ¹ | | |
| | Total | Men | Women | Total | Men | Women |
| I. Treated intermittently: | | | | | | |
| Germany | 2,409 | 1,196 | 1,213 | 7.85 (189) | 9.03 (108) | 6.68 (81) |
| Denmark | 2,262 | 1,154 | 1,108 | 3.36 (76) | 2.43 (28) | 4.33 (48) |
| United States of America | 2,174 | 1,396 | 778 | 9.75 (212) | 9.88 (138) | 9.51 (74) |
| France | 893 | 566 | 327 | 5.82 (52) | 6.71 (38) | 4.28 (14) |
| Great Britain | 2,883 | 2,087 | 796 | 2.49 (72) | 2.78 (58) | 1.76 (14) |
| S1-S4 | 10,621 | 6,399 | 4,222 | 5.66 (601) | 5.78 (370) | 5.47 (231) |
| II. Treated continuously: | | | | | | |
| Germany | 98 | 41 | 57 | 2.04 (2) | 2.44 (4) | 1.75 (1) |
| Denmark | — | — | — | — | — | — |
| United States of America | 649 | 436 | 213 | 0.77 (5) | 1.15 (5) | 0.00 (—) |
| France | 27 | 18 | 9 | — (—) | — (—) | — (—) |
| Great Britain | 81 | 78 | 3 | — (—) | — (—) | — (—) |
| S1-S4 | 855 | 573 | 282 | 0.82 (7) | 1.05 (6) | 0.36 (1) |
| III. Treated in part continuously, in part intermittently: | | | | | | |
| Germany | 52 | 17 | 35 | 1.92 (1) | 5.88 (1) | 0.00 (—) |
| Denmark | — | — | — | — | — | — |
| United States of America | 643 | 389 | 254 | 11.66 (75) | 12.85 (50) | 9.84 (25) |
| France | 77 | 44 | 33 | 5.19 (4) | 4.55 (2) | 6.06 (2) |
| Great Britain | 121 | 93 | 28 | 2.48 (3) | 2.15 (2) | 3.57 (1) |
| S1-S4 | 893 | 543 | 350 | 9.29 (83) | 10.13 (55) | 8.00 (28) |
| IV. D1 cases (first came under clinical treatment in a state of clinical relapse) (S3-S4, all five countries): | | | | | | |
| 1. Treated intermittently | 726 | 482 | 244 | 8.68 (63) | 9.13 (44) | 7.79 (19) |
| 2. Treated continuously | 60 | 41 | 19 | 8.33 (5) | 9.76 (4) | 5.26 (1) |
| 3. In part continuously, in part intermittently | 43 | 31 | 12 | 16.28 (7) | 22.58 (7) | 0.0 (—) |

¹ Absolute figures in parentheses.

Percentage¹ of the Total Cases, treated as described, which later developed Doubtful Serological Relapses.

| | Stage | | | | | |
|-----------------------------------|-----------|-----------|-----------|-----------|-----------|-----------|
| | S1 | S1 or S2 | S2 | S3 | S3 or S4 | S4 |
| I. Treated intermittently: | | | | | | |
| Germany | 1.72 (6) | 11.11 (1) | 2.79 (14) | 4.15 (28) | 4.02 (34) | 3.70 (1) |
| Denmark | 0.31 (1) | — (—) | — (—) | — (—) | — (—) | — (—) |
| United States of America | 1.24 (2) | 4.76 (1) | 2.90 (14) | 3.41 (45) | 4.31 (5) | 6.85 (5) |
| France | 1.94 (2) | 8.00 (2) | 2.48 (8) | 4.33 (13) | 5.43 (7) | 7.69 (1) |
| Great Britain | 3.46 (16) | — (—) | 4.99 (47) | 4.33 (33) | 7.79 (54) | 18.75 (3) |
| II. Treated continuously: | | | | | | |
| Germany | — (—) | — (—) | — (—) | — (—) | — (—) | — (—) |
| United States of America | 2.41 (2) | — (—) | 2.31 (3) | 4.94 (20) | 11.76 (2) | — (—) |
| France | — (—) | — (—) | — (—) | — (—) | — (—) | — (—) |
| Great Britain | — (—) | — (—) | 5.63 (4) | — (—) | — (—) | — (—) |

| | Cases | | | | | |
|---|----------------------------|--------------|--------------|--|-------------------|-------------------|
| | Treatment (Actual figures) | | | Doubtful serological relapses (Percentages) ¹ | | |
| | Total | Men | Women | Total | Men | Women |
| I. Treated intermittently: | | | | | | |
| Germany | 2,409 | 1,196 | 1,213 | 3.49 (84) | 3.01 (36) | 3.96 (48) |
| Denmark | 2,262 | 1,154 | 1,108 | 0.04 (1) | 0.0 (—) | 0.09 (1) |
| United States of America | 2,174 | 1,396 | 778 | 3.31 (72) | 3.30 (46) | 3.35 (26) |
| France | 893 | 566 | 327 | 3.70 (33) | 3.54 (20) | 3.98 (13) |
| Great Britain | 2,883 | 2,087 | 796 | 5.31 (153) | 5.08 (106) | 5.90 (47) |
| S1-S4 | 10,621 | 6,399 | 4,222 | 3.23 (343) | 3.25 (208) | 3.20 (135) |
| II. Treated continuously: | | | | | | |
| Germany | 98 | 41 | 57 | 0.0 (—) | 0.0 (—) | 0.0 (—) |
| Denmark | — | — | — | — | — | — |
| United States of America | 649 | 436 | 213 | 4.16 (27) | 3.65 (16) | 5.16 (11) |
| France | 27 | 16 | 9 | 0.0 (—) | 0.0 (—) | 0.0 (—) |
| Great Britain | 81 | 78 | 3 | 4.94 (4) | 5.13 (4) | 0.0 (—) |
| S1-S4 | 855 | 573 | 282 | 3.63 (31) | 3.49 (20) | 3.90 (11) |
| III. Treated in part continuously, in part intermittently: | | | | | | |
| Germany | 52 | 17 | 35 | 3.85 (2) | 0.0 (—) | 5.71 (2) |
| Denmark | — | — | — | — | — | — |
| United States of America | 643 | 389 | 254 | 4.98 (32) | 4.88 (19) | 5.12 (13) |
| France | 77 | 44 | 33 | 0.0 (—) | 0.0 (—) | 0.0 (—) |
| Great Britain | 121 | 93 | 28 | 4.96 (6) | 4.30 (4) | 7.14 (2) |
| S1-S4 | 893 | 543 | 350 | 4.48 (40) | 4.24 (23) | 4.86 (17) |
| IV. D1 cases (first came under clinical treatment in a state of clinical relapse) (S3-S4, all five countries): | | | | | | |
| 1. Treated intermittently | 726 | 482 | 244 | 3.17 (23) | 2.91 (14) | 3.69 (9) |
| 2. Treated continuously | 60 | 41 | 19 | 5.00 (3) | 4.88 (2) | 5.26 (1) |
| 3. In part continuously, in part intermittently | 43 | 31 | 12 | 0.0 (—) | 0.0 (—) | 0.0 (—) |

¹ Absolute figures in parentheses.

SYPHILIS TREATMENT

Percentage¹ of the Total Cases, treated as described, which later developed *Doubtful Clinical Relapses*.

| | Cases | | | | | |
|---|-------------------------------|--------------|--------------|--|------------------|-----------------|
| | Treatment (Actual figures) | | | Doubtful clinical relapses (Percentages) ¹ | | |
| | Total | Men | Women | Total | Men | Women |
| I. Treated intermittently: | | | | | | |
| Germany | 2,409 | 1,196 | 1,213 | 0.25 (6) | 0.25 (3) | 0.25 (3) |
| Denmark | 2,262 | 1,154 | 1,108 | 0.0 (—) | 0.0 (—) | 0.0 (—) |
| United States of America | 2,174 | 1,396 | 778 | 0.32 (7) | 0.29 (4) | 0.39 (3) |
| France | 893 | 566 | 327 | 0.45 (4) | 0.53 (3) | 0.30 (1) |
| Great Britain | 2,883 | 2,087 | 796 | 0.07 (2) | 0.0 (—) | 0.25 (2) |
| S1-S4 | 10,621 | 6,399 | 4,222 | 0.18 (19) | 0.16 (10) | 0.21 (9) |
| II. Treated continuously: | | | | | | |
| Germany | 98 | 41 | 57 | 0.0 (—) | 0.0 (—) | 0.0 (—) |
| Denmark | — | — | — | — | — | — |
| United States of America | 649 | 436 | 213 | 2.47 (16) | 2.04 (9) | 3.29 (7) |
| France | 27 | 18 | 9 | 3.70 (1) | 5.56 (1) | 0.0 (—) |
| Great Britain | 81 | 78 | 3 | 0.0 (—) | 0.0 (—) | 0.0 (—) |
| S1-S4 | 855 | 573 | 282 | 1.99 (17) | 1.74 (10) | 2.48 (7) |
| III. Treated in part continuously, in part intermittently: | | | | | | |
| Germany | 52 | 17 | 35 | 0.0 (—) | 0.0 (—) | 0.0 (—) |
| Denmark | — | — | — | — | — | — |
| United States of America | 643 | 389 | 254 | 1.09 (7) | 0.77 (3) | 1.61 (4) |
| France | 77 | 44 | 33 | 2.60 (2) | 4.55 (2) | 0.0 (—) |
| Great Britain | 121 | 93 | 28 | 0.0 (—) | 0.0 (—) | 0.0 (—) |
| S1-S4 | 893 | 543 | 350 | 1.01 (9) | 0.92 (6) | 1.14 (4) |

Percentage¹ of negative serological reactions obtained at the first examination in the clinic of secondary cases or cases which first came under clinical treatment in a state of clinical relapse (Sp. pallida positive).

| Country | Treated intermittently | | | Treated continuously | | |
|--------------------------------|--|------------------|------------------|----------------------|-----------------|-----------------|
| | Total | Men | Women | Total | Men | Women |
| Germany | 0.50 (12) | 0.50 (6) | 0.50 (6) | 0.0 (—) | 0.0 (—) | 0.0 (—) |
| Denmark | 0.18 (4) | 0.18 (2) | 0.18 (2) | 0.0 (—) | 0.0 (—) | 0.0 (—) |
| United States of America | 0.14 (3) | 0.21 (3) | 0.0 (—) | 0.0 (—) | 0.0 (—) | 0.0 (—) |
| France | 0.0 (—) | 0.0 (—) | 0.0 (—) | 0.0 (—) | 0.0 (—) | 0.0 (—) |
| Great Britain | 0.07 (2) | 0.0 (—) | 0.25 (2) | 0.0 (—) | 0.0 (—) | 0.0 (—) |
| S1-S4 | 0.20 (21) | 0.17 (11) | 0.24 (10) | 0.0 (—) | 0.0 (—) | 0.0 (—) |
| Country | Treated in part continuously, in part intermittently | | | D1 cases | | |
| Germany | 0.0 (—) | 0.0 (—) | 0.0 (—) | 1.17 (4) | 0.56 (1) | 1.85 (3) |
| Denmark | 0.0 (—) | 0.0 (—) | 0.0 (—) | 0.0 (—) | 0.0 (—) | 0.0 (—) |
| United States of America | 0.16 (1) | 0.26 (1) | 0.0 (—) | 0.0 (—) | 0.0 (—) | 0.0 (—) |
| France | 0.0 (—) | 0.0 (—) | 0.0 (—) | 4.62 (3) | 7.63 (3) | 0.0 (—) |
| Great Britain | 0.0 (—) | 0.0 (—) | 0.0 (—) | 0.0 (—) | 0.0 (—) | 0.0 (—) |
| S1-S4 | 0.11 (1) | 0.18 (1) | 0.0 (—) | 0.84 (7) | 0.72 (4) | 1.09 (3) |

¹ Absolute figures in parentheses.

These treatment results (the absolute totals for which are shown in Annex 11), indicate that the *best results* especially as regards the absence of clinical relapses, were secured, on the one hand *with continuous treatment* as such (*i.e.*, according to various schemes), and, on the other, with *intermittent treatment* applied according to certain particular schemes.

It should be noted that the total number of cases treated on the *continuous* plan is small compared with those treated intermittently. The cases continuously treated represent also in some respects a homogeneous group (longer prescribed minimum period of treatment, cases collected from a comparatively small number of clinics) so that any idea of ranking the various methods (intermittent and continuous) in order of merit was abandoned. It was not intended—and with the available material it would not have been possible—to recommend any one method as a standard treatment.

The record cards supplied by the United States of America comprise a considerable number of continuously treated cases. The success of continuous treatment in the *United States* is particularly striking when compared with the results obtained in the same country with intermittent treatment. This superiority is brought out even more strikingly when continuous treatment results are compared with those obtained in the United States by partly continuous and partly intermittent treatment—the number of cases treated by each method being practically the same.

Though it may, of course, be argued that the way in which the general results work out in respect of the behaviour of the serological reaction is not solely due to the merits of the treatment since a number of other factors might affect them very considerably (for instance, frequency of serological tests, nature and sensitiveness of the methods of serological testing followed in various clinics and countries, personal factor in the reading of the result, and so on), such sources of error are hardly likely to operate in the diagnosis of clinical relapse. In these cases the only matters of real importance are the regularity and duration of supervision after treatment.

Omitting for the moment the cases which first appeared for treatment in the participating clinics in as taste of clinical relapse (D1 cases), the percentage of clinical relapses noted in the United States cases is :

| | |
|---|-------|
| Continuous treatment | 0.77 |
| Intermittent treatment | 9.75 |
| Partly continuous, partly intermittent treatment... | 11.66 |

The cases treated continuously in *Germany*, *France* and the *United Kingdom*, though less numerous (about 200 in all) also yielded very satisfactory results, the percentage of clinical relapses amounting only to 0.82, whereas the corresponding percentage for intermittently treated cases in all countries still stands at 5.66 and for cases treated in part continuously and in part intermittently at 9.29.

The total number of cases that have received intermittent treatment is so great that it enables satisfactory comparisons to be made, not only between separate countries, but even between the separate stages of early syphilis.

The best results with intermittent treatment have been obtained in *Denmark* and the *United Kingdom*. In *Denmark*, the percentage of patients who remained sero-negative (S1 cases), as well as that of the patients who became and remained sero-negative, is far greater than that of any other country ; similarly the position in *Denmark* is much better in respect of serological relapses and of cases that remained sero-positive. The *United Kingdom* comes second in regard to the behaviour of the serological reaction, but shows a somewhat lower clinical relapse rate than *Denmark* (2.49 per cent as compared with 3.36 per cent). Though it may be admitted that the factors cited above as influencing the results of serological tests may also have helped to produce these differences (in other words, that in *Denmark* the serological tests were not adjusted to such a high degree of sensitiveness at one and the same level of specificity as, for instance, in the *United Kingdom*), the differences that might be ascribed to these causes would hardly be of such magnitude as those yielded by the percentage calculation.

When the results of intermittent treatment in the various stages are compared, it is seen that the percentage of cases which *became sero-negative and remained so* diminishes steadily with the age of the infection, whereas no regular trend was observable in respect of cases that *remained sero-positive* throughout. The number of *serological relapses* is almost always lowest in the sero-negative primary group, and rises considerably in the sero-positive group. This upward trend continues in the secondary syphilis groups.

Whilst such a course of events in *serological relapses* might have been expected, it is striking that *clinical relapse* does not in the least follow the same rule. Whereas (with the single exception

of Denmark) the proportion of clinical relapses among seropositive primary cases is either about the same as amongst seronegative cases (in Germany, 8.35 per cent as compared with 8.02 per cent, and, in the United States, 10.14 per cent as compared with 10.56 per cent), or is quite noticeably smaller (in France, 6.81 per cent as compared with 7.77 per cent, and, in the United Kingdom, 2.87 per cent as compared with 3.89 per cent), the percentage figures decrease in the case of secondary syphilis sometimes to a surprisingly low level. Generally, among the cases analysed, *the more recent the infection the higher the incidence of clinical relapse.*

The *comparative findings in men and women* lead to the conclusion that, *among women, the percentage of clinical relapses is appreciably less throughout than among men*, but that in the matter of serological behaviour in all comparable groups women contrast unfavourably with men. The percentage of clinical relapses among women is less than among men not only under intermittent treatment but also under continuous and under partly continuous and partly intermittent treatment.

That the results obtained by the partly continuous and partly intermittent treatment would be the least favourable in every country in which it has been practised was to be expected, since we are not dealing with a planned method or form of treatment deliberately devised by the practitioner, but rather with something brought about by the unreliability of the patients themselves. The results of these series show that, *beside the particular form of treatment, regularity is of the highest importance.* I propose to examine this point in greater detail later.

Both the continuous and the intermittent type of treatment yielded better results even when applied to *cases that were already in a state of clinical relapse when they first appeared for treatment at the clinic* than did partly continuous and partly intermittent treatment applied to the more favourable cases which came promptly under treatment. It was to be expected that a given method would yield distinctly poorer results in cases of clinical relapse than in those dealt with in the clinic from the beginning.

The groups of *doubtful serological relapses* and *doubtful clinical relapses* have been included for the sake of completeness, although their significance in the general evaluation is little more than

nominal. Doubtful serological relapses on which either a favourable or an unfavourable interpretation could be placed can the more easily be disregarded, since the percentage is astonishingly uniform in all three forms of treatment and among both men and women. The percentage of doubtful clinical relapses is very small in itself ; it is made up almost exclusively of cases in which the clinical signs after the alleged infection did not seem to afford sufficient evidence of syphilis (for instance, in the pre-Wassermann period).

Among serological relapses and doubtful serological relapses, those cases are also included in which there was a completely negative serological reaction, but in which the examination of the cerebro-spinal fluid gave a positive result in the absence of clinical signs. I shall refer to these cases later, but desire to observe here that their number is extremely small.

Consideration must now be given to a number of factors which might perhaps alter decisively the conclusions already set out. These are :

- The frequency of *re-infections* noted ;
- Undesirable complications* caused by the drugs used, or their dosage ;
- Length of observation* after the termination of treatment ;
- Behaviour of the cerebro-spinal fluid* ;
- Nature of clinical relapses and result of their treatment* ;
- Kind of serological relapses and result of their treatment.*

4. THE RE-INFECTIONS.

With regard to the returns relating to *re-infections*, it should be borne in mind that in the large majority of cases it is scarcely possible to decide with any degree of certainty whether a case is one of re-infection, super-infection, or clinical relapse. Even at the present day, there are many syphilologists who do not admit that re-infection can occur. But, even if the possibility of re-infection is allowed, and all cases presenting signs suggesting re-infection are not relegated out of hand to the category of super-infections or relapses, it would still appear altogether impossible to draw any valid conclusions under this heading from the material under review.

It is a well-known fact that a whole series of conditions must be fulfilled before a case can be pronounced to be one of re-infection, and only in the rarest instances can these be fully satisfied. The decision whether a particular clinical affection should be regarded as a re-infection or a relapse lay with the clinics supplying the returns. I have attempted no critical appraisal, nor indeed could I have done so, because the returns of the clinics, which had of course much fuller particulars of the cases, frequently record the hesitation which was felt even by them as to whether such cases should be classified as re-infections or as relapses.

To test whether the results of treatment, as set forth above, are likely to require any correction in order to allow for misjudgment in regard to re-infections, I have taken the most unfavourable hypothesis—namely, that all re-infections recorded as such might be clinical relapses. The percentage calculation of cases, as set out in Annex 12, gives the following results in respect of re-infections :

| Country | Clinical relapses (percentage) | | | Re-infections (percentage) | | | Clinical relapses + re-infections (percentage) | | |
|---|--------------------------------|-------|-------|----------------------------|------|-------|--|-------|-------|
| | Total | Men | Women | Total | Men | Women | Total | Men | Women |
| 1. Intermittent treatment (S1-S4). | | | | | | | | | |
| Germany | 7.85 | 9.03 | 6.68 | 1.14 | 1.98 | 0.29 | 8.99 | 11.01 | 6.97 |
| Denmark | 3.36 | 2.43 | 4.33 | 1.56 | 2.96 | 0.09 | 4.92 | 5.39 | 4.42 |
| United States of America | 9.75 | 9.88 | 9.51 | 0.66 | 0.94 | 0.12 | 10.41 | 10.82 | 9.63 |
| France | 5.82 | 6.71 | 4.28 | 0.52 | 0.66 | 0.28 | 6.34 | 7.37 | 4.56 |
| Great Britain | 2.49 | 2.78 | 1.76 | 0.61 | 0.61 | 0.61 | 3.10 | 3.39 | 2.37 |
| 2. Continuous treatment (S1-S4). | | | | | | | | | |
| Germany | 2.04 | 2.44 | 1.75 | — | — | — | 2.04 | 2.44 | 1.75 |
| Denmark | — | — | — | — | — | — | — | — | — |
| United States of America | 0.77 | 1.15 | 0.00 | 0.88 | 1.30 | — | 1.65 | 2.45 | 0.00 |
| France | — | — | — | — | — | — | — | — | — |
| Great Britain | — | — | — | — | — | — | — | — | — |
| 3. Partly continuous, partly intermittent treatment (S1-S4). | | | | | | | | | |
| Germany | 1.92 | 5.88 | 0.00 | — | — | — | 1.92 | 5.88 | 0.00 |
| Denmark | — | — | — | — | — | — | — | — | — |
| United States of America | 11.66 | 12.85 | 9.84 | 0.89 | 0.96 | 0.77 | 12.55 | 13.81 | 10.61 |
| France | 5.19 | 4.55 | 6.06 | — | — | — | 5.19 | 4.55 | 6.06 |
| Great Britain | 2.48 | 2.15 | 3.57 | — | — | — | 2.48 | 2.15 | 3.57 |

This table of comparative figures shows that, even if all re-infections are reckoned as clinical relapses, no appreciable change in the appraisal

of the treatment results is involved. A comparison of similar figures for primary syphilis in the various countries points to the same conclusion—with one exception, however. The number of clinical relapses following sero-negative primary syphilis is so greatly increased in Denmark by the adding in of the re-infections that it is brought very much closer to the corresponding figures for France, Germany and the United States, and becomes very nearly double that for Great Britain (referred only to intermittently treated cases).

| Country | Clinical relapses | | | Clinical relapses + re-infections | | |
|--------------------------------|-------------------|----------|-------|-----------------------------------|----------|-------|
| | Stage : | | | Stage : | | |
| | S1 | S1 or S2 | S2 | S1 | S1 or S2 | S2 |
| Germany | 8.02 | 11.11 | 8.35 | 10.89 | 11.11 | 9.94 |
| Denmark | 1.88 | 3.13 | 3.15 | 8.46 | 3.13 | 4.36 |
| United States of America | 10.56 | 9.93 | 10.14 | 11.80 | 14.29 | 11.18 |
| France | 7.77 | 8.00 | 6.81 | 8.74 | 12.00 | 7.74 |
| Great Britain | 3.89 | — | 2.87 | 4.54 | — | 3.61 |

Since, in Denmark, the number of relapses in sero-positive primary and secondary cases does not increase to the same extent when the observed re-infections are added in, it may be assumed that the re-infections in the sero-negative primary cases that were recorded in Denmark were in most cases genuine re-infections.

5. COMPLICATIONS ATTENDANT UPON ANTI-SYPHILITIC TREATMENT.

Since many different factors play a part in bringing about the accidents and complications attendant upon anti-syphilitic treatment (preparation, dosage, solvent and quantity of solvent fluid, sensitiveness of patient, etc.), it was to be expected that the statistical data on this point would display marked differences.

In two instances, however, the results under this heading are quite outside the limits of any differences to be expected from the operation of such factors. These are the unusually high proportion of icterus cases in Great Britain and of "other" (i.e., milder) subsidiary effects in France. I must be content to place the fact on record, as it would be futile to attempt any elucidation of the cause without exact knowledge of local conditions. I would merely point

out that, although it may readily be admitted that more accurate observation and the personal factor of the particular observer (*e.g.*, the noting of the slightest yellow discolouration of the sclera as icterus) may have affected the figures relating to complications, still, in my opinion, the differences found lie far outside the range of fluctuations that could be produced by such factors. The high percentage of icterus in Great Britain is found with all methods of treatment and stands at the highest level for continuous treatment. Among cases intermittently treated in Great Britain (the only form of treatment in which the total absolute number of cases allows of such a comparison), icterus occurs in men about twice as frequently as among women. It should be added that a higher frequency among men is noticeable in all countries (except France). On the other hand, *exanthem, dermatitis and the other slighter subsidiary effects are more frequently met with among women*, and this is true for all forms of treatment.

In order to judge of the practicability of the methods which have produced the most favourable results, we have to compare both the frequency and the severity of subsidiary effects in continuous treatment on the one hand and in intermittent treatment on the other ; and again to compare the figures obtained in intermittent treatment in the various countries (*cf.* Annex 13). As regards *continuous treatment*, it appears that, considering each country by itself, the really severe subsidiary effects (icterus, dermatitis) are in no way more frequent with this form of treatment than with intermittent treatment. In Germany, indeed, the subsidiary effects of continuous treatment have been even less frequent and less severe.

In the case of *intermittent treatment*, *Denmark* has the best record so far as total numbers are concerned. This is specially due to the facts that practically no slight complications have been recorded, and that the percentage of icterus, exanthem and dermatitis lies between the lower limit and the mean of the observed differences. Conditions in Great Britain are not so favourable, owing to the high percentage of icterus cases already mentioned above coupled with a rather high percentage of exanthem.

A few brief remarks may be added with regard to *deaths*. Needless to say, I have excluded all cases in which some other cause of death, such as carcinoma, could be definitely established. The position in regard to the remaining cases is as follows :

Germany :

Sero-positive primary syphilis in a woman intermittently treated ; six months after conclusion of treatment, nephritis and exitus.

Secondary syphilis in the first year after infection in a man. After the first course, dermatitis and exitus.

Denmark :

Secondary syphilis in the first year after infection in a man.

Exitus after seventh course, cause unknown.

United States :

Sero-positive primary syphilis in a man. Exitus within a year of the conclusion of intermittent treatment. Cause unknown.

Sero-positive primary syphilis in a woman. Exitus after serious disturbances of the alimentary tract and hæmorrhagic complications (intermittently treated).

Secondary syphilis in the first year after infection in a man. Exitus as a result of acute toxic hepatitis. Came forward for treatment (intermittent) when in a state of clinical relapse after earlier primary syphilis.

Secondary syphilis in the first year after infection in a woman. Exitus after dermatitis, icterus and acute yellow atrophy of the liver (intermittently treated).

Secondary syphilis in the first year of infection in a woman. Exitus after encephalitis hæmorrhagica (intermittently treated).

France :

Sero-positive primary syphilis. After fifteen courses encephalitis hæmorrhagica and exitus. Man (intermittently treated).

Great Britain :

Sero-negative primary syphilis in a man. After five courses exitus from nephritis (intermittently treated). (In addition to this, a further four cases of acute yellow atrophy of the liver in men were observed (all cases of sero-positive primary syphilis treated intermittently).)

It will be seen from the above that the connection of death with the preceding anti-syphilitic treatment does not appear to be

absolutely established in all cases. If, however, despite this, all the cases listed above are numbered among the "subsidiary effects" of therapy, the number of deaths totals 10 for 13,198 treated cases, or less than 1 per thousand. The reason why all the above cases of death are connected with intermittent treatment is probably that the number of continuously treated cases was very small.

6. THE OBSERVATION PERIOD.

The length of observation after conclusion of treatment has, needless to say, been determined for all cases, as also for the larger statistical computations built up upon them. With the approval of the Experts, only the period of observation up to the last clinical and serological examination was regarded as adequate and used statistically, and purely clinical supervision was carried on in many cases for much longer periods than would appear from the table in Annex 14. Thus, among the "0" cases (*i.e.*, cases with no observation after conclusion of treatment) there are a large number which, for some inexplicable reason, were supervised clinically for many years without a serological test ever being performed or recorded.

As the main point to be tested was whether or not the apparently satisfactory results recorded for the continuously treated cases and for the intermittently treated cases of Denmark and Great Britain may be an illusion resulting from a possible shortness of the period of observation, I have left out of account in the following comparison, on the one hand, all the cases treated in part continuously and in part intermittently and the D1 cases, and, on the other hand, the smaller groups in the other two series (the intermittently and the continuously treated cases).

In the tables which follow, the percentages are calculated even for the very small absolute numbers, but this is merely for the sake of uniformity, since in such cases they have of course no practical value. For the rest, comparison of the relevant percentages will speak for itself, and I need only emphasise once again that in the *continuously treated cases* the period of observation after the conclusion of treatment is shorter almost throughout.

Observation after the Conclusion of Treatment was carried out in the Following Percentages¹ of Cases.

| Country | 1. Intermittently treated | | | | | | | 2. Continuously treated | | | | | | | |
|--------------------------------|---|-----------------------------|---------|--------|-------|-------|------|-------------------------|---------|---------|---------|---------|-------|------|--|
| | And remaining or becoming sero-negative | | | | | | | | | | | | | | |
| | Number of cases | Years | | | | | | Number of cases | Years | | | | | | |
| 0 | | -1 | 1-2 | 2-5 | 5-10 | 10-20 | 0 | | -1 | 1-2 | 2-5 | 5-10 | 10-20 | | |
| Germany | 1,651 | 23.80 | 34.28 | 18.05 | 19.14 | 3.76 | 0.97 | 74 | 4.05 | 13.51 | 31.08 | 51.35 | | | |
| Denmark | 1,979 | 28.40 | 31.03 | 18.24 | 19.00 | 3.33 | — | — | — | — | — | — | — | — | |
| United States of America | 1,313 | 50.95 | 27.42 | 10.13 | 9.22 | 2.06 | 0.23 | 526 | 56.46 | 22.24 | 10.65 | 8.17 | 2.28 | 0.19 | |
| France | 653 | 67.53 | 19.30 | 5.97 | 6.89 | 0.31 | — | 24 | (16.67) | (41.67) | (25.00) | (16.67) | | | |
| Great Britain | 2,053 | 12.42 | 44.96 | 21.72 | 19.58 | 1.27 | 0.05 | 68 | 23.53 | 64.71 | 8.82 | 2.94 | | | |
| | | And remaining sero-positive | | | | | | | | | | | | | |
| Germany | 130 | 57.69 | 34.62 | 5.38 | 0.77 | 0.77 | 0.77 | 7 | (57.14) | (42.86) | (—) | (—) | | | |
| Denmark | 14 | (64.29) | (28.57) | (7.14) | (—) | (—) | (—) | — | — | — | — | — | | | |
| United States of America | 294 | 85.71 | 11.23 | 2.04 | 0.68 | 0.34 | — | 30 | (80.00) | (20.00) | (—) | (—) | | | |
| France | 44 | (86.36) | (13.64) | (—) | (—) | (—) | (—) | — | — | — | — | — | | | |
| Great Britain | 178 | 45.51 | 47.19 | 5.06 | 2.24 | — | — | 1 | (—) | (—) | (100.0) | | | | |

¹ Where the absolute figures are below 50, the corresponding percentages are placed in parentheses.

Observation after the Conclusion of Treatment was carried out in the Following Percentages¹ of Cases (continued).

| Country | 1. Intermittently treated | | | | | | | 2. Continuously treated | | | | | |
|--------------------------------|---------------------------|-------|-------|-------|-------|-------|------|-------------------------|------------------------|---------|---------|---------|-----|
| | With serological relapses | | | | | | | | | | | | |
| | Number of cases | Years | | | | | | Number of cases | Years | | | | |
| 0 | | -1 | 1-2 | 2-5 | 5-10 | 10-20 | 0 | | -1 | 1-2 | 2-5 | 5-10 | |
| Germany | 337 | 39.17 | 32.94 | 15.13 | 8.90 | 3.26 | 0.59 | 16 | (—) | (66.67) | (13.33) | (20.0) | (—) |
| Denmark | 158 | 36.17 | 24.47 | 15.95 | 21.81 | 1.60 | — | — | — | — | — | — | — |
| United States of America | 273 | 62.64 | 24.91 | 4.03 | 5.49 | 2.93 | — | 45 | (62.22) | (26.67) | (4.44) | (6.67) | (—) |
| France..... | 107 | 70.10 | 16.82 | 6.52 | 5.61 | 0.94 | — | 2 | (50.00) | (50.00) | (—) | (—) | (—) |
| Great Britain..... | 423 | 13.71 | 42.55 | 19.39 | 23.40 | 0.95 | — | 8 | (25.00) | (62.50) | (12.50) | (—) | (—) |
| | | | | | | | | | With clinical relapses | | | | |
| Germany | 189 | 59.79 | 23.81 | 4.23 | 6.88 | 4.76 | 0.53 | 2 | (50.00) | (—) | (—) | (50.00) | — |
| Denmark | 76 | 42.11 | 23.68 | 11.84 | 21.05 | 1.32 | — | — | — | — | — | — | — |
| United States of America | 212 | 76.42 | 7.55 | 5.19 | 7.55 | 3.30 | — | 6 | (80.00) | (—) | (20.00) | (—) | — |
| France..... | 62 | 73.08 | 10.23 | 3.85 | 1.92 | 1.92 | — | — | — | — | — | — | — |
| Great Britain..... | 72 | 18.06 | 50.00 | 9.72 | 19.44 | 2.78 | — | — | — | — | — | — | — |

¹ Where the absolute figures are below 50, the corresponding percentages are placed in parentheses.

In the *United States*, it should be said, which returned the largest absolute number of *continuously treated* cases, the difference in the period of observation as between these and the intermittently treated cases is not very great. On the other hand, *where intermittent treatment is concerned*, cases so treated in *Denmark* and *Great Britain* were kept under observation for distinctly longer than those in the *United States* and *France*, whereas the period of observation of the *German* cases equals, or approximates to, that noted for the first two countries named.

7. CEREBRO-SPINAL FLUID TESTS.

A further factor which may play an important part in the comparison of treatment results is the *behaviour of the cerebro-spinal fluid*. I was obliged, however, to abandon the idea of working up the results of lumbar puncture in any detailed manner, for the computation of comparative figures would be useless owing to the fact that the total number of cerebro-spinal fluid tests is comparatively small and, further, that the cases subjected to lumbar puncture are distributed very unevenly over the various countries and, within those countries, over the various clinics. A final reason is that in *Denmark*, *France* and *Great Britain*, save in a very few cases, lumbar puncture was performed only once. Special attention must be drawn to the fact that very little use is made of this method of test ; indeed, there are many clinics which appear to have made no lumbar punctures at all, at least so far as cases of primary and secondary syphilis are concerned. If any comparative judgment were attempted, it would have to be borne in mind that the reading of the results in cerebro-spinal fluid tests is nothing like so uniform as in the blood-serum tests, especially as we have to do with a whole series of heterogeneous separate tests.

The distribution of the figures relating to lumbar punctures and their results is set forth in the table in Annex 15. I contented myself with indicating the results as positive, doubtful or negative, since any detailed investigation into the various individual tests would not repay the trouble taken, for the reasons already mentioned.

The great differences in the frequency of lumbar puncture in the various countries will be seen from the following figures :

1. Proportion of *intermittently treated cases* (including D1 cases) in which lumbar puncture was performed :

In Germany, 28.63 per cent (779 out of 2,721 cases) ;

In Denmark, 5.95 per cent (138 out of 2,311 cases) ;

In the United States of America, 56.91 per cent (1,371 out of 2,409 cases) ;

In France, 8.26 per cent (79 out of 957 cases) ;

In Great Britain, 10.28 per cent (303 out of 2,949 cases).

2. Proportion of *continuously treated cases* (including D1 cases) in which lumbar puncture was performed :

In Germany, 4.13 per cent (5 out of 121 cases) ;

In Denmark, no cases ;

In the United States of America, 68.40 per cent (467 out of 683 cases) ;

In France, 11.11 per cent (3 out of 27 cases) ;

In Great Britain, 21.43 per cent (18 out of 84 cases) ;

Finally, a brief reference may be made to the few *cases in which, where the clinical signs and serological reaction were subsequently negative, only the cerebro-spinal fluid gave a positive result*. These cases comprise twelve with a positive reaction and two with a doubtful reaction. The latter was observed in Germany in two patients with past histories of secondary syphilis. Positive cases are distributed as follows :

Germany : 1 case (secondary syphilis) ;

United States : 9 cases (all of secondary syphilis, 2 of which only came forward for treatment at the clinic when already in a state of clinical relapse) ;

France : 2 cases (secondary syphilis).

8. THE RELAPSES.

Annex 16 gives details as to the *kinds of clinical relapse observed* and their distribution according to the stage of the disease recorded at the beginning of treatment of the particular case. Here again,

I have confined my attention to the intermittently treated and continuously treated cases (in each instance exclusive of D1 cases). In order to facilitate the understanding of these figures, the following table may be given, which shows the percentages of the different forms of clinical relapse observed for the first time.

Type of Relapse. (Intermittent Treatment.)

| Country | <i>Chancre reduz</i> | Secondary syphilis | Tertiary skin syphilis | Cardio- vascular late syphilis | Late syphilis of liver, etc. | Syphilis of the brain and spinal cord |
|---------------------------------------|--------------------------|-----------------------|------------------------------|---|---------------------------------------|---|
| Germany | 1.59 | 84.13 | 6.35 | 1.59 | 1.06 | 5.28 |
| Denmark | 5.26 | 92.11 | 2.63 | — | — | — |
| United States of America | 0.47 | 82.55 | 10.38 | 3.77 | — | 2.83 |
| France | — | 92.31 | 5.77 | — | — | 1.92 |
| Great Britain . . . | 22.22 | 70.83 | 5.56 | 1.39 | — | — |

Here again, the conditions viewed as a whole are particularly favourable in Denmark, seeing that only a very small percentage of tertiary forms of skin syphilis was observed under the heading of clinical relapses, and that no other clinical relapses whatever are recorded in the form of late syphilis of the internal organs or of the brain and spinal cord. So far as this last-named form is concerned, this circumstance may be due to the fact that cerebro-spinal fluid tests were performed in Denmark only in quite exceptional instances. The same reservation on this point is, incidentally, also applicable to France and Great Britain. Still it is noteworthy that in Denmark and particularly in Great Britain clinical relapse in the form of *chancre reduz* was observed with quite disproportionately greater frequency than in other countries. In almost every case, this form has occurred only where there has been a primary syphilitic infection, and almost exclusively in men.

In Germany, France and Great Britain, the percentage of clinical relapses in the tertiary form of skin syphilis is about twice, and in the United States about four times, the corresponding figure for Denmark. In the United States the high proportion of relapses generally, in comparison with that of other countries, is, in any case, noteworthy. The frequency and kind of repeated clinical relapses confirms the impression previously gained.

As to the kind of the (very few) clinical relapses which occur with continuous treatment, the table in Annex 16 gives sufficient particulars.

Subsequent developments in treated cases of clinical relapse as well as serological relapse are shown in Annex 14. This table indicates that, of the *clinical relapses*, the following percentages became *negative* in the course of subsequent treatment :

1. *In intermittently treated cases (exclusive of D1 cases).*

| | Total | Men | Women |
|--------------------------------|-------|-------|-------|
| Germany | 58.20 | 65.74 | 48.15 |
| Denmark | 68.95 | 57.14 | 75.00 |
| United States of America | 62.26 | 62.32 | 62.16 |
| France | 71.15 | 65.79 | 85.72 |
| Great Britain | 52.78 | 51.73 | 57.14 |

2. *In continuously treated cases (exclusive of D1 cases) (very small absolute figures).*

| | Total | Men | Women |
|--------------------------------|-------|-----|-------|
| Germany | 50 | 50 | — |
| United States of America | 80 | 80 | — |

Of the *serological relapses*, the following percentages became *negative* in the course of subsequent treatment :

1. *In intermittently treated cases (excluding D1 cases).*

| | Total | Men | Women |
|--------------------------------|-------|-------|-------|
| Germany | 62.61 | 52.35 | 70.74 |
| Denmark | 75.53 | 71.74 | 76.76 |
| United States of America | 53.48 | 52.41 | 55.14 |
| France | 81.31 | 85.29 | 74.36 |
| Great Britain | 72.34 | 74.74 | 67.16 |

2. *In continuously treated cases (excluding D1 cases) (small absolute figures).*

| | Total | Men | Women |
|--------------------------------|-------------------------------|--------|-------|
| Germany | 40.00 | 33.33 | 50.00 |
| Denmark | No continuously treated cases | | |
| United States of America | 57.78 | 51.52 | 75.00 |
| France | 100.00 | 100.00 | — |
| Great Britain | 75.00 | 75.00 | — |

9. CONCLUSIONS.

On a general review, we may say that the fact of taking into account the frequency of re-infections, the occurrence of undesirable

subsidiary effects induced by the drugs used or their dosage, the period after the conclusion of treatment, the kinds of clinical relapse and the results of their subsequent treatment, as well as the results of treatment of serological relapses, entails some slight adjustments, but is not sufficient to upset the conclusions as to the results of treatment that have previously been set forth. I would therefore repeat once more the unexpectedly clear result that has emerged from this statistical compilation.

The methods of treating primary, and early and late secondary, syphilis to be recommended as the most successful at the present day are :

1. *The continuous method of treatment as such ;*
2. *The intermittent method of treatment, as carried out in Denmark or Great Britain.*

It should be specially emphasised that *particularly satisfactory treatment results were also obtained in a number of clinics in the other countries*, and when the methods which they use are compared, they are found to agree in striking fashion with those applied in Denmark and the United Kingdom.

By way of appendix, I would like to say a few words in regard to the conclusions deduced from the material supplied by *Peiping*, which, owing to the comparative smallness of the actual number of cards, can be of value only as confirming the results otherwise reached. According to the particulars supplied in the "General Questionnaire", the treatment previously applied there was intermittent, and not until later was continuous treatment introduced. If, out of this total number of 157 cases of primary and secondary syphilis in Chinese patients, the 15 D1 cases and the 26 cases treated in part continuously and in part intermittently are discarded, the comparison shows that continuous treatment yielded far better results than the intermittent treatment previously applied. (Thus, among the 54 intermittently treated cases, there are 6 with serological and 12 with clinical relapses, whilst the corresponding figures for the 62 continuously treated cases are respectively 4 and 1.) The period of observation after the conclusion of treatment was, it is true, somewhat shorter in the continuously treated cases.

If all the effective methods of treatment are compared, then, despite individual differences, it is, in my opinion, possible to discern a number

of common features to which the uniformly good results are probably to be ascribed :

1. *The outstanding effectiveness of " 606 " or similar preparations. In order to make up for the lesser potency of " 914 " and preparations to be classed with it, the tendency is observable nearly everywhere to increase the individual dose to at least 0.6 gramme, quite frequently to 0.7 gramme and even to 0.9 gramme.*

2. *The massing of individual arsenical doses so as to give them in more or less rapid succession at the beginning of treatment (according to Ehrlich's idea), similar series being often repeated at definite intervals.*

3. *Total dose within the limits of any one course (or, in continuous treatment, the period corresponding thereto) comparatively low.*

4. *In women, individual and total dose relatively speaking only slightly lower.*

5. *Administration of Bi in high individual and total doses. (Average individual dose, 0.3 gramme metallic Bi ; total dose per course, about 3 to 4 grammes metallic Bi.) Administration either in intervals between arsenical courses or, if treatment was begun with the latter, continuation with Bi alone for a considerable time.*

6. *As regards the intervals between individual courses of intermittent treatment, it appears appropriate to make them comparatively short.*

7. *Growing tendency to make the treatment of sero-negative primary syphilis similar to that for other stages of early syphilis.*

It would seem that one factor of decisive importance to the success of the method of treatment is the *regular steadiness* of its administration. In my opinion, it is herein that the great advantage of continuous treatment or of the system of small intervals in the intermittent treatment lies ; they avoid giving the patient a certain impression that treatment has been completed.

In order to gain a general idea of the actual practice in carrying out the principles of treatment as set forth in the " *General Questionnaire* " by the various clinics, I made two investigations on which I should like to make a brief report.

Since the scheme of treatment chosen by me as a norm of comparison (cf. pages 149 and 150) is adjusted to a total dosage which is about average, or which should perhaps rather be considered a comparatively low one, judging by the international literature and the "General Questionnaire", I ascertained how many cases of S1 and S2 had been treated in a manner conforming to the requirements of that scheme. In the computation, every drug has been considered in the first place by itself, without reference to whether it was administered concurrently with another or alone; and in the second place, it was considered in combination with one or several others. The percentages thus calculated indicate throughout that, in the great majority of cases, treatment coming up to the requirements of our scheme was *not* given in intermittent therapy. The position in regard to secondary syphilis is, if anything, less favourable. This exacting work proved to be well worth the trouble entailed, as it showed that, although the total arsenical dose in the first course as well as in the following courses frequently fell below 4 grammes, good results were secured. This fact further confirms the view expressed above that high individual doses of the arsenical remedy are desirable, but that the total dose should be small.

The second investigation had to do with *the number of courses of treatment* given in the various stages of the disease (cf. Annex 17). Apart from the number, the time at which they were given was, of course, important. What I had principally in mind, however, was to show the percentages of secondary cases that were treated by one or more courses respectively. The table again shows that in Denmark and Great Britain the percentage of cases which received numerous courses—*i.e.*, more than five—is very distinctly higher than in Germany or the United States of America. Denmark, in view of the comparative smallness of the country and the enormous preponderance of its capital city in the diagnostic and therapeutic campaign against syphilis, occupies, of course, a particularly favourable position in this respect.

In this particular comparison, France takes first place in the sense that the number of courses given in all stages is quite exceptionally great in that country. Despite this very regularly applied intermittent treatment, the results are not quite so favourable as in Denmark and Great Britain.

The fact that, in the practical application of those methods of treatment which are recognised by directors of clinics to be suitable, the treatment is frequently not given in the full measure which is intended (and it may be observed that, in his reply to the "General Questionnaire", Professor FRAZIER draws attention specifically to this same difficulty, which he has observed in China), and the circumstance that this occurs *everywhere*, give me an opportunity, in conclusion, to lay stress once more upon the fact brought out by this enquiry, that the *major diagnostic methods for the detection of syphilis and the supervision of treatment—i.e., detection of the presence of Sp. pallida, regular and frequent performance of serological tests, and testing of the cerebro-spinal fluid—are not yet turned to account to the extent that would be desirable. If it should prove that this is done in the future, we may entertain the definite hope that the knowledge which has been brought to light by this enquiry will have made it possible for us to conduct the fight against syphilis and its consequences in a far more effective manner than heretofore.*

I should like to conclude my report by expressing my sincere thanks to all those who have co-operated in a spirit of devotion in its preparation, especially to Professor MADSEN, Chairman of the Health Committee of the League of Nations; to the Health Section of the League of Nations Secretariat and, in the very first place, to Dr. RAJCHMAN and Professor OLSEN; further, to the Experts, and above all to my revered master, Professor JADASSOHN, to whom I am indebted for valuable counsel and tireless support; again, and in particular, to Colonel HARRISON, Adviser to the British Ministry of Health, Professor GOUGEROT, of the Hôpital Saint-Louis, in Paris, and Professor STOKES, of the Medical School of the University of Pennsylvania; and last, but not least, to all my trusty Breslau assistants.

Figures in parentheses refer to Annex 3.

Annex 1.

| |
|----------------|
| (1) |
| CLINIC : |
| |
| |

INDIVIDUAL CASE RECORD :

[.....*]

No. of Patient Date of first attendance at this clinic (2) Duration of infection at time of first attendance at this clinic

Initials Date of birth

(3) Summary of treatment prior to attendance at this clinic (state duration of infection when treatment elsewhere first commenced)

(4) Classification of case on first attendance at this clinic

Was *Sp. Pallida* looked for ? Was *Sp. Pallida* found ?

| | Duration in weeks | (5) Serological React. | | | (6) Salv. | (7) Bl. | (8) Hg. | | | (9) Cl.R. | (10) Com. | Remarks |
|-----------------------|-------------------|------------------------|--------|-------|-----------|---------|---------|-------|-------|-----------|-----------|---------|
| | | Before | During | After | | | a | b | c | | | |
| | | | | | | | | | | | | |
| 1st course. | | | | | | | | | | | | |
| Interval | | | | | | | | | | | | |
| 2nd course. | | | | | | | | | | | | |
| Interval... .. | | | | | | | | | | | | |
| 3rd course. | | | | | | | | | | | | |
| Interval... .. | | | | | | | | | | | | |
| 4th course. | | | | | | | | | | | | |
| Interval... .. | | | | | | | | | | | | |
| 5th course (11) | | | | | | | | | | | | |

(12) Observation after suspension of treatment

(13) Results of Cerebro-Spinal Fluid Tests :

| Period | Time | S. | G. | Ly. | Coll. | |
|-------------------------------------|-------|-------|-------|-------|-------|-------|
| | | | | | P. | L. |
| At commencement of treatment | | | | | | |
| During treatment .. | | | | | | |
| After suspension of treatment | | | | | | |

Duration of observation :
From date of infection to last attendance at this clinic :

.....
From first to last attendance at this clinic :

.....
After suspension of treatment :

Date :

Signature :

* Male or Female.

Figures in parentheses refer to Annex 3.

Annex 2.

| |
|-------------------|
| CLINIC: (1) |
| |
| |

**INDIVIDUAL CARD FOR SYPHILIS.
IN PREGNANCY**

(This Card to be used for one pregnancy only. For the total treatment given apart from the period of pregnancy fill up an individual case record, and attach.)

Identification No. (*) Initials.....
 Date of birth Date of marriage.....
 Date of infection (2)..... Date of first clinical symptoms
 Date of first examination in this clinic
 Date of first serum test and result

Results of previous pregnancies (If possible, fill up a form like this for each pregnancy) }
 1st
 2nd
 3rd
 4th

Are treatment and serological reactions before and after this pregnancy shown on separate individual case record ? or uncertain ?

Classification of case when first observed in this pregnancy (4)

Treatment during this Pregnancy :

(If, during this pregnancy, treatment has been given elsewhere, please state and specify under "OBSERVATIONS").

| | Duration in weeks | (5) Serological React. | | | (6) Salv. | (7) Bi. | (8) Hg. | | | (9) Cl.R. | (10) Com. | Observations |
|---------------------------------------|-------------------|------------------------|--------|-------|-------------------|---------|---------|---|---|-----------|-----------|--------------|
| | | Before | During | After | | | a | b | c | | | |
| Interval from conception to treatment | | | | | ← (Leave blank) → | | | | | | | |
| 1st Course | | | | | | | | | | | | |
| Interval | | | | | | | | | | | | |
| 2nd Course | | | | | | | | | | | | |
| Interval | | | | | | | | | | | | |
| 3rd Course | | | | | | | | | | | | |
| Interval | | | | | | | | | | | | |
| After delivery | | | | | ← (Leave blank) → | | | | | | | |

RESULT OF PREGNANCY : Pregnancy terminated at th month.
 Result : (Give details, e.g. macerated, dead-born, living at term; symptoms at birth, healthy; duration of the observation) (**)

PLACENTA AND CORD.

Please give all available information : {

SEROLOGY OF THE CHILD. ()**

Cord blood
 Placenta blood
 Child's blood days after birth
 Subsequent tests :
 At age of months after birth.
 " " " " " " " " " " " "

Date Signature

(*) FATHER : If the father has been examined at this clinic, please fill up an individual record for his case and attach. (Father's Identification number :). Is there any other reliable evidence of infection of the father ? If so, please specify.
 (**) CHILD : If the child was infected and treated, please fill up a separate individual card and attach (child's Identification number :

Annex 3. EXPLANATORY NOTES.

(1) The name of the clinic should be stamped in block capitals. (2) If in doubt, answer with a "??". (3) If in doubt as to reliability of history, please answer with a "??".

(4) Classification of stages of syphilis for purposes of this enquiry :

(A) Acquired Syphilis.

- S.1. Primary syphilis with negative serum reactions at the time of the first injection ;
 S.2. Serodiagnostic positive primary syphilis ;
 S.3. Secondary manifestations in the first year of the disease ;
 S.4. Secondary manifestations later than the first year of the disease ;
 S.5. Latent (during the first four years after infection) : (a) treated ; (b) not treated.
 S.6. Tertiary, all later ; viz.,
 (a) Tertiary with skin and mucous membrane lesions ;
 (b) Tertiary with visceral disease except aortitis and aneurysm ;
 (c) Tertiary with aortitis and aneurysm ;
 (d) Tertiary with bone and joint disease ;
 (e) Tabes ;
 (f) General paralysis ;
 (g) With clinical signs of syphilis of the central nervous system other than the above ;
 (h) Latent treated (after the lapse of four years following on infection).
 (i) Latent untreated

(B) Congenital Syphilis.

- C.S.1. Infants with clinical signs at birth or within the first week ;
 C.S.2. Infants with signs, either clinical or serological, appearing after the first week, but within the first six months ;
 C.S.3. Children with signs, either clinical or serological, detected after the first six months, but within the first three years ;
 C.S.4. Late congenital syphilis ;
 (a) With skin and mucous membrane lesions ;
 (b) With bone and joint disease ;
 (c) Interstitial keratitis ;
 (d) With labyrinthine disease ;
 (e) Teeth ;
 (f) With visceral disease (stating type) ;
 (g) With disease of the central nervous system (stating type).

(5) State the reaction according to the notation recommended by the Laboratory Conference on the Serodiagnosis of Syphilis held at Copenhagen, 1928 (+ = positive ; ± = neither positive nor negative ; - = negative). It is important to state on the questionnaire, which you are asked to fill up, the methods of serum test employed.

(6) State total dose in grams, name of preparation (e.g., A.S. = old salvarsan ('606') ; N.S. = Neo-salvarsan ('914') ; S.S. = Silver-salvarsan ; N.S.S. = Neo-silver salvarsan. If another preparation was administered, give name using an abbreviation, with key to same in Remarks column) and the total number of injections, thus: 4A.S.(10) = 4 gm. old salvarsan in 10 injections. If another route than the intravenous was employed, please state, thus : I.M. = Intramuscular.

(7) State the dose, the preparation (give a key to abbreviations) and the number of injections, on similar lines to the above. If another route than the intramuscular was employed, please state.

(8) State (a) The preparation ; (b) The total dose and route ; (c) Number of administrations (doses).

(9) C.R. = Clinical Relapse. For purposes of this enquiry clinical relapse means any fresh manifestation of the disease. Please state any cases of recurring chancre or of re-infection and append a description, e.g., sites of old and new sores. Otherwise, use notation below :

ΣII. Secondary relapse (including Iritis).

N.S. = Neuro-relapse.

ΣIII. Tertiary syphilis of skin, mucous membrane, bones.

C.V. = Cardio-vascular relapse. (aortitis? Clin. diagnosis or X-rays?).

JΣ. Late syphilis of the liver, lungs, kidneys, etc.

C.N.S. Syphilis of brain and spinal cord.

T = Tabes.

P = Paralysis.

(10) Compl. = Accidents and complications of treatment.

J. = Icterus.

D. = Slight skin eruptions.

D'. = Severe skin eruptions.

P. = Serious pains.

GT. = Severe gastro-intestinal reaction.

ALA. = Acute yellow atrophy of the liver.

Pc. = Haemorrhagic complications (specify).

+ = Exitus (specify).

(11) If the treatment extends beyond a 5th course, please continue on another card and state that this has been done, thus "Continued" and mark the second card "Continuation". The identification number and the name of the clinic should be marked on the continuation card.

(12) Observation after suspension of treatment. If the serological reactions have been negative throughout the period of observation, state the period and the number of tests, e.g., "159 weeks. Negative 9 times". If reactions stronger than negative have occurred, please set out intervals between tests and the results of these.

(13) Tests of C.S.F. : "Time" is number of weeks from date of first attendance at this clinic.

S. = Serological, e.g., Wassermann Test.

G. = Globulin or albumin.

Ly. = Lymphocytes per cmm.

Coll. = Colloidal reaction.

P. = Paretic curve.

L. = Luetic curve.

Annex 4.

GENERAL QUESTIONNAIRE.

(Please send your replies typewritten. Should more extensive statements be required in reply to the questions marked*, you are requested to send them on separate sheets with indications to which question they refer.)

The Directors of Clinics are requested to supply the most detailed information possible with regard to the following questions, viz. :

Description of the principles governing the treatment during the entire period covered by the case record cards contributed to the present enquiry.*

(Should these principles have varied at some particular time or on several occasions during the period reported upon, please specify.)

I. Treatment.

A. PURE SALVARSAN TREATMENT.

- (a) Was it carried out throughout,
or in which special forms or stages of the disease,
or under which special conditions ?*
- (b) Which salvarsan preparation has been used exclusively or by preference ?
If several salvarsan preparations have been employed, please state from what points of view each of these preparations was selected.*
- (c) Dosage employed in pure salvarsan treatment.

Total average amount for a course of treatment (see Annex 3, under 4).

| For Stages A | 1 | For Stages B | 1 |
|---------------------|---|---------------------|---|
| | 2 | | 2 |
| | 3 | | 3 |
| | 4 | | 4 |
| | 5 | | |
| | 6 | | |

Was the amount different for men and women ?

Single doses :

What is the dose usually given at the beginning ?

Is the sequence of doses varied according to the stage of the disease ?

- (d) How long are the intervals between the injections—
in a first course of treatment of fresh syphilis,
between the first injections,
between the subsequent injections ?

- (e) How long are the intervals between the different courses of treatment, if treatment is commenced (see individual case record card, under 4)?—

| at Stage A 1 | at Stage B 1 |
|---------------------|---------------------|
| 2 | 2 |
| 3 | 3 |
| 4 | 4 |
| 5 | |
| 6 | |

B. TREATMENT WITH SALVARSAN PREPARATIONS IN CONJUNCTION WITH—

1. Bismuth.

- (a) Was this carried out throughout, or in which special forms or stages of the disease, or under which special conditions ?*
- (b) Which bismuth preparation is used exclusively or by preference ?
If several bismuth preparations have been employed, please state from what points of view each of these preparations was selected.*
- (c) Which doses of the preparation or preparations were given (in c.c. or grammes)—
as a single dose,
as total amount during a course of treatment ?
- (d) Do you administer bismuth at the same time (*i.e.*, during the same course of treatment) in which salvarsan is being injected ?
Or before ?
Or after ?
- (e) What are the intervals separating the individual bismuth injections from each other ?
- (f) If bismuth is given in the same course of treatment as salvarsan, do you inject it on the same day as the salvarsan or on alternate days ?
Which principles guide you in the method of combining the two remedies ? *
- (g) What is the average total amount of bismuth administered during a combined course of treatment ?
Is it different for men and women ?
If different doses are given in the different stages of the disease, please supply the details.
- (h) Do you also combine salvarsan—and bismuth—treatment in such manner that courses of pure salvarsan treatment are allowed to alternate with courses of pure bismuth treatment, or also with combined salvarsan-bismuth courses (see *supra*) ?
If so, according to which plan and which points of view ?

2. *Mercury.*

- (a) Was this carried out throughout, or in which special forms of stages of the disease, or under which special conditions ?
- (b) Which preparation and which method of administration is used exclusively or by preference ?
If several preparations and methods have been employed, please state what points of view govern the choice of the various preparations and methods.*
- (c) Dose of the preparation or preparations (in c.c. or grammes) given as single dose—
in injection,
in inunction,
in oral treatment ?
- (d) What is the average total amount of mercury given in a course of combined treatment,
of injection,
of inunction ?
Is it different for men and women ?
- (e) Is mercury given in the same course as salvarsan ?
or before ?
or after ?
- (f) If administered in the same course, do you give it on the same days, or alternating with the salvarsan injections ?
What principles guide you in the choice of one or the other method ?*
- (g) Do you also combine salvarsan—and mercury—treatment in such manner that a course of pure salvarsan-treatment is allowed to alternate with one of pure mercury-treatment, or also with a course of combined salvarsan-mercury-treatment ?

If so, according to which plan and which points of view ? *

- C. COMBINATION OF SALVARSAN, BISMUTH AND MERCURY
- D. PURE BISMUTH TREATMENT
- E. PURE MERCURY TREATMENT
- F. COMBINED BISMUTH AND MERCURY TREATMENT (WITHOUT SALVARSAN).

Please state, so far as possible, the principles of employment of such methods, with reference to the preceding questions.*

In case of so-called *continuous treatment*, please state—

doses, preparations and intervals between the separate administrations, etc., and, if such treatment is differentiated according to the stage of the disease, please specify.*

In preparing the questionnaire, treatment with iodine and other remedies was purposely not taken into consideration.

It is, of course, not possible in a questionnaire of this kind to deal with every modification of treatment: But any details supplied as regards indications, contra-indications, etc., will be welcomed.*

II. Diagnosis.

You are also requested to supply detailed information with respect to the following points, viz :

- (a) Which methods of serological diagnosis are employed :
- Wassermann-test,
 - Flocculation tests,
 - Turbidity tests ?
- Please state in detail the methods used.
- (b) Which criteria are relied upon for judging whether the result is considered—
- strongly positive,
 - positive,
 - doubtful ?
- (c) What indications for the treatment are deduced from the result of the serological tests ? *
- (d) Which serological and colloidal tests are employed for testing the cerebro-spinal fluid ?
- (e) What indications for the treatment are deduced from the result of the examination of the cerebro-spinal fluid ?
- (f) Is a skin-test employed ?
- Which preparation—*i.e.*, Luetin, etc.
-

Annex 5.

DISTRIBUTION OF THE CASES OF SYPHILIS.

| | Primary and secondary | | | Latent | | | Tertiary | | | Congenital | | |
|--------------------|-----------------------|-------|-------|--------|-------|-------|----------|-----|-----|------------|-----|-----|
| | Tot. | M. | W. | Tot. | M. | W. | Tot. | M. | W. | Tot. | M. | W. |
| Germany | 3,358 | 1,682 | 1,676 | 2,025 | 873 | 1,152 | 839 | 421 | 418 | 322 | 137 | 185 |
| Denmark | 2,607 | 1,355 | 1,252 | 808 | 239 | 569 | 600 | 274 | 326 | 185 | 88 | 97 |
| United States | 4,438 | 2,932 | 1,506 | 3,315 | 1,456 | 1,859 | 166 | 149 | 17 | 230 | 105 | 125 |
| France | 1,283 | 813 | 470 | 518 | 282 | 236 | 250 | 136 | 114 | 39 | 15 | 24 |
| Great Britain | 3,483 | 2,600 | 883 | 26 | 20 | 6 | 7 | 7 | — | 44 | 24 | 20 |
| Peiping | 164 | 146 | 18 | 167 | 114 | 53 | 89 | 74 | 15 | — | — | — |

The above represents the subdivision of the following total numbers of cases (arrived at after deduction of records discarded at the outset).

| | Total | Men | Women |
|---------------------|--------|--------|--------|
| Germany | 6,544 | 3,113 | 3,431 |
| Denmark | 4,200 | 1,956 | 2,244 |
| United States | 8,149 | 4,642 | 3,507 |
| France | 2,090 | 1,246 | 844 |
| Great Britain | 3,560 | 2,651 | 909 |
| Peiping | 420 | 334 | 86 |
| | 24,963 | 13,942 | 11,021 |

Annex 6.

PERCENTAGES OF CASES WITH INSUFFICIENTLY CONFIRMED DIAGNOSIS OF SYPHILIS OR WITH INSUFFICIENT SEROLOGICAL CONTROL, COMING UNDER GROUPS S1 TO S4 INCLUSIVE (PRIMARY AND SECONDARY SYPHILIS.)

| | Percentages | | |
|--------------------------|---------------------|--------|----------|
| | Of the total number | Of men | Of women |
| Germany | 13.64 | 14.75 | 12.53 |
| Denmark | 11.36 | 12.85 | 9.76 |
| United States | 15.08 | 15.66 | 13.94 |
| France | 17.23 | 18.08 | 15.74 |
| Great Britain* | 9.39 | 10.92 | 4.87 |
| All five countries | 12.90 | 13.85 | 11.35 |

* In the case of Great Britain, the percentages are really even more favourable, since the above-mentioned percentages showing the proportion of cases eliminated include 96 cases of primary syphilis, coming from a clinic which established the diagnosis "primary syphilis" merely on the basis of the histological findings (and not on the ascertained presence of *Sp. pallida* in sections). As this is a matter of the special views held by the head of the clinic, these cases occupy a position apart. If they are entirely disregarded, the corresponding percentage figures would be as follows :

| | | |
|------|------|------|
| 6.98 | 7.23 | 4.87 |
|------|------|------|

Annex 7.

STATEMENT OF THE TESTS FOR *SP. PALLIDA* CARRIED OUT IN CASES OF RECENT SYPHILIS AND THE RESULTS.

In the groups "S1" and "S1 or S2", the cases are included in the statistics only if the spirochæte test gives a positive result.

Figures relating to the group of sero-positive primary syphilis (S2).

| | Number of cases | Cases tested for <i>Sp. pallida</i> | | Positive findings | | |
|--------------------|-----------------|-------------------------------------|--------------|-------------------|----------------|-----------------------|
| | | Actual figures | % | Actual figures | In percentage | |
| | | | | | Of total cases | Of investigated cases |
| Germany | 529 | 442 | 83.55 | 338 | 63.89 | 76.47 |
| Denmark | 413 | 203 | 49.15 | 184 | 44.55 | 90.64 |
| United States .. | 765 | 400 | 52.29 | 248 | 32.42 | 62.00 |
| France | 362 | 135 | 37.29 | 105 | 29.01 | 77.77 |
| Great Britain .. | 1,084 | 656 | 60.52 | 502 | 46.31 | 76.53 |
| Total | 3,153 | 1,836 | 58.23 | 1,377 | 43.67 | 75.00 |

For cases of secondary syphilis, the corresponding figures are—

S3

| | | | | | | |
|------------------|-------|-----|-------|-----|-------|-------|
| Germany | 842 | 492 | 58.43 | 423 | 50.23 | 85.98 |
| Denmark | 1,409 | 58 | 3.98 | 54 | 3.83 | 96.43 |
| United States .. | 2,311 | 355 | 15.36 | 249 | 10.75 | 70.14 |
| France | 351 | 32 | 9.02 | 25 | 7.12 | 78.13 |
| Great Britain .. | 821 | 140 | 17.00 | 99 | 12.06 | 70.71 |

S3 or S4

| | | | | | | |
|------------------|-----|-----|-------|-----|-------|--------|
| Germany | 979 | 496 | 50.66 | 422 | 43.11 | 85.10 |
| Denmark | 68 | 2 | 3.06 | 2 | 3.06 | 100.00 |
| United States .. | 161 | 18 | 11.18 | 13 | 8.08 | 72.22 |
| France | 166 | 2 | 1.20 | 1 | 0.60 | 50.00 |
| Great Britain .. | 731 | 123 | 16.83 | 90 | 12.31 | 73.17 |

S4

| | | | | | | |
|------------------|-----|----|-------|----|-------|-------|
| Germany | 192 | 95 | 49.49 | 70 | 36.46 | 73.68 |
| Denmark | 40 | 0 | 0 | 0 | 0 | 0 |
| United States .. | 215 | 32 | 14.88 | 18 | 8.37 | 56.25 |
| France | 39 | 2 | 5.13 | 1 | 2.56 | 50.00 |
| Great Britain .. | 42 | 4 | 9.52 | 3 | 7.14 | 75.00 |

Consequently, the presence of *Sp. pallida* was proved in cases of secondary syphilis.

| | | | | | | |
|--|--------|----------|-----------------------|--------------------|-----|-----|
| Early secondary syphilis (S3). | in 850 | or 79.07 | per cent of the 1,075 | investigated cases | | |
| Secondary syphilis in which the time of infection is unknown (S3 or S4)..... | " 528 | " 82.36 | " " | 641 | " " | " " |
| Late secondary syphilis (S4) .. | " 92 | " 69.17 | " " | 133 | " " | " " |

Annex 8.

TOP SHEET FOR EACH GROUP.

Country :

Clinic :

Phase :

1. Total number of cases : of which Men Women
2. Age of patient at time of first attendance at the clinic or of infection :

| Age | Total | Men | Women | Age | Total | Men | Women |
|------------|-------|-------|-------|---------|-------|-------|-------|
| - 5 : | | | | 41-45 : | | | |
| 6-10 : | | | | 46-50 : | | | |
| 11-15 : | | | | 51-55 : | | | |
| 16-20 : | | | | 56-60 : | | | |
| 21-25 : | | | | 61-65 : | | | |
| 26-30 : | | | | 66-70 : | | | |
| 31-35 : | | | | 71-75 : | | | |
| 36-40 : | | | | 76-80 : | | | |
| Doubtful : | | | | | | | |

3. Age of infection at time of first attendance at the clinic :

| Duration | Total | Men | Women | Age | Total | Men | Women |
|------------|-------|-------|-------|------------|-------|-------|-------|
| 1-4 weeks | | | | - 3 years | | | |
| 5-8 " | | | | - 4 " | | | |
| 9-12 " | | | | - 5 " | | | |
| 4-6 months | | | | 6-10 " | | | |
| 7-9 " | | | | 11-15 " | | | |
| 10-12 " | | | | 16-20 " | | | |
| 1-1½ years | | | | doubtful : | | | |
| -2 " | | | | | | | |

4. Tests for *Sp. pallida* :

in out of cases = per cent
of which, positive : out of cases = per cent

Annex 7.

**STATEMENT OF THE TESTS FOR *SP. PALLIDA* CARRIED
OUT IN CASES OF RECENT SYPHILIS AND THE RESULTS.**

In the groups "S1" and "S1 or S2", the cases are included in the statistics only if the spirochæte test gives a positive result.

Figures relating to the group of *sero-positive primary syphilis (S2)*.

| | Number of cases | Cases tested for <i>Sp. pallida</i> | | Positive findings | | |
|--------------------|-----------------|-------------------------------------|--------------|-------------------|----------------|-----------------------|
| | | Actual figures | % | Actual figures | In percentage | |
| | | | | | Of total cases | Of investigated cases |
| Germany | 529 | 442 | 83.55 | 338 | 63.89 | 76.47 |
| Denmark | 413 | 203 | 49.15 | 184 | 44.55 | 90.64 |
| United States .. | 765 | 400 | 52.29 | 248 | 32.42 | 62.00 |
| France | 362 | 135 | 37.29 | 105 | 29.01 | 77.77 |
| Great Britain .. | 1,084 | 656 | 60.52 | 502 | 46.31 | 76.53 |
| Total | 3,153 | 1,836 | 58.23 | 1,377 | 43.67 | 75.00 |

For cases of *secondary syphilis*, the corresponding figures are—

S3

| | | | | | | |
|------------------|-------|-----|-------|-----|-------|-------|
| Germany | 842 | 492 | 58.43 | 423 | 50.23 | 85.98 |
| Denmark | 1,409 | 56 | 3.98 | 54 | 3.83 | 96.43 |
| United States .. | 2,311 | 355 | 15.36 | 249 | 10.75 | 70.14 |
| France | 351 | 32 | 9.02 | 25 | 7.12 | 78.13 |
| Great Britain .. | 821 | 140 | 17.00 | 99 | 12.06 | 70.71 |

S3 or S4

| | | | | | | |
|------------------|-----|-----|-------|-----|-------|--------|
| Germany | 979 | 496 | 50.66 | 422 | 43.11 | 85.10 |
| Denmark | 66 | 2 | 3.06 | 2 | 3.06 | 100.00 |
| United States .. | 161 | 18 | 11.18 | 13 | 8.08 | 72.22 |
| France | 166 | 2 | 1.20 | 1 | 0.60 | 50.00 |
| Great Britain .. | 731 | 123 | 16.83 | 90 | 12.31 | 73.17 |

S4

| | | | | | | |
|------------------|-----|----|-------|----|-------|-------|
| Germany | 192 | 95 | 49.49 | 70 | 36.46 | 73.68 |
| Denmark | 40 | 0 | 0 | 0 | 0 | 0 |
| United States .. | 215 | 32 | 14.88 | 18 | 8.37 | 56.25 |
| France | 39 | 2 | 5.13 | 1 | 2.56 | 50.00 |
| Great Britain .. | 42 | 4 | 9.52 | 3 | 7.14 | 75.00 |

Consequently, the presence of *Sp. pallida* was proved in cases of *secondary syphilis*.

Early secondary syphilis (S3). in 850 or 79.07 per cent of the 1,075 investigated cases
Secondary syphilis in which the time of infection is unknown (S3 or S4)..... " 528 " 82.36

Late secondary syphilis (S4) .. " 92 " 69.17 " " 641 " " " " " 133 " " "

Annex 8.

TOP SHEET FOR EACH GROUP.

Country :

Clinic :

Phase :

1. Total number of cases : of which Men Women

2. Age of patient at time of first attendance at the clinic or of infection :

| Age | Total | Men | Women | Age | Total | Men | Women |
|------------|-------|-------|-------|---------|-------|-------|-------|
| - 5 : | | | | 41-45 : | | | |
| 6-10 : | | | | 46-50 : | | | |
| 11-15 : | | | | 51-55 : | | | |
| 16-20 : | | | | 56-60 : | | | |
| 21-25 : | | | | 61-65 : | | | |
| 26-30 : | | | | 66-70 : | | | |
| 31-35 : | | | | 71-75 : | | | |
| 36-40 : | | | | 76-80 : | | | |
| Doubtful : | | | | | | | |

3. Age of infection at time of first attendance at the clinic :

| Duration | Total | Men | Women | Age | Total | Men | Women |
|------------|-------|-------|-------|------------|-------|-------|-------|
| 1-4 weeks | | | | - 3 years | | | |
| 5-8 " | | | | - 4 " | | | |
| 9-12 " | | | | - 5 " | | | |
| 4-6 months | | | | 6-10 " | | | |
| 7-9 " | | | | 11-15 " | | | |
| 10-12 " | | | | 16-20 " | | | |
| 1-1½ years | | | | doubtful : | | | |
| - 2 " | | | | | | | |

4. Tests for *Sp. pallida* :

in out of cases = per cent
of which, positive : out of cases = per cent

Annex 10.**CLASSIFICATION OF CASES.****SUBDIVISION FOR S1.**

A (—). *Cases remaining sero-negative.*

B *Cases which became sero-positive.*

(a) Changed during the first course into \pm .

1. Cases which became and remained negative *after the first course.*
2. Cases which became and remained negative *in the first interval or during the second course.*
3. Cases which became and remained negative *in the second interval or later.*

(b) Changed during the first course into +.

1. } as in (a).
2. }
3. }

(c) Changed during the first course into \pm or + thereafter *remaining positive.*

C *Serological relapse.*

(a) Cases which *remained negative during the first course and even longer; subsequently serological reaction +.*

1. Cases remaining + after serological relapse.
2. Cases which became and remained — after serological relapse.
3. Cases which became — ; then further serological relapse.

(b) *Changed during first course into \pm or + became — after first course; subsequently sero-reaction +.*

1. } as in (a).
2. }
3. }

(c) *Changed during first course into \pm or +, becoming — in the first interval or later ; subsequently serological relapse.*

1. } as in (a).
2. }
3. }

D *Clinical relapse.*

(a) *Without previous serological relapse.*

(b) *With previous serological relapse.*

Further developments to be dealt with in accordance with the scheme for the corresponding stage.

SUBDIVISION FOR S1 OR S2.

- A (—) Serological reactions throughout period of observation *remained —*.
 A (+) to D, *as in S2*.

SUBDIVISION FOR S2.

- A (+) Serological reactions throughout the period of observation *remained +*.
 B *Cases which became sero-negative :*

1. Became and remained — *during the first course.*
2. Became and remained — *after the first course.*
3. Became and remained — *in the first interval or at the beginning of the second course.*
4. Became and remained — *after the second course (i.e., at the end of the course) or later.*

C *Serological relapse :*

- (a) Cases which became — *during or after the first course ;* subsequently serological relapse.

1. Cases which became + *after the serological relapse.*
2. Cases which became and remained — *after the serological relapse.*
3. Cases which became — *after the serological relapse ;* subsequently fresh serological relapse.

- (b) *Cases which became — in the first interval or at the beginning of the second course ;* subsequently serological relapse.

- | | | |
|----|---|------------|
| 1. | } | as in (a). |
| 2. | | |
| 3. | | |

- (c) *Cases which became — after the second course or later ;* subsequently serological relapse.

- | | | |
|----|---|------------|
| 1. | } | as in (a). |
| 2. | | |
| 3. | | |

D *Clinical relapse :*

- (a)₁ *In cases belonging to the pre-Wassermann period.*

- (a) *General clinical symptoms during the first course.*

- (b) *Clinical relapse after the conclusion of the first course :*

1. Serological reactions remained + *until the clinical relapse.*
2. Serological reactions became — *before the appearance of the clinical relapse.*

- (c) *Clinical relapse after several courses :*

1. Serological reactions had previously remained +.
2. Serological reactions had previously become — *and remained — until the clinical relapse.*

3. Serological reactions had previously become — but serological relapse before the clinical relapse, and :
 - α remained + after serological relapse ;
 - β again became and remained — after serological relapse ;
 - γ became — after serological relapse, but further serological relapse preceding clinical relapse.

Repeated clinical relapses are to be correspondingly noted in the various headings.

SUBDIVISION FOR S3.

A (+) Serological reactions during the period of observation remained +.

B *Without serological and clinical relapse :*

- (a) Cases *belonging to the pre-Wasserman period.*
- (b) Serological reactions *became and remained —*
 1. *During or after the first course.*
 2. *During the first course still + after the conclusion of the first course failed to remain under treatment and observation, then after a long time — serological tests performed.*
 3. *Became and remained — in the first interval.*
 4. *Became and remained — during the second course.*
 5. *Became and remained — in the second interval, and later.*

BB *Clinical secondary syphilis, negative serological reactions ; spirochætes found to be present in first investigation in the clinic ; subsequently always negative serological-reactions.*

BC As in BB, but *subsequent relapse.*

C *Serological relapse.*

- (a) 1. }
 2. } as in S2.
 3. }
- (b) Serological reaction became — *during the first interval :*
 1. Remained + after the serological relapse ;
 2. Became and remained — after the serological relapse ;
 3. Became — after the serological relapse, then further serological relapse.
- (c) Serological relapse became — *during the second course :*
 1. }
 2. } as in (b).
 3. }
 - (d) Serological reaction became — *in the second interval and later :*
 1. }
 2. } as in (b).
 3. }

CC *Cases belonging to the pre-Wassermann period with subsequent + serological reactions (doubtful relapse).*

D *Clinical relapse :*

I.e., clinical relapse appearing during or after the clinical treatment—that is, in cases which had not been under medical observation or treatment until the first examination in the clinic ;

(a) *Occurred during the first course.*

(b) *Occurred after the conclusion of the first course :*

1. *Serological reaction remained + until the clinical relapse.*
2. *Serological reaction became — before clinical relapse.*

(c) *After several courses :*

1. *Serological reactions remained + until the clinical relapse.*
2. *Serological reactions previously became —.*
3. *Serological reactions previously became — but subsequent serological relapse before clinical relapse ; and*
 - α *remained + after serological relapse ;*
 - β *became — after serological relapse and remained — until the clinical relapse ;*
 - γ *became — after serological relapse, then further serological relapse before the clinical relapse.*

Repeated clinical relapses are to be recorded correspondingly under the individual headings.

DD *Clinical relapse in cases belonging to the pre-Wassermann period—i.e., doubtful relapse.*

D1 *Clinical relapse noted as such in the first examination in the clinic—i.e., after previous treatment outside the clinic in cases in which—*

- (a) *There was a primary manifestation (S1 or S2) at the beginning of treatment outside the clinic.*
- (b) *Secondary syphilis (S3) was present.*
- (c) *There were no detailed particulars regarding the stage of the clinical syphilitic symptoms at the beginning of the treatment outside the clinic.*

The development of these cases after the beginning of treatment in the clinic is to be recorded in accordance with the scheme which corresponds to the stage of the clinical relapse.

As regards cases with a so-called *continuous* treatment, the same schemes are applicable. In order to be able to form an opinion under approximately similar conditions, the serological results during the first twenty-six weeks after the beginning of the treatment were judged in the same manner as the serological results up to the end of the first course in cases given intermittent treatment.

Annex 11.

RESULTS OF TREATMENT.

1. RESULTS IN CASES TREATED *INTERMITTENTLY*

(excluding D₁ cases—*i.e.*, cases which first came under treatment at the clinic as clinical relapses).

Germany.

| Stage | Cases | | | Remained or became sero-negative | | | Remained sero-positive | | | Serological relapses | | | Clinical relapses | | |
|--------------------|--------------|--------------|--------------|----------------------------------|------------|------------|------------------------|-----------|-----------|----------------------|------------|------------|-------------------|------------|-----------|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. |
| S1 | 349 | 298 | 51 | 288 | 246 | 42 | — | — | — | 27 | 24 | 3 | 28 | 23 | 5 |
| S1 or S2 | 9 | 8 | 1 | 6 | 5 | 1 | 1 | 1 | — | — | — | 1 | 1 | — | |
| S2 | 502 | 326 | 176 | 352 | 234 | 118 | 17 | 12 | 5 | 77 | 43 | 34 | 42 | 28 | 14 |
| S3 | 676 | 309 | 367 | 444 | 196 | 248 | 48 | 24 | 24 | 92 | 40 | 52 | 56 | 34 | 22 |
| S3 or S4 | 846 | 242 | 604 | 544 | 151 | 393 | 63 | 16 | 47 | 134 | 39 | 95 | 61 | 21 | 40 |
| S4 | 27 | 13 | 14 | 17 | 8 | 9 | 1 | 1 | — | 7 | 3 | 4 | 1 | 1 | — |
| S1-S4 | 2,409 | 1,196 | 1,213 | 1,651 | 840 | 811 | 130 | 54 | 76 | 337 | 149 | 188 | 189 | 108 | 81 |

| Stage | Doubtful serological relapses | | | Doubtful clinical relapses | | | Secondary syphilis with negative serological reaction at the beginning of the treatment | | |
|--------------------|-------------------------------|-----------|-----------|----------------------------|----------|----------|---|----------|----------|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. |
| S1 | 6 | 5 | 1 | — | — | — | — | — | — |
| S1 or S2 | 1 | 1 | — | — | — | — | — | — | — |
| S2 | 14 | 9 | 5 | — | — | — | — | — | — |
| S3 | 28 | 10 | 18 | 3 | 2 | 1 | 5 | 3 | 2 |
| S3 or S4 | 34 | 11 | 23 | 3 | 1 | 2 | 7 | 3 | 4 |
| S4 | 1 | — | 1 | — | — | — | — | — | — |
| S1-S4 | 84 | 36 | 48 | 6 | 3 | 3 | 12 | 6 | 6 |

Annex 11 (continued).

1. RESULTS IN CASES TREATED *INTERMITTENTLY*
(excluding D₁ cases—*i.e.*, cases which first came under treatment at the clinic as clinical relapses).

Denmark.

| Stage | Cases | | | Remained or became sero-negative | | | Remained sero-positive | | | Serological relapses | | | Clinical relapses | | |
|----------------|-------|-------|-------|----------------------------------|-------|-----|------------------------|----|----|----------------------|----|-----|-------------------|----|----|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. |
| S1 | 319 | 271 | 48 | 311 | 267 | 44 | — | — | — | 1 | 1 | — | 6 | 3 | 3 |
| S1 or S2 | 64 | 58 | 6 | 59 | 54 | 5 | 1 | 1 | — | 2 | 2 | — | 2 | 1 | 1 |
| S2 | 413 | 324 | 89 | 376 | 302 | 74 | 3 | 3 | — | 21 | 11 | 10 | 13 | 8 | 5 |
| S3 | 1,396 | 468 | 928 | 1,175 | 418 | 757 | 8 | 3 | 5 | 156 | 30 | 126 | 53 | 15 | 38 |
| S3 or S4 | 64 | 31 | 33 | 53 | 27 | 26 | 2 | 1 | 1 | 8 | 2 | 6 | 1 | 1 | — |
| S4 | 6 | 2 | 4 | 5 | 2 | 3 | — | — | — | — | — | — | 1 | — | 1 |
| S1-S4 | 2,262 | 1,154 | 1,108 | 1,979 | 1,070 | 909 | 14 | 8 | 6 | 188 | 46 | 142 | 76 | 28 | 48 |

| Stage | Doubtful serological relapses | | | Doubtful clinical relapses | | | Secondary syphilis with negative serological reaction at the beginning of the treatment | | |
|----------------|-------------------------------|----|----|----------------------------|----|----|---|----|----|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. |
| S1 | 1 | — | 1 | — | — | — | — | — | — |
| S1 or S2 | — | — | — | — | — | — | — | — | — |
| S2 | — | — | — | — | — | — | — | — | — |
| S3 | — | — | — | — | — | — | 4 | 2 | 2 |
| S3 or S4 | — | — | — | — | — | — | — | — | — |
| S4 | — | — | — | — | — | — | — | — | — |
| S1-S4 | 1 | — | 1 | — | — | — | 4 | 2 | 2 |

United States of America.

| Stage | Cases | | | Remained or became sero-negative | | | Remained sero-positive | | | Serological relapses | | | Clinical relapses | | |
|----------------|-------|-------|-----|----------------------------------|-----|-----|------------------------|-----|-----|----------------------|-----|-----|-------------------|-----|----|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. |
| S1 | 161 | 155 | 6 | 131 | 128 | 3 | — | — | — | 11 | 9 | 2 | 17 | 16 | 1 |
| S1 or S2 | 21 | 18 | 3 | 17 | 15 | 2 | — | — | — | 1 | 1 | — | 2 | 2 | — |
| S2 | 483 | 401 | 82 | 298 | 250 | 48 | 74 | 58 | 16 | 48 | 41 | 7 | 49 | 41 | 8 |
| S3 | 1,320 | 749 | 571 | 763 | 432 | 331 | 188 | 106 | 82 | 181 | 103 | 78 | 133 | 73 | 60 |
| S3 or S4 | 116 | 27 | 89 | 71 | 15 | 56 | 20 | 5 | 15 | 16 | 4 | 12 | 4 | 2 | 2 |
| S4 | 73 | 46 | 27 | 33 | 22 | 11 | 12 | 8 | 4 | 16 | 8 | 8 | 7 | 4 | 3 |
| S1-S4 | 2,174 | 1,396 | 778 | 1,313 | 862 | 451 | 294 | 177 | 117 | 273 | 166 | 107 | 212 | 138 | 74 |

| Stage | Doubtful serological relapses | | | Doubtful clinical relapses | | | Secondary syphilis with negative serological reaction at the beginning of the treatment | | |
|----------------|-------------------------------|----|----|----------------------------|----|----|---|----|----|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. |
| S1 | 2 | 2 | — | — | — | — | — | — | — |
| S1 or S2 | 1 | — | 1 | — | — | — | — | — | — |
| S2 | 14 | 11 | 3 | — | — | — | — | — | — |
| S3 | 45 | 28 | 17 | 7 | 4 | 3 | 3 | 3 | — |
| S3 or S4 | 5 | 1 | 4 | — | — | — | — | — | — |
| S4 | 5 | 4 | 1 | — | — | — | — | — | — |
| S1-S4 | 72 | 46 | 26 | 7 | 4 | 3 | 3 | 3 | — |

Annex 11 (continued).

1. RESULTS IN CASES TREATED INTERMITTENTLY

(excluding D₁ cases—i.e., cases which first came under treatment at the clinic as clinical relapses).

France.

| Stage | Cases | | | Remained or became sero-negative | | | Remained sero-positive | | | Serological relapses | | | Clinical relapses | | |
|----------------|-------|-----|-----|----------------------------------|-----|-----|------------------------|----|----|----------------------|----|----|-------------------|----|----|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. |
| S1 | 103 | 97 | 6 | 79 | 75 | 4 | — | — | — | 14 | 12 | 2 | 8 | 8 | — |
| S1 or S2 | 25 | 24 | 1 | 20 | 20 | — | 1 | 1 | — | — | — | — | 2 | 1 | 1 |
| S2 | 323 | 266 | 57 | 243 | 195 | 48 | 19 | 18 | 1 | 31 | 25 | 6 | 22 | 20 | 2 |
| S3 | 300 | 125 | 175 | 215 | 82 | 133 | 13 | 5 | 8 | 37 | 21 | 16 | 18 | 8 | 10 |
| S3 or S4 | 129 | 44 | 85 | 90 | 31 | 59 | 7 | 2 | 5 | 23 | 9 | 14 | 2 | 1 | 1 |
| S4 | 13 | 10 | 3 | 6 | 5 | 1 | 4 | 3 | 1 | 2 | 1 | 1 | — | — | — |
| S1-S4 | 893 | 566 | 327 | 653 | 408 | 245 | 44 | 29 | 15 | 107 | 68 | 39 | 52 | 38 | 14 |

| Stage | Doubtful serological relapses | | | Doubtful clinical relapses | | | Secondary syphilis with negative serological reaction at the beginning of the treatment | | |
|----------------|-------------------------------|----|----|----------------------------|----|----|---|----|----|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. |
| S1 | 2 | 2 | — | — | — | — | — | — | — |
| S1 or S2 | 2 | 2 | — | — | — | — | — | — | — |
| S2 | 8 | 8 | — | — | — | — | — | — | — |
| S3 | 13 | 6 | 7 | 4 | 3 | 1 | — | — | — |
| S3 or S4 | 7 | 1 | 6 | — | — | — | — | — | — |
| S4 | 1 | 1 | — | — | — | — | — | — | — |
| S1-S4 | 33 | 20 | 13 | 4 | 3 | 1 | — | — | — |

Great Britain.

| Stage | Cases | | | Remained or became sero-negative | | | Remained sero-positive | | | Serological relapses | | | Clinical relapses | | |
|----------------|-------|-------|-----|----------------------------------|-------|-----|------------------------|-----|----|----------------------|-----|-----|-------------------|----|----|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. |
| S1 | 463 | 437 | 26 | 386 | 364 | 22 | — | — | — | 43 | 42 | 1 | 18 | 17 | 1 |
| S1 or S2 | 4 | 3 | 1 | 4 | 3 | 1 | — | — | — | — | — | — | — | — | — |
| S2 | 941 | 833 | 108 | 708 | 621 | 87 | 49 | 41 | 8 | 110 | 102 | 8 | 27 | 26 | 1 |
| S3 | 762 | 501 | 261 | 519 | 341 | 178 | 47 | 35 | 12 | 148 | 94 | 54 | 14 | 8 | 6 |
| S3 or S4 | 697 | 299 | 398 | 429 | 185 | 244 | 81 | 38 | 43 | 117 | 46 | 71 | 13 | 7 | 6 |
| S4 | 16 | 14 | 2 | 7 | 5 | 2 | 1 | 1 | — | 5 | 5 | — | — | — | — |
| S1-S4 | 2,883 | 2,087 | 796 | 2,053 | 1,519 | 534 | 178 | 115 | 63 | 423 | 289 | 134 | 72 | 58 | 14 |

| Stage | Doubtful serological relapses | | | Doubtful clinical relapses | | | Secondary syphilis with negative serological reaction at the beginning of the treatment | | |
|----------------|-------------------------------|-----|----|----------------------------|----|----|---|----|----|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. |
| S1 | 16 | 14 | 2 | — | — | — | — | — | — |
| S1 or S2 | — | — | — | — | — | — | — | — | — |
| S2 | 47 | 43 | 4 | — | — | — | — | — | — |
| S3 | 33 | 23 | 10 | 1 | — | 1 | — | — | — |
| S3 or S4 | 54 | 23 | 31 | 1 | — | 1 | 2 | — | 2 |
| S4 | 3 | 3 | — | — | — | — | — | — | — |
| S1-S4 | 153 | 106 | 47 | 2 | — | 2 | 2 | — | 2 |

Annex 11 (continued).

1. RESULTS IN CASES TREATED INTERMITTENTLY
(excluding D₁ cases—i.e., cases which first came under treatment at the clinic as clinical relapses).

Summary Table.

| Country | Cases | | | Remained or became sero-negative | | | Remained sero-positive | | | Serological relapses | | | Clinical relapses | | |
|------------------|--------|-------|-------|----------------------------------|-------|-------|------------------------|-----|-----|----------------------|-----|-----|-------------------|-----|-----|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. |
| GERMANY..... | 2,409 | 1,196 | 1,213 | 1,651 | 840 | 811 | 130 | 54 | 76 | 337 | 149 | 188 | 189 | 108 | 81 |
| DENMARK..... | 2,262 | 1,154 | 1,108 | 1,979 | 1,070 | 909 | 14 | 8 | 6 | 188 | 46 | 142 | 76 | 28 | 48 |
| UNITED STATES.. | 2,174 | 1,396 | 778 | 1,313 | 862 | 451 | 294 | 177 | 117 | 273 | 166 | 107 | 212 | 138 | 74 |
| FRANCE..... | 893 | 566 | 327 | 653 | 408 | 245 | 44 | 29 | 15 | 107 | 68 | 39 | 52 | 38 | 14 |
| GREAT BRITAIN... | 2,883 | 2,087 | 796 | 2,053 | 1,519 | 534 | 178 | 115 | 63 | 423 | 289 | 134 | 72 | 58 | 14 |
| | 10,621 | 6,399 | 4,222 | 7,649 | 4,699 | 2,950 | 660 | 383 | 277 | 1,328 | 718 | 610 | 601 | 370 | 231 |

| Country | Doubtful serological relapses | | | Doubtful clinical relapses | | | Secondary syphilis with negative serological reaction at the beginning of the treatment | | |
|--------------------|-------------------------------|-----|-----|----------------------------|----|----|---|----|----|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. |
| GERMANY..... | 84 | 36 | 48 | 6 | 3 | 3 | 12 | 6 | 6 |
| DENMARK..... | 1 | — | 1 | — | — | — | 4 | 2 | 2 |
| UNITED STATES..... | 72 | 46 | 26 | 7 | 4 | 3 | 3 | 3 | — |
| FRANCE..... | 33 | 20 | 13 | 4 | 3 | 1 | — | — | — |
| GREAT BRITAIN..... | 153 | 106 | 47 | 2 | — | 2 | 2 | — | 2 |
| | 343 | 208 | 135 | 19 | 10 | 9 | 21 | 11 | 10 |

2. RESULTS IN CASES TREATED CONTINUOUSLY (excluding D₁ cases).

Germany.

| Stage | Cases | | | Remained or became sero-negative | | | Remained sero-positive | | | Serological relapses | | | Clinical relapses | | |
|----------------|-------|----|----|----------------------------------|----|----|------------------------|----|----|----------------------|----|----|-------------------|----|----|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. |
| S1 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| S1 or S2 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| S2 | 18 | 12 | 6 | 15 | 9 | 6 | 1 | 1 | — | 2 | 2 | — | — | — | — |
| S3 | 32 | 15 | 17 | 26 | 10 | 16 | — | — | — | 6 | 5 | 1 | — | — | — |
| S3 or S4 | 44 | 12 | 32 | 32 | 8 | 24 | 4 | 2 | 2 | 6 | 1 | 5 | 2 | 1 | 1 |
| S4 | 4 | 2 | 2 | 1 | 1 | — | 2 | — | 2 | 1 | 1 | — | — | — | — |
| S1-S4 | 98 | 41 | 57 | 74 | 28 | 46 | 7 | 3 | 4 | 15 | 9 | 6 | 2 | 1 | 1 |

| Stage | Doubtful serological relapses | | | Doubtful clinical relapses | | | Secondary syphilis with negative serological reaction at the beginning of the treatment | | |
|---------------|-------------------------------|----|----|----------------------------|----|----|---|----|----|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. |
| S1 - S4 | — | — | — | — | — | — | — | — | — |

Annex 11 (continued).

2. RESULTS IN CASES TREATED CONTINUOUSLY (excluding D₁ cases).

Denmark : NO CASES TREATED CONTINUOUSLY or in part continuously and in part intermittently.

United States of America.

| Stage | Cases | | | Remained or became sero-negative | | | Remained sero-positive | | | Serological relapses | | | Clinical relapses | | |
|----------------|-------|-----|-----|----------------------------------|-----|-----|------------------------|----|----|----------------------|----|----|-------------------|----|----|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. |
| S1 | 83 | 77 | 6 | 75 | 69 | 6 | — | — | — | 3 | 3 | — | 3 | 3 | — |
| S1 or S2 | 5 | 3 | 2 | 5 | 3 | 2 | — | — | — | — | — | — | — | — | — |
| S2 | 130 | 101 | 29 | 106 | 81 | 25 | 6 | 5 | 1 | 13 | 10 | 3 | 2 | 2 | — |
| S3 | 405 | 242 | 163 | 319 | 192 | 127 | 22 | 10 | 12 | 28 | 20 | 8 | — | — | — |
| S3 or S4 | 17 | 8 | 9 | 12 | 8 | 4 | 2 | — | 2 | 1 | — | 1 | — | — | — |
| S4 | 9 | 5 | 4 | 9 | 5 | 4 | — | — | — | — | — | — | — | — | — |
| S1-S4 | 649 | 433 | 213 | 526 | 358 | 168 | 30 | 15 | 15 | 45 | 33 | 12 | 5 | 5 | — |

| Stage | Doubtful serological relapses | | | Doubtful clinical relapses | | | Secondary syphilis with negative serological reaction at the beginning of the treatment | | |
|----------------|-------------------------------|----|----|----------------------------|----|----|---|----|----|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. |
| S1 | 2 | 2 | — | — | — | — | — | — | — |
| S1 or S2 | — | — | — | — | — | — | — | — | — |
| S2 | 3 | 3 | — | — | — | — | — | — | — |
| S3 | 20 | 11 | 9 | 16 | 9 | 7 | — | — | — |
| S3 or S4 | 2 | — | 2 | — | — | — | — | — | — |
| S4 | — | — | — | — | — | — | — | — | — |
| S1-S4 | 27 | 16 | 11 | 16 | 9 | 7 | — | — | — |

France.

| Stage | Cases | | | Remained or became sero-negative | | | Remained sero-positive | | | Serological relapses | | | Clinical relapses | | |
|----------------|-------|----|----|----------------------------------|----|----|------------------------|----|----|----------------------|----|----|-------------------|----|----|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. |
| S1 | 6 | 5 | 1 | 5 | 4 | 1 | — | — | — | 1 | 1 | — | — | — | — |
| S1 or S2 | 7 | 7 | — | 7 | 7 | — | — | — | — | — | — | — | — | — | — |
| S2 | 6 | 3 | 3 | 4 | 1 | 3 | — | — | — | 1 | 1 | — | — | — | — |
| S3 | 8 | 3 | 5 | 8 | 3 | 5 | — | — | — | — | — | — | — | — | — |
| S3 or S4 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| S4 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| S1-S4 | 27 | 18 | 9 | 24 | 15 | 9 | — | — | — | 2 | 2 | — | — | — | — |

| Stage | Doubtful serological relapses | | | Doubtful clinical relapses | | | Secondary syphilis with negative serological reaction at the beginning of the treatment | | |
|----------------|-------------------------------|----|----|----------------------------|----|----|---|----|----|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. |
| S1 | — | — | — | — | — | — | — | — | — |
| S1 or S2 | — | — | — | — | — | — | — | — | — |
| S2 | — | — | — | — | — | — | — | — | — |
| S3 | — | — | — | 1 | 1 | — | — | — | — |
| S3 or S4 | — | — | — | — | — | — | — | — | — |
| S4 | — | — | — | — | — | — | — | — | — |
| S1-S4 | — | — | — | 1 | 1 | — | — | — | — |

Annex 11 (continued).

2. RESULTS IN CASES TREATED CONTINUOUSLY (excluding D₁ cases).

Great Britain.

| Stage | Cases | | | Remained or became sero-negative | | | Remained sero-positive | | | Serological relapses | | | Clinical relapses | | |
|----------------|-------|----|----|----------------------------------|----|----|------------------------|----|----|----------------------|----|----|-------------------|----|----|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. |
| S1 | 6 | 6 | — | 4 | 4 | — | — | — | — | 2 | 2 | — | — | — | — |
| S1 or S2 | 71 | 68 | 3 | 60 | 57 | 3 | 1 | 1 | — | 6 | 6 | — | — | — | — |
| S2 | 1 | 1 | — | 1 | 1 | — | — | — | — | — | — | — | — | — | — |
| S3 | 1 | 1 | — | 1 | 1 | — | — | — | — | — | — | — | — | — | — |
| S3 or S4 | 2 | 2 | — | 2 | 2 | — | — | — | — | — | — | — | — | — | — |
| S4 | 2 | 2 | — | 2 | 2 | — | — | — | — | — | — | — | — | — | — |
| S1-S4 | 81 | 78 | 3 | 68 | 65 | 3 | 1 | 1 | — | 8 | 8 | — | — | — | — |

| Stage | Doubtful serological relapses | | | Doubtful clinical relapses | | | Secondary syphilis with negative serological reaction at the beginning of the treatment | | |
|----------------|-------------------------------|----|----|----------------------------|----|----|---|----|----|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. |
| S1 | — | — | — | — | — | — | — | — | — |
| S1 or S2 | — | — | — | — | — | — | — | — | — |
| S2 | 4 | 4 | — | — | — | — | — | — | — |
| S3 | — | — | — | — | — | — | — | — | — |
| S3 or S4 | — | — | — | — | — | — | — | — | — |
| S4 | — | — | — | — | — | — | — | — | — |
| S1-S4 | 4 | 4 | — | — | — | — | — | — | — |

RESULTS IN CASES TREATED *CONTINUOUSLY* (excluding D₁ cases).

Summary Table S1-S4

| Country | Cases | | | Remained or became sero-negative | | | Remained sero-positive | | | Serological relapses | | | Clinical relapses | | |
|-------------------|-------|-----|-----|----------------------------------|-----|-----|------------------------|----|----|----------------------|----|----|-------------------|----|----|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. |
| GERMANY..... | 98 | 41 | 57 | 74 | 28 | 46 | 7 | 3 | 4 | 15 | 9 | 6 | 2 | 1 | 1 |
| DENMARK..... | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| UNITED STATES .. | 649 | 436 | 213 | 526 | 358 | 168 | 30 | 15 | 15 | 45 | 33 | 12 | 5 | 5 | — |
| FRANCE..... | 27 | 18 | 9 | 24 | 15 | 9 | — | — | — | 2 | 2 | — | — | — | — |
| GREAT BRITAIN ... | 81 | 78 | 3 | 68 | 65 | 3 | 1 | 1 | — | 8 | 8 | — | — | — | — |
| | 855 | 573 | 282 | 692 | 466 | 226 | 38 | 19 | 19 | 70 | 52 | 18 | 7 | 6 | 1 |

| Country | Doubtful serological relapses | | | Doubtful clinical relapses | | | Secondary syphilis with negative serological reaction at the beginning of the treatment | | |
|--------------------|-------------------------------|----|----|----------------------------|----|----|---|----|----|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. |
| GERMANY..... | — | — | — | — | — | — | — | — | — |
| DENMARK..... | — | — | — | — | — | — | — | — | — |
| UNITED STATES .. | 27 | 16 | 11 | 16 | 9 | 7 | — | — | — |
| FRANCE..... | — | — | — | 1 | 1 | — | — | — | — |
| GREAT BRITAIN..... | 4 | 4 | — | — | — | — | — | — | — |
| | 31 | 20 | 11 | 17 | 10 | 7 | — | — | — |

Annex 11 (continued).

3. RESULTS IN CASES TREATED IN PART CONTINUOUSLY AND IN PART INTERMITTENTLY (excluding D₁ cases).
Germany.

| Stage | Cases | | | Remained or became sero-negative | | | Remained sero-positive | | | Serological relapses | | | Clinical relapses | | |
|----------------|-------|----|----|----------------------------------|----|----|------------------------|----|----|----------------------|----|----|-------------------|----|----|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. |
| S1 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| S1 or S2 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| S2 | 9 | 5 | 4 | 3 | 1 | 2 | — | — | — | 5 | 3 | 2 | 1 | 1 | — |
| S3 | 15 | 4 | 11 | 2 | 1 | 1 | 2 | 1 | 1 | 9 | 2 | 7 | — | — | — |
| S3 or S4 | 28 | 8 | 20 | 11 | 3 | 8 | 2 | 1 | 1 | 15 | 4 | 11 | — | — | — |
| S4 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| S1-S4 | 52 | 17 | 35 | 16 | 5 | 11 | 4 | 2 | 2 | 29 | 9 | 20 | 1 | 1 | — |

| Stage | Doubtful serological relapses | | | Doubtful clinical relapses | | | Secondary syphilis with negative serological reaction at the beginning of the treatment | | |
|----------------|-------------------------------|----|----|----------------------------|----|----|---|----|----|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. |
| S1 | — | — | — | — | — | — | — | — | — |
| S1 or S2 | — | — | — | — | — | — | — | — | — |
| S2 | — | — | — | — | — | — | — | — | — |
| S3 | 2 | — | 2 | — | — | — | — | — | — |
| S3 or S4 | — | — | — | — | — | — | — | — | — |
| S4 | — | — | — | — | — | — | — | — | — |
| S1-S4 | 2 | — | 2 | — | — | — | — | — | — |

Denmark : NO CASES TREATED CONTINUOUSLY or IN PART CONTINUOUSLY AND IN PART INTERMITTENTLY.

United States of America.

| Stage | Cases | | | Remained or became sero-negative | | | Remained sero-positive | | | Serological relapses | | | Clinical relapses | | |
|----------------|-------|-----|-----|----------------------------------|-----|-----|------------------------|----|----|----------------------|----|----|-------------------|----|----|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. |
| S1 | 40 | 39 | 1 | 31 | 31 | — | — | — | — | 7 | 6 | 1 | 2 | 2 | — |
| S1 or S2 | 7 | 7 | — | 2 | 2 | — | — | — | — | 1 | 1 | — | 4 | 4 | — |
| S2 | 152 | 128 | 24 | 78 | 63 | 15 | 7 | 6 | 1 | 38 | 32 | 6 | 20 | 18 | 2 |
| S3 | 404 | 194 | 210 | 224 | 98 | 126 | 24 | 15 | 9 | 77 | 41 | 36 | 49 | 26 | 23 |
| S3 or S4 | 21 | 11 | 10 | 15 | 8 | 7 | 4 | 3 | 1 | 2 | — | 2 | — | — | — |
| S4 | 19 | 10 | 9 | 8 | 6 | 2 | — | — | — | 10 | 4 | 6 | — | — | — |
| S1-S4 | 643 | 389 | 254 | 358 | 208 | 150 | 35 | 24 | 11 | 135 | 84 | 51 | 75 | 50 | 25 |

| Stage | Doubtful serological relapses | | | Doubtful clinical relapses | | | Secondary syphilis with negative serological reaction at the beginning of the treatment | | |
|----------------|-------------------------------|----|----|----------------------------|----|----|---|----|----|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. |
| S1 | — | — | — | — | — | — | — | — | — |
| S1 or S2 | — | — | — | — | — | — | — | — | — |
| S2 | 9 | 9 | — | — | — | — | — | — | — |
| S3 | 22 | 10 | 12 | 7 | 3 | 4 | 1 | 1 | — |
| S3 or S4 | — | — | — | — | — | — | — | — | — |
| S4 | 1 | — | 1 | — | — | — | — | — | — |
| S1-S4 | 32 | 19 | 13 | 7 | 3 | 4 | 1 | 1 | — |

Annex 11 (continued).

3. RESULTS IN CASES TREATED IN PART CONTINUOUSLY AND IN PART INTERMITTENTLY (excluding D₁ cases).

France.

| Stage | Cases | | | Remained or became sero-negative | | | Remained sero-positive | | | Serological relapses | | | Clinical relapses | | |
|--------------------|-----------|-----------|-----------|----------------------------------|-----------|-----------|------------------------|----------|----------|----------------------|-----------|-----------|-------------------|----------|----------|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. |
| S1 | 9 | 9 | — | 6 | 6 | — | — | — | — | 3 | 3 | — | — | — | — |
| S1 or S2 | 1 | 1 | — | 1 | 1 | — | — | — | — | — | — | — | — | — | — |
| S2 | 32 | 15 | 17 | 16 | 7 | 9 | — | — | — | 12 | 6 | 6 | 4 | 2 | 2 |
| S3 | 9 | 7 | 2 | 5 | 4 | 1 | — | — | — | 4 | 3 | 1 | — | — | — |
| S3 or S4 | 25 | 11 | 14 | 11 | 6 | 5 | — | — | — | 12 | 3 | 9 | — | — | — |
| S4 | 1 | 1 | — | 1 | 1 | — | — | — | — | — | — | — | — | — | — |
| S1-S4 | 77 | 44 | 33 | 40 | 25 | 15 | — | — | — | 31 | 15 | 16 | 4 | 2 | 2 |

| Stage | Doubtful serological relapses | | | Doubtful clinical relapses | | | Secondary syphilis with negative serological reaction at the beginning of the treatment | | |
|--------------------|-------------------------------|----------|----------|----------------------------|----------|----------|---|----------|----------|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. |
| S1 | — | — | — | — | — | — | — | — | — |
| S1 or S2 | — | — | — | — | — | — | — | — | — |
| S2 | — | — | — | — | — | — | — | — | — |
| S3 | — | — | — | — | — | — | — | — | — |
| S3 or S4 | — | — | — | 2 | 2 | — | — | — | — |
| S4 | — | — | — | — | — | — | — | — | — |
| S1-S4 | — | — | — | 2 | 2 | — | — | — | — |

Great Britain.

| Stage | Cases | | | Remained or became sero-negative | | | Remained sero-positive | | | Serological relapses | | | Clinical relapses | | |
|----------------|-------|----|----|----------------------------------|----|----|------------------------|----|----|----------------------|----|----|-------------------|----|----|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. |
| S1 | 5 | 5 | — | 4 | 4 | — | — | — | — | — | — | — | 1 | 1 | — |
| S1 or S2 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| S2 | 72 | 65 | 7 | 49 | 44 | 5 | 7 | 6 | 1 | 12 | 12 | — | — | — | — |
| S3 | 28 | 14 | 14 | 15 | 8 | 7 | 4 | 2 | 2 | 6 | 3 | 3 | 2 | 1 | 1 |
| S3 or S4 | 15 | 8 | 7 | 9 | 5 | 4 | 1 | 1 | — | 4 | 1 | 3 | — | — | — |
| S4 | 1 | 1 | — | 1 | 1 | — | — | — | — | — | — | — | — | — | — |
| S1-S4 | 121 | 93 | 28 | 78 | 62 | 16 | 12 | 9 | 3 | 22 | 16 | 6 | 3 | 2 | 1 |

| Stage | Doubtful serological relapses | | | Doubtful clinical relapses | | | Secondary syphilis with negative serological reaction at the beginning of the treatment | | |
|----------------|-------------------------------|----|----|----------------------------|----|----|---|----|----|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. |
| S1 | — | — | — | — | — | — | — | — | — |
| S1 or S2 | — | — | — | — | — | — | — | — | — |
| S2 | 4 | 3 | 1 | — | — | — | — | — | — |
| S3 | 1 | — | 1 | — | — | — | — | — | — |
| S3 or S4 | 1 | 1 | — | — | — | — | — | — | — |
| S4 | — | — | — | — | — | — | — | — | — |
| S1-S4 | 6 | 4 | 2 | — | — | — | — | — | — |

Annex 11 (continued).

3. RESULTS IN CASES TREATED IN PART CONTINUOUSLY AND IN PART INTERMITTENTLY (excluding D₁ cases).

Summary Table S1-S4

| Country | Cases | | | Remained or became sero-negative | | | Remained sero-positive | | | Serological relapses | | | Clinical relapses | | |
|-------------------|------------|------------|------------|----------------------------------|------------|------------|------------------------|-----------|-----------|----------------------|------------|-----------|-------------------|-----------|-----------|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. |
| GERMANY | 52 | 17 | 35 | 16 | 5 | 11 | 4 | 2 | 2 | 29 | 9 | 20 | 1 | 1 | — |
| DENMARK | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| UNITED STATES ... | 643 | 389 | 254 | 358 | 208 | 150 | 35 | 24 | 11 | 135 | 84 | 51 | 75 | 50 | 25 |
| FRANCE | 77 | 44 | 33 | 40 | 25 | 15 | — | — | — | 31 | 15 | 16 | 4 | 2 | 2 |
| GREAT BRITAIN ... | 121 | 93 | 28 | 78 | 62 | 16 | 12 | 9 | 3 | 22 | 16 | 6 | 3 | 2 | 1 |
| | 893 | 543 | 350 | 492 | 300 | 192 | 51 | 35 | 16 | 217 | 124 | 93 | 83 | 55 | 28 |

| Country | Doubtful serological relapses | | | Doubtful clinical relapses | | | Secondary syphilis with negative serological reaction at the beginning of the treatment | | |
|-------------------|-------------------------------|-----------|-----------|----------------------------|----------|----------|---|----------|----------|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. |
| GERMANY | 2 | — | 2 | — | — | — | — | — | — |
| DENMARK | — | — | — | — | — | — | — | — | — |
| UNITED STATES ... | 32 | 19 | 13 | 7 | 3 | 4 | 1 | 1 | — |
| FRANCE | — | — | — | 2 | 2 | — | — | — | — |
| GREAT BRITAIN ... | 6 | 4 | 2 | — | — | — | — | — | — |
| | 40 | 23 | 17 | 9 | 5 | 4 | 1 | 1 | — |

4. RESULTS OF TREATMENT IN D₁ CASES
(i.e., those first appearing for treatment when already in a state of clinical relapse.)

Germany.

1. TREATED INTERMITTENTLY.

| Stage reached at beginning of treatment outside the clinic : | Cases | | | Since become sero-negative | | | Still sero-positive | | | Serological relapses | | | Clinical relapses | | |
|---|-------|-----|-----|----------------------------|-----|----|---------------------|----|----|----------------------|----|----|-------------------|----|----|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. |
| (a) Primary syphilis | 40 | 31 | 9 | 25 | 21 | 4 | 2 | 1 | 1 | 6 | 5 | 1 | 7 | 4 | 3 |
| (b) Secondary syphilis | 32 | 15 | 17 | 17 | 8 | 9 | 1 | — | 1 | 5 | 1 | 4 | 8 | 6 | 2 |
| (c) Clinical symptoms of syphilis without other particulars | 210 | 121 | 119 | 154 | 75 | 79 | 20 | 10 | 10 | 32 | 19 | 13 | 20 | 12 | 8 |
| S3-S4 | 312 | 167 | 145 | 196 | 104 | 92 | 23 | 11 | 12 | 43 | 25 | 18 | 35 | 22 | 13 |

| Stage reached at beginning of treatment outside the clinic : | Serological relapse doubtful | | | Relapse with negative serological reaction, <i>Sp. pallida</i> + and later still sero-negative | | |
|---|------------------------------|----|----|--|----|----|
| | Total | M. | W. | Total | M. | W. |
| (a) Primary syphilis | — | — | — | — | — | — |
| (b) Secondary syphilis | 1 | — | 1 | — | — | — |
| (c) Clinical symptoms of syphilis without other particulars | 10 | 4 | 6 | 4 | 1 | 3 |
| S3-S4 | 11 | 4 | 7 | 4 | 1 | 3 |

2. TREATED CONTINUOUSLY.

| Stage reached at beginning of treatment outside the clinic : | Cases | | | Since become sero-negative | | | Still sero-positive | | | Serological relapses | | | Clinical relapses | | | Doubtful serological relapses | | |
|---|-------|----|----|----------------------------|----|----|---------------------|----|----|----------------------|----|----|-------------------|----|----|-------------------------------|----|----|
| | Tot. | M. | W. | Tot. | M. | W. | Tot. | M. | W. | Tot. | M. | W. | Tot. | M. | W. | Tot. | M. | W. |
| (a) Primary syphilis | — | — | — | | | | | | | | | | | | | | | |
| (b) Secondary syphilis | — | — | — | | | | | | | | | | | | | | | |
| (c) Clinical symptoms of syphilis without other particulars | 23 | 11 | 12 | 17 | 7 | 10 | 5 | 3 | 2 | 1 | 1 | — | — | — | — | — | — | |
| S3-S4 | 23 | 11 | 12 | 17 | 7 | 10 | 5 | 3 | 2 | 1 | 1 | — | — | — | — | — | — | |

3. TREATED IN PART CONTINUOUSLY OR IN PART INTERMITTENTLY.

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (a) Primary syphilis | — | — | — | | | | | | | | | | | | | | | |
| (b) Secondary syphilis | — | — | — | | | | | | | | | | | | | | | |
| (c) Clinical symptoms of syphilis without other particulars | 6 | 1 | 5 | 1 | — | 1 | 1 | 1 | — | 4 | — | 4 | — | — | — | — | — | — |
| S3-S4 | 6 | 1 | 5 | 1 | — | 1 | 1 | 1 | — | 4 | — | 4 | — | — | — | — | — | — |

Annex 11 (continued).

4. RESULTS OF TREATMENT IN D₁ CASES.

Denmark.

1. TREATED INTERMITTENTLY.

| Stage reached at beginning of treatment outside the clinic : | Cases | | | Since become sero-negative | | | Still sero-positive | | | Serological relapses | | | Clinical relapses | | | Doubtful serological relapses | | |
|---|-------|----|----|----------------------------|----|----|---------------------|----|----|----------------------|----|----|-------------------|----|----|-------------------------------|----|----|
| | Tot. | M. | W. | Tot. | M. | W. | Tot. | M. | W. | Tot. | M. | W. | Tot. | M. | W. | Tot. | M. | W. |
| (a) Primary syphilis | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| (b) Secondary syphilis | 2 | 2 | — | 2 | 2 | — | — | — | — | — | — | — | — | — | — | — | — | — |
| (c) Clinical symptoms of syphilis without other particulars | 47 | 25 | 22 | 36 | 20 | 16 | 3 | 2 | 1 | 6 | 2 | 4 | 2 | 1 | 1 | — | — | — |
| S3-S4 | 49 | 27 | 22 | 38 | 22 | 16 | 3 | 2 | 1 | 6 | 2 | 4 | 2 | 1 | 1 | — | — | — |

There were no cases either treated continuously or treated in part continuously and in part intermittently.

United States of America.

1. TREATED INTERMITTENTLY.

| Stage reached at beginning of treatment outside the clinic : | Cases | | | Since become sero-negative | | | Still sero-positive | | | Serological relapses | | | Clinical relapses | | | Doubtful serological relapses | | |
|---|-------|-----|----|----------------------------|-----|----|---------------------|----|----|----------------------|----|----|-------------------|----|----|-------------------------------|----|----|
| | Tot. | M. | W. | Tot. | M. | W. | Tot. | M. | W. | Tot. | M. | W. | Tot. | M. | W. | Tot. | M. | W. |
| (a) Primary syphilis | 30 | 30 | — | 18 | 18 | — | 3 | 3 | — | 4 | 4 | — | 4 | 4 | — | 1 | 1 | — |
| (b) Secondary syphilis | 4 | 3 | 1 | 1 | 1 | — | 1 | 1 | — | 2 | 1 | 1 | — | — | — | — | — | — |
| (c) Clinical symptoms of syphilis without other particulars | 201 | 165 | 36 | 108 | 100 | 8 | 42 | 31 | 11 | 30 | 20 | 10 | 15 | 10 | 5 | 6 | 4 | 2 |
| S3-S4 | 235 | 198 | 37 | 127 | 119 | 8 | 46 | 35 | 11 | 36 | 25 | 11 | 19 | 14 | 5 | 7 | 5 | 2 |

2. TREATED CONTINUOUSLY.

| | | | | | | | | | | | | | | | | | | |
|---|----|----|---|----|----|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (a) Primary syphilis | 4 | 4 | — | 2 | 2 | — | 1 | 1 | — | — | — | — | 1 | 1 | — | — | — | — |
| (b) Secondary syphilis | 2 | — | 2 | — | — | — | 1 | — | 1 | — | — | — | — | — | — | 1 | — | 1 |
| (c) Clinical symptoms of syphilis without other particulars | 28 | 23 | 5 | 15 | 12 | 3 | 1 | 1 | — | 6 | 5 | 1 | 4 | 3 | 1 | 2 | 2 | — |
| S3-S4 | 34 | 27 | 7 | 17 | 14 | 3 | 3 | 2 | 1 | 6 | 5 | 1 | 5 | 4 | 1 | 3 | 2 | 1 |

3. TREATED IN PART CONTINUOUSLY, IN PART INTERMITTENTLY.

| | | | | | | | | | | | | | | | | | | |
|---|----|----|---|----|----|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (a) Primary syphilis | 3 | 3 | — | 3 | 3 | — | — | — | — | — | — | — | — | — | — | — | — | — |
| (b) Secondary syphilis | 3 | 2 | 1 | 2 | 1 | 1 | — | — | — | 1 | 1 | — | — | — | — | — | — | — |
| (c) Clinical symptoms of syphilis without other particulars | 28 | 22 | 6 | 14 | 10 | 4 | 2 | 1 | 1 | 5 | 4 | 1 | 7 | 7 | — | — | — | — |
| S3-S4 | 34 | 27 | 7 | 19 | 14 | 5 | 2 | 1 | 1 | 6 | 5 | 1 | 7 | 7 | — | — | — | — |

France.

1. TREATED INTERMITTENTLY.

| Stage reached at beginning of treatment outside the clinic : | Cases | | | Since become sero-negative | | | Still sero-positive | | | Serological relapses | | | Clinical relapses | | | Doubtful serological relapses | | |
|---|-------|----|----|----------------------------|----|----|---------------------|----|----|----------------------|----|----|-------------------|----|----|-------------------------------|----|----|
| | Tot. | M. | W. | Tot. | M. | W. | Tot. | M. | W. | Tot. | M. | W. | Tot. | M. | W. | Tot. | M. | W. |
| (a) Primary syphilis | 23 | 19 | 4 | 10 | 8 | 2 | 3 | 2 | 1 | 2 | 1 | 1 | 3 | 3 | — | 2 | 2 | — |
| (b) Secondary syphilis | 12 | 2 | 10 | 9 | 1 | 8 | 1 | — | 1 | 2 | 1 | 1 | — | — | — | — | — | — |
| (c) Clinical symptoms of syphilis without other particulars | 29 | 16 | 13 | 22 | 11 | 11 | 3 | 1 | 2 | 1 | 1 | — | 2 | 2 | — | 1 | 1 | — |
| S3-S4 | 64 | 37 | 27 | 41 | 20 | 21 | 7 | 3 | 4 | 5 | 3 | 2 | 5 | 5 | — | 3 | 3 | — |

Stage reached at beginning of treatment outside the clinic :

Relapse with negative serological reaction. *Sp. pallida* +, and later still sero-negative.

| | | | |
|---|---|---|---|
| (a) Primary syphilis | 3 | 3 | — |
| (b) Secondary syphilis | — | — | — |
| (c) Clinical symptoms of syphilis without other particulars | — | — | — |
| S3-S4 | 3 | 3 | — |

| Total | M. | W. |
|-------|----|----|
| 3 | 3 | — |
| — | — | — |
| — | — | — |
| 3 | 3 | — |

2. TREATED CONTINUOUSLY. (There were no such cases.)

3. TREATED IN PART CONTINUOUSLY, IN PART INTERMITTENTLY.

| Stage reached at beginning of treatment outside the clinic : | Cases | | | Since become sero-negative | | | Still sero-positive | Serological relapses | Clinical relapses | Doubtful serological relapses |
|---|-------|----|----|----------------------------|----|----|---------------------|----------------------|-------------------|-------------------------------|
| | Tot. | M. | W. | Tot. | M. | W. | | | | |
| (a) Primary syphilis | — | — | — | | | | | | | |
| (b) Secondary syphilis | — | — | — | | | | | | | |
| (c) Clinical symptoms of syphilis without other particulars | 1 | 1 | — | 1 | 1 | — | | | | |
| S3-S4 | 1 | 1 | — | 1 | 1 | — | | | | |

Summary Table (S3-S4 a-c).

1. TREATED INTERMITTENTLY.

| Country | Cases | | | Since become sero-negative | | | Still sero-positive | | | Serological relapses | | | Clinical relapses | | | Doubtful serological relapses | | |
|---------------------|-------|-----|-----|----------------------------|-----|-----|---------------------|----|----|----------------------|----|----|-------------------|----|----|-------------------------------|----|----|
| | Tot. | M. | W. | Tot. | M. | W. | Tot. | M. | W. | Tot. | M. | W. | Tot. | M. | W. | Tot. | M. | W. |
| GERMANY | 312 | 167 | 145 | 196 | 104 | 92 | 23 | 11 | 12 | 43 | 25 | 18 | 35 | 22 | 13 | 11 | 4 | 7 |
| DENMARK | 49 | 27 | 22 | 38 | 22 | 16 | 3 | 2 | 1 | 6 | 2 | 4 | 2 | 1 | 1 | — | — | — |
| UNITED STATES | 235 | 198 | 37 | 127 | 119 | 8 | 46 | 35 | 11 | 36 | 25 | 11 | 19 | 14 | 5 | 7 | 5 | 2 |
| FRANCE | 64 | 37 | 27 | 41 | 20 | 21 | 7 | 3 | 4 | 5 | 3 | 2 | 5 | 5 | — | 3 | 3 | — |
| GREAT BRITAIN | 66 | 53 | 13 | 37 | 28 | 9 | 13 | 10 | 3 | 12 | 11 | 1 | 2 | 2 | — | 2 | 2 | — |
| | 726 | 482 | 244 | 439 | 293 | 146 | 92 | 61 | 31 | 102 | 66 | 36 | 63 | 44 | 19 | 23 | 14 | 9 |

| Country | Relapse with negative serological <i>Sp. pallida</i> +, and later still sero-negative | | |
|---------------------|---|----|----|
| | Total | M. | W. |
| GERMANY | 4 | 1 | 3 |
| DENMARK | — | — | — |
| UNITED STATES | — | — | — |
| FRANCE | 3 | 3 | — |
| GREAT BRITAIN | — | — | — |
| | 7 | 4 | 3 |

2. TREATED CONTINUOUSLY.

| Country | Cases | | | Since become sero-negative | | | Still sero-positive | | | Serological relapses | | | Clinical relapses | | | Doubtful serological relapses | | |
|---------------------|-------|----|----|----------------------------|----|----|---------------------|----|----|----------------------|----|----|-------------------|----|----|-------------------------------|----|----|
| | Tot. | M. | W. | Tot. | M. | W. | Tot. | M. | W. | Tot. | M. | W. | Tot. | M. | W. | Tot. | M. | W. |
| GERMANY | 23 | 11 | 12 | 17 | 7 | 10 | 5 | 3 | 2 | 1 | 1 | — | — | — | — | — | — | — |
| DENMARK | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| UNITED STATES | 34 | 27 | 7 | 17 | 14 | 3 | 3 | 2 | 1 | 6 | 5 | 1 | 5 | 4 | 1 | 3 | 2 | 1 |
| FRANCE | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| GREAT BRITAIN | 3 | 3 | — | 3 | 3 | — | — | — | — | — | — | — | — | — | — | — | — | — |
| | 60 | 41 | 19 | 37 | 24 | 13 | 8 | 5 | 3 | 7 | 6 | 1 | 5 | 4 | 1 | 3 | 2 | 1 |

3. TREATED IN PART CONTINUOUSLY, IN PART INTERMITTENTLY.

| | | | | | | | | | | | | | | | | | | |
|---------------------|----|----|----|----|----|---|---|---|---|----|---|---|---|---|---|---|---|---|
| GERMANY | 6 | 1 | 5 | 1 | — | 1 | 1 | 1 | — | 4 | — | 4 | — | — | — | — | — | — |
| DENMARK | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| UNITED STATES | 34 | 27 | 7 | 19 | 14 | 5 | 2 | 1 | 1 | 6 | 5 | 1 | 7 | 7 | — | — | — | — |
| FRANCE | 1 | 1 | — | 1 | 1 | — | — | — | — | — | — | — | — | — | — | — | — | — |
| GREAT BRITAIN | 2 | 2 | — | 2 | 2 | — | — | — | — | — | — | — | — | — | — | — | — | — |
| | 43 | 31 | 12 | 23 | 17 | 6 | 3 | 2 | 1 | 10 | 5 | 5 | 7 | 7 | — | — | — | — |

Annex 12.

NUMBER OF CASES OF RE-INFECTION.

1. IN *intermittently* TREATED CASES.

| Stage | Germany | | | Denmark | | | United States | | | France | | | Great Britain | | |
|----------------|---------|----|----|---------|----|----|---------------|----|----|--------|----|----|---------------|----|----|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. |
| S1 | 10 | 9 | 1 | 21 | 20 | 1 | 2 | 2 | — | 1 | 1 | — | 3 | 3 | — |
| S1 or S2 | — | — | — | — | — | — | 1 | 1 | — | 1 | 1 | — | — | — | — |
| S2 | 8 | 6 | 2 | 5 | 5 | — | 5 | 5 | — | 3 | 2 | 1 | 7 | 6 | 1 |
| S3 | 5 | 5 | — | 9 | 9 | — | 8 | 7 | 1 | — | — | — | 3 | 2 | 1 |
| S3 or S4 | 7 | 6 | 1 | — | — | — | — | — | — | — | — | — | 5 | 2 | 3 |
| S4 | 1 | 1 | — | 1 | 1 | — | — | — | — | — | — | — | — | — | — |
| S1-S4 | 31 | 27 | 4 | 36 | 35 | 1 | 16 | 15 | 1 | 5 | 4 | 1 | 18 | 13 | 5 |

2. IN *continuously* TREATED CASES.

| Stage | United States ¹ | | |
|----------------|----------------------------|----|----|
| | Total | M. | W. |
| S1 | 2 | 2 | — |
| S1 or S2 | — | — | — |
| S2 | 1 | 1 | — |
| S3 | 3 | 3 | — |
| S3 or S4 | — | — | — |
| S4 | — | — | — |
| S1-S4 | 6 | 6 | — |

3. IN CASES TREATED *partly continuously and partly intermittently*.

| Stage | United States ¹ | | |
|----------------|----------------------------|----|----|
| | Total | M. | W. |
| S1 | — | — | — |
| S1 or S2 | — | — | — |
| S2 | 1 | 1 | — |
| S3 | 5 | 3 | 2 |
| S3 or S4 | — | — | — |
| S4 | — | — | — |
| S1-S4 | 6 | 4 | 2 |

¹ In other countries no re-infection under headings 2 and 3.

Annex 13.

OCCURRENCE OF UNDESIRABLE SUBSIDIARY EFFECTS AS A RESULT OF THE DRUGS USED OR THE DOSAGE.

Germany.

1. WITH INTERMITTENT TREATMENT (including D₁ cases).

| Stage | Icterus | | | Exanthem | | | Dermatitis | | | Exitus | | | Other ¹ | | | Total | M. | W. |
|----------------|---------|----|----|----------|----|----|------------|----|----|--------|----|----|--------------------|-----|----|-------|-----|-----|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. | | | |
| S1 | 17 | 15 | 2 | 19 | 16 | 3 | 2 | — | 2 | — | — | — | 25 | 24 | 1 | 63 | 55 | 8 |
| S1 or S2 | — | — | — | — | — | — | — | — | — | — | — | — | 4 | 2 | 2 | 4 | 2 | 2 |
| S2 | 22 | 19 | 3 | 23 | 14 | 9 | 5 | 3 | 2 | 1 | — | 1 | 38 | 29 | 9 | 89 | 65 | 24 |
| S3 | 26 | 17 | 9 | 31 | 14 | 17 | 11 | 3 | 8 | 1 | 1 | — | 67 | 33 | 34 | 136 | 68 | 68 |
| S3 or S4 | 21 | 5 | 16 | 51 | 6 | 45 | 8 | 2 | 6 | — | — | — | 64 | 15 | 49 | 144 | 28 | 116 |
| S4 | 2 | 2 | — | 7 | 3 | 4 | 2 | 2 | — | — | — | — | 7 | 4 | 3 | 18 | 11 | 7 |
| S1-S4 | 88 | 58 | 30 | 131 | 53 | 78 | 28 | 10 | 18 | 2 | 1 | 1 | 205 | 107 | 98 | 454 | 229 | 225 |

2. WITH CONTINUOUS TREATMENT (including D₁ cases).

| | | | | | | | | | | | | | | | | | | |
|----------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| S2 | — | — | — | 1 | 1 | — | — | — | — | — | — | — | — | — | — | 1 | 1 | — |
| S3 | — | — | — | — | — | — | — | — | — | — | — | — | 1 | 1 | — | 1 | 1 | — |
| S3 or S4 | 2 | — | 2 | 2 | — | 2 | — | — | — | — | — | — | 1 | — | 1 | 5 | — | 5 |
| S1-S4 | 2 | — | 2 | 3 | 1 | 2 | — | — | — | — | — | — | 2 | 1 | 1 | 7 | 2 | 5 |

3. WITH PARTLY CONTINUOUS, PARTLY INTERMITTENT TREATMENT (including D₁ cases).

| | | | | | | | | | | | | | | | | | | |
|----------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| S2 | 1 | 1 | — | — | — | — | — | — | — | — | — | — | — | — | — | 1 | 1 | — |
| S3 or S4 | 1 | — | 1 | 4 | — | 4 | — | — | — | — | — | — | 2 | — | 2 | 7 | — | 7 |
| S1-S4 | 2 | 1 | 1 | 4 | — | 4 | — | — | — | — | — | — | 2 | — | 2 | 8 | 1 | 7 |

Denmark.

1. WITH INTERMITTENT TREATMENT (including D₁ cases).

| | | | | | | | | | | | | | | | | | | |
|----------------|----|----|----|----|----|----|----|----|----|---|---|---|----|----|---|-----|----|----|
| S1 | 7 | 7 | — | 6 | 4 | 2 | 5 | 3 | 2 | — | — | — | 1 | 1 | — | 19 | 15 | 4 |
| S1 or S2 | 4 | 4 | — | — | 4 | — | 2 | 2 | — | — | — | — | 4 | 4 | — | 10 | 10 | — |
| S2 | 20 | 18 | 2 | 8 | 7 | 1 | 5 | 2 | 3 | — | — | — | 2 | 2 | — | 35 | 29 | 6 |
| S3 | 44 | 16 | 28 | 34 | 8 | 26 | 20 | 4 | 16 | 1 | 1 | — | 9 | 5 | 4 | 108 | 34 | 74 |
| S3 or S4 | 2 | — | 2 | — | — | — | — | — | — | — | — | — | — | — | — | 2 | 2 | — |
| S4 | 3 | 2 | 1 | — | — | — | — | — | — | — | — | — | — | — | — | 3 | 2 | 1 |
| S1-S4 | 80 | 47 | 33 | 48 | 19 | 29 | 32 | 11 | 21 | 1 | 1 | — | 16 | 12 | 4 | 177 | 90 | 87 |

2. and 3. No cases treated continuously or partly continuously and partly intermittently.

¹ E.g., nitritoid crisis, stomatitis, severe pain, albuminuria, etc.

Annex 13 (continued).

OCCURRENCE OF UNDESIRABLE SUBSIDIARY EFFECTS AS A RESULT OF THE DRUGS USED OR THE DOSAGE.

United States of America.

1. WITH INTERMITTENT TREATMENT (including D₁ cases).

| Stage | Icterus | | | Exanthem | | | Dermatitis | | | Exitus | | | Other | | | Total | M | W. |
|----------------|---------|----|----|----------|----|----|------------|----|----|--------|----|----|-------|----|----|-------|-----|-----|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. | | | |
| S1 | 4 | 4 | — | 4 | 3 | 1 | 3 | 3 | — | — | — | — | 4 | 4 | — | 15 | 14 | 1 |
| S1 or S2 | — | — | — | 1 | 1 | — | — | — | — | — | — | — | 2 | 2 | — | 3 | 3 | — |
| S2 | 14 | 11 | 3 | 8 | 5 | 3 | 3 | 3 | — | 2 | 1 | 1 | 40 | 29 | 11 | 67 | 49 | 18 |
| S3 | 36 | 17 | 19 | 36 | 20 | 16 | 26 | 11 | 15 | 3 | 2 | 1 | 99 | 47 | 52 | 200 | 97 | 103 |
| S3 or S4 | 3 | 2 | 1 | 2 | 2 | — | — | — | — | — | — | — | 13 | 3 | 10 | 18 | 7 | 11 |
| S4 | 2 | 1 | 1 | 5 | 4 | 1 | 2 | 1 | 1 | — | — | — | 7 | 4 | 3 | 16 | 10 | 6 |
| S1-S4 | 59 | 35 | 24 | 56 | 35 | 21 | 34 | 18 | 16 | 5 | 3 | 2 | 165 | 89 | 76 | 319 | 180 | 139 |

2. WITH CONTINUOUS TREATMENT (including D₁ cases).

| | | | | | | | | | | | | | | | | | | |
|----------------|----|----|---|----|----|----|----|---|---|---|---|---|-----|----|----|-----|----|----|
| S1 | 5 | 5 | — | 6 | 6 | — | 2 | 2 | — | — | — | — | 14 | 8 | 6 | 27 | 21 | 6 |
| S1 or S2 | — | — | — | — | — | — | — | — | — | — | — | — | 2 | 1 | 1 | 2 | 1 | 1 |
| S2 | 4 | 3 | 1 | 6 | 2 | 4 | 3 | 3 | — | — | — | — | 16 | 8 | 8 | 29 | 16 | 13 |
| S3 | 8 | 4 | 4 | 20 | 10 | 10 | 4 | 1 | 3 | — | — | — | 59 | 29 | 30 | 91 | 44 | 47 |
| S3 or S4 | — | — | — | 1 | 1 | — | 1 | — | 1 | — | — | — | 8 | 6 | 2 | 10 | 7 | 3 |
| S4 | — | — | — | — | — | — | — | — | — | — | — | — | 3 | 2 | 1 | 3 | 2 | 1 |
| S1-S4 | 17 | 12 | 5 | 33 | 19 | 14 | 10 | 6 | 4 | — | — | — | 102 | 54 | 48 | 162 | 91 | 71 |

3. WITH PARTLY CONTINUOUS, PARTLY INTERMITTENT TREATMENT (including D₁ cases).

| | | | | | | | | | | | | | | | | | | |
|----------------|----|----|----|----|----|----|----|---|---|---|---|---|-----|----|----|-----|-----|----|
| S1 | 3 | 3 | — | 3 | 3 | — | 1 | 1 | — | — | — | — | 3 | 2 | 1 | 10 | 9 | 1 |
| S1 or S2 | — | — | — | 2 | 2 | — | — | — | — | — | — | — | 1 | 1 | — | 3 | 3 | — |
| S2 | 5 | 4 | 1 | 7 | 4 | 3 | 1 | 1 | — | — | — | — | 28 | 21 | 7 | 41 | 30 | 11 |
| S3 | 19 | 8 | 11 | 32 | 17 | 15 | 9 | 4 | 5 | — | — | — | 61 | 23 | 38 | 121 | 52 | 69 |
| S3 or S4 | 1 | — | 1 | 3 | 2 | 1 | 1 | 1 | — | — | — | — | 13 | 6 | 7 | 18 | 9 | 9 |
| S4 | — | — | — | 2 | 2 | — | — | — | — | — | — | — | 3 | 2 | 1 | 5 | 4 | 1 |
| S1-S4 | 28 | 15 | 13 | 49 | 30 | 19 | 12 | 7 | 5 | — | — | — | 109 | 55 | 54 | 198 | 107 | 91 |

France.

1. WITH INTERMITTENT TREATMENT (including D₁ cases).

| Stage | Icterus | | | Exanthem | | | Dermatitis | | | Exitus | | | Other | | | Total | M. | W. |
|----------------|---------|----|----|----------|----|----|------------|----|----|--------|----|----|-------|-----|-----|-------|-----|-----|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. | | | |
| S1 | 7 | 7 | — | 3 | 3 | — | — | — | — | — | — | — | 18 | 18 | — | 28 | 28 | — |
| S1 or S2 | 1 | 1 | — | 2 | 2 | — | — | — | — | — | — | — | 3 | 3 | — | 6 | 6 | — |
| S2 | 8 | 8 | — | 5 | 4 | 1 | 2 | 2 | — | 1 | 1 | — | 78 | 57 | 21 | 94 | 72 | 22 |
| S3 | 15 | 6 | 9 | 10 | 2 | 8 | 3 | — | 3 | — | — | — | 107 | 30 | 77 | 135 | 38 | 97 |
| S3 or S4 | 8 | 3 | 5 | 2 | 1 | 1 | — | — | — | — | — | — | 39 | 8 | 31 | 49 | 12 | 37 |
| S4 | 1 | 1 | — | 1 | 1 | — | 1 | — | 1 | — | — | — | 17 | 8 | 9 | 20 | 10 | 10 |
| S1-S4 | 40 | 26 | 14 | 23 | 13 | 10 | 6 | 2 | 4 | 1 | 1 | — | 262 | 124 | 138 | 332 | 166 | 166 |

2. WITH CONTINUOUS TREATMENT (including D₁ cases).

| | | | | | | | | | | | | | | | | | | |
|----------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| S1 | — | — | — | — | — | — | — | — | — | — | — | — | 2 | 2 | — | 2 | 2 | — |
| S2 | 2 | 2 | — | — | — | — | — | — | — | — | — | — | 1 | 1 | — | 3 | 3 | — |
| S3 or S4 | — | — | — | — | — | — | — | — | — | — | — | — | 3 | — | 3 | 3 | — | 3 |
| S1-S4 | 2 | 2 | — | — | — | — | — | — | — | — | — | — | 6 | 3 | 3 | 8 | 5 | 3 |

3. WITH PARTLY CONTINUOUS, PARTLY INTERMITTENT TREATMENT (including D₁ cases).

| | | | | | | | | | | | | | | | | | | |
|----------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|----|---|---|
| S2 | 1 | 1 | — | — | — | — | — | — | — | — | — | — | 4 | 1 | 3 | 5 | 2 | 3 |
| S3 or S4 | 2 | — | 2 | — | — | — | — | — | — | — | — | — | 4 | — | 4 | 6 | — | 6 |
| S1-S4 | 3 | 1 | 2 | — | — | — | — | — | — | — | — | — | 8 | 1 | 7 | 11 | 2 | 9 |

Annex 13 (continued).

OCCURRENCE OF UNDESIRABLE SUBSIDIARY EFFECTS AS A RESULT OF THE DRUGS USED OR THE DOSAGE.

Great Britain.

1. WITH INTERMITTENT TREATMENT (including D₁ cases).

| Stage | Icterus | | | Exanthem | | | Dermatitis | | | Exitus | | | Other | | | Total | M. | W |
|----------------|---------|-----|----|----------|----|----|------------|----|----|--------|----|----|-------|----|-----|-------|-----|-----|
| | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. | Total | M. | W. | | | |
| S1 | 54 | 53 | 1 | 22 | 21 | 1 | 4 | 4 | — | 1* | 1 | — | 31 | 31 | — | 112 | 110 | 2 |
| S1 or S2 | 1 | 1 | — | — | — | — | — | — | — | — | — | — | — | — | — | 1 | 1 | — |
| S2 | 91 | 86 | 5 | 34 | 27 | 7 | 5 | 5 | — | — | — | — | 56 | 35 | 21 | 190 | 157 | 33 |
| S3 | 61 | 49 | 12 | 36 | 23 | 13 | 9 | 4 | 5 | — | — | — | 60 | 19 | 41 | 166 | 95 | 71 |
| S3 or S4 | 80 | 57 | 23 | 41 | 18 | 23 | 7 | 5 | 2 | — | — | — | 76 | 13 | 63 | 204 | 93 | 111 |
| S4 | 5 | 5 | — | 3 | 3 | — | 1 | 1 | — | — | — | — | 1 | 1 | — | 10 | 10 | — |
| S1-S4 | 292 | 251 | 41 | 136 | 92 | 44 | 26 | 19 | 7 | 1* | 1 | — | 224 | 99 | 125 | 683 | 466 | 217 |

2. WITH CONTINUOUS TREATMENT (including D₁ cases).

| | | | | | | | | | | | | | | | | | | |
|-------------|----|----|---|---|---|---|---|---|---|---|---|---|---|---|---|----|----|---|
| S2 | 12 | 12 | — | 5 | 5 | — | — | — | — | — | — | — | 3 | 2 | 1 | 20 | 19 | 1 |
| S1-S4 | 12 | 12 | — | 5 | 5 | — | — | — | — | — | — | — | 3 | 2 | 1 | 20 | 19 | 1 |

3. WITH PARTLY CONTINUOUS, PARTLY INTERMITTENT TREATMENT (including D₁ cases).

| | | | | | | | | | | | | | | | | | | |
|----------------|----|----|---|---|---|---|---|---|---|---|---|---|----|---|---|----|----|---|
| S1 | 1 | 1 | — | — | — | — | — | — | — | — | — | — | — | — | — | 1 | 1 | — |
| S2 | 7 | 7 | — | 3 | 3 | — | 1 | 1 | — | — | — | — | 4 | 4 | — | 15 | 15 | — |
| S3 | 1 | 1 | — | 1 | — | 1 | 2 | — | 2 | — | — | — | 5 | 1 | 4 | 9 | 2 | 7 |
| S3 or S4 | 4 | 3 | 1 | 1 | 1 | — | — | — | — | — | — | — | 1 | 1 | — | 6 | 5 | 1 |
| S1-S4 | 13 | 12 | 1 | 5 | 4 | 1 | 3 | 1 | 2 | — | — | — | 10 | 6 | 4 | 31 | 23 | 8 |

* In addition 4 cases of acute yellow atrophy of the liver (all men) were observed and are included in the total.

Recapitulation (in percentages).

1. WITH INTERMITTENT TREATMENT (including D₁ cases).

| Country | Percentages of complications relatively to the total number of cases | | | | | | |
|---------------------|--|----------|------------|--------|----------------------------|-------|-------|
| | Icterus | Exanthem | Dermatitis | Exitus | Acute yellow liver atrophy | Other | Total |
| GERMANY | 3.23 | 4.81 | 1.03 | 0.07 | — | 7.54 | 16.69 |
| DENMARK | 3.46 | 2.08 | 1.38 | 0.04 | — | 0.70 | 7.66 |
| UNITED STATES | 2.45 | 2.32 | 1.41 | 0.21 | — | 6.85 | 13.24 |
| FRANCE | 4.17 | 2.40 | 0.63 | 0.10 | — | 27.38 | 34.69 |
| GREAT BRITAIN | 9.90 | 4.61 | 0.88 | 0.03 | 0.13 | 7.63 | 23.18 |

The distribution of complications by sex is as follows : *Men.*

| | | | | | | | |
|---------------------|-------|------|------|------|------|-------|-------|
| GERMANY | 4.26 | 3.89 | 0.73 | 0.07 | — | 7.85 | 16.80 |
| DENMARK | 3.98 | 1.61 | 0.93 | 0.08 | — | 1.02 | 7.62 |
| UNITED STATES | 2.20 | 2.20 | 1.13 | 0.19 | — | 5.58 | 11.29 |
| FRANCE | 4.31 | 2.16 | 0.33 | 0.17 | — | 20.56 | 27.53 |
| GREAT BRITAIN | 11.73 | 4.30 | 0.89 | 0.05 | 0.19 | 4.63 | 21.77 |

Women.

| | | | | | | | |
|---------------------|------|------|------|------|---|-------|-------|
| GERMANY | 2.21 | 5.74 | 1.33 | 0.07 | — | 7.22 | 16.57 |
| DENMARK | 2.92 | 2.57 | 1.86 | — | — | 0.35 | 7.70 |
| UNITED STATES | 2.94 | 2.58 | 1.96 | 0.25 | — | 9.33 | 17.06 |
| FRANCE | 3.95 | 2.82 | 1.13 | — | — | 38.98 | 46.89 |
| GREAT BRITAIN | 5.07 | 5.44 | 0.87 | — | — | 15.45 | 26.82 |

2. WITH CONTINUOUS TREATMENT (including D₁ cases).

| | | | | | | | |
|---------------------|-------|------|------|---|---|-------|-------|
| GERMANY | 1.65 | 2.48 | — | — | — | 1.65 | 5.78 |
| DENMARK | — | — | — | — | — | — | — |
| UNITED STATES | 2.49 | 4.83 | 1.46 | — | — | 14.93 | 23.71 |
| FRANCE | 7.41 | — | — | — | — | 22.22 | 29.63 |
| GREAT BRITAIN | 14.29 | 5.95 | — | — | — | 3.57 | 23.81 |

As the number of cases is too small in other countries, subdivision by sex has been carried out only for the United States.

| | | | | | | | |
|---------------|------|------|------|---|---|-------|-------|
| UNITED STATES | | | | | | | |
| Men | 2.59 | 4.10 | 1.30 | — | — | 11.66 | 19.65 |
| Women | 2.27 | 6.36 | 1.82 | — | — | 21.82 | 32.28 |

3. WITH PARTLY CONTINUOUS, PARTLY INTERMITTENT TREATMENT (including D₁ cases).

| | | | | | | | |
|---------------------|-------|------|------|---|---|-------|-------|
| GERMANY | 3.45 | 6.89 | — | — | — | 3.45 | 13.79 |
| DENMARK | — | — | — | — | — | — | — |
| UNITED STATES | 4.14 | 7.24 | 1.77 | — | — | 16.10 | 29.25 |
| FRANCE | 3.85 | — | — | — | — | 10.26 | 14.11 |
| GREAT BRITAIN | 10.57 | 4.07 | 2.44 | — | — | 8.13 | 25.20 |

Subdivision by sex in the :

| | | | | | | | |
|---------------|------|------|------|---|---|-------|-------|
| UNITED STATES | | | | | | | |
| Men | 3.61 | 7.21 | 1.68 | — | — | 13.22 | 25.72 |
| Women | 4.98 | 7.28 | 1.92 | — | — | 20.69 | 34.87 |

Annex 14.

PERIOD OF OBSERVATION AFTER THE CONCLUSION OF TREATMENT.*

Germany.

1. WITH INTERMITTENT TREATMENT.

| Stage | Cases remaining or becoming sero-negative. | | | | | | | |
|----------------|--|-------|---------|-----|-----|------|-------|-------|
| | Number of cases | Years | | | | | | |
| | | 0 | up to 1 | 1-2 | 2-5 | 5-10 | 10-15 | 15-20 |
| S1 | 288 | 44 | 107 | 52 | 65 | 14 | 6 | — |
| S1 or S2 | 6 | 4 | 2 | — | — | — | — | — |
| S2 | 352 | 81 | 109 | 64 | 73 | 22 | 2 | 1 |
| S3 | 444 | 111 | 152 | 83 | 79 | 15 | 2 | 2 |
| S3 or S4 | 544 | 144 | 192 | 95 | 99 | 11 | 2 | 1 |
| S4 | 17 | 9 | 4 | 4 | — | — | — | — |
| S1-S4 | 1,651 | 393 | 566 | 298 | 316 | 62 | 12 | 4 |
| including men | 840 | 181 | 290 | 152 | 165 | 40 | 9 | 3 |
| women | 811 | 212 | 276 | 146 | 151 | 22 | 3 | 1 |

| Cases remaining sero-positive. | | | | | | | | |
|--------------------------------|-----|----|----|---|---|---|---|---|
| S1 | — | — | — | — | — | — | — | — |
| S1 or S2 | 1 | 1 | — | — | — | — | — | — |
| S2 | 17 | 10 | 6 | 1 | — | — | — | — |
| S3 | 48 | 30 | 15 | 1 | — | 1 | — | 1 |
| S3 or S4 | 63 | 33 | 24 | 5 | 1 | — | — | — |
| S4 | 1 | 1 | — | — | — | — | — | — |
| S1-S4 | 130 | 75 | 45 | 7 | 1 | 1 | — | 1 |
| including men | 54 | 30 | 18 | 4 | — | 1 | — | 1 |
| women | 76 | 45 | 27 | 3 | 1 | — | — | — |

* These tables are limited to the four main groups, and therefore leave out of account the doubtful serological and clinical relapses and the secondary cases in which, at the beginning of treatment, the serological reaction was negative whilst the test for *Sp. pallida* yielded a positive result.

Germany.

Serological relapses.

Clinical relapses.

| Stage | Number of cases | Years | | | | | |
|-------------|-----------------|-------|---------|-----|-----|------|-------|
| | | 0 | Up to 1 | 1-2 | 2-5 | 5-10 | 10-15 |
| S1 | 27 | 13 | 6 | 3 | 2 | 2 | 1 |
| S1 or S2 .. | — | — | — | — | — | — | — |
| S2 | 77 | 33 | 27 | 5 | 8 | 4 | — |
| S3 | 92 | 39 | 28 | 15 | 6 | 4 | — |
| S3 or S4 .. | 134 | 44 | 50 | 25 | 13 | 1 | 1 |
| S4 | 7 | 3 | — | 3 | 1 | — | — |
| S1-S4 .. | 337 | 132 | 111 | 51 | 30 | 11 | 2 |

| Number of cases | Years | | | | | | |
|-----------------|-------|---------|-----|-----|------|-------|-------|
| | 0 | Up to 1 | 1-2 | 2-5 | 5-10 | 10-15 | 15-20 |
| 28 | 18 | 8 | 1 | 1 | — | — | — |
| 1 | 1 | — | — | — | — | — | — |
| 42 | 21 | 12 | 3 | 5 | 1 | — | — |
| 56 | 38 | 6 | 2 | 4 | 5 | — | 1 |
| 61 | 34 | 19 | 2 | 3 | 3 | — | — |
| 1 | 1 | — | — | — | — | — | — |
| 189 | 113 | 45 | 8 | 13 | 9 | — | 1 |

Of which, after the conclusion of observation, the following number were still:

| | | | | | | | | | | | | | | | |
|-------------|----|----|----|----|---|---|---|----|----|----|---|---|---|---|---|
| Positive .. | 99 | 51 | 29 | 13 | 4 | 2 | — | 71 | 47 | 19 | 2 | 3 | — | — | — |
| Doubtful . | 27 | 19 | 6 | 1 | 1 | — | — | 16 | 16 | — | — | — | — | — | — |

The total figure comprises the following number of:

| | | | | | | | | | | | | | | | |
|-----------|-----|----|----|----|----|----|---|-----|----|----|---|---|---|---|---|
| Men | 149 | 60 | 40 | 19 | 18 | 10 | 2 | 108 | 61 | 26 | 4 | 9 | 7 | — | 1 |
| Positive. | 56 | 27 | 18 | 7 | 2 | 2 | — | 37 | 21 | 12 | 1 | 3 | — | — | — |
| Doubtful | 15 | 12 | 3 | — | — | — | — | 8 | 8 | — | — | — | — | — | — |
| Women ... | 188 | 72 | 71 | 32 | 12 | 1 | — | 81 | 52 | 19 | 4 | 4 | 2 | — | — |
| Positive. | 43 | 24 | 11 | 6 | 2 | — | — | 34 | 26 | 7 | 1 | — | — | — | — |
| Doubtful | 12 | 7 | 3 | 1 | 1 | — | — | 8 | 8 | — | — | — | — | — | — |

Annex 14 (continued).

PERIOD OF OBSERVATION AFTER THE CONCLUSION OF TREATMENT.

Germany (continued).

2. WITH CONTINUOUS TREATMENT.

| <i>Cases remaining or becoming sero-negative.</i> | | | | | | | | <i>Cases remaining sero-positive.</i> | | | | | | | |
|---|----|---|----|----|----|---|--|---------------------------------------|---|---|---|---|---|--|--|
| S2 | 15 | 1 | 4 | 1 | 9 | — | | 1 | — | 1 | — | — | — | | |
| S3 | 26 | 1 | 4 | 10 | 11 | — | | — | — | — | — | — | — | | |
| S3 or S4 .. | 32 | 1 | 2 | 12 | 17 | — | | 4 | 2 | 2 | — | — | — | | |
| S4 | 1 | — | — | — | 1 | — | | 2 | 2 | — | — | — | — | | |
| S1-S4 .. | 74 | 3 | 10 | 23 | 38 | — | | 7 | 4 | 3 | — | — | — | | |
| Including men ... | 28 | 2 | 8 | 5 | 13 | — | | 3 | 1 | 2 | | | | | |
| women . | 46 | 1 | 2 | 18 | 25 | — | | 4 | 3 | 1 | | | | | |
| <i>Serological relapses.</i> | | | | | | | | <i>Clinical relapses.</i> | | | | | | | |
| S2 | 2 | — | 2 | — | — | — | | — | — | — | — | — | — | | |
| S3 | 6 | — | 3 | 2 | 1 | — | | — | — | — | — | — | — | | |
| S3 or S4 .. | 6 | — | 4 | — | 2 | — | | 2 | 1 | — | — | — | 1 | | |
| S4 | 1 | — | 1 | — | — | — | | — | — | — | — | — | — | | |
| S1-S4 .. | 15 | — | 10 | 2 | 3 | — | | 2 | 1 | — | — | — | 1 | | |
| <i>Including, at the end of observation :</i> | | | | | | | | | | | | | | | |
| Positive .. | 9 | — | 9 | — | — | — | | 1 | — | — | — | — | 1 | | |
| <i>The total figure comprises the following number of :</i> | | | | | | | | | | | | | | | |
| Men | 9 | — | 6 | 1 | 2 | — | | 1 | 1 | — | — | — | — | | |
| Positive. | 6 | — | 6 | 1 | 1 | — | | — | — | — | — | — | — | | |
| Doubtful | — | — | — | — | — | — | | — | — | — | — | — | — | | |
| Women . | 6 | — | 4 | 1 | 1 | — | | 1 | — | — | — | — | 1 | | |
| Positive. | 3 | — | 3 | — | — | — | | 1 | — | — | — | — | 1 | | |

Denmark.

1. WITH INTERMITTENT TREATMENT.

Cases remaining or becoming sero-negative.

| Stage | Number of cases | Years | | | | | |
|-------------------|-----------------|-------|---------|-----|-----|------|-------|
| | | 0 | Up to 1 | 1-2 | 2-5 | 5-10 | 10-15 |
| S1 | 311 | 58 | 94 | 85 | 62 | 12 | |
| S1 or S2 .. | 59 | 22 | 20 | 10 | 6 | 1 | |
| S2 | 376 | 101 | 126 | 69 | 65 | 15 | |
| S3 | 1,175 | 370 | 356 | 183 | 228 | 38 | |
| S3 or S4 .. | 53 | 10 | 17 | 13 | 13 | — | |
| S4 | 5 | 1 | 1 | 1 | 2 | — | |
| S1-S4 .. | 1,979 | 562 | 614 | 361 | 376 | 66 | |
| including men ... | 1,070 | 295 | 331 | 212 | 191 | 41 | |
| women . | 909 | 267 | 283 | 149 | 185 | 25 | |

Cases remaining sero-positive.

| Number of cases | Years | | | | | | |
|-----------------|-------|---------|-----|-----|------|-------|-------|
| | 0 | Up to 1 | 1-2 | 2-5 | 5-10 | 10-15 | 15-20 |
| 1 | 1 | — | — | — | — | | |
| 3 | 2 | 1 | — | — | — | | |
| 8 | 4 | 3 | 1 | — | — | | |
| 2 | 2 | — | — | — | — | | |
| — | — | — | — | — | — | | |
| 14 | 9 | 4 | 1 | — | — | | |
| 8 | 6 | 2 | — | — | — | | |
| 6 | 3 | 2 | 1 | — | — | | |

Serological relapses.

| | | | | | | | |
|-------------|-----|----|----|----|----|---|---|
| S1 | 1 | — | 1 | — | — | — | — |
| S1 or S2 .. | 2 | — | 1 | 1 | — | — | — |
| S2 | 21 | 7 | 5 | 3 | 6 | — | — |
| S3 | 156 | 59 | 37 | 26 | 31 | 3 | — |
| S3 or S4 .. | 8 | 2 | 2 | — | 4 | — | — |
| S4 | — | — | — | — | — | — | — |
| S1-S4 .. | 188 | 68 | 46 | 30 | 41 | 3 | — |

Clinical relapses.

| | | | | | | | |
|----|----|----|---|----|---|---|--|
| 6 | 2 | 2 | — | 2 | — | — | |
| 2 | 1 | — | 1 | — | — | — | |
| 13 | 6 | 4 | 2 | 1 | — | — | |
| 53 | 23 | 11 | 6 | 12 | 1 | — | |
| 1 | — | — | — | 1 | — | — | |
| 1 | — | 1 | — | — | — | — | |
| 76 | 32 | 18 | 9 | 16 | 1 | — | |

Of which, at the conclusion of observation, the following number were still :

| | | | | | | | | | | | | | | |
|-------------|----|----|---|---|---|---|---|----|----|---|---|---|---|---|
| Positive .. | 46 | 33 | 8 | 3 | 2 | — | — | 23 | 19 | 1 | 1 | 2 | — | — |
| Doubtful . | — | — | — | — | — | — | — | 1 | — | — | — | 1 | — | — |

The total figure comprises the following number of :

| | | | | | | | | | | | | | | |
|-----------|-----|----|----|----|----|---|---|----|----|----|---|---|---|---|
| Men | 46 | 17 | 14 | 6 | 9 | — | — | 28 | 13 | 7 | 1 | 7 | — | — |
| Positive. | 13 | 11 | 1 | — | 1 | — | — | 12 | 10 | 1 | — | 1 | 1 | — |
| Women ... | 142 | 51 | 32 | 24 | 32 | 3 | — | 48 | 19 | 11 | 8 | 9 | — | — |
| Positive. | 33 | 22 | 7 | 3 | 1 | — | — | 11 | 9 | — | 1 | 1 | — | — |
| Doubtful | — | — | — | — | — | — | — | 1 | — | — | — | 1 | — | — |

Annex 14 (continued).

PERIOD OF OBSERVATION AFTER THE CONCLUSION OF TREATMENT.

United States of America.

1. WITH INTERMITTENT TREATMENT.

Cases remaining or becoming sero-negative.

Cases remaining sero-positive.

| Stage | Number of cases | Years | | | | | | Number of cases | Years | | | | | | | | |
|-------------------|-----------------|-------|---------|-----|-----|------|-------|-----------------|-------|---------|-----|-----|------|-------|---|---|---|
| | | 0 | Up to 1 | 1-2 | 2-5 | 5-10 | 10-15 | | 0 | Up to 1 | 1-2 | 2-5 | 5-10 | 10-15 | | | |
| S1 | 131 | 52 | 38 | 20 | 18 | 3 | — | — | — | — | — | — | — | — | — | — | — |
| S1 or S2 .. | 17 | 5 | 8 | 2 | 2 | — | — | 74 | 70 | 3 | — | 1 | — | — | — | — | — |
| S2 | 298 | 116 | 106 | 38 | 30 | 7 | 1 | 188 | 154 | 28 | 4 | 1 | 1 | — | — | — | — |
| S3 | 763 | 450 | 171 | 62 | 65 | 13 | 2 | 20 | 18 | 2 | — | — | — | — | — | — | — |
| S3 or S4 .. | 71 | 26 | 31 | 10 | 2 | 2 | — | 12 | 10 | — | 2 | — | — | — | — | — | — |
| S4 | 33 | 20 | 6 | 1 | 4 | 2 | — | 294 | 252 | 33 | 6 | 2 | 1 | — | — | — | — |
| S1-S4 .. | 1,313 | 669 | 360 | 133 | 121 | 27 | 3 | 177 | 153 | 18 | 4 | 1 | 1 | — | — | — | — |
| including men ... | 862 | 393 | 255 | 96 | 95 | 20 | 3 | 117 | 99 | 15 | 2 | 1 | — | — | — | — | — |
| women | 451 | 276 | 105 | 37 | 26 | 7 | — | | | | | | | | | | |

Serological relapses.

Clinical relapses.

| | | | | | | | | | | | | | | | | | |
|-------------|-----|-----|----|----|----|---|---|-----|-----|----|----|----|---|---|---|---|---|
| S1 | 11 | 7 | 1 | 1 | 2 | — | — | 17 | 13 | 3 | — | — | 1 | — | — | — | — |
| S1 or S2 .. | 1 | — | 1 | — | — | — | — | 2 | 1 | — | — | 1 | — | — | — | — | — |
| S2 | 48 | 25 | 19 | 1 | 2 | 1 | — | 49 | 35 | 1 | 5 | 6 | 2 | — | — | — | — |
| S3 | 181 | 121 | 36 | 8 | 10 | 6 | — | 133 | 106 | 11 | 4 | 8 | 4 | — | — | — | — |
| S3 or S4 .. | 16 | 10 | 5 | 1 | — | — | — | 4 | 3 | — | 1 | — | — | — | — | — | — |
| S4 | 16 | 8 | 6 | — | 1 | 1 | — | 7 | 4 | 1 | 1 | 1 | — | — | — | — | — |
| S1-S4 .. | 273 | 171 | 68 | 11 | 15 | 8 | — | 212 | 162 | 16 | 11 | 16 | 7 | — | — | — | — |

Of which, at the conclusion of observation, the following number were still :

| | | | | | | | | | | | | | | | | | |
|-------------|-----|----|----|---|---|---|---|----|----|---|---|---|---|---|---|---|---|
| Positive .. | 106 | 80 | 16 | 1 | 6 | 3 | — | 70 | 60 | 4 | 2 | 2 | 2 | — | — | — | — |
| Doubtful .. | 21 | 10 | 11 | — | — | — | — | 10 | 8 | 1 | 1 | — | — | — | — | — | — |

The total figure comprises the following number of :

| | | | | | | | | | | | | | | | | | |
|-------------|-----|-----|----|---|---|---|---|-----|-----|---|---|----|---|---|---|---|---|
| Men | 166 | 105 | 38 | 8 | 8 | 7 | — | 138 | 105 | 9 | 8 | 11 | 5 | — | — | — | — |
| Positive .. | 66 | 49 | 8 | 1 | 5 | 3 | — | 44 | 37 | 2 | 2 | 1 | 2 | — | — | — | — |
| Doubtful .. | 13 | 7 | 6 | — | — | — | — | 8 | 7 | — | 1 | — | — | — | — | — | — |
| Women ... | 107 | 66 | 30 | 3 | 7 | 1 | — | 74 | 57 | 7 | 3 | 5 | 2 | — | — | — | — |
| Positive .. | 40 | 31 | 8 | — | 1 | — | — | 26 | 23 | 2 | — | 1 | — | — | — | — | — |
| Doubtful .. | 8 | 3 | 5 | — | — | — | — | 2 | 1 | 1 | — | — | — | — | — | — | — |

2. WITH CONTINUOUS TREATMENT.

Cases remaining or becoming sero-negative.

| Stage | Number of cases | Years | | | | | |
|-------------------|-----------------|-------|---------|-----|-----|------|-------|
| | | 0 | Up to 1 | 1-2 | 2-5 | 5-10 | 10-15 |
| S1 | 75 | 40 | 15 | 12 | 7 | — | 1 |
| S1 or S2 .. | 5 | 2 | 2 | — | 1 | — | — |
| S2 | 106 | 51 | 35 | 8 | 11 | 1 | — |
| S3 | 319 | 190 | 60 | 35 | 23 | 11 | — |
| S3 or S4 .. | 12 | 10 | 2 | — | — | — | — |
| S4 | 9 | 4 | 3 | 1 | 1 | — | — |
| S1-S4 .. | 526 | 297 | 117 | 56 | 43 | 12 | 1 |
| Including men ... | 358 | 208 | 78 | 37 | 29 | 5 | 1 |
| women.. | 168 | 89 | 39 | 19 | 14 | 7 | — |

Cases remaining sero-positive.

| Number of cases | Years | | | | | |
|-----------------|-------|---------|-----|-----|------|-------|
| | 0 | Up to 1 | 1-2 | 2-5 | 5-10 | 10-15 |
| — | — | — | — | — | — | — |
| — | — | — | — | — | — | — |
| 6 | 5 | 1 | — | — | — | — |
| 22 | 18 | 4 | — | — | — | — |
| 2 | 1 | 1 | — | — | — | — |
| — | — | — | — | — | — | — |
| 30 | 24 | 6 | — | — | — | — |
| 15 | 12 | 3 | — | — | — | — |
| 15 | 12 | 3 | — | — | — | — |

Serological relapses.

| | | | | | | | |
|-------------|----|----|----|---|---|---|---|
| S1 | 3 | 1 | 1 | — | 1 | — | — |
| S1 or S2 .. | — | — | — | — | — | — | — |
| S2 | 13 | 8 | 3 | 1 | 1 | — | — |
| S3 | 28 | 18 | 8 | 1 | 1 | — | — |
| S3 or S4 .. | 1 | 1 | — | — | — | — | — |
| S4 | — | — | — | — | — | — | — |
| S1-S4 .. | 45 | 28 | 12 | 2 | 3 | — | — |

Clinical relapses.

| | | | | | | |
|---|---|---|---|---|---|---|
| 3 | 3 | — | — | — | — | — |
| 2 | 1 | — | 1 | — | — | — |
| — | — | — | — | — | — | — |
| — | — | — | — | — | — | — |
| 5 | 4 | — | 1 | — | — | — |

Of which, at the conclusion of observation, the following number were still :

| | | | | | | | |
|-------------|----|---|---|---|---|---|---|
| Positive .. | 16 | 9 | 5 | 1 | 1 | — | — |
| Doubtful : | 3 | 2 | 1 | — | — | — | — |

The total figure comprises the following number of :

| | | | | | | | |
|-----------|----|----|---|---|---|---|---|
| Men | 33 | 21 | 9 | 1 | 2 | — | — |
| Positive | 13 | 7 | 5 | — | 1 | — | — |
| Doubtful | 3 | 2 | 1 | — | — | — | — |
| Women ... | 12 | 7 | 3 | 1 | 1 | — | — |
| Positive | 3 | 2 | — | 1 | — | — | — |
| Doubtful | — | — | — | — | — | — | — |

Annex 14 (continued).

PERIOD OF OBSERVATION AFTER THE CONCLUSION OF TREATMENT.

France.

1. WITH INTERMITTENT TREATMENT.

Cases remaining or becoming sero-negative.

| Stage | Number of cases | Years | | | | | |
|-------------------|-----------------|-------|---------|-----|-----|------|-------|
| | | 0 | Up to 1 | 1-2 | 2-5 | 5-10 | 10-15 |
| S1 | 79 | 55 | 14 | 5 | 5 | — | |
| S1 or S2 .. | 20 | 11 | 5 | 1 | 3 | — | |
| S2 | 243 | 180 | 33 | 11 | 18 | 1 | |
| S3 | 215 | 141 | 45 | 16 | 12 | 1 | |
| S3 or S4 .. | 90 | 51 | 27 | 5 | 7 | — | |
| S4 | 6 | 3 | 2 | 1 | — | — | |
| S1-S4 .. | 653 | 441 | 126 | 39 | 45 | 2 | |
| including men ... | 408 | 275 | 80 | 26 | 27 | — | |
| women .. | 245 | 166 | 46 | 13 | 18 | 2 | |

Cases remaining sero-positive.

| Number of cases | Years | | | | | |
|-----------------|-------|---------|-----|-----|------|-------|
| | 0 | Up to 1 | 1-2 | 2-5 | 5-10 | 10-15 |
| — | — | — | — | — | — | — |
| 1 | 1 | — | — | — | — | — |
| 19 | 17 | 2 | — | — | — | — |
| 13 | 10 | 3 | — | — | — | — |
| 7 | 6 | 1 | — | — | — | — |
| 4 | 4 | — | — | — | — | — |
| 44 | 38 | 6 | — | — | — | — |
| 29 | 26 | 3 | — | — | — | — |
| 15 | 12 | 3 | — | — | — | — |

Serological relapses.

| | | | | | | | |
|-------------|------------------|----|----|---|---|---|--|
| S1 | 14 | 12 | 1 | 1 | — | — | |
| S1 or S2 .. | — | — | — | — | — | — | |
| S2 | 31 | 21 | 7 | 1 | 2 | — | |
| S3 | 37 | 29 | 3 | 2 | 3 | — | |
| S3 or S4 .. | 23 | 11 | 7 | 3 | 1 | 1 | |
| S4 | 2 | 2 | — | — | — | — | |
| S1-S4 .. | 107 ¹ | 75 | 18 | 7 | 6 | 1 | |

Clinical relapses.

| | | | | | | | |
|----|----|----|---|---|---|---|--|
| 8 | 7 | — | 1 | — | — | — | |
| 2 | 2 | — | — | — | — | — | |
| 22 | 17 | 5 | — | — | — | — | |
| 18 | 11 | 4 | 1 | 1 | 1 | — | |
| 2 | 1 | 1 | — | — | — | — | |
| — | — | — | — | — | — | — | |
| 52 | 38 | 10 | 2 | 1 | 1 | — | |

Of which, at the conclusion of observation, the following numbers were still :

| | | | | | | | |
|-------------|----|---|---|---|---|---|--|
| Positive .. | 12 | 8 | 4 | — | — | — | |
| Doubtful .. | 8 | 6 | 1 | 1 | — | — | |

| | | | | | | | |
|---|---|---|---|---|---|---|--|
| 8 | 5 | 3 | — | — | — | — | |
| 7 | 6 | 1 | — | — | — | — | |

The total figure comprises the following number of :

| | | | | | | | |
|-----------|----|----|---|---|---|---|--|
| Men | 68 | 50 | 9 | 4 | 4 | 1 | |
| Positive | 8 | 6 | 2 | — | — | — | |
| Doubtful | 2 | 2 | — | — | — | — | |
| Women ... | 39 | 25 | 9 | 3 | 2 | — | |
| Positive | 4 | 2 | 2 | — | — | — | |
| Doubtful | 6 | 4 | 1 | 1 | — | — | |

| | | | | | | | |
|----|----|---|---|---|---|---|--|
| 38 | 30 | 7 | 1 | — | — | — | |
| 6 | 4 | 2 | — | — | — | — | |
| 7 | 6 | 1 | — | — | — | — | |
| 14 | 8 | 3 | 1 | 1 | 1 | — | |
| 2 | 1 | 1 | — | — | — | — | |
| — | — | — | — | — | — | — | |

France.

2. WITH CONTINUOUS TREATMENT.

Cases remaining or becoming sero-negative.

Serological relapses.

| Stage | Number of cases | Years | | | | | | Number of cases | Years | | | | | | |
|-------------------|-----------------|-------|---------|-----|-----|------|--|-----------------|-------|---------|-----|-----|------|--|--|
| | | 0 | Up to 1 | 1-2 | 2-5 | 5-10 | | | 0 | Up to 1 | 1-2 | 2-5 | 5-10 | | |
| S1 | 5 | 2 | 1 | — | 2 | — | | 1 | 1 | — | — | — | — | | |
| S1 or S2 .. | — | | | | | | | — | | | | | | | |
| S2 | 7 | 1 | 1 | 4 | 1 | — | | — | | | | | | | |
| S3 | 4 | — | 3 | 1 | — | — | | 1 | — | 1 | — | — | — | | |
| S3 or S4 .. | 8 | 1 | 5 | 1 | 1 | — | | — | | | | | | | |
| S4 | — | | | | | | | — | | | | | | | |
| S1-S4 .. | 24 | 4 | 10 | 6 | 4 | — | | 2 | 1 | 1 | — | — | — | | |
| Including men ... | 15 | 2 | 5 | 5 | 3 | — | | | | | | | | | |
| women... | 9 | 2 | 5 | 1 | 1 | — | | | | | | | | | |

Of which, at the conclusion of observation, the following numbers were still :

| | | | | | | | | | | | | | | | |
|-------------|--|--|--|--|--|--|--|---|--|--|--|--|--|--|--|
| Positive .. | | | | | | | | | | | | | | | |
| Doubtful .. | | | | | | | | — | | | | | | | |

The total figure comprises the following number of :

| | | | | | | | | | | | | | | | |
|-----------|--|--|--|--|--|--|--|---|---|---|---|---|---|--|--|
| Men | | | | | | | | | | | | | | | |
| Women ... | | | | | | | | 2 | 1 | 1 | — | — | — | | |

2. WITH CONTINUOUS TREATMENT.

Cases remaining or becoming sero-negative.

| Stage | Number of cases | Years | | | | | |
|-------------------|-----------------|-------|---------|-----|-----|------|-------|
| | | 0 | Up to 1 | 1-2 | 2-5 | 5-10 | 10-15 |
| S1 | 4 | 1 | 3 | — | — | — | |
| S1 or S2 .. | — | | | | | | |
| S2 | 60 | 14 | 39 | 5 | 2 | — | |
| S3 | 1 | — | 1 | — | — | — | |
| S3 or S4 .. | 1 | — | — | 1 | — | — | |
| S4 | 2 | 1 | 1 | — | — | — | |
| S1-S4 .. | 68 | 16 | 44 | 6 | 2 | — | |
| including men ... | 65 | 15 | 43 | 6 | 1 | — | |
| women | 3 | 1 | 1 | — | 1 | — | |

Cases remaining sero-positive.

| Number of cases | Years | | | | | |
|-----------------|-------|---------|-----|-----|------|-------|
| | 0 | Up to 1 | 1-2 | 2-5 | 5-10 | 10-15 |
| — | | | | | | |
| 1 | — | 1 | — | — | — | |
| — | | | | | | |
| — | | | | | | |
| 1 | — | 1 | — | — | — | |
| 1 | — | 1 | — | — | — | |
| — | | | | | | |

Serological relapses.

| | | | | | | | |
|----------------------|---|---|---|---|---|---|--|
| S1 | 2 | — | 2 | — | — | — | |
| S2 | 6 | 2 | 3 | 1 | — | — | |
| S1-S4 (all men) | 8 | 2 | 5 | 1 | — | — | |

The total figure comprises the following number of :

| | | | | | | | |
|-------------|---|---|---|---|---|---|--|
| Positive .. | 1 | — | 1 | — | — | — | |
| Doubtful .. | 1 | — | 1 | — | — | — | |

Annex 15.

SURVEY OF THE NUMBERS AND RESULTS OF LUMBAR PUNCTURES AND THEIR DISTRIBUTION OVER THE VARIOUS STAGES.

Germany.

1. WITH INTERMITTENT TREATMENT (including D₁ cases).

| Stage | Number of lumbar punctures | | | | | | | | | | | | | | | | | | | | |
|---------------------|----------------------------|-----|-----|------------------|----|-----|---------------------------------------|---|-----|-----|---|----|------|---|----|-------|---|---|-------|---|---|
| | Total | M. | W. | During treatment | | | After conclusion of treatment (years) | | | | | | | | | | | | | | |
| | | | | + | ± | - | 0-2 | | | 2-5 | | | 5-10 | | | 10-15 | | | 15-20 | | |
| | | | | | | + | ± | - | + | ± | - | + | ± | - | + | ± | - | + | ± | - | |
| S1 | 43 | 36 | 7 | 3 | — | 17 | 1 | — | 8 | — | — | 11 | — | — | 3 | — | — | — | — | — | — |
| S1 or S2 | 2 | 2 | — | — | — | — | — | — | 1 | — | — | — | — | — | — | — | — | — | — | — | — |
| S2 | 134 | 80 | 54 | 30 | 4 | 61 | 4 | 1 | 16 | — | — | 10 | — | — | 6 | — | — | — | — | 1 | — |
| S1-S2 | 179 | 118 | 61 | 34 | 4 | 78 | 5 | 1 | 25 | — | — | 21 | — | — | 9 | — | — | — | — | 1 | — |
| including men | | 118 | | 22 | 1 | 45 | 3 | — | 19 | — | — | 19 | — | — | 7 | — | — | — | — | 1 | — |
| women | | | 61 | 12 | 3 | 33 | 2 | 1 | 6 | — | — | 2 | — | — | 2 | — | — | — | — | — | — |
| S3 | 284 | 161 | 123 | 56 | 32 | 122 | 6 | 1 | 38 | — | — | 18 | 1 | — | 9 | — | — | — | — | 1 | — |
| S3 or S4 | 249 | 80 | 169 | 54 | 16 | 123 | 7 | 3 | 31 | — | — | 11 | — | — | 2 | — | — | — | — | — | — |
| S4 | 67 | 46 | 21 | 16 | 5 | 30 | 1 | 1 | 10 | — | — | 3 | — | — | 1 | — | — | — | — | — | — |
| S3-S4 | 600 | 287 | 313 | 126 | 53 | 275 | 14 | 5 | 79 | — | — | 32 | 1 | — | 12 | — | — | — | — | 1 | — |
| including men | | 287 | | 59 | 24 | 127 | 7 | 3 | 37 | — | — | 21 | 1 | — | 7 | — | — | — | — | 1 | — |
| women | | | 313 | 67 | 29 | 148 | 7 | 2 | 42 | — | — | 11 | — | — | 5 | — | — | — | — | — | — |
| Total S1-S4 | 779 | 405 | 374 | 160 | 57 | 353 | 19 | 6 | 104 | — | — | 53 | 1 | — | 21 | — | — | — | — | 2 | — |
| including men | | 405 | | 81 | 25 | 172 | 10 | 3 | 56 | — | — | 40 | 1 | — | 14 | — | — | — | — | 2 | — |
| women | | | 374 | 79 | 32 | 181 | 9 | 3 | 48 | — | — | 13 | — | — | 7 | — | — | — | — | — | — |

2. WITH CONTINUOUS TREATMENT (including D₁ cases).

| | | | | | | | | | | | | | | | | | | | | | |
|---------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Total S1-S4 | 5 | 1 | 4 | 1 | — | 4 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| including men | | 1 | | — | — | 1 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| women | | | 4 | 1 | — | 3 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |

3. WITH PARTLY CONTINUOUS, PARTLY INTERMITTENT TREATMENT (including D₁ cases).

| | | | | | | | | | | | | | | | | | | | | | |
|---------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Total S1-S4 | 6 | 1 | 5 | 2 | — | 4 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| including men | | 1 | | 1 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| women | | | 5 | 1 | — | 4 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |

Denmark.

1. WITH INTERMITTENT TREATMENT (including D₁ cases).

| Stage | Number of lumbar punctures | | | | | | | | | | | | | | | | | |
|---------------------|----------------------------|----|----|------------------|---|----|---------------------------------------|---|----|-----|---|----|------|---|----|-------|--|--|
| | Total | M. | W. | During treatment | | | After conclusion of treatment (years) | | | | | | | | | | | |
| | | | | + | ± | — | 0-2 | | | 2-5 | | | 5-10 | | | 10-15 | | |
| | | | | | | | | | | | | | | | | | | |
| S1 | 17 | 15 | 2 | 1 | — | 1 | — | — | 5 | — | — | 6 | — | — | 4 | | | |
| S1 or S2 | 2 | 2 | — | — | — | — | — | — | 1 | — | — | 1 | — | — | — | | | |
| S2 | 15 | 11 | 4 | — | — | 2 | — | — | 7 | — | — | 6 | — | — | — | | | |
| S1-S2 | 34 | 28 | 6 | 1 | — | 3 | — | — | 13 | — | — | 13 | — | — | 4 | | | |
| including men | | 28 | 6 | 1 | — | 2 | — | — | 11 | — | — | 10 | — | — | 4 | | | |
| women | | | 6 | — | — | 1 | — | — | 2 | — | — | 3 | — | — | — | | | |
| S3 | 95 | 37 | 58 | 12 | — | 25 | — | — | 31 | 1 | — | 19 | — | — | 7 | | | |
| S3 or S4 | 1 | — | 1 | 1 | — | — | — | — | — | — | — | — | — | — | — | | | |
| S4 | 8 | 4 | 4 | 1 | — | 2 | — | — | 2 | — | — | 2 | — | — | 1 | | | |
| S3-S4 | 104 | 41 | 63 | 14 | — | 27 | — | — | 33 | 1 | — | 21 | — | — | 8 | | | |
| including men | | 41 | 63 | 5 | — | 11 | — | — | 14 | — | — | 6 | — | — | 5 | | | |
| women | | | 63 | 9 | — | 16 | — | — | 19 | 1 | — | 15 | — | — | 3 | | | |
| Total S1-S4 | 138 | 69 | 69 | 15 | — | 30 | — | — | 46 | 1 | — | 34 | — | — | 12 | | | |
| including men | | 69 | 69 | 6 | — | 13 | — | — | 25 | — | — | 16 | — | — | 9 | | | |
| women | | | 69 | 9 | — | 17 | — | — | 21 | 1 | — | 18 | — | — | 3 | | | |

2 and 3. No continuous or partly continuous and partly intermittent treatment.

United States of America.

1. WITH INTERMITTENT TREATMENT (including D₁ cases).

| | | | | | | | | | | | | | | | | | | |
|---------------------|-------|-----|-----|-----|-----|-----|----|---|-----|---|---|----|---|---|----|---|---|---|
| S1 | 98 | 96 | 2 | 13 | 6 | 51 | 2 | — | 19 | — | — | 6 | 1 | — | — | — | — | — |
| S1 or S2 | 14 | 11 | 3 | 1 | — | 10 | — | — | 3 | — | — | — | — | — | — | — | — | — |
| S2 | 164 | 135 | 29 | 17 | 16 | 104 | 3 | — | 18 | — | — | 5 | 1 | — | — | — | — | — |
| S1-S2 | 276 | 242 | 34 | 31 | 22 | 165 | 5 | — | 40 | — | — | 11 | 2 | — | — | — | — | — |
| including men | | 242 | 34 | 28 | 17 | 143 | 4 | — | 37 | — | — | 11 | 2 | — | — | — | — | — |
| women | | | 34 | 3 | 5 | 22 | 1 | — | 3 | — | — | — | — | — | — | — | — | — |
| S3 | 972 | 543 | 429 | 165 | 88 | 587 | 8 | 5 | 85 | — | — | 23 | — | — | 9 | 1 | — | 1 |
| S3 or S4 | 28 | 6 | 22 | 6 | — | 18 | 1 | — | 2 | — | — | 1 | — | — | — | — | — | — |
| S4 | 95 | 69 | 26 | 27 | 8 | 44 | 3 | — | 11 | — | — | — | — | 2 | — | — | — | — |
| S3-S4 | 1,095 | 618 | 477 | 198 | 96 | 649 | 12 | 5 | 98 | — | — | 24 | — | — | 11 | 1 | — | 1 |
| including men | | 618 | 477 | 107 | 58 | 355 | 9 | 4 | 63 | — | — | 14 | — | — | 6 | 1 | — | 1 |
| women | | | 477 | 91 | 38 | 294 | 3 | 1 | 35 | — | — | 10 | — | — | 5 | — | — | — |
| Total S1-S4 | 1,371 | 860 | 511 | 229 | 118 | 814 | 17 | 5 | 138 | — | — | 35 | 2 | — | 11 | 1 | — | 1 |
| including men | | 860 | 511 | 135 | 75 | 498 | 13 | 4 | 100 | — | — | 25 | 2 | — | 6 | 1 | — | 1 |
| women | | | 511 | 94 | 43 | 316 | 4 | 1 | 38 | — | — | 10 | — | — | 5 | — | — | — |

Annex 15 (continued.)

SURVEY OF THE NUMBERS AND RESULTS OF LUMBAR PUNCTURES AND THEIR DISTRIBUTION
OVER THE VARIOUS STAGES.

United States of America (continued).

2. WITH CONTINUOUS TREATMENT (including D₁ cases).

| Stage | Number of lumbar punctures | | | | | | | | | | | | | | |
|---------------------|----------------------------|-----|-----|------------------|----|-----|---------------------------------------|---|----|-----|---|----|------|---|---|
| | Total | M. | W. | During treatment | | | After conclusion of treatment (years) | | | | | | | | |
| | | | | + | ± | — | 0-2 | | | 2-5 | | | 5-10 | | |
| | | | | | | | | | | | | | | | |
| S1 | 52 | 47 | 5 | 4 | — | 27 | 1 | — | 17 | — | — | 2 | — | — | 1 |
| S1 or S2 | 5 | 4 | 1 | 2 | 1 | 1 | — | — | 1 | — | — | — | — | — | — |
| S2 | 70 | 53 | 17 | 4 | 4 | 44 | — | — | 17 | — | — | 1 | — | — | — |
| S1-S2 | 127 | 104 | 23 | 10 | 5 | 72 | 1 | — | 35 | — | — | 3 | — | — | 1 |
| including men | | 104 | | 9 | 4 | 58 | 1 | — | 28 | — | — | 3 | — | — | 1 |
| women..... | | | 23 | 1 | 1 | 14 | — | — | 7 | — | — | — | — | — | — |
| S3 | 324 | 189 | 135 | 35 | 9 | 201 | 1 | 1 | 62 | — | — | 11 | — | — | 4 |
| S3 or S4 | 5 | 5 | — | — | — | 3 | — | — | 1 | — | — | — | — | — | — |
| S4 | 11 | 8 | 3 | 3 | 2 | 5 | — | — | 1 | — | — | — | — | — | — |
| S3-S4 | 340 | 202 | 138 | 39 | 11 | 209 | 1 | 1 | 64 | — | — | 11 | — | — | 4 |
| including men | | 202 | | 30 | 7 | 116 | 1 | 1 | 38 | — | — | 7 | — | — | 2 |
| women..... | | | 138 | 9 | 4 | 93 | — | — | 26 | — | — | 4 | — | — | 2 |
| Total S1-S4 | 467 | 306 | 161 | 49 | 16 | 279 | 2 | 1 | 99 | — | — | 14 | — | — | 5 |
| including men | | 306 | | 39 | 11 | 174 | 2 | 1 | 66 | — | — | 10 | — | — | 3 |
| women..... | | | 161 | 10 | 5 | 105 | — | — | 33 | — | — | 4 | — | — | 2 |

3. WITH PARTLY CONTINUOUS AND PARTLY INTERMITTENT TREATMENT (including D₁ cases).

| | | | | | | | | | | | | | | | |
|---------------------|-----|-----|-----|----|----|-----|---|---|----|---|---|----|---|---|---|
| S1 | 35 | 34 | 1 | 8 | — | 16 | 2 | — | 5 | 1 | — | 2 | — | — | 1 |
| S1 or S2 | 8 | 8 | — | 2 | — | 3 | — | — | 2 | — | — | 1 | — | — | — |
| S2 | 119 | 106 | 13 | 17 | 14 | 68 | 2 | — | 14 | — | — | 4 | — | — | — |
| S1-S2 | 162 | 148 | 14 | 27 | 14 | 87 | 4 | — | 21 | 1 | — | 7 | — | — | 1 |
| including men | | 148 | | 24 | 13 | 78 | 4 | — | 20 | 1 | — | 7 | — | — | 1 |
| women..... | | | 14 | 3 | 1 | 9 | — | — | 1 | — | — | — | — | — | — |
| S3 | 396 | 211 | 185 | 57 | 20 | 255 | 2 | 2 | 53 | — | — | 5 | — | — | 2 |
| S3 or S4 | 7 | 4 | 3 | 1 | — | 4 | — | 1 | 1 | — | — | — | — | — | — |
| S4 | 25 | 20 | 5 | 6 | 1 | 11 | — | — | 4 | — | — | — | — | — | — |
| S3-S4 | 428 | 235 | 193 | 64 | 21 | 273 | 2 | 3 | 58 | — | — | 5 | — | — | 2 |
| including men | | 235 | | 39 | 10 | 144 | 2 | 3 | 34 | — | — | 2 | — | — | 1 |
| women..... | | | 193 | 25 | 11 | 129 | — | — | 24 | — | — | 3 | — | — | 1 |
| Total S1-S4 | 590 | 383 | 207 | 91 | 35 | 360 | 6 | 3 | 79 | 1 | — | 12 | — | — | 3 |
| including men | | 383 | | 63 | 23 | 222 | 6 | 3 | 54 | 1 | — | 9 | — | — | 2 |
| women..... | | | 207 | 28 | 12 | 138 | — | — | 25 | — | — | 3 | — | — | 1 |

France.

1. WITH INTERMITTENT TREATMENT (including D₁ cases).

| Stage | Number of lumbar punctures | | | | | | | | | | | | | | |
|---------------------|----------------------------|----|----|------------------|---|----|---------------------------------------|---|----|-----|---|---|------|---|---|
| | Total | M. | W. | During treatment | | | After conclusion of treatment (years) | | | | | | | | |
| | | | | + | ± | - | 0-2 | | | 2-5 | | | 5-10 | | |
| | | | | | | | + | ± | - | + | ± | - | + | ± | - |
| S1 | 7 | 7 | — | 1 | — | — | — | — | 6 | — | — | — | — | — | — |
| S1 or S2 | 2 | 2 | — | — | — | — | — | 1 | — | — | — | 1 | — | — | — |
| S2 | 25 | 25 | — | — | — | 5 | 1 | — | 17 | — | — | 2 | — | — | — |
| S1-S2 | 34 | 34 | — | 1 | — | 5 | 1 | — | 24 | — | — | 3 | — | — | — |
| all men | | | | | | | | | | | | | | | |
| S3 | 35 | 21 | 14 | 1 | — | 4 | 1 | — | 26 | — | — | 3 | — | — | — |
| S3 or S4 | 5 | 4 | 1 | — | — | 2 | — | — | 3 | — | — | — | — | — | — |
| S4 | 5 | 4 | 1 | — | — | 3 | — | — | 2 | — | — | — | — | — | — |
| S3-S4 | 45 | 29 | 16 | 1 | — | 9 | 1 | — | 31 | — | — | 3 | — | — | — |
| including men | | 29 | | 1 | — | 7 | 1 | — | 19 | — | — | 1 | — | — | — |
| women... | | | 16 | — | — | 2 | — | — | 12 | — | — | 2 | — | — | — |
| Total S1-S4 | 79 | 63 | 16 | 2 | — | 14 | 2 | — | 55 | — | — | 6 | — | — | — |
| including men | | 63 | | 2 | — | 12 | 2 | — | 43 | — | — | 4 | — | — | — |
| women... | | | 16 | — | — | 2 | — | — | 12 | — | — | 2 | — | — | — |

2. WITH CONTINUOUS TREATMENT (including D₁ cases).

| | | | | | | | | | | | | | | | |
|---------------------|---|---|---|---|---|---|---|---|---|--|--|--|--|--|--|
| Total S1-S4 | 3 | 2 | 1 | — | — | — | — | — | 3 | | | | | | |
| including men | | 2 | | — | — | — | — | — | 2 | | | | | | |
| women... | | | 1 | — | — | — | — | — | 1 | | | | | | |

3. WITH PARTLY CONTINUOUS, PARTLY INTERMITTENT TREATMENT (including D₁ cases).

| | | | | | | | | | | | | | | | |
|---------------------|---|---|---|---|---|---|---|---|---|---|---|---|--|--|--|
| Total S1-S4 | 7 | 5 | 2 | 1 | — | 2 | 1 | — | 2 | — | — | 1 | | | |
| including men | | 5 | | 1 | — | 2 | 1 | — | 1 | — | — | 1 | | | |
| women... | | | 2 | — | — | — | — | — | 1 | — | — | — | | | |

Annex 15 (concluded).

**SURVEY OF THE NUMBERS AND RESULTS OF LUMBAR PUNCTURES AND THEIR DISTRIBUTION
OVER THE VARIOUS STAGES.**

Great Britain.

1. WITH INTERMITTENT TREATMENT (including D₁ cases).

| Stage | Number of lumbar punctures | | | | | | | | | | | | | | |
|---------------------|----------------------------|-----|----|------------------|---|----|---------------------------------------|---|-----|-----|---|----|------|---|---|
| | Total | M. | W. | During treatment | | | After conclusion of treatment (years) | | | | | | | | |
| | | | | + | ± | — | 0-2 | | | 2-5 | | | 5-10 | | |
| | | | | | | + | ± | — | + | ± | — | + | ± | — | |
| S1 | 88 | 88 | — | 2 | — | 27 | — | — | 42 | — | — | 16 | — | — | 1 |
| S1 or S2 | 82 | 79 | 3 | — | — | 18 | 3 | — | 40 | 1 | 1 | 19 | — | — | — |
| S2 | 170 | 167 | 3 | 2 | — | 45 | 3 | — | 82 | 1 | 1 | 35 | — | — | 1 |
| S1-S2 | 167 | 167 | 3 | 2 | — | 42 | 3 | — | 82 | 1 | 1 | 35 | — | — | 1 |
| including men | | | | — | — | 3 | — | — | — | — | — | — | — | — | — |
| women | | | 3 | — | — | — | — | — | — | — | — | — | — | — | — |
| S3 | 88 | 68 | 20 | 6 | 1 | 24 | — | — | 29 | — | — | 28 | — | — | — |
| S3 or S4 | 42 | 36 | 6 | 5 | 1 | 15 | — | — | 13 | — | — | 7 | — | — | 1 |
| S4 | 3 | 2 | 1 | — | — | 1 | — | — | 1 | — | — | 1 | — | — | — |
| S3-S4 | 133 | 106 | 27 | 11 | 2 | 40 | — | — | 43 | — | — | 36 | — | — | 1 |
| including men | | 106 | | 9 | 2 | 37 | — | — | 40 | — | — | 17 | — | — | 1 |
| women | | | 27 | 2 | — | 3 | — | — | 3 | — | — | 19 | — | — | — |
| Total S1-S4 | 303 | 273 | 30 | 13 | 2 | 85 | 3 | — | 125 | 1 | 1 | 71 | — | — | 2 |
| including men | | 273 | | 11 | 2 | 79 | 3 | — | 122 | 1 | 1 | 52 | — | — | 2 |
| women | | | 30 | 2 | — | 6 | — | — | 3 | — | — | 19 | — | — | — |

2. WITH CONTINUOUS TREATMENT (including D₁ cases).

| | | | | | | | | | | | | | | | |
|-------------------|----|----|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Total S1-S4 | 18 | 18 | — | — | — | 9 | — | — | 9 | — | — | — | — | — | — |
| all men | | | | | | | | | | | | | | | |

3. WITH PARTLY CONTINUOUS, PARTLY INTERMITTENT TREATMENT (including D₁ cases).

| | | | | | | | | | | | | | | | |
|-------------------|----|----|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Total S1-S4 | 11 | 11 | — | 1 | — | 4 | — | — | 6 | — | — | — | — | — | — |
| all men | | | | | | | | | | | | | | | |

Annex 16.

SURVEY OF THE VARIOUS KINDS OF CLINICAL RELAPSE.

Germany.

1. WITH INTERMITTENT TREATMENT (excluding D₁ cases). *Stage of relapse.*

| Stage at the beginning of treatment | Chancre redux | | | Secondary syphilis | | | Tertiary syphilis | | | | | | Late syphilis of the liver, etc. | | | Syphilis of the brain and spinal marrow | | | | |
|-------------------------------------|---------------|----|----|--------------------|----|----|-------------------|----|----|-----------------|----|----|----------------------------------|----|----|---|----|----|-------------------------------------|--|
| | Total | M. | W. | Total | M. | W. | Of the skin | | | Cardio vascular | | | Total | M. | W. | Total | M. | W. | | |
| | | | | | | | Total | M. | W. | Total | M. | W. | | | | | | | | |
| S1 | 1 | 1 | — | 26 | 21 | 5 | 1 | 1 | — | — | — | — | — | — | — | — | — | — | — | |
| S1 or S2 | — | — | — | 1 | 1 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | |
| S2 | 1 | 1 | — | 38 | 24 | 14 | 3 | 3 | — | — | — | — | — | — | — | — | — | — | — | |
| S3 | 1 | 1 | — | 41 | 23 | 18 | 5 | 3 | 2 | 2 | 2 | — | 2 | 2 | — | — | — | 4 | 3 | |
| S3 or S4 | — | — | — | 52 | 17 | 35 | 2 | — | 2 | 1 | 1 | — | — | — | — | — | — | 6 | 3 | |
| S4 | — | — | — | 1 | 1 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | |
| S1-S4 | 3 | 3 | — | 159 | 87 | 72 | 11 | 7 | 4 | 3 | 3 | — | 2 | 2 | — | — | — | 10 | 6 | |
| | | | | | | | | | | | | | | | | | | | 4 | |
| | | | | | | | | | | | | | | | | | | | (Including 1 tabes and 1 paralysis) | |

Relapses under secondary syphilis include :

3 cases of iritis (men).

5 neuro-relapses (2 men and 3 women).

Repeated relapses in the same case have been excluded, as follows :

| | Total | M. | W. |
|--|-------|----|----|
| Tertiary syphilis of the skin | 3 | 3 | — |
| Late syphilis of the liver, etc. | 2 | 2 | — |
| Syphilis of brain and spinal marrow (paralysis) | 1 | 1 | — |

2. WITH CONTINUOUS TREATMENT (excluding D₁ cases). *Stage of relapse.*

| | | | | | | | | | | | | | | | | | | | | |
|-------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| S1-S4 | — | — | — | 1 | 1 | — | 1 | 1 | — | — | — | — | — | — | — | — | — | — | — | — |
|-------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|

Annex 16 (continued).

**SURVEY OF THE VARIOUS KINDS OF CLINICAL RELAPSE.
Denmark.**

1. WITH INTERMITTENT TREATMENT.

| Stage at the beginning of treatment | Chancere redux | | | Secondary syphilis | | | Tertiary syphilis | | | | | | Late syphilis of the liver, etc. | | | Syphilis of the brain and spinal marrow | | | |
|-------------------------------------|----------------|----------|----------|--------------------|-----------|-----------|-------------------|----------|----------|-----------------|----------|----------|----------------------------------|----------|----------|---|----------|----------|----------|
| | Total | M. | W. | Total | M. | W. | Of the skin | | | Cardio vascular | | | Total | M. | W. | Total | M. | W. | |
| | | | | | | | Total | M. | W. | Total | M. | W. | | | | | | | |
| S1 | 1 | 1 | — | 5 | 2 | 3 | — | — | — | — | — | — | — | — | — | — | — | — | — |
| S1 or S2 | — | — | — | 2 | 1 | 1 | — | — | — | — | — | — | — | — | — | — | — | — | — |
| S2 | 2 | 2 | — | 9 | 4 | 5 | 2 | 2 | — | — | — | — | — | — | — | — | — | — | — |
| S3 | — | — | — | 53 | 15 | 38 | — | — | — | — | — | — | — | — | — | — | — | — | — |
| S3 or S4 | 1 | 1 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| S4 | — | — | — | 1 | — | 1 | — | — | — | — | — | — | — | — | — | — | — | — | — |
| S1-S4 | 4 | 4 | — | 70 | 22 | 48 | 2 | 2 | — | — | — | — | — | — | — | — | — | — | — |

Repeated relapses in the same case have been excluded as follows :
Tertiary syphilis of the skin : total 5, no men, 5 women.

2. WITH CONTINUOUS TREATMENT (not used).

United States of America.

1. WITH INTERMITTENT TREATMENT (excluding D₁ cases). Stage of relapse.

| | | | | | | | | | | | | | | | | | | | |
|--------------------|----------|----------|----------|------------|------------|-----------|-----------|----------|-----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
| S1 | — | — | — | 17 | 16 | 1 | — | — | — | — | — | — | — | — | — | — | — | — | — |
| S1 or S2 | — | — | — | 2 | 2 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| S2 | 1 | 1 | — | 40 | 35 | 5 | 5 | 4 | 1 | 2 | 1 | 1 | — | — | — | — | 1 | — | 1 |
| S3 | — | — | — | 110 | 63 | 47 | 14 | 4 | 10 | 6 | 4 | 2 | — | — | — | — | 3 | 2 | 1 |
| S3 or S4 | — | — | — | 2 | 2 | — | 1 | — | 1 | — | — | — | — | — | — | — | 1 | — | 1 |
| S4 | — | — | — | 4 | 2 | 2 | 2 | 1 | 1 | — | — | — | — | — | — | — | 1 | — | — |
| S1-S4 | 1 | 1 | — | 175 | 120 | 55 | 22 | 9 | 13 | 8 | 5 | 3 | — | — | — | — | 6 | 3 | 3 |

Relapses under secondary syphilis include :
39 neuro-relapses (28 men, 11 women).

Repeated relapses in the same case have been excluded, as follows :

| | Total | M. | W. |
|---|-------|----|----|
| Tertiary syphilis of the skin..... | 5 | 4 | 1 |
| Tertiary cardio vascular | 1 | — | 1 |
| Syphilis of brain and spinal marrow | 2 | 1 | 1 |

2. WITH CONTINUOUS TREATMENT (excluding D₁ cases). Stage of relapse.

| | | | | | | | | | | | | | | | | | | | |
|--------------------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
| S1 | — | — | — | 3 | 3 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| S1 or S2 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| S2 | — | — | — | 1 | 1 | — | — | — | — | — | — | — | — | — | — | — | 1 | — | — |
| S1-S4 | — | — | — | 4 | 4 | — | — | — | — | — | — | — | — | — | — | — | 1 | — | — |

Relapses under secondary syphilis include :
2 neuro-relapses (men).

France.

1. WITH INTERMITTENT TREATMENT (excluding D₁ cases). Stage of relapse.

| Stage at the beginning of treatment | Chancre redux | | | Secondary syphilis | | | Tertiary syphilis | | | | | | Late syphilis of the liver, etc. | | | Syphilis of the brain and spinal marrow | | | |
|-------------------------------------|---------------|----|----|--------------------|----|----|-------------------|----|----|-----------------|----|----|----------------------------------|----|----|---|----|----|---|
| | Total | M. | W. | Total | M. | W. | Of the skin | | | Cardio vascular | | | Total | M. | W. | Total | M. | W. | |
| | | | | | | | Total | M. | W. | Total | M. | W. | | | | | | | |
| S1 | — | — | — | 8 | 8 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| S1 or S2 | — | — | — | 1 | — | 1 | 1 | 1 | — | — | — | — | — | — | — | — | — | — | — |
| S2 | — | — | — | 19 | 17 | 2 | 2 | 2 | — | — | — | — | — | — | — | — | — | — | — |
| S3 | — | — | — | 18 | 8 | 10 | — | — | — | — | — | — | — | — | — | — | — | — | — |
| S3 or S4 | — | — | — | 2 | 1 | 1 | — | — | — | — | — | — | — | — | — | — | — | — | — |
| S4 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| S1-S4 | — | — | — | 48 | 34 | 14 | 3 | 3 | — | — | — | — | — | — | — | — | — | — | — |

Relapses under secondary syphilis include :
1 neuro-relapse (man).

Repeated relapses in the same case are excluded as follows :

| | Total | M. | W. |
|---|-------|----|----|
| Tertiary syphilis of the skin | 1 | 1 | — |
| Syphilis of brain and spinal marrow | 1 | 1 | — |

2. WITH CONTINUOUS TREATMENT (excluding D₁ cases). No relapses.

Great Britain.

1. WITH INTERMITTENT TREATMENT (excluding D₁ cases). Stage of relapse.

| | | | | | | | | | | | | | | | | | | | |
|----------------|----|----|---|----|----|----|---|---|---|---|---|---|---|---|---|---|---|---|---|
| S1 | 9 | 8 | 1 | 9 | 9 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| S1 or S2 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| S2 | 7 | 7 | — | 18 | 17 | 1 | 1 | 1 | — | 1 | 1 | — | — | — | — | — | — | — | — |
| S3 | — | — | — | 12 | 6 | 6 | 2 | 2 | — | — | — | — | — | — | — | — | — | — | — |
| S3 or S4 | — | — | — | 12 | 6 | 6 | 1 | 1 | — | — | — | — | — | — | — | — | — | — | — |
| S4 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| S1-S4 | 16 | 15 | 1 | 51 | 38 | 13 | 4 | 4 | — | 1 | 1 | — | — | — | — | — | — | — | — |

Relapses under secondary syphilis include :
2 neuro-relapses (men).

2. WITH CONTINUOUS TREATMENT (excluding D₁ cases). No relapses.

SYPHILIS TREATMENT

Annex 17.

SURVEY OF THE NUMBER OF COURSES OF TREATMENT GIVEN
TO INTERMITTENTLY TREATED CASES (EXCLUDING D, CASES)
IN THE PARTICIPATING COUNTRIES, DIVIDED BY STAGES.

| | One | Two | More than two courses in the percentage of cases shown | |
|---------------------|-------|-------|---|--|
| S1 : | | | | |
| Germany | 37.82 | 35.24 | 26.94 | |
| Denmark | 17.24 | 22.88 | 59.88 | |
| United States | 24.22 | 39.75 | 36.06 | |
| France | 1.94 | 1.94 | 96.12 | |
| Great Britain..... | 8.86 | 47.73 | 43.41 | |
| | | | | |
| | One | Two | Three to five | More than five (six to twenty) courses |
| S1 or S2 : | | | | |
| Germany | 11.11 | 44.44 | 44.44 | — |
| Denmark | — | 4.69 | 51.56 | 43.75 |
| United States | 14.29 | 42.86 | 33.33 | 9.52 |
| France | — | 4.0 | 48.00 | 48.00 |
| Great Britain..... | — | 25.0 | 75.00 | — |
| | | | | |
| | | | | More than five courses |
| S2 : | | | | |
| Germany | 23.91 | 32.07 | 39.24 | 4.78 |
| Denmark | 7.99 | 13.08 | 61.02 | 17.92 |
| United States | 14.49 | 36.03 | 42.65 | 6.83 |
| France | 0.93 | 2.48 | 44.89 | 51.70 |
| Great Britain..... | 10.20 | 31.57 | 51.86 | 6.37 |
| | | | | |
| | | | | More than five (six to twenty) courses |
| S3 : | | | | |
| Germany | 17.15 | 33.16 | 45.14 | 4.55 |
| Denmark | 3.62 | 10.43 | 58.20 | 27.75 |
| United States | 8.30 | 28.69 | 50.03 | 12.97 |
| France | — | 2.38 | 39.58 | 58.04 |
| Great Britain..... | 9.26 | 28.08 | 50.19 | 12.45 |
| | | | | |
| | | | | More than five (six to twenty) courses |
| S3 or S4 : | | | | |
| Germany | 16.26 | 29.18 | 51.11 | 6.45 |
| Denmark | 7.58 | 13.64 | 51.52 | 27.26 |
| United States | 6.67 | 20.83 | 67.50 | 5.00 |
| France | — | 5.01 | 45.11 | 51.88 |
| Great Britain..... | 5.31 | 24.62 | 55.94 | 14.13 |
| | | | | |
| | | | | More than five courses |
| S4 : | | | | |
| Germany | 13.53 | 30.59 | 45.29 | 10.59 |
| Denmark | 7.50 | 17.50 | 50.00 | 25.00 |
| United States | 16.17 | 29.34 | 43.11 | 11.28 |
| France | — | 2.70 | 35.14 | 62.16 |
| Great Britain..... | — | 28.21 | 46.15 | 25.64 |
| | | | | |
| TOTAL FIGURES | | | | |
| S1 to S4 : | | | | |
| Germany | 20.51 | 31.79 | 43.70 | 4.01 |
| Denmark | 6.36 | 12.68 | 58.42 | 22.54 |
| United States | 11.12 | 30.68 | 47.86 | 10.34 |
| France | 0.52 | 2.51 | 48.28 | 48.69 |
| Great Britain..... | 8.41 | 31.43 | 51.03 | 9.13 |

Part Two.**RECOMMENDATIONS.**

The above report was examined by the group of Experts referred to on page 129, whose composition had since undergone the following modifications :

Professor L. QUEYRAT (deceased) was succeeded by Professor H. GOUGEROT, Director of the " Clinique des maladies cutanées et syphilitiques de la Faculté de Médecine de Paris " (Hôpital St.-Louis), who took part for the first time in the work of the Group.

Professor C. RASCH was replaced by Dr. Svend LOMHOLT, Director of the Dermatological Clinic of " Finsens Lysinstitut (Copenhagen) ".

The report and the following recommendations were also examined and approved from the statistical point of view by Professor Harald WESTERGAARD (Copenhagen).

In adopting the report, the Experts extended to Professor MARTENSTEIN their heartiest congratulations and warmest thanks upon the truly distinguished performance of his difficult task.

They agreed upon the following recommendations dictated by their experience and the principles brought out by the international study of the records submitted by the various clinics :

1. *Treatment should be recommended as early as possible in the sero-negative primary stage. In this connection, the fullest possible use should be made, for purposes of diagnosis, of the microscopical examination of secretions from primary lesions or from lymph glands.*

2. *It should be emphasised that, prior to the institution of either of the systems of treatment outlined below, there should be an adequate physical examination to determine the absence or otherwise of any indication for caution in respect of the dosage.*

3. *It is essential that, in carrying out the treatment, a strict supervision of the patient be exercised, especially in respect of mucous membranes, skin, kidneys and liver.*

4. *Observation, clinical and serological, after completion of treatment should be adequate and in any case for not less than three years.*

5. *Adequate examination of the spinal fluid, at least before dismissal from observation, is essential.*

6. *The principles to be followed in carrying out the actual treatment should be as follows :*

(a) *To employ a comparatively heavy individual dosage of the arsenobenzene and of the bismuth or mercurial compounds, the doses being administered in comparatively rapid succession, especially at the commencement ;*

(b) *To maintain a persistent attack on the disease, avoiding intervals of such length as to afford the parasite an opportunity of recovering ;*

(c) *To administer approximately as much treatment to primary as to secondary cases.*

7. *The material studied does not enable a clear decision to be made as to the relative merits of intermittent treatment with courses of injections in rapid succession separated by rest intervals of some weeks and continuous treatment as defined on pages 149 and 150 of Professor MARTENSTEIN's report, or between the simultaneous employment of both arsenical and bismuth or mercury, and the system in which bismuth and mercury are withheld until a number of arsenical injections have been administered.*

Nevertheless, it seems practicable, from the results of the analysis and from the personal experience of the Experts, to formulate a system of intermittent treatment and one of continuous treatment, either of which can be expected to yield satisfactory results in ordinary cases or early syphilis.

It seems possible that the intermittent treatment which is suggested below may in effect be continuous, or practically continuous, treatment, owing to the continued absorption of bismuth from the sites of the injection for some weeks after any temporary suspension of the treatment.

PLAN OF INTERMITTENT TREATMENT.

1. MALES.

For adult males of average weight aged less than 50 years and in whom there is no contra-indication, a number of courses of injections

on the plan described below. It should be said that, at the beginning of this course, some administer at once the full weekly dose (0.60 gramme to 0.75 gramme), whilst others divide it into two doses (e.g., 0.30 gramme and 0.45 gramme) so far as the first week is concerned.

| Week | " 914 " | " 606 " | Insoluble compound of bismuth * containing bi-metal |
|----------------|--------------------|----------------------|---|
| 1st | 0.6 to 0.75 gramme | or 0.4 to 0.5 gramme | and 0.20 to 0.24 gramme |
| 2nd | " | " " | " " |
| 3rd | " | " " | " " |
| 4th | " | " " | " " |
| 5th | " | " " | " " |
| 6th | " | " " | " " |
| 7th | " | " " | " " |
| 8th | " | " " | " " |
| 9th | | | 0.20 to 0.24 gramme |
| 10th | | | 0.20 to 0.24 gramme |

It is recommended that :

(a) In cases which remain or become serologically negative during, or by the end of, the first course, four such courses be administered, with intervals of three to five weeks between any two courses.

(b) In cases which have not become sero-negative by the end of the first course, in addition to the amount of treatment shown in (a), further courses should be administered until the patient has received as a minimum three beyond that which has ended with negative serum reactions. At the option of the individual clinician, this treatment may be prolonged as may be considered necessary.

(c) Cases presenting signs of clinical relapse of an early type should be dealt with on principles similar to those enunciated in (b).

* (1) By *insoluble* bismuth is here meant compounds of a very slight solubility in water. They should therefore be given in suspension—those of extremely slight solubility (the oxychloride, etc.) usually in a watery suspension, those that are more soluble (the subsalicylate, the iodo-bismuthate of quinine, the alkaline tartrates, etc.) suspended in a vegetable oil. If a *liposoluble* compound (e.g., the camphocarboxylate, etc.) is preferred, it is desirable that the injection be given twice weekly in half-doses.

The dosage of all bismuth compounds should be calculated according to their content in bismuth metal.

(2) As an alternative to bismuth, a course of mercury may be given, either in the form of inunctions (forty days at 3 grammes of *Unguentum hydrargyri*) or of injections (70 milligrammes calomel or 120 milligrammes salicylate of mercury, etc., suspended in a suitable base).

2. FEMALES.

For females (non-pregnant), treatment should be administered on the plan outlined for males, with the exception that the single dose of "914" should be reduced by 0.15 gramme and that of "606" by 0.1 gramme.

In the event of any reduction in the amount of treatment being indicated, it is recommended that this be effected by reducing the number of arsenical injections rather than by reducing the individual dose or increasing the interval.

**PLAN OF ALTERNATING CONTINUOUS TREATMENT
FOR EARLY SYPHILIS.**

| Day or week | "606" | Interim treatment | Serol. test | Remarks |
|-------------|---------|--|-------------|---|
| Day | | | | |
| 1 | 0.3-0.6 | | 1 | "606" dosage for first three injections at level of 0.1 gramme for each 25 pounds (11.3 kg.) body weight. Average subsequent dosage, 0.4 gramme, men; 0.3 gramme, women, the fourth and subsequent injections in the first course at weekly intervals. In average patient, all lesions heal rapidly and blood serological reaction becomes negative during first course. If "606" cannot be used, substitute 8 to 10 doses 0.3 gramme silver arsphenamine (silver salvarsan, silver arsenobenzol, etc.) or 10 to 12 doses "914" (0.45-0.6 gramme maximum for women and 0.6-0.75 gramme for men). This applies also to subsequent courses. |
| 5 | 0.3-0.6 | | | |
| 10 | 0.3-0.6 | | | |
| Week | | | | |
| 3 | 0.4 | | | |
| 4 | 0.4 | | | |
| 5 | 0.4 | | | |
| 6 | 0.4 | | | |
| 7 | 0.4 | | | |
| 8 | | Bismuth, 4 doses, | 1 | |
| 9 | | 0.2 gramme and | | |
| 10 | | K I., or Ungt. | | |
| 11 | | Hg. and K.I. | | |
| 12 | 0.4 | | 1 | If mercury is used, note overlap of one week at end of first and start of second "606" courses. At this point, a few days without treatment may be dangerous. Neuro-relapse. |
| 13 | 0.4 | | 1 | |
| 14 | 0.4 | | | "606" starts, bismuth stops. Watch for provocative serological reaction after first dose of "606". |
| 15 | 0.4 | | | |
| 16 | 0.4 | | | |
| 17 | 0.4 | | 1 | |
| 18-23 | | Bismuth, 6 doses (or Ungt. Hg.) and K.I. | | Try to prevent short lapses in treatment, especially at this early stage. |
| | | | | Bismuth is better than mercury. Use it if possible. Examine cerebro-spinal fluid if patient's co-operation can be secured at about this time. If found to be abnormal, continue or intensify treatment as required, re-examining fluid within six months. |

| Day or week | "606" | Interim treatment | Serol. test | Remarks |
|-------------|--|---|-------------|---|
| Week | | | | |
| 24 | 0.4 | | | |
| 25 | 0.4 | | | |
| 26 | 0.4 | | | |
| 27 | 0.4 | | | |
| 28 | 0.4 | | | |
| 29 | 0.4 | | | |
| 30-37 | | Bismuth, 8 doses (or Hg.) and K.I. | | |
| 38 | 0.4 | | 1 | |
| 39 | 0.4 | | | |
| 40 | 0.4 | | | |
| 41 | 0.4 | | | |
| 42 | 0.4 | | | |
| 43 | 0.4 | | 1 | |
| 44-53 | | Bismuth, 10 doses (or Ungt. Hg.) and K.I. | | Note that bismuth or mercury courses are gradually getting longer—four, six, eight and now ten weeks. |
| 54 | 0.4 | | 1 | |
| 55 | 0.4 | | | The average sero-negative, sero-positive primary or early secondary patient should have at least five courses of "606". |
| 56 | 0.4 | | | |
| 57 | 0.4 | | | |
| 58 | 0.4 | | | |
| 59 | 0.4 | | 1 | |
| 60-69 | | Bismuth, 10 doses (or Ungt. Hg.) and K.I. | | It is safer to finish treatment with bismuth or mercury rather than with "606". |
| 70-122 | Probation | No treatment | 6-12 | |
| 123 | Complete physical and neurological examination, lumbar punctures, and, if possible, fluoroscopic examination of heart and great vessels. | | | |

As an optional scheme more in harmony with the trend toward longer courses, three series of ten to twelve injections each of the arsenical drugs may be given. To secure an overlapping of the heavy metal and the arsenical, believed by some observers to protect against neuro-relapses, begin the bismuth two, three, or even four injections before the end of the longer arsenical course, continue it through the period in which the arsenical is suspended, and on into the beginning of the next arsenical course. The bismuth is then suspended while the arsenical course is completed.

The bismuth salt advised for this system is bismuth salicylate in oil suspension, in full adult dosage with due regard for weight. Other preparations of bismuth may be used only with due regard for an equivalent metallic content and for their rate of elimination. The mercurial

inunction is 50% metallic mercury in a suitable fatty base, dose 4 grammes per inunction, five to six inunctions per week. The use of the iodide is optional, depending on indications.

The use of insoluble mercurials intramuscularly in this system is not recommended.

It should be further understood that, when heavy metal is employed after the last "606" course, the heavy metal courses are to be separated by rest intervals of six to eight weeks between each series of ten weeks' injections, or each course of forty inunctions.

In cases of primary syphilis which have remained sero-negative throughout, a minimum of 5 courses of "606" or "914" should be given. Cases of sero-positive primary syphilis should receive the full treatment called for by this system.

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THE BLOOD CULTURE OF THE TUBERCLE BACILLUS ACCORDING TO LOEWENSTEIN

INTRODUCTION.

In August 1932, Professor LOEWENSTEIN of the Austrian State Serotherapeutic Institute drew the attention of the League of Nations Health Committee to his research work and, in particular, to the fact that he had found the tubercle bacillus, not only in a high proportion of blood samples from reliably diagnosed tuberculosis cases, but in the blood of subjects suffering from acute or chronic polyarthritis, chorea, dementia præcox, multiple sclerosis, and retrobulbar neuritis. He proposed that, in order to establish beyond doubt the tuberculous ætiology of dementia præcox, the Health Section of the League of Nations Secretariat should ask institutions for the insane in various countries to send blood samples taken from dementia præcox cases to the Vienna laboratory for examination by the Loewenstein method.

In view of the importance attaching to Professor LOEWENSTEIN'S statements, which adduced tuberculosis as an operative factor in the pathogenesis of affections hitherto regarded as non-tuberculous, the President of the League of Nations Health Committee, Dr. Th. MADSEN, considered that the first step, before proceeding any further, should be to have control tests made. He met Professor LOEWENSTEIN in Milan in September 1932, and they both agreed that arrangements should be made in various laboratories specialised in tuberculosis research for comparative tests to ascertain the causes of the discrepancies that had been noted between Professor LOEWENSTEIN'S results and those recorded by other experimenters using his process.

At the invitation of Dr. MADSEN, the following scientific workers expressed their willingness to assist in these researches :

Professor CALMETTE and Dr. A. SAENZ, Pasteur Institute, Paris ;
Dr. A. Stanley GRIFFITH, Cambridge ;
Dr. K. A. JENSEN, Statens Seruminstitut, Copenhagen ;
Professor W. KOLLE, Staatliches Institut für experimentelle
Therapie, Frankfort-on-Main ;
Professor P. UHLENHUT, Hygienic Institute, Freiburg-in-
Breisgau.

In November 1932, Professor LOEWENSTEIN kindly allowed Dr. K. A. JENSEN to work for a spell in his laboratory in order to acquaint himself fully with the details of the Vienna technique. Jointly with Professor LOEWENSTEIN, Dr. K. A. JENSEN then drew up the plan of work detailed on pages 253 to 256.

In December 1932, Professor CALMETTE, commenting on the plan of work set forth above, made the following remarks :

"It is quite conceivable that the discrepancies in the results obtained may proceed from the manner in which the inoculation of the tubes is performed.

"The execution of the plan will not enable that point to be settled.

"It appears to me that, in order to remedy this defect, it should be provided that, just as LOEWENSTEIN is to send tubes of his medium to each expert, so each expert should also send tubes prepared in his institute to LOEWENSTEIN, and that the latter should inoculate each of the blood samples supplied to him, first, on two tubes of his own preparation and, secondly, on two tubes prepared by the expert supplying the blood.

"If, in these circumstances, the results should differ, it will doubtless be possible to detect the cause, and that cause will have to be sought elsewhere than in the technique of inoculation."

This suggestion was communicated in January 1933 to the experimenters, who unanimously accepted it.

The comparative research, which was centrally controlled from the Copenhagen Institute, was then undertaken on the lines of the plan thus completed. All the institutes sent a portion of the blood samples taken to Professor LOEWENSTEIN in Vienna. In order to make the results still more precise, the institutes in Copenhagen, Freiburg-in-Breisgau and Frankfort-on-Main divided their blood samples into

a certain number of portions which were subjected to comparative examination in the other institutes, and some of which were also examined by Professor Ludwig LANGE, of the Reichsgesundheitsamt, Berlin.

Disturbing differences soon appeared, however, between the results secured by Professor LOEWENSTEIN, on the one hand, and Dr. GRIFFITH and Dr. JENSEN, on the other. Thus, the strains of tubercle bacilli isolated in Vienna from the blood of animals artificially injected at Cambridge belonged to types other than those used at Cambridge to inoculate the said animals. In the circumstances, it was thought necessary to bring these discrepancies to Professor LOEWENSTEIN'S knowledge. An exchange of views consequently took place on October 22nd, 1933, in the tuberculosis laboratory of the Pasteur Institute, between Professor CALMETTE, Dr. GRIFFITH, Professor LOEWENSTEIN, Dr. MADSEN and Dr. SAENZ.

As Professor LOEWENSTEIN maintained his particular view, it was decided that, in order to eliminate the possibility of any error of technique, he should himself, at the Pasteur Institute, seed some 50 blood samples from cases of tuberculosis, rheumatism and dementia præcox. On October 23rd, six samples from the blood of tuberculous patients in Professor Léon BERNARD'S ward were ready for inoculation; Professor LOEWENSTEIN preferred, however, to let Dr. SAENZ conduct the experiment. Once the inoculations had been performed, Professor LOEWENSTEIN definitely stated that the manipulations had been perfectly carried out and that the differences between the Paris and the Vienna results could not be ascribed to the technique followed.

The next day, further blood samples were ready for inoculation, and again, though pressed by Dr. SAENZ, Professor LOEWENSTEIN did not consent to conduct the experiment himself. On October 25th, he left Paris, holding that his presence at the Pasteur Institute would serve no useful purpose, since no error of technique had been detected.

Whilst at the Pasteur Institute, Professor LOEWENSTEIN had endeavoured to explain the discrepancy between the Paris and Vienna results by adducing the following two reasons: first, that the consistency of the media prepared in Paris was too great, despite the presence of the same quantity of water of condensation as in the media sent from Vienna; secondly, that close co-operation between clinic and laboratory had not been ensured.

In reply to the first objection, Dr. SAENZ pointed out to Professor LOEWENSTEIN that the comparative tests carried out in parallel series

on media sent from Vienna and media prepared in Paris had yielded results that were in all respects coincident. With the blood of tuberculous patients, no matter what medium was used, the proportion of positive results had never exceeded 4 to 5 per cent. Nevertheless, in order to take account of Professor LOEWENSTEIN'S remark, the media subsequently prepared at the Pasteur Institute were coagulated in steam in order to secure the requisite consistency.

To the second objection, Dr. SAENZ replied that more than 400 of the blood samples examined had been supplied by the Barcelona Institute of Professor SAYÉ, who enjoys Professor LOEWENSTEIN'S complete confidence, and who was careful to send only the blood of clinically diagnosed cases of tuberculosis.

The research work conducted according to the plan prepared by Dr. K. A. JENSEN by agreement with Professor LOEWENSTEIN had been completed, and the reports of the late Professor CALMETTE and Dr. SAENZ, of Dr. A. Stanley GRIFFITH and of Dr. K. A. JENSEN were about to be sent to print—the memoranda of the Institute of Experimental Therapy at Frankfurt-on-Main¹ and of the Hygienic Institute of Freiburg-in-Breisgau² having already been published—when, on July 31st, 1934, Professor LOEWENSTEIN approached Dr. MADSEN and asked him to organise a fresh series of tests, in order to settle beyond doubt the still controversial question of the intervention of tuberculosis in the genesis of affections such as rheumatic polyarthritis, chorea and dementia præcox.

Being desirous of meeting the request thus made to him by Professor LOEWENSTEIN, Dr. MADSEN engaged in certain preliminary discussions to secure the assistance of the Tuberculosis Service of the Pasteur Institute, in providing premises and facilities for the experiments. At the same time, in order that the proposed tests might be of decisive value, he submitted to Professor LOEWENSTEIN a draft contract which provided, inter alia, that the inoculations should be carried out by Dr. SAENZ in the presence of Professor LOEWENSTEIN and of a third party, and the results, whatever they might be, should be regarded as unchallengeable and final. With great fair-mindedness, Professor LOEWENSTEIN expressed himself as willing to sign such a contract.

¹ W. KOLLE and E. KÜSTER: "Ueber das Vorkommen der Tuberkelbazillen in strömenden Blute". *Deutsche Mediz. Wochenschrift*, 1934, No. 9, page 309.

² W. SEIFFERT: "Zur Züchtung von Tuberkelbazillen aus dem strömenden Blut nach Loewenstein". *Deutsche Mediz. Wochenschrift*, 1934, No. 35, page 1314.

The negotiations had reached that stage when, on November 26th, 1934, the Director of the Pasteur Institute, Dr. LOUIS MARTIN, advised Dr. MADSEN that he had consulted the heads of the Tuberculosis Service, Dr. BOQUET and Dr. NÈGRE, and that, in their opinion, "further research work would not bring any fresh evidence to light".

Conveying the results of this consultation to Professor LOEWENSTEIN, on November 27th, 1934, Dr. MADSEN added that it appeared to him impossible to organise the proposed tests in any other institute and that, such being the case, there was no reason to delay the publication of the reports of Dr. CALMETTE and Dr. SAENZ, Dr. GRIFFITH and Dr. K. A. JENSEN, which would appear in the March 1935 issue of the Quarterly Bulletin of the Health Organisation.

These reports the conclusions drawn by their authors and were communicated to Professor LOEWENSTEIN before publication, together with the present covering note.

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*
*

If the examinations of blood and cerebro-spinal fluid samples effected by the various experimenters are grouped by diseases, the results work out as follows :

| | Calmette and Saenz | | Kolle and Küster | | Jensen | | Seiffert | | Griffith ¹ | | Totals | |
|--|--------------------|----|------------------|---|--------|---|----------|----|-----------------------|---|--------|----|
| | Cases | + | Cases | + | Cases | + | Cases | + | Cases | + | Cases | + |
| Tuberculosis (all forms) | 756 | 12 | 631 | 5 | 309 | 0 | 277 | 17 | 8 | 0 | 1,981 | 34 |
| Dementia præcox (blood) | 83 | 0 | 128 | 1 | 43 | 0 | 22 | 1 | — | — | 276 | 2 |
| Dementia præcox (cerebro - spinal fluid) | 60 | 0 | — | — | — | — | — | — | — | — | 60 | 0 |
| Rheumatism and erythema nodosum | 37 | 0 | 111 | 1 | 83 | 0 | 4 | 0 | — | — | 235 | 1 |
| Multiple sclerosis | — | — | 15 | 0 | — | — | — | — | — | — | 15 | 0 |
| Other affections .. | — | — | 68 | 0 | 44 | 0 | 40 | 2 | — | — | 152 | 2 |

¹ For the reasons stated in his report, Dr. GRIFFITH sent mainly blood samples from animals which had been injected with known strains of tubercle bacilli.

CONCLUSIONS.

In the unanimous opinion of the experimenters who took part in the research work, the facts given in their reports warrant the following conclusions :

1. The inoculation by the Loewenstein technique of blood samples taken from definitely diagnosed cases of tuberculosis did not, in the hands of the experimenters, yield the high percentages of positive results previously reported by Loewenstein.

2. From these same blood samples, Loewenstein obtained a percentage of results which exceeds, it is true, that of the other experimenters but falls far short of those reported in his previous papers.

3. The inoculation by the Loewenstein technique of blood samples obtained from patients suffering from dementia præcox, carried out by the experimenters, yielded negative results, with two exceptions. Blood samples from patients suffering from rheumatism or erythema nodosum also gave negative results, with one exception.

4. The discrepancies between Loewenstein's results and those of the experimenters are not attributable to defects of technique on the part of the latter nor to errors in diagnosing the condition of the donors of blood.

5. In several cases, the types of tubercle bacilli isolated by Loewenstein from the blood of tuberculous patients or of artificially infected animals did not correspond to the types of bacilli carried by the patients or injected into the animals.

PLAN OF COMPARATIVE RESEARCH INTO THE ISOLATION OF
B. TUBERCULOSIS FROM THE BLOOD
BY THE LOEWENSTEIN TECHNIQUE.

Preparation of the Medium.

1. Twenty eggs are cleaned by immersion for half-an-hour in a soap solution to which 5 per cent of NaHCO_3 has been added. They are then carefully cleaned and rinsed for one hour in running water.

2. Stock solution of asparagine :

| | |
|---|------------|
| Asparagine (Merck) | 3 gm. |
| Di-potassium phosphate (Kahlbaum) K_2HPO_4 | 1 gm. |
| Tribasic citrate of soda (Kahlbaum) | 1 gm. |
| Magnesium sulfuricum pur. cryst. (Kahlbaum) | 1 gm. |
| Glycerin. redistil. pur. cryst. 28° (Oesterreichische Heil- mittelstelle A.G., Wien, III) ,..... | 60 c.c. |
| Distilled water | 1,000 c.c. |

This solution is sterilised in steam for two hours. It keeps well.

3. Potato-starch.

4. Congo red (Grübler and Co., Leipzig) in a 2 per cent solution in water, sterilised by fifteen minutes' autoclaving.

5. Malachite green (Grübler and Co.) in a 2 per cent solution in water, sterilised in steam for two hours.

Add to 600 c.c. of the stock solution of asparagine, 10 c.c. of a 50 per cent potato-starch solution. Boil for two hours in a water-bath.

After cooling down to 50° C., add 16 eggs and the yolks only of 4 eggs. Shake thoroughly and add 20 c.c. of the congo red solution or 20 c.c. of the malachite green solution. LOEWENSTEIN now recommends congo red for preference.

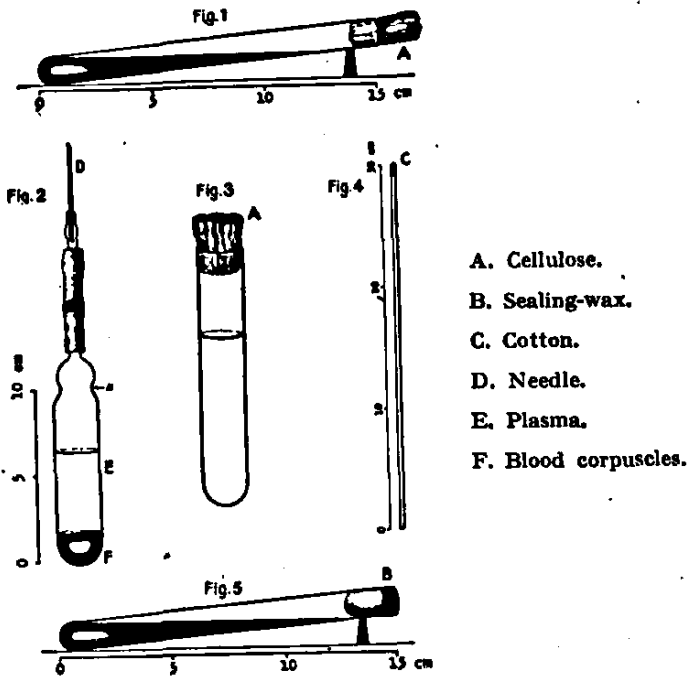
After shaking again, filter through four layers of gauze ; the medium will run through more easily if the gauze is slightly lifted away from the funnel.

The medium should be distributed into sterile tubes (Jena glass, diameter about 1½ cm., height about 15 cm.).

Coagulate by heating to 75-80° C. in steam for two hours; then place tubes in incubator. The following day, heat again to 75-80° C. in steam for two hours.

Plug the tubes with cellulose. Allow the medium to solidify on the slant (Figure 1) in order to secure a larger surface.

When inoculated, the medium should be fresh (not more than two weeks old). LOEWENSTEIN keeps it in a dark and cool place, but not in the ice-chest ; otherwise there is a risk of mould-growth.



- A. Cellulose.
- B. Sealing-wax.
- C. Cotton.
- D. Needle.
- E. Plasma.
- F. Blood corpuscles.

The Inoculation of the Media.

The blood sample is taken, with every precaution to ensure sterility, in a "Haemaut" (Figure 2).

While the blood sample is being taken, the container should be held as vertically as possible so that the blood may run down into the citrated solution. When sufficient blood has been taken, the container is shaken in order to mix the blood with the citrated solution.

The "Haemaut" is kept in a dark place until the blood corpuscles have formed a sediment. The neck of the "Haemaut" is then cut off with a diamond or glass file.

The plasma is poured out, care being taken that it does not carry any of the deposit with it. The latter is then briskly shaken and poured into sterile centrifuge tubes already containing 10 c.c. of distilled water. (If more than 5-10 c.c. of blood is to be treated, it must be divided into two parts, since it is not possible to deal with such a quantity in one centrifuge tube.)

The centrifuge tubes of 40 c.c. capacity are closed with a solid plug of cellulose and remain closed during centrifugation; if one of the plugs becomes moist, it must be replaced by a fresh sterile plug.

The "Haemaut" is rinsed out by briskly shaking up a few c.c. of distilled water in it. The rinsings are poured into the centrifuge tube, which is then filled with distilled water up to the mark (see Figure 3). If the blood is not evenly distributed throughout the liquid, it should be stirred with a sterile pipette in order to hasten hæmolysis (see Figure 4).

It should be centrifuged for about twenty minutes at 1,300 r.p.m.

LOEWENSTEIN considers it greatly important that the centrifuging should not be too vigorous ; otherwise the sediment becomes unduly compacted. Since, however, his centrifuge has a very large diameter, the speed indicated should correspond to about 2,000 r.p.m. in an ordinary centrifuge.

After centrifuging, the supernatant fluid should be decanted, care being taken that it does not carry any of the deposit with it ; rather than that it is preferable to allow some of the fluid to remain. The sediment is washed again with distilled water. (First a few c.c. are added and shaken vigorously, then the tube is filled up to the mark (see Figure 3).) Centrifuge again. If the sediment is not entirely free of hæmoglobin, the washing must be repeated. (When no more hæmoglobin is left, the sediment turns grey, but a faintly reddish tint is of no consequence.) As a general rule, it will be sufficient to wash twice. After the last washing, remove any coagula that may remain. If the blood is to a large extent coagulated, it is unsuitable and must be discarded.

The sediment is then shaken briskly for three minutes with 1-2 c.c. of 15 per cent dilute sulphuric acid (100 c.c. distilled water to 15 c.c. sulphuric acid—Acid. sulfuric. concentrat. pur. Ph. A VIII — Oesterreichische Heilmittelstelle, A.G., Wien, III, Rennweg 12). While still shaking the tube, add distilled water up to the mark (Figure 3) and centrifuge for fifteen minutes. After the deposit has again been washed with distilled water and centrifuged once more, it is ready for inoculation.

From $\frac{1}{2}$ to 1 c.c. of distilled water is left on the surface of the deposit to enable it to be thinned at the moment of inoculation.

The deposit should be seeded on to 3 or 4 tubes by being evenly spread on the surface of the medium without, however, scraping the latter. The pipettes used for seeding are long, thin glass tubes (Figure 4).

The culture tubes are hermetically sealed with sealing-wax and slanted to prevent the seeded deposit from running down into the bottom (Figure 5).

The tubes are kept in this position until the following day, either at room temperature and protected against the light, or in the incubator. They are then placed vertically in racks at 38° C. Growth usually occurs during the third or fourth week. A small residue of the deposit is kept for direct microscopy. Stain by the ZIEHL-NEELSEN method.

All the processes should be carried out with precautions to ensure sterility. The necks of the centrifuge tubes and of the bottle of distilled water should always be passed through the flame.

Plan of Work.

The institutes will themselves prepare culture media exactly as described above. The chemicals and stains should be of the same brands as those used by LOEWENSTEIN.

In addition to these, LOEWENSTEIN will send every week or every fortnight a sufficient number of tubes of his own medium to the institutes concerned.

The various institutes will themselves take the blood samples by means of the "Haemauts" supplied to them. Replacement "Haemauts" should be obtained by direct application to Professor LOEWENSTEIN. When the "Haemaut" is full, the quantity of blood it contains is sufficient to be divided into two parts.

The container is opened, with sterile precautions, after being vigorously shaken. The neck is scratched with a glass file all the way round (Figure 2(a)). A bent piece of red-hot steel wire is pressed into the crack and the neck snaps off of itself.

With a sterile 10-c.c. pipette, half of the blood is transferred into a sterile test-tube, which should be at once sealed hermetically, marked with a serial number and the name of the institute, *but with no mention of the clinical diagnosis*, and sent to Professor LOEWENSTEIN. The rest of the blood will be treated in the manner already described.

In all, four tubes will be inoculated, two containing the medium prepared by the institute concerned and two containing that supplied by LOEWENSTEIN.

Microscopical preparations will be made and kept (particularly the positives), so that they may be gone over together later on.

If any macroscopically visible growth occurs, the colonies will be examined under the microscope, reinoculated into tubes and inoculated into guinea-pigs. If the guinea-pig test is negative, the pathogenic properties of the strain will be investigated according to the rules for the determination of types.

All preparations as well as primary and secondary cultures must be preserved for the purpose of a later comparison.

If the cultures have not become macroscopically positive after six weeks, a preparation will be made with scrapings from the whole surface of the tubes. If this preparation is found to contain elements resembling the tuberculosis bacillus, inoculation into the guinea-pig and a reinoculation of tubes will be resorted to.

All these preparations must also be preserved.

It is considered adequate for each institute to examine a total of 50 blood samples (at the proposal of Professor LOEWENSTEIN, this figure was subsequently raised to 200).

Blood samples from patients suffering from the following diseases are particularly suitable for this kind of research :

- (1) Schizophrenia ;
- (2) Tuberculosis of the skin ;
- (3) Tuberculosis of the bones ;
- (4) Pulmonary tuberculosis ;
- (5) Rheumatism and other diseases of the joints.

The acute phases of these diseases are the most favourable for this work.

As far as possible, blood samples will be taken on several occasions from each patient.

The institutes concerned are requested to send, on the first of each month, to Dr. Th. MADSEN, Statens Seruminstitut, Copenhagen, a list of the blood samples taken, together with their serial numbers, the name of the institute and the indication of the clinical diagnosis. They will also report to Dr. MADSEN, on the first of each month, the results of their research.

Professor LOEWENSTEIN will also communicate to Dr. MADSEN, on the first of each month, the list of blood samples sent to him by the various institutes, together with their serial numbers and the results he has obtained himself.

1. REPORT ON THE DETECTION OF TUBERCULOUS BACILLÆMIA BY THE LOEWENSTEIN METHOD.

By

A. CALMETTE and A. SAENZ.

The purpose we had in view was :

(1) To study the method recommended by Professor LOEWENSTEIN, which is stated to demonstrate bacillæmia in 100 per cent of acute or disseminated forms of pulmonary, intestinal or meningeal tuberculosis, in 70 per cent of renal tuberculosis and in 55 per cent of cases of bone or skin tuberculosis ;

(2) To make cultures from the blood or cerebro-spinal fluid of dementia præcox patients, as recommended by Professor LOEWENSTEIN, who thereby succeeds in demonstrating the tuberculous ætiology of this disease in at least 50 per cent of the cases ;

(3) Further to apply the said method to the bacteriological study of acute or chronic rheumatism and other arthritic diseases of obscure ætiology, in which Professor LOEWENSTEIN has detected bacillæmia in a really impressive proportion (60 per cent) of cases ;

(4) To verify, by means of the results of our blood cultures in the above-mentioned cases, the facts adduced by Professor LOEWENSTEIN. Also to ascertain whether this method can be relied upon in order to detect a possible tuberculous ætiology in these morbid conditions. This is the essential purpose of the present report.

Before undertaking these experiments, we had already familiarised ourselves with this kind of research. One of us had proceeded to Vienna immediately after Professor LOEWENSTEIN'S first publications in 1930, with the object of learning the technique

employed by him, and had brought back from his laboratory the products required for the preparation of the culture media.

We shall therefore, in this report, expound first the results collected by us before the intervention of the League of Nations Health Committee, and thereafter those which were obtained by following with the greatest care the details of the plan drawn up by Dr. K. A. JENSEN, of the Copenhagen State Serum Institute, up to October 20th, 1933, at which date they were communicated by M. CALMETTE, in a preliminary report, to the experts who met at the Pasteur Institute to discuss the results with Professor LOEWENSTEIN.

Finally, we shall report upon the fresh research work decided at that meeting, which was prosecuted up to the month of July 1934.

Before, however, embarking upon this statement, we must indicate the experimental basis of the method and the conditions under which we carried out our work.

CULTURE MEDIUM.

LOEWENSTEIN successively recommended several modifications of his initial 1930 formula. We used these as described by him, and were thus able to compare them both among themselves and with various other media, particularly those of DORSET, LUBENAU, PETROFF, HOHN and PETRAGNANI. It should be said at once that PETROFF's egg and gentian-violet medium proved so consistently inferior to the others that we soon abandoned it altogether. PETRAGNANI's is good, on condition, however, that, as one of us (A. SAENZ) proposed, asparagine is substituted for peptone.

Generally speaking, the LOEWENSTEIN medium proved definitely superior to all other egg media.

The formula we adopted, and which we still find in every way satisfactory, is that recommended in the plan sent by the Health Section of the League of Nations Secretariat.

A nutrient liquid is first prepared as follows :

| | |
|---|------------|
| Di-potassium phosphate K_2HPO_4 (Kahlbaum)..... | 1 grm. |
| Asparagine (Merck) | 3 grm. |
| Tribasic citrate of soda (Kahlbaum) | 1 grm. |
| Neutral glycerine at 30° B' | 60 grm. |
| Sulphate of magnesium (Kahlbaum) | 1 grm. |
| Distilled water | 1,000 c.c. |

When these various ingredients have been dissolved, the solution is heated to 100° C. for 2 hours. It keeps well.

To 150 c.c. of this solution there should be added, in a sterile flask containing glass beads :

6 gm. of Merck's potato starch,
12 gm. of neutral glycerine at 30° B° sterilised.

The flask is shaken and heated to 100° C. for 15 minutes and then for an hour at 58° C.

To this mixture, which is kept at 56° C. and is maintained in constant motion by means of the glass beads in the jar, the following are added :

4 complete eggs plus the yolk of 1 egg (eggs washed and disinfected as indicated by LOEWENSTEIN), and
5 c.c. of a sterile 2 : 100 solution of malachite green (Merck) in water.

LOEWENSTEIN substitutes for the malachite green .5 c.c. of a 2 : 100 solution of *congo red* in water, but we have long abandoned this practice, since this substance is devoid of any antiseptic properties.

The liquid is filtered through sterile gauze and distributed in sterile test-tubes in the proportions of 5 to 6 c.c. per tube. These are tyndallised in damp steam for 2 hours a day, on two successive days at 80 to 85° C.

The tubes are left in the incubator for 24 hours at 38° C. to control their sterility.

During the past 3 years we have conducted varied and numerous experiments in order to determine the sensitiveness of this culture medium. These experiments warrant us in saying that it owes its superiority over other media to its asparagine content. Furthermore, comparative research undertaken by one of us with L. COSTIL showed that, with liquids of low bacillary content, having only 20 bacilli per c.c., culture on LOEWENSTEIN medium and inoculation into sensitive animals yield concordant results.

TECHNIQUES USED.

For the seeding of blood samples, among the various techniques recommended by LOEWENSTEIN, we adopted, up to January 1933,

the following :

In a sterile test-tube of 22 mm. diameter containing 3 c.c. of a 10 per cent solution of citrate of soda, 5 or 10 c.c. of blood are obtained by aseptic venous puncture. After decantation of the blood plasma, 10 to 20 c.c. of a 3 per cent sterile solution of acetic acid is added. The ingredients are left in contact for 10 minutes and the hæmolysed blood is removed by means of a sterile ball-pipette. It is poured into a large sterile centrifuge tube of 300 c.c. capacity, into which 20 c.c. of sterile distilled water has previously been delivered. The tube is then filled up with sterile distilled water and the contents centrifuged at 3,000 r.p.m. for 15 minutes. The supernatant fluid is poured off, and the blood corpuscle deposit is washed by brisk stirring with a sterile glass rod in 200 to 250 c.c. of sterile distilled water. A further centrifugation after this washing suffices to eliminate the hæmoglobin entirely. If the deposit has been well prepared, it then presents a greyish white appearance. It is sucked up into a pipette of fairly large calibre and seeded on to 6 to 8 tubes of the LOEWENSTEIN medium, prepared as described above.

In the investigations which one of us conducted with M. SADETTIN, hæmoglobin was not found to exert any inhibitory effect on the culture of the bacilli, notwithstanding what LOEWENSTEIN has written on the subject. Moreover, we obtained different results according to the strain studied.

Thus, when using BCG, we observed that the quantity of microbial bodies developed in 125 c.c. of SAUTON medium which had been left in the incubator for 25 days at 38° C. was roughly the same as in the flasks to which there had been added from 1 to 5 c.c. of blood obtained from healthy or tuberculous persons, sheep or rabbits untreated or vaccinated with BCG, or infected with virulent bacilli. We found, however, that the corpuscle extract prepared according to LEGROUX's formula had a definitely favourable influence. The weight of microbial bodies developed in the control flask and weighed in a dry state averaged 1 grm. 40, whereas the flasks to which 1 to 5 c.c. of corpuscle extract had been added yielded from 1 grm. 60 to 1 grm. 70 of bacilli under the same conditions.

As regards cultures of bacilli of the bovine type, while the corpuscle extract and the blood of sheep and rabbits suffering from tuberculosis or vaccinated with BCG displayed no definite growth-promoting property, the blood of healthy or tuberculous persons, and the blood of untreated rabbits and sheep, had an inhibitory effect upon the development of the strain used (VALLÉE strain).

As regards the strain of human bacilli (RATTI) or bird bacilli (Avian IV), we found that blood and corpuscle extract are definitely favourable to the culture of these types. We had some series in which the development of microbial bodies in SAUTON blood medium was nearly double that observed in the control flasks.

This research work enables us to conclude that, whilst the presence of blood is a matter of indifference so far as the CALMETTE-GUÉRIN strain is concerned, it exerted an inhibitory influence, under certain conditions, upon the development of bacilli of bovine origin. As regards strains of human or bird origin, however, our observations are entirely contrary to those of LOEWENSTEIN, since they showed us that blood promotes the growth of these bacillary types.

Further, we were able on one occasion to secure a very abundant growth of fine colonies of human type bacilli in tubes directly seeded, without preliminary preparation, with total liquid blood extracted from the heart of a patient who had died of chronic progressive tuberculosis.

On the other hand, experiments made with L. COSTIL convinced us that, in citrated centrifuged blood, the bacilli are most numerous, not in the layer of leucocytes, but in the red-black subjacent mass of corpuscles.

BLOOD CULTURES MADE IN 1931 AND 1932.

The results of the first 300 blood cultures made by one of us (A. SAENZ) were communicated to the Société de Biologie.¹ Eighteen positive cultures of acid-fast bacilli had then been obtained—that is, 6 per cent.

Since then we have studied under the same conditions a further 200 samples. In the course of this first series of experiments, we seeded more than 3,000 tubes of LOEWENSTEIN medium.

¹ C. R. Soc. de Biol., 1931, 107, page 1455.

The blood samples available were obtained from persons suffering from or suspected of tuberculosis among the patients of MM. L. SAYÉ (Barcelona), F. BEZANÇON, LÉON BERNARD, SERGENT, LEMIERRE, DEBRÉ, LAIGNEL-LAVASTINE, LAEDERICH, WEILL-HALLÉ, HOCQUART, CHEVALLIER, ABRAMI, ARMAND-DELILLE, COSTE and MOZER, etc. (Paris).

The last 200 blood samples yielded only 8 positive cultures, or 4 per cent. In all, over the whole range of the 500 patients in this first series, we immediately obtained macroscopic colonies in 9 cases only, of which 7 showed this result in 1 out of 6 seeded tubes, and 2 in 2 tubes. These colonies were visible, in 1 instance on the twelfth day, in 2 on the nineteenth, and in all other cases between the thirtieth and fortieth day after seeding. In 17 cases there were discernible micro-colonies only on the ZIEHL-stained smears, the value and significance of which will be discussed in the second part of this report. In one instance such micro-colonies yielded macroscopically visible colonies when re-seeded on LOEWENSTEIN medium.

IDENTIFICATION OF THE TYPES OF BACILLI ISOLATED IN OUR FIRST SERIES OF BLOOD CULTURES.

Up to now, we succeeded in identifying the types of bacilli both by biological tests and by inoculation in 9 cases. Now, in 3 cases these were bacilli presenting the characteristics of the para-tuberculous type ; in one case a bacillus of the bird type isolated from the blood of a patient suffering from tuberculosis of the bone and joints (JAQUEZ) ; and, in all others, bacilli of the human type isolated from cases of pulmonary or bone tuberculosis. Furthermore, we have been keeping under investigation, for the last two years, a special group of acid-fast bacilli whose dissociation into a number of different types of colonies will perhaps enable us to determine their significance.

Since, of the 9 strains which immediately yielded macroscopic colonies, 3 are para-tuberculous bacilli, the total proportion of positive macroscopic results is thus reduced by 30 per cent to 1.2 per cent for the whole.

It should be said at once, with regard to the para-tuberculous types isolated by us, that there could be no question of any accidental contamination during the manipulations, as these strains are completely different from the strains kept in the laboratory. We came to the conclusion that they really did come from the patient's blood. Moreover, LOEWENSTEIN, TIDEMANN, POPPER and Lydia RABINOWITSCH are of the same opinion as regards the paratuberculous types isolated by them in the course of their experiments.

As regards our bird strain, since certain experimenters—in particular LICHTENSTERN, PAULTAUF, etc.—have frequently found that ordinary market eggs were contaminated (up to 10 per cent), it was conceivable that the eggs used in preparing our culture media might contain some acid-fast bacilli which might have survived owing to insufficient heating. Smears made with the scrapings of several hundreds of unseeded egg-medium tubes which we left in the incubator for several weeks never showed the presence of such bacilli. Furthermore, we mixed with the LOEWENSTEIN medium, before coagulation, para-tuberculous bacilli, bird type bacilli and mammal bacilli of the bovine type, in doses of 1 mgrm. per c.c. We heated part of these tubes to 75° C. for half an hour once only; another series to 85° C. for half an hour on two occasions with 24 hours' interval; and a third series at 75° C. for half an hour on three occasions, also with 24 hours' interval. We left these tubes in the incubator at 38° and kept them under observation for three months. Of the 150 tubes, none showed any macroscopic culture. Furthermore, in order to make certain that mammal type bacilli were not present in our medium, we ground it up after it had remained to all appearances sterile for three months and inoculated it into a batch of guinea-pigs. These animals, which we observed for four months, never reacted to tuberculin and showed no discernible trace of tuberculosis on post-mortem examination.

If there is any factor of error in the results of the LOEWENSTEIN method, our research work therefore enables us to assert that it is certainly not connected with the culture medium.

In our publications on this question, we have several times compared our results with those obtained after us by other scientific workers. Among the first 500 blood cultures, the total percentage

recorded in our laboratory was 5.2. That arrived at elsewhere,¹ after some hundred investigations, involving 6,000 blood cultures, was, on the average, 5.35. The agreement between the two figures is obviously a very striking one.

SERIES OF BLOOD CULTURES MADE UP TO OCTOBER 1933
(date on which the preliminary report was presented).

We may now turn to the results of the blood cultures made by us in 1933, in accordance with the particulars laid down in the plan of research communicated by the Health Section of the League of Nations Secretariat. The only important modification made in the technique previously used has reference to the treatment of the centrifugation deposit for seeding. We proceeded as follows :

20 c.c. of blood are collected by aseptic venous puncture in a "Haemaut" apparatus of 30 c.c. capacity containing 2 c.c. of a 1-in-10 solution of citrate of soda. The requisite precautions having been taken for the opening of the neck of the apparatus, the supernatant plasma is decanted by means of a ball-pipette, after sedimentation has been allowed to take place by leaving the apparatus in a vertical position in the laboratory for 24 hours. The deposit of corpuscles is briskly shaken and transferred, by means of another ball-pipette, to a 200 c.c. capacity centrifuge tube containing 10 c.c. of distilled water. The Haemaut apparatus is rinsed with sterile distilled water, and the centrifuge tube is filled up with the rinsings. The liquid is centrifuged for 20 minutes at 2,000 r.p.m. The supernatant fluid is poured off, and the deposit is again washed by vigorous stirring up in 200 c.c. of sterile distilled water with a sterile glass rod. The liquid is again centrifuged, and the resulting deposit is treated for 3 minutes with 2 c.c. of 15 per cent dilute sulphuric acid. The tube is then filled up with sterile distilled water, the deposit is again shaken and centrifuged a third time for 15 minutes. This same

¹ In both cases the percentage covers total results, both macroscopic and microscopic.

washing and centrifugation procedure is repeated for the fourth time. The hæmoglobin is then completely eliminated and the deposit has assumed a greyish-white colour.

In most of our experiments, the deposit thus obtained was divided into two parts : the first half was seeded on to 6 tubes of *malachite-green* LOEWENSTEIN medium. The other half, diluted in 3 c.c. of physiological saline solution, was subcutaneously injected into 3 guinea-pigs.

With this technique we studied :

1. The blood of 90 patients suffering from various forms of definitely diagnosed pulmonary tuberculosis, most of whom had bacilli in the sputum. These blood samples were obtained from the clinics of Professor L. SAYÉ (Barcelona), Professor LÉON BERNARD and Dr. AMEUILLE (Paris).

2. The blood of 30 patients suffering from dementia præcox, under the care of Professor LAIGNEL-LAVASTINE (Salpêtrière) and Mlle. PASCAL (Asile de la Maison-Blanche, Neuilly-sur-Marne).

3. The blood of 14 persons suffering from rheumatism, under the care of Professor COSTE (Paris).

Of the 90 blood samples of the first group we were able to inoculate 50 into guinea-pigs, and the animals remained under observation for periods varying from 5 to 7 months. All were periodically tested with the intradermal tuberculin test (1/10th c.c. of tuberculin diluted to 1 in 10). The results were as follows :

Direct examination.—No acid-fast bacilli were ever found in films made of the deposit and stained by the ZIEHL-NEELSEN process. In one only of the 90 cases did we secure the immediate development of a macroscopic culture, which appeared on the twentieth day ; 15 colonies were counted in one only of the 6 seeded tubes. These were *human type* bacilli, as was demonstrated by biological tests and inoculation into guinea-pigs and rabbits. This positive culture was obtained from the blood of a patient from Professor LÉON BERNARD's clinic, suffering from febrile, cavernous, pulmonary tuberculosis in the progressive stage. A few days after the taking of the blood sample, the patient developed acute disseminated tuberculosis.

In the case of 9 other patients of this group, scrapings from the tubes seeded within the time-limit laid down by LOEWENSTEIN were found on direct microscopic examination to present acid-fast bacilli in clumps. These micro-colonies, reseeded and inoculated into guinea-pigs, did not develop under culture and did not produce tuberculosis in any of the animals.

As regards the 50 samples of blood in this first group, which included the 9 just mentioned, inoculation of the centrifugation deposit into guinea-pigs yielded no positive result.

The same is true of the patients of the second and third groups. Blood from the 30 cases of dementia præcox produced neither the growth of cultures nor tuberculosis in the guinea-pig. Three samples yielded micro-colonies of acid-fast bacilli, which could be detected by scraping, but none of these colonies could be cultivated or produce tuberculosis in guinea-pigs.

The 14 blood cultures from rheumatism patients proved similarly negative.

If we compare these results with those recorded for our previous research work, it appears that, using either LOEWENSTEIN's original technique or the second technique described in the programme of work communicated by the Health Section of the League of Nations Secretariat, we secured much the same percentage of immediately developing macroscopically visible and virulent cultures (1.1 per cent). If, however, sulphuric acid is substituted for acetic acid for purposes of blood hæmolysis, the effect is to prevent the development of the saprophytic para-tuberculous bacilli which proved so definitely a hindrance in our first research. Our experiments show, in fact, that acetic acid, which is highly toxic for the tuberculosis bacilli of mammals, has little or no toxicity for para-tuberculous saprophytes. The latter survived, in SAUTON solution, three-quarters of an hour's contact with 1 in 10 dilute acetic acid !

THE QUESTION OF MICRO-CULTURES.

LOEWENSTEIN recommends that culture tubes seeded with the blood deposit should be scraped when, after 6 weeks in the incubator, no development of macroscopic colonies is observed. These scrapings should, after fixation and ZIEHL-NEELSEN staining,

be examined for acid-fast bacilli. When this examination is positive it must be inferred, according to LOEWENSTEIN, that tubercle bacilli were present in the blood sample from which the culture was prepared. A glance at the literature on the subject of blood cultures shows that many workers base their positive results on these microcultures, which cannot be reseeded and do not produce tuberculosis in guinea-pigs.

We must therefore discuss the question—still a very obscure one—of the micro-cultures which appeared in larger numbers when we employed the new technique.

We saw above that the bacilli which are detected simply by direct examination in stained scrapings of such micro-colonies certainly do not originate in the culture medium.

On the other hand, we must always bear in mind the facts recorded by CORNET, MEYER, GOTTSTEIN, KAHN and other authors, which show that fragments of the covering membrane of blood corpuscles, as well as certain leucocytic granules which are rich in lipoids, are acid-fast, and that their morphological likeness to Koch's bacillus may lead to gross errors.

And especially must we beware of the ubiquitous acid-fast saprophytic bacilli in the various chemical products, staining reagents, tap-water, etc., used by workers in laboratories which conduct investigations into tuberculosis. This is proved by the experiments we shall relate below.

With a new sterilised bistoury we scraped the inside of 10 so-called "anti-splash" rubber tubes fitted to the cold-water taps in our laboratories and rubbed up the scrapings in each case in a conical glass, which was also new and sterile and had previously been washed in alcohol and ether and subsequently with the water from these same taps. The emulsions from the several glasses were then centrifuged and the deposits spread into a film each on a separate new slide and ZIEHL-NEELSEN stained.

The results of this examination were as follows : on 1 slide numerous clumps of acid-fast bacilli ; the microscopic fields literally covered with enormous colonies ; on 6 slides numerous clumps of acid-fast bacilli ; on 2 slides a few clumps ; on 1 slide no acid-fast bacilli visible.

The same test performed with the "anti-splash" tubes of 7 hot-water taps gave the following result : 1 slide with very numerous

clumps of acid-fast bacilli ; 2 slides with numerous clumps ; 2 slides with a few clumps ; 2 negative slides.

Other tests brought to light the presence of dead acid-fast bacterial organisms in our distilled water and in our sterile SAUTON solution.

The presence of these acid-fast bacilli is explained by the fact that, when apparatus is washed in the wash-house of our laboratory, acid-fast bacilli, either living or killed by sterilisation, are left adhering to the surface of the glass or steel beads or lead shot used in the cleaning process. They are frequently found there in very great numbers and they remain on the sides of the containers or pass into the liquids which are poured into those containers before sterilisation.

These considerations and other well-known facts concerning the precautions to be taken with cedar oil, the front lenses of immersion objectives, slides, solutions of stains, etc., in order to avoid acid-fast bacilli, lead us to believe that such microbial elements, simply ZIEHL-stained for purposes of direct examination, must frequently have been confused with true tuberculosis bacilli.

We gained the conviction that what is mistaken for micro-colonies obtained by scraping the surface of LOEWENSTEIN or other media is mostly simple clumps of acid-fast bacilli, usually killed by the heating of the media.

Throughout our researches, we only once found micro-colonies which developed after reseeded. As regards all other micro-colonies of acid-fast bacilli detected by the simple process of the scraping of culture media followed by direct examination after staining, we are now certain that these were acid-fast saprophytes not capable of cultivation.

We are therefore of opinion that, in future research, account should be taken only of micro-colonies which are *capable of cultivation* or which become so by reseeded, and of such colonies as prove capable of engendering tuberculosis either directly in the guinea-pig or by passage through that animal.

RESULTS OF THE THIRD SERIES OF BLOOD CULTURES CARRIED OUT WITH DUE ALLOWANCE FOR LOEWENSTEIN'S CRITICISMS.

Following the meeting of experts held in October 1933 in the tuberculosis laboratories of the Pasteur Institute, under the Chairmanship of M. CALMETTE, Professor LOEWENSTEIN endeavoured

to explain the discrepancies between our results and his by adducing the following two reasons :

(1) The consistency of our culture media was firmer than that of the media prepared at Vienna, though both contained the same quantity of water of condensation.

(2) We had not worked in sufficiently close contact with skilled clinicians.

To meet these two objections, we proceeded, in the first place, under the guidance of Professor LOEWENSTEIN himself, to change the system of coagulation of our media and to adopt the running-steam method used at Vienna. Furthermore, the deposit of the blood sample was in most cases seeded in equal parts on to tubes sent to us from Vienna by Professor LOEWENSTEIN and on to tubes prepared at the Pasteur Institute.

In the second place, we worked in close contact with eminent clinical specialists, who carefully established the clinical diagnoses of tuberculosis (Professors LÉON BERNARD, SAYÉ, AMEUILLE, etc.), dementia præcox (Dr. PASCAL), and rheumatism (Dr. COSTE).

Proceeding on these lines, we studied :

(1) The blood of 166 patients suffering from various forms of pulmonary, renal, bone or skin tuberculosis. In 71 of these cases, a culture grown from the centrifugation deposit was simultaneously inoculated by the subcutaneous route into 2 guinea-pigs. In the remaining 95 cases, the deposit was seeded into 6 tubes, three containing the medium sent by LOEWENSTEIN and three containing that prepared in our laboratory. After a period of observation of 3 months, we had obtained in all but 2 positive results. In one case, five colonies appeared in a single tube 24 days after seeding. The morphological characteristics of the culture, as well as its virulence for animals, showed that it was a strain of the human type. The blood had been obtained from a female patient suffering from severe bilateral progressive ulcerative pulmonary tuberculosis, according to information supplied by Professor SAYÉ. The second positive culture was also isolated from a case of lung and bone tuberculosis under the care of Professor SAYÉ ; the inoculation and seeding of the blood enabled us to isolate a strain of mammal bacilli, virulent for guinea-pigs, but not yet fully investigated.

(2) 113 cases of dementia præcox, 53 of which were the subject of blood cultures, and 60 of cerebro-spinal fluid cultures, with simultaneous inoculation into guinea-pigs.

Among the 53 blood cultures studied, we were able to detect no acid-fast bacilli, either by seeding or in ZIEHL-NEESEN-stained films made with the centrifuge deposit of the blood. The media seeded with the 60 cerebro-spinal fluids never showed macroscopic cultures; similarly, the inoculated guinea-pigs remained free, after 3 months' observation, from any lesion suggesting tuberculosis.

(3) Finally, blood taken from 23 patients suffering from various forms of acute or chronic rheumatism. In this group, although several of the patients showed obvious signs of tuberculosis—and most of them were strongly allergic—the seedings and inoculations remained negative.

Now that we have set forth the results of the research work we have conducted over a period of 3 years, it will be easy to compare the figures of our 3 series of blood cultures in order to determine the practical value of LOEWENSTEIN'S method as a means of detecting tuberculous bacillæmia. In this general table we shall not take account of the cases in which the presence of acid-fast bacilli was demonstrated only in the tube scrapings, since we are now clear as to the value and significance of these so-called non-reseedable micro-cultures.

Total number of blood cultures made *in vivo* : 946.

Total number of tubes seeded : 5,676.

| | Number of cases | Positive results | Percentage |
|---|-----------------|------------------|------------|
| A. <i>First Series</i> : | | | |
| Various forms of tuberculosis and rheumatism | 500 | 9 | 1.8 |
| B. <i>Second Series</i> : | | | |
| Definitely diagnosed pulmonary, skin or bone tuberculosis | 90 | 1 | 1.1 |
| Dementia præcox | 30 | 0 | |
| Acute or chronic rheumatism | 14 | 0 | |
| C. <i>Third Series</i> : | | | |
| Fairly advanced pulmonary, skin or bone tuberculosis | 166 | 2 | 1.2 |
| Dementia præcox, blood | 53 | 0 | |
| Dementia præcox, cerebro-spinal fluid .. | 60 | 0 | |
| Acute or chronic rheumatism | 23 | 0 | |
| Total | 936 | 12 | 1.2 |

This table shows a total of 12 positive results among 936 samples examined—that is, 1.2 per cent. It will also be observed that all the blood cultures in cases of dementia præcox and rheumatism remained negative.

Before discussing these results, we should like to give an account of the new series of investigations we have undertaken, in co-operation with M. COSTIL, in order to ascertain whether our failure might be due to some errors of technique, which might have occurred inadvertently in the course of our experiments. With these considerations in view, and by agreement with the author of the method, M. COSTIL proceeded to Vienna, where he worked for a week in LOEWENSTEIN'S laboratory. During this time, he had an opportunity of applying LOEWENSTEIN'S technique to 32 blood samples, in accordance with the following experimental plan :

Each treated sediment was seeded on the surface of 4 to 6 tubes of a medium supplied, in equal parts, by the Vienna laboratory and the Pasteur Institute. Part of these tubes remained under observation in LOEWENSTEIN'S laboratory, whilst the remainder were brought back to the Pasteur Institute by M. COSTIL.

The 32 examinations made related to :

- (1) 24 blood samples which had been sent to Professor LOEWENSTEIN ;
- (2) 8 blood samples which had been obtained from the Pasteur Institute.

The results of these blood cultures have been derived exclusively from the reading of the tubes observed in our laboratory ; they are set forth in the table on the following page 272.

We observe that, of the 24 seedings of the first group, 20 yielded negative results, both in the Vienna and in the Pasteur Institute tubes. The 4 other blood samples yielded four positive cultures ; direct examination of the centrifugation deposits had, however, already shown in two cases enormous masses of acid-fast bacilli, the appearance of which is shown in Figures 1 to 5.

These two cultures referred to patients suffering, one of them (W. R., No. 18,204) from acute polyarthritis, and the other (B. H., No. 18,206) from erythema induratum of Bazin. The colonies, which were very numerous in all the tubes supplied by LOEWENSTEIN'S laboratory, appeared after 20 days ; whilst, in the tubes supplied

by the Pasteur Institute, 16 colonies were noted in one instance and two in another. It should be said at once that this difference is easily explainable by the fact that the former were seeded with ten times the dose used for the latter.

BLOOD CULTURES MADE AT VIENNA IN PROFESSOR LOEWENSTEIN'S LABORATORY.

| Blood sample No. | Source of supply | Date of seeding | Direct examination of deposit | Results, number of colonies thirty days after seeding | |
|--|------------------|-----------------|-------------------------------|---|-------------------|
| | | | | Pasteur Institute tubes | Loewenstein tubes |
| <i>First Series consisting of Samples supplied by LOEWENSTEIN.</i> | | | | | |
| 18,203 | Prof. Falla | 3.V.34 | — | 0 | 0 |
| 18,204 | Pr. Loewenstein | 3.V.34 | +++ | 16 | Numerous |
| 18,205 | Prof. Neumann | 3.V.34 | — | 0 | 0 |
| 18,206 | Prof. Neumann | 3.V.34 | +++ | 2 | Numerous |
| 18,207 | Prof. Neumann | 3.V.34 | — | 0 | 0 |
| 18,208 | Prof. Neumann | 3.V.34 | — | 0 | 0 |
| 18,209 | Prof. Neumann | 3.V.34 | — | 0 | 0 |
| 18,210 | Prof. Neumann | 3.V.34 | — | 0 | 0 |
| 18,211 | Prof. Neumann | 3.V.34 | — | 0 | 0 |
| 18,214 | Prof. Reitter | 3.V.34 | — | 0 | 0 |
| 18,216 | Prof. Neumann | 4.V.34 | — | 0 | 0 |
| 18,217 | Prof. Neumann | 4.V.34 | — | 0 | 0 |
| 18,218 | Prof. Vilardell | 4.V.34 | — | 0 | 0 |
| 18,219 | Prof. Berger | 4.V.34 | — | 0 | 0 |
| 18,220 | Prof. Berger | 4.V.34 | — | 0 | 0 |
| 18,221 | Prof. Berger | 4.V.34 | — | 0 | 0 |
| 18,222 | Prof. Berger | 4.V.34 | — | 0 | 0 |
| 18,223 | Prof. Berger | 4.V.34 | — | 0 | 0 |
| 18,224 | Prof. Berger | 4.V.34 | — | 0 | 0 |
| 18,225 | Prof. Berger | 4.V.34 | — | 0 | 0 |
| 18,226 | Prof. Berger | 4.V.34 | — | 0 | 0 |
| 18,227 | Prof. Berger | 4.V.34 | — | 0 | 0 |
| 18,228 | Prof. Meller | 4.V.34 | — | Numerous | Infected |
| 18,229 | Prof. Meller | 4.V.34 | — | Numerous | 0 |
| <i>Second Series consisting of Samples brought from the Pasteur Institute.</i> | | | | | |
| 18,233 | Pasteur Inst. | 4.V.34 | — | 0 | 0 |
| 18,234 | Pasteur Inst. | 4.V.34 | — | Numerous | 0 |
| 18,235 | Pasteur Inst. | 4.V.34 | — | 16 | 0 |
| 18,236 | Pasteur Inst. | 4.V.34 | — | 0 | 0 |
| 18,237 | Pasteur Inst. | 4.V.34 | — | 0 | 0 |
| 18,238 | Pasteur Inst. | 4.V.34 | — | Numerous | A few col. |
| 18,239 | Pasteur Inst. | 4.V.34 | — | 0 | 0 |
| 18,240 | Pasteur Inst. | 4.V.34 | — | 3 | 4 |

Nos. 18,233, 18,236, 18,237 and 18,239, blood of fresh rabbits.

No. 18,234, blood of rabbit artificially infected with 1/10,000th mgrm. of human bacilli.

No. 18,235, blood of rabbit inoculated with 1/1,000th mgrm. of BCG.

No. 18,238, blood of a rabbit infected with 1/1,000th mgrm. of human bacilli.

No. 18,240, blood of a rabbit infected with 1/1,000th mgrm. of bovine bacilli.

The two other positive cases, which relate to two patients (P. I., No. 18,228, and S. A., No. 18,229) suffering from sympathetic ophthalmia, yielded very numerous colonies in the tubes supplied by the Pasteur Institute ; those of Vienna were either desiccated or affected by secondary contamination, and it is possibly these circumstances which prevented the development of Koch's bacillus.

The biological reactions and inoculations into the guinea-pig enabled us to ascertain that all four strains were tubercle bacilli of mammals.

As regards the 8 samples of the second group, 4, which were fresh rabbit blood, were used as controls and remained sterile in the tubes procured from both sources. The 4 remaining samples, which were blood of fresh rabbits inoculated with 1/1,000 or 1/10,000 mgrm. of bacilli of human or bovine origin, or of BCG, all gave positive results in the tubes prepared in Paris. The number of colonies obtained, except for BCG, was proportionate to the quantity of material used for seeding. On the other hand, in two cases, these samples, seeded on to the tubes of Professor LOEWENSTEIN's laboratory, produced no growth of microbes.

This table brings out clearly the following three facts :

(1) The presence of Koch's bacillus in 16 per cent of patients suffering from various diseases, detected by blood culture in Professor LOEWENSTEIN's laboratory.

(2) Presence in the centrifugation deposit of the blood of persons suffering from erythema induratum and acute polyarthrititis of large quantities of bacilli detected by direct examination of the smears.

(3) As regards the culture media, the Pasteur Institute tubes proved at least as sensitive as those supplied by the Viennese author.

DISCUSSION.

Having now completed the account of our work, we can proceed to consider whether an analysis of all the various factors that have operated in the course of our investigations will yield an explanation of our negative results.

In the first place, it is unlikely that differences of technique can be the cause of our failure. We have familiarised ourselves

with the method over a period of four years, and the regularity of our experimental results warrants the belief that we are fully conversant with its every detail.

Moreover, it may be supposed that this factor does not play an essential part, since the successive modifications which Professor LOEWENSTEIN introduced in the course of two years in the various phases of the treatment of the centrifugation deposit for seeding purposes have not prevented him from regularly obtaining a high percentage of positive blood cultures, relating alike to cases of tuberculosis, dementia præcox, rheumatism and other diseases of nervous origin or of obscure ætiology like erythema induratum.

Besides, if some errors have crept into the technique we have followed in applying the method, they are not discernible, for Professor LOEWENSTEIN, who twice witnessed the preparation of the blood cultures in our laboratory, has himself testified to the correctness of the procedure followed both by our assistants and ourselves.

We would point out, moreover, that, as far back as 1930, one of us, who was then barely acquainted with the details of blood culture, secured in Professor LOEWENSTEIN'S laboratory abundant cultures, which we have been subsequently unable to obtain in the Pasteur Institute. Again, it sufficed for our assistant, M. COSTIL—who worked in Paris for months on more than a hundred seedings of blood samples from selected tuberculosis and other patients, and failed—to apply the very same technique at Vienna to obtain after a few days, with a group of heterogeneous diseases, a high percentage of positive results (16 per cent).

Finally, the question of technique is irrelevant to the consideration that Professor LOEWENSTEIN is able fairly frequently to detect considerable numbers of bacilli by direct examination of the centrifugation deposit of the blood or cerebro-spinal fluid of patients suffering from dementia præcox, rheumatism, chorea or erythema induratum. We ourselves have never found this in any of the hundreds of smears we have examined.

In the second place, let us consider whether the culture medium we used may be made responsible for the discrepancy in the results.

With this object in view, we made numerous seedings, for comparative purposes, on equal numbers of culture tubes from Vienna

and from Paris. These tubes were seeded either with bacillary emulsions or with artificially infected blood samples, or with the blood of tuberculous guinea-pigs and rabbits. These experiments demonstrated the absolute equivalence of the two media in point of sensitiveness. Our seedings proved fertile in the Paris and Vienna tubes alike whenever the substance examined contained not less than twenty bacilli per cubic centimetre.

On the other hand, when the LOEWENSTEIN technique is applied to the heart blood of patients who have died of progressive tuberculosis, our frequently very high positive results (40 per cent) agree perfectly with Professor LOEWENSTEIN's experiments on cadavers. Furthermore, it is in these cases only that we secured the development of numerous colonies in all the tubes seeded with each sample.

Again, we saw that, whilst our culture medium proved identical with that of Professor LOEWENSTEIN in the first series of blood cultures made by our assistant, M. COSTIL, at Vienna (see table, page 272), it proved much more sensitive in the second series, since the Pasteur Institute tubes yielded 4 positive results for 8 seedings, whereas those of Vienna yielded but 2.

A difference in the sensitiveness of the medium can thus also not be adduced to explain our complete failure in cultures made with 60 cerebro-spinal fluid samples from dementia præcox patients, for the simple reason that half of the seedings were on tubes supplied from Vienna ; here, again, technique plays no part. Now, Professor LOEWENSTEIN obtains fairly frequently, under like conditions and using the same media, positive results both by direct examination and by culture ; the latter is so luxuriant that it seems to point to a bacillary density comparable with that sometimes observed in sputum (see Plate 6).

There remains now to analyse the objection concerning the co-operation that should be maintained between the clinicians and the biologists in order to determine the most likely moment of the passing of Koch's bacillus into the blood, such conditions being essential for the success of the blood cultures. It will have been observed that, in the third series of blood cultures, we took particular care to secure that co-operation between the clinic and the laboratory but the percentage of positive results (among 290 cases studied in this series) was more or less identical (1.2 per cent) with that previously obtained.

On the other hand, identical samples of blood, that were sent both to ourselves and to Professor LOEWENSTEIN by Professor SAYÉ, of Barcelona, gave positive results on several occasions in the Vienna laboratory, whereas they proved negative throughout at the Pasteur Institute.

The same thing happened in October last with samples taken from twelve persons suffering from acute disseminated tuberculosis selected by Professor LÉON BERNARD. The blood culture was made in our laboratory under the guidance of Professor LOEWENSTEIN himself, and the seedings were made in tubes which he had brought, but no single culture was isolated.

In view of the fact that Professor LOEWENSTEIN finds so high a percentage of positive blood cultures in the diseases we have studied, it is difficult to conceive that the propitious moment for the taking of the blood sample can be determined only by Viennese clinicians and not by those of Paris or elsewhere.

There is even a striking contrast between our positive results and those of Professor LOEWENSTEIN. Among the 12 strains isolated from the 936 blood samples examined by us, there was none which was represented by a positive culture in the whole of the 6 tubes seeded with each sample ; in most cases we noted the development of bacilli in one single tube, and in 2 instances on 2 tubes. The colonies were always few in number—*i.e.*, 5, 8, or 25 colonies at the outside. Now, Professor LOEWENSTEIN, in his positive results, secures cultures in all the tubes, and they nearly always show innumerable colonies.

Plate 6 shows tubes corresponding to 12 blood cultures made at Vienna by M. COSTIL during his stay in Professor LOEWENSTEIN'S laboratory and brought back by him. A glance at these cultures will enable what we have just said to be clearly appreciated.

Moreover, it will be noticed that these blood cultures were obtained with samples from patients suffering from such different diseases as tubercle, dementia præcox and rheumatism.

At first sight, one naturally wondered whether these were really cultures of tuberculosis bacilli of the mammal type. Now, we identified 12 strains which were brought to us in October last by Professor LOEWENSTEIN himself and had been obtained from patients suffering from the same diseases, and are able to say that they were really virulent and that most belonged to the human

type. This is also true of the strains shown in figures 1 to 5 and already discussed above.

In conclusion, we would say one word as regards positive results by direct examination disclosing an abundance of bacilli that will be appreciated by a glance at the photographs reproduced on pages 279 to 282. Their quantity is at times so considerable that several clumps, each containing thousands of the bacilli, are sometimes found within one and the same microscopic field; closer examination has shown them to belong to strains of human origin. It is inconceivable how such masses of virulent bacilli can thus circulate freely in the blood stream without producing microbial embolism.

CONCLUSIONS.

(1) Very numerous and varied experiments enable us to assert that, without a doubt, the culture medium the composition of which has been laid down by Professor LOEWENSTEIN proves superior to all the media so far proposed for the culture of tuberculosis bacilli of human, bovine or avian origin.

(2) 936 blood samples, seeded on to this medium in about 6,000 tubes, subject to the most careful observance of Professor LOEWENSTEIN'S directions, only yielded a total number of twelve positive results, or 1.2 per cent. The blood samples had been obtained from patients suffering from various forms of acute or chronic tuberculosis, rheumatism and dementia præcox.

(3) If consideration is limited to the blood cultures with samples from tuberculous patients, the positive results total 1.58 per cent. The appearance of the cultures showed every case to be one of invasion of the blood by small numbers of microbes only. In most cases, the isolated strain was of a human type.

(4) Cultures with 37 blood samples from patients suffering from acute or chronic rheumatism, and 83 blood samples and 60 cerebro-spinal fluid samples from patients suffering from dementia præcox, remained negative.

(5) The considerable difference between the percentage of our positive results with tuberculous patients and that of Professor LOEWENSTEIN, as well as our complete failure with patients suffering from rheumatism and dementia præcox, could not be explained by adducing errors of technique, or differences in the sensitiveness

of the culture media, or, finally, insufficient co-operation between clinics and laboratory.

(6) The luxuriant appearance of the cultures obtained in Professor LOEWENSTEIN's own laboratory, as well as the positive results noted on direct examination of the centrifugation deposit in cases of dementia præcox, erythema induratum and polyarthritis, were never found by us, or in the other laboratories, despite the combined efforts of a large number of qualified research workers.

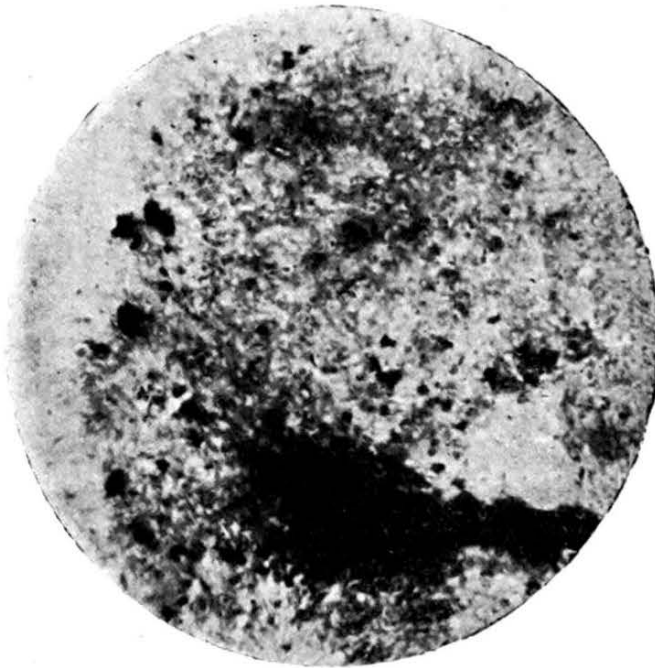
(7) Despite its superiority, on the practical side, over the other methods of culture, the method advocated by LOEWENSTEIN is less sensitive as a means of detecting tuberculous bacillæmia than inoculation into the guinea-pig¹. The latter method, when used by us in connection with patients suffering from progressive forms of tuberculosis, yielded us a higher percentage of positive results than blood cultures. We believe that the many processes through which the blood passes in LOEWENSTEIN's method, as well as the laking, successive washings and repeated centrifugation to which it is subjected, are injurious to the preservation of the vitality of the bacilli, which, according to our investigations, are most commonly present in isolated units.

Our experiments, and others which we have published with COSTE and COSTIL,² show that, without a doubt, LOEWENSTEIN's theories concerning the alleged inhibitory effect of hæmoglobin upon the cultures are not justified, and that the seeding on LOEWENSTEIN's egg medium, of pure blood (in co-operation with COSTIL) which has simply been rendered incoagulable by citrate of soda and laked with distilled water—and especially its immediate inoculation of that blood into the guinea-pig (without exceeding a dose of 5 cubic centimetres by the subcutaneous route)—yields more frequent and more reliable positive results. It is along these lines that we propose to conduct our future research into tuberculous bacillæmia.

¹ SAENZ, COSTIL et SADETTIN, *C. R. Soc. de Biol.* 1935, 118, p. 1159.

² SAENZ, COSTE and COSTIL, *C. R. Soc. de Biol.*, 1932, 111, page 934.

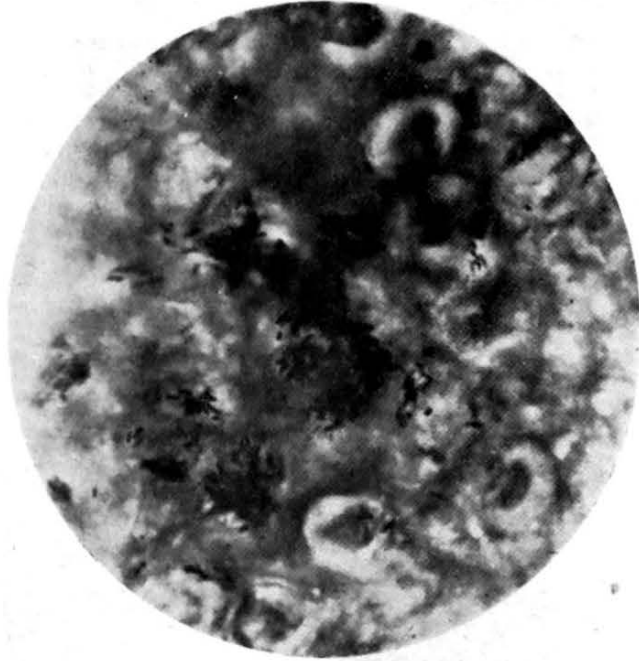
No. 1. MICROSCOPIC FIELD SHOWING THE SMEAR PREPARED FROM THE CENTRIFUGATION DEPOSIT OF BLOOD BEFORE SEEDING, IN PROFESSOR LOEWENSTEIN'S LABORATORY (PATIENT No. 18,206, SUFFERING FROM ERYTHEMA INDURATUM OF BAZIN, UNDER TREATMENT BY PROFESSOR NEUMANN).



The culture showed that the bacilli in question were tubercle bacilli virulent for sensitive animals. The enormous number of black spots will be observed ; each of these corresponds to a clump of acid-fast bacilli.

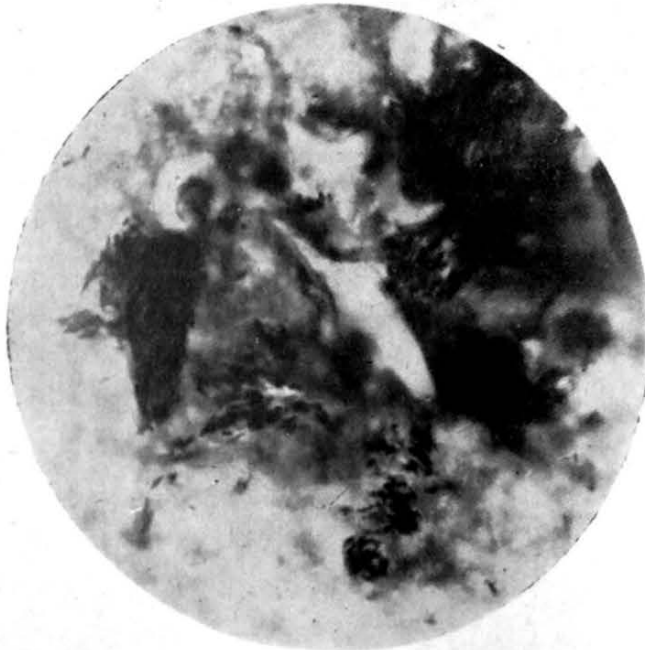
In one of these clumps below and to the right, thousands of bacilli were counted.

No. 2. ONE OF THE CLUMPS OF THE PREVIOUS PREPARATION GREATLY MAGNIFIED
(No. 18,206).

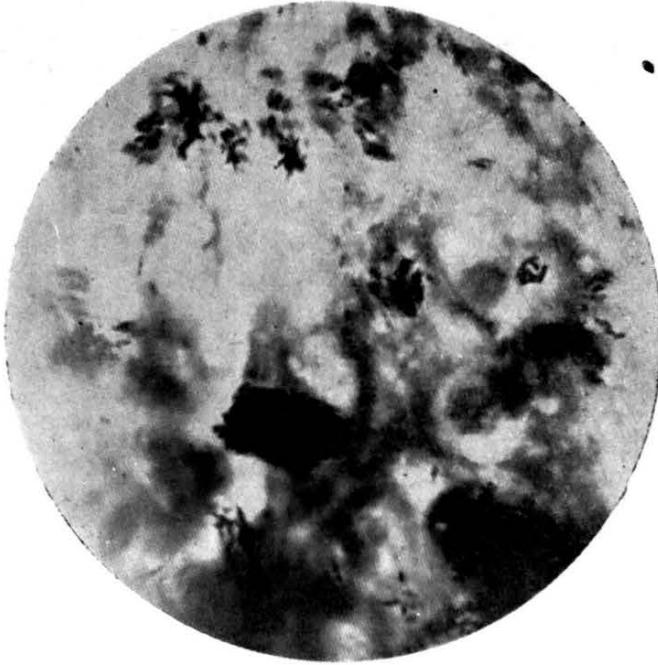


The distribution of the clumps of bacilli over the microscopic field should be observed.

No. 3. ANOTHER VIEW OF THE SAME SLIDE (No. 18,206).

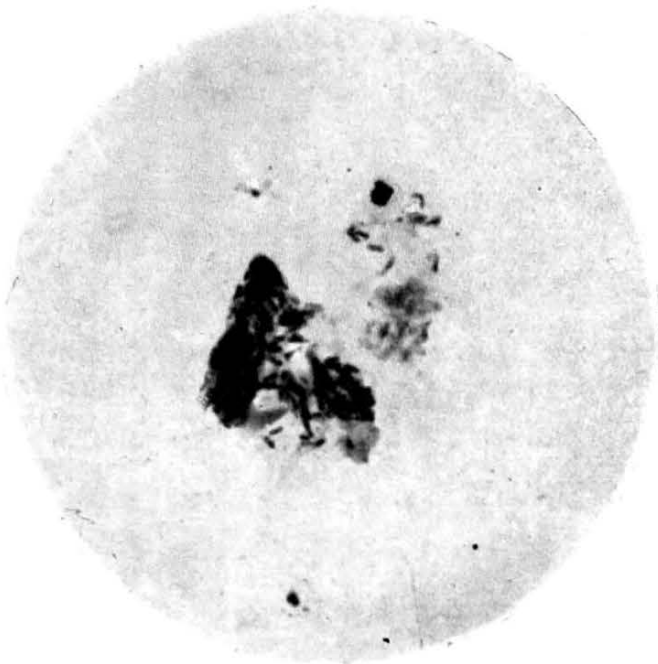


No. 4. MICROSCOPIC FIELD OF A SMEAR PREPARED FROM THE CENTRIFUGATION DEPOSIT OF BLOOD BEFORE SEEDING, IN PROFESSOR LOEWENSTEIN'S LABORATORY (PATIENT W. R., No. 18,204, SUFFERING FROM ACUTE POLYARTHRITIS UNDER TREATMENT BY PROFESSOR LOEWENSTEIN).

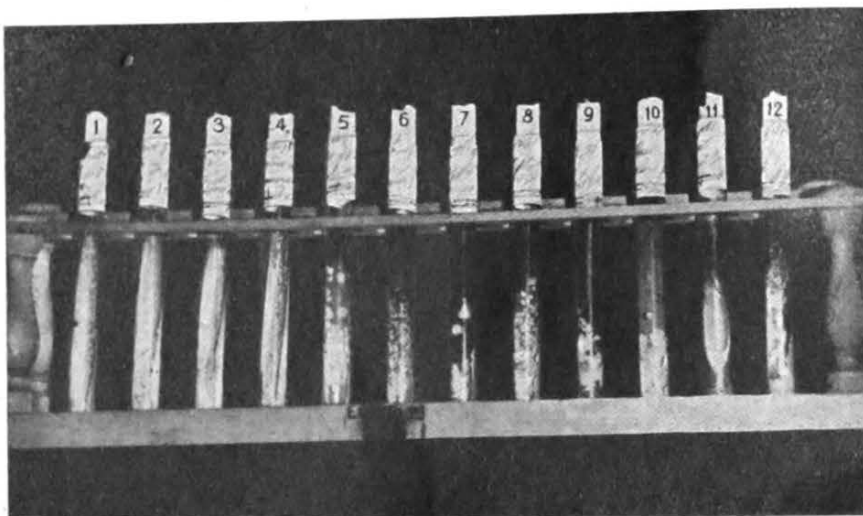


The examination of this culture showed that the bacillus was a tubercle bacillus of the human type.

No. 5. AN ISOLATED CLUMP FROM THE PREVIOUS PREPARATION (No. 18,204).



No. 6. ORIGINAL TUBES OF THE CULTURES FROM PROFESSOR LOEWENSTEIN'S LABORATORY.



The luxuriant and confluent nature of the innumerable colonies invading the whole surface of the medium will be noticed. All these cultures proved virulent for the guinea-pig.

- Tube 1. No. 15,266, Patient N. J., Rheumatism, Prof. Reitter.
- Tube 2. No. 16,807, Patient H. F., Dementia præcox.
- Tube 3. No. 16,573, Patient W. K., Rheumatism, Prof. Reitter.
- Tube 4. No. 13,683, Patient A., Tuberculosis.
- Tube 5. No. 16,506, Patient A. H., Rheumatism.
- Tube 6. No. 16,488, Patient S. J., Tuberculosis of tongue, Dr. Markus.
- Tube 7. No. 16,616, Patient K. E., Tuberculosis of eye, Prof. Meller.
- Tube 8. No. 16,244, Patient 209, Dementia præcox, New York.
- Tube 9. No. 16,299, Patient W., Skin tuberculosis, Prof. Kren.
- Tube 10. No. 16,613, Patient W. K., Rheumatism, Prof. Reitter.
- Tube 11. No. 16,810, Patient K. E., Dementia præcox.
- Tube 12. No. 16,493, Patient M. M., Rheumatism, Prof. Reitter.

2. TUBERCULOUS BACILLEMIA.

By

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There are at the present day two opposed conceptions regarding the sequence of events following invasion of the body by the tubercle bacillus.

According to the more general view, tuberculosis manifests itself by characteristic morbid processes, of which tubercles are the most conspicuous, and is at the outset invariably a local disease, its primary manifestations (known as the primary complex) occurring at the points of invasion of the bacilli or in the lymphatic glands in immediate relation or both. After the setting-up of the primary complex, the course of the infection depends very much upon the natural powers of resistance of the individual. In highly resistant individuals, the bacilli are retained within the region of the primary complex, the bacilli are walled off and the tuberculous process is arrested.

During the earliest phase of an infection in a resistant individual, it is possible that bacilli in small numbers may enter the blood, but, if so, they die out, since no distal lesions indicative of such invasion can be found in persons who have died from causes other than tuberculosis, but who show at autopsy healed local tuberculous lesions.

In less resistant individuals, the few bacilli which at this early stage of the infection pass through the first line of defence into the efferent lymphatics and so enter the blood stream settle in some distant part—either a bone, or a kidney or the brain—multiply and give rise to lesions which themselves may become centres of diffusion, the primary complex often undergoing retrogressive changes. In the highly susceptible person, the primary lesions extend, the disease becomes generalised and death ensues from acute general miliary tuberculosis of all the organs of the body,

a condition which could only have been caused by the entry of tubercle bacilli in large numbers directly into the blood.

Between the two extremes of a single distal lesion and profuse general miliary tuberculosis an infinitude of degrees of dissemination have been observed. Thus, from anatomical-pathological observations it is certain that, in a case of disseminated tuberculosis, there must have been a period between the inception of the primary complex and generalisation of the disease when the blood contained tubercle bacilli in greater or less abundance and for a longer or a shorter time.

The second conception, held by a minority, is that tubercle bacilli invade the blood very soon after infection, multiply and produce a septicæmia of variable intensity and often considerable duration before the stage of nodular formation. The clinical picture of this form of bacillary invasion is that of a general infection resembling typhoid fever and was interpreted by LANDOUZY as a tuberculous bacillæmia and designated by him typho-bacillosis. CALMETTE, as is well known, supported this view and, moreover, believed that it could occur without causing symptoms. The tubercle bacilli, entering the body usually through the mucous membranes of the mouth, nose, throat or intestines, remained latent in the lymphatics or in the blood for a period more or less prolonged before setting up the first primary lesion which might be in some part very distant from the point of entry of the bacilli. On clinical grounds, other French observers have upheld this hypothesis of pre-nodular invasion of the blood ; but it has remained for LOEWENSTEIN to affirm it boldly on the ground of the results of his blood cultures. As recently as October 1933, he writes :

“ The first stage of tuberculosis is not characterised by the primary complex, but by the bacillæmia, and there exist tuberculous infections unaccompanied by nodule formation.”

METHODS OF DEMONSTRATING TUBERCLE BACILLI IN THE BLOOD.

The occurrence, the duration and the intensity of a tuberculous bacillæmia have been the subjects of laboratory investigations over a very long time.

The methods adopted of revealing the presence of tubercle bacilli in the circulating blood have been three—namely, microscopical examination, cultivation and animal inoculation, the whole blood or centrifuged deposits being utilised.

Microscopical examination is so beset with pitfalls and sources of error, which have been fully exposed by WILSON, that no reliance at all can be placed on the results of observations of this kind.

With regard to the comparative reliability of the other two different opinions have been expressed, but the consensus of opinion is in favour of the animal inoculation test. With this view I agree if it is restricted to infections with virulent mammalian tubercle bacilli. When in comparative investigations of duplicate samples of blood the one or the other method has appeared to give better results, the differences may be attributed to chance distribution of the scanty tubercle bacilli resulting in the presence of a bacillus or two in one portion of the blood and not in the other.

RESULTS OF PUBLISHED INVESTIGATIONS.

WILSON¹, in his very useful review of the literature of tuberculous bacillæmia, has divided the investigators of the blood into two groups—those who obtained uniformly negative results and those who succeeded in demonstrating tubercle bacilli in the peripheral blood.

Leaving out of account for the moment the work of LOEWENSTEIN and his collaborators, one finds that the negative results far outnumber the positive, in spite of the fact that most of those who got negatives strictly followed LOEWENSTEIN'S technique. The successful searchers may be subdivided into those who have found the bacilli rarely and sparsely and those who, like LOEWENSTEIN, have found them frequently and more or less abundantly.

The workers who have never succeeded and those who have demonstrated them in only a small proportion of the cases examined have concluded that a tuberculous bacillæmia occurs only as an inconstant and transient phenomenon. The tubercle bacilli which enter the circulation during the course of the infection do not remain for long in the blood, but are rapidly filtered off by the tissues.

¹ *Med. Res. Council. Sp. Rep. Series; No. 182, 1933.*

In striking contrast to the results of most other observers are those of LOEWENSTEIN, who, since 1930, has reported successes in ever-increasing proportion and in the most diverse clinical conditions, both tuberculous and non-tuberculous. In 1933, his investigations had extended to 15,000 samples of blood, and they now exceed 17,000.

Among the diseases not generally regarded as tuberculous, LOEWENSTEIN (with REITTER) has recently been paying particular attention to acute rheumatism, one of a group of serous inflammatory conditions which he believes are caused by the tubercle bacillus. In acute rheumatism he states that he has found tubercle bacilli, not only in the blood, but also in the tonsils and the articular cavities. He also claims to have found the bacilli in the blood and the cerebro-spinal fluid of cases of chorea, dementia præcox and retro-bulbar paralysis, and in the blood of a series of ocular and skin affections.

DISCUSSION OF TECHNIQUE.

LOEWENSTEIN attributes the failure of other workers to demonstrate tubercle bacilli in the blood to three main causes: (1) not following his technique of media-making sufficiently closely, a technique which he himself is constantly changing; (2) not freeing the blood deposits from hæmoglobin; and (3) not taking the blood samples at the right moment or frequently enough.

For growing tubercle bacilli from the blood, LOEWENSTEIN insists upon the importance of using his synthetic asparagin egg medium, coagulated at 80° C. in flowing steam. There is no doubt that this medium is good for the primary cultivation of tubercle bacilli. But it is not superior to the plain egg medium which F. GRIFFITH and I, independently of DORSET, found, when working for the Royal Commission on Tuberculosis, to be much more reliable for primary cultures of tubercle bacilli than the coagulated serum media which had up till then been used for this purpose.

LOEWENSTEIN was good enough to send me 20 tubes of his medium prepared in Vienna, and I made a series of comparative tests. I found that all three types grew on his medium in primary culture, but in some of the tests growth was much more luxuriant on the

Cambridge 5 per cent glycerine egg than on the Vienna "synthetic egg" (the percentage of glycerine in the latter was not stated). Moreover, on several occasions I obtained cultures from blood on plain egg medium when the Vienna medium sown with the same blood deposits failed.

LOEWENSTEIN also emphasises the importance of removing all traces of hæmoglobin from the centrifuged deposits before sowing the tubes because, in his view, hæmoglobin inhibits the growth of the tubercle bacillus. My observations do not entirely bear out this statement. On many occasions I have obtained cultures directly from the heart blood of experimentally tuberculous animals and from blood artificially infected with tuberculous pus. In these experiments, however, the amount of blood used was not more than sufficient to spread very thinly over the surface of the medium. When thick layers of blood, containing numerous tubercle bacilli, are put on, growth is scanty and may be completely inhibited.

In the course of these tests a method of preparing a blood medium was devised which brings out clearly the inhibitory action of hæmoglobin. A blood egg medium was prepared in the following way: Tubes of plain egg were taken and all the condensation water was removed by pipette. Over the surface of each tube about 0.1 c.c. (2 large drops) of citrated goat's blood was made to flow evenly, and the tubes were kept in a horizontal position for 2 days or until the blood had become so adherent that when the tube was stood vertically none of the blood slipped from the surface. After from 2 to 3 weeks all the blood is absorbed into the medium, which is then ready for use. It was found that when tubes of this blood medium were sown with tuberculous pus from a guinea-pig and incubated, no growth was obtained, although on ordinary egg (or on egg to which goat's blood plasma or sodium citrate had been added in the same way as the blood) sown with equivalent amounts of the pus the colonies were numerous. The tubercle bacilli not only fail to grow on this medium, but eventually they die. If scrapings are taken from the surfaces of blood tubes which have been sown with pus and incubated for more than 2 months, and spread upon ordinary egg, the bacilli, demonstrable microscopically in the scrapings, do not produce colonies. Moreover, if the scrapings are injected into guinea-pigs, they do not cause tuberculosis.

The explanation of the inhibitory action of the medium may perhaps be that the hæmoglobin, having a strong affinity for oxygen, absorbs this from the egg medium itself, thus fixing an element which is essential for the vitality and growth of the tubercle bacillus. The necessity of using only small quantities of untreated blood for success in the culture of tubercle bacilli by directly smearing on the surface of coagulated egg makes impracticable the use of whole blood for demonstrating slight degrees of bacillæmia. One must, as LOEWENSTEIN has recommended, hæmolyse the blood, centrifuge and sow the deposits (I have used the distilled water technique).

The claim of LOEWENSTEIN to have demonstrated tubercle bacilli in the blood of a high proportion of persons suffering from tuberculosis or from certain other affections not hitherto regarded as tuberculous has been contested mainly on two grounds. In the first place, about 30 per cent of his cultures are described as "microscopic positives". COURMONT¹ also has recently reported that the great majority of the 62 positive blood cultures which he obtained from 151 cases were of this kind. What is the nature of these so-called "microscopic cultures"? Nothing is visible in the shape of colonies, but, on scraping the surface of the medium and making a film preparation, acid-fast bacilli are found in greater or less abundance. On subculture they may, according to COURMONT, persist and grow scantily for 2 or 3 generations, but finally they disappear. As WILSON has pointed out, there are many sources of error in the microscopical demonstration of tubercle bacilli, though LOEWENSTEIN and COURMONT are convinced that they were tubercle bacilli from the blood. To account for the failure of the bacilli to develop, COURMONT advances the hypothesis that tubercle bacilli which normally circulate in the blood are attenuated in their virulence and lowered in vitality as the result of the action of bactericidal and other defensive substances in the blood. He also thinks that these bacilli circulating in the blood are young forms which have not yet acquired their protective waxy envelope, and, being, as it were, naked, are very vulnerable. I have never found in my own work that attenuated tubercle bacilli are any less capable of developing colonies than virulent bacilli, and they are also able to multiply in the guinea-pig, though they

¹ *Journal de Médecine de Lyon*, 1933, No. 331, page 627.

do not always produce typical lesions. I therefore cannot accept COURMONT'S hypothesis.

In the second place, it is contended, LOEWENSTEIN has not proved, except in a minority of instances, that his macroscopic cultures were really tubercle bacilli; they may have been acid-fast saprophytes. Among the considerable number of his strains, LOEWENSTEIN reports that 14 were, in fact, acid-fast saprophytes which grew rapidly and abundantly and with a yellow or orange pigment, and there may have been other saprophytic strains which, in the absence of virulence tests, he failed to recognise. But, nevertheless, there is, I think, very little doubt that the majority of the strains which he has obtained, at any rate in the last two or three years, were tubercle bacilli. In the spring of 1932, I was in Vienna, and Professor LOEWENSTEIN showed me a large number of cultures, many of recent origin. They all appeared to me to be cultures of tubercle bacilli, but, in order to make sure, I asked him to send me a selection. He sent me 24 cultures, and I found that 17 were typical human and 7 were typical avian strains. These results were reported in the *Lancet* of September 9th, 1933.

Although his findings had not received any important corroboration, LOEWENSTEIN remained convinced that the tubercle bacilli which grew in his culture tubes actually came from the blood, and, in 1932, at his request, the President of the Health Committee of the League of Nations arranged an international inquiry into his technique of blood cultures, in which I was invited to assist.

THE AUTHOR'S INVESTIGATIONS.

The plan of the investigation, so far as it related to me, was to examine in Cambridge specimens of human blood, taken from persons in England, duplicate portions of which had been sent to Vienna, and to study in Cambridge every strain of acid-fast bacillus obtained at the two places. Professor LOEWENSTEIN asked that each collaborator should send at least 50 specimens of human blood, as failure might attend the earlier efforts of one unused to the technique of blood culture. On account of other work I could not undertake to examine so many specimens of human blood. Moreover, recalling the almost complete failure of English workers to demonstrate tubercle bacilli in human blood and the discordant

results obtained by LOEWENSTEIN and other workers when duplicate specimens of the same blood were examined, I doubted whether final conclusions could be reached by examining human blood only.

For example, the cultivation of 50 or more blood specimens might not yield a single positive result either at Cambridge or at Vienna. On the other hand, some specimens might be positive in Vienna and not in Cambridge and my failure in these instances to obtain cultures could be attributed, as in so many previous independent inquiries, to an imperfect technique. Moreover, mere confirmation subsequently of the fact that the acid-fast organisms obtained in Vienna were tubercle bacilli would not prove that the bacilli had come from the blood.

In order, therefore, to ensure that some of the specimens would contain tubercle bacilli and at the same time to obviate all uncertainty regarding the origin of the tubercle bacilli cultivated from the blood specimens, I arranged, with the full approval of Professor LOEWENSTEIN, to send blood from animals as well as from human beings. By taking serial samples of blood from animals inoculated either intravenously or subcutaneously, one could be certain that a proportion of the specimens submitted to examination would contain tubercle bacilli, and, what was of greater importance, one would be in a position to check the results by comparing the characters of each blood culture with those of the original inoculum.

EXPERIMENTS WITH HUMAN BLOOD.

Previous to this investigation my observations on human blood were limited to four specimens. They were obtained through the kindness of Dr. R. COLLIS from children under 6 years of age ; three were suffering from tuberculous meningitis and one from chorea and a tuberculous hip. The blood, in total about 70 c.c., was used for cultures and the inoculation of ten guinea-pigs. The results of all these tests were negative.

For the present investigation, 15 specimens of human blood were kindly sent to me by Mrs. SCHWABACHER from London and by Dr. STOTT from Papworth, by kind permission of Sir Pendrill VARRIER-JONES. The specimens were obtained from 8 cases of advanced phthisis pulmonalis, 3 cases of tuberculosis of bone or

joint, 3 cases of acute rheumatism and one case of erythema nodosum. One of the phthisis cases died soon afterwards of general tuberculosis and tuberculous meningitis.

Results in Cambridge.

Cultivation Experiments.—Owing either to the small amount of blood supplied or for other reasons, I was unable to make cultures from 7 specimens. The cultures from 8 specimens remained sterile.

Guinea-pig Inoculations.—All the specimens were tested by subcutaneous injection on the guinea-pig, 12 each on two and 3 each on one, the total amount of blood inoculated being 115 c.c. The 27 guinea-pigs were killed in periods ranging from 70 to 305 days and on autopsy were found to be free from any sign of tuberculosis. Cultures sown from the inguinal glands of 4 guinea-pigs which lived from 277 to 305 days remained sterile. My results with human blood therefore were entirely negative.

Results in Vienna.

Of the 15 tubes of human blood sent to Vienna one was broken in the post. Professor LOEWENSTEIN reported that, of the 14 specimens examined by him, 11 were negative and 3 produced macroscopic cultures. He sent me primary cultures from these three specimens. One tube showed about a dozen raised creamy warty colonies. The others were closely studded with raised creamy colonies, aggregated together in places to form warty masses. Two of the cultures were contaminated and were freed from the contaminants by treatment with potassium hydrate or sulphuric acid.

In subculture, each strain produced the luxuriant growths of the eugonic human type of tubercle bacillus and each strain was virulent for the guinea-pig, producing general tuberculosis of the type which usually follows inoculation of human bacilli.

I call special attention to the number of colonies which grew on Professor LOEWENSTEIN'S tubes, although the actual amount of blood dealt with was no more than 1.5 c.c. in one and 2.5 c.c. in another instance ; I have already stated that the cultures were of virulent human bacilli. It is impossible to believe that 3 samples of blood containing tubercle bacilli in such abundance could each be so divided that the Vienna portion contained tubercle bacilli

and the Cambridge none, or that blood infected with virulent tubercle bacilli to that degree could fail to produce tuberculosis in any of 5 guinea-pigs.

EXAMINATION OF ANIMAL BLOOD.

Forty-six samples of blood from 3 goats and 2 calves were taken. Goats were used in 3 experiments because of the ease with which large serial samples of blood can be obtained from the jugular vein in this species of animal. The amount of blood taken for each observation was 20 c.c., which was immediately run into a tube containing 3 c.c. of 10 per cent citrate of soda. Half of the citrated blood was sent to Vienna and half was retained in Cambridge. The subcutaneous method of inoculating 2 of the goats was chosen because previous experiments on other species of animals had shown that a tuberculous bacillæmia of not too great an intensity can be produced with certainty in this way.

The experiments to which I refer were done in 1906 by F. GRIFFITH and myself. Nineteen animals of 8 different species (1 calf, 1 monkey, 5 pigs, 3 rabbits, 3 guinea-pigs, 3 cats, 2 rats and 1 chicken) were inoculated subcutaneously with cultures of bovine or human bacilli in doses of 5 to 44 mg. Fifteen of the animals were killed 24 to 48 hours after inoculation and cultures and guinea-pig inoculations were made with the blood and various tissues of the body, including in all cases the spleen.

Cultures of tubercle bacilli were obtained directly from the untreated blood in 4 instances, and from the spleen in 14 instances, the number of colonies from the blood ranging from one to eight and from the spleen from one to numerous. All the blood samples except one—the guinea-pig in this case dying prematurely—caused tuberculosis in guinea-pigs.

The experiments showed that tubercle bacilli were distributed over the body of an animal within 24 hours after subcutaneous inoculation and that this dissemination occurred in every species tested, whether the bacilli were fully virulent or not virulent for that species. It is probable that most, if not all, of the bacilli found in the blood soon after subcutaneous inoculation entered the blood stream directly at the seat of inoculation through capillaries

which had been injured by the needle or ruptured by the swelling caused by the fluid injected.

One experiment was done to determine the duration of the bacillæmia which follows immediately after subcutaneous inoculation. Five swine were inoculated subcutaneously behind the ear, each with 20 mg. of virulent bovine bacilli. They were killed at intervals of 1, 3, 5, 8, and 14 days and the heart blood was used for cultivation and inoculation experiments. A few colonies were cultivated from the blood of the animal killed 24 hours after inoculation, but none from any of the other specimens. Blood from the swine was found to be infective for the guinea-pig up to the fifth day and possibly the eighth, but not the fourteenth. It should be stated here that the amount of blood used for cultures in all the experiments was just sufficient to spread thinly over the surface of the medium, whereas each guinea-pig received 2 c.c. The evidence showed that tubercle bacilli were numerous in the blood 24 hours after inoculation and gradually diminished subsequently. One could not say whether or not the bacilli had disappeared completely from the blood between the eighth and fourteenth days, since the amount of blood tested was very small.

Further experiments were obviously necessary to determine more precisely the duration of the initial dispersal of bacilli which occurs after subcutaneous inoculation and, if this is fleeting, as the experiment on pigs seemed to indicate, whether there are in the later stages of an experiment repeated invasions of the blood from the secondary foci which are set up.

The occasion of my collaboration with Professor LOEWENSTEIN afforded the opportunity of gaining such further information, with an improved technique of blood culture, on tuberculous bacillæmia in experimentally infected animals.

Experiment I.

The first goat was inoculated on the left side of the neck with 5 mg. of a virulent dysgonic bovine strain derived from a case of renal tuberculosis in a woman of 37.

The goat died 69 days later of tuberculosis of the lungs, which were consolidated and closely beset with coalescing caseating nodules; the caudal lobes contained cavities, the pus in which was

swarming with tubercle bacilli. The thoracic glands were moderately enlarged and tuberculous and there were two small caseous nodules in the spleen.

At intervals of 24 hours during the first 8 days, and of 3, 4 or 7 days subsequently till the death of the goat, 20 c.c. of blood were withdrawn from the right jugular vein, the total number of samples being 22.

Results in Cambridge.

The results are summarised on page 302. It will be seen from this table that all the cultures with quantities of blood varying from 2 to 7 c.c. were negative and that only one of 38 guinea-pigs inoculated with blood became tuberculous. This guinea-pig was one of two which had been inoculated with blood drawn on the second day of the experiment. A culture obtained from the guinea-pig was dysgonic and virulent for the rabbit and identical in every respect with the strain inoculated into the goat.

Results in Vienna.

Professor LOEWENSTEIN reported 11 positives, of which 5 were macroscopic and 6 were microscopic. He sent me one or more tubes from each positive blood.

The macroscopic cultures showed numerous greyish white or creamy colonies, in places aggregated, which proved on investigation to be composed of typical human tubercle bacilli. The cultures were virulent for the guinea-pig and produced slight tuberculosis only in rabbits inoculated subcutaneously (doses 5 to 20 mg.). The rabbits, killed 96 to 98 days later, showed local abscesses, small purulent foci in the adjacent scapular gland in 4 instances and a few small trivial foci in the lungs; the kidneys and other organs and glands were free from macroscopic lesions.

The microscopic cultures are considered later, together with other similar cultures obtained in the other experiments.

Experiment II.

A second goat was inoculated subcutaneously on the left side of the neck with approximately 5 mg. of culture of bovine bacilli obtained directly from the sputum of a girl of 20 with phthisis

pulmonalis. The goat died, 35 days after inoculation, of general miliary tuberculosis, very severe in the lungs.

Nine specimens of blood taken at intervals of 24 hours during the first 4 days and of 7 days afterwards, the last specimen directly from the right ventricle after the death of the animal, were examined.

Results in Cambridge.

Cultures were made from each specimen, except the second and the last, which were used wholly for the inoculation of guinea-pigs. Quantities of 4 to 6 c.c. of blood were used for each culture test but only one positive result was obtained, a single colony growing on one of the tubes sown with 24-hour blood.

Thirteen guinea-pigs in all were inoculated and one became tuberculous. This was one of the three inoculated with second-day blood. The culture recovered from the guinea-pig and the single colony direct strain were identical with that inoculated. Each strain was inoculated subcutaneously into a rabbit and produced typical bovine general tuberculosis, the rabbits dying in 64 and 75 days respectively.

The results show that there was a tuberculous bacillæmia 24 and 48 hours after the inoculation of the goat and not subsequently. The number of bacilli present in the blood on these two occasions must have been very small, since, in the first instance, only one colony was cultivated from 4 c.c. of citrate blood, while 8 c.c. of the same sample was not infective for two guinea-pigs, and in the second only one of three guinea-pigs each inoculated with 4 c.c. of citrate blood became tuberculous.

Results in Vienna.

Professor LOEWENSTEIN reported that the first- and second-day specimens had given microscopic positives and that the seventh-day specimen was macroscopically positive. He sent me two tubes from the first specimen, both grossly contaminated with other bacteria but showing acid-fast bacilli in moderate number, and a subculture of the macroscopic culture. I was unable to cultivate anything from this last tube, and a guinea-pig inoculated with a washing of its surface did not develop tuberculosis. I, however,

obtained a culture through the guinea-pig from one of the microscopic cultures. The results of testing this strain are given later.

Experiment III.

The third goat was inoculated intravenously in the left jugular vein with 50 mg. of BCG. The goat died of pneumonia 9 days after inoculation, the lungs being in a state of red hepatisation without visible tubercles.

Blood was withdrawn from the right jugular vein 1, 5 and 24 hours and 2, 3, 5, 6 and 9 days after inoculation.

Results in Cambridge.

The cultivation method only was employed. BCG was recovered from all the specimens, the 1-hour blood producing numerous colonies and the others colonies in progressively diminishing number. From the last specimen one colony only of BCG was obtained.

Results in Vienna.

Two tubes (5-hour and 2-day specimens) were broken in the post. The 1-, 6- and 9-day specimens were reported negative. The 1-hour and the 3- and 5-day specimens were macroscopic positives.

I investigated these cultures, all of which were luxuriant, and found the first (from the 1-hour blood) to be composed of BCG only. The other two were identical culturally with tubercle bacilli of human type and were virulent for guinea-pigs. Each strain was tested on four guinea-pigs, one being inoculated with a general scraping and three with single colonies. All the guinea-pigs developed progressive general tuberculosis.

Experiment IV.

Blood was drawn from a calf 1, 3 and 24 hours after revaccination intravenously with 100 mg. BCG.

Results in Cambridge.

Cultures of the blood drawn 1 and 3 hours after inoculation were negative. A positive result was obtained with the 24-hour blood, 8 c.c. of which produced one colony of BCG on 12 tubes sown.

Results in Vienna.

Professor LOEWENSTEIN reported that the 1- and the 24-hour specimens were negative and that the 3-hour specimen had given a microscopic positive. The results of examining the latter culture are given later.

Experiment V.

Blood was drawn from a calf $\frac{1}{2}$ hour and $22\frac{1}{2}$ hours after revaccination intravenously with 100 mg. BCG.

Results in Cambridge.

Four colonies of BCG were obtained from 8 c.c. of the $\frac{1}{2}$ -hour blood and three colonies from 10 c.c. of the $22\frac{1}{2}$ -hour blood.

Results in Vienna.

Professor LOEWENSTEIN obtained a positive result with the $\frac{1}{2}$ -hour specimen. The tube he sent to Cambridge had one colony, which proved to be BCG. His experiments with the $22\frac{1}{2}$ -hour blood were negative.

RESULTS WITH PROFESSOR LOEWENSTEIN'S MICROSCOPIC CULTURES.

As already stated, Professor LOEWENSTEIN submitted 8 microscopic cultures, 6 from one goat, 1 from another goat and 1 from a calf. On examining film preparations of scrapings from two of the cultures, I was unable to find acid-fast bacilli; subcultures from these tubes remained sterile, the guinea-pigs inoculated did not develop tuberculosis and cultures from their inguinal glands remained sterile. The film preparations from the six other cultures showed acid-fast bacilli varying in number from scattered to nume-

rous. In 3 tubes acid-fast bacilli were the only organisms found, while in the other 3 there were also numerous spore-bearing bacilli or cocci.

As the cultures when I received them were more than 6 months old I did not attempt direct subcultures but instead injected in each instance an emulsion of a scraping from the surface subcutaneously into a guinea-pig.

The guinea-pigs died or were killed after periods ranging from 66 to 85 days. The one killed 85 days after inoculation showed no sign of disease; cultures, however, from its inguinal glands yielded a moderate number of colonies of acid-fast bacilli. The remaining five guinea-pigs showed lesions at the seats of inoculation of the emulsions, either a focus of pus or a minute ulcer discharging pus or, in two cases, a pea-sized caseo-purulent abscess in the thigh muscles. Two inguinal glands of one guinea-pig contained each a pea-sized caseo-purulent abscess. The inguinal glands of the others were normal in size and free from macroscopic lesions. None of the guinea-pigs showed any sign of visceral tuberculosis. Acid-fast bacilli were found in the pus from each guinea-pig.

Cultures were made from the inguinal glands of each guinea-pig and colonies of acid-fast bacilli were obtained. In primary culture and in subculture, the six strains exhibited the cultural characters of the avian type of tubercle bacillus. They were each tested on the fowl and produced rapidly fatal general tuberculosis, the lesions swarming with acid-fast bacilli. Four of the strains were tested intravenously on the rabbit and caused acute rapidly fatal septicæmic tuberculosis.

The six strains were therefore typical avian strains.

RECIPROCAL INVESTIGATION OF STRAINS AT CAMBRIDGE AND COPENHAGEN.

The importance of corroboration in the classification of the strains submitted by Professor LOEWENSTEIN was recognised. I therefore sent to the State Serum Institute, Copenhagen, cultures of ten Vienna strains (from Cambridge blood samples 22, 24, 25, 26, 29, 32, 36, 37, 38 and 39) which Dr. K. A. JENSEN kindly typed. He also typed the two strains which I had recovered from Cambridge specimens 3 and 23. In every instance my classification of these strains was confirmed by Dr. JENSEN.

In return, Dr. K. A. JENSEN sent to me 4 strains which had been obtained in connection with 2 Copenhagen cases. Two of the strains were cultivated in Vienna, each from a different specimen of blood. The other 2 were obtained in Copenhagen from the same 2 cases, not however from the blood specimens with which JENSEN had had negative results, but from the sputum in one case and from lupoid skin in the other. The results of my examination of the strains are as follows : JENSEN's culture from the sputum was of the human type, while LOEWENSTEIN's culture from the blood was an acid-fast saprophyte. JENSEN's culture from the lupoid skin was an attenuated bovine strain. LOEWENSTEIN's culture from the blood in this case belonged to the human type. My results with these strains were in accordance with those obtained by Dr. K. A. JENSEN.

SUMMARY OF BLOOD EXAMINATIONS AT CAMBRIDGE.

Fifteen specimens of human blood and 45 specimens of animal blood were examined for tubercle bacilli by cultivation and animal inoculation.

The results with human blood (from 11 cases of tuberculosis, 3 of acute rheumatism and 1 of erythema nodosum) were entirely negative.

Of the 45 specimens of animal blood, 32 were from 2 goats which had been inoculated subcutaneously with tubercle bacilli. A tuberculous bacillæmia was demonstrated in one goat 24 hours and in both goats 48 hours after inoculation but not subsequently, though both animals died of general tuberculosis and the last specimen in one instance was taken directly from the heart.

Eight specimens were from a goat which had been injected intravenously with a large dose of BCG. The organisms were cultivated from the blood during the 9 days the animal lived after injection, but in steadily decreasing numbers.

The remaining 5 specimens were from two calves which had been revaccinated intravenously each with 100 mg. of BCG and were taken during the 24 hours following injection. Three specimens from one calf yielded one colony only of BCG and two specimens from the other produced altogether seven (4 and 3).

My results therefore corroborate the conclusions of other English observers—that it is rarely possible to demonstrate tubercle bacilli

in the blood of human beings and that in animals inoculated subcutaneously a tuberculous bacillæmia is transient, the tubercle bacilli being rapidly filtered off by the tissues.

SUMMARY OF RESULTS IN VIENNA WITH CAMBRIDGE BLOOD SPECIMENS.

Professor LOEWENSTEIN reported positive results with 22 of the 57 specimens received by him, 3 having been lost in the post. He sent cultures from 21 of these to Cambridge for identification.

Three of the cultures were from 3 out of 14 specimens of human blood (one lost in post). These proved to be of eugonic human tubercle bacilli.

Fourteen of the cultures were from 14 of the 32 specimens of blood from the two goats inoculated subcutaneously with bovine tubercle bacilli and 13 of these (6 macroscopic and 7 microscopic) were sent to Cambridge. Of the 6 macroscopic cultures 5, all from one goat, were of eugonic human bacilli and one failed to produce subcultures, the tube sent to me showing no growth or bacilli microscopically. Of the 7 microscopic cultures 5 yielded cultures of avian bacilli and 2 gave negative results.

Three of the cultures were from 3 out of 6 specimens of blood from the goat injected intravenously with BCG. One of the cultures was composed of BCG only and was not virulent for the guinea-pig. The other two were virulent for the guinea-pig.

The remaining two cultures were obtained from the two calves injected intravenously with BCG. One culture from one calf was of BCG. The second culture (microscopic) from the other calf was of avian tubercle bacilli.

COMPARISON OF RESULTS.

The experiments with 29 specimens were negative both at Cambridge and Vienna.

With 6 specimens (of animal blood) positive results were obtained at Cambridge and negative results in Vienna. The cultures recovered from the animals at Cambridge were identical with those injected.

With 16 specimens (3 human and 13 animal), the results were positive in Vienna and negative at Cambridge. Of the 13 cultures

from animals 10 were typed at Cambridge and each proved to be different in character from that injected.

With 6 specimens (of animal blood) positive results were obtained both at Cambridge and Vienna. In two instances, both in animals injected with BCG, the findings were in agreement, BCG being recovered at both places. In 3 instances the results were discordant. The three strains recovered from the specimens at Cambridge were identical with those inoculated. The three strains from Vienna were different in type from those injected—namely, two human strains from a goat injected with BCG, and one avian strain from a goat injected with bovine bacilli. In the remaining instance no comparison could be made, as the Vienna culture was not sent to Cambridge.

Summary of Results with Human Blood.

| Number of sample | Sex and age of patient | Clinical diagnosis | Cambridge | | | Vienna | |
|-------------------------------|------------------------|---------------------------------------|------------|-------------------------|---|----------|---------------|
| | | | Cultures | Guinea-pig inoculations | | Cultures | |
| Amount of blood tested (c.c.) | Number of guinea-pigs | Result | | | | | |
| 10 ... | F.11 | Erythema nodosum | Negative | 4.0 | 2 | No T. | Negative |
| 12 ... | M.40 | Advanced phthisis | " | 5.5 | 2 | " | " |
| 14 ... | M.23 | Chronic phthisis | " | 5.0 | 2 | " | " |
| 15 ... | M.24 | Chronic phthisis | " | 3.5 | 2 | " | " |
| 25 ... | M.22 | Pulmonary and abdominal tubercle | Not tested | 2.8 | 2 | " | Human culture |
| 36 ... | M.45 | Advanced phthisis | " | 2.5 | 1 | " | " |
| 40 ... | M.30 | Pulmonary tuberculosis ; died of G.T. | " | 9.5 | 2 | " | " |
| 41 ... | M.47 | Chronic phthisis | Negative | 8.0 | 1 | " | Tube broken |
| 44 ... | M.10 | Acute rheumatism | " | 14.0 | 2 | " | Negative |
| 45 ... | M.14 | Acute tonsillitis and rheumatism | " | 10.0 | 2 | " | " |
| 46 ... | M ? | Acute rheumatism | Not tested | 10.0 | 2 | " | " |
| 47 ... | M.10 | Tb. hip and kidney | " | 10.0 | 2 | " | " |
| 48 ... | M.7 | Tb. hip | " | 14.0 | 1 | " | " |
| 49 ... | M.4 | Tb. spine | " | 14.0 | 2 | " | " |
| 52 ... | M.24 | Tb. pyopneumothorax | Negative | 6.0 | 1 | " | " |

Experiment I.—Goat 154 (inoc. subcut., 5 mg. bovine culture).

| Sample number | Cambridge | | | | | | Vienna Cultures |
|---------------|---|-------------------------------|----------|-------------------------------|-----------------------|------------------------|----------------------|
| | Interval after inoculation of goat (days) | Cultivation experiments | | Guinea-pig inoculations | | | |
| | | Amount of blood tested (c.c.) | Result | Amount of blood tested (c.c.) | Number of guinea-pigs | Result | |
| 1 ... | —* | — | — | 2.0 | 1 | No T. | — |
| 2 ... | 1 | 3 | Negative | 8.0 | 2 | " | — |
| 3 ... | 2 | 2 | " | 9.0 | 2 | (a) No T. (b) G. T. | — |
| 4 ... | 3 | 4 | " | 7.0 | 2 | No T. | Micro + (avian) |
| 5 ... | 4 | 2 | " | 10.0 | 2 | " | — |
| 6 ... | 5 | 2 | " | 10.0 | 2 | " | Micro + (avian) |
| 7 ... | 6 | 4 | " | 7.5 | 2 | " | — |
| 8 ... | 7 | 4 | " | 9.5 | 2 | " | — |
| 9 ... | 8 | A few drops directly | " | 10.0 | 2 | " | — |
| 11 ... | 11 | 4 | " | 6.0 | 1 | " | Micro + (avian) |
| 13 ... | 14 | 3 | " | 9.0 | 2 | " | Micro + (avian) |
| 16 ... | 18 | 4 | " | 7.0 | 2 | " | — |
| 21 ... | 21 | 4 | " | 7.5 | 2 | " | — |
| 24 ... | 25 | 4 | " | 7.5 | 2 | " | Macro + (human) |
| 26 ... | 32 | 7 | " | 5.0 | 1 | " | Macro + (human) |
| 27 ... | 39 | 5 | " | 6.0 | 1 | " | Macro + (human) |
| 28 ... | 43 | 5 | " | 6.0 | 2 | " | — |
| 29 ... | 46 | 6 | " | 6.0 | 1 | " | Macro + (human) |
| 30 ... | 50 | 3 | " | 9.0 | 2 | " | Micro + ¹ |
| 31 ... | 53 | 6 | " | 6.0 | 2 | " | Micro + ¹ |
| 37 ... | 56 | 4 | " | 8.0 | 2 | " | Macro + (human) |
| 43 ... | 61 | 6 | " | 5.0 | 1 | " | — |
| 51 ... | 65 | 6 | " | 5.0 | 1 | " | — |

Experiment II.—Goat 160 (inoc. subcut., 5 mg. bovine culture).

| Sample number | Cambridge | | | | | | Vienna Cultures |
|---------------|---|-------------------------------|------------------|-------------------------------|---------------------------------------|--------|----------------------|
| | Interval after inoculation of goat (days) | Cultivation experiments | | Guinea-pig inoculations | | | |
| | | Amount of blood tested (c.c.) | Result | Amount of blood tested (c.c.) | Duration of life of guinea-pig (days) | Result | |
| 53 ... | 1 | 4 | 1 colony of T.B. | 4.0 | D.44 | No T. | Micro + (avian) |
| 54 ... | 2 | None | — | 4.0 | K.73 | " | — |
| | | | | 4.0 | K.79 | " | |
| | | | | 4.0 | K.78 | G.T. | |
| | | | | 4.0 | K.79 | No T. | |
| 55 ... | 3 | 6 | Negative | 6.0 | K.102 | " | — |
| 56 ... | 4 | 6 | " | 4.5 | K.101 | " | — |
| 57 ... | 7 | 6 | " | 5.0 | D.201 | " | Macro + ² |
| 58 ... | 14 | 6 | " | 6.0 | D.184 | " | — |
| 59 ... | 21 | 6 | " | 6.0 | D.180 | " | — |
| 60 ... | 28 | 6 | " | 6.0 | K.223 | " | — |
| 61 ... | 35 | None | — | 2.5 | D.225 | " | — |
| | | | | 2.0 | D.107 | " | — |

* Before inoculation.

¹ The tubes sent gave negative results at Cambridge.² Not sent to Cambridge.³ Subculture sent to Cambridge proved sterile.

Experiment III.—Goat 159 (inoc. intrav., 50 mg. BCG).

| Sample number | Interval after inoculation of goat | Culture results in Cambridge | Culture results in Vienna |
|---------------|------------------------------------|---|---|
| 32 | 1 hour | Numerous colonies on all tubes | Moderately numerous BCG colonies |
| 33 | 5 hours | All tubes produced colonies, from a dozen up to numerous | Tube broken in post |
| 34 | 24 hours | 100 colonies from 9 c.c. blood | Negative |
| 35 | 2 days | 96 colonies from 7 c.c. blood | Tube broken in post |
| 38 | 3 days | 37 colonies from 10 c.c. blood | Culture eugonic, virulent for guinea-pigs |
| 39 | 5 days | 3 colonies on 2 tubes, 4 tubes sterile, 4 tubes contaminated; 10 c.c. blood | Culture eugonic, virulent for guinea-pigs |
| 42 | 6 days | 10 colonies on 5 tubes, 5 tubes sterile; 10 c.c. blood | Negative |
| 50 | 9 days | One colony from 5 c.c. blood | Negative |

Experiment IV.—Calf 160 (revaccinated intrav. with 100 mg. BCG).

| | | | |
|----------|----------|-------------------------------|-----------------|
| 18 | 1 hour | Negative | Negative |
| 19 | 3 hours | Negative | Micro + (avian) |
| 20 | 24 hours | One colony of BCG on 10 tubes | Negative |

Experiment V.—Calf 164 (revaccinated intrav. with 100 mg. BCG).

| | | | |
|----------|-----------|---|-------------------|
| 22 | ½ hour | 8 c.c. blood; 4 colonies BCG on 11 tubes | One colony of BCG |
| 23 | 22½ hours | 10 c.c. blood; 3 colonies BCG (one colony on each of 3 tubes) on 12 tubes | Negative |

3. REPORT ON INVESTIGATIONS REGARDING THE LOEWENSTEIN TECHNIQUE OF CULTIVATING TUBERCLE BACILLI FROM BLOOD

by

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The technique followed has been, in the main, that described on pages 253 to 256. We have departed from it only in respect of a few minor details that may be summed up as follows :

A large number of blood-samples were collected in the double *haemauls* recommended by the Loewenstein Institute. One part of each sample was sent to LOEWENSTEIN and the remaining one examined at the Copenhagen State Serum Institute. Beside the four tubes with the special LOEWENSTEIN medium, we inoculated two of our own routine tubes.

Some of the later blood-samples (Nos. 208-235) were inoculated only on our medium, since we found this more efficient than LOEWENSTEIN'S own medium, as will be shown later. After six weeks' incubation, we made smears from half of the tubes by scraping the surface of the medium, staining with the Ziehl-Neelsen stain, and examining them very thoroughly under the microscope. The remaining tubes were kept in the incubator for at least four months before final examination.

The results of the investigation are given in Table I. All the cases of dementia præcox were examined clinically six months after the blood-samples had been taken, to ensure that the diagnosis could be maintained and to find out whether the case-histories and other examinations suggested tuberculosis. The results of these enquiries are also to be found in Table I. It is to be remarked that in only 2 out of these 40 cases of dementia præcox did the clinical examination disclose the existence of tuberculosis.

Forty-one of the blood-samples entered in Table I were also sent to Professor KOLLE, Staatliches Institut für experimentelle

Therapie, Frankfort-on-Main, and 8 of these again were reforwarded thence to Professor UHLENHUT, Hygienisches Institut, Freiburg-in-Breisgau. The results obtained at these institutes are also given in Table I.

Abbreviations used in the tables :

Ma = Macro-colonies—*i.e.*, macroscopically visible colonies of tubercle bacilli, observed for at least four months.

Mi = Micro-colonies—*i.e.*, acid- and alcohol-fast rods resembling *B. Koch* and found in smears of surface material from the tubes.

Mi + subc. = Micro-colonies which were subcultured.

Mi - subc. = Micro-colonies which could not be subcultured.

D. M. = Direct microscopy of blood sediment.

Table I.

| Diagnosis | COPENHAGEN | | | VIENNA | | | | FRANKFORT A/M. | | |
|---|------------|-----|-----|--------|------------|---------------|---------------|-------------------|-----|-----|
| | No. | Ma. | Mi. | No. | Ma. | Mi + subc. | Mi - subc. | No. | Ma. | Mi. |
| Pulm. Tb. T.B. + | 5 | 0 | 0 | 11753 | 0 | 0 | 0 | | | |
| " " T.B. + | 6 | 0 | 0 | 11722 | 0 | 0 | 0 | | | |
| " " T.B. + | 7 | 0 | 0 | 11716 | 0 | 0 | 0 | | | |
| " " T.B. + | 8 | 0 | 0 | 11715 | + | | | | | |
| " " T.B. + | 9 | 0 | 0 | 11721 | + | | | | | |
| " " T.B. + | 10 | 0 | 0 | 11720 | 0 | 0 | 0 | | | |
| " " T.B. + | 11 | 0 | 0 | 11752 | 0 | 0 | 0 | | | |
| " " T.B. + | 12 | 0 | 0 | 11717 | 0 | 0 | 0 | | | |
| " " T.B. + | 13 | 0 | 0 | 11718 | 0 | 0 | 0 | | | |
| " " T.B. + | 14 | 0 | 0 | 11719 | 0 | 0 | 0 | | | |
| Bursitis trochant. T.B. + | 35 | 0 | 0 | 11942 | coagulated | | | | | |
| Lupus vulgaris T.B. + | 36 | 0 | 0 | 11926 | 0 | + | | | | |
| " " T.B. + | 37 | 0 | 0 | 11941 | 0 | 0 | 0 | | | |
| " " T.B. + | 38 | 0 | 0 | 11928 | 0 | 0 | 0 | | | |
| " " T.B. + | 39 | 0 | 0 | 11924 | 0 | 0 | 0 | | | |
| " " T.B. + | 40 | 0 | 0 | 11925 | 0 | 0 | 0 | | | |
| " " T.B. + | 41 | 0 | 0 | 11927 | 0 | + | | | | |
| " " T.B. + | 54 | 0 | 0 | 12139 | 0 | + | | | | |
| Tb. of the conjunctiva and of the cervical glands T.B. + | 55 | 0 | 0 | 12123 | 0 | 0 | 0 | | | |
| Lupus vulgaris | 56 | 0 | 0 | 12126 | 0 | 0 | 0 | | | |
| Lupus erythemat. | 57 | 0 | 0 | 12127 | 0 | 0 | 0 | | | |
| Pulm. Tb. T.B. + | 58 | 0 | 0 | 12124 | 0 | 0 | 0 | | | |
| " " T.B. + | 59 | 0 | 0 | 12125 | 0 | 0 | 0 | | | |
| " " T.B. + | 60 | 0 | 0 | 12129 | 0 | 0 | 0 | | | |
| " " T.B. + | 61 | 0 | 0 | 12122 | 0 | 0 | 0 | | | |
| " " T.B. + | 62 | 0 | 0 | 12128 | + | | | | | |
| " " T.B. + | 63 | 0 | 0 | 12137 | 0 | 0 | 0 | | | |
| Tb. of the hip T.B. + | 64 | 0 | 0 | 12138 | 0 | 0 | 0 | | | |
| Tb. of the cervical glands T.B. + | 65 | 0 | 0 | 12196 | 0 | 0 | 0 | | | |
| Tb. of the spine T.B. + | 66 | 0 | 0 | 12194 | 0 | 0 | 0 | | | |
| Pulm. Tb. T.B. + | 67 | 0 | 0 | 12195 | 0 | 0 | 0 | | | |
| Tb. of the cervical glands T.B. + | 68 | 0 | 0 | 12197 | 0 | 0 | 0 | | | |
| Pulm. Tb. T.B. + | 69 | 0 | 0 | 12198 | 0 | 0 | 0 | | | |
| " " T.B. + | 83 | 0 | 0 | 12334 | 0 | 0 | 0 | | | |
| Dementia præcox | 84 | 0 | 0 | 12337 | 0 | 0 | 0 | | | |
| " " " | 85 | 0 | 0 | 12305 | 0 | 0 | 0 | | | |
| " " " | 86 | 0 | 0 | 12304 | 0 | 0 | 0 | | | |
| " " " | 87 | 0 | 0 | 12303 | 0 | 0 | 0 | | | |
| " " " | 88 | 0 | 0 | 12341 | 0 | 0 | 0 | | | |
| " " " | 89 | 0 | 0 | 12336 | 0 | 0 | 0 | | | |
| " " " | 90 | 0 | 0 | 12339 | 0 | 0 | 0 | | | |
| Mania depress. | 91 | 0 | 0 | 12301 | 0 | 0 | 0 | | | |
| Dementia præcox | 92 | 0 | 0 | 12300 | 0 | 0 | 0 | | | |
| " " " | 93 | 0 | 0 | 12302 | 0 | 0 | 0 | | | |
| Pulm. Tb. T.B. + | 94 | 0 | 0 | 12333 | 0 | 0 | 0 | | | |

BLOOD CULTURE OF B. TUBERCULOSIS

| Diagnosis | COPENHAGEN | | | VIENNA | | | | FRANKFORT A/M. | | |
|--------------------------------------|------------|-----|-----|-------------------------|-----|---------------|---------------|-------------------|-----|-----|
| | No. | Ma. | Mi. | No. | Ma. | Mi + subc. | Mi - subc. | No. | Ma. | Mi. |
| Urogenital Tb. T.B. + | 95 | 0 | 0 | 12335 | 0 | 0 | 0 | | | |
| Psychogenic psychosis | 96 | 0 | 0 | 12338 | 0 | 0 | 0 | | | |
| Dementia præcox | 97 | 0 | 0 | 12340 | 0 | 0 | 0 | | | |
| | 98 | 0 | 0 | 12366 | 0 | 0 | 0 | | | |
| | 99 | 0 | 0 | 12369 | 0 | 0 | 0 | | | |
| | 100 | 0 | 0 | 12385 | 0 | 0 | 0 | | | |
| | 101 | 0 | 0 | 12367 | 0 | 0 | 0 | | | |
| | 102 | 0 | 0 | 12362 | 0 | 0 | 0 | | | |
| | 103 | 0 | 0 | 12363 | 0 | 0 | 0 | | | |
| Urogenital Tb. T.B. + = 95 | 104 | 0 | 0 | 12383 | 0 | 0 | + | | | |
| Dementia præcox | 105 | 0 | 0 | 12368 | 0 | 0 | 0 | | | |
| | 106 | 0 | 0 | 12381 | 0 | 0 | 0 | | | |
| | 107 | 0 | 0 | 12382 | 0 | 0 | 0 | | | |
| | 108 | 0 | 0 | 12384 | 0 | 0 | 0 | | | |
| Tb. of the cervical glands T.B. + | 109 | 0 | 0 | 12386 | 0 | 0 | 0 | | | |
| Tb. of the knee T.B. + | 110 | 0 | 0 | 12364 | 0 | 0 | 0 | | | |
| T.B. + = 110 | 111 | 0 | 0 | 12365 | 0 | 0 | 0 | | | |
| Pleurisy T.B. + | 124 | 0 | 0 | 12498 | 0 | 0 | 0 | | | |
| T.B. + | 125 | 0 | 0 | 12496 | 0 | 0 | 0 | | | |
| Lupus vulgaris T.B. + | 136 | 0 | 0 | 12494 | 0 | 0 | 0 | | | |
| | 137 | 0 | 0 | 12501 | 0 | 0 | 0 | | | |
| | 138 | 0 | 0 | 12500 | 0 | 0 | 0 | | | |
| | 139 | 0 | 0 | 12503 | 0 | 0 | 0 | | | |
| | 140 | 0 | 0 | 12497 | 0 | 0 | 0 | | | |
| | 141 | 0 | 0 | 12499 | 0 | 0 | 0 | | | |
| | 142 | 0 | 0 | 12502 | 0 | 0 | 0 | | | |
| | 143 | 0 | 0 | 12495 | 0 | 0 | 0 | | | |
| | 144 | 0 | 0 | 12642 | 0 | + | 0 | | | |
| Pulm. and urogenital Tb. T.B. + | 145 | 0 | 0 | 12756 | 0 | 0 | 0 | | | |
| Tb. of the elbow T.B. + | 146 | 0 | 0 | 12755 | 0 | 0 | 0 | | | |
| Lupus vulgaris | 147 | 0 | 0 | 12641 | 0 | 0 | 0 | | | |
| | 150 | 0 | 0 | 12798 | 0 | 0 | 0 | | | |
| | 151 | 0 | 0 | 12801 | 0 | 0 | + | | | |
| Erythema multiforme | 152 | 0 | 0 | 12643 | 0 | 0 | 0 | | | |
| Lupus vulgaris | 153 | 0 | 0 | 12803 | 0 | 0 | 0 | | | |
| | 154 | 0 | 0 | 12799 | 0 | 0 | 0 | | | |
| | 155 | 0 | 0 | 12800 | 0 | 0 | 0 | | | |
| | 156 | 0 | 0 | 12802 | 0 | 0 | 0 | | | |
| Pulm. Tb. T.B. + | 157 | 0 | 0 | 12805 | 0 | 0 | 0 | | | |
| Lupus vulgaris | 158 | 0 | 0 | 12804 | 0 | 0 | 0 | | | |
| Dementia præcox | 160 | 0 | 0 | 12913 | 0 | 0 | + | | | |
| | 161 | 0 | 0 | 12901 | 0 | 0 | 0 | | | |
| | 162 | 0 | 0 | 12897 | 0 | 0 | 0 | | | |
| | 163 | 0 | 0 | 12900 | 0 | 0 | 0 | | | |
| | 164 | 0 | 0 | 12915 | 0 | 0 | 0 | | | |
| | 165 | 0 | 0 | 12908 | 0 | 0 | 0 | | | |
| | 166 | 0 | 0 | 12899 | 0 | 0 | 0 | 403 | 0 | 0 |
| | 167 | 0 | 0 | 12898 | 0 | 0 | 0 | 404 | 0 | 0 |
| | 168 | 0 | 0 | 12905 | 0 | 0 | + | 405 | 0 | 0 |
| | 169 | 0 | 0 | 12907 | 0 | 0 | 0 | 406 | 0 | 0 |
| | 170 | 0 | 0 | 12917 | 0 | 0 | 0 | 407 | 0 | 0 |
| | 171 | 0 | 0 | 12912 | 0 | 0 | 0 | 408 | 0 | 0 |
| | 172 | 0 | 0 | 12906 | 0 | 0 | 0 | 409 | 0 | 0 |
| | 173 | 0 | 0 | 12904 | 0 | 0 | 0 | 410 | 0 | 0 |
| | 174 | 0 | 0 | 12902 | 0 | 0 | 0 | 411 | 0 | 0 |
| | 175 | 0 | 0 | 12903 | 0 | 0 | 0 | 412 | 0 | 0 |
| | 176 | 0 | 0 | 12916 | 0 | 0 | 0 | | | |
| | 177 | 0 | 0 | 12918 | 0 | 0 | 0 | | | |
| | 178 | 0 | 0 | 12911 | 0 | 0 | 0 | | | |
| | 179 | 0 | 0 | 12914 | 0 | 0 | 0 | | | |
| Tb. verrucosa T.B. + | 180 | 0 | 0 | 13050 | 0 | 0 | 0 | 421 | 0 | 0 |
| Lupus vulgaris T.B. + | 181 | 0 | 0 | 13051 | 0 | 0 | 0 | 422 | 0 | 0 |
| Tb. verrucosa T.B. + | 182 | 0 | 0 | 13052 | 0 | 0 | 0 | 423 | 0 | 0 |
| Erythema nodosum, rheumatic fever | 183 | 0 | 0 | 13126 | 0 | 0 | 0 | 426 | 0 | 0 |
| Lupus vulgaris T.B. + | 184 | 0 | 0 | 13127 | 0 | 0 | 0 | 427 | 0 | 0 |
| Rheumatic fever | 185 | 0 | 0 | not sent to Loewenstein | | | | 428 | 0 | 0 |
| Lupus vulgaris T.B. + | 186 | 0 | 0 | 13144 | 0 | 0 | 0 | 429 | 0 | 0 |
| Chron. polyarthritis | 187 | 0 | 0 | 13147 | 0 | 0 | 0 | 430 | 0 | 0 |
| (infect.) | 188 | 0 | 0 | 13146 | 0 | 0 | 0 | 431 | 0 | 0 |

| Diagnosis | COPENHAGEN | | | VIENNA | | | FRANKFORT A/M. | | | |
|--|------------|-----|-----|--------|-----|--------------------------|----------------|------------|-----|---|
| | No. | Ma. | Mi. | No. | Ma. | Mi + Mi - subc. subc. | No. | Ma. | Mi. | |
| Chron. polyarthritis (rheum.) ... | 189 | 0 | 0 | 13145 | 0 | 0 | 0 | | | |
| Lupus vulgaris | 190 | 0 | 0 | 13274 | 0 | 0 | 0 | 434 | 0 | 0 |
| " " T.B. + | 191 | 0 | 0 | 13273 | 0 | 0 | 0 | 435 | 0 | 0 |
| " " " " | 192 | 0 | 0 | 13275 | 0 | 0 | 0 | 436 | 0 | 0 |
| " " " " | 193 | 0 | 0 | 13272 | 0 | 0 | 0 | 437 | 0 | 0 |
| " " " " | 194 | 0 | 0 | 13388 | 0 | 0 | + | 457 | 0 | 0 |
| " " T.B. + | 196 | 0 | 0 | 13872 | + | 0 | 0 | | | |
| " " " " | 197 | 0 | 0 | 13873 | + | 0 | 0 | | | |
| " " " " | 198 | 0 | 0 | 13874 | + | 0 | 0 | | | |
| Lupus follicularis | 199 | 0 | 0 | 13870 | 0 | 0 | 0 | | | |
| Tb. of the spine T.B. + | 202 | 0 | 0 | 13871 | 0 | 0 | 0 | | | |
| Erythema induratum Bazin | 208 | 0 | 0 | 13988 | 0 | 0 | 0 | | | |
| Sympathetic Ophthalmia | 213 | 0 | 0 | 14250 | + | 0 | 0 | | | |
| Pleurisy T.B. + | 216 | 0 | 0 | 14617 | 0 | 0 | 0 | 539 | 0 | 0 |
| Pulm. Tb. T.B. + | 217 | 0 | 0 | 14619 | 0 | 0 | 0 | 540 | 0 | 0 |
| " " T.B. + | 218 | 0 | 0 | 14620 | 0 | 0 | 0 | 541 | 0 | 0 |
| " " " " | 219 | 0 | 0 | 14618 | 0 | 0 | 0 | 542 | 0 | 0 |
| Tb. of the cervical glands T.B. + | 220 | 0 | 0 | 14616 | 0 | 0 | 0 | 543 | 0 | 0 |
| Pulm. Tb. T.B. + | 221 | 0 | 0 | 14681 | 0 | 0 | 0 | | | |
| Tb. of the cervical glands T.B. + | 222 | 0 | 0 | 14680 | 0 | 0 | 0 | 545 | 0 | 0 |
| Bone Tuberculosis T.B. + | 223 | 0 | 0 | 14679 | 0 | 0 | 0 | 546 | 0 | 0 |
| " " " " | 224 | 0 | 0 | 14759 | 0 | 0 | 0 | 549 | 0 | 0 |
| Tub. of the lumbar spine T.B. + | 225 | 0 | 0 | 14760 | 0 | 0 | 0 | 550 | 0 | 0 |
| Lupus vulgaris T.B. + | 226 | 0 | 0 | 14863 | 0 | 0 | 0 | | | |
| Pulm. Tb. T.B. + | 227 | 0 | 0 | 14858 | 0 | 0 | 0 | cultivated | 0 | 0 |
| Tb. of the cervical glands T.B. + | 228 | 0 | 0 | 14865 | 0 | 0 | 0 | by Prof. | 0 | 0 |
| Pulm. Tb. T.B. + | 229 | 0 | 0 | 14859 | 0 | 0 | 0 | Uhlenhut | 0 | 0 |
| " " T.B. + | 230 | 0 | 0 | 14861 | 0 | 0 | 0 | | | |
| " " " " | 231 | 0 | 0 | 14864 | 0 | 0 | 0 | | 0 | 0 |
| " " " " | 232 | 0 | 0 | 14866 | 0 | 0 | 0 | cultivated | 0 | 0 |
| Pleurisy T.B. + | 233 | 0 | 0 | 14860 | 0 | 0 | 0 | by Prof. | 0 | 0 |
| Pulm. Tb. T.B. + | 234 | 0 | 0 | 14862 | 0 | 0 | 0 | Uhlenhut | 0 | 0 |
| " " T.B. + | 235 | 0 | 0 | 14867 | 0 | 0 | 0 | | 0 | 0 |
| " " " " | 236 | 0 | 0 | | 0 | 0 | 0 | | | |
| Tb. of the cervical glands T.B. + | 237 | 0 | 0 | | 0 | 0 | 0 | | | |
| Pulm. Tb. T.B. + | 238 | 0 | 0 | | 0 | 0 | 0 | | | |
| " " T.B. + | 239 | 0 | 0 | | 0 | 0 | 0 | | | |

In addition we received 71 blood-samples from Professor KOLLE, Frankfort-on-Main. Thirty-seven of these were also sent to Professor LOEWENSTEIN. The results are shown in Table II.

Table II.

BLOOD SAMPLES FROM PATIENTS IN FRANKFORT A/M. EXAMINED JOINTLY IN THE FRANKFORT, VIENNA AND COPENHAGEN LABORATORIES.

| Diagnosis | FRANKFORT A/M. | | | VIENNA | | | COPENHAGEN | | |
|--|----------------|-----|-----|--------|-----|-----|------------|------|---------|
| | No. | Ma. | Mi. | No. | Ma. | Mi. | No. | D.M. | Ma. Mi. |
| Tb. Keratitis | 117 | 0 | 0 | | | | 1 | | 0 |
| Pulm. Tb. | 133 | 0 | 0 | | | | 2 | | 0 |
| " " " " | 131 | 0 | 0 | | | | 3 | | 0 |
| " " " " | 130 | 0 | 0 | | | | 4 | | 0 |
| Erythema nodosum | 138 | 0 | 0 | 11677 | 0 | 0 | 15 | | 0 |
| Pulm. Tb. | 136 | 0 | 0 | 11678 | 0 | 0 | 16 | | 0 |
| " " " " | 135 | 0 | 0 | | | | 17 | | 0 |
| " " " " | 141 | 0 | 0 | 11758 | 0 | 0 | 18 | | 0 |
| " " " " | 140 | 0 | 0 | 11757 | 0 | 0 | 19 | | 0 |
| " " " " | 139 | 0 | 0 | 11754 | 0 | 0 | 20 | | 0 |
| " " " " | 147 | 0 | 0 | 11779 | 0 | 0 | 21 | | 0 |

| Diagnosis | FRANKFORT A/M. | | | VIENNA | | | COPENHAGEN | | |
|-------------------------------------|----------------|-----|-----|--------|-----|-----|------------|------|-------|
| | No. | Ma. | Mi. | No. | Ma. | Mi. | No. | D.M. | Ma. M |
| Pulm. Tb. | 145 | 0 | 0 | | | | 22 | | 0 |
| " " | 148 | 0 | 0 | 11783 | + | | 23 | | 0 |
| " " | 144 | 0 | 0 | 11782 | 0 | 0 | 24 | | 0 |
| Lupus vulgaris | 165 | 0 | 0 | 11837 | + | | 25 | | 0 |
| Myocarditis | 167 | 0 | 0 | 11838 | + | | 26 | | 0 |
| Pulm. Tb. | 169 | 0 | 0 | 11835 | + | | 27 | | 0 |
| Polyarthrits (arrested) | 170 | 0 | 0 | 11840 | + | | 28 | | 0 |
| Myalgia (before Tonsillectomy)... | 172 | 0 | 0 | 11879 | 0 | 0 | 31 | | 0 |
| Myalgia (after ") .. | 173 | 0 | 0 | 11877 | 0 | 0 | 29 | | 0 |
| Pulm. Tb. | 174 | 0 | 0 | 11878 | 0 | 0 | 30 | | 0 |
| Paraphrenia | 177 | 0 | 0 | 11880 | 0 | 0 | 32 | | 0 |
| Endocarditis | 183 | | | 11882 | 0 | 0 | 33 | | 0 |
| Pulm. Tb. | 184 | 0 | 0 | 11883 | 0 | 0 | 34 | | 0 |
| Lupus vulgaris | 185 | 0 | 0 | 11887 | 0 | 0 | 42 | | 0 |
| Pulm. Tb. | 186 | 0 | 0 | 11888 | 0 | 0 | 43 | | 0 |
| " " | 187 | 0 | 0 | 11889 | 0 | 0 | 44 | | 0 |
| Dementia præcox | 188 | 0 | 0 | 11890 | + | | 45 | | 0 |
| Pulm. Tb. | 195 | 0 | 0 | 11948 | 0 | 0 | 46 | | 0 |
| " " | 198 | 0 | 0 | 11946 | 0 | 0 | 47 | | 0 |
| " " | 194 | 0 | 0 | 11949 | 0 | 0 | 48 | | 0 |
| " " | 201 | 0 | 0 | 11945 | 0 | 0 | 49 | | 0 |
| " " | 203 | 0 | 0 | 11950 | 0 | 0 | 50 | | 0 |
| " " | 204 | 0 | 0 | 11947 | 0 | 0 | 51 | | 0 |
| Acute Polyarthrits | 217 | 0 | 0 | 11938 | 0 | 0 | 52 | | 0 |
| Dementia præcox | 220 | 0 | 0 | | | | 53 | | 0 |
| Tb. Keratitis | 261 | 0 | 0 | | | | 70 | | 0 |
| Pulm. Tb. | 262 | 0 | 0 | | | | 71 | | 0 |
| " " | 263 | 0 | 0 | | | | 72 | | 0 |
| " " | 267 | 0 | 0 | | | | 73 | | 0 |
| Lupus erythem. | 247 | 0 | 0 | | | | 74 | | 0 |
| Lupus vulgaris | 248 | 0 | 0 | | | | 75 | | 0 |
| Lupus erythem. | 249 | | | | | | 76 | | 0 |
| " " | 250 | | | | | | 77 | | 0 |
| Tb. Iritis | 254 | 0 | 0 | | | | 78 | | 0 |
| Tb. of the spine and Pulm. Tb. | 265 | 0 | 0 | | | | 79 | | 0 |
| Polyarthrits | 269 | 0 | 0 | | | | 80 | | 0 |
| " " | 274 | 0 | 0 | 12219 | 0 | 0 | 81 | | 0 |
| " " | 275 | 0 | 0 | 12222 | 0 | 0 | 82 | | 0 |
| Pulm. Tb. | 278 | 0 | 0 | | | | 112 | | 0 |
| " " | 279 | 0 | 0 | | | | 113 | | 0 |
| " " | 280 | 0 | 0 | | | | 114 | | 0 |
| " " | 281 | 0 | 0 | | | | 115 | | 0 |
| " " | 283 | 0 | 0 | 12309 | 0 | 0 | 116 | | 0 |
| " " | 284 | 0 | 0 | 12307 | + | | 117 | | 0 |
| Cutaneous Tb. | 255 | 0 | 0 | | | | 118 | | 0 |
| Polyarthrits | 290 | 0 | 0 | | | | 119 | | 0 |
| " " | 292 | 0 | 0 | | | | 120 | | 0 |
| Pulm. Tb. | 295 | 0 | 0 | | | | 121 | | 0 |
| " " | 296 | 0 | 0 | | | | 122 | | 0 |
| Polyarthrits | 297 | 0 | 0 | | | | 123 | | 0 |
| Dementia præcox | 301 | 0 | 0 | | | | 126 | | 0 |
| Pulm. Tb. | 307 | 0 | 0 | | | | 127 | | 0 |
| " " | 309 | 0 | 0 | | | | 128 | | 0 |
| " " | 311 | | | | | | 129 | | 0 |
| " " | 313 | 0 | + | | | | 130 | | 0 |
| " " | 318 | 0 | 0 | 12394 | 0 | 0 | 131 | | 0 |
| " " | 319 | 0 | 0 | 12396 | 0 | 0 | 132 | | 0 |
| " " | 320 | 0 | 0 | 12395 | 0 | 0 | 133 | | 0 |
| " " | 321 | 0 | 0 | 12393 | 0 | 0 | 134 | | 0 |
| Retrobulbar Neuritis | 322 | 0 | 0 | | | | 135 | | 0 |

In the cases in which we did not succeed in finding any tubercle bacilli, we applied for other cultures to Professor LOEWENSTEIN, who replied that no more cultures of these strains were available.

The Institut für experimentelle Therapie, Frankfort-on-Main, the Hygienisches Institut, Freiburg-in-Breisgau, and the Statens Serum Institut, Copenhagen, were thus unable to secure a single micro- or macro-culture.

Table IV shows the percentage of cases in which Professor LOEWENSTEIN succeeded in growing tubercle bacilli from the blood-samples sent to him. By way of comparison, the percentage of positive results from Professor LOEWENSTEIN'S former publications (see *Acta Path. and Micr. Scand.*, 1933, Vol. X, page 60; *Deutsche mediz. Wochenschrift*, 1933, No. 38, page 1468; *Wiener klin. Wochenschrift*, 1931, No. 13, page 1; *Münchener mediz. Wochenschrift*, 1930, No. 39, page 1662) has been entered in the same table.

The data of Tables I and II have been grouped in Tables III and IV so as to make the general survey easier.

Table III.
BLOOD SAMPLES EXAMINED SIMULTANEOUSLY BY :

| Disease | COPENHAGEN | | | | VIENNA | | | | FRANKFORT A/M. | | |
|---|------------|------------------|----------|----------|----------|------------|----------------|----------------|-------------------|------------------|----------|
| | Number | Positive results | | | Number | Ma. | Mi + subc. | Mi - subc. | Number | Positive results | |
| | | D.M. | Ma. | Mi. | | | | | | | |
| Exsudative Pleurisy | 4 | 40 | 0 | 0 | 0 | 40 | 3 ¹ | 1 ² | 0 | 11 | 0 |
| Pulm. Tb. | 36 | 40 | 0 | 0 | 0 | 40 | 3 ¹ | 1 ² | 0 | 11 | 0 |
| Lupus vulgaris | 36 | 40 | 0 | 0 | 0 | 40 | 3 ¹ | 5 ⁴ | 0 | 10 | 0 |
| Lupus erythemat. | 1 | 40 | 0 | 0 | 0 | 40 | 3 ¹ | 5 ⁴ | 0 | 10 | 0 |
| Lupus follic. | 1 | 40 | 0 | 0 | 0 | 40 | 3 ¹ | 5 ⁴ | 0 | 10 | 0 |
| Tb. verrucosa | 2 | 40 | 0 | 0 | 0 | 40 | 3 ¹ | 5 ⁴ | 0 | 10 | 0 |
| Other forms of non-pulmonary Tb. | 21 | 0 | 0 | 0 | 0 | 20 | 0 | 1 ³ | 0 | 6 | 0 |
| Dementia præcox | 40 | 0 | 0 | 0 | 0 | 40 | 0 | 0 | 2 | 10 | 0 |
| Various | 10 | 0 | 0 | 0 | 0 | 9 | 1 ⁵ | 0 | 0 | 4 | 0 |
| Total | 151 | 0 | 0 | 0 | 0 | 149 | 7 | 7 | 2 | 41 | 0 |
| After elimination of the strains mentioned below | | | | | | | 4 | 2 | 0 | | |

¹ One of these three strains was a luxuriantly-growing orange-tinted *saprophyte*. Simultaneously a *human* strain was isolated from the sputum of the same patient.

² *Human* type.—From the sputum of this patient, pure cultures of the *bovine* type had been isolated on three occasions before and after the blood-taking, in the last instance a year later.

³ One of these three strains was a *human* type. At the time when the blood was taken, a pure culture of an *attenuated bovine* strain was isolated from the patient's focal lesion.

⁴ One strain of these five was a *human* strain. At the same time, a pure culture of *bovine* type was isolated from the lesion of the patient concerned. Of the remaining 4 subcultures, 2 did not show any tubercle bacilli (microscopy and culture).

⁵ This subculture contained no tubercle bacilli (microscopy and culture).

⁶ This primary culture contained no tubercle bacilli (microscopy and culture).

Table IV.

| | Percentage of positive cultures | | Percentage of positive results formerly published |
|---------------------------------------|---------------------------------|-------------------------------|---|
| | All included | Without the strains specified | |
| Pleurisy and Pulm. Tb. | 10 | 5 | 80-100 Progressive pulm. Tb. Stage 3 with fever. |
| Cutaneous Tb. | 20 | 10 | 75-82 Examined once. |
| Other forms of non-pulmonary Tb. | 5 | 0 | 50 Tb. of the bone |
| Dementia præcox | 5 | 0 | 39.6 Examined once. |
| Other forms | 11.1 | 0 | |
| Total | 10.7 | 4 | |

Finally, the total number of blood-examinations carried out by the LOEWENSTEIN method in the "Statens Serum Institut" in the past three years is given in Table V.

A great many of the blood-samples were examined by J. HOLM who studied the special technique during a visit to LOEWENSTEIN'S laboratory (see *Acta Tub. Scand.*, 1932, Vol. VI). The rest of the blood-specimens were examined by ourselves.

A large proportion of the cases of pulmonary tuberculosis examined were in the third stage and febrile. Most of the samples which were inoculated into guinea-pigs (figures in parentheses) were obtained from such cases.

Table V.

| | Number of tests | Macro-cultures | Micro-cultures | Positive guinea-pig inoculations |
|---|-----------------|----------------|----------------|----------------------------------|
| Pulm. Tb. | 96 (26) | 0 | 0 | 0 |
| Exsudative Pleurisy | 16 (6) | 0 | 0 | 0 |
| Articular urogenital and glandular Tb. | 77 (11) | 0 | 0 | 0 |
| Lupus vulgaris | 81 | 0 | 0 | 0 |
| " erythemat. | 25 | 0 | 0 | 0 |
| Tb. of the eye | 10 (2) | 0 | 0 | 0 |
| Miliary Tb. | 4 (3) | 0 | 0 | 0 |
| Erythema nod. | 30 (13) | 0 | 0 | 1 |
| Acute and chronic Polyarthritia | 53 (6) | 0 | 0 | 0 |
| Dementia præcox | 43 | 0 | 0 | 0 |
| Various | 44 (8) | 0 | 0 | 0 |
| Total | 479 (75) | 0 | 0 | 1 |

Consideration of the material here presented discloses once again the great discrepancies which are characteristic of investigations on tuberculous bacillæmia. It is, however, unnecessary for me to

give a full survey of the literature as a very detailed bibliography has recently been published (G. S. WILSON : "Tuberculous bacillæmia", *Med. Res. Council, Spec. Report Series*, No. 182, London 1933).

The discrepancies observed are as follows :

1. In several series of investigations, which included the examination of about 500 blood-samples, J. HOLM and we ourselves tried out the culture method strictly observing Loewenstein's directions, but with completely negative results. *We never obtained any macro- or micro-cultures.* Both of us thoroughly studied the LOEWENSTEIN method in LOEWENSTEIN's own laboratory.

From the same blood-specimens, LOEWENSTEIN succeeded in a number of cases in cultivating tubercle bacilli.

2. The results of LOEWENSTEIN's latest series of cultures set forth in Table III, differ considerably from those obtained in his former investigations, which showed a much higher percentage.

3. There are discrepancies between the strains LOEWENSTEIN has cultivated from the blood and the strains isolated from the lesions of the same patients.

Regarding the first point, LOEWENSTEIN has emphasised again and again that the explanation of the discrepancies lay in the great technical difficulties of the blood-culture method, and that small deviations from the proper technique were the cause of the negative results obtained by most other investigators. These technical difficulties, he said, resided in part in the preparation of the medium, in part in the procedure of culture.

In the course of his work, LOEWENSTEIN has made many changes in his medium. We compared the medium first described in *Deutsche medizinische Wochenschrift*, 1930, with most other media and found that, in our hands, it is by far the best existing solid medium for cultivating the human as well as the bovine type of tubercle bacilli. The main reason for its excellence is that *unlike other similar media it contains 0.75 per cent of glycerine*, a proportion which, in our experience, yields the best results in the culture of the human as well as the bovine type.

LOEWENSTEIN has however repeatedly changed his medium ; for a long time he worked with from 5 to 6 per cent of glycerine

without, for all that, experiencing any deterioration in his results. Lately, however, he has reduced the amount of glycerine to 2 to 3 per cent. We repeatedly compared these different media with his first medium containing 0.75 per cent, sometimes by using them in our routine work, sometimes by inoculating tubes with decreasing doses of recently isolated human and bovine strains. In this way, it was demonstrated that the medium with 5 to 6 per cent of glycerine was so inefficient that the bovine strains hardly grew on it at all and that the growth even of human strains, which usually stand a fairly high percentage of glycerine, was inhibited. Table VI gives a summary of these investigations.

Table VI.

COMPARISON BETWEEN OUR ROUTINE MEDIUM MADE WITH VARYING PROPORTIONS OF GLYCERINE AND THE MEDIUM DESCRIBED BY LOEWENSTEIN IN REPORT 1.

| Type of inoculated strain | Days of observation | Our routine malachite-green medium with a percentage of glycerine of | | | | | The Loewenstein medium with congo red (about 2.4 % glycerine) |
|---|---------------------|--|---------------|-----|-----|-----|---|
| | | 0 | $\frac{1}{2}$ | 2 | 4 | 8 | |
| Bovine : 1 : 100,000 mg. T.B. per tube . | 13 | 9 | 4 | 2 | 0 | 0 | 0 |
| | 15 | 44 | 11 | 9 | 0 | 0 | 1 |
| | 21 | 278 | 127 | 19 | 1 | 0 | 13 |
| | 28 | 383 | 294 | 40 | 7 | 1 | 43 |
| Human : 1 : 100,000 mg. T.B. per tube . | 11 | 42 | 33 | 33 | 18 | 2 | 2 |
| | 14 | 262 | 404 | 259 | 110 | 4 | 115 |
| | 19 | 580 | 830 | 560 | 320 | 127 | 675 |
| | 25 | c. 900 | c. 1,000 | 735 | 555 | 408 | c. 1,000 |

The figures give the total number of colonies on five tubes.

In order to clear up this point finally, we had taken some tubes of our own medium to Professor LOEWENSTEIN's laboratory and inoculated them with 18 of the ordinary blood-samples which came there for examination. On leaving Professor LOEWENSTEIN's laboratory, we took with us one of our own and one of LOEWENSTEIN's tubes in respect of each sample inoculated. The result of this experiment is given in Table VII.

Table VII.

BLOOD CULTURE INOCULATIONS CARRIED OUT DURING MY VISIT TO LOEWENSTEIN'S LABORATORY (NOVEMBER 5TH TO 9TH, 1932).

| No. | INOCULATED TUBES BROUGHT BACK TO COPENHAGEN. | | | | INOCULATED TUBES REMAINING IN VIENNA | |
|-------|--|---|---|---|--|---|
| | Petraghani medium + serum prepared by the Loewenstein laboratory | | The Loewenstein medium with 0.75 % glycerine prepared in Copenhagen | | Loewenstein's congo-red medium | The Loewenstein medium with 0.75 % glycerine prepared in Copenhagen |
| | Macroscopical growth | Microscop. exam. of scrapings | Macroscopical growth | Microscop. exam. of scrapings | | |
| 10514 | 23/XII 0 | 23/XII 0 | 23/XII 0 | 23/XII 0 | 0 | 0 |
| 10515 | " 0 | " 0 | " 0 | " 0 | 0 | 0 |
| 10517 | " 0 | " 0 | " 0 | " 0 | 0 | 0 |
| 10518 | " 0 | " 0 | " 0 | " 0 | 0 | 0 |
| 10519 | " 0 | 23/XII + f.B. in clumps (GP inocul. positive) | " 0 | 23/XII + f.B. in clumps (GP inocul. positive) | 0 | 0 |
| 10520 | " 0 | 23/XII 0 | " 0 | 23/XII 0 | 0 | 0 |
| 10525 | " 0 | " 0 | " 0 | " 0 | 0 | 0 |
| 10526 | " 0 | " 0 | " 0 | " 0 | 0 | 0 |
| 10527 | " 0 | " 0 | " 0 | " 0 | 0 | 0 |
| 10528 | " 0 | " 0 | " 0 | " 0 | 0 | 0 |
| 10529 | " 0 | " 0 | " 0 | " 0 | 0 | 0 |
| 10530 | " 0 | " 0 | " 0 | " 0 | 0 | 0 |
| 10533 | 28/XI + (ab. 100 colonies) | + T.B. | 24/XI + (innumerable colonies) | + T.B. | 0 | 28/XI + |
| 10534 | 29/XII 0 | 29/XII 0 | 29/XII 0 | 29/XII 0 | 10/XII + f.B. microscopical examination of scrapings | 0 |
| 10535 | " 0 | " 0 | " 0 | " 0 | 0 | No tubes |
| 10536 | 28/XI + (ab. 100 colonies) | + T.B. | 25/XI + (innumerable colonies) | + T.B. | 5/XII + | " |
| 10537 | 5/XII + (10 colonies) | + T.B. | 29/XII 0 | 29/XII 0 | 5/XII + | " |
| 10538 | 29/XII 0 | 29/XII 0 | 25/XI + (innumerable colonies) | + T.B. | ? | " |

As will be seen from this table, the first growth was observed as early as 15 days after inoculation (this period including the two days the tubes were kept at room temperature). It will also be seen that the colonies in the case of the three positive samples were very abundant and that our medium was perhaps better than that of LOEWENSTEIN. We have observed such abundant growth only in cultures from microscopically positive sputa or in pure cultures.

After our return to Copenhagen, we received, according to plan, media prepared in LOEWENSTEIN'S laboratory and we compared some of these tubes with our own routine medium and with the medium prepared by us according to LOEWENSTEIN'S directions.

Table VIII shows that our medium is at least as good as LOEWENSTEIN'S so far as human tubercle bacilli are concerned, and much superior to his for the cultivation of bacilli of the bovine type.

Table VIII.

EXPERIMENT 1.

Varying amounts of human tubercle bacilli were mixed with guinea-pig's blood (3 c.c. in each centrifuge-tube). The blood was treated according to Loewenstein's prescriptions and inoculated partly on to our own medium and partly on to the medium prepared in Loewenstein's laboratory.

| Amount of tubercle bacilli per centrifuge-tube | Our own medium | Loewenstein's medium |
|--|--|--|
| About 300 million | Tube 1 : + (5-12) : innumerable colonies Tube 2 : + (5-12) : innumerable colonies | 1 : + (5-12) : innumerable colonies 2 : + (5-12) : innumerable colonies |
| About 3 million | Tube 1 : + (5-12) : innumerable colonies Tube 2 : + (5-12) : innumerable colonies | 1 : + (5-12) : ab. 200 colonies 2 : + (5-12) : ab. 200 colonies |
| About 1,000 | Tube 1 : + (5-12) : 46 col. (14-12) : 75 col. Tube 2 : + (5-12) : 41 col. (14-12) : 59 col. | 1 : (5-12) : 3 col. (14-12) : 11 col. 2 : (5-12) : 3 col. (14-12) : 13 col. |

Inoculated November 24th, 1932.

EXPERIMENT 2.

A comparison between results obtained with media prepared in our laboratory and in Loewenstein's.

| Type (freshly isolated strains) | Number of days of observation | Dosage of inoculated tubercle bacilli in milligrammes | Media prepared in | | | |
|---------------------------------|-------------------------------|---|----------------------------------|----------------------------------|----------------------------|--------------------------------|
| | | | Copenhagen | | Vienna | |
| | | | Routine medium with 1% glycerine | Loewenstein's formula (report 1) | Modified Petragrani medium | Loewenstein's congo-red medium |
| Human | 23 | 1 : 100,000 | 66 col. | — | 1 col. | 13 col. |
| | | 1 : 1 million | 8 " | 8 col. | 0 " | 5 " |
| Bovine | 30 | 1 : 100,000 | 59 " | 0 " | 0 " | 0 " |
| | | 1 : 1 million | 4 " | 0 " | 0 " | 0 " |
| | 42 | 1 : 100,000 | 76 " | 13 " | 0 " | 0 " |
| | | 1 : 1 million | 4.6 " | 1.8 " | 0 " | 0 " |

The figures give the average number of colonies per tube.

On a general review of these investigations, one thing stands out clearly. *The divergence between LOEWENSTEIN'S results and ours cannot depend upon the quality of the medium.*

The only possibility remaining to be considered is that, in spite of all our precautions, there still exists a difference between LOEWENSTEIN's technique and ours as regards the treatment and the seeding of the blood-samples. It seems, however, that LOEWENSTEIN over-estimates the difficulties attaching to this part of the cultivation method. Mere technical deviations might perhaps explain the discrepancies if LOEWENSTEIN secured the growth of but a single colony, but this is not the case. We saw, ourselves, in LOEWENSTEIN's laboratory, that most of the positive samples yielded in every tube a number of colonies such as can be obtained as a rule only in cultures prepared from microscopically positive sputum.

During our visit to the LOEWENSTEIN laboratory, we were present at the reading of the blood-culture tests, and it was found that, of about 89 blood-samples, 28 were positive. In most of these 28 cases, the tubes were riddled with countless colonies and, in some instances, the colonies were so numerous that even in the young cultures they formed a continuous film.

As a further illustration of the extremely large numbers of tubercle bacilli concerned, the following observation may be adduced. Before the inoculation of the tubes, a tiny fraction of each blood sediment was taken for direct microscopy (*i.e.*, the deposit remaining after hæmolysis, centrifuging and treatment with sulphuric acid). Under the microscope, 3 out of 8 such slides prepared from blood of patients with schizophrenia proved positive. The slide did not, as might have been expected, show just a few tubercle bacilli discernible here and there after careful scrutiny but, strange to say, was red all over with acid-fast bacilli. These were massed in clumps as regularly as those which can be seen under the microscope on glycerine broth cultures. Some of the clumps occupied a third of the field, and we estimated the number in such clumps at more than a thousand. LOEWENSTEIN has described such cultures in *Zentralblatt f. Bakt.*, 1933, Abt. I, Orig., Vol. 128, page 297. He explains the great clumps as originating by multiplication of the tubercle bacilli in thrombotic capillaries. The clumps of tubercle bacilli which we observed are, however, far from resembling the formations which LOEWENSTEIN has photographed. Figure 1 is a micro-photograph of one of the three slides mentioned above, which LOEWENSTEIN kindly allowed us to bring away from Vienna.

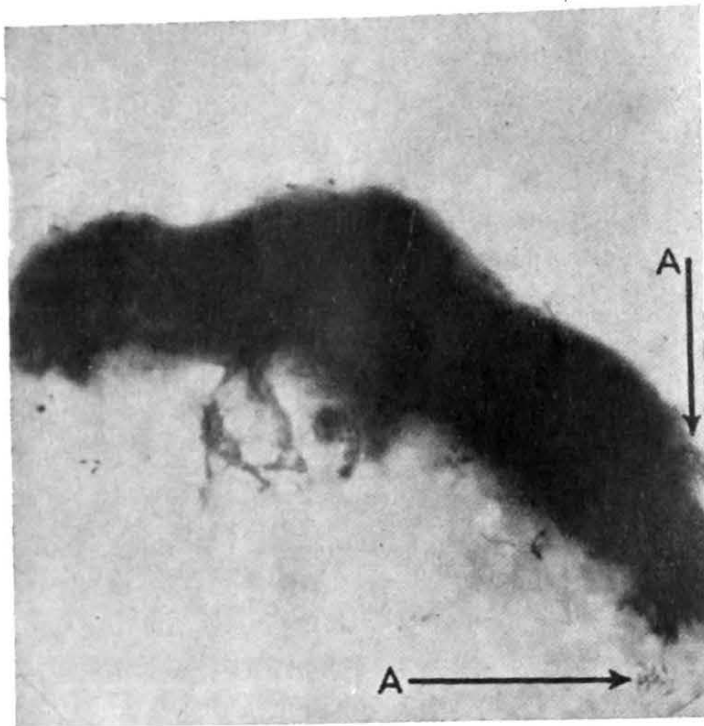


Figure 1.

The huge lump of tubercle bacilli shown in the micro-photograph is so solid that finer details cannot be seen because of the refraction of light. Judging by the size of the single bacilli at the points marked A, the enormous number in the main mass can be imagined.

This slide is the one mentioned above and represents only an insignificant fraction of the whole sediment recovered from 5 to 10 c.c. blood. A systematic examination of the slide disclosed 195 large clumps of bacilli, nearly all of the size of that shown in Figure 1, 9,500 medium-sized clumps, all containing at least 10 bacilli, besides innumerable single tubercle bacilli and small groups of less than 10 bacilli.

By mixing tubercle bacilli with guinea-pig's blood and treating the mixture as indicated above, we found that, even when 100 million tubercle bacilli are added to 1 c.c. blood and a total quantity of 3 c.c. is treated, it was impossible to produce slides showing anything approaching the same abundance of bacilli.

Where luxuriant growths and microscopical findings of this kind are concerned, it is absolutely inconceivable that small technical subtleties can be the cause of the great discrepancies already mentioned. In our opinion, there remains but one possible explanation of LOEWENSTEIN'S findings—viz., that, in his laboratory, there must exist some source of error which has escaped his notice.

In support of this conclusion, we may mention the following observation. During the past four years, we have isolated from man and typed a great number of strains of tubercle bacilli. Certain of the blood-samples sent by us to LOEWENSTEIN came from patients from whose focal lesions we had at the same time isolated and cultivated tubercle bacilli. In the cases in which LOEWENSTEIN secured the growth of cultures from these blood-samples, we compared his strains with those which we had isolated from the focal lesions. The result of these comparisons is shown in Table IX.

It is evident from this table that, in three cases only, the cultures obtained by LOEWENSTEIN from the blood appear to be identical with the cultures isolated in our laboratory from the focal lesions of the patients.

In each of 4 cases (Nos. 8, 41, 54 and 197), the differences between the two strains are so wide that the cultures can hardly have been obtained from the same patient.

With regard to case 8, it must be assumed that LOEWENSTEIN'S finding of an acid- and alcohol-fast saprophyte is due to an accidental contamination. In our laboratory, we have now and again cultivated such saprophytes from various materials received for routine tests for tubercle bacilli. Since these specimens are partly derived from tuberculous patients, it is quite natural that an acid-fast saprophyte should be occasionally isolated from a patient with undoubtedly tuberculous lesions ; but this establishes no definite relation between the saprophyte and the patient's tuberculosis. Much more frequently, we have isolated saprophytes from non-tuberculous patients. In this connection, we may cite an example of the sort of mistake to which any laboratory may be exposed. From a certain hospital, we received 5 specimens of stomach lavage water. We isolated in every case quite identical strains of an acid- and alcohol-fast saprophyte. There is no doubt that this finding was due to a contamination, and it shows how cautious one must be in attaching any importance to the occurrence of such saprophytes.

With regard to the other three cases (Nos. 41, 54 and 197) mentioned above, we can see no other possible explanation than a serious error. In the three cases in which LOEWENSTEIN succeeded in cultivating tubercle bacilli from the blood of patients with a definite bovine infection, his strains were all of the human type.

Table IX.

| No. | Diagnosis | Material | Culture | GUINEA-PIG | | RABBIT | | |
|-------|-------------|----------|--|---------------------------------------|---|---------------------------------------|--|---------------------------------------|
| | | | | Route of inoculation, dosage and date | Autopsy | Route of inoculation, dosage and date | Autopsy | Type |
| 8 | Pulm. Tb. | Sputum | Primary culture : eugonic human. | Subcutaneous 1 mg. 4/X/1933 | Died 12/XII/1933 Generalised tuberculosis. | | | Human. |
| 11715 | | Blood | Secondary culture : roughly folded orange-coloured colonies. | Subcutaneous 1 mg. 17/VII/1933 | Killed 10/X/1933 No tuberculosis. | Intravenous 1 mg. 17/VII/1933 | Killed 26/X/1933 No tuberculosis. | Acid-fast saprophyte. |
| 9 | Pulm. Tb. | Sputum | Primary culture : eugonic human. | | | | | Human. |
| 11721 | | Blood | Secondary culture : eugonic human. | Subcutaneous 1 : 10 mg. 3/VIII/1933 | Died 6/XI/1933 Generalised tuberculosis. | Subcutaneous 10 mg. 3/VIII/1933 | Killed 2/XI/1933 Locally a plum-sized abscess, no other tuberculous changes. | Human. |
| 36 | Lupus vulg. | Skin | Secondary culture : dysgonic human. | Intraperitoneal 1 : 10 mg. 15/IX/1933 | Killed 13/XII/1933 Very slight changes in omentum only. | Subcutaneous 10 mg. 15/IX/1933 | Killed 13/XII/1933 No tuberculosis. | Dysgonic human. Very little virulent. |
| 11926 | | Blood | Secondary culture : eugonic human. | Intraperitoneal 1 : 10 mg. 30/IX/1933 | Died 24/X/1933 Generalised tuberculosis. | Subcutaneous 10 mg. 30/IX/1933 | Killed 20/I/1934 Locally an abscess. In lungs 3-4 fibrous nodules. No other tuberculous changes. | Human. Normal virulence. |
| 41 | Lupus vulg. | Skin | Secondary culture : dysgonic bovine. | Homogenised skin specimen 31/I/1933 | Died 17/III/1933 Generalised tuberculosis. | Subcutaneous 10 mg. 1/IV/1933 | Died 2/VIII/1933 Generalised tuberculosis. | Bovine. |
| 11927 | | Blood | Secondary culture : eugonic human. | Subcutaneous 1 : 10 mg. 13/IX/1933 | Killed 3/XI/1933 Generalised tuberculosis. | Intravenous 1 : 10 mg. 3/XI/1933 | Killed 7/II/1934 In lungs 5-6 fibrous nodules. No other tuberculous changes. | Human. |
| 54 | Pulm. Tb. | Sputum | Primary and secondary culture : dysgonic bovine. | | | Subcutaneous 10 mg. 25/I/1933 | Died 25/III/1933 Generalised tuberculosis. | Bovine. |
| 12139 | | Blood | Secondary culture : eugonic human. | Intraperitoneal 1 : 10 mg. 28/X/1933 | Died 15/XII/1933 Generalised tuberculosis. | Intravenous 1 : 10 mg. 28/X/1933 | Killed 7/II/1934 No tuberculosis. | Human. |

| | | | | | | | | |
|-------|----------------|--------|--|---|--|---|---|------------------------------|
| 62 | Pulm. Tb. | Sputum | Primary and secondary culture : eugonic human. | | | | | Human. |
| 12128 | | Blood | Secondary culture : eugonic human. | Subcutaneous 1 : 10 mg. 3/VIII/1933 | Died 9/IX/1933 Generalised tuberculosis. | Subcutaneous 10 mg. 3/VIII/1933 | Killed 2/XI/1933 Locally a plum-sized abscess. No other tuberculous changes. | Human. |
| 144 | Lupus vulg. | Skin | Secondary culture : eugonic human. | Intraperitoneal 1 : 10 mg. 28/VI/1933 | Died 12/VIII/1933 Generalised tuberculosis. | Subcutaneous 10 mg. 28/VI/1933 | Killed 30/IX/1933 Locally an apple-sized abscess only. | Human. |
| 12642 | | Blood | Secondary culture : eugonic human. | Intraperitoneal 1 : 10 mg. 22/IX/1933 | Died 17/XII/1933 Generalised tuberculosis. | Intravenous 1 : 10 mg. 22/VI/1933 | Killed 20/I/1934 No tuberculosis. | Human. |
| 196 | Lupus vulg. | Skin | Secondary culture : eugonic human. | Intraperitoneal 1 : 10 mg. 28/VI/1933 | Killed 2/I/1934 Slight chronic tuberculous changes in the omentum without caseous changes. Lymph glands normal. In lungs a few fibrous nodules. | Subcutaneous 10 mg. 28/VI/1933 | Killed 30/IX/1933 No tuberculosis. | Human. Slightly virulent. |
| 13872 | | Blood | Secondary culture : eugonic human. | Subcutaneous 1 : 10 mg. 5/VIII/1933 | Died 22/X/1933 Generalised tuberculosis. | Subcutaneous 10 mg. 5/VIII/1933 | Killed 8/XI/1933 An abscess locally. No other tuberculous changes. | Human. Normal virulence. |
| 197 | Lupus vulg. | Skin | Secondary culture : dysgonic bovine. | Intraperitoneal 1 : 10 mg. 4/VII/1933 Intraperitoneal 1 : 10 mg. 18/X/1933 | Died 22/VIII/1933 Slight tuberculosis. Died 22/XII/1933 Generalised tuberculosis. | Subcutaneous 10 mg. 18/X/1933 Intravenous 1 : 10 mg. 18/X/1933 | Killed 20/I/1934 Slight tuberculosis. Died 28/XII/1933 Generalised tuberculosis. | Bovine "attenuated". |
| 13873 | | Blood | Secondary culture : eugonic human. | Intraperitoneal 1 : 10 mg. 17/VIII/1933 | Died 18/IX/1933 Generalised tuberculosis. | Intravenous 1 : 10 mg. 17/VIII/1933 | Killed 21/XI/1933 No tuberculosis. | Human. |
| 198 | Lupus vulg. | Skin | Secondary culture : eugonic human. | Subcutaneous 1 : 10 mg. 16/IX/1933 | Killed 2/I/1934 Regional gland, pea-sized with caseous centre. Portal gland enlarged. Spleen very large ; hyperæmic. Liver degenerated without tubercles. Lungs normal. | Subcutaneous 10 mg. 16/IX/1933 | Killed 20/I/1934 No tuberculosis. | Human. Slightly virulent. |
| 13874 | | Blood | Secondary culture : eugonic human. | Subcutaneous 1 : 10 mg. 17/VIII/1933 | Died 14/X/1933 Generalised tuberculosis. | Subcutaneous 10 mg. 17/VIII/1933 | Killed 21/XI/1933 No tuberculosis. | Human. Normal virulence. |

An attempt to explain this incongruity by a transformation of the bovine type to the human with such regularity must be based upon very well substantiated evidence. Well-known authorities on this subject, such as A. Stanley GRIFFITH, NEUFELD and Bruno LANGE, have all maintained that the type characters of the human and bovine strains are extremely constant. Our own experiences, which will shortly be published, confirm this anew. We have so far never observed that a typical bovine strain can be transformed into a human strain or *vice versa*.

We may add a few details about case 54. The case was one of pulmonary tuberculosis. From the sputum, pure strains of bovine type were isolated on December 22nd, 1932, February 6th, 1933, and January 3rd, 1934, whereas LOEWENSTEIN isolated a human type from a blood-sample taken on February 1st, 1933.

Lastly it should be mentioned that the strains from the remaining 3 cases (Nos. 36, 196 and 198) also show some dissimilarity. These divergencies may not be quite so great as in the case of the 4 discussed above, but they are more definite than we have ever observed in repeated cultivations from the same patients. Thus, LOEWENSTEIN isolated fully virulent human tubercle bacilli from blood-samples Nos. 196 and 198, while the strains isolated by ourselves from the local processes (lupus nodules) were of the human type but of low virulence. From the blood-sample No. 36, LOEWENSTEIN cultivated a *eugonic* human strain, but the strain isolated from the local lesion (a lupus nodule) was a *dysgonic* human strain of low virulence.

SUMMARY.

1. In November 1932, we obtained cultures of tubercle bacilli from 5 out of the 18 blood-samples supplied to us in LOEWENSTEIN's laboratory by his assistant.
2. After our return to Copenhagen, we examined 222 blood-samples by the same technique and with the same media as LOEWENSTEIN, and obtained completely negative cultures, both macroscopic and microscopic.
3. 101 of these blood-samples were concurrently examined by Staatliches Institut für experimentelle Therapie, Frankfort-on-

Main. In one case only, a micro-culture was found, but it could not be subcultured and failed to produce tuberculosis in the guinea-pig.

4. 186 of these blood-samples were examined in Professor LOEWENSTEIN's laboratory and they yielded 14 macro- and 9 micro-cultures, of which two could not be subcultured.

5. At the Statens Serum Institut, Copenhagen, J. HOLM and ourselves have in the last three years carried out 479 cultivations from blood by the LOEWENSTEIN technique and *in no single case demonstrated a macro- or a micro-culture, or acid-fast saprophytes.*

75 blood-specimens mostly from patients with very advanced tuberculosis have been inoculated into guinea-pigs and only in one case was tuberculosis found in the guinea-pig.

6. The discrepancies between LOEWENSTEIN's results and ours cannot be attributed to the unsuitability of our medium.

7. Considering the results of cultivation and microscopy described in this paper after we had seen them personally in LOEWENSTEIN's laboratory, it is absolutely inconceivable that the discrepancies should be due to niceties of technique in connection with the hæmolysis, the homogenisation and the centrifuging of the blood.

8. From 149 Danish blood-samples Professor LOEWENSTEIN obtained 16 positive results—viz., 2 micro-cultures which he was unable to subculture, 7 micro-cultures which could be subcultured, and 7 macro-cultures.

14 of these cultures were sent to us : in 4 instances (2 primary cultures and 2 sub-cultures) we were unable to demonstrate tubercle bacilli either by microscopy or by culture.

The remaining 10 cultures were typed and compared with cultures isolated from the focal lesions of the same patients.

In 4 cases, the cultures differed so widely that it is impossible to believe that they could have originated from the same patient. In 3 other cases, the disagreement was such as to make this doubtful. Concordance was established in 3 cases only.

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Authors are alone responsible for views expressed in signed articles.

NUTRITION AND PUBLIC HEALTH

by

Et. BURNET and W. R. AYKROYD.

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PREFACE.

In the present report we have dealt with only one aspect of the rapidly expanding science of nutrition—its relation to public health. The report is addressed to public health authorities rather than to the specialised student of nutrition. We hope that in some degree it may help the reader to visualise public health work in nutrition as an integral and highly important part of public health activity in general.

We are, of course, aware of the superficialities of our survey ; any one of its sections could be expanded into a book. For detailed knowledge the reader must go to text-books, to the scientific and medical journals, to journals dealing exclusively with nutrition, etc. From the enormous mass of information available, we have selected a limited amount of data in support of the main theme—that the remarkable advance of the science of nutrition during recent years demands a new orientation of public health activity.

To give a complete account of existing public health nutrition activities in all countries of the world was clearly impossible. The examples chosen are largely those about which information happened to be most accessible, and in many instances this is the only reason why one country is referred to rather than another. At the same time, stress has been laid on special contributions made by certain countries to the advance of public health work in this field.

The problem of malnutrition is largely a social and economic problem, and as such concerns politicians, economists, agriculturists, social workers, etc., as closely as it concerns the medical profession. It is possible that non-medical readers may find something of interest and value to them in our report.

I. THE PLACE OF NUTRITION IN PUBLIC HEALTH AND PREVENTIVE MEDICINE.

As science advances, knowledge accumulates about the relation of man to his physical environment. The purpose of public health work, in its early days, was envisaged as the defence of populations against infectious diseases menacing them from without. But PASTEUR himself, at the outset of his career, and long before he undertook the study of microbic infections, conceived the modern idea that nutrition may play an important part in ensuring (development and) freedom from disease. His work on the chemical conditions necessary to ensure the growth in culture media (and his investigations relating to resistance to infection and immunity) tended to emphasise the idea that the food consumed by the organism has an importance apart from the provision of energy, and that the physical state of the organism largely dependent on its nutrition has a bearing on immunological reactions. It followed that the task of medicine and hygiene is not only to defend human beings against external noxious agents by effecting a sort of artificial isolation, but also to build up healthy and vigorous bodies. At about the same date, Claud BERNARD was insisting on the importance to health of the "internal environment" and "la synthèse organique" and defined nutrition as "perpetual creation".¹

Thirty years ago it was generally believed that the dietary requirements of human beings are satisfied so long as they have enough to eat ; any illnesses or physical disabilities from which men not actually hungry might suffer were ascribed to causes other than diet. We now know that the adequacy of a dietary depends on the presence of a considerable number of factors and that mere quantitative sufficiency may co-exist with a whole series of qualitative defects, any one of which may produce the most serious physical consequences.

Faulty or insufficient diet leads to serious diseases, such as rickets, beri-beri, pellagra, dental caries, certain types of anæmia ; further,

¹ "La nutrition et le développement ne sont rien autre chose qu'une création organique" (Cl. BERNARD, *Rapport sur la Physiologie en France*, 1867, page 93).

it appears to pave the way for certain infectious diseases, including tuberculosis. But diet is not only a factor in the prevention and treatment of disease ; there is also a close relation between it and physical development and efficiency. In so far as public health activity is concerned not only to defend populations against disease, but also to create a maximum of physical well-being, nutrition is perhaps the most important subject with which it has to deal. In this connection, the public health worker can learn useful lessons from the attitude of the agriculturist and stock-raiser.

Public health authorities to-day are no less concerned with nutrition than with water supply and control of infectious diseases. The protection of the public against dangerously contaminated foodstuffs and fraudulent practices in connection with the sale of food, and the feeding of population groups in schools, prisons, asylums, naval and military establishments, etc., have long been among the recognised duties of the State. During the war, Governments had to feed great armies whose physique and morale had to be maintained at all costs, and at the same time responsibility for providing food for the civilian population had to be assumed. Within recent years, the economic crisis and unemployment have imposed on Governments enormous responsibilities in the sphere of public assistance, of which the most urgent has been the combating of malnutrition. The emergency situations produced by the war and the depression have helped to make clear the importance of public health nutrition work in so-called normal times.

It is useless to ask whether governmental control in this field is legitimate or desirable ; it is sufficient to remark that in many countries it exists and is developing. In the field of public health, more and more attention is being given to the problems of nutrition ; in the course of our report, we shall describe some of the activities that result. Whether present tendencies are likely to prove permanent, or whether they are dependent on temporary and emergency conditions, it is impossible to say ; in each country, the course of economic events will influence the issue. But even to-day . it is possible to observe that State control in dietary matters is becoming more systematic and less of an "emergency" activity and that in many countries, for public health and economic reasons, a definite policy as regards the feeding of the population is being developed.

The inhabitant of a prosperous country, consuming his dinner in tranquillity, rarely pauses to reflect that millions of his fellows are at the same moment similarly occupied (or, if less fortunate, would wish to be) ; that the satisfaction of his primary need for food is made possible only by the regular production and distribution of mountains of provisions, which do not automatically take place everywhere and always ; that, in fact, vast numbers of human beings are malnourished and undernourished ; that, indeed, famine itself has not yet disappeared from the world.

II. CERTAIN ASPECTS OF THE PROBLEM.

1. PHYSIOLOGY AND ECONOMY.

Nutrition is an economic, agricultural, industrial and commercial problem, as well as a problem of physiology.

2. THE INDIVIDUAL AND THE MASS.

With the help of schedules of dietary requirements according to age, sex, intensity of work, etc., it is relatively easy to determine the quantity and quality of food required to nourish a city or an army. For such purposes, figures are commonly used which, as we shall see later, have little value except as averages ; they are largely based on mass observations and their application is to the mass, in which the individual disappears. But it is the individual who eats. Public health workers in general have a tendency to consider the individual case as a pathological case, for which the physician is responsible, but this is scarcely true as regards diet. Digestion and assimilation are not mechanical acts which are precisely the same in all human beings ; within the bounds of the normal, great scope for variation may exist. Might it not be possible, in this as in other fields, to approach the knowledge of the individual by the definition of categories or types ? It is possible that varying types exist, knowledge of which would throw light on the problem of the "normal" diet.

3. THE NORMAL AND THE PATHOLOGICAL.

Clearly, it is impossible to define with precision normal standards of health and physical developments, all deviation from which is regarded as pathological. A physician, even after prolonged examination of a subject, may find it difficult to say whether he is in "normal" health. Many diseases (*e.g.*, rickets) may manifest themselves in latent border-line conditions, which are difficult to detect, but it is just conditions of this nature which, from the standpoint of preventive medicine, it is most useful to recognise. Difficulties increase when the "normality" or otherwise of large numbers has to be rapidly assessed. In such circumstances, it has been found necessary to establish and employ methods of assessment which are questionable from a scientific point of view, but nevertheless useful as a basis for practical action. We may recall the endless discussions which have taken place with regard to the validity of "indices of nutrition" dependent on measurements of height, weight, chest width, hip and arm girths, etc.

Physical standards which are considered in current practice as reflecting the normal state may in reality, if based solely upon averages, be subnormal relatively to the optimum or ideal state that might be conceivable.

4. DIFFERENCES IN DIETARY HABITS DEPENDENT ON RACE, CLIMATE AND CUSTOM.

All diets which support life in human beings contain protein, fat, carbohydrate, mineral salts and vitamins, but the relative amounts in which these food factors are present vary greatly from one country to another. Broadly speaking, the principal cause of such variation seems to be climate ; what we call race has little influence on diet. Climatic and such different geographical conditions as are represented by mountains, plains, inland areas, coastal areas, etc., largely determine the production of foodstuffs. Man adapts his dietary habits to his surroundings and, in the balance which must be struck between physiological demand and environment, the environmental factor weighs heavily. It seems likely that national dietary habits are determined less by choice and instinct than by economic necessity, and, for this reason, it is quite

irrational to give them the status of physiological laws. In normal times populations will not readily change their mode of diet, but they will often change it quickly enough under stress of compulsion or economic crisis. The comparative ease with which human beings pass from one regime to another makes it possible to imagine great changes in the distribution and consumption of foods throughout the world taking place without serious opposition. Undernourished populations will not long reject good food because it is unfamiliar to them and conflicts with their traditional dietary habits.

5. THE EVOLUTION OF DIET.

What we know of the history of food and diet suggests that in the past, as at present, the dietary habits of mankind have varied enormously under the influence of geographical and economic circumstances. But, while man adapts himself to his environment, he also adapts his environment to himself. As the population of the world has increased, the production of certain types of animal and vegetable food has increased concurrently ; for example, the progress of civilisation has hitherto consistently been accompanied by increase in the production and consumption of wheat. At times the desire of human beings to secure certain articles of food may have influenced the course of history ; thus, one of the motives underlying the adventurous explorations of the fifteenth and sixteenth centuries was to obtain spices to relieve the monotonous diet of the day. We shall consider in a later section the relation between diet and the enormous increase in the production of foodstuffs made possible by modern science.

Remarkable changes in food habits are taking place in the modern world. It is obvious, for example, that the growth of industrialism has greatly influenced, and continues to influence, dietary customs in a large number of ways. It seems that, until very recently, the diet of the mass of the working population contained very little meat and was largely composed of foods rich in carbohydrate ; this description might still be applied to the regime of the European peasant. We may picture the heavy manual worker in the past (like the modern peasant) consuming a bulky diet containing much unassimilable material, and stopping work to eat very frequently—every two or three hours, in fact. Physiologically

such dietary habits may conform with the requirements of heavy labour ; a man working hard in the open air can tolerate a bulky indigestible diet more readily than a sedentary office-worker. At the same time, economic factors must play a part in determining the nature of the diet consumed by the peasant and manual labourer. Carbohydrate derived from cereals is the cheapest form of food energy.

Industrialisation influences diet through many channels. It tends, for example, to develop housing conditions which make the preparation of palatable meals a discouraging task. The high cost of rent in large cities reduces the proportion of the family budget which can be devoted to food.

Mechanisation reduces the need for the expenditure of human energy ; it becomes the industrial worker's task simply to tend the machine. At the same time, the development of industry and commerce involves the multiplication of sedentary office-workers. The modern industrial worker and employee find a bulky carbohydrate-rich diet quite unsuitable to their circumstances ; they demand a lighter, more concentrated regime rich in animal protein, fat, and green vegetables, and the number of meals is reduced to three a day. The modern tendency towards a more concentrated and nutritious diet is well illustrated in Germany, where, in spite of the economic depression, the consumption of meat and fat has, during recent years, continued to rise. With the development of industry, the population tends to discard its ancient bulky cereal diet—the traditional diet of the poor—in favour of a type of regime once enjoyed only by the wealthy [1].

In the United States of America, which a hundred years ago was a land of pioneers rather than peasants, the evolution of diet has followed a slightly different course. In the first half of the nineteenth century, according to MENDEL [2], there was an enormous preponderance of flesh foods in the national diet. To-day, the consumption of meat and cereals is falling, while that of dairy products, sugar, eggs, fruit or green vegetables is rising. Of late years a new factor, other than complex forms of supply and demand, has arisen to influence national dietary habits—namely, the education of the public in the scientific principles of nutrition. The effects of such education on national diet trends are particularly evident in the United States.

Within recent years, a number of factors have operated to disturb family life in general and to alter traditional customs, including dietary customs, based on the family. Such factors include : the increase of industrialisation, the material and moral results of the war, the entry of women into employment in relatively greater numbers, the increasing distances between the home and the place of work. In the working-class quarters of great cities and in towns devoted to industry, the home, the centre of family life in which the mother worked all day and prepared the family meals which all consumed round a common board, tends to disintegrate and disappear. All meals may be consumed outside the home ; or, if eaten at home, they tend to be irregular and hastily prepared, and to be largely made up of cold and tinned foods. Systematic investigation of such modern tendencies as regards diet (which have, in particular, excited the interest of German workers) might yield interesting information of an economic and physiological nature.

As a result, on the one hand, of the weakening of family ties and the partial disappearance of regular family meals, and, on the other, of the desire of employers that the working-day should be subject to a minimum of interruption, there has arisen a necessity for the provision of meals away from home, and this, in turn, has led to the development of what may be termed "mass feeding". Mass feeding raises problems of importance in the sphere of public health, to which considerable attention has already been given in certain countries, though not so much in others. The term "mass feeding" may include collective dietary arrangements in religious institutions, schools, colleges, asylums, orphanages, prisons, barracks, etc. ; but we refer particularly to mass feeding in connection with industry—in big shops, in offices and in factories, for example. It is especially in Japan and the U.S.S.R. and Germany that industrial mass feeding has developed within recent years.

6. THE PRESENT STATE OF OUR KNOWLEDGE OF NUTRITION.

There is a science of nutrition which is the necessary basis of all practical action. But it cannot be said that fundamental principles in this field are as firmly established as, let us say, the

principles which underlie the science of engineering. Many "generally accepted" facts are, in reality, debatable; "laws" which seemed fully established twenty years ago are open to question. In the absence of certainty on many points, it is necessary to make shift with probability.

The thermodynamic principles, for example, established by LAVOISIER and a long series of scientific workers rest on a secure foundation and provide the basis of indispensable methods of measurement. It is often essential, for practical purposes, to regard human beings as thermodynamic machines. But they are not thermodynamic machines; they are organisms with complicated functions to perform, endowed with imagination and will, and capable of adapting themselves in a remarkable manner to changes in their environment and mode of diet. It is not surprising that the problems of energy and protein requirements still give rise to infinite discussion. There are so many variable factors operating in the domain of physiology and psychology that the interpretation of dietary experiments in general is extremely difficult. Laboratory experiments, and particularly experiments on rats, have supplied valuable and necessary information. But in themselves they are often insufficient to clarify the problems of human nutrition, and the need for their confirmation by experiments on human beings (which need involve no danger or discomfort) is becoming more and more obvious. As soon as we leave the laboratory and attempt to study the problems of nutrition in the field, complicated by a variety of economic and social factors, difficulties increase. To assess the value of diet, we must employ standards about which there is little agreement among physiologists, and the statistical methods which are commonly employed in gathering information about the dietary habits of population groups provide only average figures relating to large numbers, and are often open to criticism on the ground that they do not conform with the requirements of statistical science.

There are, however, a number of facts about nutrition which are firmly established on a scientific basis. Such are :

The organism needs to be supplied daily with a certain quantity of food energy, evaluated in Calories. A considerable amount of information exists with regard to Calorie requirements. The discovery of food factors—vitamins and mineral salts—which

supply no appreciable energy and yet are essential to health has not affected the fundamental problem of energy needs.

The diet must yield protein, fat and carbohydrate. The proportion of these is variable, but only within limits, which are tolerably well established. (We omit here reference to special therapeutic and experimental diets which may lack fat or carbohydrate.)

Minerals are an indispensable part of the diet, though the quantities necessary are relatively small. From a practical point of view, the most important minerals in human nutrition are phosphorus, calcium, iron and iodine.

There are a number of vitamins which are necessary for growth, health, and even for life itself. Vitamins were once known as accessory food factors ; it is now clear that they are very essential food factors.

7. PSYCHOLOGICAL ASPECTS OF THE PROBLEM.

Psychological factors should not be ignored in the sphere of practical dietetics. Appetite is influenced, not only by the body's need for food, but also by mental attitudes ; prejudices, theories, philosophical and mystical ideas may all strongly affect dietary habits. We may recall the existence of numerous dietary "sects", of which the best known are perhaps the vegetarians and the enthusiasts for raw food. Certain sects are inspired by the ideal of protecting the body from uncleanness, which becomes the basis of religious scruples and of principles of asceticism, abstinence or temperance, involving the protection of the body—and not only the body, but also the soul—from "pollution".

One of the commonest dietary superstitions of the day is a belief in instinct as a guide to dietary excellence. Its partisans believe that nature has provided man with a specific instinct which infallibly prompts him to consume the kind of diet most suited to his well-being ; it follows as a corollary that the diets of primitive peoples are superior to diets approved by science. It is urged that civilised man, to avoid degeneration, must base his food habits on those of savages, who, if not completely free from all disease, are at least immune from the diseases of nutrition. It has been seriously suggested that light might be thrown on the problems of human nutrition by study of what chimpanzees eat in their native forests.

Such notions are derivative of the eighteenth-century fiction of the happy and noble savage. Those who have lived among the native populations in Equatorial Africa, for example, are aware of the value of such legends.

Dietary superstitions are perhaps not without influence on economic problems in connection with food.

III. STANDARDS.

First, what constitutes an adequate diet? What are human requirements as regards Calories, fat, protein, vitamins, etc., and in what proportion should the various food factors be combined? Again, by what means can the "state of nutrition" of an individual be assessed, and how can "malnutrition" be detected?

Both dietary and physical standards are necessary as a basis for practical action. The former may enable us, for example, roughly to gauge the value of the diet consumed by this or that section of the community. They make it possible to draw up dietary schedules for groups which have no free choice of food (*e.g.*, armies, inmates of institutions): They have been used as the basis of large-scale war-time rationing schemes; they may be used as a foundation of agricultural policies. Physical standards are employed by physicians to select from a given group those suffering from malnutrition and in need of dietary treatment. They assist us in assessing the effect on human beings of this or that dietary regime.

The problems of establishing satisfactory dietary and physical standards are intimately interconnected. The ultimate test of a satisfactory diet is its effect on the physique and health of human beings. In seeking an answer to the question, Is this or that population group adequately fed? two methods of investigation may be followed: (1) the diet of the group may be compared with arbitrary standards put forward by physiologists, or (2) clinical or anthropometric enquiries may be carried out, the purpose of which is to assess the physical condition of the group and to discover whether there exists evidence of physical defect and disease which experience has taught us may arise as a result of defective diet.

No two physiologists, in attempting to establish standards representing an adequate diet, are likely to reach precisely the

same conclusions, nor is there any general agreement as to what constitutes the physical state of "malnutrition", or methods for detecting malnutrition in individuals which are above scientific reproach.

But it is perfectly possible to establish standards of adequate or optimum food intake which are sufficiently accurate for use in practice. With regard to the assessment of "state of nutrition" and the detection of malnutrition, the position is somewhat less satisfactory, but at least it may be said that the application of current methods in this field may supply the public health worker with useful information.

1. DIETARY STANDARDS.

Dietary needs can be considered either in terms of Calories and food factors or, from a qualitative angle, in terms of actual food-stuffs. The latter method has the advantage of simplicity, but it can usually be employed only in conjunction with the former. In certain countries, for example, standards of necessary milk intake for children have been widely adopted by public health authorities ; it is often more convenient, in practice, to think of milk as milk rather than as a source of valuable food factors ; but, at the same time, the use of milk can be defended on a physiological and chemical basis. The second method of approach, useful for rough qualitative judgments, is, in fact, a development and simplification of the first to meet the requirements of practice.

Energy Requirements.

Two methods have been employed in the study of human Calorie requirements. By direct and indirect calorimetry, it is possible to discover the energy output of subjects at rest or performing various kinds of work. Work performed by an experimental subject may be measured and expressed in terms of Calories. Observation of the number of Calories expended on work or heat-production under experimental conditions provides data for the establishment of quantitative standards of food intake.

Another widely employed means of assessing dietary requirements is by the observation of what healthy individuals living under various conditions and performing various kinds of work,

who have no reason to restrict their food intake, consume. In making use of such observations to establish quantitative standards, we take it for granted that appetite adjusts food intake to energy requirements.

It has been observed that the energy intake of men of average size not engaged, on the one hand, in very strenuous labour, or, on the other, following an entirely sedentary life, is usually in the neighbourhood of 3,000 Calories a day. This figure agrees well enough with that derived from energy expenditure budgets based on physiological data, for the compilation of which the basal metabolism rate—*i.e.*, the rate of energy exchange at rest in a warm atmosphere twelve hours after a meal—is used as the foundation. It is well established that the B.M.R. of an average European is from 65 to 75 Calories per hour; during sleep, the energy exchange is on a lower level; during nearly all waking activities, it is considerably higher. The increase of energy exchange, in relation to the basal, which takes place during the performance of various activities, has been carefully investigated in the laboratory; as a result, it is possible to draw up energy budgets the various items of which consist of figures representing the energy exchanges of an average individual during an average day. The sum total of all the items, where average men at average work are concerned, is found to be somewhere about 3,000 Calories per day.

This figure, or something closely approximating to it, has been widely used in practical dietetics. The well-known dietary standards of VOIT, ATWATER and RUBNER, based both on calorimetric and statistical investigations, evaluate the daily energy requirements of a man at "moderate" work at 3,055, 3,315 and 3,093 Calories respectively. The figure 3,000 has been put forward as standard by the Advisory Committee on Nutrition of the British Ministry of Health [3] and by v. TYZSKA [1], one of the most influential of German workers in this field. It is to be found in a number of standard text-books on nutrition. The Conference convened by the League of Nations in Rome in September 1932, for the "standardisation of certain methods used in making dietary studies", in adopting the figure 3,000, made the following reservations:

It will be noted that the historic 3,000 Calories have been accepted as the basis of the coefficients. Certainly, the majority of the members of the Conference were definitely of the opinion that 3,000 Calories, gross or

brutto, as the basal value, even for a man during a good day's work, is definitely high. (Probably a figure of 2,700 to 2,800 would be nearer the mark.) The only defence of the continued use of this figure is that the majority of studies in the past have been based upon it, and its retention allows of some—admittedly indifferent—comparison of new investigations with the old. [4]

Does this figure, 3,000, represent *gross* or *net* requirements? The standards of VOIT, ATWATER and RUBNER are based on food as eaten (Calories net). In practice, however, we are usually more concerned with food as purchased (Calories gross), and it has been reckoned that, to allow for losses in cooking and digestion, food as purchased should have a Calorie value 10% higher than actual requirements. This is a liberal estimate, but we can at least say that, whatever figure is accepted as representing net requirements, food as purchased should yield a somewhat greater number of Calories to allow for waste.

The application of the generally accepted 3,000 Calorie standard is largely a matter of common sense. Energy requirements vary enormously according to the type of work performed—from perhaps 6,000 to 7,000 in the case of a lumberman to 2,200 in the case of a sedentary office-worker. Any standard of caloric requirements is applicable only to large numbers; where individuals are concerned it has little significance, except perhaps a rough *point d'appui*. It cannot even be applied indiscriminately to population groups, unless these are very large and contain people engaged in a variety of manual and sedentary occupations; when numbers are large, individual differences and differences due to occupation tend to cancel each other out. Public health nutrition work is, as a rule, to be carried out on a large scale, and for this reason a standard figure of Calorie intake has its uses; but there is, of course, no reason why any public health administration, about to engage in such work, should adopt the figure 3,000 without further question. Even considered as a very general average, it is open to attack. VOIT's Calorie standard was originally put forward as suitable for a man doing "moderate work", by which was meant the work performed by a man, like a joiner or mechanic, doing a good ten hours of work per day. In modern civilised communities, as mechanisation spreads, the proportion of men carrying out "strenuous" or even "moderate" work continually decreases.

All that can be said is that the figure 3,000 has been very widely accepted, and, in view of the general consensus of opinion, founded to some extent on physiological evidence, any extreme departure from it requires defence.¹

The indefiniteness of our information in this field makes it possible to criticise *any* officially adopted figure representing Calorie requirements. In connection with the food requirements of the unemployed, a question in which political passions are involved, much controversy has taken place within recent years, the bitterest controversialists being, as a rule, those incapable of distinguishing between individual cases and a statistical average.

The energy requirements of women and children are, in general, less than those of an adult man. Both statistical and calorimetric data exist with regard to caloric intake and requirements in both sexes in different age-groups; data of this nature assist in the construction of *scales of family coefficients*, in which the needs of women and children are stated in terms of those of an average man, the latter being usually taken as unity. Over twenty different scales of family coefficients have been proposed by various workers. Such scales probably correspond to reality only very roughly, and no one scale can reflect the relationship between dietary requirements according to age and sex which exists in all parts of the world. For example, in most scales, the energy requirements of women are taken to be about 0.8 of those of an adult man; this may be roughly true in industrial communities, but it is less likely to represent reality in peasant communities where the housewives work side by side with their husbands in the fields.

But, in spite of the disadvantages of such scales, they fulfil useful purposes. When it is necessary to calculate the dietary requirements of mixed population groups, it is convenient to have a *consumption unit* (usually the needs of an adult man) in terms of which the requirements of the entire group can be reckoned. For the investigation of family dietary habits, a scale of family coefficients is essential; since families differ in size and composition, it would be impossible to compare the *total* food intake of families with that of other families as with some accepted standard. To make such comparison possible, the total food intake of each family

¹ See Annex 1.

must be divided by the number of consumption units which it contains. A further use of scales of family coefficients is in enabling any figure taken as indicating the energy requirements of an average man to be applied to mixed population groups.

In large-scale public health nutrition work, it is usually necessary to employ some "scale of family coefficients".

In 1932, an expert Committee, convened by the Health Organisation of the League of Nations, drew up a scale, which is as follows:¹

| Age | Coefficient | | |
|----------|-------------|------------|--------|
| | Male | Both sexes | Female |
| 0-2 | | 0.2 | |
| 2 and 3 | | 0.3 | |
| 4 „ 5 | | 0.4 | |
| 6 „ 7 | | 0.5 | |
| 8 „ 9 | | 0.6 | |
| 10 „ 11 | | 0.7 | |
| 12 „ 13 | | 0.8 | |
| 14 to 59 | 1.0 | | 0.8 |
| over 60 | | 0.8 | |

(1.0 = 3,000 Calories gross.)

The Committee claimed no absolute accuracy for this scale; it could not be defended figure by figure, and it was not the scale that any member of the Committee put forward as his ideal scale. The international scale has been fairly widely employed, and its use makes the results of different workers more easily comparable. In the present instance, we would simply draw attention to its existence as a reasonably accurate scale for use in practice.

In the scale of BIDGWOOD and JACQUEMYNS [5], the unit of consumption is the housewife, and the adult male coefficient varies from 1.14 to 1.2 according to hours of work. These workers apply the coefficient 0.9 to an adult *unemployed* man, on the grounds that in an unemployed family the wife works more strenuously than the husband.

¹ In any case, the Conference was of the opinion that no scale can be formulated which will correspond accurately to the relative food consumption of family members in all countries and in all circumstances of life. The variation, from country to country and from class to class, of such factors as height, weight, age of maturity, amount of work performed by women and children, etc.—factors which influence the relative food intake of different family members—make it impossible that one particular scale should everywhere correspond with real values. (*Quart. Bull. Health Organ., League of Nations, 1: 480, 1932.*)

Protein Requirements.

There is no existing "standard of protein intake" which rests on the sure ground of experimental evidence, and the question, What is the optimum protein intake? hotly debated by physiologists, physicians, economists, and dietary faddists, cannot be answered. On the one hand, there are those who advocate a high intake; on the other, we find schools which seek to emphasise the desirability of "restricted" consumption.

On the effect of a high protein diet on the kidneys and on the organism generally, laboratory and clinical evidence is contradictory. NEWBURGH and his associates [6] observed that diets containing 30% of protein produced signs of kidney damage in rabbits and human beings, but their observations have been criticised on the grounds that the experimental diets were incomplete as regards dietary factors other than protein. POLVOGT, McCOLLUM and SIMMONDS [7] have shown that hypertrophy and congestion of the kidneys, with hyaline casts, occurred in rats fed diets containing 30-40% of protein, but complete as regards vitamins and mineral salts; in spite, however, of morphological evidence of kidney damage, the animals were in excellent general condition at the close of the experiment. We may mention also the experiments of ADDIS, MACKAY and MACKAY [8], in which rats lived a year in good health, showing no evidence of renal lesions, upon a diet containing 70% of protein. Many other relevant observations might be quoted. While certain experiments suggest that a high protein intake may cause renal hypertrophy and injury, such experiments are often open to criticism on the grounds that the diets employed were incomplete; further, it is not clear that the effects on the kidney noted were actually detrimental to health. In nearly all such experiments, the proportion of protein in the diet greatly exceeded that in the ordinary freely chosen diets of civilised man.

On the whole, the races of mankind with a high protein intake are superior in physique to those with a low intake, but no inference can thereby be drawn as to optimum protein consumption, since freely selected "high protein" and "low protein" diets differ in many important respects besides protein content. ORR and GILKS [9], for example, have observed that the Masai tribe in East

Africa, which lives on a diet composed mainly of meat, milk and blood, is greatly superior in physique and energy to a neighbouring tribe, the Akikuyu, the diet of which consists of cereals, tubers, plantains, legumes and green leaves. But the diet of the Akikuyu, as compared with that of the Masai, is deficient, not only in protein, but also in fat, and certain vitamins and mineral salts.

In support of a low intake, it is possible to quote numerous examples of population groups consuming less than 70 grammes of protein per day. According to ALBERTONI and ROSSI, the frugal and poverty-stricken (yet healthy) peasants of Southern Italy have a protein intake not exceeding 60 to 70 grammes per day. CAMPBELL, carrying out investigations on medical students in Singapore, including Brahmins and Hindus, vegetarians except for a little milk, accorded average figures of nitrogen excretion as low as 5 to 6 grammes per day. EIJKMAN found that the protein intake of eight young Javanese did not exceed 54 grammes ; KUMAGAWA observed equally low intakes among the poorer classes in Japan ; and A. BASLER, among soldiers of 50 kg. body-weight (53 grammes) [10]. Millions of human beings do not consume more than 50 to 70 grammes of protein per day. It must, however, be remembered that such examples tell us nothing except that human beings can exist at a low level of protein intake. An observer may describe groups as healthy, although he knows little of their vital statistics, resistance to disease, or of their physical potentialities with a richer diet.

We must also recognise that similar arguments in favour of a high protein intake may be equally fallacious. The Eskimos are often cited as an example of a people who live in health on a diet yielding from 260 to 300 grammes of protein per day. But we have only very general knowledge about the health of the Eskimos or, for that matter, about their diet. Similarly, the oft-quoted case of the arctic explorer, STEFANSSON [11], who lived on a meat diet for nine years without visible injury to health, and that of McCLENNAN and WALTER, who lived on a similar diet for a year in the United States of America, do not provide really useful data for the solution of the problem of protein requirements. Too many complex factors were involved.

The minimum amount of protein required to ensure nitrogenous equilibrium has often been investigated. HINDHEDE claims to have

shown that health and nitrogenous equilibrium can be maintained on a diet of cereals, potatoes, margarine and fruit containing only 32 grammes of absorbable protein, which seems to be the lowest figure ever put forward in this connection. Hindhede's assistant, MADSEN, is said to have lived on this regime in good health for many months, but the fact that this period was interrupted by intervals of ordinary feeding seems to detract from the value of this experiment [12].

Subsequently, Hindhede proposed a protein standard of 60 grammes, combined with a Calorie standard of 2,500. Of recent years he has, so to speak, attacked animal protein rather than protein in general.

Hindhede's dietetic theories are associated with the idea of a "return to nature" and their advocates are inclined to display a certain sectarian and missionary spirit. Some of his followers have stressed the value of his low protein diets in the treatment of ill-health and disease, but clearly we have no scientific evidence to enable us either to affirm or to deny their utility (much the same might be said of religious fasts). In the economic sphere, Hindhede's views have been the centre of considerable controversy. Hindhede maintains that countries could effect great economies by adopting his regime, and that it is a profound error to transform cheap food into dear by feeding pigs on cereals which could with advantage be fed direct to human beings. At the same time, he urges the consumption of unmilled cereals. He claims to have saved Denmark from famine during the war and the blockade by his advice to kill off four-fifths of the pigs and one-third of the cows in the country; the Germans, on the other hand, maintained their live-stock, with the result that neither human beings nor animals could be sufficiently fed. "A million human beings", wrote Hindhede, "died in honour of science". According to F. CHRISTIANSEN, the population of Denmark during the war did not consume a diet deficient in protein—in cities the average protein intake was 108 grammes per day and in the country 139—and the lowered mortality observed during the war period must be ascribed to causes other than restricted intake of animal protein.

The questions which Hindhede raises are very complex, and indeed little precise information with regard to optimum or minimum protein consumption can be drawn from his work. The difference between the type of diet recommended by Hindhede and

the type of diet recommended by more orthodox physiologists is not solely a question of protein intake. Hindhede's type of diet is relatively poor in vitamin B₂ and probably in calcium (since it contains little milk). It is doubtful, Christiansen remarks, whether it would be as suitable for children as for adults.

On the whole, laboratory experiments suggest that the long-continued use of a diet very low in protein produces enfeeblement : but here, again, other factors may be involved.

Between the two extremes of a very high and a very low protein intake, it is difficult to *prove* that one level of intake is preferable to another. SHERMAN, from an exhaustive examination of the literature, has reckoned that the protein requirements of a man weighing 70 kilos are in the neighbourhood of 44 grammes a day. This figure is an average, derived from many investigations, and Sherman further concludes that it is " somewhat above the actual need for maintenance in the average man or woman ". Since, however, it is not advisable to adopt as a standard the lowest amount of protein to which the body can adjust itself, the same worker proposes 1 gramme of protein daily per kilo of body-weight, or about 70 grammes per average man, as a suitable standard of protein needs.

The authority of VOIT, RUBNER, ATWATER and others is responsible for the very general acceptance (in Europe) of a " protein standard " of 100 grammes. Actually, the figures originally suggested by these physiologists were somewhat above this level ; Atwater's protein standard, for example, was 125 grammes. The modern tendency in America is towards the adoption of a lower protein standard (such as that suggested by Sherman)—a fact which suggests that physiologists, in drawing up dietary standards, are largely influenced by the dietary habits of their time and country. In the closing years of the last century, when Atwater put forward his standard, the American diet included more meat than it does now ; milk and green vegetables, fruit and other foods are tending to displace meat to-day. When CHITTENDEN in 1905 vigorously advocated what he called " economy in nutrition "—*i.e.*, a daily Calorie intake of 2,800 and a protein intake of about 60 grammes—his views were regarded as revolutionary. They appear less so in America to-day, for in the interval the dietary habits of the American people have swung in the direction of " economy in nutrition " as defined by him. It would seem that much the same has taken

place in Germany. TYSZKA has reckoned, on the basis of gross consumption statistics, that average daily Calorie intake in Germany in 1912 was 3,642, as compared with 2,835 in 1932, while the corresponding figures for protein were 91.9 and 74.5. Dietary standards, far from being absolute, bear the impress of the date and place of their origin.

It is usually assumed that some of the protein contained in a satisfactory diet should be of animal origin. The basis for this assumption is a long series of experiments on man and animals, which on the whole show that animal protein is of higher biological value than vegetable protein. Experiments on rats carried out by McCOLLUM and others have indicated that, while vegetarian diets, if very carefully devised, can support growth and maintain the animal in a fairly good condition, such diets are on the whole inferior in these respects to mixed diets containing a proportion of animal food. It seems reasonable to assume that the inferiority of vegetarian diets observed was related to their deficiency in animal protein. On the other hand, we know that it is possible for adult human beings to live in health on a vegetarian diet. TYSZKA suggests that the sedentary yet busy existence of modern civilised man calls for a concentrated diet rich in animal protein which can be rapidly consumed, involves a minimum of digestive effort, and gives a feeling of satiety enabling meals to be widely spaced. The Advisory Committee on Nutrition of the British Ministry of Health has suggested 37 grammes as a suitable daily allowance of "first class" or animal protein for an average man, which would represent about 5% of total Calories on a diet yielding 3,000 Calories per day. Tyszka proposes as standard 40 grammes of *animal* protein. This is a far higher intake of animal protein than is customary in peasant communities throughout the world. The question of animal protein requirements is in fact quite insoluble on the basis of existing knowledge, and a diet deficient in animal protein cannot logically be condemned for that fact alone. There can, however, be no disadvantage in adopting a standard of protein intake which includes a reasonable proportion of animal protein such as that, for example, proposed by the Advisory Committee on Nutrition. In ordinary freely selected diets, 100 grammes of protein would supply from 12 to 15% of total Calories; if protein requirements are stated in terms of the percentage of Calories

yielded by protein, then the fact that the protein requirements of children, relative to total energy intake, are greater than those of adults should be borne in mind.

Protein Requirements according to Age and Sex.—During growth, protein needs are relatively greater than in adult life. This is also true of mineral salts. For this reason, certain workers have deemed it irrational to apply scales of family coefficients, based on energy needs, to protein and mineral requirements. In an attempt to meet this difficulty, HAWLEY [13] has drawn up the following scale.

Hawley's Scale for Protein and Mineral Requirements.

| Age and Sex. | | Coefficient |
|--------------|---------------|-------------|
| Man | 18 to 60..... | 1.0 |
| Woman | 18 to 60..... | 0.8 |
| Youth | 15 to 17..... | 1.5 |
| Girl | 15 to 17..... | 1.2 |
| Boy | 10 to 14..... | 1.3 |
| Girl | 13 to 14..... | 1.3 |
| Girl | 10 to 12..... | 1.2 |
| Child | 6 to 9..... | 1.0 |
| Child | under 6..... | 0.8 |

Protein Standard for Public Health Work.—For practical public health work, a standard of from 70 to 100 grammes of protein may well be employed, and the desirability that a reasonable proportion should be of animal origin may be emphasised. We may add that, although the generous classical estimates of protein needs are still widely used, the modern tendency, in many countries, is towards a decreased consumption of meat, and therefore of animal protein.

Carbohydrate and Fat.

We have no knowledge as to the optimum proportions of these food factors in the diet. It is clear that they are isodynamically interchangeable within wide limits. Carbohydrate fulfils other functions in the body besides the provision of energy. It spares the breakdown of protein and assists in the metabolism of fat. The proportion of fat to carbohydrate in the diet may vary within wide limits without producing metabolic disturbance, but, if the

limits are overstepped and fat supplies too high a proportion of the energy value of the diet, incomplete oxidation of fat—ketosis—may result. It has been well said that “ fat burns in the fire of carbohydrate ”.

KROGH [14] has shown that effective work at lowest cost to the organism can be best accomplished when the liver is well stored with carbohydrate. Before a severe athletic contest, the diet should be rich in carbohydrate.

Standards of fat intake proposed by physiologists show wide variation, as does the actual intake of human beings in various parts of the world. The standard fat allowances of VOIT, RUBNER and others are about half the actual consumption of average men in Western civilisation to-day. Fat has a high satiety value ; its high caloric content reduces the bulk of food consumed ; it is the vehicle of fat-soluble vitamins ; infants at the breast receive about half of their Calories in the shape of fat ; it may yet be shown to possess some intrinsic quality of value to the organism. For these and other reasons, it seems advisable that standards of fat intake should not be too low.

*Standard Dieteries put forward by Various
Authorities as suitable for Average Men.*

| | Protein | Fat (grammes) | Carbohydrate | Calories |
|---|---------------------|------------------|--------------|----------|
| Voit | 118 | 56 | 500 | 3,055 |
| Rubner | 127 | 52 | 509 | 3,092 |
| Atwater | 125 | 125 | 450 | 3,520 |
| Advisory Committee (Ministry of Health)... | 100 ¹ | 100 | 400 | 3,000 |
| Playfair | 119 | 51 | 531 | 3,140 |
| Tyszka | 80-100 ² | 60-80 | 500 | 3,000 |

¹ Including 37 grammes of animal protein.

² Including 40 grammes of animal protein.

In connection with the problem of human requirements of Calories, protein, carbohydrate and fat, the emphasis may lie in two different directions—towards liberality or towards frugality. For children, for pregnant and lactating women, for those engaged in hard manual work, abundance is essential. On the other hand, the ideal of frugality, of a “ moderate asceticism ”, is more appropriate in the case of middle-aged and elderly men and women leading a sedentary life. A diminution in food intake, and particularly intake

of protein, in middle life may be salutary in that it minimises the risk of certain diseases associated with "over-feeding" and of premature senility.

Mineral Salts.

No diet is adequate unless it contains a sufficiency of the mineral elements found in human tissues, which are constantly leaving the body and need to be replaced. This fact has long been recognised as a general principle, but it is only recently that the rôle played by mineral deficiencies in producing disease has been generally realised. As far as present knowledge goes, the elements which are most commonly defective in ordinary diets are calcium and iron. It is generally accepted that there is a relation between certain types of goitre and iodine deficiency in soil, water and food. Considerable public health work designed to prevent this food-deficiency disease has been carried out in a number of countries.

Phosphorus.—SHERMAN has suggested 1.32 grammes per day as a suitable standard of phosphorus requirements for an adult. This figure is 50% higher than the average phosphorus output of 21 subjects in 95 "balance" experiments. The needs of growing children are relatively higher than those of adults.

Most human diets, at any rate as far as Western civilisation is concerned, seem to contain a sufficiency of phosphorus. Phosphorus deficiency is, however, of paramount importance in connection with the feeding of live-stock. On millions of acres of grazing-land throughout the world, the mineral content of the pasture, and most commonly its phosphorus content, is the limiting factor in stock-raising. In areas of phosphorus deficiency, the diet of human beings may tend to be deficient in that element.

It would appear that the rachitogenic or anti-calcifying action of cereals, and particularly oatmeal, which MELLANBY [15] has described is virtually due to phosphorus deficiency. BRUCE and CALLOW [16] have shown that the phosphorus in cereals is present in a chemical form which is very poorly utilised. A diet rich in cereals is therefore a diet poor in available phosphorus, which intensifies rickets in the absence of vitamin D.

Calcium.—Calcium constitutes a larger proportion of the body-weight than any other of the inorganic elements, over 99% of the

total being located in the bones. SHERMAN and his colleagues, having made a compilation of all "calcium balance" experiments recorded in the literature, discovered that, in 97 experiments, the average daily calcium output was 0.459 gramme. This, Sherman takes to be the minimum requirement. Since dietary standards should be set above the minimum, he proposes a figure 50% higher—0.68 gramme—to represent the calcium requirements of the average man. The needs of children and pregnant and lactating women are higher; 1 gramme has been proposed for children, and it appears that the optimum requirements of pregnant women may be as high as 1.6 grammes. We shall later discuss the practical significance of these figures.

There is evidence that vitamin D is concerned in the economical utilisation of calcium by the organism, from which it follows that an abundant intake of calcium is of peculiar importance when vitamin D intake is at a minimum—*e.g.*, in winter, or in countries which enjoy little sunshine throughout the year.

Iron.—The problem of iron metabolism and exchange has been less fully investigated than similar problems in the case of calcium and phosphorus. 15 milligrammes of food iron per day has been very tentatively proposed as standard by SHERMAN. Human milk contains from 1 to 2 milligrammes per litre, and cow's milk from 0.36 to 1 milligramme.

The recent discovery that hypochromic microcytic anæmia, one of the causes of which is a diet poor in iron-containing foods, is a very common disease among infants, and in adult women in the child-bearing period, indicates that this food factor is of importance in the sphere of public health.

Iodine.—It has been estimated that the body of an adult man weighing 70 kilos contains about 25 milligrammes of iodine; of this, the thyroid gland contains about 10 milligrammes. VON FELLEBERG has reckoned the daily iodine requirements of an adult as 14 γ . The iodine content of foodstuffs varies with locality; we have little information as to the extent of the variation. Sea foods, in general, are richly supplied.

Endemic goitre is most prevalent in mountainous areas far from the sea, in which, for reasons still under discussion, the iodine

content of soil and water is low. It is generally accepted that lack of iodine is the principal factor in producing the disease, though other possible factors, such as contaminated water supply and unhygienic conditions, have been emphasised by McCARRISON. Effective public health work designed to prevent goitre has been carried out in a number of countries, notably Switzerland and the U.S.A. The method of prophylaxis which has achieved most success has been the regular administration of iodine compounds to schoolchildren and the encouragement of the use of table salt containing sodium iodide. It may be recalled that in goitrous areas domestic animals are likely to suffer from goitre, which may be prevented by a variety of methods.

In practice, it is generally admitted that the prevention of goitre is effectively ensured by the intake of a total of 50 milligrammes of iodine per year, administered in several courses interrupted by periods of rest. In endemic areas, doses as high as 5 to 10 milligrammes per week have been administered.

Vitamins.

It is at present impossible to deal satisfactorily with the problem of vitamin requirements from a quantitative standpoint. Several of the vitamins have now been isolated in a pure condition ; one, vitamin C, can now be produced synthetically in the laboratory. The time may shortly arrive when, in the words of the " Report of the Second International Conference on Vitamin Standardisation " [17], the vitamin activity of substances will be expressed in terms of the exact amount of pure active vitamin present. Such an advance would allow the problem of vitamin requirements to be investigated on the same plane as the problem of mineral requirements.

The establishment of arbitrary vitamin units has already introduced a quantitative element into this field. International units for vitamins A, B₁, C and D, based on standard substances, have been adopted by two Conferences convened by the Permanent Commission on Biological Standardisation of the Health Organisation of the League of Nations, and widely used throughout the world. For an account of existing international vitamin standards and units, the reader may be referred to the report of the second Conference on Vitamin Standardisation.

Attempts have been made to estimate human requirements of certain of the vitamins in terms of various units. We have included two of these estimates in the following sections, translated roughly into international units. The practical value of such figures is at present small, since tables giving the vitamin content of common foods in terms of international units are not yet generally available.

Satisfactory quantitative data being absent, we must emphasise the necessity of a very abundant supply of the known vitamins. There is no evidence that any diet composed of natural foodstuffs contains vitamins in such excess as to produce harmful effects, and, on the other hand, we know that vitamin deficiency produces the most serious consequences.

Vitamin A.—Vitamin A and carotene appear to have the same physiological action, the latter being converted into the former in the liver.

Among the most abundant sources of one or other of these food factors are whole milk and fat-containing milk products, tissue fats, liver and liver oil, green vegetables, carrots, certain fruits (*e.g.*, tomatoes, bananas, dates, mangoes), and pine and fir needles.

Except during the war, the severest results of vitamin A deficiency—*e.g.*, keratomalacia—have seldom been observed in Western civilisation, but evidence is accumulating that, in the tropics and the East, vitamin A deficiency produces severe and widespread cutaneous and ocular disease.

In recent years, there has been considerable discussion as to whether partial vitamin A deficiency is common in the children of the poor in Europe and North America, decreasing their resistance to skin and respiratory infections and producing general ill-health. Whatever may be the answer to this question, it is clear that in many parts of the world impaired immunity to infectious agents, resulting from vitamin A deficiency, is an important factor in the production of disease.

ROSE [18] suggests 3,000 U.S. Pharmacopœia units as representing the vitamin A needs of an average man. This would correspond to about 4,200 international units.

Vitamin B₁.—This vitamin is widely distributed in nature, being particularly abundant in the germ and pericarp of cereal grains and in legume seeds. There is no doubt that infantile beri-beri,

which produces an enormous infantile mortality in many tropical countries, is due to vitamin B₁ deficiency. Most observers ascribe adult beri-beri to the same cause, and even those who hesitate to accept the explanation of the disease in its entirety admit that vitamin B deficiency plays a part in its production. Certain workers have sought to show that minor forms of vitamin B deficiency are common in the West, but on the whole it appears that this vitamin is sufficiently present in the ordinary mixed diets of Europe and North America. COWGILL [19] has devised a formula by means of which the vitamin B₁ requirements of an individual of known weight and caloric intake may be predicted, and he finds its accuracy confirmed by available data about beri-beri-producing diets. According to Cowgill's formula, the minimum vitamin B₁ requirements of a man weighing 70 kilos and consuming 3,000 Calories a day are about 300 international units.

Vitamin C (or ascorbic acid).—Vitamin C, the anti-scorbutic vitamin, is found in fresh fruit and vegetables, in germinated cereals and legumes, and to some extent in fresh milk and meat. Paprika or Hungarian pepper contains ascorbic acid in abundance and has been used for making preparations on a large scale. It was found, in the U.S.S.R., in pine and fir needles, in sorrel and whortleberry.

Vitamin C is of interest to public health authorities for a number of reasons. It is the most unstable of the vitamins, and readily impaired in the process of food preservation. Considerable progress has been made in the development of canning processes which do not destroy the vitamin C originally present in fruits and vegetables, and it would seem advisable that public health authorities, in drawing up regulations about food preservation and sterilisation, should bear the problem of vitamin C destruction in mind. A quotation from a recent report of the Committee on Fruit and Vegetables of the American Public Health Association will illustrate their responsibilities in this connection: "It is possible", the report remarks, "to express and bottle or can tomato juice and preserve a high concentration of vitamin C. It is also possible to produce a well-flavoured juice practically devoid of it. If we buy the juice for the vitamins and salts it contains, it is important that we give critical attention to the methods of production and the character and source of these new juice preparations."

The practice of supplying infants, particularly artificially fed infants, with vitamin C, usually in the form of fruit juice, is now becoming common throughout the civilised world, and imposes on health administrations the duties of ensuring supplies of vitamin C for this purpose and inculcating awareness of its advisability. In certain Northern countries—*e.g.*, Norway and Sweden—widespread vitamin C deficiency of minor degree is common during the early spring months, giving rise to an interesting public health problem capable of solution by simple measures. The discovery by SZENT-GYÖRGYI and others of the chemical nature of vitamin C, and the subsequent synthesis of vitamin C in the laboratory, making possible production on a large scale, promise shortly to bear valuable fruit in the realm of medicine and public health. Some workers consider that minor manifestations of vitamin C deficiency are more widespread than is generally supposed.

ROSE [18], defining the unit of vitamin C as “ the smallest dosage which will permit growth and prevent scurvy in guinea-pigs on a scurvy-producing diet ”, proposes 30 units as the standard adult requirement, an amount contained in 45 to 60 c.c. of orange juice. This estimate of adult requirements corresponds roughly to 500-600 international units per day. Szent-Györgyi has reckoned the protective daily dose of ascorbic acid for an infant as 25 milligrammes. A liberal estimate of the protective dose for a man would be 50 milligrammes per day.

Vitamin D.—There are few common foodstuffs which contain vitamin D or the anti-rachitic vitamin in abundance. It is to be found in liver, eggs, summer milk and butter ; liver oils are its most abundant natural source. Vitamin D requirements are increased when the diet is deficient in calcium, when it contains much cereal, and when little sunlight is available. In countries which enjoy abundant sunshine throughout the year, rickets rarely occurs in infants and children, although the diet may be low in calcium or contain no foods rich in vitamin D. In such circumstances, the bones show osteoporosis but no marked rachitic changes [20].

Infants in the temperate zone, whether breast- or bottle-fed (but particularly the latter), are in danger of rickets if they do not receive additional supplies of vitamin D. The amount of “ additional ” vitamin D necessary to prevent rickets (in England) has

been reckoned as from 1,000 to 2,000 international units, and the curative dose as about 5,000 units (HARRIS [21]). It is pointed out later that vitamin D requirements, in terms of international units, depend on the form in which vitamin D is given.

In recent years, it has been shown that the development of the teeth, like that of other bony structures, is dependent on vitamin D. An ample supply of this vitamin ensures strong, glistening, shapely teeth. Further, evidence is accumulating that vitamin D is a potent factor in the prevention of dental caries, which may be described as one of the major scourges of modern civilisation.

There can be no question that recent discoveries in connection with vitamin D are of extreme importance to the public health worker.

Vitamin B₂ (G).—It is generally held that vitamin B₂ is identical with GOLDBERGER'S P-P, or pellagra-preventive, factor. The richest sources of the vitamin are lean meat, fish, liver, milk, cheese, eggs, peas, yeast, peanut meal and certain vegetables—*e.g.*, collards, kale, tomatoes and turnip greens [22]. The supply of foods rich in the P-P factor is an important public health activity in pellagra-stricken areas.

Certain workers consider that a high vitamin B₂ intake tends to improve general health and development, and that the remarkable value of milk in improving physical status may be partly due to the vitamin B₂ contained in this food.

Vitamin E.—We need not lay stress on this vitamin, which is necessary for successful reproduction in both sexes. There are indications that it is of practical importance to the farmer and stock-breeder, but so far no conclusive clinical observations have been published indicating that vitamin E deficiency is a common cause of human sterility.

In a word, it is desirable that, in all those fields in which the health authorities take charge of the public health—*viz.*, maternal and infant welfare, school hygiene, social medicine clinics—they should provide for the administration of vitamins. For the population as a whole, it is desirable that they should test the value of the prepared foods that are being placed on the market in ever-increasing numbers and bar those that are found wanting; the League recommendations provide the necessary standards and

technique for the purpose. There is useful work to be done in connection with the canning industry with a view to securing the best possible preservation of the vitamins. It would be an extremely good thing if the public were warned against the vitamin craze, deficiency-disease phobia and the consumption, otherwise than on definite medical advice, of highly expensive medical preparations. This is a point of some importance in education in hygiene.

Dietary Requirements in Simple Terms.

The essence of modern practical dietetics can be briefly expressed in simple language in terms of actual foodstuffs.

One of the principles which emerges is the desirability of a mixed diet ; the many food factors which are necessary for life and health are more likely to be supplied by a varied diet than by a monotonous one. A second important principle is the value of a large intake of the "protective foods"—milk and green vegetables (to which may be added fruit). Milk and cheese are rich in calcium and supply proteins of high biological value and vitamin B₂. Milk fat in its various forms is an important source of vitamin A. On account of its high content of valuable food factors, milk is a necessary food for children and for pregnant and nursing mothers, making good the deficiencies of meat, root vegetables, tubers and cereals. We shall later refer to the effect of "extra-milk" in accelerating growth and enhancing well-being in children. One of the most essential tasks of public health administrations is to ensure that children receive an abundant supply of uncontaminated milk. Adults as well as children may benefit from a high milk consumption.

In general, green vegetables resemble milk as regards protective food value ; they are moderately rich in calcium, vitamin A and the water-soluble vitamins, notably C. As a source of iron, they are superior to milk. Fruits are valuable in that they supply vitamin C, and for other reasons. The encouragement of the production and consumption of these "protective" foods is a valuable public health activity.

Once the consumption of "protective" foods is assured, elasticity in the remainder of the diet is permissible and choice may be allowed free range. Meat, which some class among the protective foods, in moderation is a useful and palatable article of diet, supplying first-class protein and vitamin B₂ ; glandular organs and blood

are, however, richer in vitamins and mineral salts. Unmilled cereals are richer than milled cereals in protein, mineral salts and vitamins, and, for this reason, American workers have recommended that one-third of the cereal should be in "unmilled form"; the same opinion is also being advanced in France. This, applied to the reasonably varied diets of Western civilisation, seems a reasonable idea, to which may be added the suggestion that children and pregnant women should consume wholemeal bread. The greater the quantity of cereal in the diet, the more important it becomes that the more nutritive parts of the grain should be consumed.

In temperate lands, it is difficult to provide sufficient vitamin D through the medium of a diet composed of ordinary foodstuffs. Infants and children fed according to the usual dietary customs of Western civilisation need to be supplied with "extra" vitamin D in some form—*e.g.*, cod-liver oil. Such provision will ensure freedom from rickets and, assuming the hypothesis of Mrs. MELLANBY and her school is correct, from dental caries.

A well-balanced diet containing abundance of the various food factors is particularly necessary to children, expectant and nursing mothers, and those required to make exhausting physical efforts. It has repeatedly been observed that hard work disposes an individual on a defective diet to deficiency diseases. A diet which may keep an adult living an unexacting life in fair health may fail to meet fully the requirements of a growing boy and be inadequate for times of stress (pregnancy, hard manual work, exposure to infection, etc.).

Dietary requirements, thus stated, seem remarkably simple ; there is nothing here that could not be readily grasped by an uneducated peasant or manual labourer. The real problem lies in the fact that in all countries the great mass of the people, mainly because of ignorance and poverty, do not reach the simple standard of dietary excellence demanded by modern nutritional science.

2. PHYSICAL STANDARDS.

Physical standards of comparison, by means of which the degree of health and development of an individual may be assessed, fulfil several important purposes. Parents and family physicians wish to know whether children in their care are developing normally.

School medical officers, concerned with larger groups of children, require working methods which enable them to select those suffering from retarded development and malnutrition. It is logical to combine enquiries into the dietary habits of population groups with investigations of the physique and health of the group concerned, and, for carrying out the latter, physical standards are necessary. The problems of assessing physical condition and development and detecting malnutrition are essentially similar in nature.

The "State of Nutrition".

The terms "state of nutrition" and "malnutrition" have different meanings for different authorities. Sir George NEWMAN [23] connects the term "nutrition" with the "total well-being and right functioning of the whole body". Height, weight, substance, colour, elasticity, balance and carriage of body, the effective functioning of the nervous system, heart, lungs and alimentary tract, the readiness and relative strength of the muscular system—all these, he implies, must be taken into account in judging an individual's "state of nutrition". The physician, in estimating the state of nutrition of a child by clinical examination, does in fact do so. There are many factors which adversely influence an individual's state of nutrition in this wide sense of the term—*e.g.*, faulty diet, lack of sleep, overwork, chronic infective processes. Of these, diet is one of the most important. In the "Annual Report of the Chief Medical Officer of the Ministry of Health for the Year 1933", it is pointed out that :

"The physiological effects even of a single deficiency are usually of a complex nature. Thus, a deficiency of calcium during the growth period, when the effects of inadequate diet are particularly liable to become manifest, would result in defective development of the bony skeleton. This is the most obvious effect of such a deficiency, but others less striking, though just as important, would occur. The proper functioning of the contractile tissues depends on the presence of a certain concentration of calcium ions in their environment, and as the calcium in the blood is lowered by a calcium-poor diet, the contractile elements in the body—*e.g.*, the musculature of the circulatory and alimentary systems, would not play their requisite parts in a proper fashion. There is also evidence for believing that absorption of carbohydrates would be reduced by deficiency of calcium in the blood. Further, the metabolism of calcium is intimately bound up with that of phosphorus and with the function of the parathyroid gland, so that any disturbance in the former is bound to lead to disturbances

in the metabolism of phosphorus and in parathyroid function. In addition, since calcium plays a dominant rôle in maintaining the selective permeability which is an essential characteristic of all living cells, there is probably not a function in the body which would not be adversely affected by continued ingestion of diets low in calcium. Widespread and far-reaching effects may thus be liable to result from even a single dietary deficiency.

Some workers, however, give the term "state of nutrition" a much more restricted meaning. The German word *Ernährungs-zustand* refers solely to the amount of fleshy covering which envelops the skeleton. For practical purposes, children with a good or bad *Ernährungszustand* are fat and thin children respectively. The same limited definition of the term "state of nutrition" has been adopted by some English and American workers.

It is also necessary to distinguish between existing states of malnutrition and stigmata of past malnutrition. Thus, a child may show evidence of having suffered from rickets or some other deficiency disease in infancy, and yet at the time of examination its state of nutrition may be excellent. As a rule, public health workers and school medical officers are concerned to assess existing states of nutrition.

Basis of Standards used for judging the State of Nutrition.—The individual may be compared with the average or with the optimum. If standards of height, weight, chest girth, etc., are based on unselected groups, they represent the average; if on selected groups of exceptionally well developed people, they tend rather to represent the "optimum". This is as true of subjective as of numerical standards. The physicians with different social backgrounds may have very different ideas of what a healthy, well-nourished child should be.

Methods of assessing the State of Nutrition.—Three different methods may be mentioned: (1) the comparison of certain measurements (or the relation between certain measurements) with a chosen standard; (2) the formulation of a general clinical impression of the state of health and development (it may be noted that the judgment of those in close contact with the child supplements that of the physician and is often of great value); (3) more refined clinical tests designed (*a*) to assess physiological efficiency and (*b*) to detect early deficiency disease.

In practice, clinical and anthropometric methods are usually associated.

Anthropometric Measures.

The height of a child provides little information about his state of nutrition. Many hold that height is entirely dependent on heredity and little affected by diet ; this is scarcely true, for faulty feeding, if prolonged, must lead to stunting in height.¹ Nevertheless, height is so variable that a single comparison of an individual's height with a chosen standard (*e.g.*, the average of his class) can give little information as to his state of nutrition. Rate and regularity of gain in height may provide more useful information, though these criteria cannot be used in assessing the state of nutrition of a child not previously the object of investigation, and their employment is complicated by seasonal variations in growth rate. Growth is not uniform, it proceeds by fits and starts at different ages in both sexes ; the various divisions of the body—the lower limbs, the trunk, the head—each have their phases of growth at different times in the course of development.

While it may be fallacious to assess the state of nutrition of an individual by comparing his height or weight with a chosen standard, comparisons of height or weight averages of groups of children with averages of other groups of similar racial origin may provide useful information where large groups are concerned ; individual variations cancel each other out. Height and weight averages in different age-groups have been used by English workers for assessing the state of nutrition of miners' children, the children of the unemployed, etc. [24].

Simple comparisons of weight with a chosen standard are of little value. A child fed on a diet over-rich in carbohydrate may be over weight and yet in a state of malnutrition. Another child may be thin, yet "wiry" and in excellent health. The use of rate of gain in weight as a criterion of malnutrition is subject to the same limitations as the use of rate in gain in height. It is, of course, of great value in infancy.

¹ "The upper limit of the size of an animal is determined by heredity. The stature to which an animal may actually attain, within definitely fixed limits, is directly related to the way in which it is nourished during its growing period." (WATERS, cited by SHERMAN, *Chemistry of Food and Nutrition*, 1934, page 478).

Weight in relation to height (or height and age) has been much used in assessing nutritional status. In the U.S.A., it has been common practice to class a child as malnourished if he is 10% below standard weight for height (or for height and age). Sometimes the higher limit of 7% is chosen.

EMERSON [25] employs the following classification :

1. 10% or more below average weight for height = "malnutrition" ;
2. Under average but less than 10% = "borderline" ;
3. Average to 20% above = normal (about 10% above is considered ideal) ;
4. 20% or more above average = over-weight.

More complicated relationships between height, weight and other measurements are expressed in the many "indices of nutrition" which have been formulated. The following may serve as examples :

Quetelet

$$\frac{\text{Weight}}{\text{Height}_3} \text{ or } \frac{\text{Weight}}{\text{Height}_2^{\frac{1}{3}}} = N.$$

Livi (index ponderalis)

$$\frac{100 \times \sqrt[3]{\text{weight in grammes}}}{\text{Height in cm.}} = N.$$

Pignet (coefficient de robusticité)

$$\text{Height} - (\text{Breast circumference in cm.} + \text{Weight in kilos}) = N.$$

Pirquet (pelidisi)

$$\frac{\sqrt[3]{10 \text{ wt. in grammes}}}{\text{sitting height in cm.}} = N.$$

In using most indices of nutrition, the index of the individual is compared with the average or ideal for his age. The normal pelidisi was stated by PIRQUET to be 100 for well-developed adults and 94 for growing children. BARDEN, however, showed that the pelidisi

of average American children fluctuates more considerably according to age. The relation of the cube root of the weight in grammes to the sitting height in centimetres is only approximately linear during the period of growth.

Fallacies arising from the use of "indices of nutrition" have been repeatedly described [26]. The pelidisi index is such that a very slight error in the measurement of heights greatly affects the result. PATON and FINDLAY [27] reach the conclusion that a simple comparison of an individual's weight with the average for his height and age provides more useful information than the use of more complicated indices of nutrition.

Clinical Methods.

It is generally agreed that the most satisfactory method of assessing nutritional status is clinical examination by an experienced physician. The disadvantage of this method for public health purposes lies in the fact that no two observers employ the same criteria as the basis of judgment. They will probably be in agreement as to which children are very well or very badly nourished, but there will be divergencies of opinion in regard to children who fall between these extremes. In England, the diagnosis of malnutrition in schools is based on clinical examination, and the subjective element which enters into the assessment is illustrated by the following: Bootle (which is for all practical purposes an integral part of greater Liverpool) returns a malnutrition rate twelve times as high as Liverpool itself; Leeds and Wigan, containing very similar industrial populations, return rates of 31 and 9 per 1,000 respectively; the relatively prosperous borough of Twickenham returns a rate of 10 per 1,000 [28].

The well-known DUMFERLINE scale, used for grading state of nutrition by clinical examination, includes the following categories: (1) excellent; (2) good; (3) nutrition requiring supervision; (4) nutrition seriously impaired and requiring treatment. PIRQUET's "sacratama" method is essentially similar in principle. Four diagnostic elements—the colour of the skin, the amount of fat, the water content of the tissues, and the state of the muscles—each represented by a consonant, are graded into five degrees of excellence each represented by a vowel. The results of the examination of

each individual are enshrined in a word of four syllables easily understood by those familiar with the system.

One of the advantages claimed for the A.C.H. index, elaborated by FRANZEN [29] and his colleagues on behalf of the American Child Health Association, is that it is more successful than any other system of measurement in grading children into nutrition categories which correspond to categories based on clinical assessment. The A.C.H. index involves measurement of arm, chest and hip girths. Further investigation is required before its practical utility can be estimated.

Physiological and Clinical Tests.

Since malnutrition involves inefficiency and disharmony in many functions of the body, it is logical that physiological tests should be employed to detect it. A number of such tests were recommended by the Berlin Conference [30], to whose report the reader may be referred. Special mention may be made of tests of physical efficiency and "fatigability". A great deal more investigation, however, is required before the use of such tests can be confidently recommended to public health authorities.

A number of tests have been proposed for the detection of very early evidence of vitamin deficiency, such as HESS's capillary resistance test for the discovery of incipient scurvy (Hess himself recognised that this test was unreliable in practice) and JEANS and ZENTMIRE's visual test for detecting early vitamin A deficiency. Other similar tests were suggested by the Berlin Conference. The clearest evidence of defective diet and poor nutritional status is provided by the existence of active food deficiency diseases.

For the detection and assessment of malnutrition, anthropometric methods supplement clinical and physiological methods. No existing method of assessment is above criticism, yet many have proved useful in practice. Pirquet's system, which involves both measurement and clinical examination, while unquestionably open to criticism on many grounds, nevertheless proved very serviceable in Vienna after the war; in America, its use has not been attended with success. This system of assessing nutritional status was recommended by the Berlin Conference. We may venture to suggest that, for practical public health purposes, it is advisable that clinical, anthropometric and physiological methods should be applied in association.

IV. FOOD SUPPLY.

1. PRODUCTION.

The type of diet consumed by human beings depends to a large extent on their geographical position. Population groups naturally tend to consume the foods which are produced most easily under local conditions of soil, temperature and social organisation. The influence of such factors is of course largely modifiable, and is indeed daily being modified by modern developments in transport, agricultural methods, irrigation or its opposite, the draining of water-logged areas, and in many other fields. But while great alterations in human ecology in relation to food production are taking place around us, and still more fundamental changes may be envisaged in the future as science advances, food habits will continue to vary throughout the world in accordance with geographical position, though perhaps the variation will be smaller than at present.

National plans of food production and distribution, having as their object the provision to the entire population of a diet pronounced adequate by physiological science, are already being envisaged in certain countries ; theoretically, there is no reason why a plan of this nature should not be extended to involve the whole world. It could not, however, be formulated without taking into account the facts of food production as they at present exist, and its aim would be to bring about modifications and improvements in existing dietary habits rather than drastic alterations. Thus, if the staple diet of an Eastern Asiatic country is rice, and rice happens to be the only cereal which can easily be grown in that country, the dietary reformer will seek to make available a satisfactory and well-balanced diet the basis of which is rice, rather than wheat imported from Canada or Australia.

On the one hand, there is the fact that, in almost all countries, food production falls short of the needs of the population either

as regards quantity or variety ; on the other, the possibility, not inconceivable, of pooling food resources in accordance with a plan embracing the entire world. It is evident that, if such a plan could be formulated, the problem of distribution would be as important as the problem of production.

Each of the cereals thrives best under certain conditions of climate and soil ; rye flourishes best in the cooler lands of the temperate zone ; maize demands a moderate degree of warmth and moisture ; rice, the cereal of the tropics, will grow only in damp and swampy regions, where the soil is under water during part of the year. Except in a few highly organised countries, the breeding of domestic animals on a large scale to supply meat requires abundant green pasture, and it is only in rich countries that domestic animals are reared up to adult age ; in countries where populations live densely under comparatively primitive conditions, and most of the available fertile land is used for the production of cereals and other vegetable foods, the production of meat is small. In China, fertile valleys are cultivated to the last square inch to supply the teeming population with cereals and other vegetable foods, and in such circumstances meat becomes a luxury. The Chinese diet is relatively deficient in both meat and milk. Except in the temperate zone, a successful dairy industry is attended with many difficulties ; in very warm and very cold countries, good pasturage is available only at certain seasons, and milk output fluctuates accordingly. Further, a hot climate makes fresh liquid milk liable to excessive contamination.

The " production " of that valuable food, fish, is dependent on locality in an obvious manner.¹ Fruit and green vegetables are seasonal products ; only a highly developed transport and preservation system will ensure a regular supply throughout the year. In arid countries and the Far North, the production of either may be difficult or impossible.

As the following table shows, the production of staple foodstuffs varies greatly from continent to continent. Such figures, while doubtless very rough, indicate broadly the contribution of the various parts of the world to production.

¹ And yet there are countries bordered by seas rich in fish of which no advantage is taken, such as Chile, according to E. SANHABER. (*Ztschr. f. Volks-ernahrung*, 9 : 399, 1934).

*Percentage Production of Various Foodstuffs
in Different Areas of the World (1932).¹*

| | Europe, excluding U.S.S.R. | Europe, including U.S.S.R. | North America | Latin America | Africa | Asia | Oceania |
|--|----------------------------------|----------------------------------|------------------|------------------|--------|-------|---------|
| Crude foodstuffs | 31.9 | 43 | 25.3 | 8.8 | 3.2 | 17.4 | 2.3 |
| Cereals (excluding rice). | 31.4 | 47.6 | 34.6 | 6.6 | 2.7 | 6.7 | 1.8 |
| Cereals and other food crops (including su- gar) | 28.4 | 41.2 | 24.4 | 5.8 | 2.4 | 24.6 | 1.6 |
| Meat | 36.1 | 45.7 | 29.7 | 11.9 | 3.4 | 5.6 | 3.7 |
| Coffee, tea and cocoa . . . | | | | 42.4 | 12.3 | 45.7 | 0.2 |
| Populations, in millions | 385 | 549 | 137 | 124 | 144 | 1,114 | |
| Area (million sq. km.). | 5.4 | 26.5 | 19.6 | 21 | 30 | 41.9 | |

¹ Based on *World Production and Prices, 1925-1933*. League of Nations, 1934, page 127.

Population figures from the *Statistical Year-Book of the League of Nations, 1933-1934*.

At present, only very general information exists about the production of foodstuffs throughout the world. Statistics are incomplete and do not embrace all kinds of foodstuffs. More detailed investigation of food production and consumption in many countries might yield unexpected results. It is widely thought, for example, that Japan cannot produce enough food to nourish her teeming population (Japan proper, 147,600 square miles and 67 million inhabitants). In 1926, Ch. Egerton GREY [31], after studying export, import and production statistics, arrived at the conclusion that Japan could feed herself, provided the decortication of rice and its use for distilling purposes were abandoned (both of which cause a loss of 10% of its total Calorie value), and provided no use was made of fish and soya-bean products as manure. But even if these conditions were fulfilled and the food production of the countries were made quantitatively sufficient, the problem of quality would remain. The Japanese diet contains excess of carbohydrate and insufficiency of fat, mineral salts and vitamins. Consumption of milk, meat and animal fat is very small.

A rise in the production and stocks of foodstuffs took place during the years immediately preceding the economic depression

and this tendency was continued for some time after the depression had established itself. To combat the downward trend of prices, production was to some extent diminished. But it is clear that the fall of prices was not so much due to increased production as to a sharp and unexpected decrease in purchasing power and, consequently, in demand. The existence of surplus stocks and over-production in general, at certain moments in certain countries, does not in any way prove that the world produces too much food, or even enough, to meet the needs of its population [32].

There can be no question that a great part of the population of the world at present consumes a diet which is unsatisfactory when compared with dietary standards put forward by physiologists. The diet of the vast majority of mankind is largely composed of cereals, and there is evidence that such a diet is incompatible with *optimum* nutrition ; it will not adequately support growth in the *young* and is relatively deficient in several essential food factors. The results of dietary surveys and investigations in India, China, Japan, Ceylon, the Philippines, Porto Rico, and many other of the poorer countries of the world, could be quoted here as showing that the diet of the masses in such countries is composed of cheap cereal foods and lacks meat, milk, green vegetables and other products rich in essential food factors [33]. The prevalence of food deficiency diseases throughout the world is further proof of the existence of widespread malnutrition. Even in the most advanced countries, there is room for great improvement in diet.

The imagination is struck by accounts of the destruction of food in countries in which there is over-production, while at the same time serious malnutrition or semi-starvation exists elsewhere. It seems iniquitous that thousands of human beings should die of famine in a flood-devastated area in China, while the food which would have saved them is being destroyed elsewhere. The fact that localised famine might be combated by action on the part of highly organised and highly productive countries leads to the conviction that the world produces ample food for its inhabitants. The deduction cannot be justified : in the first place, our knowledge of production is limited and inexact ; in the second place, the approach to the problem depends on the standard of food requirements adopted.

While it is true that surplus food stocks might with advantage be diverted to sustain limited population groups suffering from famine or serious under-nutrition (and we cannot insist too strongly on this point), it cannot be assumed that a simple redistribution of existing surplus would solve all dietary problems throughout the world.

Recent valuable studies carried out in the United States of America throw much light on this point [34]. Using current American standards of satisfactory nutrition, STIEBELING and WARD drew up 4 dietaries : (1) a restricted diet for emergency use, (2) an adequate diet at minimum cost, (3) an adequate diet at moderate cost, and (4) a liberal diet. The following estimates were made of the amount of land *per capita* per year required to produce each of the four diets :

| Diet | Amount of land <i>per capita</i> per year required | |
|---------|---|--|
| | Acres | |
| 1 | 1.2 | |
| 2 | 1.5 | |
| 3 | 1.8 | |
| 4 | 2.1 | |

Diets 2, 3 and 4 are similar in energy value, but 3 and 4 contain more meat, eggs, fruit and vegetables and less cereal than 2, and thus require more land for their production.

In America, at present, there is not enough land under cultivation, or used for food production, to supply the entire population with diet 4. 335,108,000 acres would be required to produce it, whereas, in 1933, only 294,219,000 acres were cultivated. An increase in the production of all animal foods would be involved, and a decrease in that of cereals, particularly wheat. If the entire population were suddenly to demand this liberal diet, there would be under-production rather than over-production in the American agricultural industry.

At the present time, owing to the incompleteness of available figures of food production, it would be difficult to extend the method of reckoning adopted by Stiebeling and Ward in America to the entire world. But it is only too clear that the result of such a calculation would indicate that the amount of food at present produced is enormously less than the amount required to provide all mankind with a satisfactory diet.

Engineering and biological science can turn deserts and swamps into fertile land. The chemist provides fertilisers which not only greatly increase the yield of land already under cultivation, but can also make land hitherto considered entirely useless for food production yield magnificent crops. The living species, animal or vegetable, on which man depends for food, can be modified by selective breeding into more productive forms, or into forms capable of resisting drought, parasites and other inimical conditions. In Java, the Dutch, by selective breeding along Mendelian lines, have within recent years produced a sugar-cane which has quadrupled the output of the island. Pests and parasites can be eliminated by spraying or dusting with fungicides or insecticides, or by the remarkable method of hyperparasitisation—the introduction of species which, in various ways, eliminate destructive or obstructive animal and vegetable parasites. Many striking examples of the triumphs of this method could be cited.

An interesting development is the possibility of improving the nutritive value of foods, in respect of some particular food factor—*e.g.*, certain of the vitamins—by selective breeding and other methods.

Selection has made it possible to obtain varieties of wheat not affected by blight, varieties of potatoes and tomatoes richer in vitamin C than ordinary kinds.

The extent in the increase of, and improvement in, food production which modern scientific knowledge has made possible is not as yet generally realised.

“ It would scarcely be an exaggeration”, says Dr. Enid CHARLES [35], “ to say that the world’s food production could be increased many times without increasing the area of cultivation, if mankind exploited to the fullest extent all the scientific knowledge now available. Lest this statement should appear to be exaggeration or mere surmise, it is sufficient to remark that the Cambridge School of Agriculture, under normal working conditions, consistently obtains a yield of 60 bushels per acre of wheat, as compared with an average of 32 for the whole country. ”

Malthusian nightmares of an overcrowded world living on the brink of food scarcity need trouble us no longer. We are entering an era of plenty. It must not, however, be assumed that the vast improvements in the technique of food production which are now

taking place will automatically and *per se* reduce malnutrition throughout the world. Their first effect can be seen in the economic crisis, which has resulted, in certain countries at least, in an increase in malnutrition. In backward countries, increase in food production has hitherto often had the effect of increasing numbers without appreciably improving living standards ; more are fed, but the dietary level remains unaltered. Anxiety is often expressed by public health authorities in India at the pressure of increasing numbers on the available food supply ; it is asserted that improvement in the state of nutrition of the Indian masses can be brought about only by a reduction of population. Not infrequently, the introduction into primitive communities of the cheap surplus foods of modern civilisation results in a change for the worse. Primitive dietary habits, which have stood the test of long practice, are disturbed. We may cite here the deterioration of the diet of the Labrador Eskimo and the inhabitants of certain South Pacific islands which has taken place as a result of contact with civilisation.

The physiologist can estimate the dietary requirements of mankind ; the chemist, the biologist and the engineer are devising methods which may make it possible to satisfy them. A planless economy may nullify their efforts. Improvement in the diet of the great mass of the world's population can be brought about only by rational planning on an international or national scale, based on a knowledge of the principles of nutrition. If, for example, increased agricultural efficiency throughout the world results only in a greater production of the cheaper foods (*e.g.*, cereals), an aggravation of the present economic chaos is likely to occur and new problems of dietary deficiency may be created.

2. DISTRIBUTION.

Modern developments in communication and transport, which have so materially assisted the progress of civilisation, help to eliminate differences in diet due to geographical position and to adjust available food supply to the needs of mankind. A Londoner may consume at a single meal Canadian flour, New Zealand butter, Danish eggs, French vegetables, Argentine beef, West Indian sugar and Colombian or Brazilian coffee.

As the result of such developments, seasonal changes in diet are largely disappearing in the great centres of civilisation. The modern city dweller takes it for granted that he should be able to obtain fresh vegetables, fruit, fish, meat, butter, etc., cheaply all the year round ; he forgets the elaborate organisation which makes present abundance at all seasons possible, and how much more closely diet depended on season a few short years ago. Elderly people still talk about " spring sickness ", in all probability a condition of debility occurring in early spring as a result of consuming a limited dietary, lacking in vitamin C and other elements, throughout the winter.

The freedom of distribution made possible by transport is hampered by financial and political impediments. The products which a nation requires are not to be had for nothing, and the poorest countries, with inadequate resources for feeding their populations, are just those which can least afford to import foodstuffs from elsewhere. Nations, striving to foster their own agricultural industries, and sometimes influenced by fear of war or blockade, are impelled towards an ideal of self-sufficiency. Customs barriers are thrown up which raise the price of foodstuffs, unless, indeed, they make them a drug on the market by immobilising them. In an era when great benefits might be derived from an unimpeded distribution of foodstuffs, nations are retiring into voluntary isolation and falling back on their own resources. Transport is perfected within countries, but paralysed between them.

The economic policy of a country in connection with foodstuffs deeply concerns public health authorities. The claims of the farmer may conflict with public health ideals in the field of nutrition. When this is so, it is surely desirable that attempts should be made to reconcile the two by close co-operation between the respective authorities concerned.

Brief mention may be made of another aspect of food distribution—its cost. In countries where housewives purchase much of the food they require in retail markets and carry it home with them, distribution costs are low. But when food reaches the consumer through the medium of large-scale commercial organisations, distribution cost may form a higher proportion of total cost. But this is not always the case in every country, and from this point of view it would be useful to compare wholesale and retail trades.

Distribution costs are likely to be particularly high in the case of rapidly perishable foods—*e.g.*, milk—the delivery of which to the consumer in a satisfactory state involves elaborate organisation and technique.

3. PRESERVATION OF FOOD.

Even when living in primitive conditions, man preserves food by various methods. The surplus of seasons of abundance must be set aside for use in times of scarcity. The cause of putrefactive changes in organic matter has been known only for half a century, but in very early times man discovered empirically ways of checking or preventing the disintegration of foodstuffs by saprophytes. In our complicated modern civilisation, in which only a few live in contact with the soil and consume food they have themselves produced, the necessity of preserving food has multiplied a million-fold. To-day, vast industries are concerned with storing fresh foodstuffs under suitable conditions and in converting them into such a form that they may be transported for long distances and distributed to the consumer without falling a prey to putrefactive and other organisms. The food-preserving industry helps to produce the same result as improved transport by greatly increasing the variety and availability of foodstuffs throughout the year. FELLARS [36], speaking of frozen foods, says that “ their ready availability at all seasons gives balance to the human diet and should aid in decreasing nutritional deficiency diseases ”. The use of many valuable foods would be greatly restricted if these could be consumed only in the fresh state.

The high intake of milk and milk products of many modern civilised communities is directly dependent on the conversion of fresh liquid milk into other more stable forms : cheese is preserved milk. In certain parts of the world, whole milk is available only in the “ dried ” state. Similarly, by means of cold storage, drying, salting, canning, etc., that very nutritious food, sea fish, can be included in the dietary of the city dweller.

Food can be preserved in a large variety of ways, according to its nature and destination : by physical methods, such as cooling, heating and drying ; by chemical methods, such as salting, smoking,

sugaring, souring, addition of alcohol and other chemical substances. Preserved food, in general, demands vigilant control from the public health standpoint, because any error or carelessness in manufacturing methods may readily convert it into a source of infection ; it may be free from saprophytes and yet contaminated by other dangerous micro-organisms. It may contain poisonous amounts of chemical preservatives or chemical substances derived from the container (*e.g.*, lead). Public health authorities already give much attention to these and similar questions. We are concerned here rather with the problem of the physiological value of preserved foods, as compared with fresh.

It seems that, in general, the physical and chemical changes produced in food by preserving processes do not in any serious measure impair its nutritive value as regards its content of protein, fat, carbohydrate and mineral salts. Knowledge on this point is somewhat incomplete, for most investigations of the results of preserving processes have been concerned with palatability and commercial attractiveness. Vitamin C is sensitive to heat, particularly when the medium is alkaline and access of air permits oxidation ; under suitable conditions, however, it is possible to use heat to sterilise fruits and vegetables and leave vitamin C unimpaired. The effect of drying is variable ; commercially dried vegetables, in general, are devoid of vitamin C, but dried fruits retain considerable anti-scorbutic potency. Here, again, it is possible to minimise destruction by suitable means. Vitamin B₁ value may be reduced by the heat required for canning, but only in small measure, unless there has been addition of alkalis. As far as present knowledge goes, methods used in the preservation of food do not exercise a destructive effect on the other known vitamins.

Sweeping condemnations of preserved foods are usually based on the vaguest grounds. It is urged, for example, that a diet containing large quantities of such foods, and particularly canned foods, is a *devitalised* diet. Others will maintain that widespread ill-health, or even certain diseases of unknown origin—*e.g.*, cancer—are caused by chemical preservatives. These are speculative, or more or less mystical, ideas, often closely related to vegetarianism and other food fads, and to the idea that the diet of primitive man is the perfect diet.

Nevertheless, the modern tendency to substitute "something out of a tin" for a well-prepared meal composed of fresh foodstuffs cannot be applauded. It tends to diminish variety, which is physiologically so useful, and leads to atrophy of the arts of cooking and housewifery. Preserved foods raise a question of price: they may or may not be dearer than the fresh article; there is no rule in this matter. But if a poor housewife makes a habit of buying more expensive canned foods for convenience, she may be seriously impairing the family dietary. We may wholeheartedly condemn expensive "patent" foods, often cleverly advertised as "concentrated nourishment", which provide the same food factors as bread, butter and meat at ten or even fifty times the price.

We touch here on the question of "buying for appearance". Food well packed in small attractive containers is usually dearer than food packed in larger bulk. STIEBELING [34], comparing (in the United States of America) the prices of foods packed in large and small containers, finds that savings ranging from 8 to 38% may be effected by buying the former. There is considerable room for the education of the public on such questions.

Canned foods are essential to fighting forces and explorers, and in all emergencies when large quantities of food have to be collected and transported. They should, perhaps, be regarded as an auxiliary or supplementary type of food, often indispensable, but it does not seem desirable that they should form the ordinary staple part of the diet in ordinary circumstances. The place which they occupy in the diet is largely determined by geographical and economic circumstances, but the public health problems involved by their use cannot be disregarded. In most countries, the law requires that they should be free from bacteriological and chemical contamination. Methods of manufacture which tend to leave vitamins (particularly B₁ and C) unimpaired might be encouraged and the public educated on this point. To facilitate control, commercial firms might be required to state on the labels of tins the manufacturing processes involved.

In the Union of Soviet Socialist Republics, the Institute of Nutrition, which is a technical department of the Government, has taken the following line. The best food, it is held, is undoubtedly fresh food; the food-preserving industry should none the less be developed, since, in an immense agricultural country like Russia, there are

vast areas which produce little or nothing and, under present conditions, are hardly accessible to fast transport that would make a supply of fresh food possible. In the northern or Arctic regions, however, the preponderance of preserved food should be offset by an adequate supply of vitamins in the form of the concentrated products which can be prepared by modern scientific processes. This supply will be organised by the public health administration.

4. POINTS OF CONTACT BETWEEN NUTRITION AND ECONOMICS.

Our object in the following sections will be to emphasise, and illustrate by a few chosen examples, the dependence of national diets on a great variety of factors—political, economic, agricultural, etc.—and to outline very roughly what may be termed the public health approach to the complex issues involved.

Bread.

For many years, physiologists and others have urged that the habit of consuming bread made from refined wheat-flour is reprehensible, since the germ and pericarp of the grain, which are richer in protein, vitamins and mineral salts than the endosperm,¹ have been eliminated from such flour. There can, indeed, be no question but that wholemeal flour is of higher nutritive value than refined flour. The fact that the former contains more indigestible material (roughage) in the form of cellulose can scarcely be considered in its disfavour; the average human stomach and intestine are capable of dealing with wholemeal bread and, indeed, it would appear that the presence in the diet of a reasonable amount of roughage is usually advantageous. Doubtless there are a small number of individuals with impaired digestive functions in whom the consumption of wholemeal flour induces uncomfortable symptoms. The taste for white bread is often supported by prejudice; there is a fashionable

¹ According to LAPICQUE, the presence of a certain proportion of indigestible matter is not a drawback.—“ In preferring wheat to barley, in ceasing to add barley, in discarding the layers nearest to the husk of the grain, civilised man makes mistake after mistake ” (TERROINE).

“ It is a singular fact that in the preparation of animals for human consumption, as in the preparation of cereals, those parts which are less in demand are the parts having the greatest nutritive value on account of certain constituents ” (MITCHELL and BEADLER).

preference for white purified preserved foods and even natural foods, such as honey. Until lately, white bread was the bread of the rich ; brown or black bread, that of the poor : to eat white bread was to rise in social scale. On the other side, it must not be forgotten that white bread is an excellent cheap concentrated food containing protein and carbohydrate in suitable proportions. Refined flour is more easily transported and consumed than wholemeal flour.

The importance of this question in any given country depends on the nature of the diet habitually consumed by the mass of the population. As long as white bread is eaten as part of an abundant and varied diet, its disadvantages as regards mineral and vitamin content are minimised. From the public health point of view, the more varied the diet the less important becomes the question of the degree of milling to which wheat is subjected.

On the economic side, there are many problems relating to wheat production and consumption. In certain countries—*e.g.*, France and the United States of America—there is “over-production” of wheat, due in part to a lowered consumption (in France, consumption per head was 224 kilogrammes in 1914, 195 in 1922-23—a diminution of 13%). On the other hand, the world consumption of wheat is steadily rising. In Europe, production increased from 324 million quintals in 1921-1928 (yearly average) to 470.7 millions in 1933. In France, it has been proposed that, in order to dispose of surplus wheat, the use of very highly refined flour (50%) should be encouraged. Supporters of the scheme do not tell us what is to be done with the millings ; whether, for example, they are to be used for feeding live-stock, or for the manufacture of vitamin preparations to replace the vitamins removed from the original wheat.

In Germany, owing to peculiar conditions of climate and agriculture, the question has tended to assume a special form—namely, that of competition between home-grown rye and imported wheat, so that the propaganda in favour of wholemeal bread becomes more especially a campaign for whole rye bread. In support of the latter, physiologists assert that every part of the grain is digestible and that the integuments should not be discarded. At the same time, they argue that the use of grain as cattle-food involves a wasteful conversion into animal tissue which is highly expensive for the nation.

The fact that a number of countries are producing more wheat than they can at present consume is of interest in connection with the problem of beri-beri and pellagra. The latter occurs among populations consuming whole maize, the former for the most part among those whose staple cereal is rice. The partial replacement of rice and maize by whole wheat would do something to check the ravages of beri-beri and pellagra. Under present economic and commercial circumstances, however, there seems little possibility of sufferers from these diseases benefiting from "surplus" wheat supplies.

Meat.

The increase of less strenuous "machine-minding" jobs and of clerical work in industry and trade seems to have promoted the demand for, and consumption of, meat, which is a palatable and stimulating food and, according to certain physiologists, particularly suitable to take a prominent place in the diet of sedentary or light workers. If a line be drawn from East to West, starting in the Far East, passing through Europe and continuing to the United States, the meat consumption per inhabitant will be found to increase roughly from country to country.

The increase in food production which has taken place in the last few years in Europe has affected meat as much as food crops (the Union of Soviet Socialist Republics is not included in this statement). Up to 1932, in fact, the production of meat rose more rapidly than that of cereals. There has been an increase in the amount of live-stock raised in Africa, Asia and Oceania, but a temporary diminution in the Union of Soviet Socialist Republics. In both the Americas, it has remained stationary [37].

Because of the relatively large amounts of labour and land required for its production, meat is an expensive food, and throughout Europe its consumption is roughly proportionate to the wealth of the country concerned.

If the annual requirements of an adult are estimated at 1,400,000 Calories, the number of acres required to produce this in the form of meat is much greater than the number needed to yield the same amount of food energy in cereal form.

*Acres needed to produce 1,400,000 Calories of Certain Foods.
United States of America, 1922-1924.*

| Product | Number of acres | |
|----------------------|-----------------|---------|
| | Crop | Pasture |
| Potatoes | 0.76 | |
| Corn meal | 0.79 | |
| Wheat-flour | 1.45 | |
| Pork and lard | 3.70 | 0.7 |
| Milk | 2.35 | 1.6 |
| Beef (dressed) | 11.30 | 2.5 |

(“ Land Utilisation and the Farm Problem.” U.S. Department of Agriculture, 1930.)

In 1933, in Czechoslovakia, the following could be purchased for 1 crown :

| | Calories |
|-------------|----------|
| Bread | 1,191 |
| Beef | 172 |
| Pork | 90 |

The 2.85 million hectares under potatoes in Germany could supply the energy needs of 50 million people, but only of 6 million if the potatoes are used to feed pigs. A chicken yields 1 lb. of meat in return for 14 lb. of grain [38]. Sir Thomas More, contemplating the transformation of fifteenth-century England from an agricultural to a pastoral country, said : “ Sheep are eating men ”. It has been said in certain countries that “ Pigs are eating men ”.

But the old idea, often strenuously upheld, that it is simply wasteful to convert vegetable into animal food through live-stock, is quite outmoded. A loss of Calories may occur, but it is usually accompanied by a beneficent change in quality.

When wages fall, the proportion of meat in the dietary tends to decrease ; in Germany, in 1924, as soon as the new mark was established and the monetary situation improved, the consumption of meat increased.

The relatively high cost of animal protein is further enhanced by the uneconomic utilisation of the animal. The civilised European consumes scarcely more than muscle meat, and even then is more and more inclined to despise the “ inferior cuts ”. The animal would naturally yield much more, both quantitatively and qualitatively, if the liver, blood and the glands were more widely consumed.

In an industrially and thickly populated country such as Germany, which is now reaching the point at which one out of every three of the population is a town-dweller, and in which some 40 million people are tending to demand more and more fat and animal protein, meat consumption steadily increases (except in times of depression); notwithstanding the development of national production, 28% of the protein and 20% of the Calories in the national diet have to be purchased abroad. The expenditure involved will become more and more difficult to meet, if the export of industrial products decreases [39]. National production in crop and live-stock might be increased, but can be promoted only at the expense of the urban populations; it would be difficult to raise the price of agricultural produce whilst wages are falling. On the other hand, it is impossible to revert to the old form of vegetarian diet, to which we have already referred. It will be realised that phases of industrial and agricultural depression may have a serious effect upon the food supply of the masses.

Fat.

The War demonstrated the ill-effects which ensue from a deficiency of fat and fat-soluble vitamins in the food supply. The Western European is accustomed to a diet in which from 20 to 25% of the energy is provided in the form of fat. Among modern industrial populations, the desire for an increased consumption of fat has developed *pari passu* with the desire for increased consumption of animal protein.

The fat supply has been latterly one of the major nutritional and economic problems in Germany. Germany has to buy about 50% of its fat requirements; in 1932, it was short of some 1,200,000 tons [39]. The will for economic independence here comes into conflict with nutritional demands. Faced with the impossibility of transferring 100,000 hectares from wheat to the production of oleaginous plants, certain German economists have proposed, in order to resolve the problem of fat requirements within the national sphere, that milk production should be increased at all costs, that pig-breeding should be developed, and that $2\frac{1}{2}$ million hectares of bog and marsh land should be brought under cultivation or laid down to grass [40]. To prevent foreign fats from entering the country would not solve the problem; it would be necessary to

increase production and keep a balance between the interests of the urban consumers (the working-class population) and of the peasants. It was thought that the imposition of import duties on the raw materials used for the manufacture of margarine would afford a steady stimulus to the production and consumption of native butter.¹ As a matter of fact, once a certain point was reached, the increase in the Customs duties on foreign foods reduced the consumption of butter. If margarine is inexpensive, the consumer buys margarine and a little butter ; if margarine is expensive, though cheaper than butter, quantitative needs outweigh considerations of taste and quality and the consumer buys only margarine [41].

In Germany, experiments have been carried out for several years on the cultivation of soya beans. These are already being cultivated in the Union of Soviet Socialist Republics.

The production and consumption of butter and margarine, which are rival products on the European market, raise questions of far-reaching economic importance. Reduction in butter consumption, redounding to the advantage of the less expensive margarine, and the increase in the consumption of tropical vegetable fats are regarded as a threat to the stock-breeding industry and consequently to agriculture. If the production of butter and lard is reduced, the problem arises of the disposal of low-grade cereal products that are not used up by human consumption. In France, in 1933, the turnover of the margarine trade was 1,500 million francs ; that of the butter trade, 2,500 million francs. In order to increase the consumption of butter, recourse has been had to the device of making the addition of a certain proportion of butter to margarine compulsory—10% in France and 25% in Holland being required by law. (Such an addition is prohibited in Germany.) An increase in the consumption of butter would react upon the cattle and cereal markets and would, to some extent, remedy the agricultural depression. " One of the most effective ways of coping with over-production in cattle and pig breeding and cereal-growing countries would be to replace vegetable fats and whale-oil by butter and lard

¹ " At the present time, certain qualities of margarine do not contain any animal fats at all, while in others the proportion is quite high, amounting to about 40%, the average for the whole being in the neighbourhood of 10%." *Report on Dairy Produce, 1926.* Imperial Economic Committee.

and increase the annual butter consumption from 500 to 1,000 grammes per inhabitant " (in Europe) [42].

The production of tropical vegetable oils (apart from olive oil) amounted to 68 million quintals in the year 1931-32 and that of whale-oil to $1\frac{1}{2}$ million quintals (LAUR).

Confronted with facts and figures of this nature, we may ask ourselves how much attention the question of the quality of children's meals and their need of vitamins is likely to claim. All fats are not equivalent in nutritive value. Governmental control of fats, however, is usually based on economic policy, and consideration of its resulting effects on the growth of children and the health of adults is not to be neglected. An important new factor in the situation is the possibility of enhancing the food value of margarine by the addition of fat-soluble vitamins. Brands of margarine so enriched, and equal in vitamin value to summer butter, are now on the market in several countries.

Milk.

The questions of milk supply and of animal fat supply are closely interconnected, since milk stands pre-eminent among animal fats. But milk, *qua* milk, is a highly important food, the wider use of which may be strongly supported on public health grounds. While whole milk and its products are particularly valuable as food for children, there can be no doubt that adults, and especially perhaps the aged, may benefit from their liberal consumption. We shall later discuss the nutritional qualities of milk and its place in the diet of infants and children.

As a result of the War and its aftermath, consumption of milk in Europe temporarily declined. To-day, however, it is steadily on the increase in Western European countries and in the United States of America ; of these countries, Sweden, Denmark, Norway and the United States of America have the highest consumption, and France the lowest, while England, Germany and Holland come in between. In each country, the production and consumption of milk are influenced by many factors : the areas under crops, potatoes and grass, considered in relation to the size of population, means of transport and distribution, and the wholesale and retail cost of milk.

V. HÖSSLIN [43] reckoned that, in Germany, in 1933, a given sum of money, spent on milk, could purchase twice as much animal protein, and five times as many Calories, as the same sum spent on meat.

The relation between the price of milk and its products and that of other foods varies from time to time and from country to country, but, in general, milk, considering its richness in valuable food factors, is not an expensive food. In highly organised countries, in which elaborate arrangements exist for the delivery of milk daily to the consumer in a safe condition, distribution costs form a large proportion of total cost. The present door-to-door method of delivery may add as much as a third to the retail price of milk. In Denmark, milk distribution has been raised to a very high level of hygienic perfection, but the price of milk delivered in the home is comparatively high, and it seems that something will have to be done to devise a more economical form of distribution if milk is to remain a popular food.

In England, one of the aims of the Milk Marketing Board, which, under the Milk Act of 1934, controls the sale of all milk in England and Wales, is to encourage the consumption of milk in liquid form. This would benefit the dairy farmer, because wholesale prices of liquid milk are much higher than prices obtained for milk sold for manufacturing purposes. In Germany, it is hoped to increase the average annual yield of the country's 10 million milch cows from 2,300 to 3,000 litres, a valuable addition to the national dietary in that the extra milk produced would yield, in addition to other food factors, 250,000 tons of animal fat rich in vitamin A [40].

In Italy, a ten-year "nutrition plan", designed to increase the consumption of milk and other foods, is in effective operation [44].

It seems desirable that every country should have its "milk policy", covering production, distribution, preservation and control. Closely connected with economic problems of production and consumption is the question of a safe milk supply, to which great attention is being given by public health authorities. Milk is so important a food from a public health point of view that "milk policies" should be governed by considerations of health rather than of political economy.

5. NUTRITION AND POVERTY.

The influence of poverty on diet and nutrition is a question which has long attracted attention ; the economic depression and the widespread unemployment accompanying it have lent fresh importance to the subject and afforded opportunity for closer investigation. Poverty affects diet in a number of ways. In the first place, lack of means may make it impossible to buy sufficient food of any kind, and semi-starvation will result. Again, the quality of a diet is related to its cost ; the cheapest foods—*e.g.*, cereals, root vegetables and vegetable fats—are those which are most deficient in first-class protein, vitamins and mineral salts, while the “ protective ” foods are, in general, dearer. The fact that, in certain countries, it is possible to buy certain types of nutritious animal food (*e.g.*, liver sausage) very cheaply, does not effectively neutralise the general tendency for very inexpensive diets to be poor in quality, even if adequate in quantity.

Further, poverty influences diet in that it is usually associated with general ignorance, and, in particular, with ignorance of how available resources may be used to the best advantage.

The relations between income and diet are well described in the following passage from *Planning* [28] :

“ Amongst the lowest income groups (in England) are still some who suffer from actual hunger, but these are a declining element which could and should be lifted out of their present situation without delay. Immediately above is a much larger group, estimated to cover between 10 and 25% of the population, who can afford enough food to fill their bellies, but cannot afford a diet of the type and quality now known to be essential as a safeguard against malnutrition and disease. On the next step upwards, measured by incomes, comes another large group which commands enough purchasing power to obtain an adequate diet for the whole family, provided that this purchasing power is completely spent on the lines suggested by such applications of modern research as the report of the British Medical Association Committee on Nutrition. Actually, many of the incomes in this group, and especially the lower ones, are often unwisely spent, at any rate from the strict standpoint of nutrition, and thus a further large number of families falls, for practical purposes, into the zone of malnutrition. The higher the income and the more money spent on food, the smaller this risk becomes, but there is reason to suppose that even among super-tax payers a standard based upon the optimum established by recent research would disclose the presence of malnutrition due to a faulty diet.”

The effects of malnutrition due to poverty may only become apparent after a long interval ; a child whose diet contains too high a proportion of cheap carbohydrates may retain a " normal " weight for a fairly long time, even though a state of anæmia and debility has already set in. The actual duration of the inadequate nutrition is a very important factor.

A number of examples may be cited illustrating certain relationships between poverty, diet, and malnutrition.

SPENCE [45] has recently drawn comparisons between two groups of children belonging to the professional and labouring classes respectively in Newcastle-upon-Tyne. The former group included 125 children, the latter 124. Height and weight comparisons in both groups with an arbitrary " normal " standard produced the following results :

| | Poor children Per cent | Well-to-do children Per cent |
|----------------------------|---------------------------|------------------------------------|
| Below normal weight | 55 | 13 |
| Above normal weight | 11 | 48 |
| Below normal height | 47 | 5 |
| Above normal height | 2 | 11 |
| Hæmoglobin below 65% | 23 | 0 |

The clinical state of the group of poor children was assessed as follows :

| | Per cent |
|---------------------------------|----------|
| In good general condition | 33 |
| In bad general condition | 20 |
| Intermediate | 47 |

5 out of 103 working-class children examined showed evidence of rickets. It was concluded that the defective physical condition found in a large proportion of the " poor " group was due in equal measure to previous infectious disease and to dietetic deficiency.

In the same survey, an examination of the budgets of 16 families in receipt of relief showed that weekly expenditure on food per consumption unit was from 4s. to 5s. 8d., the British Medical Association standard being 5s. 7½d. A rise in the price of milk to 7d. per quart sufficed to increase the percentage of families who bought only condensed milk from 27 to 35 (observations on 1,452 families).

A survey of 277 families, living in a poor district of New York City, was carried out in 1933 by WIEHL [46] on behalf of the Milbank Memorial Fund. It was found that, on the average, the Calorie intake of families with an income below 4 dollars a week was 20% below standard requirements (*i.e.*, 3,000 Calories per consumption-unit per day). Families receiving food allowances had a diet about 10% below, and those on "work relief" a diet 20% below, the accepted energy standard. As income declined, the average consumption of each type of food in the dietary was reduced, but the greatest reductions were in the use of milk, eggs, fish, vegetables and fruit.

SINGER and RUSS [47] studied the relation between diet and income in Czechoslovakia. After investigation of the budgets of a number of very poor families, they arrived at the conclusion that the type of diet consumed was largely determined by the number of Calories yielded by different foodstuffs for a given sum. Families at this income level, it was maintained, can purchase a diet sufficient in quantity only at the expense of quality, so that educational effort designed to improve diet is bound to fail. The authors declared that it was irrational to recommend a higher intake of "protective" foods to people who were only just able to purchase sufficient Calories in the form of carbohydrate-rich foods, and who could not afford greater expenditure on food except by economies on rent and clothes.

The effect of high rent in reducing food expenditure has been emphasised by CROWDEN [48], MCGONIGLE [49] and ROGERS [50]. This factor operates most strongly in large cities. It has been suggested that the removal of families from slum areas to new housing estates where the rent is high may actually lower health standards, because the proportion of income available for food is diminished.

On the other hand, it has been amply demonstrated that, even among the very poor, diet may be influenced by other factors besides income level. PATON and FINDLAY [27] have rightly stressed the importance of "maternal efficiency"; they observed that the height and weight of children belonging to a series of very poor Glasgow families were more closely correlated with "maternal efficiency" than with any other factor, including income, whose influence was studied.

CATHCART and MURRAY [51], who carried out dietary surveys in certain English and Scottish towns, observed only a very general correspondence between income and Calories purchased per penny ; yield per penny was greater in low than in high income groups, but within the same group large variations were observed.

It is clear that a mere increase in wages or relief would not eliminate all dietary deficiency associated with poverty ; education is also necessary (and not only for the poor), and should include instruction in marketing, food values, cooking, and methods of preservation. " Maternal efficiency " is a complex factor, depending on the number of children, on housing conditions, and the health of the mother herself. But most of all, it depends on education. There is no reason to doubt that valuable results can be obtained, even among families with very small incomes, by educational means. Studies by VILLETTE and RICE [52], in New York, have demonstrated the beneficial effect on dietary habits of suitable methods of instructions.

V. EDUCATION IN NUTRITION.

While our knowledge of the scientific fundamentals of nutrition is still incomplete in many respects, public health technique designed to put existing knowledge into practice is still more under-developed. In this section, we propose to consider education in nutrition as a means for hastening the practical application of recent scientific advances.

It is the task of central and local public health services, the medical profession and its ancillaries (nurses, dietitians, social workers, etc.), to instruct the public, but these cannot teach unless they have the requisite knowledge and enthusiasm. There are, therefore, two aspects of the subject : the education of those responsible for educating the public and the education of the public itself.

1. NUTRITION IN THE MEDICAL CURRICULUM.

At present, medical students, during the early years of their course, are given a few lectures and demonstrations dealing with

the physiology of nutrition and perhaps carry out a little practical laboratory work in this field ; the subject is presented as a chapter of physiology, and not as an integral part of preventive medicine. The medical practitioner learns to treat nutritional diseases, but he is at present less interested in the preventive and general public health aspects of the subject. We are far from suggesting that yet another speciality should be added to the already congested medical curriculum. It is rather a question of orientation. In the course of ordinary clinical teaching, for example, interest in diet in relation to health may be aroused. The student is taught how to supervise the feeding of infants ; he might well be encouraged to extend his interest in the subject to the feeding of schoolchildren, adolescents and adults.

The subject of nutrition in relation to public health might well be included in the curriculum of post-graduate medical schools, particularly schools of public health and tropical medicine. It is of particular importance to the public health worker in the tropics.

2. PUBLIC HEALTH NUTRITION WORKERS.

Advisory.

If it is admitted that the subject of nutrition is an important branch of public health, then it follows that public health organisations should employ personnel and develop machinery for furthering work in this field. Nutrition specialists, acquainted with the latest developments of research and capable of formulating and carrying out schemes for their practical application, would be a valuable addition to the personnel of public health organisations. Such specialists are already employed in a number of countries.

Advisory Committees on nutrition, formed of physiologists, practical cooking experts, medical officers of health, etc., may fulfil a useful rôle. Among the primary duties of such committees, which might suitably be attached to central public health authorities, would be the issue of sound educational material and the advising of other Departments of State on matters connected with nutrition.

In certain countries (*e.g.*, Japan and the Union of Soviet Socialist Republics), one finds institutes of nutrition, or institutes of hygiene, possessing a department of nutrition, which are connected both with the public health authority and with the universities. The

ideal institute of nutrition would include laboratories, a statistical department, lecture rooms for students and the public, a cookery department, an educational department containing models, posters, diagrams, etc. Such institutions or departments would obviously play a prominent part in educating nutrition workers and the public.¹

Educational material issued by responsible authorities, which lays down suitable dietary standards, is of particular value as a basis for practical action. We may quote, as an example, two pamphlets [53] issued by the British Ministry of Health in 1932: "Diet in Poor Law Children's Homes" and "The Criticism and Improvement of Diets". These pamphlets, drawn up by an expert committee, discuss in simple language the principles of adequate nutrition and translate these into terms of ordinary foodstuffs and menus. Mention may also be made of STIEBELING and WARD's excellent pamphlet "Diet at Four Levels of Nutritive Content and Cost", published by the U.S. Department of Agriculture [34].

3. FIELD WORKERS.

While State and local authorities, expert committees, the medical profession, etc., are, in general, responsible for the initiation and support of public health nutrition work, such work is, in large measure, social work, and cannot be carried out effectively without the assistance of "nutritionists", "dietitians", nurses, social workers, etc., in contact with the population.

"Nutritionists" and "Dietitians" in the United States of America.

In the United States of America, the practical side of public health nutrition work is largely in the hands of a type of worker usually called a "nutritionist". The term "dietitian" is usually applied to those who supervise dietary arrangements in hospitals and other institutions. Both categories are exclusively female. The following table indicates the number of nutritionists employed in the United States of America in 1932:

¹ It is remarkable how little attention has been given to the subject of nutrition at the various conferences of Directors of Schools of Hygiene. (League of Nations document C.H.888.)

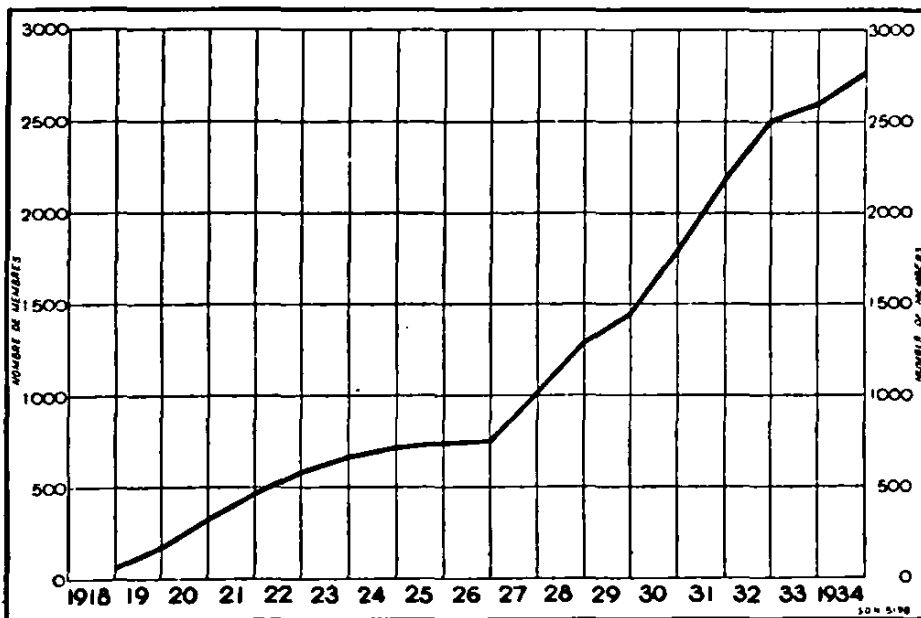
Number of Nutritionists in the United States of America in 1932 and Agencies employing them [54].

| Type of organisation or agency | Number of organisations | Number of nutritionists |
|---|-------------------------|-------------------------|
| Co-operative Extension Service in Agriculture and Home Economics | 1 | 56 |
| American Red Cross | 1 | 55 |
| Boards of Health (State and City)..... | 5 | 9 |
| Clinics, dispensaries, hospitals and dental centres | 31 | 31 |
| National health organisations..... | 2 | 1 |
| Public and private health and welfare agencies, including health centres... | 96 | 122 |
| Commercial organisations | 59 | 109 |

This list does not include nutritionists and dietitians employed in the wards and kitchens of hospitals, in institutions for child care, in schools and in education departments. Within the last three years, there has been a great increase in the number of nutritionists employed by organisations dealing with unemployment relief.

In 1934, there were over 2,700 members of the American Dietetic Association, the professional organisation of nutritionists and dietitians, which includes few members not actually earning their living by nutrition work. The following graph illustrates the growth of the American Dietetic Association during the last seventeen years.

Membership Growth of the American Dietetic Association, 1919-34 (American Dietetic Association Reports for 1933-34)



The nutritionist is a college graduate who, before specialising in nutrition, has had a training in the fundamental sciences—physics, chemistry and biology. Her work at the university, which extends over a number of years, includes advanced lecture courses on nutrition in health and disease, laboratory work and demonstrations, a training in cooking, and demonstrations of practical nutrition work in hospitals, schools, etc. In the larger universities, nutrition is usually taught in association with home economics. "All departments of home economics in the 311 colleges, universities and other higher institutions offering this subject in the United States give some training in nutrition, and many of these have well-developed food and nutrition courses" [55]. Sometimes, the student engages in a little elementary research under the supervision of her teachers; a few of the more gifted students may write a thesis and take a Ph.D. degree. Columbia University now offers a Ph.D. degree in nutrition.

Before taking employment, the nutritionist must usually supplement her academic course by acquiring practical experience in her profession during a year or more. For membership of the American Dietetic Association, two years' practical experience subsequent to graduation, including a period of internship in an approved hospital, is obligatory.

Nutritionists attached to Public Health Organisations in the United States of America.

The number of public health bodies throughout the United States of America which now employ nutritionists has increased since the figures given on page 389 were collected. The duties of those so employed are manifold. The nutritionist acts as a consultant in connection with all public health activities which demand a knowledge of nutrition, such as tuberculosis, infant welfare, care of pre-school children, pre- and post-natal work, etc. She responds to requests from prisons, orphanages and other kinds of residential institutions which ask for advice about the regulation of catering methods on scientific and economical lines. A large part of her work is educational; she prepares propaganda and gives talks and lectures, attempting to reach the community through school-teachers, public health nurses and social workers. She lectures to graduate and undergraduate nurses. In addition, she replies to

requests for information from individuals and groups, and often takes part in health demonstrations and in field nutritional studies.

In general, she is an advisory and not an executive officer. She has no administrative powers ; she is not *legally* responsible, for example, for the regulation of feeding in State institutions.

A number of educational authorities employ nutritionists. " In New York State, there is a nutritionist in the State Department of Education. Her work includes developing nutrition instruction in training-schools for teachers of the elementary grades ; preparing courses of study and helpful material for the use of teachers ; serving on committees for curriculum construction ; co-operating with outside organisations interested in promoting child health. At present, as many as 25 nutritionists are under her supervision in school systems in the State " [55].

Relief Work.

In 1933, the Federal Emergency Relief Administration requested State administrations concerned with relief to seek the services of fully qualified nutrition specialists to superintend the part of the relief programme concerned with food and nutrition. By April 1934, all States but five had complied with this request. Nutritionists employed in connection with public relief draw up schedules of " adequate diets at minimum cost " ; instruct social workers ; advise families how best to lay out relief money on food ; superintend the distribution of foods, such as milk or cod-liver oil ; and, in general, play an important rôle in ensuring that those requiring relief are adequately fed.

Nutritionists and Dietitians in Hospitals and Other Institutions.

The function of the hospital dietitian is to supervise the feeding of patients and staff. It is her task to provide, in a palatable form, special diets ordered by the physician and to give advice about diet to out-patients and to patients leaving the hospital. She gives lectures to nurses and provides practical training for them in kitchens and wards.

The " diet therapy " clinic, sometimes known as the " food " or " nutrition clinic ", is a special department of a general hospital or an out-patient dispensary designed to deal with cases requiring

dietary treatment. The "diet therapy" clinic has reached its highest development in the United States of America. One of its main functions is to translate the general dietary recommendations of the physician into terms of actual foodstuffs for the benefit of the patient. For example, an underweight anæmic factory girl attends the hospital for medical advice. The physician prescribes iron and a diet rich in vitamins. She is then referred to the diet clinic, where a trained worker inquires into her usual dietary habits and gives exact instructions as to how these should be modified to meet the recommendations of the physician. She will be provided with a carefully explained dietary schedule, drawn up to meet her case and, as far as possible, consonant with her means. A little elementary teaching of dietary principles will be given. If she is unable to purchase the necessary food, arrangements may be made for charitable assistance.

This method of imparting instruction in diet has proved particularly useful in the case of diabetics, but many other conditions requiring dietary treatment can be effectively dealt with by the diet therapy clinic. The patient, instead of being vaguely told to "eat less meat" or to "eat plenty of vegetables"—commands which may mean little or nothing to him—is provided with precise instructions and made to take an interest in his regime.

For imparting dietary instructions to slow-minded patients, wax models fulfil a useful purpose. Such expressions as "a slice of bread" or "a helping of cabbage" have a different meaning for everybody. Models help the teacher to provide an exact description of the regime to be followed.

Nutritionists employed in residential institutions other than hospitals, in commercial organisations providing meals for employees, etc., supervise catering and cooking with the object of improving nutrition values or palatability and of reducing cost. In general, in the United States of America and elsewhere, it has been found that the regulation of collective feeding by a worker trained in scientific and practical dietetics results in economy and in increase of comfort and satisfaction, and for this reason a number of large commercial organisations have found it advantageous to employ nutritionists.

Status of the Nutritionist.

The nutritionist is not a scientific worker, though she often takes part in scientific enquiries. She must know how to make reliable dietary surveys. She is, in general, expected to keep up with the latest developments of her subject. Although she deals largely in matters closely associated with medicine and often works in close contact with the medical profession, she has had, as a rule, little medical or nursing training. It is only to be expected that there should be members of the medical profession who resent the intrusion of a non-medical worker into medical fields ; such critics complain, rightly or wrongly, that the training and knowledge of the nutritionist is too academic, that she lacks the background necessary for the application of laboratory results to human beings. It is to be noted that the inspiration of the " nutrition " movement in the United States of America has come from distinguished scientists who are not members of the medical profession. In general, however, medical men feel that the nutritionist is a useful assistant in hospital, in the out-patient department, and in public health work of all kinds.

The following statement, recently made by the President of the American Dietetic Association [56], illustrates the relation which the nutritionist strives to maintain between herself and the medical profession :

" Our profession is concerned with the health and well-being of mankind. Whether we emphasise the application of our knowledge to the preventive or to the curative aspects of nutrition, it has been well for us to recognise as our leaders that wise and humane profession so ably represented by the American Medical Association and the American College of Surgeons. These organisations have pointed the way for us. The demands for scientific accuracy and medical knowledge made upon our members by physicians in the early days of our organisation forced the Association to recognise the imperative need for high membership requirements for new and younger members."

It may be urged that a nurse who has received, in addition to her ordinary hospital training, post-graduate instruction in dietetics

could successfully fulfil most of the functions of the nutritionist. Some consider, indeed, that the training of the former would better qualify her to deal with problems of malnutrition in the home and elsewhere. There is some truth in this view. Nevertheless, nutrition workers with a sound knowledge of physiology and scientific methods, while at first they may be bewildered by the gulf between theory and practice, should, in the long run, prove more useful in the sphere of public health than specially trained nurses. At the same time, the contribution which "health visitors" and public health nurses can make to the improvement of dietary habits in the home and elsewhere need not be belittled. More emphasis might well be placed on nutrition in the training of the "health visitor". She can provide valuable assistance in the campaign against rickets, dental caries, infantile scurvy, and other deficiency diseases; she can supervise the diet of infants and pregnant and nursing mothers. Social workers of all kinds can also help in the campaign against malnutrition. In the Union of Soviet Socialist Republics, nutritionists are trained mainly for collective feeding.

4. EDUCATION IN NUTRITION IN SCHOOLS.

In all civilised countries, simple instruction in the rules of health is given to schoolchildren; it is obviously essential that such teaching should include the subject of diet. But since dietary habits and problems differ from country to country, there can be no general rules as to the type and amount of instruction in nutrition which schoolchildren should receive.

Perhaps the keynote should be simplicity. The child need not be given the impression that correct feeding is a difficult problem requiring vigilant attention throughout life. Elementary principles may be taught, but the emphasis will naturally be on foods rather than food factors. The child may learn that milk and green vegetables are healthy foods, that bread and margarine is not a satisfactory meal, that it is better to spend pocket-money on fruit rather than sweets, and so on. Models and posters can reinforce verbal instruction. In the United States of America, posters are often exhibited to children comparing large sleek milk-fed laboratory rats with less fortunate litter mates, undersized and scraggy, whose diet lacked that food.

When food is provided in schools by educational authorities, an excellent opportunity of teaching dietetics arises. The giving of milk at the midday interval is an object lesson of the value of that food, and teachers can readily drive the lesson home with a few remarks. If meals are provided, children can learn much from the nature of the meal and from the method by which it is served and cooked. The child can be encouraged to eat slowly, and graceful table manners can be inculcated.

The Nutrition Class.

The "nutrition class" for malnourished schoolchildren was conceived by EMERSON, of Boston, in 1908 [25]. Emerson, while working in a children's out-patient clinic, noted the existence of a large number of delicate children, belonging to all social classes, who appeared to derive little benefit from ordinary medical treatment. Having confirmed this impression by the study of 5,000 children attending the clinic, he chose 15 children showing evidence of debility and malnutrition in a marked degree, and formed these into a "class" for treatment by education in nutrition. Children attending the "nutrition class" are given a note-book in which to record the nature of meals and their duration, hours of sleep, and the amount of time spent playing in the open air. At the same time, a nurse or social worker visits their homes and notes the hygienic conditions in which each child lives.

Each child is presented with a chart bearing its name, on which two curves are inscribed, one being the child's actual weight curve and the other an ideal weight curve. The children themselves record on the chart their weight week by week, and their parents are invited to attend the class in order that its purpose may be explained to them. Rewards are given to children who make the best progress. If a child is not progressing favourably, an attempt is made to discover the reason; lack of sufficient food, over-rapid meals, faulty hygiene or infectious conditions (*e.g.*, colds) may be held accountable. The parents are informed of the cause of the child's lack of progress. Nutrition classes were at first attached to clinics, but subsequently they have been developed in schools. They are sometimes supplemented by open-air "nutrition camps". It has been found that the influence of the nutrition class often makes itself felt in the home.

The nutrition class involves an abridgment of school-hours. The programme includes a rest and a meal at 10.30, half an hour's rest before the midday meal, and a small meal in the middle of the afternoon. KAISER, NORTON and WALKER [57] attempted to assess the results obtained in nutrition classes in Rochester, U.S.A., during the years 1921-1926. It was found that 80% of children attending the class regained average weight, while only 35% of poorly nourished children outside the classes made similar gains during a similar period. It was claimed that the beneficial effects of the nutrition class extended to children not actually enrolled and to the children's homes. ROBERTS [58], in a book written before the "economic crisis", urges that nutrition classes in school should be organised for all children without distinction.

The Education Committee of the London County Council has recently announced its intention of establishing five nutrition clinics in London during the next three years. Cases will be referred to the clinics by school doctors, teachers and child care committees, and each child will have a thorough medical examination to ascertain whether it is suffering from dietetic deficiency. If so, advice will be given to the parents and, when necessary, treatment in the form of cod-liver oil, malt, iron, etc., will be provided [59].

5. SCHOOLS OF DOMESTIC SCIENCE.

Schools of "domestic science" or "home economics", largely attended by young women, provide excellent opportunity for teaching rational dietetics. The pupil, in learning how to purchase and prepare attractive meals for her future family, can also be taught the elements of nutritional science, with particular reference to the relative price and nutritive value of foodstuffs. It is often said that maternal ignorance is the main cause of malnutrition in children. This is not strictly true, for no amount of knowledge and skill on the part of housewives makes it possible to purchase a satisfactory diet when income is grossly insufficient. There can, however, be no doubt that the inefficiency of housewives is an important contributing factor in producing malnutrition in the children of the very poor and unemployed. The satisfactory education of women in "domestic science", which includes cooking, marketing and dietetics, is an important public health activity.

6. EDUCATIONAL WORK AMONG RURAL POPULATIONS.

An example of energetic educational work in the field of nutrition is provided by the Co-operative Extension Service in Agriculture and Home Economics in the United States of America. The function of the Extension Service is to apply to the local problems of the farm and the rural community the results of scientific research in agriculture and nutrition, and, in particular, research carried out by the United States Department of Agriculture and one of its subsidiary branches, the Bureau of Home Economics. The latter undertakes much nutritional research with a strictly practical bearing, such as the investigation of the vitamin and mineral content of foodstuffs, the effect of cooking on nutrition value, and suitable methods of food preservation. It carries out family budget enquiries, studies food consumption trends, works out "adequate diets at minimum cost" and so on. In order that the community may derive benefit from the results of such investigations, the Extension Service employs (1934) 61 "extension nutritionists" in 45 States. All these workers are college graduates and a considerable number have taken advanced degrees. "Most have a background of high-school or college teaching, a few have been hospital dietitians, and an increasing number have had, in addition, several years of work as country home demonstration agents. Salaries range from 2,100 to 3,770 dollars, with the average of 2,770 dollars" [54].

To some extent, the rural community is reached by ordinary publicity methods, but the spearhead of the campaign is the "home demonstration agent", who achieves contact with the population through clubs and other local organisations. A good deal of information is disseminated through specially organised clubs for boys and girls and by trained volunteer-leaders chosen from rural communities.

Malnutrition is attacked in a variety of ways. The growing of vegetables for home consumption is taught and encouraged, an activity of special importance in the pellagra-stricken areas in the Southern States. Methods of preserving meat, vegetables, fruit and other foods are taught, with the object of assisting the small farmer to eliminate waste and to make full use of potential wealth

at his disposal. In Texas, in 1931, 3,500,000 quarts of food were stored and 500,000 lb. of meat were cured as a result of the activities of home demonstration agents [60]. Education is given in food values, in wise purchasing of foodstuffs, in cooking, menu planning and so on. Mothers are taught the dietary requirements of growing children, special attention being given to the school lunch prepared at home, which the child consumes at the midday interval.

It would appear that the Extension Service has done much to prevent the lowering of health standards during recent years of economic stress. Such activities are of interest in that they represent an attempt to improve the diet of rural populations. Contrary to general belief, malnutrition is as common among the poor of the countryside as among the poor in great cities.

Educational work in nutrition among rural populations is a promising field of activity. The peasant all too rarely makes full use of the possibilities at his disposal for obtaining a varied, nutritious and attractive diet. Even in the absence of extreme poverty, his food is often monotonous and ill-cooked. Cooking-classes in rural communities, at which some instruction in the principles of diet is given, have been organised in a number of European countries. Housewives, as a rule, are eager to attend such classes, to the great benefit of themselves and their families.

7. PUBLICITY AND PROPAGANDA.

Useful dietary knowledge may be imparted directly to individuals through the medium of infant welfare and ante-natal clinics, nutrition clinics, nutritionists, nurses and social workers, or it may be disseminated through schools as part of health education programmes. Or, again, the publicity methods of modern civilisation—pamphlets, lectures, exhibitions, the cinema, radio, posters, Press articles, etc.—may be employed. Well-prepared, tactful and interesting publicity material has an obvious value in educating the public in wise dietary habits.

Sound educational material relating to diet, issued by responsible authorities,¹ is liable to be parodied by commercial advertisements.

¹ The Institut scientifique d'Hygiène alimentaire, in Paris, gives a course in cooking every year, with demonstrations in which the connection is shown

It is difficult for the half-educated to distinguish between ingenious advertising and genuine health propaganda. If anything, the former makes more use of scientific terms ; advertisements of expensive patent food products will discuss Calories, protein, vitamins, etc., with an appearance of profound knowledge. During recent years, there has been, in many countries, a tightening-up of regulations designed to ensure that food preparations, advertised as being rich in this or that food factor, do, in fact, possess the quality stated : preparations alleged to contain vitamins, for example, may be subject to official approval and control on the basis of the standards and units established by the League of Nations. But there is, as yet, no machinery for controlling advertising which is false, not verbally, but by implication such advertising, for example, as attempts to give mothers the idea that, if they do not buy the article in question, their children's health will suffer. Those engaged in teaching dietetics to the public find that the ingenuity of the modern advertisement adds greatly to their difficulties.

Results and Goal of Education in Nutrition.

During the economic crisis, vigorous attempts have been made in many countries to disseminate dietary knowledge, the effectiveness of which it is naturally impossible to assess. But the fact that the infantile mortality rate and the death rate from tuberculosis have not ceased to fall suggests that they have not been without result.¹

It is not only the poorer classes which require education as regards diet. But since the poor suffer from malnutrition more than the well-to-do, much public health nutrition work is at present concerned with saving the indigenes from the worst effects of improper and insufficient feeding. Under existing economic circumstances,

between the culinary art and physico-chemical phenomena. There is at Moscow a higher school of "kitchen engineers", in addition to a number of other schools. In Paris, each newly created "school-group" includes a domestic science class.

¹ " Compared with the average of 1924-1927, our 1932 *per capita* consumption of margarine fell by 20.8% and of flour by 2% (bread remaining unchanged), while consumption of fruit rose by 8.2%, of milk by 15.5%, of eggs by 32.7% and of butter by 40.3%. These changes are not parallel to changes in price : consumption of bread has not increased, in spite of the fall in price ; and the consumption of milk and eggs has increased considerably faster than prices have fallen. " *Nature*, 135 : 322, 1935.

spreading knowledge of how an adequate if unpalatable diet may be obtained at very low cost is a valuable activity.

But those concerned with educating the public should also envisage a wider goal—that of a population consuming a diet, not merely just sufficient, but the best, both as regards nutritive value and palatability, which the vast resources of the modern world can produce. In a world suffering from over-production of foodstuffs, emphasis should be placed on the *optimum* rather than on the minimum.

In the United States of America, public health nutrition workers sometimes confess to the ambition of making the nation “food-conscious”. If by “food-conscious” is meant a constant pre-occupation with diet, a perpetual nervousness lest the breaking of some rule should entail disastrous consequences, then we have little sympathy with such an ideal.

In educating the public in nutrition, the simplicity of the principles involved should be emphasised: it should be made clear that it usually requires a little more knowledge, but no more effort and anxiety, to prepare and consume a well-balanced diet than a defective one.

VI. VARIOUS EXAMPLES OF PUBLIC HEALTH NUTRITION WORK.

The best proof that diet can be organised by the public health administrations is the fact that it is already so organised. The public authorities, seconded by private institutions, have intervened, more or less recently, in matters in which the need for their action was most strongly felt. Examples of such action, which is tending to become more and more systematic, will be found in this chapter.

1. NUTRITION IN CHILDHOOD.

Infants.

From the nutritional point of view, the pre-natal period is perhaps the most important in the human life-span. Included among the duties of maternity and child welfare services is the supervision of the diet of pregnant women and infants. Nutrition work with

mothers and infants can readily be co-ordinated with other activities. The same machinery used for the prevention of tuberculosis in infants and young children can be employed for the prevention of rickets.

The diet of pregnant women requires regulation in many respects. Particular attention should, however, be given to vitamin D, calcium and iron (phosphorus being usually adequately supplied by ordinary mixed diets), with the object of preventing rickets in the infant and anæmia in both mother and child. The calcium needs of a pregnant woman in the later stages of pregnancy, during lactation, have been assessed by K. U. and G. TOVERUD at the very high figure of 1.6 grammes per day [61]. A high consumption of "protective food"—in particular, of whole milk, green vegetables and fruits—will ensure that the most important dietary requirements of pregnancy are fulfilled. Sufficiency of vitamin D can be provided for by the giving of cod-liver oil or other preparations rich in vitamin D, or by sun-baths, etc.

If the child at the breast is to be adequately nourished, not only its health and diet, but those of its mother, require supervision. STRAUSS [62] and his colleagues, for example, have drawn attention to the possibility that gastro-intestinal disturbances occurring in women during lactation may promote vitamin deficiency in the mother and react upon the health of the child.

Most pædiatricians are in agreement that breast feeding remains the ideal method of nourishing an infant. For the poorer classes of the population, which cannot easily afford the better grades of fresh cow's milk or dried milk preparations, it has particular advantages. Where sanitary standards are low, it minimises the danger of infection. It must not be forgotten, however, that the quality of milk provided by the mother is to a considerable extent dependent on the quality of her own diet.

Within recent years, great improvement has taken place in the technique of "artificial" feeding, and "humanised" dried milks, well supported by average infants, are widely available. "Feeding with artificial milk mixtures", remark GRULEE, SANFORD and HERRON [63], "has had such success that, in the minds of many physicians and perhaps a large proportion of the public, there has grown up the idea that artificial formulas can safely replace breast milk without detrimental results to the child." These workers

studied mortality and morbidity in a large series of infants (20,061) under the care of the Infant Welfare Society of Chicago. From birth to nine months, 48.5% received only breast milk, 43% were partially breast fed, and 8.5% artificially fed on cow's milk mixtures. All three groups received accessory food, including orange juice beginning at four weeks, cod-liver oil beginning at four weeks, cereal at five weeks and vegetable at six months. Mortality and morbidity in the three groups were as follows :

Mortality and Morbidity in Breast-fed, Partially Breast-fed and Artificially-fed Infants (Grulee et al.).

| | Breast-fed | Partially breast-fed | Artificially-fed |
|----------------------------------|------------|----------------------|------------------|
| Per cent of total | 48.5 | 43.0 | 8.5 |
| Morbidity per cent | 37.4 | 53.8 | 63.6 |
| Per cent of total mortality | 6.7 | 27.2 | 66.7 |

In this particular group of infants, it seems clear that breast feeding was associated with a higher standard of health than artificial feeding. Other factors may, however, have influenced morbidity and mortality in the various groups.

There is a tendency to-day to give infants solid food, as an addition to their milk regime, at an earlier age than formerly—a practice which is of prophylactic value in connection with hypochromic anæmia, a disease which infants on a diet entirely composed of milk tend to develop in the latter months of the first year [64]. Towards the end of the fourth month, a little fruit pulp—apple, banana—is often given ; and at the end of the fifth month, egg yolk and mashed vegetables. Fruit juice and cod-liver oil are often given as early as the second month.

The suggestion of a *milkless* diet during infancy has even been advanced. Except in special cases of intolerance, such a diet could scarcely be permissible before the sixth month and, even in later infancy, is indefensible on scientific grounds. Milk, and, if possible, breast milk, during the first nine months of infancy, remains the best dietary.

The steady fall in the infantile mortality rate which has taken place throughout the last half-century is a recognised triumph of modern hygiene. Infant welfare clinics, designed to supervise the feeding and general development of infants, have long been a

valuable, and indeed an essential, part of public health organisation. As a result of the better education of mothers in the principles of infant feeding, to which many agencies besides the infant welfare centre have contributed, the incidence of nutritional disorders in infancy has been greatly reduced in many countries. We may refer here especially to the increasing rarity of certain diseases common in infancy, which are related to faulty feeding—*e.g.*, rickets and scurvy.

The Pre-School Child.

Maternity and child welfare services, as at present organised, do not, as a rule, follow the child beyond its second year. At the age of 6 or 7, it enters school and comes under the control of school medical services. The fact that, during the interval, it may be without medical supervision has aroused the concern of public health authorities, but, in most countries, machinery for safeguarding the health of the pre-school child remains to be invented. Several schemes have been proposed : maternity and child welfare services may be called upon to prolong their period of control, or school medical services may undertake the care of the child at an earlier age. Whatever plan of campaign is adopted—whether the main line of approach is through health centres, dispensaries, nursery schools or kindergartens, or through health visitors and social workers in direct contact with the home—it is clear that it must involve the greatest attention to diet.

J. Ch. Roux¹ makes the interesting suggestion that the faculty of adaptation to different forms of diet develops slowly, and that children up to the age of 12 are extremely sensitive to any change of food and to the effects of certain fermentations. This is perhaps another way of saying that it is during the period of most rapid growth that the ill-effects of an unbalanced diet show themselves most readily.

MCGONIGLE and MCKINLAY [65] have observed, from an examination of the records of the Child Welfare Service in Stockton-on-Tees, that a correlation exists between unsatisfactory diet and the occurrence of bone defects, pharyngeal conditions and dental decay in children under the age of 5 years. It follows that many physical

¹ Private communication.

defects among schoolchildren could be *prevented* by attention to diet during the earliest years ; at present, defects are often discovered only when the time for prevention is past. The same workers found that " dietary disturbances " (including anæmia) were most commonly recorded in children attending child welfare stations during the second half of the first year ; bone defects were most frequently observed for the first time during the second year, pharyngeal conditions during the third, and dental decay was frequently detected during the second year.

In a recent investigation, a high percentage of physical defects was noticed in an unselected group of London elementary school-children aged 5 [66].

The survey revealed the following :

- 87.5% showed one or more signs of bony rickets ;
- 66.1% two or more signs of bony rickets ;
- 82.4% presented some abnormality of the nasal pharynx ;
- 67.1% had " adenoids " in some degree ;
- 93.8% had dental caries ;
- 88.2% had a certain degree of dental hypoplasia.

A great proportion of such defects is attributable to faulty diet.

Children of School Age.

The period of school attendance is growing longer in most civilised countries (extending up to 13 and 14 years in elementary schools, and up to about 17 years in secondary schools). During the whole of their school career, children are under medical control, and an opportunity is thereby provided for improving their state of nutrition.

In the following sections, four questions will be discussed : the prevalence of malnutrition among schoolchildren at the present time ; the organisation of school meals ; the value of milk in the diet of children ; the importance of sunlight and ultra-violet radiation.

Observations on " Malnutrition " in Childhood.

A number of investigations have been carried out in Europe and America, which tend to show that malnutrition is common

in schoolchildren. In interpreting the results of such investigations, it must be remembered that the term "malnutrition" has a different meaning to different observers. Where a child is defined as malnourished, it may mean, according to the context, that it falls below a recognised standard as regards height, weight and other measurements, that it displays certain clinical symptoms, or that its diet is defective. Further, malnutrition as diagnosed clinically and anthropometrically may be due to other factors besides faulty feeding.

ROBERTS [58] summarises the results of large-scale investigations on malnutrition among schoolchildren carried out in the United States of America during the years 1906-1924. In 13 investigations, each involving thousands of children, the percentage judged to be suffering from malnutrition on the basis of clinical examination averaged 22.3. The highest figure was that of GILL, who, in 1909, found that 40% of schoolchildren in the "East Side" of New York were suffering from malnutrition. In 17 investigations carried out during the years 1918-1924, weight in relation to height was used as the criterion of nutritional status (see pages 360-362); the percentage judged malnourished on this basis was 32.7; JACOBS [67] has recorded that malnutrition (assessed clinically) among Jewish children attending a Community Health Centre in Chicago rose from 15 to 30% during the years 1928-1932.

In 1921, ROBERTS [68] investigated the dietary habits of 6,015 pre-school children in Gary, Indiana. It was found that 90% were living on diets which were judged insufficient by current American standards; 57% had no milk to drink; 16% had no milk in any form, either in food or as a beverage; 59.5% had no eggs and 60% no fruit; 50% consumed no vegetables other than potatoes. Many were given large quantities of tea and coffee, and, in general, sleep and rest were inadequate.

In England, the first general recognition of the extent of malnutrition among the children of the poorer classes came with the passing of the *Education Act* of 1870, which filled the elementary schools with sickly and emaciated children from the slums of the great cities. Later, during the Boer War, recruitment revealed a formidable amount of physical disability, and the question of malnutrition among schoolchildren was forced upon the public notice. In 1907, when the School Medical Service was started,

10% of the schoolchildren were assessed as malnourished on clinical examination. (In Edinburgh, Alistair McKENZIE reported $33\frac{1}{8}\%$.) The percentage of malnourished children has fallen since 1907. During the last ten years, it has remained stationary at about 1% ; to put it in another way, of the 5 million children attending elementary schools in England every year, 50,000 may be expected to show evidence of malnutrition.

The percentage of malnutrition recorded among schoolchildren is much higher in America than in England. The difference may be largely due to the employment of a higher standard of satisfactory nutrition by American physicians, and illustrates the confusion which at present reigns in this field.

McCOLLUM [33] has suggested the following criteria as evidence of a satisfactory nutritional state in any given population group : capacity for uninterrupted growth to maturity ; a high degree of fertility (in the biological sense) ; a low infantile mortality ; satisfactory development and condition of the bones and teeth ; a high resistance to infection ; and ability to retain to an advanced age the characteristics of youth.

School Meals.

The provision of meals to schoolchildren is to-day a recognised public health activity in many countries, though the methods employed vary greatly from place to place. It is no new departure. As long ago as 1870, voluntary associations known as the *caisses des écoles* were founded in France for the purpose of providing destitute elementary-school children with books, clothes and food. Later, the functions of these associations were assumed by the State. The *caisses des écoles* organised school canteens, and children were provided with a midday meal of soup, with one vegetable and 40 to 60 grammes of meat, according to age. Older children received meat every day and younger children twice a week. Sometimes soup was provided to children in the morning on arrival and tea (a light meal) in the afternoon.¹ This system of school feeding still exists in France. As a general rule, parents who can afford to do so pay for the meals, while poor children are fed free of charge.

¹ Sum included in the budget of the City of Paris in 1931, in addition to contributions from the school funds : 3,900,000 francs.

A system of tickets is employed, so that the children themselves do not know which child is paid for and which not. The tendency is towards free feeding for all. In order to inculcate cleanly habits and good table manners, a good deal of care is given to the method of serving ; the meals are intended to have an educational value.

In the United Kingdom, the feeding of elementary-school children was initiated by voluntary associations (335 in 1905) and was continued and developed by the Board of Education. After some discussion, Parliament, in 1906, accepted the principle that school feeding is " educational " in character, and not in the nature of relief (Education (Provision of Meals) Act, 1906). It was held that the principle of compulsory education obliged the authorities to supplement the dietary of undernourished children, even during school holidays.

In 1907-8, the number of meals provided by the local education authorities was 2,751,326. In 1914-15, the number had risen to 29,560,316. During the year 1932-33, the number of meals provided rose from 47,858,200 (1931-32) to 62,304,600, and the number of children fed to about 400,000 (as compared with 320,000 in 1931-32, 295,000 in 1930-31, 265,000 in 1929-30). The meals included 3,118,613 breakfasts, 22,116,042 dinners, 1,236,965 teas, 32,255,262 " milk meals " and 3,577,789 " other meals ", the last-named consisting usually of supplementary nourishment in some such form as extract of cod-liver oil and malt. About 95% of the ordinary meals, 65% of the " milk meals " and 72% of the " other meals " were provided free of charge [69].

The composition of the meals has to be approved by the school medical officer. The average dinner comprises 33 grammes of protein and 21 grammes of fat, representing about 850 Calories. The children are selected on the basis of two tests : physical condition and poverty. Children showing definite evidence of malnutrition may be given cod-liver oil or some similar preparation which supplies fat-soluble vitamins. In a number of large cities, the food is prepared in central kitchens ; in a certain number of schools, by the schoolgirls themselves during their cookery lessons. The meal is, so far as is possible, rendered educational and attractive and parents are invited to attend.

As a result of co-operation between the Board of Education, the National Milk Publicity Council and the Milk Marketing Board,

there has recently been a great increase in the number of children consuming milk in schools in England (see Annex 3).

Dr. SCHIOTZ [70], Chief Medical Officer of Oslo, has organised school feeding on interesting and novel lines. The hot midday meal which the schools provided for a certain number of children before 1927 was judged unsatisfactory : of the 2,220 Calories deemed necessary for children between 7 and 14 $\frac{1}{2}$ years of age, it yielded only 640, or 28% ; the food, which was boiled to excess, was poor in vitamins and provided no work for jaws and teeth ; from 65 to 75% of the children went back to exactly similar meals at home ; on the other hand, up to 45% of the children did not receive any milk at home, and the majority very rarely consumed fresh fruit and vegetables, so that the school lunch did not in any way make up for the deficiency of the home diet.

In 1927, breakfasts were provided comprising :

- 400 to 500 c.c. of fresh whole milk (in winter 200 c.c. of cocoa made with skimmed milk) ;
- 2 scones made of wholemeal, wheaten or rye flour ; whole wheat or whole rye bread *ad lib.*, a little fat cheese and vitaminised margarine (*i.e.*, margarine which is equivalent in vitamin A and D value to good summer butter) ; half an apple or half an orange ; during other seasons, a raw carrot may alternate with these fruits.

The meal must be taken slowly and with due regard to social elegance. Its Calorie value is between 700 and 1,000, according to the amount of bread eaten ; it is rich in vitamins and salts and exercises the teeth and jaws. It costs about 30 öre.¹ Children begin school with a feeling of repletion, and the meal is stated to improve their capacity for sustained attention. In Oslo, about 30% of children attending the public school partake of the breakfast. In the poorer districts, the percentage is as high as 50%.

WESTERGAARD [71] has produced the following figures which he interprets as demonstrating the superiority of the school breakfasts to school luncheons : An experiment was carried out in two schools, in one of which the children were supplied with the old-fashioned " lunch " and, in the other, with modern " Oslo school

¹ At present, about 0.40 gold franc.

breakfast". At the end of six weeks it was found that the boys in the former school had put on 600 grammes in weight, those of the latter 886. Among the girls, the corresponding figures were 429 and 1,029 grammes. There was no other variable besides the difference of meals.

In the United States of America, while school feeding along excellent lines is widespread, there is some tendency to attack malnutrition via the home and not to make up by school meals what is lacking in the home diet. Attempts are made to teach mothers to supply the children with a well-balanced and adequate lunch to carry with them to school.

The midday school-meal is the rule in the U.S.S.R., where about one third of the children receive it free of charge. School meals are given in Kindergartens; schools of the first and second degree provide one or two meals according to the number of hours of attendance.

Experience has shown that certain methods and principles make for success in connection with the feeding of schoolchildren. The improvement of health, and not charity, should be the underlying motive. As a rule, school meals are provided for malnourished and undernourished children, and not for all children without distinction. In certain countries, special attention is given to the feeding of mentally retarded children (LABBÉ, in France). The organisation of school feeding is the concern of health and education authorities and not of private philanthropy, and it is the task of school medical officers to supervise menus. Meals consumed at school have an educational value. As regards the composition of the meals, the emphasis should be on the protective foods—milk, green vegetables, fruit, etc. Children suffering from the severer degrees of malnutrition may be given cod-liver oil, or some similar preparation which supplies fat-soluble vitamins.

It is not only children in cities who may benefit from well-organised school feeding; such feeding may be equally valuable in country districts where children often have a long journey to school and may bring with them a quite unsuitable midday "snack" (*e.g.*, white bread and jam or some preserve).

School authorities, school medical officers, and health visitors should not overlook the importance of the child's home diet; it might happen, for example, that parents, relying on an abundant

school meal, would send their children to school without breakfast. The provision of school meals is a valuable public health activity, but it is not a panacea for all the ills from which schoolchildren suffer. Many factors besides diet may influence a child's "state of nutrition"—*e.g.*, excessive play and over-exertion, lack of sleep, open air and sunshine.¹

Milk in Schools.

CHICK [72] has pointed out that cow's milk, but for its high nutritive value, would long ago have disappeared from the dietary of civilised peoples, particularly those living in cities. Its richness as a foodstuff makes it an excellent medium for the growth of bacteria, and for this reason it is potentially the most dangerous of foods. It is often an efficient agent for the spread of infectious diseases, particularly tuberculosis. One of the most important problems with which public health authorities have to deal is that of a pure milk supply.

The proteins of cow's milk, lactalbumin and casein, have an amino-acid composition which renders them suitable to supply the nitrogenous elements needed for growth and repair. Milk fat (*e.g.*, butter) is palatable and digestible, and, under certain circumstances, a vehicle for vitamins A and D. Cow's milk contains 0.15 to 0.2% of lime and, among foodstuffs, is equalled in this respect only by certain leafy vegetables. It is relatively poor in iron.

The protein, fat and mineral content of milk does not seem to be greatly influenced by the diet of the cow, but the same cannot be said of its vitamin content. There is an extensive literature on this point. In general, the milk of cows fed on summer pasture is richer in vitamins than the milk of stall-fed cows, but, under modern conditions, it has become possible to control the vitamin content of milk at all seasons by suitable feeding methods. No

¹ In France, there is a growing demand for the establishment of a Ministerial Commission to organise and supervise feeding in educational establishments of all kinds and to prepare standard menus and tables of food values. The Fédération nationale de l'Enseignement ménager, which represents forty-two voluntary organisations, was appealed to to take steps in the same direction. (A. MOLL-WEISS, *Bull. Acad. Méd.*, April 22nd, 1930.)

assumption as to the vitamin content of milk can be made, unless the circumstances under which it is produced are taken into account.

Mention may be made of the value of milk as a source of vitamin B₂ emphasised by SHERMAN, who remarks that, "when account is taken of the amounts ordinarily eaten in a reasonably well-balanced dietary and food supplies, milk is doubtless the most important source of vitamin B₂ (G) for the American and European peoples" [73]. HUNT and KRAUS [74] have observed that the vitamin B₂ content of milk varies in accordance with the diet of the cow.

TERROINE and VALLA [75], attempting to throw light on the "growth-promoting" value of various proteins, drew comparisons on the basis of three coefficients: the "coefficient of digestibility" ($\frac{N \text{ absorbed}}{N \text{ ingested}}$), the "coefficient of retention" (N absorbed — urinary N), and the "coefficient of effective utilisation" combining the first two. Judged by these coefficients, milk proteins were found to be superior to proteins contained in a number of common foods.

Milk as compared with Other Protein Foods.

(Table by TERROINE and VALLA.)

| | Coefficients | | | Comparison Milk = 100 | | |
|---|---------------|-----------|-----------------------|--------------------------|-----------|-----------------------|
| | Digestibility | Retention | Effective utilisation | Digestibility | Retention | Effective utilisation |
| Total milk albumins . | 96.5 | 67.6 | 62.7 | 100.0 | 100.0 | 100.0 |
| Casein | 99.8 | 50.4 | 50.3 | 100.1 | 78.4 | 78.6 |
| Beef | 94.7 | 49.5 | 46.9 | 97.8 | 77.0 | 75.3 |
| Total albumin of white of egg | 96.0 | 46.3 | 44.6 | 99.2 | 71.9 | 70.8 |
| Fine barley flour | 95.2 | 45.6 | 43.5 | 98.4 | 65.9 | 64.7 |
| Wholemeal barley flour | 83.3 | 41.3 | 34.0 | 85.6 | 65.1 | 55.1 |
| Wholemeal wheat flour (Graham's flour) ... | 91.2 | 34.3 | 31.9 | 94.9 | 51.6 | 49.6 |
| High-grade wheat flour (74%) | 96.8 | 28.7 | 28.0 | 99.6 | 38.0 | 37.8 |
| Soya flour | 91.3 | 51.6 | 47.1 | 94.3 | 70.0 | 66.5 |
| Pea flour | 95.5 | 40.6 | 38.8 | 97.8 | 55.2 | 53.2 |

It is not yet clear wherein lies the peculiar virtue of milk as a food for growing children. It may depend for its richness on a particular

dietary factor : protein, calcium or certain of the vitamins. On the other hand, its dietary value may result from the balance of its chemical constituents and be enhanced by its digestibility. These are interesting points for further study.

Effect of Heating on the Nutritive Content of Milk.

At present, in most civilised countries, milk is pasteurised to prevent the spread of milk-borne diseases. A great many laboratory and clinical investigations have been carried out in order to determine whether and how far the food value of milk is altered by heating, and the point has been discussed for many years. The food factor in milk most readily affected by heating is vitamin C. When milk is rapidly heated to boiling-point and allowed to cool, little loss of vitamin C takes place [76]. The effect of aerobic pasteurisation is, in general, more serious, but much depends on the metal with which the milk comes into contact in the process [77]. Temperatures above 100° C. cause a rapid destruction of the vitamin C in milk [78]. In general, dried and condensed milks contain less vitamin C than fresh milk. Heating, in addition to impairing vitamin C, brings about a reduction of diffusible calcium [79].

Without going deeply into the matter, it may be said that there is no conclusive evidence that heated milk is in any marked degree inferior to fresh milk, except in respect of vitamin C, a food factor that can readily be made good from other sources. With regard to calcium, the natural richness of cow's milk in this element tends to diminish the importance of the losses which occur on heating.

FRANK and his colleagues [80] could find no significant differences in the mean height and weight of two groups of schoolchildren fed on raw milk and heated milk (including pasteurised, boiled and evaporated milk) respectively. While there are observations on record which suggest that raw milk may, in certain respects, be superior to heated milk, the high nutritive value of the latter cannot be denied. In present circumstances, public health authorities cannot accomplish the task of ensuring an abundant, cheap and pure milk supply, except by the employment of pasteurisation.¹

¹ " We have an immense amount of clinical evidence gathered from many countries which shows that pasteurised milk has fulfilled the needs for feeding infants and children over many years, with no evidence of damage, provided the loss of vitamin C is made good. The opponents of pasteurised milk have

Clinical Evidence of the Nutritive Value of Milk.

During recent years, some very important observations have been made in a number of countries of the value of cow's milk as a food for growing children. It has been shown that, when children living on diets usually considered adequate in the country concerned are given an additional amount of milk per day (usually about 500 c.c.) for periods varying from three to four months to a number of years, the result is an acceleration of growth and an improvement of well-being. A simple technique has been employed. A group of children living in an institution or attending school from home is selected. One-half of the group is given, in addition to the ordinary diet, 500 to 1,000 c.c. of milk per day, while the other half, whose diet remains unaltered, provides a control. Records of height and weight in both groups are kept, and, at the end of a certain period, the height and weight increments in both groups are compared.

The well-known experiment of Cory MANN [81] was carried out on boys living under excellent hygienic conditions in a charitable institution near London. Six groups of 30 to 60 healthy children between the ages of 7 and 11 were formed, all of which received the same basal diet, containing 56 to 71 grammes of protein (a quarter being animal protein), 29 to 47 grammes of fat, and 288 to 347 grammes of carbohydrate, and yielding, on an average, 1,900 Calories. In addition, each group was given as supplement one of the following: 90 grammes of sugar (pure carbohydrate); 50 grammes of margarine (fat); 50 grammes of butter (fat + fat-soluble vitamins); 21 grammes of fresh watercress (rich in various vitamins); 21 grammes of casein (equivalent to the amount of casein in a pint of milk); and a pint of milk. The children were observed for one to three years and records of height and weight were kept. The group receiving milk showed the most rapid increases in height and weight, and remained relatively free from minor ailments and infections, which were fairly common among the rest of the boys. It

conspicuously failed to make a case against it in favour of the raw product. The marked lessening of the incidence of intestinal troubles and contagious diseases carried by raw milk through pasteurisation makes it hard to understand how opposition can longer be justified."—McCOLLUM, *Am. J. Pub. Health*, 9: 956, 1934.

was observed that the milk-fed boys, as compared with the remainder, were high-spirited and mischievous.

Height and Weight Increases during a Year in Six Groups receiving Various Supplements
(Cory Mann).

| Group | Increase in | |
|---|--------------|-----------------|
| | Weight (lb.) | Height (inches) |
| 61 children receiving the basic diet..... | 3.85 | 1.84 |
| 41 boys : basic diet plus milk | 6.98 | 2.63 |
| 41 boys : basic diet plus butter | 6.30 | 2.22 |
| 41 boys : basic diet plus margarine | 5.23 | 1.84 |
| 41 boys : basic diet plus watercress | 5.42 | — |
| 41 boys : basic diet plus sugar | — | 1.94 |

LEIGHTON and CLARK's [82] experiment related to 1,425 children aged from 5 to 13 years, in six centres in Scotland and Northern Ireland. The children belonged to average working-class homes, and their home diet was of the kind customary under such conditions. At each centre, four groups of children were selected and each group was given, in addition to the ordinary diet, one of the following : whole milk (about 500 c.c.) ; separated milk (about 500 c.c.) ; a biscuit ration of the same Calorie value as the separated milk ; no supplement at all (control group).

The experiment was continued for two years. At all ages, the children given milk show greater increases of height and weight than the biscuit-fed group or the controls.

Height and Weight Increments of Children given " Extra Milk " compared with those of Children receiving a Supplementary Biscuit Ration or no Dietary Supplement. (All age-groups.)

| | No. | Increase in one year | |
|----------------|-----|----------------------|--------------|
| | | Height (inches) | Weight (lb.) |
| Milk | 567 | 1.4585 | 3.5716 |
| Non-milk | 526 | 1.1810 | 2.4610 |

It is interesting to note that the children given separated milk did as well as children given whole milk.

One of the medical officers in charge of the investigation reported :

" In practically every case, it was noted that the children receiving milk showed, even where there was obviously poor maternal care, that sleekness peculiar to a well-nourished animal. Their hair had a glossy and bright

appearance. Their nails were smooth, resilient and looked as if polished. General alertness was common to all the children fed on milk. No difference could be detected with regard to these points between the children receiving milk, irrespective of the kind of milk. It was gathered from teachers and janitors that the children receiving milk were much more alert and very much more boisterous and difficult to control than the others. This latter fact was only too evident when they were waiting in small groups to be weighed."

A considerable number of similar experiments are on record. Mention may be made of that carried out by McCOLLUM, PARSONS and KALMBACH [83] at an orphanage for negro children in Maryland ; of G. LEIGHTON and P. L. MCKINLAY'S [84] experiment on 20,000 children in Scotland,¹ and of others in Japan [85], in France [86], and in New Zealand among Maori children [87].

In Paris, in 1931-32, an experiment was carried out by the Direction de l'Enseignement, the Office national d'Hygiène sociale and the Office du Lait on about 1,200 children, whole classes being taken without special selection. In the results, only those children were considered who had been taking milk regularly for six months : 400 grammes (250 for the smaller children) of pasteurised milk, boiled and allowed to cool, given in two portions, at 10 a.m. and 4 p.m.

| | | Increase in weight (kg.) | Percentage of weight | Difference in favour of milk | Increase in height % |
|----------------------------------|----------|--------------------------------|-------------------------|------------------------------------|----------------------------|
| <i>Elementary schools :</i> | | | | | |
| 6-12 years, 400 grammes of milk | | | | | |
| Boys | 169..... | 1.670 | 6.6 | 2.0 | 1.7 |
| Controls | 179..... | 1.190 | 4.6 | | |
| Girls | 205..... | 1.630 | 6.8 | 2.9 | 0.9 |
| Controls | 221..... | 0.990 | 3.9 | | |
| <i>Open-air school :</i> | | | | | |
| During 3½ months only. | | | | | |
| Boys and girls | 52..... | 1.920 | 8.3 | | |
| <i>Nursery School :</i> | | | | | |
| 3-6½ years, 250 grammes of milk. | | | | | |
| Boys and girls | 80..... | 1.330 | 8.9 | | |

The experiment shows the advantages of open-air schools in large towns.

¹ Fresh milk did not prove superior to pasteurised milk. The effect was the same on boys and girls of various ages ; the younger children did no better than the older children.

The benefit derived from milk was so manifest that, in many cases, the habit having been formed, the mothers continued the practice of giving milk twice daily, which had been found of such advantage during the children's school years.

Some of these investigations on the effect of "extra milk" in the diet of schoolchildren have been criticised on statistical grounds. One single unconfirmed experiment of this nature, however clear-cut its results, might fail to carry conviction. But the cumulative effect of so many experiments with similar results cannot fail to convince. Two conclusions emerge which are of importance in the field of public health. First the value, particularly to schoolchildren, of an abundant consumption of pure milk, and, secondly, the failure of diets usually regarded as "normal" to produce "optimal" health and well-being. If the schoolchildren concerned had been properly fed, no such dramatic results could have been obtained.

Sunshine and Ultra-Violet Rays.

The series of investigations on rickets and the relationship between vitamin D, ergosterol, ultra-violet light and the metabolism of calcium and phosphorus have confirmed and explained the observation of PALM, made as early as 1870, that rickets is a disease of the less sunny countries of the world. Lack of sunlight predisposes to rickets and osteomalacia; both diseases are seasonal in character, tending to appear during the winter months and to grow milder and disappear in summer. The victims of rickets are often those children who, in addition to consuming a diet deficient in vitamin D, live in circumstances which deprive them of abundant sunshine. Studies in osteomalacia in India and China, and in Vienna after the war, have shown that the disease tends to occur in malnourished women who spend most of their life indoors. In India, the habit of keeping purdah is an important factor in the ætiology of the disease.

Rays possessing anti-rachitic activity are present only at the limit of the sun's spectrum. The shortest rays which have been detected at the earth's surface in the middle of summer with the atmosphere at its clearest and the sun at its zenith are of the wavelength of 290 m μ . In December and February, in the northern hemisphere, the shortest observed waves have been given as of

wave-length 312 $m\mu$; from March till May, as of 301 $m\mu$. Since the shorter ultra-violet rays coming from the sun are absorbed by the ozone present in the upper atmosphere, the lowest limit as regards wave-length of rays reaching the earth rises as the obliquity of the sun's light increases. At Baltimore, U.S.A., the intensity of the sun's anti-rachitic radiations in July is fourteen times greater than their intensity in December [88].

Sunlight is necessary for the pregnant mother, the nursing mother, the infant and the child. This need for sunlight has led to the development of open spaces and playing-grounds in cities, and it is revolutionising school architecture. Schools are now built to catch as much of the sun as possible.¹ In countries of temperate climate, play-hours should, as suggested by CHICK, be arranged to coincide with the period round 'about noon, when sunshine contains its maximum anti-rachitic radiation [89].

Various types of glass transparent to ultra-violet rays are on the market. It would appear that effective anti-rachitic radiation through windows fitted with such types of glass is possible only in a small area quite close to the window. At a distance of 5 metres from the window, it would be necessary to remain for twenty hours in order to receive the same amount of irradiation as would be obtained by two minutes' exposure to direct sunlight. Glass permeable to ultra-violet rays might well prove of value as a cover for "boxes" in which infants could be placed in crèches. In order to permit transmission, such glass must be kept extremely clean.

Artificial sources of radiation must be handled with caution, since they emit rays of which little is known and which fall outside the solar spectrum.

In the large cities, smoke abatement is something more than a mere attempt to ease respiration. It is a means of rendering accessible the physiologically active ultra-violet rays, thereby contributing to the prevention of rickets.

¹ An interesting example can be seen at Suresnes Garden City, near Paris. Each classroom is double : one of the rooms (which is well lighted) is sheltered, for use during bad weather ; the other, the open-air classroom, is regarded as the normal classroom.

2. FOOD DEFICIENCY DISEASES.

The aim of public health nutrition work is to raise dietary and physical standards, and also to eliminate food deficiency diseases. While a generalised attack on malnutrition is also an attack on food deficiency disease, each of these may with advantage be regarded as representing a public health problem in itself, calling for special measures of prevention. We shall refer briefly here to a number of clearly recognised food deficiency diseases which cause widespread ill-health and disablement, and yet could be eliminated by technically very simple means. These diseases are to be numbered among the so-called social diseases. It must be remembered that for each outspoken and easily recognised case of food deficiency disease, there may be (as in tuberculosis) several latent cases.

Hypochromic Microcytic Anæmia.

Thirty years ago, one of the commonest diseases met with in general practice and out-patient departments was "chlorosis" or "green sickness", so called because the patient exhibited characteristic pallor with a greenish tint. The disease was confined to the female sex and was most frequently met with in working girls, particularly waitresses, shop assistants and domestic servants, between the ages of 15 and 25. The underlying cause of the pallor and weakness of the patient was recognised to be a very marked fall in the hæmoglobin level, with a relatively very small decrease in the erythrocyte count. The origin of the disease was ascribed to many causes, including constipation, lack of fresh air and exercise, and the commencement of menstruation. It could be effectively treated by large doses of iron.

It is now very widely recognised that the fundamental cause of "chlorosis" was the consumption of a diet deficient in iron; other factors, such as unhygienic surroundings, played a subsidiary rôle. Many of the victims of the disease lived on a diet composed of white bread, margarine, potatoes and tea. The total disappearance of chlorosis in the space of a few years (in England) may be ascribed to the raising of wages and living standards and the dissemination of knowledge about the relation between nutrition and health.

The diet of the modern shop-girl may not be perfect, but it is greatly superior to that of her predecessor of thirty years ago.¹

MACKAY has shown that 50% of infants in the East End of London develop some degree of nutritional anæmia from the fourth month onward. The liver at birth contains sufficient iron to satisfy requirements for three or four months, but after this time, if the diet is deficient in iron, anæmia tends to develop. Milk is a food deficient in iron, and infants fed exclusively on milk for a prolonged period are likely to become anæmic; the danger is greater if they are fed exclusively on cow's milk or the milk of an anæmic mother. Children of anæmic mothers show a satisfactory hæmoglobin level at birth, but it appears that their iron stores may be below normal. A great deal of infantile ill-health seems to be associated with anæmia of various degrees, for Mackay observed that the morbidity rate from colds, sore throats, pneumonia and other conditions was 50% lower in a group of London infants receiving iron medication than in an untreated control group.

Nutritional anæmia of infants may be exceptionally common in London, but it may, on the other hand, be a more serious public health problem in other great cities than is commonly realised. Prophylaxis is simple. The disease may be diminished by dietetic treatment of the pregnant and nursing mothers, by providing infants with prophylactic iron from the third or fourth month onward, or by feeding them on a mixed diet before anæmia has had time to develop.

Recent observations in Aberdeen [90] suggest that hypochromic microcytic anemia in adult women may be hypoglobular and that it is an extremely important, if hitherto neglected, problem of public health. Of 1,000 women belonging to the poorer classes in Aberdeen, 50% showed some degree of anæmia, 15% being severely anæmic. The sufferers were for the most part women in the child-bearing period, subject to loss of blood during labour and in the puerperium, and to menorrhagia between pregnancies, who at the same time consumed a diet deficient in iron—i.e., a diet rich in

¹ "This extraordinary victory of nutrition over disease", DAVIDSON and LEITCH remark, "presents a perfect example of preventive medicine and deserves widespread recognition. What has been achieved in the nutritional anæmia of adolescents can most certainly be accomplished in the similar anæmias associated with infancy and adult life." (*Nutrition Abstracts and Reviews*, 4 : 901, 1934.)

starchy foods and containing little meat and green vegetables. Many of these women considered their condition of chronic ill-health and wretchedness as normal and accepted it with resignation.

Anæmia of this nature can be more rapidly and effectively treated by iron medication than by an iron-rich diet, because the former method ensures a larger iron intake.¹ In the prevention of anæmia in adult women, the importance of a diet rich in iron may be stressed.

WERDINIUS [91] has shown that anæmia in women, associated with a defective diet, is common in North Sweden, and in all probability this deficiency disease is common in other parts of the world.

There appears to be at least one type of microcytic hyperchromic anæmia which may justifiably be described as a disease due to dietary deficiency—pernicious anæmia of pregnancy. Pernicious anæmia, as it occurs in Western civilisation, has been shown to be due to defective production of a specific enzyme, an “intrinsic factor” in gastric juice which interacts with an “extrinsic factor” in food to produce the specific “anti-anæmic principle”. Treatment in this disease consists either in supplying the “anti-anæmic principle” (*i.e.*, by liver therapy) or in giving gastric tissue products which supply the intrinsic factor and enable the patient to manufacture the anti-anæmic principle for himself. The work of WILLS [92] suggests that a type of pernicious anæmia occurring among Indian women, particularly in pregnancy, may be due to the consumption of a diet containing insufficiency of the extrinsic factor, which appears to be found in association with protein. Pernicious anæmia of pregnancy is clearly an important addition to the roll of food deficiency diseases.

Rickets.

Brief mention may be made here of some public health problems in connection with the prophylaxis and treatment of rickets. Interest in this disease has now shifted from the scientific to the public health problem. As a result of intensive work by many scientific workers in many countries, the scientific problem of rickets has been triumphantly elucidated, vitamin D has been

¹ It has been observed that sulphate, carbonate and chloride of iron are more effective than iron and ammonium citrate, probably because more ferrous ions are liberated from the former in the intestine.

isolated in pure form, and the public health worker has been presented with a large variety of effective weapons to carry on the fight against the disease.

During recent years, there has been a marked fall in the incidence of rickets. But, by its nature, the disease cannot be wiped out and forgotten as certain infectious diseases have been wiped out and almost forgotten in the advance of civilisation ; a permanent and untiring effort of prevention is necessary. It is clear that infants in the temperate zone, even infants living under the best sanitary conditions, tend to develop rickets unless specific means are taken to prevent it. Even breast-fed infants may contract the disease, though in a milder form than artificially fed infants. Breast and cow's milk are poorly endowed with vitamin D, and in the temperate zone there is not enough sunlight at all seasons of the year to provide sufficiency of vitamin D via the skin.

The multiplicity of anti-rachitic agencies adds to the responsibilities of public health officials. We may quote here from a recent article by that distinguished investigator, the late A. F. Hess :

“ There are, in all, five reliable and well-established anti-rachitics, each one of which represents a distinct and different pharmacologic point of view. The first to be established was cod-liver oil, a natural product ; the second to be introduced was direct irradiation of the body by means of ultra-violet energy ; the third was irradiated food, particularly milk, activated by exposure to ultra-violet radiations ; the fourth, an irradiated basic substance, ergosterol, extracted from yeast ; the fifth, representing still another method, was yeast milk, a biologic product endowed with anti-rachitic potency as a result of feeding irradiated yeast to the cow (or by irradiating the cow directly). In addition to these five established agents, there are numerous others which consist of various modifications or combinations ; for example, the addition of a concentrate of cod-liver oil to milk, or of viosterol to cod-liver oil. Whether one or the other of these several anti-rachitics should be adopted in the campaign to eradicate rickets from the community will depend not so much on their efficacy in preventing rickets as on their availability, which involves their cost

to the community, the readiness with which they are accepted by the public, their palatability and other non-medical considerations. " [93]

There is a tendency in the United States of America to-day to regard irradiated fluid milk as the most valuable anti-rachitic agent (from a public health point of view). If mothers can be taught to give their children such milk, rickets is automatically eliminated without further effort on anyone's part, while anti-rachitic measures involving daily dosing require more active supervision.

In Europe, cod-liver oil, which has the advantage of familiarity and of containing vitamin A, still holds its own, although it is less potent in vitamin D than artificial preparations, so that a larger preventive or curative dosage is required, and not all infants can be persuaded to take it. As curative agents, there seems little doubt that preparations of irradiated ergosterol are the most effective.

Whatever preventive method or methods are ultimately found to be the most convenient, active public health effort will be required for their supervision. If, for example, vitamin D is supplied through the medium of liquid milk, the purity of the milk must be controlled. Perhaps the most important public health activity in this field is the control of all preparations which purport to contain vitamin D, in order to ensure their vitamin D potency. The establishment of widely accepted national vitamin D units, and later of an international vitamin D unit, has simplified this problem, but unexpected difficulties have arisen. The international vitamin D unit is defined as the anti-rachitic activity of 1 milligramme of a standard solution of irradiated ergosterol, and the number of international units in a test substance is estimated by comparing its activity with that of the standard, the rat being the experimental animal employed. It appears that the concentration of international (rat) units in different preparations is not a constant criterion of their value in preventing and curing human rickets. According to HESS and LEWIS, 50 to 56 international (rat) units daily in the form of irradiated milk will prevent rickets. To be equally effective, " yeast milk " (*i.e.*, milk from cattle fed with irradiated yeast) must supply not less than 90 units, cod-liver oil

not less than 250 units, and viosterol (a preparation of irradiated ergosterol) from 600 to 800 units. The clinical curative or protective anti-rachitic dose cannot therefore be generally established in terms of rat units ; it can, however, be established in terms of the number of rat units in various anti-rachitic agents. It is clear that the rat unit can retain its usefulness only if its limitations are widely understood, and that there is great scope here for difficulty and confusion. A committee of the American Public Health Association [94] has recently suggested the establishment of a " clinical unit " for different vitamin D products, which should not be difficult if it can be shown that there is a constant relation between the content in rat units of each *type* of anti-rachitic agent and its clinical effect.

TONNEY and DEYOUNG [95] have underlined the importance of smoke eradication in order to ensure urban dwellers a maximum of ultra-violet light. In our great cities, smoke shuts off a very considerable proportion of the actinic rays of the sun. The discovery that vitamin D can be produced by the action of ultra-violet light on the skin lends the question of smoke abatement a new importance in the sphere of public health.

Rickets is probably the food deficiency disease of most interest to the public health worker in temperate countries. The available data about the prevalence of the disease throughout the world were collected by A. F. HESS and given in his book " Rickets, Osteomalacia and Tetany ", published in 1929. In 1921, HESS and UNGER wrote that " rickets is the most common nutritional disease occurring among the children of the temperate zone. Fully three-fourths of the infants in the great cities, such as New York, show rachitic signs of some degree." The same authors reported in 1917 that *almost all* the infants in the negro community in New York City, whether breast-fed or bottle-fed, were found to have rickets, and the same was true, to a slightly less extent, of the Italian districts in the city. In New Haven, Connecticut, ELIOT [96] found that, in 1923, 83% of infants showed evidence of rickets. In the early years of the present century, rickets was wellnigh universal among the children of the poor in the cities and towns of England. According to MARFAN [97], writing in 1912, in Paris one out of every two infants showed rachitic symptoms. There is abundant testimony as to the high incidence of rickets in Central

Europe at the same period and of its accentuation as a result of food shortage during and after the war. Recently, KLOSTER [98] has observed that, in a number of villages in the north of Norway, within the Arctic Circle, signs of rickets were present in 163 out of 376 children under 7 years of age (43.4%). The incidence of rickets was highest in a relatively prosperous village inhabited by a population of Finnish origin, who consumed more milk and meat than their less prosperous neighbours, but much less fresh fish, fish liver and cod-liver oil. WILSON [99] has shown that rickets is common in children in certain districts of Northern India, and the same appears to be true of Northern China and Manchuria [100]. In both Northern India and Northern China, adult rickets, or osteomalacia, represents a serious public health problem. While rickets is, in general, rare in countries which enjoy abundant sunshine, it is by no means unknown, particularly in cities, among ill-fed infants reared indoors; thus, Jean BAPTISTE [101] has noted its occurrence in the city of Algiers, particularly among the indigenous population practising "purdah".

As a result of the practical application of scientific discoveries, severe rickets has recently become rarer in Europe and North America. The public health problem presented by rickets, however, is still far from solved.¹

Diet and the Teeth.

It has been shown by M. MELLANBY and her associates that the teeth, like the bones, require for their proper formation adequate supplies of calcium and phosphorus and an ample provision of vitamin D. Further, a tooth which is ill formed as a result of vitamin D deficiency is more prone to decay than a structurally perfect tooth, so that children who are liberally supplied with

¹ "Rickets is still one of the greatest social evils of this country [England], in spite of the fact that its ætiology and methods of prevention are known. It is probably true that, in London, there has been a great diminution in the number of gross rachitic defects in the young during recent years, but in the industrial towns of the Midlands and North, the disease is still rampant. A rickets clinic has, in recent years, been established in Sheffield, and there are never fewer than 500 children attending for treatment." (MELLANBY, E., *Brit. Med. J.*, II: 865, 1932.)

vitamin D during the period of tooth formation are less likely to suffer from dental caries in later life than children not so supplied. There is also evidence that abundant provision of vitamin D not only checks caries by producing well-formed teeth ; independently of structure, the resistance of teeth to decay is directly influenced by the character of the diet ; further, suitable dietary measures can assist healing in teeth already carious.

Not all are agreed that vitamin D is the most important single corrective factor in connection with the immunity of the teeth to caries. In a recent editorial in the *American Journal of Public Health* [102], the remark is made that " there are almost as many opinions on the causation and prevention of dental caries as there are workers on the subject ". Theories that a specific organism is concerned, or that the consistency of the food is of paramount importance, are still widely held. Nevertheless, the idea that there is a close relation between dental caries and dietary deficiency is steadily gaining ground, and must influence the future direction of public health activity in connection with the prevention of dental decay.

We must remember that, in most countries, the problem of providing adequate dental treatment in schools for already existing caries is an insoluble one, and that for this reason it behoves public health authorities to give the closest attention to other possible methods of combating the disease.¹

If we accept the theory that dental caries is related to dietary defects, and in particular to deficiency of vitamin D, then a new orientation of public health effort in this field is indicated. Less emphasis must be placed on oral hygiene, and more on diet. While encouraging the use of the toothbrush for social and æsthetic reasons, we may, at the same time, reflect that most of the sound teeth in the world are in the mouths of people who have never seen a tooth-

¹ In the preface to Mrs. Mellanby's latest publication on the subject of diet and teeth, we find the following statement :

" The very novelty of the situation created by this work has caused it to be subjected to vigorous criticism and often to disbelief. This can be readily understood, for it involves the mental contortion of those interested in the problem of dental decay from the firmly established conception of oral hygiene, with its emphasis on the toothbrush and dental antiseptics, to a new view of the importance of correct feeding of the pregnant and nursing woman, of the growing child, and, indeed, of people of all ages. " *Med. Res. Council, Special Report Series, No. 191, 1934.*)

brush in their lives. Dental caries may be attacked by improving the diet of expectant and nursing mothers, infants and growing children, particularly in respect of its content of calcium, phosphorus and vitamin D.

It would be cheaper to supply schoolchildren regularly with vitamin D in some form than to supply them with dental treatment—treatment which, for the most part, consists in an attempt to repair the ravages of already existent caries. This is a question which merits the closest attention on the part of public health authorities. A number of large-scale experiments have indicated the possibility of preventing dental caries by dietary means [103], but more are required. We may hope that such experiments may shortly be undertaken in a number of countries.

The following table, taken from M. MELLANBY [104], indicates the extent of dental caries in Europe :

Dental Caries in Europeans.

| Source | Number of individuals examined | Percentage of individuals with carious teeth |
|--|--------------------------------|--|
| British Dental Association investigation, 1891-1897 | 12,318 | 84.0 |
| Birmingham schoolchildren (Richards)..... | 1,424 | 94.7 |
| Kettering schoolchildren (Leyton) | 5,724 | 93.0 |
| English Public Schools (large) | 560 | 87.0 |
| Cambridge Dental Clinic (Cunningham) | 1,403 | 96.5 |
| Shropshire Poor Law cases (S.M.O., Salop) .. | 7,374 | 95.9 |
| Baden and Hamburg residents (Rose) | .. | 98.7 |
| North German schoolchildren (Schleswig-Holstein Dent. Assn.) | 19,725 | 95.0 |
| Würzburg children (Berlin) | .. | 83.0 |
| Hungarian children (Unghrari) | .. | 87.2 |
| Northern Italy : Milano | .. | 92.0 |
| Valle di Non | .. | 82.7 |
| Torino | .. | 54.0 |
| Genova | .. | 79.1 |
| Brescia | .. | 46.0 |
| Central Italy : Bologna | .. | 67.7 |
| Livorno | .. | 55.0 |
| Siena | .. | 89.1 |
| Rieti | .. | 64.0 |
| Parma | .. | 85.0 |
| Ravenna | .. | 70.0 |
| Roma | .. | 50.0 |
| Finland (children) | 5,903 | 95.3 |

Pellagra.

Italian physicians have long envisaged pellagra as a public health problem open to attack on a large scale by dietary measures [105]. Public health measures against pellagra in Italy took shape during the second half of last century, and were crystallised in a law passed in 1902, their basis being the theory that pellagra is due to the excessive consumption of spoiled maize. The sale of spoiled maize as human food was strictly prohibited, and local authorities were obliged to acquire public desiccators and municipal reservoirs in which maize could be kept in good condition. In 1910, there were 546 public maize desiccators in Italy. Rural bakeries were set up, the purpose of which was the furnishing of cheap wheat bread to those whose staple food was maize ; by 1916, there were 1,300 of these bakeries. Charitable kitchens of two kinds were established. One kind, which supplied soup, and sometimes bread and meat, free, or at very low prices, during the whole year or before and during the pellagra season, was designed for a generalised preventive action ; the other kind supplied bread free to persons in the initial stage of pellagra. In 1910, there were 127 of the former, 533 of the latter. As a result of the 1902 Ordinance, "pellagrosari", or pellagra hospitals, and asylums for the children of pellagrins were founded.

Pellagra is a comparatively rare disease in modern Italy, whether on account of public health measures of the kind outlined, or because of a general rise in the standard of living involving a more varied diet. According to SCHMIDT-LEMBERG [106], a ten-year "nutrition plan", having as its object an increase in the consumption of milk and fish, is in operation in Italy and has already achieved very appreciable results. A further development of the plan is the encouragement of vegetable production. Though not specially designed to eliminate the possibility of a widespread recurrence of pellagra in Italy, the "ten-year plan" will, in fact, operate in this direction, for milk, fish and green vegetables are valuable pellagra preventive foods.

Pellagra in Italy (1896-1928).

| Year | Deaths from pellagra | | Year | Deaths from pellagra | |
|--------------|----------------------|------------------|------|----------------------|------------------|
| | Total number | Rate per 100,000 | | Total number | Rate per 100,000 |
| 1896-1900 | 3,426 | 10.7 | 1921 | 222 | 0.6 |
| 1901-1905 | 2,563 | 7.8 | 1922 | 198 | 0.5 |
| 1906-1910 | 1,545 | 4.5 | 1923 | 138 | 0.4 |
| 1911-1915 | 956 | 2.7 | 1924 | 158 | 0.4 |
| 1916 | 793 | 2.2 | 1925 | 108 | 0.3 |
| 1917 | 691 | 1.9 | 1926 | 108 | 0.3 |
| 1918 | 627 | 1.8 | 1927 | 96 | 0.2 |
| 1919 | 537 | 1.5 | 1928 | 85 | 0.2 |
| 1920 | 331 | 0.9 | | | |

The work of the United States Public Health Service, carried out under the inspiration of Joseph GOLDBERGER, has simplified the problem of pellagra prevention. It has been shown that pellagra can be prevented by the adequate consumption of certain foods, which include lean meat and fish, milk, some green vegetables, peas, peanut flour, yeast and wheat germ. In the Southern United States, anti-pellagra work takes the form of spreading knowledge of the relation between diet and pellagra, and in particular knowledge of the foods which will prevent the disease. Efforts are made to encourage the growing of vegetables ; the Extension Service in Home Agriculture and Home Economics, to which reference has been made in another section, has played a part in this activity. A number of State Boards of Health have distributed brewers' yeast to potential pellagrins, but it is clear that such a measure is only palliative, and that the aim of pellagra preventive work should be to bring about more radical and permanent dietary alterations.

Official figures of death from pellagra in the United States of America during the years 1922-1932 are as follows :

Deaths from Pellagra in the United States of America.

| Year | Actual figures | Rate per 100,000 inhabitants |
|----------------|----------------|------------------------------|
| 1922 | 2,640 | 2.8 |
| 1923 | 2,352 | 2.4 |
| 1924 | 2,347 | 2.3 |
| 1925 | 3,344 | 3.2 |
| 1926 | 3,854 | 3.7 |
| 1927 | 5,418 | 5.0 |

| Year | Actual figures | Rate per 100,000 inhabitants |
|-----------------------------|---|------------------------------|
| 1928 | 6,969 | 6.1 |
| 1929 | 6,703 | 5.8 |
| 1930 | 6,332 | 5.3 |
| 1931 | 5,090 | 4.3 |
| 1932 | 3,691 | 3.1 |
| 1933 | 3,955 | 3.1 |
| 1930 in six southern States | Alabama Arkansas North and South Carolina Georgia Mississippi | 29.4 |

It will be noted that the death rate from pellagra reached its peak in 1928 and that since then there has been a steady decline. This is the more encouraging in that the years 1929-1932 were years of economic depression and poverty. It is, of course, impossible to say how far the diminution in the pellagra death rate has been due to public health educational effort. WHEELER and SEBRELL [107] have suggested that the fall in the price of cotton, which makes the small farmer devote more of his land to growing vegetables and become less dependent on the local stores for his food, may have played a notable part.

Pellagra is extremely common in Roumania. In a number of villages in Moldavia, familiar to one of us (W. R. A.), some 5 to 6% of the population suffers from pellagra every spring. In the following table are presented figures supplied by the Roumanian public health authorities, giving the mortality from pellagra in Roumania during the years 1930-1933. These figures certainly represent an understatement, for many deaths actually due to pellagra, which first invalidated the patient, are ascribed to terminal causes.

Pellagra in Roumania, 1930-1933.

| | Deaths from pellagra | Death rate per 100,000 |
|------------|----------------------|------------------------|
| 1930 | 2,087 | 11.7 |
| 1931 | 2,075 | 11.4 |
| 1932 | 1,964 | 10.7 |
| 1933 | 2,800 | 15.0 |

The recorded mortality rate per 100,000 from pellagra in 1930 in six American States (North Carolina, South Carolina, Georgia, Alabama, Mississippi and Arkansas) was 29.4. In Moldavia and Oltenia, the two Roumanian provinces which suffer most severely

from pellagra, the death rates from pellagra in the same year were recorded as 19 and 27.7 respectively.

Pellagra is widespread in Yugoslavia, South Russia, Turkestan, Egypt, and certain of the West Indian islands.

Any campaign to eradicate pellagra must be of long duration, for poor and ignorant people cannot have their dietary habits changed overnight. The continued widespread existence, in many parts of the world, of a disease which can be prevented by simple dietary means illustrates the necessity of developing public health work in the field of nutrition.

Beri-beri.

Beri-beri is exceedingly common throughout Eastern Asia, including Japan, China, the Malay Peninsula, the East Indies and the Philippines. It has been reported from all parts of Africa and from Newfoundland and Labrador. It is a serious problem in Brazil, Venezuela, Panama, the West Indies and the Antilles.

Deaths from Beri-beri in Japan and Manila (Philippines), 1928-1932.

| Year | Population (in millions) | JAPAN | | | | MANILA | | | | |
|------|-----------------------------|--------------|---------------------------------|------------------------|--------------------------|----------------------------|--------------|---------------------------------|------------------------|--------------------------|
| | | Total deaths | Rate per 100,000 inhabitants | Deaths under 1 year | Rate per 1,000 births | Population (in 100,000) | Total deaths | Rate per 100,000 inhabitants | Deaths under 1 year | Rate per 1,000 births |
| 1928 | 62.522 | 19,036 | 30.4 | 9,582 | 4.5 | 325 | 368 | 113.2 | 340 | 21.6 |
| 1929 | 63.478 | 15,456 | 24.3 | 8,267 | 4.0 | 329 | 552 | 167.8 | 519 | 32.2 |
| 1930 | 64.450 | 15,419 | 23.9 | 7,897 | 3.8 | 333 | 326 | 97.9 | 286 | 17.2 |
| 1931 | 65.366 | 17,767 | 21.2 | 9,398 | 4.5 | 337 | 196 | 58.2 | 173 | 9.1 |
| 1932 | 66.296 | 11,805 | 17.8 | 6,834 | 3.1 | 341 | 222 | 65.1 | 200 | 10.1 |

Control of Beri-beri in the East.—It has been shown, in a long series of investigations, that beri-beri can be largely prevented by the consumption of unmilled or slightly milled rice. The beri-beri problem in the tropics should not, however, be regarded as being solely a question of polished or unpolished rice. McCARRISON has observed that the vitamin B₁ content of unmilled rice may, by washing, be reduced to that of milled rice, and under-milled rice

of poor commercial quality may require vigorous washing before it is fit for consumption. Human beings rarely live upon rice alone, and the presence of other foods in the diet prevents an absolute correlation between the incidence of beri-beri and the vitamin B₁ content of rice.

The anti-neuritic vitamin resides mainly in the germ and pericarp of the rice grain. A number of methods of testing the vitamin B₁ content of rice have been proposed, in which the amount of germ and pericarp present is used as the criterion. Of these, the P₂O₅ test, depending on the fact that a large proportion of the total phosphorus content of the grain is found in its integuments, is the most familiar. In 1910, FRASER and STANTON [108] proposed that rice containing less than 0.40% of P₂O₅ should be regarded as "dangerous" rice—*i.e.*, rice liable to cause beri-beri.

The Far Eastern Association of Tropical Medicine, at its fourth Congress, held in Batavia in 1921, passed the following resolutions:

Whereas beri-beri is known to prevail extensively in the following countries:

Dutch East Indies, Japan, Malaya, Siam, Borneo, Philippines, Indo-China, Hong-Kong, China and other territories in the Far East;

Whereas there is enormous annual loss of human life, with corresponding invalidism and disability, due to deficient diet in the above countries, and whereas the deficiency is mainly due to the over-milling of rice, which removes a vital part of the essential food factors, and whereas nothing has been put forward in the last ten years which proves that beri-beri cannot be controlled by substituting under-milled for polished rice in countries in which rice is a staple article of diet;

Whereas it has been demonstrated by Fraser and Stanton, and others, that a satisfactory standard of milling is the presence of a minimum of 4% of P₂O₅ in rice:

Therefore be it resolved that this fourth Congress of the Far Eastern Association of Tropical Medicine considers it urgently desirable that the Governments concerned should take action to discourage the use of rice which is below the standard; therefore be it further resolved that, with a view to taking united action, the Far Eastern Association of Tropical Medicine recommends the appointment of a Commission, to which each country is asked to send a delegate, which shall put forward recommendations as to the best methods of bringing beri-beri under control.

As a result of the resolution, official representatives of the various Governments named attended the next Congress of the Far Eastern Association of Tropical Medicine, held in Singapore in 1923. At

this meeting, concrete proposals with regard to beri-beri control were submitted by the Philippine delegation. The official representatives, however, all declared that *international* legislative action designed to discourage or prohibit the use of highly milled rice was, for the time being, impossible. Grounds for objection included the following :

- (a) Since all the facts about the ætiology of beri-beri have not yet been discovered, legislation would be premature ;
- (b) Unmilled rice cannot be recommended for general use, because of its unpleasant taste and because it deteriorates more rapidly than milled rice ;
- (c) A reliable test for distinguishing rice liable to cause beri-beri is essential as a basis for legislation. The P_2O_5 test is not reliable ;
- (d) The prohibition of highly milled rice in Far Eastern countries would meet with great resistance from the rice trade, which, in general, is organised to produce that article.

The Association, in accepting the adverse decision of the Government representatives, recommended further research into the following questions :

- (a) The standardisation of rice ;
- (b) The effects of transport and storage on rice ;
- (c) Economic considerations.

It emphasised the desirability of discouraging the excessive use of highly milled rice by native populations, and the need for a vigorous educational campaign against beri-beri.

At the next meeting of the Far Eastern Association of Tropical Medicine (Tokio, 1925), the problem of the international control of beri-beri was fully discussed by DE LANGEN. De Langen showed that the P_2O_5 test is unreliable as an indication of the vitamin B_1 content of rice, for several reasons ; the same objections apply to any method of estimating vitamin content by the amount of pericarp present, such as, for example, SAIKI's method of staining with phenolated fuchsin. He further stated that unmilled or " silver-skin " rice would keep only for a month, and is therefore an unsatisfactory article for trade ; rice in the husk (paddy) and highly milled rice, on the other hand, would keep for several years. Beri-beri

in the East does not commonly occur among those who grow their own rice and mill it partially by primitive means ; it is a disease which follows the consumption of factory-milled rice imported in the highly milled state. As a possible solution of the beri-beri problem, he proposed an international agreement that only rice in the husk should be imported, which could subsequently be milled locally to a slight degree and immediately consumed.

Mention may be made of another possible solution of the beri-beri problem, in so far as this is associated with the consumption of highly milled rice. It has been shown by ΑΥΚΡΟΥΔ [109] that, when unmilled rice is steamed or parboiled, vitamin B₁ diffuses throughout the grain, so that parboiled rice retains the vitamin even when highly milled.

It is difficult to persuade native communities to discard the more attractive and palatable polished rice in favour of an unmilled variety ; prejudice might, however, be overcome by the substitution of milled rice of good quality and appearance, previously parboiled.

Up to the present, no serious attempt has been made to attack beri-beri on a large scale by legislative measures. The problem of the international control of beri-beri, while highly complex, is nevertheless worthy of further study.

3. COLLECTIVE FEEDING.

“ Meals in common ” have probably existed in all historical eras and among all peoples. We may roughly distinguish three kinds in existence to-day :

(1) Collective feeding in residential institutions, public or private, civil or religious ; in armies and navies ; in “ boarding ” establishments of all kinds—*e.g.*, hotels ; in hospitals, sanatoria, homes for the aged, asylums, prisons, etc. ; in educational establishments where pupils reside.

(2) Meals given as relief in times of unemployment and economic distress to unemployed, or to impoverished students and artists, needy intellectual workers, etc.

(3) Mass-feeding organised by industry or the State in accordance with economic and physiological principles.

Feeding in Institutions.

The task of ensuring that the diet provided in residential institutions is physiologically satisfactory is one which falls within the province of health authorities. Whether such authorities exercise direct administrative control, or simply act in an advisory capacity, will depend on the laws and customs of each country. A special organisation or department for such purposes is scarcely necessary; public health administrations could readily add the supervision of institutional diets to their existing activities. Naval and military health services, hospital services and school medical services are particularly concerned with this question, and it would be easy to arrange that such services should include men or women who have special knowledge of dietetics. A useful new departure in most countries would be the employment by public health authorities of subordinate workers—such as the “nutritionists” and “dietitians”, whose activities we have already described (Chap. V)—to develop the practical side of nutrition work. In certain countries, for example, hospital dietitians, in collaboration with the medical staff, supervise the feeding of staff and patients, prepare special diets, conduct out-patient clinics, etc.

Mention might be made, as an example of action by the central authorities, of the instructions of the British Ministry of Health on the principles to be observed in the feeding of assisted children [110] and the system applied in Denmark (Annex 2).

Meals for the Relief of Unemployment and Distress.

Food relief given in periods of economic depression is usually an extension of similar relief given in normal times. In France, the so-called “soupes populaires” and “fourneaux économiques” have long furnished meals to the needy, and similar organisations have existed in other countries. The recent period of economic distress has simply increased the number of applicants for this form of relief, and has led to inclusion amongst these of persons drawn from social classes which hitherto have never, or almost never, had recourse to charitable assistance: members of the intelligentsia, artists, students, etc. It is to be regretted that fuller information does not exist on the question of food relief during

the economic crisis ; the experience gained might be useful as a guide in " normal " times.

As an example of mass-feeding in Germany, that organised in Cologne during the winter 1932-33 may be cited. The *Caritas* Association lent its kitchens to volunteers who prepared each day meals for 20,000 persons, served in 67 places. Meals costing 20 and 25 pf. were provided for 15 and 20 pf. respectively. A card entitling the bearer to 6 meals cost those living on relief RM. 0.60 or 1.20, according to the nature of the food provided. Persons not in receipt of relief, but in want, could purchase 6 meal tickets for RM. 1.80. The cheapest meal consisted of a litre of soup or stew, half of which could be taken home ; the demand for the more varied meal for 20 pf. (6 tickets for RM. 1.20) was considerably greater. Weekly schedules of the meals provided through the organisation were distributed to housewives in the hope that they would learn therefrom variety in catering methods. Simultaneously, in Cologne, special diets were distributed from hospital kitchens to indigent patients undergoing dietary treatment. Charitable donations enabled the *Nothilfe* and the Public Assistance authorities in the same city to provide a midday meal to 1,000 schoolchildren during winter and spring, the meal being prepared in kitchens situated near the schools. During the summer holidays, a portable midday meal was provided every second day for 15,000 children (one-fifth of the entire school population) spending the whole day in the country [111].

JUSATZ and WEISE [112] have described a system for the provision of cheap meals to students in a university town (Marburg) at a time when 5 to 10% of the students could afford only one warm meal a day and were going without breakfast. At midday, students could buy for RM. 0.58 a meal yielding 1,200 to 1,300 Calories. Supper was available for RM. 0.35. Thick nutritive soups, which contain a variety of food factors, are rich in fat and give a feeling of satiety, were found to be very suitable for large-scale feeding.

MACKENZIE [113] has described the various systems designed to combat malnutrition among the poor in Great Britain—systems which were in existence long before the so-called economic depression and were found to be capable of extension to meet the demands imposed by growing unemployment. He mentions the provision of meals through central kitchens to schoolchildren and to pregnant

and nursing mothers. The central kitchens at Glasgow, for example, supplied (1932) food for necessitous children attending ordinary schools at 48 centres, and special schools for physically and mentally defective children at 26 centres. Meals are delivered in some cities by special lorries owned by the local authorities, in others by milk vans (free in the middle of the day) or by cars used for the transport of defective children to school. The cost of each meal provided by the Newcastle-upon-Tyne Education Committee in 1932 was 3.2*d.*, the cost of foodstuffs being 1.65*d.*, of preparation 0.5*d.*, of service 0.72*d.*, of transport 0.24*d.* Pregnant and nursing women are provided, not only with milk, but also with meals ; in Birmingham, meals for mothers are prepared in a central kitchen and sent by motor-car, in special containers, to 7 child welfare centres situated in poor areas, where they are reheated and served under the supervision of health visitors. During 1932, in Birmingham, 26,000 dinners were served to expectant and nursing mothers, who paid 2*d.* for a meal costing 6.8*d.* Every attempt is made to vary menus, which always include fruit and fresh vegetables when these are available at reasonable prices.

In Birmingham, the active "Citizens' Society" has founded a number of canteens in occupational centres, both centres and canteens being run by the unemployed themselves. Food is bought wholesale and sold at 1-2*d.* per meal.

Systematic Mass-feeding other than that organised for the Relief of Distress.

We are but slowly realising that the rapid development of industrialisation necessitates a series of social adaptations which, in practice, tend to take place more slowly. It is only within recent years, for example, that the new housing problems created by industrialisation have been clearly envisaged. Allusion has already been made to the breaking-up of traditional dietary customs, based on the family, as a result of the demands of the office and the factory. Distances between the place of employment and the home tend to grow greater. The employment of women in factories and offices is on the increase. Employers, aware that output is influenced by the diet of the employee, are disposed to facilitate the provision of meals, organised on a "rational" basis, at the

place of work itself. Members of the working-classes, when guided only by their inclinations, often consume a diet far removed from the physiological ideal. Poverty and ignorance, sometimes combined with a tendency towards alcoholism, may exercise a baneful effect on dietary habits.

A good meal prepared and consumed at home may be ideal, and at some future date new dietary customs, based on the home, may be evolved. But, meanwhile, civilised humanity is tending more and more to consume meals prepared in restaurants rather than in private kitchens, and " collective feeding ", in general, is becoming more common. Properly organised, mass-feeding may promote health and well-being, and at the same time lead to economy of time and money. There is, indeed, little point in discussing whether the modern tendency to consume meals away from home is desirable or not, since it already exists and is rapidly growing.

Factory canteens often develop into factory restaurants. It would be interesting to study the factory canteen or restaurant from a physiological and psychological point of view. Such questions as the following would be worthy of investigation : the influence of the nature of work on choice of dishes ; the influence of season and temperature ; the variety of food supplied ; the influence of the traditional dietary habits of the country on the type of meal provided ; administration, whether this is wholly or partly in the hands of the workers. As the result of a series of such enquiries, a useful " dietary handbook " for factories might be drawn up.

In general, the organisation of mass-feeding in industrial concerns is profitable to employers. There is less interruption of work in the middle of the day, and output in the afternoon tends to be increased. In all probability, the provision of a good meal to employees lowers invalidity rates. Employees themselves profit, in that they obtain good meals at a low price ; the hot meal provided by the factory may be as cheap as sandwiches brought from home. The number of hours spent away from home may be reduced. Profits obtained in the restaurant may be paid into workmen's funds. Intestinal troubles are less frequent.

In some commercial organisations which provide meals for employees, " extra " milk ($\frac{1}{2}$ litre) and fresh butter are supplied to women and young girls with a tendency to anæmia. It appears

that, in general, manual workers display a preference for foods rich in animal protein.

We have visited, in France, restaurants in big shops which have been created for the benefit of the employees, and which provide 3,000-5,000 meals per day. In France, there exist sound dietary traditions which influence both those who consume and those who prepare restaurant meals, and these traditions help to ensure that mass-feeding is organised on a reasonably satisfactory, if empiric, basis. But such traditions do not exist everywhere, and it would often be advantageous if catering in employees' restaurants were organised in accordance with the principles of modern dietetics. In this connection, the services of a competent dietitian are invaluable. Through her, the use of the "protective" foods can be encouraged and the consumption of less valuable tinned and preserved foods decreased.

The same remarks may be applied to the "bars" and "cafeteria" which are often found to-day connected with commercial organisations. American in origin, they have spread to Europe. Sometimes, they are run purely for profit; in other cases, they are established by employers for the benefit of their staffs and managed so as to provide food of good quality at minimum prices. The habit of consuming *all* meals in such places is scarcely commendable, but they may provide a good midday meal, the evening meal being taken at home. They are particularly convenient for solitary workers, bachelors and widowers. It is to be desired that meals in such places should be eaten seated and not standing, as is to-day necessary through lack of space in certain establishments. Space is expensive in great cities. If there is not enough room for tables, a certain degree of comfort can be assured by chairs fitted with arms on which trays of food can be placed.

These different types of restaurant, if well run on rational lines, and perhaps supervised by trained dietitians, could help to educate the public in nutrition and improve that part of the diet which is consumed away from home.

In the course of a series of experiments designed to improve diet in Japanese rural districts, it was observed that the population was ready to make use of co-operative purchasing schemes and common kitchens, particularly at times of great activity—*e.g.*, during the sowing and reaping of rice [114].

*Collective Feeding in the Union of Soviet Socialist Republics.*¹

In the Union of Soviet Socialist Republics, collective feeding forms an integral part of a deliberate, specific and State-directed alimentary policy. It is included in the political and social programme of the Government in the first and second Five-Year Plans and in the budget. It is applied, under the direction of the Commissariats of Commerce, Finance, Public Health and Education, by the big factories, co-operatives, municipalities, educational institutions and by the collective farms (Sovkhozes and Kolkhozes), which seem destined to play a part of ever-increasing importance in this sphere.

Collective feeding is not, therefore, a mere empirical effort of secondary social importance ; it is one of the great public services. Its scientific bases are supplied by the Institute of Nutrition ; its technical personnel by the schools ; a directing organ, the Narpit, links it up with the economic administration of the country.

The Narpit first established collective feeding in 1923 by creating the first kitchen-factories, which, in 1925, were not yet mechanised. On the governing body of the Narpit sit the People's Commissary for Commerce, a member of the Supreme Economic Council and a doctor. It is aided by the Commission on Mass-Feeding. The Narpit is the guide and mainstay of the kitchens and co-operatives. The kitchen-factories receive their victuals, on the order of the Commissariat of Commerce, from the foodstuff depots, the meat "Combinat" and the great bakeries. The rules or standards of alimentary requirements defined by the Scientific Institute determine the quantities which agricultural and industrial production must endeavour to supply.

Collective feeding is not planned solely for persons in good health, but also for those whose capacity for work has been diminished by disease. A large number of individuals suffering from rheumatic, cardiac or renal complaints, and even consumptives, can continue to work or recuperate their energies if submitted to treatment ; nutrition is a means of protection and treatment. In most of the public restaurants, there are special corners set apart for customers on diet.

¹ See Annex 1.

The building of kitchen-factories, supplemented by restaurants, began in 1928 ; there were already 79 of these in 1932, in addition to some 9,000 restaurants created by workers' groups. At the beginning of 1935, collective feeding provided daily meals for 20 million persons (about 40 millions in the summer, during the busy time on the farms) (in the Sovkhozes and Kolkhozes). It occupies over 500,000 employees of every category. The annual purchases of foodstuff on its behalf have amounted to 10,000 million roubles in the towns and 3,000 millions (without counting a quantity of produce obtained directly on the spot) in the country.

The kitchen-factory in Leningrad Avenue, Moscow, occupies 1,080 employees. It serves an aircraft factory, a watch factory and, on certain days, a racecourse and an athletic sports ground ; in the four refectories (1,000 places), 15,000 meals are served daily from midday to 6 p.m. Dishes are sent out to 55,000 school-children. The factory does not, therefore, merely function as a kitchen for the four refectories attached to it. At 6 p.m., it becomes a café-restaurant for rest and amusement and, in this capacity, also serves 6,000 dishes a day.

Since, roughly speaking, last year, the kitchen-factories have, at any rate in part, been working on new lines. The tendency is to replace the manufacture of prepared dishes (ready to eat) by " half-prepared " dishes which are easier to transport : the ingredients for soup without the water ; meat and fish cut up and dressed but not cooked.

Each kitchen-factory possesses a bacteriological and chemical laboratory. Every day and at all times in the day, dishes are taken away and tested by the laboratory for their bacteriological condition, Calorie value and alimentary composition.

A meal of two courses, one being a meat course, costs slightly under or slightly over 1 rouble, according to the meat. A meal without meat costs from 0.60 to 0.70 rouble. The workers show a preference for meat and fish. The consumption of vegetables is, however, increasing on the whole. These restaurants do not serve alcoholic drinks.

The diet section has a special staff with a specialised doctor and male nurse when the participants are sufficiently numerous. It prepares regularly a number of diets (for instance, in one Moscow factory, 7 diets for 150 persons), in addition to individual

prescriptions. In 1933, about 600,000 workers were on one diet or another. The diets are prescribed mainly in the following cases : abnormal gastric secretions ; ulcers of the stomach and duodenum ; rheumatic affections ; disease of the kidneys ; diabetes ; heart and vascular affections ; tuberculosis. There is a special dining-room and scullery for consumptives.

Workers eat at small tables for 2, 4 or 8 persons ; they are allowed thirty minutes for a meal. The refectories are large and well lighted ; almost all these installations are new. They are very clean and tidy. The kitchen staff take a shower-bath and change their clothes before and after work.

Kitchen-factories are under constant medical supervision. In certain factories, this special medical service forms part of the general curative and preventive service of the factory, so that the kitchen, with its diet section, becomes part of a veritable health centre. There are factories (for instance, the " Red Giant " india-rubber factory, at Moscow) with a complete centre comprising a general and specialised dispensary open to factory workmen and the residents of the neighbourhood. This centre even possesses a neuro-psychiatric consulting department, a department for guidance in occupational questions and a department where legal advice can be obtained. These matters have, of course, nothing to do with nutrition, but they show how nutrition can occupy a place in the general scheme of curative and preventive medicine.

The restaurants and kitchen-factories are not the only institutions for collective feeding : similar institutions exist in the Sovkhozes and Kolkhozes, co-operatives, universities and schools, which themselves prepare food or receive it in whole or in part from a kitchen-factory which delivers half-prepared meat. There were at Moscow, in January 1935, 26 kitchen-factories (one for each " radius " or district) and 2,000 smaller " stolovaias " or refectories.

The above facts were observed at Moscow, but trustworthy information shows that collective feeding on the same lines is spreading throughout the country. It will be applied by the Sovkhozes and Kolkhozes to two-thirds or three-quarters of the rural population, at any rate during the busy season.

VII. NEW QUESTIONS.

1. THE NORMAL AND THE INDIVIDUAL : " DIETARY TYPES ".

The conception of " normality " is necessary for the establishment of dietary and physical standards, and in connection with the latter the term " normal " often means more than " average ". It may include the idea of perfect development and health and harmonious functioning of all the organs of the body.

On this question, R. BENSUADE and J. Ch. ROUX¹ write as follows :

" It is unlikely that there exists a 'normal' human type, all variations from which, whether morphological, mechanical or chemical, should be considered as pathological. With regard to the internal organs, there are no canons of perfection such as painters and sculptors have created for the shape of the body and the limbs. Indeed, one of the most essential characteristics of healthy men, and perhaps especially of men belonging to the white races, is capacity for adaptation to highly variable circumstances. This is specially true of the digestive tube."

So-called " normal " height and weight standards should not be based on the measurement of unselected groups, but on that of specially selected groups of well-developed individuals. Bensaude and Roux propose that, for the establishment of standards of normality for the digestive organs, exhaustive clinical and biochemical examinations of the whole digestive tube, and the glands connected with it, should be carried out on a group of a hundred or more young and healthy subjects. It is suggested that the investigation should include different races, living in their normal habitat or transferred to a different environment the negroes in the temperate or cold zone and the white people of the temperate countries in the tropical zone. In order to obtain comparable

¹ Private communication.

results, it would be necessary to lay down standard methods of investigation. The researches would concern, not only the stomach and the colon, but the whole of the digestive tube and the glands connected therewith.

“ It is clear ”, write Bensaude and Roux, “ that, even in a small group of a hundred people, one would observe large variations in, for example, the shape and the secretions of the stomach. But averages might be established, and, while stomach shape and secretions may vary within wide limits, there is much less individuality as regards motor function. The same applies to the duodenum and ileum, and especially to the colon.”

The various techniques of examination might be determined by an international committee of experts (see Annex 6).

A deficiency disease may be caused, not only by insufficient intake of a necessary food factor, but also by failure of absorption or utilisation.

Alcoholism, cancer of the stomach and intestine, œsophageal stricture, dilatation of the colon (Hirschsprung's disease ?), gastro-enterostomy and amœbic dysentery have all been recorded as predisposing to pellagra-like symptoms. In northern States of the United States of America, polyneuritic conditions associated with digestive disturbances have been observed which were found to be curable by administration of vitamin B₁. Vomiting during pregnancy may cause a beri-beri syndrome which can be treated by vitamin B. Stenosis of the pylorus, or an operation which immobilises a segment of the intestine, may cause a beri-beri syndrome which can also be successfully treated by vitamin B. Cases of rickets have been observed caused by peptic ulcer, and cases of tetanus and osteomalacia due to the absence of intestinal absorption of vitamin D in coeliac disease and sprue¹ may occur, apparently as a result of defective absorption of vitamin D.

¹ The question has even been raised (MARCHOUX : “ L'alimentation des indigènes aux Colonies ”, *Rev. Col. M. Chir.*, September 15th, 1933) whether (in the Congo) accidents hitherto included in the category of beri-beri are due solely to malnutrition or whether there may be a syndrome due to various causes.

The digestibility of one of the commonest human foods, bread, shows astonishing variations in different individuals. According to RUBNER and THOMAS, fibrous "cell membrane" substances are digested in different proportions and in different ways, depending on the foodstuffs consumed at the same time, the intestinal flora, and the exact nature of the chemical reactions occurring in the intestine of each individual.

To restore a subject suffering from a deficiency disease in any form to a state of normality or health, individual preventive or curative treatment is often necessary.

Brief mention may be made of the possibility of defining what might perhaps be called dietary "classes" or "types", each reacting in a different way to the same diet. In groups of the same sex, age and race, different physical types can be distinguished—tall, short, thin, fat, etc. In thin subjects, the axis of the heart is more nearly vertical than in thick-set types and the heart is relatively smaller; in the former, the stomach tends to take a "fish-hook" shape and lies lower in the abdomen, while, in the latter, the long diameter of the stomach is nearly equal to its transverse diameter. In the thin, the transverse colon has a tendency to hang in "garland" shape. In young children, the viscera are placed as in the thick-set adult, while at puberty their position approximates more nearly to that observed in thin adult types [115]. It may be that the effects of defective feeding differ in different human types. It has been observed, for example, that thin people are, in general, more sensitive to dietary deficiency than those of a more robust type. VOGT has suggested that, in supervising the feeding of athletes, the question of physical type should be taken into account.¹

The establishment of dietary "types" would simplify the task of school doctors and that of medical men entrusted with the supervision of the health of manual workers. Taking into consideration the already known facts relating to the period of growth, it is not unlikely that an individual may pass from one dietary "type" to another during the course of life.

Special dietary regimes are devised to suit abnormal individual conditions and circumstances, which may be of several kinds. Constitutional anomalies in respect of absorption and assimilation

¹ VOGT, private communication, 1931.

give rise to dietary "types" of the kind discussed in the last paragraph. Disease of the heart, rheumatism, diabetes, etc., may call for therapeutic dietary regimes. Again, certain types of work may necessitate special kinds of diet. In all these cases, it is legitimate to speak of types or classes, because resemblances exist between considerable numbers of individual cases, which fall into groups. Since, in any population group, the number of individuals whose dietary requirements are "abnormal" for constitutional, medical or social reasons may be considerable, the importance of special dietary regimes should not be overlooked, particularly in connection with "mass" and "collective" feeding.

In the Union of Soviet Socialist Republics, where the State has undertaken the task of organising the feeding of the population on scientific lines, the principle that the same type of diet will not suit all workers has been accepted; it is considered necessary to take into account, not only age and occupation, but also physiological and pathological variations between individuals. The National Institute of Nutrition includes a section for the study of special diets, which may be either therapeutic or "professional". Attention is given to the same question in the Diet Therapy Clinic attached to the National Institute of Nutrition. As an example of an attempt to modify diet to suit occupation, we may cite the protein intake recommended for metallurgical workers, who work in a very warm atmosphere: 130 to 150 grammes per day, instead of 120 as supplied to ordinary manual workers. In the "collective" restaurants, as many as 7 to 10 kinds of special diets are regularly supplied, and others can be obtained to meet the needs of particular cases. In January 1935, the Diet Therapy Clinic was engaged in the study of 40 special diets in workshops and factories in Russia. 600,000 workers were reported to be receiving special regimes. Most of the collective restaurants have a separate "corner" for those who need special diets, and such diets are supplied through a specialised department of the main kitchens. (See Annex 1.)¹

¹ One of the four Chairs of Clinical Medicine of the Paris Faculty of Medicine will have, at the end of 1935, a Therapeutic Dietetics Section, with special consultation centre, dietitians, laboratory and kitchen. A Dietetics Clinic, specially for children, exists at the Lyons Faculty of Medicine. A Clinical Dietetics Division has been instituted at the Ospedale dello Spirito Santo, at Sassia (Rome): it includes a hospital pavilion and consultation clinic.

2. DIET IN RURAL COMMUNITIES.

We propose in this section to consider particularly the diet of the farmer and peasant in Europe and North America. The question of diet in rural communities, like rural hygiene, is worthy of special study. While in certain countries the inhabitants of rural localities can obtain—as far as Customs restrictions allow—the products of distant lands, their diet, as compared with that of the city worker, is naturally less affected by commercial currents and more closely dependent on the productive capacity of the soil. In normal times, it is perhaps less varied than that of the city dweller, but it was, on the whole, less influenced by the disasters and crises which followed the war—for example, in Germany and in the Union of Soviet Socialist Republics. With the development of civilisation, the food supply of the peasant has become more regular and secure. We may picture the inhabitants of mediæval Europe, living before the days of organised transport and centralised administration, enjoying a liberal diet after good harvests and fasting after poor ones : prolonged wars (*e.g.*, the Hundred Years' War, the Thirty Years' War) ravaged the countryside and caused famine. One may surmise that the meat consumption of peasants during the Middle Ages and down to the nineteenth century was, in general, small. Probably, their diet was a bulky vegetable diet like that of many peasants in Europe to-day. The " chicken in the pot ", which Henry IV of France wished every peasant to enjoy, signified an amelioration of diet. Since the middle of the nineteenth century, the diet of peasants has included much more meat and fat.

Poverty influences the diet of the peasant in much the same way as it influences the diet of the city dweller ; the peasant sells his butter and buys margarine ; he sells his poultry and eggs ; he sells his milk fat to the creamery, obtaining perhaps some skim milk for his own use. Such tendencies have been observed in rural Denmark, for example. Poverty does not usually prevent the consumption of a certain quantity of fresh vegetables and fruits, but this may be insufficient to make good the deficiency of the diet in other foods. During the present economic crisis, the diet of rural communities in certain countries has improved because the

peasant, not being able to sell his produce, has consumed it himself and, in consequence, has been better fed than workers in cities and industrial centres. Elsewhere, it seems that the extremely low prices obtainable for agricultural produce have had an opposite effect. In order to pay certain fixed charges—*e.g.*, rent, taxes, etc.—and provide himself with the necessities of life other than food, the peasant has been compelled to sell more of his food products, and particularly more butter and eggs, than was formerly his habit.

More dietary studies in rural areas, of the kind which have been carried out in urban districts, are called for. It is more difficult to obtain precise data as to the consumption of one food of primary importance—milk—in the countryside than in the city. The International Conference on Rural Hygiene in 1931 [116] did not deal specially with nutrition (although it stresses the importance of milk and of food inspection), but the lines which it lays down are suitable for the action of hygiene experts in the matters of a national diet.

The general programme of work drawn up—studies, enquiries, education, control—was intended to be carried out by primary health centres (which were specially concerned with education) and by secondary centres (the latter specially concerned with field investigations). The Conference recommended (Chapter III, paragraph 7) statistical enquiries into economic and social conditions. Educational work in nutrition could be furthered by the existence of advisory committees composed of representatives of local authorities and public health organisations (Chapter III, paragraph 8). The laboratories connected with secondary health centres might collect information and make observations on the subject of diet for the benefit of State or provincial public health institutes. The type of advisory health commission recommended (paragraph 12) by the Conference, which includes representatives of local authorities, education authorities, the medical profession, the clergy, charitable organisations, insurance societies, might further education and even research in the field of nutrition.

The same Conference stressed the importance of milk supply in connection with rural health, and it declared that the relation between milk supply and “state of nutrition”, infantile mortality, and the prevalence of certain diseases (whether infectious or due to dietary deficiency) was worthy of close study.

Recent enquiries in Japan have shown that mortality rates may be higher in villages than in towns in the same province. In the villages, there is a higher proportion of young men unfit for military service and much sickness and disability due to diseases of the respiratory and digestive organs. Deficiency diseases are common.

Professor MIYAJIMA [117] reported to the Health Committee an interesting experiment by Tamaki and Yamaka, which shows the possibility of raising the standard of health in a rural community by improving the diet. The experiment was carried out in a poor village, where the public health administration instituted, for a period of one year, improved standards of Calories and protein, collective purchases of foodstuffs and group kitchens. The average of morbid manifestations per inhabitant dropped from 2.7 to 0.92. The increase in height and weight in young people was greater than in a control village. There is no mention of milk in the report. The results are specially noteworthy, as the village was rated fairly low from the standpoint of well-being and health.

3. COLONIAL DIETARY PROBLEMS.

Explorers, doctors, etc., have collected fairly extensive general information about the diet of native populations in European and North American colonies in Africa, Asia and Oceania. It is only within recent years, however, that attempts have been made to analyse the available data and to carry out qualitative dietary studies. It is now clear that "colonial" populations, in general, are under nourished, and Governments have begun to recognise this fact and take steps to deal with the situation.

It is not possible to give a comprehensive picture, as there are so many differences between the countries.

In certain Asiatic colonies, there is a tendency towards overpopulation, while in Africa, and particularly Oceania, the opposite trend is visible. In certain parts of Africa, the native is not always assured of a regular and constant food supply; his food supply may vary in abundance like that of the European peasant in the Middle Ages. There have been great economic and social changes in the life of many African peoples during the last fifty years; while inter-tribal strife has disappeared, portage work, work on roads and railways, etc., have disturbed the easy traditional routines of the

native and have often subjected him to unaccustomed physical strain¹; at the same time, there has been a spread of indigenous diseases, such as sleeping-sickness, relapsing fever and malaria, and also of diseases of Western civilisation, including tuberculosis. In spite of differing local circumstances, the diets of native populations in African, Asiatic and Oceanic colonies tend to show the same defects: they are often insufficient in quantity and unsatisfactory as regards quality, in that they contain inadequate amounts of animal protein, mineral salts and vitamins. As a result, resistance to infection is low and infantile mortality high. It is scarcely fanciful to ascribe the low birth rate observable in certain parts of Africa and Oceania to dietary deficiency.

The protein intake of native populations in the tropics and the East is usually small. The Masai, in British East Africa, who live mainly on meat, milk and blood, and whose protein consumption is from 200 to 300 grammes a day, are exceptional. In parts of Africa, particularly Equatorial Africa, cattle are symbols of wealth and honour, and, as such, are rarely killed for meat. Trypanosomiasis prevent stock-breeding over wide areas. Big game is partly lost, owing to rapid putrefaction, in the absence of means of preservation. The pastoral tribes, such as the Masai, are better nourished than tribes living by agriculture.

Long before modern times, travellers ascribed the fine physique of Arabs in Asia Minor to a high milk intake (LARREY). According to ATKEY [118], in British Sudan, there is a relation between milk intake and resistance to leprosy. In East Africa, ORR and GILKS studied the causes and effects of the different diets of the Masai, pastoral tribe living on milk and meat and the Kikuyu who only eat meat from time to time.

The problem of an adequate milk supply, so important in densely populated Europe, is not less so in Africa and Asia. In the absence of milk derived from live-stock, the only milk available is human milk, the quality of which depends to a considerable extent on the diet of the mother.

The bulk of the diet of most native African populations is composed of cereals. In Morocco, according to GAUD, increase of prosperity brings about a rise in the consumption of wheat at the expense

¹ In Morocco, according to GAUD, the effects of malnutrition become noticeable in the natives when the latter are engaged in regular work on European lines.

of that of barley ; at the same time, meat consumption remains low, being about 250 grammes *per capita* per week in Mogador (RAULT). In South Africa [119], maize is as important a cereal as rice in Southern Asia and occupies 40% of the land under cultivation. It forms a large part of the native diet, which contains an insufficiency of meat, milk, grain and vegetables. Prejudice in favour of white maize, corresponding to the European prejudice in favour of white bread and that of the Asiatic in favour of white rice, is found in South Africa. White maize is deficient in vitamin A. "Mealie food" also lacks vitamin C, and, as a result, native labourers often arrive in mines in a state of latent scurvy, which is cured (in spite of heavy work output) by the liberal diet supplied in the mines—daily, about 250 grammes of meat, 100 grammes of germinated broad beans or haricots and 140 grammes of fresh vegetables. According to CLUVER [120], dental caries, pellagra and incipient pellagra are common among the Bantu and the natives of Zululand and Transkei, whose diet is largely mealies, whereas no cases of caries were observed among the 200 inhabitants of the island of Tristan da Cunha, who have practically no cereals and live chiefly on milk and potatoes [121].

In general, the diet of the African native lacks animal fat. The few inhabitants of the Sahara consume a small quantity of rendered butter. The fats most commonly consumed in many districts are palm oil and peanut oil. The former contains vitamin A. Peanuts contain, in addition to protein, some vitamin A, and are fairly well endowed with vitamin B₁ and B₂.

In many parts of Africa, insufficient amounts are available of sodium chloride, which may, as a result, become valuable merchandise (as in the Andes in the days of the Incas and the first period of Spanish conquest). McCULLOUGH has suggested that, by the replacement of native salts by impure rock salts, the provision of iodine might be assured. The diet of the Kikuyu (one of the tribes studied by ORR and GILKS) and that of numerous other tribes is deficient in calcium but not in phosphorus ; in certain samples of East African maize, the proportion of calcium to phosphorus was 1 to 300, which may be compared with the average figure, based on American samples, of 1 to 10. The natives have learnt to consume a salt rich in calcium which is prepared by the women by burning roots and swamp plants. The diet of the Masai, on the

other hand, is rich in calcium. The following table, based on the work of ORR and GILKS [9], gives the percentage incidence of different bony and dental defects in Kikuyu and Masai children :

Percentage Incidence of Different Defects in Kikuyu and Masai Children.

| | Kikuyu | | Masai | |
|-------------------------------|--------|--------|-------|--------|
| | Male | Female | Male | Female |
| Bony deformities | 62.6 | 43.7 | 11.7 | 14.6 |
| Dental caries | 13.7 | 13.1 | 1.6 | 3.6 |
| Dental defects in general . . | 40.0 | 28.8 | 8.3 | 7.3 |

Over large areas in Africa and in other parts of the world, the soil and its products are deficient in phosphorus. Such soil deficiency raises an obstacle to stock-raising and provides a formidable problem of nutrition [122].

Disease and ill-health due to vitamin deficiency are common throughout the tropics and the Far East. Xerophthalmia exists in Uganda and Kenya. Night blindness and keratomalacia, due to vitamin A deficiency, have been observed in many parts of Asia and Africa. Other manifestations of vitamin A deficiency, affecting the mouth and the skin, have been noted in Ceylon and West Africa and probably exist in many other regions. Adult and infantile beri-beri, closely related to vitamin B₁ deficiency, are found wherever milled rice is used as staple cereal ; many observers have commented on the waste and danger involved in the decortication of rice consumed by native populations. Pellagra is endemic in maize-eating areas throughout Asia, Africa and the West Indies. Scurvy has been observed among native adults in South and East Africa. Deficiency of vitamin E may play a part in reducing fertility in many tropical and Eastern countries. Apart from the recognised food deficiency diseases, there can be little doubt that a vast amount of ill-health in the tropics and the East is due to the consumption of diet deficient in vitamins and other food factors. There is evidence, for example, that the fundamental cause of tropical ulcer may be faulty and insufficient diet. W. E. McCULLOCH [123] has adduced reasons for ascribing tropical ulcer in West Africa to the " chronic semi-starvation of the vast majority of the population ".

In districts which suffer from avitaminoses, means of prevention may be found close at hand. In Nauru, in the Pacific, the distribution

of yeast "toddy", a native drink, reduced infantile mortality and beri-beri and increased the birth rate [124]. In many parts of the tropics, extracts of rice polishings are employed in the treatment of beri-beri. In Porto Rico [125], extracts of *Bixa orellana* grains can supply vitamins B₁ and C. Many other similar examples might be quoted.

"La meilleure politique coloniale est la politique alimentaire." More scientific research on the subject of diet in colonial territories is required, and campaigns against nutrition, based on public health and economic considerations and adapted to local conditions, might with advantage be initiated. The fact that the greater part of the population of Africa and Asia—to mention only these two continents—suffers from insufficient or faulty feeding is no longer a secret, and there is more honour to be gained in attempting to improve the situation than in concealing it. In the tropics and the East, one finds, as in Europe, a variety of nutritional problems—a lack of meat, fat, milk, vitamins, etc. "In order to solve these problems, economic development must be assured; roads, railways, ports, irrigation canals are required; considerable effort on the part of native populations, and this cannot be made unless they have the muscular vigour which is created only by a good diet" [126].

Many workers who have called attention to the existence of malnutrition among native populations, and who are seeking for remedies, recommend that policies of prevention should not involve unnecessary disturbance of traditional dietary habits. It is preferable that the foodstuffs necessary to supplement native diets should be sought locally. Something may be achieved by education; national and tribal dietary customs are not inviolable physiological laws. Colonial medical workers have observed that native populations readily develop the habit of consuming three meals a day in imitation of Europeans. Populations consuming millet have readily accepted distributions of rice, which they had not had the trouble of sowing or reaping, in times of food shortage.

The nature of the soil—its content of phosphorus and other minerals—the amount of pasture-land available, the possibility of employing fertilisers, methods of developing the productivity of the native population—all these are problems worthy of extensive study in the various countries which make up modern colonial empires. GAUD has drawn up for Morocco a progressive programme

which includes seed selection, "water policies", reforestation, the creation of fodder reserves, the development of sea-fisheries, the formation of native agricultural co-operative societies for the purpose of minimising the ill-effects of bad harvests. In certain colonies, there is a possibility of teaching practical nutrition during the period of military service. GILKS suggests that, in British East Africa, colonial policy should aim at turning the native into a self-supporting small-holder who has a surplus of vegetable products to sell. MARAZ proposes that, whenever native workers are assembled for some particular task, schools of cookery, at which an "amended" type of native cookery can be taught, should be established, even before the workshops themselves.

Organisations concerned with maternal and child welfare have good opportunity of dealing with the problem of malnutrition, and the same might be said of auxiliary medical services which have been for some time in existence in Africa, in French and British possessions.

The remarkable study of ORR and GILKS [9] on two East African tribes was carried out under an agreement between the Colonial Office and the Government of Kenya, with the assistance of two successive subsidies, each of £3,000, from the Empire Marketing Board; it was completed with the assistance of the Rowett Research Institute, of Aberdeen, the Imperial Bureau of Animal Nutrition and the Chemical Laboratories of Nairobi, and was published under the patronage of the Dietetics Committee of the Economic Advisory Council (formerly the Committee of Civil Research) of the Medical Research Council.

In considering a report of ROUBAUD, the French Académie des Sciences coloniales emphasised the desirability of developing fisheries, animal husbandry, centres for food preservation, and popular education. The Minister for the Colonies has laid down the lines of preliminary enquiries which are to be carried out by technical workers (doctors, pharmacologists, veterinarians, agricultural experts) with laboratory facilities at their disposal [127].

In French Africa, the Governments have taken action regarding the nutrition of the native workers employed in the public services and in private undertakings by insisting on compulsory rations and the distribution of fresh vegetable foodstuffs, and, for sickly individuals, of additional food, taken under the supervision of

medical orderlies [128]. In Togoland, relatively over-populated regions have been decongested by "internal colonisation"—that is to say, the transfer of part of the population to other regions.

The Far Eastern Association of Tropical Medicine, at its congress held in Nanking in 1934, decided to create a section on diet. It was recommended that, during the interval between the 1934 and 1937 Congresses, information about native dietaries should be collected in Far Eastern countries. The Association envisages the continuance of dietary studies after the presentation of preliminary reports at the next meeting.

VIII. NATIONAL AND INTERNATIONAL ORGANISATION.

It does not seem necessary to suggest schemes for the national organisation of public health nutrition work ; we may confine ourselves, in the present report, to attempting to show that such organisation is desirable. Of its nature, public health nutrition work is but one of the functions of public health services, which in many countries have already created agencies and developed institutions for the improvement of nutrition. If the subject of diet comes to occupy its due position in the teaching programmes of medical faculties, and is given the attention which its importance warrants by maternity and child welfare services, school medical authorities and administrative authorities and committees, a special branch of the public health services to deal with the question seems scarcely necessary. Various examples of work in this field described in our report may suggest directions in which existing organisations might usefully develop.

The desirability of attaching a specialist in nutrition, familiar with the physiological and economic aspects of the subject, to central public health administrations may again be emphasised. Further, the value of national "institutes of nutrition", specialising in research and teaching, and possessing laboratories, a library, and exhibits suitable for popular education, seems undeniable. Such institutes may be expected to assume in any country a shape and form suitable to their purpose, and to be influenced in their development by national traditions and existing organisations.

Experience has already shown that subordinate "executive" nutrition workers, such as the "nutritionist" and the "dietitian", may fulfil a useful rôle, and greater use might be made of agents of this kind by public services and private organisations. Even a small number of such workers may be valuable, in that they can obtain the co-operation of health visitors, etc., in educational work, in out-patient departments, in schools and in the home.

The utility of domestic science training for girls, already developed in many countries, cannot be over-stressed. Such training may take several forms : special hours may be devoted to it in school curricula ; it may be given in domestic science schools ; special classes for all ages may be organised outside the ordinary educational system altogether. Cooking is obviously an important branch of domestic science, as are the arts of wise purchasing of foodstuffs and of food preservation.

The activities of public health services in the field of nutrition must be based on as complete a knowledge as possible of the food requirements and resources of the country and the state of nutrition of its inhabitants. Gross consumption statistics, prepared for economic purposes, and general and infantile mortality statistics do not provide the public health nutrition worker with sufficiently detailed information. During the last hundred years, Governments have come to require data as to living standards, including information about diet in relation to wage levels and economic conditions. For this latter purpose, it is necessary to make inventories and analyses of national food products, to study dietary habits and traditional customs, to learn something of the prevalence of food deficiency diseases and the educational level of the masses. One method of collecting data on such points is by family enquiries, which are carried out among different classes of the population and which have both a public health and an economic aspect. Family budget enquiries are often conducted by means of questionnaires, and may include several hundreds or even thousands of families ; when enquiries are based on questionnaires, social workers may be necessary to help the housewife to fill in the forms. Sometimes, responsibility for the enquiry is wholly assumed by specialised workers of the "health visitor" or "social worker" type, who visit families at home and note their food intake over a chosen period. A quarter in a city, a rural district, a group

of families connected with some particular industry, etc., may be made the subject of dietary enquiries, which naturally tend to be more detailed when their range is small. The Conference of Experts convened in Rome in 1931 [129] put forward suggestions as to the conduct of dietary enquiries, which were necessarily very general, because each such enquiry involves, according to its goal, the population studied, living conditions, etc.—a series of difficulties peculiar to itself which can be solved only by common sense.

Ordinarily, data about food consumption are translated into terms of Calories and energy-yielding food factors; less frequently, analyses are made of the intake of certain mineral elements—*e.g.*, calcium, phosphorus and iron. With the establishment of vitamin units, there is no reason why vitamins should not be dealt with quantitatively in future dietary enquiries. It often happens that standard text-books do not contain analyses of all the foods consumed by a particular population group, and, naturally, all figures contained in such books are not entirely dependable for use in all investigations; there is evidence that the chemical composition and vitamin content of the same foodstuff or the same class of foodstuff may vary at different times and places. Difficulties of this nature are met with in all family dietary investigations.

Whether such studies are made to provide a basis for public health work and economic planning, or whether they are made in order to assess the value of measures already in operation, it is obviously important that physical and clinical examinations of the group investigated should be carried out simultaneously. Control groups are usually necessary, even when it is possible to draw comparisons between conditions existing in a particular group and those existing in the same group at an earlier period.

From the international point of view, needs, resources and customs of different peoples and population groups are so varied that there can be no question of putting forward uniform plans for the organisation and reform of public health nutrition work in different countries or of establishing standards which are universally applicable. But despite this diversity, or perhaps indeed because of it, it is possible to conceive an international organisation which could render considerable service to physiologists and public health workers occupied with practical nutrition problems.

Much might be learned by the organisation of nutrition enquiries

and experiments to be carried out on parallel lines in different countries. Experiments on the effect of "extra" milk in the diet of schoolchildren, similar to those already described, might be initiated in a number of countries; the value of other foods as additions to national dietaries could be tested in the same way. There is, at present, a great need for large-scale dietary experiments to be carried out on schoolchildren, family groups, in institutions, etc. The value of the various public health methods used in the prevention and treatment of food deficiency diseases—*e.g.*, pellagra—might be studied on an international scale, along the lines already followed by the Malaria Commission of the League of Nations.

The lack of uniform methods of calculation and assessment makes it difficult to compare the results of enquiries, carried out in different places, which are concerned with food intake or physical "state of nutrition". The Rome Conference drew up an international scale of family coefficients for use in dietary enquiries; this scale is conventional in nature, and the Conference emphasised the obvious impossibility of putting forward a scale corresponding accurately to the relative food consumption of family members in all countries and in all circumstances. Its purpose was rather to obtain the conventional acceptance of a scale deriving its value from the fact that it exists and is used. The Conference expressed the hope that nutritional research workers, "though they may prefer to use other scales in making their particular dietary studies, should also calculate food intake per consumption unit in terms of the international scale". Similarly, the Berlin Conference [30] outlined a conventional method of studying "state of nutrition", of which it can be said that it is no worse and no better than most other current methods employed for the same purpose. For enquiries and experiments on an international scale, it would seem necessary to elaborate standard methods which are at once simple and easily applicable and which, at the same time, conform adequately with scientific knowledge.

International effort might secure a more uniform approach to the following questions: standards of dietary requirements; categories of energy expenditure: "heavy", "medium" and "light" work; methods of assessing "state of nutrition".

For the purpose of special enquiries carried out simultaneously in different countries, a conventional method of investigation may

serve (for example, that suggested by the Berlin Conference), but further research on this subject, which might well be organised on an international scale, is required, with the object of discovering tests which will evaluate "state of nutrition" with a minimum of error. Model schemata for dietary enquiries, and the publication of the results of such enquiries, without rigidity and easily adaptable to different circumstances, might be drawn up.

The vitamin units established by the recent International Vitamin Conferences [17] can already be used in dietary enquiries.

The establishment by the Health Committee of a permanent commission to study the problems of nutrition has already often been proposed. Co-operation between such a commission and specialists in different countries could be assured through the medium of national institutes of nutrition or special branches of national schools of hygiene, the directors of which could meet in conference from time to time like the directors of national schools of hygiene, whose meetings led to the International Conference on Rural Hygiene in 1931.

We may even envisage a further goal. During recent years, the idea of an International Institute of Nutrition has often been suggested in printed articles and in documents sent to the Health Organisation (See Annex 6). Such an institute could be serviceable, in that it could help to maintain contact between technical workers in different countries, collect and co-ordinate documentation, study methods of enquiry and facilitate the investigation of the relation between diet and economic circumstances.

We should like to enlarge on this last point. If we might be allowed to suggest the lines that seem to us desirable, particularly at the present juncture, for dealing with the practical problem of nutrition, we would say that production, distribution and consumption have hitherto been considered mainly as economic phenomena, without sufficient regard to their effect on public health, but that the fact of the economic depression has directed attention to the gap which almost everywhere exists between dietetic needs, as determined by physiology, and the means of satisfying them possible under existing economic conditions. The general problem of nutrition, as it presents itself to-day, is that of harmonising economic and public health development.

ANNEX 1.

GENERAL SURVEY OF NUTRITION IN THE UNION OF SOVIET SOCIALIST REPUBLICS.

Food supply is a public service. The State does not merely inspect foodstuffs from a health point of view and punish fraud (as in all other civilised countries); in conformity with the doctrine of the Communist Party, it aims at organising the nutrition of the people in accordance with the laws of physiology and the norms of hygiene.

The nutrition of each individual should be determined, not by his income, but by his needs.

Nutrition should supply one of the fundamental needs of man : ensure resistance of the organism to disease, maintain and increase capacity for work, promote general well-being.

With a view to ensuring the rational nutrition of the greatest possible number there are the following institutions and bodies :

| | | |
|---|---|---|
| Laws | } | Law on foodstuffs. |
| | | Inspection. |
| Economy | } | The " Gosplan ". |
| | | The People's Commissariats for Commerce, Education, Public Health, the <i>Centrosoyuz</i> , the <i>Narpit</i> . |
| | | |
| Scientific research. Technical advice to the Government | } | The National Institute of Nutrition. |
| Application to preventive and curative medicine | | } |
| Dietaries | | |
| Training of staff | | Technical schools. |
| Training of doctors | } | Nutritional hygiene branch of the Faculty of Hygiene. |
| | | |
| Popular education | } | School museums. |
| | | Exhibitions. |
| | | Propaganda. |
| Collective feeding | } | Kitchen factories. |
| | | Courses of individual diets. |
| Special activities | } | Infants : milk dispensaries. |
| | | Schoolchildren : school meals. |
| | | Sick : special diets. |

A consolidated law is in preparation. Inspectors will be empowered to close any establishments that do not conform to this law.

Economy.—The norms or standards of alimentary requirements govern production and supply : foodstuffs for collective feeding are bought by the *Centrosoyuz* and the Commissariat of Commerce (10,000 million roubles for kitchen factories in the towns in 1934 ; 3,000 million roubles—excluding foodstuffs locally collected—for those in rural districts).

The Commissioner for Commerce and a member of the Supreme Economic Council sit on the *Narpit*, the directing organ for collective feeding.

There are enough cereals and fats. Bread is manufactured in large bakeries under the supervision of the health authorities. At present, there is a shortage of meat and milk, the consumption of these commodities having increased much more rapidly than production.

The amount of foodstuffs imported is negligible. Within the country, however, the traffic in foodstuffs is considerable.

The *National Institute of Nutrition* is not an administrative organ but an institute for scientific research. It also acts as technical adviser to the Government. It studies the nutrition of man, both in health and illness. It is divided into the following sections : physiology and biology ; food hygiene, cooking technique ; dietetics and therapeutic nutrition ; feeding of infants and mothers ; general education and training of technical staff ; economy : plans and statistics.

The physiological section lays down the norms or standards. The standards it has adopted are about 15% higher than the standards allowed in Western Europe or in the United States of America.

| | Protein | Fat | Carbo- hydrates | Total Calories | |
|--|----------------------|-----|--------------------|-------------------|-------|
| <i>Workmen and Residents of Cities :</i> | | | | | |
| Maximum for very heavy work | — | — | — | 4,300 | |
| Average { | adults | 120 | 108 | 525 | 3,644 |
| | 1 to 3 years | 52 | 54 | 200 | 1,530 |
| | 4 to 7 years | 72 | 57 | 300 | 2,060 |
| | 8 to 13 years | 83 | 52 | 380 | 2,380 |
| | 14 to 18 years | 118 | 60 | 536 | 3,250 |
| <i>Rural Districts :</i> | | | | | |
| Average, adults | 115 | 96 | 592 | 3,800 | |
| Workmen in overheated premises .. | 130-150 | — | — | — | |

No difference is made between the sexes, whether for children or for adults. These norms have been laid down after prolonged observations on factory workmen who ate whatever they wanted and whose work was measured by the calorimetric process. Most of these observations were made in Moscow factories and some in other towns (*e.g.*, Tashkent).

Less protein and more carbohydrates are given in rural districts than in the cities ; 20% of the protein must be animal protein.

The food must not be taken at random hours or in random quantities. The following schedule is recommended :

| | |
|---|-----|
| Towards 7 a.m. before work, about | 25% |
| • 10.30-11 a.m. | 20% |
| • 5 p.m. (dinner) | 40% |
| • 9 p.m. | 15% |

Its researches are concerned particularly with the composition of proteins and the association of amino-acids and testing national products for vitamins : carotene and vitamin C in pine and fir needles. The food hygiene section

is concerned with processes for the *rapid* analysis of raw and prepared foodstuffs. Preserved foodstuffs are necessary as a reserve. The section of technology studies both the theory and practice of the preparation of foodstuffs, condiments and sauces ; it lays down standards for the manufacture of utensils ; it manufactures *models* for the instruction of the public.

The *Clinic of Therapeutical Dietetics* studies diet as a means of treating and preventing disease : diseases of the digestive tract, heart and blood vessels, and the various forms of rheumatism and nephritis, with a view to preserving and restoring capacity for work. About 600,000 persons in the U.S.S.R. are in receipt of special diets. Most kitchen factories and every restaurant have their "special diet section". The clinic studies mainly the relationship between nutrition and the reactions of the body (allergy and anaphylaxis) and the introduction of prophylactic diets for the prevention of those deficiencies to which workers in mines, peateries and the transport industry are particularly liable (additional protein for workers working in a hot atmosphere).

The *High School for Foodstuffs Engineers* trains technical experts for kitchen factories and laboratories.

Five years' study, about 120 pupils per annum ; pupils can obtain a diploma at the end of the course. Three branches of training : alimentary technology, chemistry and physics, economy.

There are schools of cookery of various grades.

There are in the U.S.S.R. officials corresponding to the "nutritionists" and "dietitians" in England and the United States of America ; they receive a good scientific and technical education and are trained mainly for the collective feeding services.

The *feeding of children* is studied at the Maternal and Infant Welfare Institute, which possesses a nutrition section and a clinic for instructional and research purposes. The nutrition section includes a "milk kitchen", breast-milk store and a section concerned with the feeding of older children.

The Institute of Nutrition studies the requirements of schoolchildren from the angle of physiology and standards of nutrition. At the Narkomzdrav, there is an institute for the protection of schoolchildren. *School meals* are provided in kindergartens and primary and secondary schools—in kindergartens one, two or three meals per diem, according to the hours of attendance, which may be four, six or ten. In the schools, the midday meal constitutes about one-third of the daily ration. Schoolchildren of the "first degree" receive one meal (five hours' attendance at school); those of the "second degree", two meals (eight hours' attendance), providing 70% of the daily ration. The midday meal is a compulsory minimum for all schools.

The system of *collective feeding* is outlined in the report. It is followed, not only in the restaurants of kitchen factories, but also in the restaurants of co-operatives, schools, universities, and, in the country, in the Sovkhozes and Kolkhozes ; these rural organisations are destined to form a framework for the development of collective feeding and dietetic hygiene in the U.S.S.R.

This organisation should be judged in the same light as the organisations of other countries—*i.e.*, bearing in mind the past and present situation of the

nation and, above all, of the mass of the population. The organisation forms a whole, in which the State, directing the total activity of the country, is alone qualified to settle the relationship between alimentary needs and production, and between production and the general economy of the country. The State directs, and is everywhere present. The *State* does not, however, necessarily mean the central power : workmen's committees, co-operatives, syndicates, educational institutions—each, in their own sphere, administer this system of collective feeding. The main characteristic of the system is that the supply of food is a public service, like the financial, commercial, educational, public health and economic services. It is organised with a view to securing the greatest benefit for the greatest number. *Therapeutic* dietetics for the protection of public health is given as much attention as normal nutrition. Collective feeding is regarded as one of the most efficient methods of applying the results of science and ensuring a rational nutrition of the people. The U.S.S.R. can produce from its soil all that it requires to maintain its population.

ANNEX 2.

DIET IN DANISH RESIDENTIAL INSTITUTIONS.

Towards the end of the last century, a beginning was made in the direction of the scientific regulation of diet in certain Danish public institutions, which included poor-houses, municipal hospitals and prisons. The Government, advised by the Royal College of Health, issued regulations ultimately based on the dietary standard for a labourer put forward in 1876 by Vorr : protein 118 grammes, fat 56 grammes, carbohydrate 500 grammes : Calories, 3,000.

The National Board of Health, established in 1909, has control over most Danish public institutions, and its approval of the diet provided by each institution must be secured. There are, however, certain private institutions under State control, such as sanatoria for consumptives and homes for the feeble-minded, which do not fall under its jurisdiction, and in small rural communes the dietary regimes in poor-law institutions are supervised by the County Medical Officer. The Professor of Hygiene in the University of Copenhagen, who is *ex officio* a member of the National Board of Health, has, in practice, the duty of supervising the diet in the public institutions concerned.

The original dietary regulations drawn up for Danish public institutions have been modified (a) as knowledge of the dietary habits of the people has accumulated, (b) in accordance with certain experience gained during the War and (c) with the advance of the science of nutrition.

A number of family budget enquiries, carried out between 1900 and 1920, provided exact information about the dietary customs of various social classes in Denmark, both urban and rural. On this basis, it was possible to calculate, not only the Calorie, protein, fat and carbohydrate content of the various diets, but their composition as regards actual foodstuffs. It was found that the consumption of protein and fat in all classes is rather higher than the Vorr

standard ; it approximates, in fact, more closely to ATWATER'S American standard.

During the War, however, when a rigid system of rationing was introduced and scrupulously enforced, the amount of meat (beef, mutton, and especially bacon and pork) in the diet of the people was greatly reduced ; in other words, their intake of protein and fat became considerably smaller. Less bread made from refined wheat-flour was consumed and more rye bread (the latter mixed with wheat-bran). These changes were without apparent ill effects on the health of the population, and the whole experience has influenced the dietary regulations for public institutions. Reduction of the quantities of beef, mutton, pork, bacon and fish in the diet of an institution reduces cost, and there has been a tendency to make this reduction, especially in drawing up regulations for institutions in which the greatest economy must be practised. The provision of rye bread instead of wheat bread, encouraged by the existing regulations, also makes for economy.

The influence of recently gained knowledge in the field of nutrition can be traced in the various dietary schedules at present in force. During the early years of the War, BLOCH observed the occurrence of xerophthalmia in Copenhagen children fed on a diet entirely deficient in milk fats ; when the rationing system, ensuring a supply of milk fat to all the population, was instituted, xerophthalmia disappeared. In 1920, however, cases of xerophthalmia occurred in certain Danish asylums. To ensure adequate provision of vitamin A and the avoidance of such symptoms of vitamin A deficiency as xerophthalmia, a certain amount of milk is included in the poorest dietaries, and stress is laid on the necessity of supplying green vegetables as generously as possible ; as a rule, however, margarine is given in preference to butter for reasons of economy, in spite of the superior vitamin content of the latter. In general, dietary schedules at present in force are reasonably satisfactory as regards their content of energy, energy-yielding food factors, mineral salts and vitamins.

Apart from the regulation of diet in public institutions, the Professor of Hygiene in the University of Copenhagen, who directs the University Hygienic Institute, assumes the responsibility of advising private institutions the authorities of which may wish to have their system of feeding organised on scientific lines. When such advice is asked for, a "dietitian" (a woman graduate of University standing) is sent from the University Hygienic Institute to the institution concerned. She stays there a few weeks, and then returns to the University Hygienic Institute, where, in collaboration with the Professor, she draws up a scheme of scientifically satisfactory nutrition. This is provisionally tried out for three months. During the last fifteen years, many private institutions have taken advantage of such advice.

In general, the dietary regimes drawn up in the Hygienic Institute have given satisfaction to the boards of management concerned. It has been noted that when catering is organised by untrained individuals, the result is often dullness and uniformity, whereas in the schedules drawn up in the Hygienic Institute, a varied and interesting diet is aimed at. It has also been observed that the scientific control of diet results in economy, a fact which makes institu-

tions ready to take advantage of the assistance of the Hygienic Institute in this matter.

Eventually, it is hoped that all residential institutions in Denmark will have their systems of catering organised on scientific lines. Regulations have recently been framed for temporary "houses of detention" and suitable schedules will be drawn up for certain boarding-schools in the near future. A scheme is on foot to set up standards with regard to all foods supplied to public institutions, which would take nutritional quality into account as well as purity.

ANNEX 3.

PROPAGANDA IN FAVOUR OF THE CONSUMPTION OF MILK AND CHEAP MILK FOR SCHOOLCHILDREN.

In the United-Kingdom, the Milk Marketing Board controls the sale of all the milk in England and Wales. To this Board is affiliated the National Milk Publicity Council, which comprises representatives of milk producers and distributors, doctors, medical officers of health and representatives of the Ministries of Agriculture and Public Health.

The National Milk Publicity Council issues propaganda literature which emphasises the nutritional value of milk. Attempts have been made to popularise the use of milk in industrial centres and mining areas.

Some years ago, the National Milk Publicity Council, with the approval of the Board of Education, originated a scheme for increasing the milk consumption of schoolchildren. For a penny a day, the children can belong to a "Milk Club" and receive one-third of a pint of milk daily. This scheme was extended by the Milk Act of 1934: all schools under the control of State or education authorities may participate in the scheme; in other words, it is working-class children who mainly benefit by it. The milk must be approved by the school medical officers concerned. There is no distribution of milk to schoolchildren in the absence of a local milk supply which satisfies the conditions laid down. About 3 million children benefit by the present organisation.

In France, propaganda in favour of milk and the distribution of milk in schools is carried out by or under the auspices of two organisations similar to those in existence in England: the Office du Lait and the Office National de Propagande pour l'Organisation et le Développement de la Production et la Consommation du Lait, du Beurre et des Fromages.

These organisations were State subsidised from their very foundation. The Office National de Propagande has issued an interesting propaganda publication under the title of "La France Laitière", to which is appended a year-book. It also sets up committees in the Departments which organise clean milk competitions and conduct propaganda: these Committees number at present 47. The Office National de Propagande has also organised "Milk Days" in connec-

tion with the great regional fairs and markets (at Bordeaux, Lille, Lyons and Toulouse) and has produced a talking film. The two Offices have contributed to the provision of cheap milk for schoolchildren in conjunction with the schools' administrative authorities and the *Caisses des Écoles*; hitherto, this movement has been particularly pronounced in the Department of the Seine, but it is already beginning to make headway in the provinces. Attention may also be drawn to an effort which is being made to provide soldiers in barracks with *café au lait* in the morning instead of black coffee. The Office National has distributed hundreds of thousands of copies of posters and pamphlets.

According to its articles of foundation, the Office du Lait is required to study all the economic, scientific, social and technical questions relating to milk.

In France, as in England, the distribution of milk to schoolchildren has been encouraged by an agreement between the producers and hygienists such as J. RENAULT and the leading exponents of "School Hygiene".

In Italy, there are analogous institutions with similar programmes. The National Milk Committee, founded in 1931 in connection with the National Syndicate of Agricultural Experts presided over at its inception by the Minister of Agriculture, aims at organising enquiries and research with a view to bringing about better and more rational production and consumption of milk and its derived products. This Committee comprises agricultural, industrial, commercial, mechanical, economic and scientific sections. In 1932, it organised the first National Dairy Produce Congress. From its foundation, the National Committee has aimed at developing the consumption of milk in schools and barracks.

ANNEX 4.

FRANCE.

SCIENTIFIC SOCIETY OF ALIMENTARY HYGIENE (SOCIÉTÉ SCIENTIFIQUE D'HYGIÈNE ALIMENTAIRE).

The Scientific Society of Alimentary Hygiene and Rational Nutrition, recognised by law as a public utility association, aims at the encouragement and teaching of the sciences in their application to human and animal nutrition. It has undertaken the teaching of advanced cookery. At the time of its foundation, it was also invested with an economic and social function—namely, the protection of public health and well-being in times of economic depression and high cost of living.

It includes a laboratory of bio-energetics and a physiological laboratory (for research into the chemical composition of foodstuffs, their nutritional value and their combination into well-balanced diets; researches on vitamins) and an experimental station, the special purpose of which is to investigate questions relating to the feeding of live-stock in the form in which they arise in agricultural practice.

It publishes a *Bulletin*, which serves as a link between the members of the Society and the general public.

It has attempted to make a contribution to the study of nutrition on the international plane. During the War, the Allied Governments set up an Inter-Allied Scientific Foodstuffs Supplies Commission, which laid down directives of a scientific nature to serve as a basis for the decisions taken by the general foodstuffs supplies services. The Scientific Society of Alimentary Hygiene has resumed this practice and, in consideration of the vital importance of research on nutrition, has caused official representations to be made to the League of Nations with a view to the creation of a permanent body to co-ordinate, encourage and make known the efforts of all research workers who have made useful contributions to the science of nutrition from whatever point of view.

The duties of this International Scientific Nutrition Commission would be :
(1) to consider the standardisation of methods of enquiry and research regarding the production and use of foodstuffs, and subsequently to collect on this subject the most complete scientific, practical and administrative information possible ;
(2) to promote experiments, research work and enquiries in the contracting countries, and, with the co-operation of the competent administrative authorities, institutions and associations, to contribute to the development, teaching and popularisation of the sciences in their application to nutrition.

In this way, the contracting States would be enabled to take advantage of the results obtained ; each of them would be able to adopt, at its own discretion and in its own time, any measures, in harmony with the laws of nature, regarded as desirable in the general interests of the human race.

In 1933, a Centre of Economic Nutrition Research (Centre d'études économiques de l'alimentation) was set up in Paris, with a membership consisting mainly of engineers, former pupils of such important schools as the École polytechnique, École centrale des Arts et Manufactures and the Institut agronomique. The Centre publishes a *Bulletin* ; it concerns itself more particularly with " questions relating to nutrition from the point of view of agricultural production and consumption, and more especially the maintenance of a balance between the two ". This new Centre is actively supported by the Scientific Society of Alimentary Hygiene.

ANNEX 5.

ORGANISATION FOR IMPROVING NUTRITION IN JAPAN.

The organisation for improving nutrition in Japan consists of two sorts of institutions : an Institute of Nutrition and organisations in the prefectures. The Institute is subordinate to the Ministry of the Interior ; it was inaugurated on December 17th, 1921, as a national institute, at that time unique in the world.

I. INSTITUTE OF NUTRITION AND ITS ACTIVITIES.

It conducts enquiries and studies regarding the nutrition of the people and the relationship between nutrition and public health, economy, labour and general alimentation. The results of the researches made by the Institute and their dissemination exercise a direct or indirect influence on the well-being of the people.

The organisation of the Institute is as follows :

1. Section for elementary research :
 - (a) Chemical analysis ;
 - (b) Examination of nutritive exchanges (metabolism) ;
 - (c) Physiology and pathology ;
 - (d) Physics.
2. Section for research into the practical use of foodstuffs :
 - (a) Natural foodstuffs (including foodstuffs used in times of emergency or famine), manufactured foodstuffs and the growing of cereals ;
 - (b) Economic feeding ;
 - (c) Conservation and distribution of foodstuffs ;
 - (d) Cooking and utensils ;
 - (e) Nutrition of children ;
 - (f) Utilisation of refuse.
3. Enquiries section :
 - (a) Enquiries, statistics and material drawn from history ;
 - (b) Courses, exhibitions, propaganda in the matter of nutrition.
4. Section for general questions.

Summary of the Main Work of the Institute.

1. Researches with a view to improving the manner in which rice is consumed
2. Researches with a view to improving the manner in which wheat is consumed.
3. Researches with a view to improving the manner in which millet is consumed.
4. Researches on the adsorbing clay used for treating rice and wheat polishings.
5. Research with regard to standardised food in Japan.
6. Research into the nutrition of intellectual workers.
7. Research work in connection with economic feeding.
8. Research work in connection with the utilisation of refuse.
9. Research with regard to foodstuffs used in times of emergency and famine.
10. Researches concerning the improvement of the human constitution.
11. Research into the production of foodstuffs.
12. Research into the manufacture of foodstuffs.
13. Research with a view to improving the quality of foods.

Papers have been read on these subjects to the "Dietetics Society" (forty-two general assemblies have been held up to date), summaries of the same being published in the *Bulletin of the Institute of Nutrition* or in other scientific reviews. The Institute also publishes from time to time a *Report of the Institute of Nutrition*, in which this work is described in detail.

Practical activities of the Institute.—The Institute plays a great part in improving conditions of daily life ; consequently, practical work must not be overlooked. A special training-course would be an excellent means to achieve this end but, for reasons of economy, the Institute has not yet been in a position to organise it. Nevertheless, when public or private societies, or schools or factories, desire to organise a training-course or lecture on nutrition, the Institute is always prepared to send one or two organising specialists. From January 1921 until August 1934, the Institute had lent its assistance at 938 meetings and 1,257 lectures.

As a result of the efforts made by the Institute for research and propaganda in the matter of the nutrition of the people, the State has adopted a law concerning the despatch of "nutrition officers" to the local Governments for the purpose of giving practical instruction to the inhabitants. These officers are increasingly sought after by hospitals, boarding-schools, etc.

The Institute has also studied the problem of improving the nutrition of the rural population.

Dr. SAIKI, Director of the Institute of Nutrition, has organised a school of nutrition. "Nutrition officers" who have studied there now act as advisers in the local governments, factories, schools, hospitals and agricultural villages.

II. ORGANISATION IN THE PREFECTURES.

Attention has been devoted to the following subjects : enquiries on nutrition, nutrition statistics, school meals, courses and lectures, pamphlets, exhibitions. Thirty-three "nutrition officers" took part.

III. SCHOOL MEALS IN JAPAN.

The State Treasury decided to grant a minimum of 880,000 yen to improve the nutrition of schoolchildren, in accordance with current requirements and educational conditions. This sum was intended to provide for 100,000 children per annum, that being the minimum number of children who are unable to pay for school meals.

After one year—that is to say, at the end of March 1933—380,548 children had been given school meals (338,329 free of charge and 42,268 for payment). At the end of March 1934, the total number of children who had received school meals was 637,425 (512,632 free of charge and 124,793 for payment). The surprising increase in the number of meals paid for proved that teachers and parents have realised the importance of school meals.

The Ministry of Public Instruction allocated 1,089,536 yen for meals for the year 1933. If to this amount is added expenditure and gifts by the prefectures,

communes and other bodies, the amount exceeds 1,592,000 yen, including expenditure on meals paid for by over 120,000 children ; the total amount per annum exceeds 2 million yen. The institution of school meals may be compared to the system which has been in force in England for a very long time.

ANNEX 6.

RECOMMENDATIONS IN FAVOUR OF AN INTERNATIONAL NUTRITION INSTITUTE.

In May 1926, on the motion of the League of Austrian Women, the eighth meeting of the International League of Women voted a resolution in favour of an International Institute for Research on Nutrition. The idea has been frequently supported in the review *Die Volksernährung*. The following sections have been proposed : statistics and records ; economic section ; enquiries and epidemiology ; standards ; physiological research ; clinical research. Scientific expeditions. Education. Museum and exhibitions.

In a note addressed to the Health Section in 1931, Professor ABDERHALDEN demonstrated the need for an International Centre for nutrition studies, with particular reference to the nutrition of children, the relations between nutrition and economics, between nutrition and wages, and between nutrition and infectious diseases, and, in the last place, to the standardisation of the methods applied to nutrition problems.

“ The problem of the relationship between nutrition and health throughout the world is of sufficient importance to merit the attention of the League of Nations ” and also to be made the subject of an organised international effort.¹

The National Nutrition Institute at Moscow is in favour of an international conference of experts.

(See Annex 4 for the recommendation of the Scientific Society of Alimentary Hygiene, Paris.)

ANNEX 7.

STUDY OF THE NORMAL FUNCTIONING OF THE ALIMENTARY CANAL.

Summary of the scheme suggested by R. BENS AUDE and J. Ch. ROUX in a note to the Health Section :

1. Establish, by methods of research previously agreed upon, the normal type of digestive system : morphology, mechanical work, digestive secretions, microbic flora, excretions.

¹ J. B. ORR, of the Rowett Institute, Aberdeen ; Address to the Dundee Section of the British Medical Association, *Medical Record*, May 1st, 1931.

2. Apply this first test to groups of young subjects belonging to different countries—for instance, young European and American (United States) soldiers. Comparison of results by an international commission of experts.

Establish the best methods for estimating the normal condition of the digestive system.

3. Apply the latter test to the study of nutrition among the different races or countries. Study the morphological or functional changes in the alimentary canal under the influence of different diets :

(a) Research should bear first on a specific food : secretions, passage through the alimentary canal, utilisation, waste, assimilation ;

(b) Then on the various foods employed by man : to what extent are they in keeping with the alimentary canal's means of adaptation ?

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TUBERCULIN STANDARDISATION AND TUBERCULIN TESTS

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Considerable divergencies appear in the results of certain of the series of tuberculin tests carried out recently, but as there was no uniformity in the tuberculin used or the type of test employed, it is hardly possible to compare the results, and valuable material is thus lost for the study of tuberculosis epidemiology. The obvious remedy to this state of affairs would be the adoption of the standard tuberculin and of a standardised test.

1. TUBERCULIN.

Examination of the various commercial tuberculins having shown that their strength differs considerably, the Health Committee of the League of Nations, desiring to bring about uniformity in this field, requested CALMETTE, in 1924, to go into the whole question. The results of his work appeared in a report by CALMETTE and DE POTTER entitled "On the Titration of Tuberculin" (League of Nations, document C.H.429.1926). The authors recommended an intracutaneous test in sensitised guinea-pigs for titration, and emphasised the importance of obtaining a standard preparation. Accordingly, the Health Committee made arrangements for comparative tests of the different tuberculin preparations in a number of laboratories.¹ These tests having showed that the standard

¹ HUSTED, Erik : *Acta path. et micr. Scand.*, Suppl. III, 167, 1930.

tuberculins used in Frankfort-on-Main, London, Paris and Tokio were of equal strength, it became possible to propose the adoption of an international standard tuberculin, and the proposal was made at a session of the Health Committee held in Frankfort in April 1928.

The National Institute of Medical Research, London, offered to place a certain amount of standard tuberculin at the disposal of the Health Committee to be distributed by the State Serum Institute, Copenhagen, acting as central laboratory. Later on, standard tuberculin in suitable quantities for distribution was prepared at Copenhagen, and the international standard tuberculin has since then been distributed from the latter institute. Detailed studies designed to throw light on the mechanism of standardisation have been carried out by Johs. HOLM : " Resultater over Tuberkulin, lokale Tuberkulinmetoder og disses Anvendelse paa Mennesker " (" Investigations on Tuberculin, the Local Skin Tuberculin Tests and their Application in Man "), Copenhagen, 1934.

Several methods exist for the standardisation of tuberculin : notably, the shock method in tuberculous guinea-pigs and the intracutaneous test in guinea-pigs or in man.

As tuberculin is mostly used in man for diagnostic purposes, it might appear to be sufficient to test the cutaneous effect. But as it is also employed for other purposes, it was considered useful to standardise by the shock reaction as well ; this appeared specially important in view of the recent hypothesis that shock activity and cutaneous activity are dependent on two different substances in the tuberculin.

The shock test in tuberculous guinea-pigs is by far the most expensive and the most unreliable of these methods ; the intracutaneous test in man, when it is possible to apply it, is obviously the method of preference.

The present international standard tuberculin is prepared in the same way as Koch's *Alltuberculin*. However, efforts are being made to obtain a purer preparation and two interesting proposals have appeared in recent years ; Douglas and Hartley have prepared tuberculin on a synthetic medium and have titrated it against the international standard tuberculin, while the Americans, Long, Seibert and Aronson, going still farther, have worked out a purified

and dried tuberculin (Purified Protein Derivate) which they suggest should be the international standard. Even if a purer standard preparation should be obtained, it should always be titrated against the present international standard preparation.

Another important question, that of the preparation of stable tuberculin dilutions, appears to have been practically solved by the use on the one hand of a buffer solution, and on the other of dried tuberculin.

Finally, it must be pointed out that, for diagnostic purposes, no differences have been detected between tuberculins prepared from a human or from a bovine strain.

2. THE TUBERCULIN TEST.

Three practical methods of carrying out the tuberculin test exist at present :

- The intracutaneous (Mantoux) reaction ;
- The cutaneous (Pirquet) reaction ;
- The percutaneous (Moro) reaction.

(a) THE INTRACUTANEOUS (MANTOUX) REACTION.

The intracutaneous (Mantoux) reaction has, in our experience, based on about 11,000 individuals,¹ proved to be far superior to the others when it is performed as follows :

- (1) Injection of $\frac{1}{100}$ milligramme standard tuberculin ;
- (2) Reaction read 3 days later, and, if negative, $\frac{1}{10}$ milligramme of the same tuberculin is injected ;
- (3) 3 days later the reaction is read, and, if negative, 1 milligramme is injected.

In Denmark, the reading is taken on the third instead of on the second day, as recommended by Opie and others, in order better to distinguish between a possible pseudo-reaction (disappearing by the second day), and the specific reaction which remains and may even persist for several days.

¹ These extensive experiments have been greatly facilitated by a grant from the Rockefeller Foundation.

We did not dare to adopt the simplest procedure, that of two injections going directly from $\frac{1}{100}$ mg. to 1 mg., because there were a good number of severe enough reactions after the second injection. Therefore in a non-tuberculous environment, where it is essential that disagreeable reactions should be avoided, we prefer the system of three injections.

The great advantage of the intracutaneous test is the simplicity of the technique, for it is possible to see immediately whether the injection has been made correctly. Furthermore, it can be performed rapidly, a point of considerable interest when a large number of schoolchildren are to be tested. An investigator with a little experience can perform 200 tests in an hour. Finally, this method has the considerable advantage over all others that it permits of an increase in the amount of the tuberculin introduced. The importance of this factor is demonstrated in Figure 1, which shows the incidence of tuberculin sensitivity to the introduction of the three different amounts in positive individuals between 7 and 17 years. Of these, 50 to 68% were positive with $\frac{1}{100}$ milligramme ; 89 to 97%, with $\frac{1}{10}$ milligramme ; and the remainder only positive with 1 milligramme.

Figure 2 shows the distribution of positive reactors at different ages in various population groups. It is particularly interesting to note the result of the test in older persons (69 to 93 years). Of all tuberculin-positives, only one-third reacted positively with $\frac{1}{100}$ milligramme ; another third, with $\frac{1}{10}$ milligramme ; and to obtain a positive reaction in the remainder, it was necessary to increase the amount of tuberculin to 1 milligramme.

(b) THE CUTANEOUS (PIRQUET) TEST.

This classical test may, as is well known, give comparable results, especially in cases of recent tuberculosis. The Pirquet test, however, has the drawback, if employed for mass investigations performed by a number of persons, that it is exceedingly difficult to obtain a uniform technique, whether the drilling or the scarification method is used.

A more serious disadvantage, however, is that a graduated test with increasing doses is impossible, and therefore the total number of tuberculin-positive reactors is not ascertained. To illustrate

this, an investigation at Rønne (Dr. HELSTED) is described hereafter (Figure 3).

It appears that of 549 tuberculin-positives only 42% reacted to the Pirquet test performed with standard tuberculin, whereas the Mantoux test (with $\frac{1}{100}$ milligramme), performed at the same time, gave 53%. To ascertain whether better results would be obtained by repeating the Pirquet test with a strong tuberculin (three times the international standard tuberculin), the negative reactors were tested with Pirquet (P II) and Mantoux tests ($\frac{1}{10}$ milligramme) (Mx II). By this means, the percentage of tuberculin-positives was increased to 65 and 80 respectively, but only when the Mantoux test of 1 milligramme (Mx I + II + III) was used was the total number of reactors obtained. This shows clearly the number of tuberculin-positives which would be missed by performing only the usual Pirquet test. The last experiment was carried out on individuals between 15 and 25 years. In younger persons, the difference is generally less pronounced, the ordinary Pirquet test corresponding to a Mantoux test with $\frac{1}{100}$ milligramme.

Similar experiences based on extensive examinations are reported from many other quarters—*e.g.*, England (D'ARCY HART), the United States of America, Germany and Sweden. OPIE, who has had very considerable experience in this field, claims that for mass investigations the intracutaneous test must be completed by the use of a dose of 1 milligramme standard tuberculin.

It must be concluded that for mass investigations the Pirquet test is not to be recommended.

(c) THE PERCUTANEOUS (MORO) TEST.

This test has the advantage of not requiring any instruments, and is therefore more popular, especially for tests on children. The work in Denmark reveals the interesting fact that the sensitivity of the test decreases after about 12 years and becomes less and less marked with increasing age. To illustrate this fact, we cite the following investigation on 2,153 persons from 7 to 18 years, in whom the Moro test was first performed, followed by a Mantoux test with $\frac{1}{50}$ milligramme (Figure 4). It shows to what extent the Moro test is defective in older individuals.¹ In order to obtain

¹ Had the Mantoux test been made with 1 milligramme, the difference would have been still more pronounced.

maximum results with the Moro test, the use of a strong preparation is necessary—for example, a tuberculin three times as strong as the international standard.

* * *

The general conclusion which emerges from the investigations we have summarised is *that the sensitivity of the Pirquet and Moro tests corresponds to a Mantoux test performed with $\frac{1}{100}$ milligramme standard tuberculin*. To determine all the tuberculin-positives, the negative reactors must be re-tested with an intracutaneous injection of $\frac{1}{10}$ milligramme, and eventually with 1 milligramme.

Only a complete intracutaneous test ending with a dose of 1 milligramme can be considered a standard method for mass investigations.

MANTOUX TEST.

Fig. 1. — POSITIVE SCHOOL CHILDREN.
Percentage reacting to 1/100 ; 1/10
and 1 mg tuberculin.

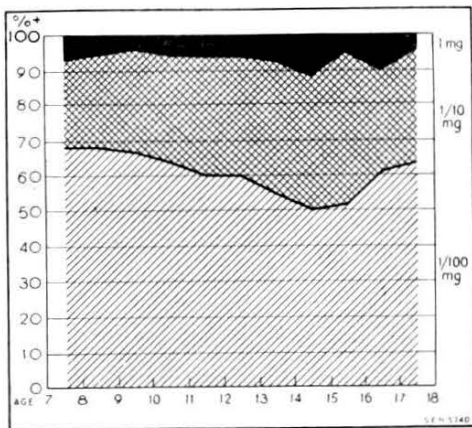


Fig. 2. — POSITIVE REACTORS IN DIFFERENT AGES.
Percentage reacting to 1/100, 1/10
and 1 mg tuberculin.

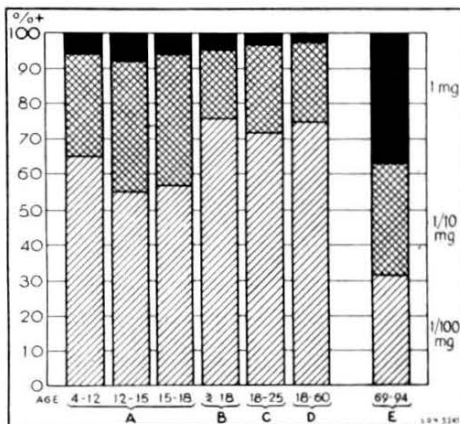


Fig. 3. — PIRQUET AND MANTOUX TESTS.

Percentage of positive reactions with each test.
(540 tuberculin positive individuals 15-25 years old tested in Rønne in 1934).

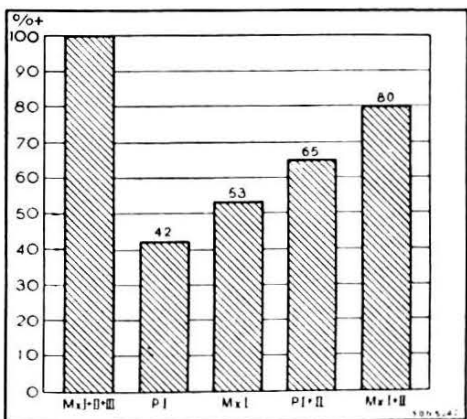
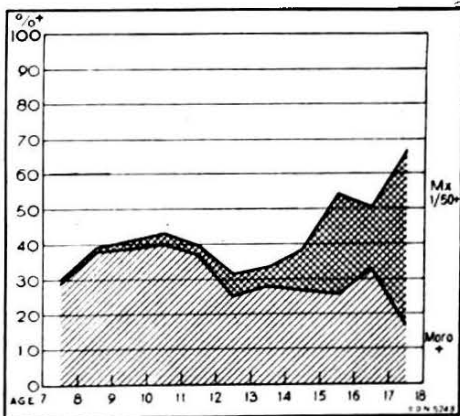


Fig. 4. — MORO AND MANTOUX TESTS IN SCHOOL CHILDREN.

Percentage of positive Reactors with each test.



Mx I : Mantoux, 1/100 mg.
Mx II : " 1/10 mg.
Mx III : " 1 mg.
P I : Pirquet, standard tuberculin.
P II : " , tuberculin 3 times standard strength.

LATEST RESULTS OF TYPHOID SEROLOGY.

(Their bearing upon the production and testing of typhoid vaccines and therapeutic sera as well as upon typhoid diagnosis.)

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The discovery of the new typhoid Vi antigen (virulence antigen) by A. FELIX and R. M. PITT, as well as the detection of the new serological V-W change of form by F. KAUFFMANN, has introduced such vitally important improvements in the experimental basis upon which the production and testing of typhoid vaccines and therapeutic sera rests that they must necessarily be taken into account in such production and testing. At the same time, this accession of new knowledge has completely eliminated the difficulties and irregularities formerly encountered in serological typhoid diagnosis. We may therefore say that great progress has been made both in the diagnostic and in the therapeutic field.

This paper cannot claim to give more than a general survey of the whole field, and the reader is referred for details to the literature quoted at the end.

THE ANTIGEN STRUCTURE OF THE TYPHOID BACILLUS.

Nowadays, we can distinguish three kinds of typhoid bacillus antigen :

- (1) The O antigen—*i.e.*, the thermostable body antigen;
- (2) The H antigen—*i.e.*, the thermolabile flagellum antigen;
- (3) The Vi antigen—*i.e.*, the thermolabile body antigen.

In accordance with the nomenclature first applied to *B. proteus* by WEIL and FELIX, the thermostable body antigen of the typhoid

bacillus—the principal representative of the Salmonella group—has been designated by O.

This O antigen is to be found in all smooth forms of the typhoid bacillus, since it represents the body substance of the bacillus, whereas the H antigen corresponds to the flagellar organ. The H form should therefore more correctly be termed O H form, since it contains both antigens. The O form, on the contrary, contains O antigen alone, since it has no flagellum. Pure O forms can occur spontaneously or can be produced artificially by growth on carbonised media. The flagellum antigen of the H form is thermolabile, whereas the O antigen is thermostable. The O antigen will stand two hours' heating at 100° C., whereas the H antigen is destroyed. The O antigen is also unaffected by treatment with absolute alcohol, which destroys the H antigen. If, therefore, it is desired to produce pure O antigen from normal flagellate bacilli (O H forms), the simplest procedure is to heat the bacilli to 100° C. or treat them with alcohol.

When used on animals and human beings for purposes of immunisation, the O and H antigens produce qualitatively different agglutinin—viz., O and H agglutinins.

H agglutinin yields a floccular flagellar agglutination which occurs rapidly and is easily disaggregated on shaking; this contrasts with the granular O agglutination, which is established more slowly, is more difficult to disaggregate by shaking and resembles the dysentery type of agglutination. It can be shown by direct microscopy on the hanging drop that there are real qualitative differences as between H and O agglutination. Whereas H agglutination produces complete immobilisation at a stroke and results in a loose kind of agglutination, motility is preserved in O agglutination, even for the agglutinated bacilli, which adhere at their poles (polar agglutination) and produce highly characteristic figures such as chains, stars, garlands, etc., which swim about in the field of vision.

The point of action of the H agglutinins is the flagellum; that of the O agglutinins, the poles of the bacillary body.

Whilst the O antigen usually develops in a satisfactory way upon the ordinary media, the H antigen makes a greater demand on the medium. To secure a good development of H antigen, a soft agar (about 2%) should be used which has been prepared from meat

broth and must be poured out in thick dabs and used in a damp state. Nevertheless, freshly isolated typhoid strains may, on occasion, be of the O form, and consequently non-motile, in which case no agglutination in H serum will occur. We should then speak of *H inagglutinability* attributable to the absence of flagella.

On the other hand, we speak of *O inagglutinability* if no agglutination in O serum occurs, despite the presence of O antigen. This O inagglutinability is of comparatively frequent occurrence with fresh typhoid strains and proves somewhat disturbing in routine work, especially if accompanied by H inagglutinability. These two kinds of inagglutinability have nothing in common; they can occur independently of each other, but also simultaneously. In the latter case, it has been usual to speak of "*inagglutinable*" strains.

Whilst H inagglutinability was explained by the absence of flagella, the cause of O inagglutinability had remained a mystery until recently. It was known that this O inagglutinability could be eliminated by various procedures—for instance, by heating—but the real cause remained unexplained. The explanation was furnished by the discovery of the new Vi antigen, which produces this O inagglutinability, though it has not been possible so far to explain why. An explanation which suggests itself at once is that this Vi antigen is a sheath-antigen enclosing the body of the bacillus in a kind of capsule, thereby preventing the fixation of the O agglutinins. Indeed, it can be proved under suitable experimental conditions that O-inagglutinable bacilli do not fix O antibodies, or do so only to a limited extent. It has, however, not been possible up till now to demonstrate the presence of a capsule or an outer slimy covering. The Vi antigen has been given that name because the O-inagglutinable forms of typhoid bacilli which contain Vi antigen are more virulent on white mice than the readily agglutinable forms which are devoid of Vi antigen.

THE DETECTION OF Vi ANTIGEN.

For the detection of Vi antigen, a Vi-immune serum is necessary—that is to say, an immune serum containing Vi agglutinins. In order to produce such a serum, rabbits are immunised with live typhoid bacilli in which the Vi antigen is developed to a maximum.

This maximum development of Vi antigen is shown by their O inagglutinability, since these strains, in a live state, produce no O agglutination. For purposes of immunisation, bacilli killed by formalin or formalin extracts can be used instead of live bacilli ; the latter would, however, appear to be more suitable for the attainment of higher Vi titres. The immune sera produced by means of such O-inagglutinable typhoid strains contain, however, in addition to the Vi agglutinins, O and H agglutinins as well ; so that these sera must be exhausted with a typhoid strain having no Vi antigen—*e.g.*, with strain H 901—in order that pure Vi serum may be secured. When Vi serum (Vi-O-H) is exhausted by means of strain H 901, all O and H agglutinins are thereby removed and only the Vi agglutinins remain. The agglutinations obtained with such Vi sera consequently afford complete evidence of the presence of Vi antigen.

If no Vi serum is available, the presence of Vi antigen can be inferred from the O inagglutinability of any given serum with a degree of probability which verges on certainty. On the other hand, Vi antigen may be present, notwithstanding good O agglutination—a point which we shall discuss below.

Vi agglutination can be demonstrated either with living bacilli or with formalin bacilli, but not with heated bacilli. Vi agglutination can therefore be carried out either with living bacilli on the slide or else in the form of a test-tube agglutination with living or formalin bacilli. In the latter case, the tube is placed in the incubator for two hours at 37° C. and allowed to stand at room temperature for twenty hours, after which the reading is taken. The presence of Vi antigen can also be detected by microscopical agglutination, just as the microscope can be used to demonstrate O inagglutinability.

Without going into details, it should be emphasised that Vi agglutination, like O agglutination, is a body agglutination, which therefore results, not in the immobilisation of the bacilli, but in polar agglutination. The Vi antigen should, therefore, be regarded as a thermolabile body antigen.

The development of Vi antigen depends on a number of factors :

- (1) The nature and previous history of the particular strain ;

- (2) The medium ;
- (3) The temperature of incubation ;
- (4) The V-W change of form.

THE SEROLOGICAL CHANGES OF FORM OF THE TYPHOID BACILLUS.

The term "serological change of form" means a change of the antigen occurring in accordance with a regular law within the limits of the several constant *Salmonella* types.

In the case of the typhoid bacillus, we can distinguish three kinds of change of form :

- (1) The H-O change of form
- (2) The S-R change of form ;
- (3) The V-W change of form.

The H-O change of form consists in the transient or permanent loss of the flagellum, or H antigen, so that the particular strain presents either the flagellate, or H form, or the aflagellate, or O form. This change is largely dependent upon the medium; when the bacilli are grown on carbolised media, O forms may be produced; these may, however, also occur spontaneously when the most suitable media are used. The best medium for the development of H antigen has been found to be a soft ascitic agar. The change from H to O may prove reversible or irreversible.

The S-R change of form consists in a change from the smooth to the rough form. The rough form represents a modification of the normal thermostable O antigen characterised, according to BRUCE WHITE, by the loss of the normal carbohydrate and by the production of a new thermostable substance—the R antigen. The flagellum antigen either remains entirely unaffected or is partly or wholly lost.

Rough forms may occur, even when the bacilli are first isolated from man, and are usually to be recognised by the duller, rougher appearance of the colony and its more irregular outline. They may occur to all degrees of rugosity and usually flocculate spontaneously in 0.85% NaCl solution. In addition to this, there may be some modification of the morphology of the bacilli, of their agglutinating

capacity, virulence and other properties. Rough forms are unsuitable for the preparation of vaccines and therapeutic sera, since they are wholly or partly devoid of the O antigen, which is necessary for immunisation.

The V-W change of form takes place between three different serological forms—*i.e.*, (1) the V form ; (2) the W form ; (3) the V-W form.

The V form has the Vi antigen fully developed, and is consequently O-inagglutinable. The W form has no Vi antigen and is well agglutinated by an O serum. The V-W form has the Vi antigen, but is nevertheless well agglutinated by an O serum, since it consists of a mixture of V and W forms.

In all three forms, H agglutination may or may not occur.

The V, W and V-W forms can be quickly and easily identified by slide agglutination with O and Vi sera (see Table 1).

TABLE 1.

| Form | Sera | |
|-----------|------|----|
| | O | Vi |
| V | — | + |
| W | + | — |
| V-W | + | + |

The serological forms (V, W and V-W) are evolved one from the other by a process which is usually reversible. The proportion in which the forms are produced by the various strains is variable. While some strains maintain their serological form in very constant fashion, there are others which frequently change over into the other form.

Under like external conditions, this change of form is largely dependent upon the nature of the particular strain. In addition to this, the medium and the temperature of incubation also play an important part.

The best form of medium for the preservation of the Vi antigen, and therefore of the V form, is soft ascitic agar, whereas on casein agar or carbolised agar full development of the Vi antigen does not take place, but a high proportion of V-W or W forms is developed. Similarly, a temperature of about 22° or 40° C. promotes an evolution of W forms; whilst, for the preservation of the V form, incubation must take place at 37° C.

Almost all typhoid strains freshly isolated from man have been found to possess Vi antigen and to be either V or V-W forms. When they are further cultivated on artificial media, W forms begin to develop in varying proportions, this entailing a loss of Vi antigen. In order to prevent this, from 1 to 3 passages through active guinea-pig serum (complement) are sufficient, since the full development of the Vi antigen is thereby restored. This process fails, however, with strains H 901 and O 901, which appear to have permanently lost the capacity for developing Vi antigen. With all other typhoid strains, however, we can maintain the V form of the typhoid bacillus constant—that is to say, obviate the V-W change of form—by passage through complement and growth on ascitic agar at 37° C.

It will be seen hereafter that, in practical typhoid diagnosis, especially in the performance of Widal tests, we shall endeavour to produce the contrary result—namely, to eliminate V forms and to maintain the O-agglutinable forms.

CHART OF THE CHANGES OF FORM OF THE TYPHOID BACILLUS.

Antigen

| | | | |
|----|-----|-----|--|
| O | < + | = S | = Smooth form (contains the specific carbohydrate). |
| O | < - | = R | = Rough form (does not contain the specific carbohydrate). |
| H | < + | = H | Form (motile). |
| H | < - | = O | Form (non-motile). |
| Vi | < + | = V | = O-inagglutinable and virulent. |
| Vi | < - | = W | = O-agglutinable and of low virulence. |

CHART OF DIFFERENCES BETWEEN O, H AND Vi ANTIGENS.

| | O | H | Vi |
|--|---|------------------------------------|---|
| Thermostability of the agglutinogens. | + | ± | — |
| Thermostability of the agglutinins .. | — | + | — |
| Alcohol-stability of the agglutinogens. | + | — | — ? |
| Formalin-stability of the agglutinogens | + | + | + |
| Development at 22° C. | + | + | ± to — |
| Development at 37° C. | + | + | + |
| Development on damp agar | + | + | + |
| Development on ascitic agar | + | ++ | ++ |
| Development on carbolised agar | + | — | ± to — |
| Type of agglutination | Granular = polar aggluti- nation | Floccular = immobi- lisation | Granular = polar aggluti- nation |
| Consequence as regards virulence and toxicity | + | — | ++ |
| Consequence as regards immunity ... | + | — | ++ |

THE SEROLOGICAL DIAGNOSIS OF TYPHOID STRAINS.

Control of the V-W change of form has made it possible to free the serological diagnosis of typhoid strains of all the irregularities and difficulties which have hitherto beset it.

By means of slide agglutination of colonies from the original fæces and urine plates, successful serological typhoid diagnosis can now be made with ease, provided Vi-immune serum is available and the old O and H sera are used in conjunction with it. In cases where the V form occurs whilst, at the same time, the flagellum antigen is absent, it was previously impossible to secure a positive slide agglutination. This can now be done by means of the Vi serum. If it is desired to demonstrate the presence of O and H antigens, in addition to that of Vi antigen, by means of microscopical slide agglutination, the strain is reseeded on to (1) ascitic agar and (2) carbolised agar.

On ascitic agar—if we except the pure O forms—a very good development of H antigen, as well as of Vi antigen, is secured, whilst with growths on carbolised agar good O agglutination can be obtained, owing to the ensuing V-W change of form. At the same time, with growths upon carbolised agar, H agglutination is completely absent. In order that this behaviour may be shown in tabular form, the typical results of microscopical slide agglutination with fresh typhoid strains have been set forth in Table 2 below.

TABLE 2.

| Medium | O | H | Vi |
|-----------------------|---|----|----|
| Ascitic agar | — | +* | + |
| Carbolised agar | + | — | + |

* In the case of O forms, H agglutination is absent.

In order, therefore, that an exact serological diagnosis of typhoid strains may be quickly made, three separate immune sera are necessary :

- (1) An O serum obtained by the immunisation of rabbits with the O form ;

- (2) An *H* serum prepared by the immunisation of rabbits with a formalin broth culture of the H form ;
- (3) A *Vi* serum prepared by the immunisation of rabbits with the V form.

If no *Vi* serum is available, the diagnosis can also be made—except for O forms—with the help of the old O and H sera and using carbolised agar and ascitic agar. O agglutination in the test-tube can indeed be obtained with all smooth forms, provided the bacillary emulsion is first boiled for ten minutes in the water-bath, in order to destroy the *Vi* antigen. On the other hand, *Vi* serum is absolutely necessary in dealing with aflagellate forms which cannot be diagnosed as typhoid strains on the strength of O agglutination alone. Thanks to the *Vi* serum, the concept of “inagglutinability” of typhoid bacilli has now been completely eliminated. Up to the present, no strain of typhoid bacilli has been found which does not yield a distinct agglutination with one, at least, of the three sera (O, H or *Vi*). It follows, therefore, that, if agglutination tests yield negative results, the tested strain can be definitely pronounced to be not of the typhoid type.

THE WIDAL TEST.

These new results of typhoid serology have led to the following conclusion in connection with the Widal test. *The use of freshly isolated living typhoid strains and the practice of agglutination testing at 37° C. are completely mistaken procedures. At that temperature, the Vi antigen contained in these strains in variable proportions is not destroyed and prevents the detection of the O agglutinin.*

Those who desire to perform Widal tests with living bacilli must, in any case, use H 901 and O 901 strains, since these are devoid of *Vi* antigen. If it is desired to work with killed cultures, it is advisable to use a formalin broth culture of strain H 901 for H agglutination, since, unlike most fresh typhoid strains, this particular strain develops H antigen extremely well. For purposes of O agglutination in such cases, bacilli heated to 100° C. or treated with alcohol are recommended.

In any case, however, the O and H agglutinins should be tested for separately.

These remarks apply to the search for agglutinins O and H, not to that for Vi agglutinins, for which living or formol-killed bacilli of the V form must be used, and the agglutination reading made after the tubes have been incubated for two hours at 37° C. and kept for twenty hours at room temperature.

It is not yet possible to say whether Vi agglutinins play a part in the serological diagnosis of typhoid fever—that is, whether typhoid sera exist in which the only agglutinins present are of the Vi form. Dr. FAARUP and I have succeeded, on several occasions, in demonstrating Vi agglutinins, in sera which also contained O and H. In these cases, however, the Vi titre was quite low (1 : 10 to 1 : 60) and these agglutinins, which had no diagnostic significance, were only demonstrable by means of the saturation test.

The experience we have gained so far affords us a reliable basis for the following proposals concerning an internationally uniform Widal test :

- (1) That all investigators should use the same strains, which should be supplied from one single centre and distributed afresh once a year ;
- (2) That the strains should, in all cases, be reseeded on the same medium, and the emulsions prepared and preserved according to the same recipe ;
- (3) That the Salmonella tests should be performed separately with O and H antigens ;
- (4) That killed emulsions be used for O and H agglutinations, since these emulsions are in every case specific and easy to read, that they remain stable for a long time and are safe and cheap ;
- (5) That formalin broth cultures be used for purposes of H agglutination, alcohol emulsions for O agglutination, and living or formol-killed bacilli of the V form for possible Vi agglutination ;
- (6) That specified dilutions of the serum, specified temperatures of incubation, specified periods of incubation and a specified technique of reading and appraisal of results be used.

TYPHOID VACCINES AND THERAPEUTIC SERA.

The researches of ARKWRIGHT, SCHÜTZE, IBRAHIM, SCHÜTZE and others having shown that only the smooth forms (S forms) of typhoid bacillus could be used for the preparation of typhoid vaccines, we now know, more especially as a result of the work of PERRY, FINDLAY and BENSTED, as well as FELIX and PITT, that O-inagglutinable smooth forms—that is to say, smooth V forms—should be used for the preparation of such vaccines and sera.

The reason why the O-inagglutinable forms exert a better immunising action is to be sought in the presence of Vi antigen, although the highly thermolabile Vi agglutinin must not be placed on a par with the Vi immunogen. It has, in fact, been shown that vaccines prepared from V forms still give effective protection after the cultures have been heated to 60° or 100° C., although this heating destroys the Vi agglutinin. On the other hand, vaccines prepared from the W form of the typhoid bacillus gave no protection against a subsequent infection with V-form typhoid strains. Further investigation will be required in order to show whether this higher immunising efficacy is regularly associated with a higher virulence of the V forms of typhoid bacillus.

If white mice are intraperitoneally injected with living typhoid bacilli, the V forms of the bacilli are found to be about ten times as virulent as the W forms. For instance, whilst, when a W form is used, 500 million living bacilli may be required to kill the mouse, 50 million of the V form will prove fatal. Intraperitoneal injection of lethal doses into mice usually produces acute illness resulting in death within one to two days, so that the delaying of death cannot be achieved by the administration of smaller doses. In these tests, the typhoid bacillus behaves quite differently from the mouse-typhoid bacillus (Breslau bacillus), which is so highly pathogenic for white mice that even minimum doses prove fatal, since they multiply rapidly in the mouse's body and lead to septicæmia. The typhoid bacillus, on the other hand, is less pathogenic for white mice. It cannot multiply within the organism to an unlimited extent, even though intraperitoneally injected bacilli can still be found in the internal organs several weeks later. So far as can be

seen from exploratory experiments, the Vi antigen does not confer upon the typhoid bacillus a capacity for development within the organism of the mouse akin to that of the mouse-typhoid bacillus. The property considered is consequently not "virulence" in the strict sense of the term, if virulence is taken to mean the enormous capacity of multiplication of the bacilli coupled with an intense power of invasion and a consequent pathogenicity. It would appear, rather, as though the Vi antigen produces a toxic effect and, when administered in sufficient doses, brings about death by acute poisoning. Some caution should therefore be exercised in applying the results of mice tests by inference to human beings, since the conditions of pathogenicity and virulence of the typhoid bacillus in man do not correspond to those in the mouse. This does not mean, however, that the results of the mice tests are valueless, for we believe that they will none the less afford valuable guidance as to the efficacy of a vaccine or therapeutic serum when administered to human patients.

As already mentioned, only vaccines prepared from V forms can protect mice against subsequent infection with V typhoid strains, whereas vaccines prepared from W forms prove wholly inadequate in this respect. This gives us the possibility of testing the comparative efficacy of vaccines on mice and of determining thereby the most suitable method of killing or preservation. So far, only a few exploratory experiments have been made; they should be further developed and confirmed.

Since human typhoid infections would appear to be exclusively infections with V forms, it follows that, for protective purposes, only such vaccines should be used as have been shown, by animal tests, to be capable of affording protection against V forms, vaccines should therefore be prepared from V forms. It would be premature, however, to give indications at this stage concerning methods for the preparation of vaccines and their preservation.

The same applies to the preparation of therapeutic sera, as to which we can only say that V typhoid forms should be used in any case for the immunisation of the animals, in order that the resultant immune serum may contain Vi antibodies. As shown by the experiments reported by FELIX and PITT, immune serum containing Vi antibodies gives protection against infection with V typhoid forms.

The mouse test provides a method for comparing the potency of various therapeutic sera and so arriving at an international standard unit.

All the details must be held over for further experimental work. For the present, we can only give the following principle :

- (1) *The V forms of typhoid bacilli should be used for the preparation of typhoid vaccines and therapeutic sera ;*
- (2) *The potency of typhoid vaccines and therapeutic sera should be tested on mice against a lethal dose of V-typhoid forms.*

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Errata to No. 1 (March 1935).

Page 241, last line of the Table, and without indication of date, add the words :
“ *Serum Tests* ”.

At the end of para. (b) add : “ *Before discontinuance of treatment the cerebro-spinal fluid should have been found to be normal* ”.

Page 242. First part of the page up to Table “ *PLAN OF ALTERNATING CONTINUOUS TREATMENT FOR SYPHILIS* ”, read :

(d) *In the event of any reduction in the amount of treatment being indicated, it is recommended that this be effected by reducing the number of arsenical injections rather than by reducing the individual dose or increasing the interval.*

(e) *After cessation of treatment a physical examination, with serum tests, should be carried out at least every two months for a year and thereafter every three months until at least two years have elapsed since suspension of treatment. At this time a complete physical examination, with tests of both serum and spinal fluid, is desirable.*

2. FEMALES.

For females (non-pregnant), treatment should be administered on the plan outlined for males, with the exception that the single dose of “ 914 ” should be reduced by 0.15 gramme and that of “ 606 ” by 0.1 gramme.

Page 244. Delete para 4.

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Authors are alone responsible for views expressed in signed articles.

**THE HEALTH ORGANISATION
AND BIOLOGICAL STANDARDISATION**

By

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on Biological Standardisation.

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INTRODUCTION.

Our object in the following pages is to give a general conspectus of the work accomplished under the auspices of the League of Nations Health Organisation in the field of biological standardisation. We have endeavoured to keep strictly to essentials, eliminating from our account, so far as possible, the purely technical details, for which specialists are referred to the reports listed in Annex 1.

By "biological standardisation" we mean the assay in relation to a single stable standard preparation of substances whose specific activity can only be estimated by comparative tests on laboratory animals.

The activity of the standard preparation is not always appraised by biological methods; for certain vitamins and hormones, for instance, it has already been found possible to take the active substance in chemically pure form as the standard, and to define this by its physical and chemical constants. If titration relatively to such a standard is still effected by biological means, the reason is that preparations issued for therapeutic use do not usually contain the active substance in its pure form and are frequently mixtures; so long as these conditions prevail, any method of assay other than the biological will accordingly be unpracticable. As soon, however, as the action of such preparations can be measured by physical or chemical processes, it is clear that the biological method must be discarded.

But to have a standard preparation is not enough; its action must also be measurable and expressible in terms of a unit of activity, the latter being defined as an arbitrarily selected volume or weight of the standard preparation.

Experience—and war-time experience in particular—has shown the difficulties in which physicians, public health services and manufacturers alike are involved through the existence of a variety of different units expressing the potency of one and the same drug.

The physician, confronted with a number of preparations from various sources, must choose. Being anxious to make his treatment effective, he will select the most potent. How is he to recognise

it, however, if the drugs have all been titrated on a different basis ? How can he compare the therapeutic results he achieves with those reported by a foreign colleague if there is no common measure for substances used on different sides of a frontier ? Finally—an even more serious consideration—many deaths could have been averted if the sera used during the war had been assayed in relation to a single standard. Doctors would not have been betrayed by the unitage given on foreign ampoules into injecting quantities of serum which they had good reason to regard as sufficient, but which were in fact inadequate, since the assay had been effected in terms of a unit of lesser potency than that to which they were accustomed.

It is the duty of the public health departments responsible for the control of medical remedies to reject ruthlessly all preparations of inadequate therapeutic value, whether they be of local or of foreign origin. In this work, uniformity of titration will be of valuable assistance to them.

Manufacturers who do not supply the home market alone but intend to export have to take account of the conditions which each country lays down for the import of drugs. Now, if all countries adopted the same unit, matters would be greatly facilitated for the producing firms, who would be relieved of the trouble of adjusting their assays to the national units which subsist here and there.

* * *

The decision to have the question of biological standardisation internationally studied was taken by the League of Nations Health Committee at its second session (Geneva, 1921). From that date onwards there have been held a series of conferences, which are listed below.

International Conference on the Standardisation of Sera and Serological Tests, London, 1921.

International Conference on the Standardisation of Sera and Serological Tests, Paris, 1922.

Technical Conference for the Study of Certain Methods of Biological Standardisation, Edinburgh, 1923.

Conference for the Standardisation of Anti-dysentery Sera, Geneva, 1924.

International Conference for the Biological Standardisation of Certain Drugs, Geneva, 1925.

Laboratory Conference on Blood Groups, Paris, 1930.

Conference for the Standardisation of Vitamins, London, 1931.

Conference for the Standardisation of Sex Hormones, London, 1932.

Second Conference for the Standardisation of Vitamins, London, 1934.

Second Conference for the Standardisation of Sex Hormones, London, 1935.

In 1924, the Health Committee decided, in order to secure continuity of work, to set up a Permanent Commission on Biological Standardisation, which has so far held six sessions (Paris, 1924 ; Geneva, 1926 ; Frankfort, 1928 ; Geneva, 1930 ; London, 1931 ; Copenhagen, 1934). Up to 1934, it consisted only of six regular members and one associate member for the study of veterinary questions,¹ but the Health Committee has just decided to reorganise it on a wider basis.

The Commission's method of work is founded entirely on international co-operation. When the state of our knowledge concerning a given substance seems to warrant an attempt at standardisation, the Commission entrusts the conduct of the preliminary work to a certain number of official and private laboratories having special experience of this branch of research, the experimental results being co-ordinated at the Copenhagen Institute in the case of serological questions and at the Hampstead Institute in other cases. As soon as it appears from the whole of the material thus collected that the solution of the problem is at hand, the experimenters concerned are convened in conference, and any remaining divergences are then

¹ Dr. Th. MADSEN, Director of the "Statens Serum Institut", Copenhagen, *Chairman*.

Professor J. BORDET, Director of the Brabant Pasteur Institute, Brussels.

Sir Henry H. DALE, Director of the National Institute for Medical Research, Hampstead.

Professor W. KOLLE, Director of the "Staatliches Institut für Experimentelle Therapie", Frankfort-on-Main.

Dr. G. W. MCCOY, Director of the National Institute of Health, Washington.

Professor L. MARTIN, Director of the Pasteur Institute, Paris.

Professor E. LECLAINCHE, Director of the "Office international des Épizooties", Paris.

easily smoothed out. The Commission thereupon makes recommendations, which are submitted to the Health Committee of the League of Nations for approval.

* * *

It is accordingly the business of the Biological Standardisation Commission first to establish standard preparations and second to select units to express their potency. This done, there remains to secure the acceptance of such standards and units for international use. Two cases may occur : either one or several standards and units are already in use for the substance to be standardised. In this case, some caution is required in order to avoid coming into conflict with the official regulations and alienating the medical profession, which may be accustomed to prescribe a given serum in doses of, say, 500 units, or insulin titrated in rabbit units. Some compromise must be arrived at which will satisfy both these requirements and will consist either in adopting an intermediate value between the extremes of the units in use or in determining a ratio of potency as between the international standard and a national standard which some country may be anxious to keep.

Or the field is clear, and the Commission can propose the standard preparation and unit which seem to it best suited for international requirements.

From the establishment of a standard and the selection of the unit to the adoption of a standard method of assay there was but a step ; nevertheless, in most cases the Commission refused, on principle, to take it, arguing that methods are liable to modification and improvement according to the indications furnished by research and that it is therefore the standard which should be immutable whilst the method may vary. Moreover, to attempt to impose some particular method, which will never be perfectly accurate since it is based on biological processes, is to restrict research. Now, it is important to leave full freedom to research workers who endeavour to improve existing methods of assay or devise new ones. This is why, whenever several methods might be used, the Commission has merely mentioned them, though it has specified which one appeared to have given the best results.

There is another principle already current in serology, though it had not yet been generally recognised in other branches, by which the Commission has been guided throughout—namely, that the potency of a preparation must not be judged in relation to a given biological action, but compared with that of a specified weight of a standard preparation. Indeed, any attempt to define a unit through the reaction induced in the animal would merely tend to perpetuate certain ideas which it is desired to eliminate, such as that of the “physiological” unit or “clinical” unit, the effect of which is difficult to appraise and which are liable to vary, not only from one animal species to another, but even in one of the same species.

* * *

So far, although the Commission's recommendations have been put forward merely by way of indication, they have been followed by the large majority of laboratories—a result that may be ascribed to the high scientific standing of its members and of the numerous experts of many countries which it has been its privilege to associate with its work.

Now, however, considering the long list of substances for which international standards have been established under its auspices, it appears desirable that its recommendations should receive official sanction. A number of countries have, it is true, already introduced the standards and units proposed into the recent editions of their pharmacopœiæ, acting upon the recommendation of the Second International Conference for the Standardisation of the Formulæ of Heroic Drugs (Brussels, 1925). It will be for the Inter-Governmental Conference on Biological Standardisation, which will meet at Geneva in October 1935, to consider what measures should be taken in order that the recommendations of the Permanent Commission on Biological Standardisation may be duly acted upon by national authorities.

I. STANDARDISATION OF SERA AND BACTERIAL PRODUCTS.

At the present time, the preservation and distribution of all standard sera and bacterial products established by the Commission are in the hands of the Danish State Serological Institute of Copenhagen, which has a specialised department of biological standardisation working with the support of the League of Nations Health Organisation under the control of Dr. Cl. JENSEN.

On application to the Copenhagen Serological Institute, all public health departments or laboratories responsible for the official testing of sera are supplied, free of charge and periodically, with a sample of the international standards of :

- Diphtheria antitoxin ;
- Tetanus antitoxin ;
- Anti-dysentery serum (Shiga) ;
- Gas-gangrene antitoxin { *B. perfringens*,
Vibrion septique,
B. œdematiens ;
- Anti-pneumococcus serum { Type I,
Type II ;
- Staphylococcus antitoxin ;
- Tuberculin.

In order that research workers may be relieved of the delicate work of dissolving a specified weight of dry standard serum in a given volume of liquid, the standard sera are henceforward supplied in glycerol-saline solution (glycerol, 2 parts ; physiological saline solution, 1 part) of carefully adjusted titre, numerous tests having shown that the addition of glycerol increases stability without affecting the accuracy of assay.

We will now give a summary account of the work which led up to the standardisation of these sera and of the attempts which have so far not led to success. For the sake of conciseness, we propose to designate the institutes which took part in the research merely by the name of the town in which they are situated. They may easily be identified from Annex 2.

1. DIPHTHERIA ANTITOXIN.

The standardisation of diphtheria antitoxin presented a comparatively simple problem, for, ever since the beginnings of the era of serotherapy, one method and one unit—those of EHRlich—had been generally recognised for the assay of this antitoxin.

Up to 1914, the standard serum of the Ehrlich Institute at Frankfurt-on-Main was supplied regularly to most producing institutes, as well as to national departments responsible for the official testing of sera. The war brought this practice to an end, and, in 1921—the date of the London Conference, which took up the study of the unification of diphtheria antitoxin titration—there were two rival units in the field—that of EHRlich and that used by the Washington laboratory. Preliminary research work had made it clear that, if any difference existed between these two units, it could only be very small ; further, that it must have come about in the course of the seven years during which the periodical assays had been interrupted, since the tests prior to 1914 had demonstrated the identity of the EHRlich and American units. This, however, had to be verified.

The tests, which were entrusted to the Copenhagen, Paris, Rome and Washington Institutes, showed that there was no appreciable difference between the two units and that that of EHRlich might be finally adopted for international use (Paris, 1922).

Furthermore, in order to make certain that the various national standard sera should always remain identical *inter se*, it appeared desirable that the Copenhagen Institute, in its capacity as central laboratory, should proceed, at least once a year, to the comparative assay of such standard sera against the authentic sample in its safe-keeping. It was understood that institutes would be free to send samples of their standard serum to Copenhagen at any time for comparison with the international standard (Geneva, 1922). Since then, the Copenhagen Institute has on very many occasions tested such national standards against the international standard.

2. TETANUS ANTITOXIN.

The standardisation of tetanus antitoxin was beset with considerable difficulties, owing to the existence of three different (American, French and German) units and four principal methods of assay. The exact ratio of these units to each other had not been ascertained and the four methods did not proceed from the same basis. Nevertheless, it appeared possible to arrive at some common measure by agreeing to select one particular standard serum. Before this, however, the relation in which the three units stood to each other had to be determined experimentally (London, 1921).

Comparative assays performed by the Copenhagen, Frankfort, Paris, Rome and Washington Institutes showed that, if the German serum was taken as having a titre of one unit, the unitage of the American serum would be from 60 to 66 and that of the French serum about 2,500.

The Commission then decided to choose a unit which would be intermediate between these two extremes (Geneva, 1922).

Had the ratios been exactly 1 : 50 and 1 : 2,500, they might have been accepted as affording the most convenient measurement. Since this was not so, the units in current use had to be modified. To this end, Professor W. KOLLE offered to adjust the German unit so that the ratio to the American unit should be exactly 1 : 50. He further suggested that, for the convenience of medical practitioners, the German unit be divided by a hundred in order to reduce it to the same order of magnitude as the unit adopted for diphtheria antitoxin.

The ratio between the various units was thenceforward as follows :

50 American units = 100 new German units = 2,500 French units.

Since, therefore, the ratio of potency as between the American unit and the new German unit was now 2 : 1, Professor Louis MARTIN proposed that the new German unit be adopted as the international unit. In this way, an international unit was established in principle (Paris, 1922).

There remained to determine experimentally, in terms of this new unit, the exact relation between the standard sera used in various laboratories.

Certain discrepancies having been brought to light by these tests (Paris, 1924), the Commission endeavoured to eliminate them by recommending the use of the same test-toxin in laboratories making such assays.

The definition of the new international unit as given by the Commission is as follows : 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 (Geneva, 1926).

Dr. McCoy then declared that he had no authority to approve the new unit for the United States of America, but that he could see no objection to American producers of tetanus antitoxin for export indicating on the labels the content of the serum in international units as well as in American units.

The various institutes began to prepare standard sera titrated in terms of the new international unit as defined, and the Copenhagen Institute, acting here again as central laboratory for the Health Organisation, undertook the periodical comparative assay of such sera in order to control the uniformity of the unit in which their titre was expressed. The tests conducted up to 1928 demonstrated that the unit remained identical all round ; accordingly, in consideration of this research work, the Commission finally adopted for international use the tetanus antitoxin unit as defined above (Frankfort, 1928).

In the course of the ensuing years, however, differences in the value of certain national units appeared, despite repeated assays. It had to be recognised, therefore, that, from causes so far unknown, the titre of certain national standard sera had slightly altered, or, alternatively, that the units were not absolutely equivalent when the assays were conducted with toxins other than those originally used to determine their potency.

The Commission, after considering the numerous tests conducted on parallel lines at Copenhagen, Frankfort and Hampstead, therefore instructed the Copenhagen Institute to draw up a new plan of comparative research (Copenhagen, 1934). This plan was to eliminate so far as possible the variable factors from the experiments ; with that object in view :

- (1) The purity of the strains used for the preparation of the toxins was to be verified ;

(2) The same toxin was to be used by all institutes taking part in the comparative assays ;

(3) The manner in which the toxin was preserved was to be stated ;

(4) The p_H of the toxin dilutions was to be that of the toxin ;

(5) The time elapsing between the preparation of toxin-antitoxin mixtures and their injection, as well as the temperature at which such mixtures should be kept during that time, were to be stated ;

(6) The guinea-pig and mouse were to be used simultaneously for titration.

This plan is being carried into effect. The Copenhagen Institute submitted to Professor ZEISSLER (Hamburg) the strains which it uses for the preparation of toxin, and asked him to test them. They were found pure, but endowed with varying antigenic power. The most active of these strains was therefore selected for the preparation, at Copenhagen, of a dry serum which is to be used for the comparative tests. These will be performed on five sera prepared by the Copenhagen, Hampstead, Paris, Frankfort and Washington Institutes. Each serum will be assayed, first, against the Copenhagen dry serum, in accordance with uniform methods, the details of which remain to be fixed, and, second, against the toxins used in these institutes by the method they currently employ.

3. ANTI-DYSENTERY SERUM (SHIGA).

Before the standardisation of this serum could even be taken in hand, two questions of principle had to be settled : first, Was a polyvalent serum acting against the various types of the dysentery bacillus to be selected ? and, second, Should the antitoxic or the anti-microbial potency, or both, be measured ?

The London Conference (1921) decided to deal only with monovalent anti-Shiga serum and to have its antitoxic potency assayed against toxin or killed cultures. Once this had been decided, there remained, however, a number of technical problems for which a solution had to be sought—viz., What method should be followed for the preparation of the toxin ? What technique should be

adopted to immunise horses ? In the determination of the anti-toxin content of the serum, should the method of the toxin-anti-toxin mixture or that of separate injections be used ? Should the rabbit or the mouse be selected as the experimental animal ? How many animals should be used for each dose ? How many minimum lethal doses of toxin should be administered ? Should the titration be made relatively to L_+ or L_0 ? What should be the route of injection ?

It will be seen that this plan of study was both extensive and complex. Several institutes had already begun to carry it into effect when the Paris Conference met (1922). The latter decided that the tests should be directed to establish what animal species, rabbit or mouse, should be used, and to determine exactly how liquid toxin, dry toxin and heat-killed microbes acted. The toxin-antitoxin mixture left in contact half an hour at room temperature was to be administered by the subcutaneous, intravenous or intraperitoneal route.

By co-operation between the institutes of Basle, Berlin, Bucarest, Copenhagen, Cracow, Frankfort, Hampstead, London, Paris, Tokio and Warsaw, it was found possible, after many laborious efforts, to clear up a number of problems and to set the standardisation of anti-dysentery serum on a solid scientific foundation (intravenous injection of a toxin-antitoxin mixture into mice). One fact was made abundantly clear by the experimental work—namely, that the requisite regularity in the assays could only be achieved by using the same toxin. Hence the need for preparing and distributing a test toxin at the same time as a standard serum.

The Copenhagen Institute having advocated a method of assay based on this principle, the Commission adopted it and recommended that the experiments be continued with the serum of the Copenhagen Institute as the standard, on the understanding that this institute would send a supply every two months during a whole year to the laboratories concerned, with instructions for its use and an indication of its titre in terms of a provisional unit of potency. If all the results of the assays agreed, it would then be possible to adopt a definitive international unit in terms of this standard serum (Geneva, 1926).

Since these tests gave concordant results, the Commission adopted the standard serum prepared at Copenhagen for international use

and decided that one international unit should be defined as the specific activity contained in $\frac{1}{200}$ c.c. of this serum (Frankfort, 1928), this corresponding to 0.05 mgrm. of dry standard serum.

During the following years, certain criticisms were levelled at the international standard serum, of which it was alleged that the titre had fallen. This assertion was based upon the comparison of the standard international serum with the German standard serum, the ratio of these two standards having originally been fixed at 1 to 60. Fresh comparative assays of the standard sera kept at the Copenhagen, Hampstead and Frankfort Institutes had to be undertaken and the statisticians of these institutes instructed to make a fresh examination of the documentary material collected (Copenhagen, 1934). They concluded that there was nothing in the experiments to show that the titre of the international standard serum had varied. The value of the international unit hence remains unchanged.

In order that the ratio between the international and the German standards may be fixed for the future, it has been agreed that the activity of a solution containing 100 mgrm. of German standard serum in 4.3 c.c. of physiological saline solution is indistinguishable from that of a solution of international standard serum having a titre of 200 units per c.c.

4. GAS-GANGRENE ANTITOXINS.

Gas-gangrene antitoxins having come more and more into use since the war and the number of producing laboratories being already considerable, the Commission was bound to turn its attention to the titration of these sera; it therefore decided to arrange for a comparison of the standards of the various types of gas-gangrene antitoxins that were in use in the various countries (Frankfort, 1928).

(a) *B. perfringens*.—As regards *perfringens* antitoxin, the Hampstead Institute was selected by the Commission (Geneva, 1930) to supply samples of dry serum of known and unknown titre, together with a test toxin, to the Beckenham, Berlin, Copenhagen, Elstree, Frankfort, Paris and Washington laboratories. One of these antitoxins was the standard which had been in use for some years

in the United States of America and, the unit originally adopted to express its potency being inconveniently large, a new unit équivalent to $\frac{1}{100}$ of the old had come into force in 1930. According to the tests performed at Hampstead, this new American unit was equivalent to 0.322 mgrm. of the American standard preparation.

In consideration of the whole of the assays effected, the Commission recommended that the standard preparation and unit in use in the United States be accepted as the international standard and unit of perfringens antitoxin (London, 1931).

(b) *Vibrio septique*.—Under the terms of a decision of the Commission (London, 1931), the possibilities of standardising vibrio septique antitoxin were to be explored in accordance with the same principles as had been adopted for perfringens antitoxin. Accordingly, the Hampstead Institute prepared, from a quantity of antitoxin placed at its disposal by Professor WEINBERG (Paris), a dry standard with a view to its adoption for international use.

This preparation, together with a provisional standard prepared at Washington, an antitoxin of unstated potency and a test toxin, were distributed to the institutes of Beckenham, Copenhagen, Elstree, Frankfort, Paris and Washington. The following table, which is reproduced in order to show the measure of agreement that can be attained in such assays, gives the values assigned by the various research workers to the antitoxin of unstated potency :

| | Units per c.c. |
|------------------|----------------|
| Copenhagen | 154-167 |
| Paris | 170 |
| Frankfort | 160 |
| Beckenham | 160 |
| Elstree | 150-155 |
| Hampstead | 155 |
| Washington | 160-170 |

In consideration of these assays, the Commission recommended that the Hampstead dry preparation of vibrio septique antitoxin be accepted as the international standard and that the activity contained in 0.2377 mgrm. of the dry standard be defined as one international unit (Copenhagen, 1934).

(c) *B. œdematiens*.—The Copenhagen Institute having been asked to prepare a dry standard œdematiens antitoxin and to propose a unit for international use, it sent a supply of this standard,

an œdematiens antitoxin of unstated potency and a test toxin to the institutes of Beckenham, Berlin, Elstree, Hampstead and Washington for purposes of comparative assay. The results obtained were in every way concordant. The Commission accordingly recommended that the Copenhagen dry œdematiens antitoxin be accepted as the international standard and that the activity contained in 0.2681 mgrm. of this standard be defined as one international unit (Copenhagen, 1934).

(d) *B. histolyticus*.—The Copenhagen Institute also undertook the preparation of a dry histolyticus antitoxin suitable for use as an international standard. The unit proposed was that defined by Professor WEINBERG, of the Paris Pasteur Institute.

Comparative assays are proceeding, and the Commission will be able to decide on the choice of an international standard and unit at one of its next sessions.

5. ANTI-PNEUMOCOCCUS SERA.

The work of standardisation of anti-pneumococcus sera has been carried out in two phases.

The first opened at the London Conference (1921), which drew up a plan of work concerning the technique to be applied in the assay of the sera and the distribution of various types of pneumococcus in the world. Research on this subject was conducted at Berlin, Copenhagen, London and Paris, and the results were submitted to the Paris Conference (1922), which made the following decisions. In the first place it adopted, for the classification of pneumococci into various serological types, the three principal types I, II and III, as defined by the research workers at the Rockefeller Institute of New York, strains not conforming to these three types to be classed in a group *x*. In the second place, it recommended that a study of the geographical distribution of pneumococci should be undertaken, not merely in Europe and in the United States, but also in tropical countries.

Finally, without pronouncing any opinion as to the therapeutic value of the serum in the treatment of pneumonia, the Conference considered that the assay against a standard serum by the mouse test afforded a sufficient basis to justify an attempt at international

standardisation, and instructed the Copenhagen Institute to furnish standard cultures as well as standard sera both agglutinating and therapeutic. Trial assays were carried out at Albany, Berlin, Copenhagen and London, without, however, yielding satisfactory results (Paris, 1924). The Commission accordingly expressed the opinion that the question of the standardisation of anti-pneumococcus sera had not yet reached a stage permitting of the adoption of recommendations on international lines (Geneva, 1926).

The second phase opened in 1930. At this time, in view of the growing therapeutic use of anti-pneumococcus sera types I and II in certain countries, and of the practice which had developed of assaying sera relatively to a bivalent serum F.146, prepared by Dr. D. L. FELTON, of Harvard University, the Commission took up once more the question of the choice of international standards for anti-pneumococcus sera.

(a) *Type I.*—By agreement with the Washington Institute, the Hampstead Institute prepared a dry standard anti-pneumococcus serum type I titrated in terms of the type I Felton unit as contained in $\frac{1}{200}$ c.c. of serum F.146.

The Hampstead Institute then sent the standard preparation and serum F.146 to Dr. FELTON and to the Albany, Beckenham, Detroit, Elstree, New York and Toronto Institutes, requesting them to determine the ratio of potency of the anti-type-I fraction of serum F.146 to the dry standard preparation. These assays having entirely confirmed the Hampstead results, the Commission adopted the dry type I anti-pneumococcus serum prepared by the Hampstead Institute as the international standard, and decided that the activity contained in 0.0886 mgrm. of this serum be defined as one international unit.

(b) *Type II.*—The Hampstead Institute also prepared a dry type II anti-pneumococcus standard serum and determined its potency in relation to anti-type-II component of serum F.146. Though it was not possible for similar comparative tests to be carried out by other authorities, the Commission nevertheless recommended that the Hampstead dry serum be adopted as the international standard and that the activity contained in 0.0894 mgrm. of this serum be defined as one international unit (Copenhagen, 1934).

6. STAPHYLOCOCCUS ANTITOXIN.

Being convinced that it would be of advantage, now that the staphylococcus antitoxin and toxoid are frequently used in treatment, for an international standard and unit for staphylococcus antitoxin to be adopted, the Hampstead Institute took the initiative of submitting to the Commission a dry antitoxin and proposing a unit for international use (Copenhagen, 1934).

The institutes of Beckenham, Brussels, Copenhagen, Elstree, Frankfort, Marburg, Melbourne, Paris, Toronto and Washington were supplied with samples of this provisional standard preparation and antitoxins of unstated potency, but no test toxin. They were consequently obliged to carry out their comparative assays with toxins of different origin and potency.

The reports of these institutes showed that the potency of staphylococcus antitoxin relative to that of a standard antitoxin can be determined with a high degree of accuracy and that the various methods of titration used give concordant results. This confirms the view already advanced above—that the standard should be immutable whilst the method may vary. In the case under consideration, the tests were performed by five different methods—hæmolysis, intradermal injection into the guinea-pig or rabbit, and intravenous or intraperitoneal injection into the mouse—but the results were none the less the same.

Since, moreover, the unit proposed appeared to be suitable, the Commission recommended that the Hampstead dry staphylococcus antitoxin be accepted as the international standard and that the specific antitoxic activity contained in 0.5 mgrm. of this antitoxin be defined as one international unit.

7. TUBERCULIN.

At its meeting in October 1924, the Health Committee decided to call for a study of the methods of assay of tuberculin (KOCH'S *All Tuberkulin*) in use in various laboratories, to compare their results and determine whether any one of them could be recommended as the standard method. The investigation of this question was entrusted to Professor A. CALMETTE, who, jointly with Dr. DE POTTER,

drew up a report entitled *Sur le titrage (Standardisation) des Tuberculines*,¹ based upon the comparative examination of thirty-four samples of commercial tuberculin. This memorandum brought to light considerable differences in the method of preparing tuberculin. Thus, there were differences in the types of tuberculosis bacillus used, the composition of culture media, their pH, the period of incubation, the method of filtering, sterilisation and concentration. Reviewing various methods of titration, the authors pronounced in favour of intradermal inoculation performed in parallel series on the same, previously sensitised, animal (tuberculous guinea-pigs or cattle), since by this means the toxic potency and the antigenic potency of several tuberculins can be measured on the same subject in relation to one tuberculin selected as standard. This method is, moreover, strictly specific, requires only the use of a small number of animals and yields results that are more accurate, more quickly obtained and easier to interpret than those of any other method of titration.

Having this report before it, the Commission decided (Geneva, 1926) to arrange for a comparison of the standard tuberculin preparations used in the Frankfort, Hampstead, Paris and Tokio Institutes. The tests showed that these various standards were identical in toxic and antigenic potency (Frankfort, 1928).

The Hampstead Institute having provided a considerable quantity of tuberculin suitable for use as a standard at the Copenhagen Institute, the latter conducted comparative tests extending over a number of years, which again demonstrated the equivalence of the various national standards.

These results determined the Conference to adopt as the international standard the tuberculin preparation made at Hampstead and kept at Copenhagen ; it is suitable for the comparative titration of tuberculins on sensitised subjects (London, 1931).

From various quarters the desire was expressed that a tuberculin standard be set up which would serve exclusively for skin tests and from which the toxic potency would have been eliminated leaving only the cutaneous potency, since these two properties are bound up with the presence of different substances which may be separated. This problem is at present under investigation.

¹ Document C.H.429.1926.

8. DIPHTHERIA TOXINS USED FOR THE SCHICK TEST.

"The test dose" to be used for the Schick test was originally defined as a fiftieth part of the minimum lethal dose for the guinea-pig of a mature diphtheria toxin. Since this definition continues in use in the United States of America, titration in that country is entirely based upon the lethal action of the toxin of the guinea pig.

Opinions differed as to the need for a further adjustment of the test dose in regard to neutralising power. In certain countries—the United Kingdom, for instance—this adjustment was required by law. This additional proviso precluded the use of numerous toxins which would have been allowed under American regulations. In order to arrive at international agreement on the definition of the test dose, the Commission investigated the question of the necessity of titration in regard to neutralising power (Geneva, 1930).

Two diphtheria toxins having a different toxoid content were selected for the tests with the assistance of the Beckenham laboratory. The Hampstead Institute, which directed and co-ordinated this research, arranged for these toxins to be tested clinically at the Birmingham, London and Motherwell hospitals, and experimentally in the Copenhagen, Milan, New York, Prague, Toronto, Vienna, Warsaw and Washington laboratories.

The Schick reaction was to be tested for on actively immunised persons, on convalescents recovering from diphtheria, on healthy subjects who had been given preventive treatment with diphtheria antitoxin, and, finally, on normal persons. Out of 1,457 persons examined, the number of Schick-positives was 594 with Toxin A, and 660 with Toxin B.

The international enquiry thus showed that the number of persons classified as Schick-positive or Schick-negative depended upon the nature of the toxin used in the test. The Commission therefore recommended (London, 1931) that, in the choice of a diphtheria toxin, account should be taken of its neutralising power as well as of its toxicity. It further laid down a definition of a toxin possessing the properties required for use in Schick tests, and specified the dose of toxin to be used in the tests.

9. BLOOD GROUPS.

In 1927, the Health Committee, at the suggestion of its President, Dr. Th. MADSEN, instructed the Commission to consider the standardisation of the sera used in blood-group determinations, and laid stress on the desirability of securing a uniform nomenclature for these groups. With regard to this last-named point, the Commission pronounced in favour of the system of notation advocated by von DUNGERN and HIRSZFELD (O, A, B, AB) and recommended its adoption for international use. As for the denominations of the test sera, they should, in the Commission's opinion, be as follows :

Test serum A (anti-B),
Test serum B (anti-A),

test serum A (anti-B) to be delivered in containers of white glass, and test serum B (anti-A) in containers of brown glass, in order to avoid any risk of confusion.

The Commission further proposed that the Copenhagen Institute should arrange for research in regard to the preparation, preservation and titration of the test sera (Frankfort, 1928).

Two series of iso-agglutinin titrations were then undertaken by twelve different research workers, but the results were widely divergent; the discrepancies observed were probably due to slight undetected differences in the technique of the tests and the method of reading the results. In an endeavour to achieve greater uniformity, Dr. MADSEN took advantage of the presence in Paris of numerous specialists who were attending the Microbiological Congress (1930) and brought them together in the laboratories of the Pasteur Institute, where fourteen of them consented to perform simultaneously the titration of the iso-agglutinin content of twelve different samples of serum.

The conclusion which emerged was that, despite the care given to these titrations, which were performed under strictly identical experimental conditions, the degree of uniformity reached was not yet sufficient. The experts consequently laid down the general lines of an investigation into the technique of the tests, the methods of preventing the deterioration of sera during transport, and the

accidents, mortal or other, which occur on the occasion of blood transfusion. The possibility of standardising iso-agglutinating sera appears, however, to be still remote.

10. STREPTOCOCCUS ANTITOXIN (ANTI-SCARLATINA SERUM).

As early as 1922, the Paris Conference expressed the hope that the question of standardising streptococcus antitoxin would be studied. In 1926, the Commission recommended that the question of immunisation against scarlet fever should be investigated by the American, British and Polish Institutes in collaboration with the Copenhagen Institute.

By 1927, the Hampstead Institute had prepared a provisional dry standard antitoxin and had distributed this together with a test toxin to various laboratories. At about the same time, Dr. McCoy offered to place at the Commission's disposal the standard antitoxin that had been officially accepted in the United States.

Without expressing an opinion on the ætiology of scarlet fever or on the methods of testing sera prepared by means of hæmolytic streptococci, the Commission felt that, in order to make future research more readily comparable, it would be advantageous to select the American standard serum as a basis for study (Frankfort, 1928).

Reverting to the matter at its Copenhagen session (1934), the Commission had to recognise that all attempts to create or adopt an international standard for streptococcus antitoxin were crippled by the fact that patents covering the preparation of this serum and the toxin used in producing and testing it existed in the United States of America and in several other countries. By the terms of the licences granted by the patentees, Drs. George and Gladys Dick, of Chicago, the producers are bound to submit a sample from every batch of such serum for a determination of its value in terms of a unit defined by them as the quantity required to neutralise in man five skin-test doses of streptococcus toxin. Even in countries, such as the United States, where a standard serum and unit have been officially accepted, manufacturers are therefore bound to submit samples from each batch of their serum to the patentees, who proceed to an independent determination of its value in terms of their own unit.

In these circumstances, the Commission decided that it was useless for it to proceed with work preparatory to an agreement on an international standard and unit, the use of which might conflict in some countries with the authority exercised by the patentees. It recommended that this decision, and the circumstances in which it had felt itself obliged to take it, should be reported to the Health Committee of the League of Nations.

11. ANTI-MENINGOCOCCUS SERUM.

In view of the variety of types of meningococcus encountered in different countries, the London Conference (1921) proposed that the several experimenters should exchange and compare, one with the other, the strains of meningococcus isolated by them from the cerebro-spinal fluid, as well as their agglutinating sera. It further suggested that research be undertaken as regards the determination of the anti-endotoxic and bactericidal potency of therapeutic serum. Unfortunately, none of the six main methods of assay applicable to these properties was capable of yielding satisfactory results by itself. In the circumstances, therefore, recourse had to be had to several methods, as the official regulations of certain countries prescribe.

The Paris Conference (1922), having before it reports drawn up by the institutes of Albany, Berlin, Copenhagen and Paris, recommended that, in order that a uniform nomenclature might be arrived at, the classification of meningococci be based on a primary division into groups, designated by roman figures, and a subdivision of these groups into types denoted by a letter added to the group figure (*Ia*, *Iib*, etc.). It further proposed that the various methods of assay continue to be tested on monovalent and polyvalent heated and unheated sera, and that special attention be given to strains isolated from cases in which sero-therapeutic treatment had failed.

Four years later no new facts had come to light on the subject, and the Commission (Geneva, 1926) took the view that the state of our knowledge held out no hope of any international agreement on the standardisation of anti-meningococcus serum. This still holds good at the present time.

12. DIPHTHERIA FORMOL-TOXOID.

What preparation of formol-toxoid could be adopted as an international standard and what amount of this standard should be taken as the unit? Such were the questions which the Commission had decided to study (Frankfort, 1928). In order to facilitate research, the Paris Pasteur Institute had kindly placed a number of samples of formol-toxoid (anatoxine) at the disposal of the Commission. In the first place, however, agreement had to be reached on the method to be adopted for titration, since this could be effected either by RAMON'S flocculation test or by animal tests. In order to facilitate comparison of the results obtained by these two means, the Copenhagen Institute prepared a standard serum to be used for the determination of the flocculating power of various samples of formol-toxoid. Although a very large number of tests have been performed in the Copenhagen, Frankfort, Garches, Hampstead, Toronto and Washington Institutes, no final result has yet been reached.

13. STAPHYLOCOCCUS FORMOL-TOXOID.

At its Copenhagen session (1934), the Commission heard a statement by Dr. D. T. FRASER (Toronto), who stressed the desirability, now that an international standard was available for staphylococcus antitoxin, of securing agreement as to the conditions which should be satisfied by staphylococcus formol-toxoid, the clinical use of which had now passed the experimental stage.

The method employed at Toronto to demonstrate whether the antigenic potency of staphylococcus formol-toxoid samples is adequate is to administer two spaced injections intravenously into rabbits and to measure the antitoxin content of the animal's serum at a fixed interval after the second injection.

The discussion which ensued upon this statement showed the need for determining the part played by various factors, such as the choice of animal species, the number of injections to be given, the route of administration, the dose to be injected and the interval between injections.

Acknowledging the importance of the question, the Commission considered that it would be desirable to arrive, at the earliest possible

moment, at an international agreement as to the antigenic potency of staphylococcus formol-toxoid to be issued for practical use. To that end it recommended that the investigations carried out by Dr. FRASER should be taken as a basis for further studies.

14. SWINE ERYSIPELAS SERUM.

There are sera which are of equal moment to medicine and to veterinary therapeutics, since their specific action is directed against pathogenic micro-organisms that are capable of attacking both man and domestic animals. Accordingly, the Commission decided (London, 1931) to undertake, with appropriate veterinary advice, studies on the standardisation of such sera, among which must be included that which is active against swine erysipelas.

The Frankfort Institute having offered to place at the Commission's disposal a certain quantity of the German standard preparation of this serum, the Cambridge and Zagreb Institutes used it in comparative assays performed both by the German official method and in other ways. Since the results of these titrations were not in agreement with those secured at Frankfort, further tests will have to be carried out.

II. STANDARDISATION OF CERTAIN DRUGS.

We now have to consider a far more diversified group of products—alkaloids, glucosides, arsenical derivatives, gland extracts—whose only common feature is the biological character of the methods of assay which are applicable to them. The reason why they are grouped together is an historical one: they were enumerated in the memorandum which Sir Henry DALE submitted to the League Health Committee in 1923. Now this memorandum was the starting-point of the whole of the work which has been accomplished under the auspices of the Committee in the field of biological standardisation of drugs. That same year, a technical conference met at Edinburgh which earmarked for study, as regards the possibility of standardised titration, the cardiac drugs, the anthelmintics, ergot of rye, the arsenobenzenes, insulin, posterior lobe pituitary, thyroid and suprarenal extracts.

The International Conference on the Biological Standardisation of Certain Remedies (Geneva, 1925) continued the work that had been mapped out at Edinburgh. Finally, at its Frankfort session (1928), the Permanent Commission on Biological Standardisation proceeded to a revision of certain recommendations previously adopted.

We propose to give, in respect of each of the remedies considered, a brief account of the experimental work upon which the decisions taken at these three meetings are based. In this way some idea will be gained of the intricacy of the work accomplished, which, whilst it may still present certain imperfections, none the less stands as a fine example of what may be achieved by international scientific co-operation.

In the first place, however, we wish to indicate that the institution which at present undertakes, on behalf of the Health Organisation, the work of distributing centre for the international standards of digitalis, strophanthus (ouabain), insulin, sulpharsphenamine and posterior lobe pituitary extract¹ is the National Institute for Medical Research at Hampstead (London, N.W. 3).

This institute has a biological standards department—under the control of Dr. P. HARTLEY—and sends free samples of the international standards in its safe-keeping periodically, to any public health service or recognised scientific institution which applies therefor.

1. DIGITALIS.

Some uncertainty still prevailed in regard to the assay of digitalis. In the first place, it had not been demonstrated that the active principles measured by the different methods were the same. Secondly, it remained to be determined which method would yield the most accurate titration of the active principle responsible for the therapeutic effect of digitalis. Among the numerous methods of titration submitted to it, the Edinburgh Conference selected two—that which consists in determining the lethal dose for the frog, by injection into the lymph-sac, and that which is based upon slow infusion into the cat until stoppage of the heart is produced—and recommended that further research work be undertaken with a

¹ See page 533.

view to establishing the relationship between the biological effect measured by these methods and the therapeutic action.

The Conference further recommended that the unit of digitalis activity be expressed in terms of a given weight of a standard preparation and not in terms of the lethal dose for any animal species. It accordingly accepted the proposal of Professor R. MAGNUS (Utrecht), who offered to facilitate the further progress of the research work by making a stable preparation of dried digitalis leaves which might serve as the international standard.

Three preparations of this kind—one of which was the proposed standard—were distributed for purposes of comparative examination to various experimenters at Ann Arbor, Berlin, Copenhagen, Edinburgh, Ghent, Hampstead, London, Manila, Munich, Utrecht, Vienna and Washington, some using the frog method, others the cat method, whilst others again applied a technique of their own.

The results yielded by the frog method were as concordant as could be expected considering that the preparation of the extracts had not been uniform (mean variation up to 20%).

The cat method proved more accurate, the mean variation not exceeding 10% when aqueous infusions were used.

The therapeutic tests performed with these three samples of digitalis on patients suffering from heart disease, in the hospitals at Edinburgh and Baltimore, showed that it is not possible to arrive at any quantitative appraisal of the action of a digitalis preparation through tests on human beings by present-day clinical methods. The only inference that can be drawn from these experiments was that the sample which was least active on animals also produced the least effect on man. It would seem, therefore, from a clinical standpoint, that there is no need to assay digitalis preparations with strict accuracy ; and that digitalis leaves whose activity is within $\pm 25\%$ of that of the standard preparation would satisfy therapeutic requirements.

The whole of these experimental results were submitted to the Geneva Conference, which felt unable either to decide as between the frog and the cat methods or to recommend any particular method of extraction. In its view, a satisfactory comparison could be made by any method which is properly adjusted, provided the preparation to be tested and the standard preparation have been treated in the same way.

The Conference decided that this standard preparation should consist of a powdered preparation of digitalis leaves of the same strength (within $\pm 10\%$) as the powder prepared in accordance with the decisions of the Edinburgh Conference. For the preparation and assay of this new standard, it approached Professor MAGNUS requesting him to control the titre of the standard powder annually and, in the event of any deterioration or exhaustion of the supply, to prepare a new standard of equal activity.

Professor MAGNUS then procured ten different samples of digitalis leaves from German, American and Netherlands sources, which he mixed, powdered and dried between 50° and 60° C. Tests showed that the lethal dose of the standard powder as prepared was 82.5 mgrm. per kg. body-weight of cat—that is to say, that 1 gramme of powder contained 12.1 lethal doses for the cat.

The standard preparation was distributed into brown glass ampoules and held at the disposal of the various countries, which have thus been able to set up their national standard by comparative assay.

At that stage of the research work, the Conference did not feel able to set up an international unit, but suggested that digitalis leaves should not differ in strength from the standard powder by more than 25%. The drawback of this proposal is that highly active digitalis leaves have to be mixed with less active leaves, in order to adjust the mixture to the desired titre ; on the other hand, it has a great advantage in that any dispensary can always prepare digitalis of this titre, since it represents a mean.

The standard powder having proved entirely suitable for practical purposes, the Commission decided (Frankfort, 1928) to adopt it finally for international use, the Hampstead Institute being entrusted with its preservation and distribution on behalf of the Health Organisation.

Owing to the lamented death of Professor MAGNUS, the Commission requested Professor BIJLSMA (Utrecht) to prepare and assay a new standard powder when the present supply should be exhausted. Further, it considered that more stringent precautions should be taken than had previously been the case as regards the water content of the standard international powder. In future, this product must not contain more than 3% of water, whereas the present standard contains from 7 to 8%.

Finally, the Commission recommended that, when the titre of digitalis or its preparations is expressed in units of activity, the unit employed should be the international unit defined as the specific activity contained in 0.1 gm. of international standard powder.

2. STROPHANTHUS (OUABAIN).

For strophanthus and its preparations, the Edinburgh Conference adopted as standard pure crystallised strophanthin (ouabain), and the Geneva Conference confirmed this decision.

The Commission (Frankfort, 1928), considering the variable activity of different preparations of crystallised ouabain due to varying proportions of water of crystallisation, recommended that, when strophanthus preparations are assayed in relation to ouabain, the activity of the latter should be expressed in terms of water-free ouabain. To facilitate such assays it was decided to establish an international standard preparation of ouabain having an accurately determined content of water-free ouabain. Professor TIFFENEAU (Paris) kindly undertook to prepare the standard, which is kept by the Hampstead Institute and distributed by it on behalf of the Health Organisation.

3. INSULIN.

Though insulin is a comparatively new acquisition in our armoury of therapeutic weapons, the units advocated to express its activity were already numerous when the Edinburgh Conference met in 1923. At that time "physiological" units, "clinical" units, "rabbit" units, or even "mouse" units were in current use, all these values being based on biological reactions which are delicate to measure and are especially difficult to compare *inter se*.

The first thing for the Edinburgh Conference was to make a choice from among these units ; it decided to take that introduced by the Insulin Committee of Toronto University. According to this Committee, one insulin unit was equivalent to one-third of the quantity which reduces the blood-sugar percentage to 0.045—that is to say, to the point at which convulsions occur in a normal rabbit of 2 kg. body-weight from which all food has been withheld for twenty-four hours.

The question was, however, whether a unit thus defined would maintain the necessary uniformity in tests performed in different laboratories in different countries on animals kept under different conditions.

It appeared to the Conference that the best way of stabilising the unit would be to express it in terms of a specified weight of a dried standard preparation which might be distributed, without any risk of variation, to all laboratories concerned.

The Hampstead Institute thereupon undertook to prepare such a standard. By 1924 it had been able to collect a supply of insulin representing approximately 500,000 Toronto units, thanks to the generosity of the Connaught Laboratories of Toronto University, Eli Lilly and Company (Indianapolis), British Drug Houses Ltd. (London), Burroughs, Wellcome and Co. (London) and the Nordisk Insulin Laboratorium (Copenhagen). The problem was now to convert this stock into a stable and perfectly soluble dry powder, a delicate piece of work which the Hampstead Institute carried out with complete success. This standard powder having been distributed to various institutes for the purpose of comparative assay in relation to a sample of insulin whose potency had been accurately determined by the method in use at Toronto, the remarkably concordant results obtained by five different laboratories were as follows :

| | Number of units per mgrm. of standard powder. |
|---|---|
| Insulin Committee of the University of Toronto | 8.5 |
| Lilly Research Laboratories (Indianapolis) | 8.5 |
| Squibband Sons' Research Laboratories (New York) | 8.4 |
| Wellcome Physiological Research Laboratories (Becken- ham) | 8.8 |
| National Institute for Medical Research (Hampstead) ... | 8.8 |

In consideration of these tests, the Insulin Committee of the University of Toronto suggested that, in order to avoid calculations in fractions, it might be agreed that the standard powder contained 8 units per mgrm. The unit was consequently defined as the activity contained in 0.125 mgrm. of the standard preparation.

This proposal was submitted, in 1925, to the Geneva Conference, which recommended that the dry preparation of insulin hydrochloride prepared by the Hampstead Institute be accepted as the international standard, the insulin unit to be represented by

0.125 mgrm. of that preparation. The Hampstead Institute was asked to keep and distribute this international standard.

For the biological assay of insulin, the Conference advocated three methods—two based on the determination of the blood-sugar content in rabbits and one on the determination of the dose producing convulsions in mice.

Samples of 0.1 gm. of this standard were sent in each country to the Government institutes responsible for their distribution to laboratories working on insulin. The latter were then able to set up a national standard by means of comparative assays.

At Frankfort (in 1928) the Commission had under review the uniformly favourable results obtained since 1925 in laboratories of countries which use the international insulin standard. It was happy to note that the international unit is now in use all over the world and adopted as the only unit of insulin.

The original standard had been prepared at a time when the titre of the best insulin obtainable did not exceed 8 units per mgrm. In course of time, the purity of the insulin produced, even in industrial quantities, rapidly improved, and manufacturers began to deliver solutions prepared from insulins containing as much as 18 or 20 units per mgrm. Later, the discovery of insulin in crystalline form by Professor ABEL made it clear that the maximum attainable degree of purity was not much above that already obtained industrially. Finally, last year, the knowledge—as demonstrated by Dr. D. A. SCOTT, of Toronto—that crystallised insulin is a zinc salt of the hormone still further facilitated the production of chemically pure preparations, with the result that a number of producers now supply solutions prepared from the crystalline substance.

Evidence was accumulating, however, to show that, when insulins of a high degree of purity were assayed in relation to the comparatively impure standard, significant differences appeared in the value of the unit according to the method of assay employed; thus, the convulsion method on mice yielded titres from 20 to 25% higher than those given by the method of blood-sugar determination in the rabbit. The need for a new standard, more appropriate to the present state of our knowledge, was consequently felt.

The Insulin Committee of Toronto thereupon offered to provide a large supply (about 50 grms.) of insulin purified by successive crystallisations according to Scott's method. This new preparation,

intended to be used as a standard, was carefully dried and distributed in 20 mgrm. ampoules by the Hampstead Institute, and then assayed in relation to the old standard by both the mouse and rabbit methods, the tests being carried out in six different laboratories at Copenhagen, Indianapolis, London and Toronto. The results of these titrations were submitted to Professor BEST (Toronto), Sir Henry DALE (Hampstead) and Professor KROGH (Copenhagen) as representatives of the three institutes whose research work had made it possible, in 1925, to define the unit in terms of the standard preparation then adopted. Two of these scientists concluded that, if a potency of 22 units per mgrm. were assigned to the new crystalline standard, the unit would remain identical, at all events to the highest degree of approximation attainable, in view of the differences of potency observed in the two standards when the assay is performed by different methods. If, at its forthcoming meeting, the Commission endorses that view, it will have to redefine the insulin unit, since this will henceforward be equivalent to the specific activity contained in $\frac{1}{22}$ mgrm. of the new standard preparation.

4. ARSENOBENZENES.

The problem as propounded at the Edinburgh Conference was twofold : first, to initiate titration of arsenobenzene derivatives in terms of a standard preparation and unit ; secondly, to prevent any preparation of salvarsan or its derivatives from having an appreciably higher toxicity or a definitely lower therapeutic potency than the standard.

After considering a report by Professor KOLLE (Frankfort), the Geneva Conference adopted the principle of the biological standardisation of remedies belonging to the arsenobenzene group, by means of a series of standard preparations which would, severally, serve for the titration of the following drugs :

1. Dioxydiamino-arsenobenzene dihydrochloride (syn. salvarsan, arspenamine, arsénobenzol, etc.) ; and
2. Its metallic derivatives (silver-salvarsan) ; and
3. Its sodium salts (sodium salvarsan) ;
4. Dioxydiamino-arsenobenzene-sulphoxylate of sodium (syn. neosalvarsan, neoarsphenamine, novarsénobenzol, etc.) ;

5. Neo-silver-salvarsan ;
6. Sulpharsphenamine (syn. sulfarsénol).

Professor KOLLE (Frankfort) kindly agreed to keep and distribute standard preparations 1 to 5 on behalf of the Health Organisation and Professor VOEGLIN (Washington) undertook to prepare the sulpharsphenamine standard.

The Conference further decided that every batch of salvarsan or its derivatives, before issue for therapeutic purposes, should be tested on normal animals for toxicity and on artificially infected animals for curative potency.

The toxicity test is based upon the administration of samples from each batch of the preparation to be tested to not less than ten mice or five rats, or simultaneously to both. Only preparations which have proved under identical experimental conditions to have been not more toxic than the corresponding standard preparation, should be passed for issue.

The test for therapeutic potency is to be performed on rats or mice infected with a suitable strain of pathogenic trypanosomes (*T. brucei*, *T. equiperdum*, etc.) in the following way. A series of mice or rats is taken having the same degree of infection with the same strain of trypanosomes, as determined by the parasite count per unit volume of blood. On a series of animals thus infected, each batch is tested for therapeutic potency by two to four increasing doses, with at least three animals for each dose, and the result is evaluated by comparison with the effects obtained with similar doses of the standard preparation.

Finally, before any batch of ampoules is certified for general use, samples must have been used on a series of human patients under clinical supervision.

At the Frankfort meeting (1928), these recommendations were modified on certain points. Firstly, provision was made to meet the contingency of the neosalvarsan and sulpharsphenamine standards being exhausted. In addition to the assays required to establish the equivalence of a new standard with the present one, certain precautions are to be taken to ensure its stability (resistance to a temperature of 60° C. for several days, drying in vacuo over P₂O₅, preservation in ampoules filled with neutral gas and kept at a temperature not higher than 0° C.).

Secondly, the experimental therapeutic action may be tested, not only on animals infected with trypanosomes, but also upon animals infected with spirochætes.

Finally, the maximum permissible excess of toxicity above the standard was fixed at 20%.

Quite recently, obstacles have arisen which prevent the five standards of salvarsan and its derivatives maintained at the Frankfort Institute from being distributed as heretofore on behalf of the Health Organisation. It is to be hoped that the Hampstead Institute will be ready to undertake the distribution of some of these standards in the future.

5. PITUITARY EXTRACT (POSTERIOR LOBE).

Preparations of posterior lobe pituitary extract exert three totally distinct physiological actions : increase of the tonus of the uterus (oxytocic action), vaso-constriction (pressor action) and reduction of water diuresis accompanied by an increase in the mineral salt concentration of the urine (anti-diuretic action) ; hence the intricacy of attempting to standardise these preparations, since, at the time when the question was raised, it was not yet known whether all three actions were related to a single factor or to several factors and, in the latter alternative, how many.

At the Edinburgh Conference, Professor VOEGTLIN (Washington) presented a survey of the principal methods in use for the determination of the oxytocic action of pituitary preparations, pronouncing in favour of titration on the uterus of the virgin guinea-pig in relation to a standard consisting, not of a fresh watery organic extract, as advocated by various authors, but of a dry powder obtained by the acetone-extraction of the fresh lobe. This dry preparation is stable and contains all the active principles of the posterior lobe.

The Conference agreed to Professor VOEGTLIN's suggestion as to the choice of a standard preparation, but considered that it would be desirable to proceed also to a determination of the pressor and anti-diuretic actions, at least from the qualitative standpoint, and to work out appropriate methods for the purpose.

A plan of research work designed more especially to elucidate the question of the number of factors involved in the complex action

of posterior lobe pituitary was submitted to American, Belgian, English, German and Netherlands experimenters.

The Geneva Conference, after noting the results of their work, decided to adopt finally as the international standard the dry powdered acetone-extracted posterior pituitary lobe, as it had been recommended at Edinburgh by Professor VOEGTLIN. This standard had, incidentally, already been adopted in the tenth edition of the United States Pharmacopœia. By following the indications given therein, it was possible to prepare, at any time and in any country, as a national standard, a sample equal in activity to the standard powder.

In order to permit of the comparison of these standards with the authentic international standard, Professor VOEGTLIN was requested to hold a certain quantity of the original standard preparation in his safe-keeping.

Some discussion took place regarding the accuracy and practical application of the method of assay which is based upon the use of the uterus of the virgin guinea-pig. The Conference therefore agreed that, when this method was used, it should be supplemented by a control test to make sure that the action exercised was not due to the presence of non-specific active substances such as histamine.

The Conference thereupon considered what concentration of pituitary extract, expressed in terms of the standard powder, should be recommended for official adoption. One suggestion that two different concentrations should be taken, in order to meet the requirements of various therapeutic uses, did not find general acceptance. On the other hand, various members of the Conference, mindful of current prescribing practice in their respective countries, were reluctant to accept a concentration of 0.5% of the standard powder, as suggested by Professor VOEGTLIN, as suitable for international use. Such a concentration appeared to them too high for obstetrical use and liable to imperil the life of the child.

In order to overcome this difficulty, Sir Henry DALE suggested a method of indicating the concentration of the extract which, whilst ensuring a uniform international notation, would none the less allow some latitude as regards the content of preparations to be included in the various pharmacopœiæ, so as to allow for the therapeutic practice current in various countries. To achieve this object

it was necessary to express the strength of the extract in units of activity, one unit of activity being defined as the specific action exercised by 0.5 mgrm. of the standard powder. This proposal was unanimously approved.

At its Frankfort session (1928), the Commission supplemented the 1925 decisions on a number of points. For the determination of oxytocic activity, it recommended the test on the isolated uterus of the virgin guinea-pig, as described in the tenth edition of the United States Pharmacopœia. For the determination of pressor activity, comparative tests were to be made on the anæsthetised dog or on the decapitated cat ; finally, for the determination of antidiuretic activity, tests might be carried out on the unanæsthetised dog, on the normal man or on the patient with *diabetes insipidus*.

The Commission considered the effect on the recommendations of the Geneva Conference of the experimental evidence showing that the oxytocic and pressor activities of posterior lobe pituitary extract were due to different active principles that might be separated, and of indications that the anti-diuretic activity seems to be bound up with the presence of a third active principle. It noted with interest that the discoverers of the method of separating the pressor and the oxytocic principles had found no difficulty in expressing the activity of various preparations in pressor and oxytocic units of the international standard. If, therefore, it could be proved that the anti-diuretic action was ascribable to a third constituent, it would be possible to contemplate that the anti-diuretic activity of any preparations might also be expressed in anti-diuretic units in relation to that same standard.

Consequently, and in the light of the uniformly favourable experience obtained since 1925, the Commission recommended that the dry powder obtained from the acetone-extracted fresh posterior lobe substance of ox pituitary be definitely adopted as the international standard preparation for the biological assay of pituitary preparations, whether containing all three active principles or the pressor or oxytocic principle only (Frankfort, 1928).

The activity of the latter preparations was to be expressed in relation to the international standard either in pressor or oxytocic units ; in each case the unit of such activity to be that of 0.5 mgrm. of the standard powder.

As to the suitability of the same standard for the measurement of the anti-diuretic power, the Commission expressed as yet no final opinion.

It will be seen that the situation had cleared up considerably since 1925. It had been shown that at least two of the physiological actions of posterior lobe pituitary are due to distinct and chemically separable principles. It was found that these two principles remained in normal proportions one to the other in the powder chosen as an international standard. Any pituitary preparation can accordingly be assayed in relation to this standard if a method is used which brings into play the physiological action upon which its therapeutic efficacy rests.

The Commission has not, so far, officially requested any laboratory to prepare, keep and distribute, on behalf of the Health Organisation, the international standard of posterior lobe pituitary. There is no reason to doubt that it will make this selection in the near future.

At the same time, a number of laboratories have applied to the Hampstead Institute, in its capacity as distributing centre, for samples of the pituitary standard. In the absence of an international standard preparation, this institute has distributed to them the British standard preparation of posterior lobe pituitary, which is equal in activity to the international standard, as numerous assays have shown.

6. ERGOT OF RYE.

The estimation of the therapeutic activity of ergot preparations presents special difficulties, since ergot contains two groups of substances which exert a marked effect upon the uterus. They are, on the one hand, the non-specific amines (histamine and tyramine), which are derived from amino-acids by the action of bacteria, and, on the other hand, the specific alkaloids (ergotoxine, ergotamine). Since the relative proportions of these active ingredients are highly variable, a very elaborate form of titration becomes necessary.

Chemical methods are too inaccurate, colorimetric methods insufficiently sensitive; as for the biological methods that had previously been used, and which measured either the effect exerted upon the uterus, isolated or *in situ*, or the change in arterial pressure,

or, finally, the necrotic action on the cock's comb, they had not given satisfactory results, so that none of these could be recommended.

The Edinburgh Conference took the view that the determining factor in the assay of ergot should be the specific alkaloid content, and that only methods directed to the measurement of this should be considered. The Conference was also of opinion that only ergot preparations containing the full amount of ergotoxine or ergotamine should be accepted in the pharmacopœiæ.

A new method, that of BROOM and CLARK, based upon the antagonism of the actions severally exerted by ergotoxine and adrenaline upon the isolated rabbit uterus, appeared to satisfy these requirements; the Conference accordingly thought it desirable to test its value. The results of the investigations conducted in American, English, German and Netherlands laboratories were submitted to the Geneva Conference, which concluded that the question of the biological standardisation of ergot was not yet ripe for final decision. It was held desirable, at the stage reached, to give further study to the various biological methods of assay and to compare their results with those obtained by the chemical method presented by Professor STRAUB (Munich).

Research work having shown that Broom and Clark's method enabled the action of the specific alkaloids of ergot to be appraised with a margin of error of 10 to 25%, according to the sensitiveness of the uterus, the Commission (Frankfort, 1928) recommended this as being at once convenient and accurate. It again stressed the need for arriving at a standardisation of ergot by measurement of the ergotoxine and ergotamine content.

Quite recently a new development has taken place which may affect the Commission's decision—namely, the discovery by DUDLEY and MOIR of a new alkaloid—ergometrine—which is responsible for most, if not all, of the therapeutic action exerted by ergot of rye. It is probable that the activity of ergot preparations can be judged from their ergometrine content and that this titration can be carried out by chemical methods. If this is so, the question of the standardisation of ergot will have been removed from the field of work which the Commission has assigned to itself.

7. SUPRARENAL EXTRACT.

Adrenaline may be isolated in pure form from the suprarenal gland or synthetically prepared in crystalline form. The Edinburgh Conference (1923) consequently adopted this substance as the standard in relation to which preparations containing the active principle of the suprarenal gland should be assayed.

In the conduct of this assay, the biological method is far more sensitive than chemical methods ; this is why the Conference advocated a method which is based upon the determination of the doses necessary to produce equal submaximal increases of blood-pressure in a decapitated or anæsthetised and atropinised mammal.

Since adrenaline can be easily prepared in pure form in all countries and the degree of purity can be chemically estimated, it did not seem necessary to establish an international standard preparation of that substance.

8. THYROID EXTRACT.

The administration of thyroid, by raising the metabolism, increases the resistance of the organism to hydrocyanic poisoning induced in the mouse by the intravenous injection of aceto-nitrile. On the other hand, the administration of thyroid gland exerts an action on the metamorphosis of amphibians. Such are the two principles upon which a determination of the potency of thyroid preparations could be based.

The Edinburgh Conference requested Professors REID HUNT, of Boston, and STRAUB, of Munich, to compare the value of these methods and to investigate whether the biological effect of which they give the measure runs parallel with the therapeutic action.

Professor REID HUNT's investigations having shown that the potency of thyroid preparations was proportional to their iodine content, there was no further need to contemplate a biological assay, except as a protection against possible fraud. Professor REID HUNT accordingly proposed that the assay be based upon a determination of the iodine content by chemical methods.

The Geneva Conference endorsed this view whilst recommending that, whenever the biological method appeared to be needed, as in the case of preparations artificially enriched with iodine, recourse

be had to the aceto-nitrile test ; it further adopted as standard of activity that of a dried preparation of thyroid gland with a natural iodine content of 0.2%. Professor REID HUNT was invited to obtain and keep a sufficient quantity of thyroid-gland substance corresponding to that definition, for use as an international standard.

9. ANTHELMINTHICS.

(a) *Filix Mas*.—A proposal to use for the assay of *Filix mas* earthworms immersed in an ethereal solution of given titre was adopted at the Edinburgh Conference and further developed by that of Geneva. Experience had shown, in fact, that small fish could replace the earthworm, since the lethal concentration was identical for both.

A recommendation to that effect was adopted for use in pharmacopœiæ (Geneva, 1925) ; it provided that a 0.002% watery solution of the official ethereal extract of *Filix mas* should be the minimum lethal concentration for earthworms (*Lumbricus terrestris*, *Allolobophora foetida*) or for small fish (*Carassius*, *Gobio*, *Scardinius*) of from 5 to 10 cm. in length.

(b) *Oil of Chenopodium*.—It seemed that the test on earthworms might also yield an indication as to the relative potency of various samples of this oil. The Geneva Conference therefore suggested that this test be used, whilst holding it desirable that further research should be undertaken to establish a relationship between toxicity for earthworms and anthelmintic properties in man.

Experiments conducted with a series of oils of chenopodium prepared from different sources have now shown that neither earthworms nor fish are suitable for assays. As for other practicable biological methods of determining the ascaridol content of oil of chenopodium, these have proved inferior to the colorimetric method (Frankfort, 1928).

III. STANDARDISATION OF VITAMINS.

As far back as 1925, the problem of standardising the assay of vitamins was raised before the second Conference for the biological standardisation of certain remedies. Professor POULSSON (of Olso)

having been invited to review the whole position, came to the conclusion that only the growth-promoting factor contained in vitamin A could at that time form the subject of international agreement.

Since then, knowledge has rapidly accumulated ; six years later the progress achieved was such as to justify the convening of a Conference for the standardisation of vitamins (London, 1931). In the first place, it had to decide a question of principle : Were vitamin units to be defined in relation to their biological action or expressed by a given weight of standard preparation ? The Conference decided in favour of the second alternative, which was, moreover, in keeping with the general practice previously followed.

The Conference took the view that it might appropriately consider the fat-soluble vitamin A, the anti-neuritic vitamin B, the anti-scorbutic vitamin C and the anti-rachitic vitamin D. Nevertheless, in view of the rapid progress of science, it was anxious that its recommendations should be recorded as merely provisional in character, assigning to them a validity of from two to five years, according to cases.

The second Conference for the standardisation of vitamins (London, 1934) was called upon to take more lasting decisions, although it may well be asked whether it will not be necessary—possibly even in the near future—to revise some of its decisions. Indeed, the time is fast approaching when the procedure of assaying a vitamin preparation in relation to a standard will be regarded as obsolete and the titre will be expressible in terms of the pure vitamin content of the preparation. The second Conference thought it preferable, however, to continue to measure the vitamin potency by biological methods based upon comparison with a standard, even in cases in which substances possessing a high degree of vitamin activity have been isolated in pure form, thus enabling a sufficiently accurate titration to be effected by chemical or physical methods.

We shall now see that for each of the four vitamins considered (A, B₁, C and D), an international standard preparation has been adopted and a unit selected. These standards are preserved and distributed by the National Institute for Medical Research at Hampstead, which acts for the purpose as central laboratory for the Health Organisation.

1. VITAMIN A.

The 1931 Conference recommended that carotene be accepted as a provisional international standard and that a selected sample of cod-liver oil be held in view as a possible secondary standard.

The preparation of carotene to be used as standard was to be made from carrots by WILLSTÄTTER'S method, and to consist of a mixture of the two isomers α and β , whose biological action appeared to be similar. Samples of carotene of this type were prepared in the laboratories of the United States of America, France, Germany, the United Kingdom, the Netherlands, Sweden and Switzerland. They were subsequently mixed with a view to obtaining a uniform preparation having the requisite degree of purity. The delicate work of dissolution, crystallisation and filling into ampoules was successfully carried out by the Hampstead Institute. The unit recommended for adoption was the activity of one *gamma*.

The Conference did not recommend any one particular method of conducting the biological assay, but merely suggested that further attention be given to methods based on the curative action of carotene for xerophthalmia.

In current use, the provisional standard, consisting as it did of a mixture of isomers, did not prove entirely satisfactory. The second Conference consequently decided that pure optically inactive β -carotene should be adopted as the international standard. As for the unit, it was not modified; assays showed that it corresponds to the vitamin A activity of 0.6 *gamma* of the new standard preparation. The latter is distributed in the form of an oily solution of such strength that one gramme contains 500 international units.

In making up the standard preparation, the Hampstead Institute received the generous support of Professor KARRER, of Zurich, who, on three occasions, placed the necessary quantities of β -carotene at its disposal.

As regards the cod-liver oil suitable for use as a subsidiary standard, the 1934 Conference, following a recommendation put forward by the 1931 Conference, selected the oil described in the United States Pharmacopœia. This oil—which has been accurately assayed in relation to the provisional carotene standard—has been officially used in the United States for some time past.

The United States Pharmacopœia Committee, under the chairmanship of Dr. E. FULLERTON COOK, having been approached on the subject, has kindly consented to supply to applicants a 30 c.c. bottle of its standard cod-liver oil at the price of \$2.50.

2. VITAMIN B₁.

The adsorption product of this vitamin prepared according to SEIDELL's method was selected by the first Conference as a provisional international standard. This product is obtained by extracting rice polishings with acidulated water. After two days, fuller's earth is added in appropriate quantities to the solution, which is then stirred for twenty-four hours. Subsequently it is filtered off and the fuller's earth, after being washed with water and alcohol, is dried. In order that an adequate supply might be available, the hygienic laboratory of Batavia was asked, through Professor JANSEN (of Amsterdam), to place at the disposal of the Hampstead Institute a batch of 25 kg. of this adsorption product, and kindly complied with this request.

The unit provisionally adopted was the anti-neuritic activity of 10 mgrm. Daily doses of 10 to 20 mgrm. of this preparation will maintain normal growth in young rats on a diet deficient in vitamin B ; at doses of 20 to 30 mgrm. it will cure pigeons suffering from polyneuritis induced by a diet of polished rice.

The Conference expressed no opinion on the relative merits of biological methods for the estimation of vitamin B₁. It considered that all the methods advocated, either of the prophylactic or curative type, and employing either the rat or the pigeon, might yield equally valid results.

The second Conference merely confirmed the decisions of the first ; accordingly, the standard and unit selected in 1931 are henceforward adopted for international use. It will be desirable, however, that the potency of the standard adsorption product should be determined in relation to that of the crystalline vitamin B₁ preparations which have recently been produced by various experimenters, with a view to the subsequent adoption of pure crystalline B₁ vitamin as an international standard.

3. VITAMIN C.

In the opinion of the first Conference, fresh lemon-juice was to be used as the provisional standard for the anti-scorbutic vitamin C, the unit being defined as the activity of 0.1 c.c. of that juice.

This unit represents about one-tenth of the daily dose necessary to prevent the development of serious macroscopic scorbutic lesions in a young guinea-pig maintained on a scurvy-producing diet.

In 1933, however, the discovery by Professor SZENT-GYÖRGYI (of Szeged) of a new substance, ascorbic acid, which is derived from *Capsicum annuum* and is none other than vitamin C in pure form, completely changed the position. Consequently, abandoning lemon-juice, the second Conference adopted lævo-ascorbic acid as the international standard, the unit being defined as 0.05 mgrm. of this acid and exerting a biological effect equivalent to that of the lemon-juice unit.

The Hampstead Institute now holds a supply of ascorbic acid which was prepared in Professor SZENT-GYÖRGYI's laboratory and is used as international standard.

Thus, a pure and chemically defined substance has replaced, as the international standard, a complex product like lemon-juice, which is liable to vary in composition according to the ripeness and place of origin of the fruit. This represents an undoubted step forward.

4. VITAMIN D.

The anti-rachitic vitamin D standard adopted provisionally by the first Conference was the standard solution of irradiated ergosterol then available at the Hampstead Institute, the unit being defined as 1 mgrm. of this solution. When doses equivalent to one unit are administered for eight successive days to a rachitic rat, the formation of a wide line of calcium deposits can be observed in the metaphysis of the proximal ends of the tibiæ and of the distal ends of the radii.

The Conference provided that, for the determination of the anti-rachitic potency of unknown preparations, recourse might be had to methods of assay based either on the prophylactic or on the therapeutic action of vitamin D, such as the calcification "line" test,

X-ray examination or determination of the bone ash. For the preparation of a future standard, the ultra-violet irradiation of the ergosterol was to be carried out in ethereal solution in the absence of any traces of oxygen, the product to be subsequently dissolved in a natural vegetable oil which has given a negative test for vitamin D.

Finally, the Conference recommended that further tests should be made to determine whether the physical properties of crystalline products recently isolated from ergosterol were constant ; if so, one of these substances might eventually replace the irradiated ergosterol as international standard.

The exhaustion of the standard irradiated ergosterol solution prepared by the Hampstead Institute—which had, moreover, been foreseen—made it necessary to prepare a fresh batch according to the technique described above. The potency of the new solution has been compared with that of the original solution in American, British, French, German and Swedish laboratories and found to be equivalent.

The second Conference upheld the decisions of the first concerning the choice of irradiated ergosterol as the international vitamin D standard. Nevertheless, if the present standard solution were to be exhausted or if it became unsatisfactory for any reason, it should be replaced by a solution of pure crystalline vitamin D (calciferol) in olive oil, of such strength that 1 mgrm. contains 0.025 *gamma* of crystalline vitamin D.

The unit remains defined as corresponding to the activity of 1 mgrm. of the international standard solution of irradiated ergosterol, which has been found equivalent to 0.025 *gamma* of crystalline vitamin D.

To assay preparations for vitamin D content and express their potency in international units, recourse should be had to comparative tests on rats. If other species are employed the values cannot be expressed in international units.

Certain anomalies have recently been detected in the action upon some animal species of preparations containing the same number of international units of vitamin D. Thus, given quantities of cod-liver oil and of irradiated ergosterol which are found to be equivalent in their action upon the rat may not prove equal to each other in the activity exerted when they are assayed on chickens, for instance. This brings out clearly the value of cod-liver oil as

a subsidiary standard. Moreover, in certain countries, the United States in particular, cod-liver oil standards are at present in use.

Nevertheless, having regard to the large quantities that would be required for the use of such oil for international purposes, the Conference did not recommend its adoption as a subsidiary standard. It did recommend, however, that the national centres of distribution—to which reference will be made below—should prepare subsidiary reference samples of cod-liver oil. In order to keep uniform the value of the international unit, the vitamin D activity of such oils was to be titrated in international units in relation to that of the standard irradiated ergosterol by tests on at least twenty rats of the same age and body-weight for each titration. Thanks to the experience gained in the use of such subsidiary cod-liver oil standards, it is hoped that the anomalous action on certain species of different sources of vitamin D will be explained.

Quite recently the question of the choice of an appropriate cod-liver oil sample has been settled, since the Pharmacopœia Committee of the United States has declared its readiness to supply, on application, at the price of \$2.50, 30 c.c. of the standard cod-liver oil which appears in the pharmacopœia of that country for vitamin D assays and is titrated in terms of international units.

* * *

The second Conference further examined the possibility of standardising vitamins B₂ and E, but it did not prosecute this matter any further, considering that our knowledge of the nature of these products and of the pathological phenomena produced by their deficiency is still too limited.

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Being desirous of simplifying the somewhat heavy work which devolves upon the Hampstead Institute in its capacity as distributing centre of vitamin standards, both Conferences recommended in turn that an institution be selected in each country to carry out that distribution and, if possible, to prepare a national standard equivalent to the international standard, thus permitting of a more economical use of the authentic international standard.

This recommendation is now being carried into effect. There are at present national centres of distribution in the following twenty-two countries : United States of America, Argentine, Australia, Austria, Belgium, Canada, China, Czechoslovakia, Denmark, France, Germany, Hungary, India, Italy, Japan, Netherlands, New Zealand, Norway, Poland, Spain, Sweden and Switzerland, and there will be further additions to this list.

IV. STANDARDISATION OF SEX HORMONES.

In 1931, the Permanent Commission on Biological Standardisation requested Sir Henry DALE to explore the possibility of international agreement concerning the assay of sex hormones, and to arrange in due course for a Conference of experts on the subject.

The only sex hormone which had been prepared in pure form at the time was the œstrus-producing hormone, originally detected in the fluid from ovarian follicles but later found to be present in the human placenta and to be excreted in the urine of pregnant women and mares.

1. ŒSTRUS-PRODUCING HORMONE.

In scientific literature as well as on the labels of therapeutic preparations, the activity of the œstrus-producing hormone had been indicated in physiological units corresponding to the quantity required to produce œstrus in the ovariectomised rat or mouse. Now it is clear that this quantity cannot be the same for the rat and for the mouse, even when methods of administration and of appraising the result are identical.

Even with one species of test animal, however, the unit will have a wide range of values according to the method of administration of the hormone—in watery or in oily solution, in a single dose or in divided doses—or to the degree of œstrus accepted as indicating a positive effect.

The only basis for international agreement on a common unit of activity for the œstrus-producing hormone was, as in many other cases, to be found in the choice of a standard preparation in terms of which the unit can be defined.

The substance which seemed most suitable as a standard was the hydroxy-ketonic form of the hormone. Opinions differed, however, as to whether this standard should be kept in and distributed from one centre ; it was argued that, since its chemical and physical characters were perfectly defined, it might be prepared in any country.

It had, further, become clear that the hydroxy-ketonic form of the hormone consists of at least two isomeric substances of unequal biological activity. If, therefore, that substance were to be adopted as international standard, the creation of a standard sample, for distribution from a single source, was essential.

Such were the main questions which had to be considered by the Conference which met in London in 1932. It was attended by American, British, French, German and Netherlands scientists.

In the first place, that Conference accepted the principle of an international standard of œstrus-producing hormone and the definition of a unit in terms thereof. In the second place it decided that the standard should be of the hydroxy-ketonic form. In the third place it defined the international unit as the specific œstrus-producing activity contained in 0.1 *gamma* of the standard preparation. Lastly, it entrusted the preservation and distribution of the standard to the Hampstead Institute.

The Conference took the view that the changes in the cellular contents of the vaginal secretion observable in rats or mice deprived of their ovaries should be the criterion upon which the assay of an unknown preparation in relation to the standard preparation should be made. For this purpose it was necessary for the two preparations to be administered in identical solvents and by a method ensuring slow absorption at identical rates. Vaginal smears were to be taken at least once a day until the animals had returned to the diœstrus condition.

Finally, the Conference emphasised the fact that the unit selected could not be used to determine the activity on other forms of the œstrus-producing hormone.

The standard preparation was made up at the Hampstead Institute by the mixing of four samples kindly supplied by Professor BUTENANDT (Danzig), Dr. DOISY (St. Louis), Dr. GIRARD (Paris) and Professor LAQUEUR (Amsterdam). It was afterwards subjected to control tests and distributed as the international standard.

Meanwhile, research work in the field of sex hormones was making great strides, and more active oestrus-producing preparations made from di-hydroxy or tri-hydroxy derivatives and from the esters—especially the benzoates—of these derivatives were being artificially prepared and placed on the market, these being preparations which could not be assayed in relation to the hydroxy-ketonic standard. A certain amount of confusion had consequently arisen which needed to be cleared up.

The solution adopted by a second Conference, which met in London in July 1935—and was attended by experts from the United States of America, the United Kingdom, Canada, Danzig, France, the Netherlands and Switzerland—was the establishment of a subsidiary standard consisting of the mono-benzoate of the di-hydroxy form of the hormone. The unit, which will be labelled “benzoate unit”, will be represented by the specific activity contained in 0.1 *gamma* of that substance. Professor BUTENANDT (Danzig), Dr. GIRARD (Paris), Professor LAQUEUR (Amsterdam) and Dr. MARRIAN (Toronto) have generously offered to contribute towards the accumulation of a stock of this standard.

The assay of the benzoyl preparations of the oestrus-producing hormone—which are among the most important—can therefore now be effected in relation to this new standard, the preservation and distribution of which have been entrusted to the Hampstead Institute.

On the other hand, the Conference did not feel that the time had come to select standards for the other forms in which the oestrus-producing hormone can be prepared.

2. MALE HORMONES.

The reason why the 1932 Conference put forward no recommendation concerning the assay of male hormones was that the question did not appear to be ripe for international agreement and that it would have been extremely difficult at the time to collect an adequate supply of the active principle. Therefore, in order to prepare the ground, it merely questioned American, British, French, German and Netherlands specialists as to the possibilities of future action.

In the meanwhile, however, fresh knowledge was accumulating. BUTENANDT (Danzig) extracted from the urine of males a crystalline

substance of testicular origin which promotes the growth of the capon's comb—androsterone—and established its empirical formula ; RUZICKA (Zurich) succeeded in obtaining the same active principle by synthetic methods.

The establishment of an international standard preparation and unit then appeared possible and even highly desirable. Androsterone being a pure crystalline substance, it was adopted by the second Conference as the international standard for the titration of substances having the specific activity of male hormones. The international unit is to be equal to the activity of 0.1 mgrm. of this standard. In the opinion of the Conference, the test based on the induction of growth in the comb of the capon is, at present, the only one sufficiently specific to permit of comparison with the standard ; it would be desirable, however, to perfect the method of assay on mammals.

The Hampstead Institute was asked to preserve and distribute the international standard, which is to be made up of a mixture of samples of pure androsterone supplied by Professor BUTENANDT (Danzig), Professor LAQUEUR (Amsterdam) and Dr. MIESCHER (Basle).

3. " CORPUS LUTEUM " HORMONE.

Whilst the 1932 Conference had held discussion of *corpus luteum* hormones to be premature, the second Conference had before it a quantity of experimental material, which had been accumulated in the meanwhile, the most important of which was the isolation in pure crystalline form of the progestational hormone of the *corpus luteum*. The assay of preparations containing this hormone can be effected by a sufficiently accurate method based upon the degree of proliferation produced in the endometrium of the rabbit, which may be either an adult female rabbit deprived of the ovaries after coitus, or an immature female rabbit previously treated with œstrus-producing hormones.

In these circumstances, there was no further obstacle to the choice of an international standard. The Conference selected the pure crystalline progestational hormone in the form of needles, for which it proposed the name of " progesterone ". As for the international unit, it is to be represented by the progestational activity of 1 mgrm.

of this substance. The Hampstead Institute kindly undertook to keep and distribute the progestational standard on behalf of the Health Organisation.

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Before completing this statement we should like to show the place which the work of the Permanent Commission on Biological Standardisation occupies in the general setting of the League Health Organisation's activities. These are essentially of two kinds : first, those demanding continuity of effort, and, second, those which may be of an occasional nature, such as a Government's request for co-operation in carrying into effect a plan of health reorganisation or enquiries into a technical subject of general interest. Now the term "permanent" in the title of the Commission under consideration is, in itself, sufficient indication that its work is assignable to the former category. Work of this kind, which should keep pace with the advance of science, adapt itself to new knowledge and promote discovery by facilitating research, would indeed be inconceivable unless it were endowed with continuity. Far from pursuing any pure scientific aims, such research is pre-eminently practical, since its purpose is, in the last resort, to help physicians, public health departments and producers, as we explained at the outset.

But this is not all, the work is based entirely on mutual agreement. Now the bringing together of men of goodwill from many different countries to consider problems whose solution will be of benefit to all is neither more nor less than the application—in a limited field, it may be—of those methods of international co-operation which represent the essential working principle of the League.

No doubt this work is far from finished, and, while certain chapters may be closed, others remain, and will perhaps long remain, open, quite apart from the fact that there will be still others to add whenever the standardisation of other therapeutic agents may appear expedient. Experience has shown, at all events, that the method followed has been the right one and that, given a sound case to argue on the international scientific plane, there is no difficulty in arriving at a consensus of opinion.

ANNEX 1.

PUBLICATIONS OF THE HEALTH ORGANISATION
ON BIOLOGICAL STANDARDISATION.

- Report of the International Conference on the Standardisation of Sera and Serological Tests. London, 1921 (document C.533.M.378.1921.III).
- Report of the Second International Conference on the Standardisation of Sera and Serological Tests. Paris, 1922 (document C.H.48).
- Report of the Technical Conference for Consideration of Certain Methods of Biological Standardisation. Edinburgh, 1923 (document C.4.M.4.1924.III).
- Reports on Serological Investigations presented to the Second International Conference on the Standardisation of Sera and Serological Tests. Paris, 1922 (document C.168.M.98.1923.III).
- The Standardisation of Dysentery Serum, by K. SHIGA, H. KAWAMURA and K. TSUCHIYA.
First Report (document C.177.M.49.1924.III).
Second Report (document C.177(a).M.49(a).1924.III).
- Beiträge zur Standardisierung des Dysenterieserums.
1. Ueber Eigenschaften, Wirkungsart und Wertbestimmung des Dysenterieserums. Von W. KOLLE, H. SCHLOSSBERGER und R. PRIGGE.
2. Ueber die Auswertung der antitoxischen Dysenteriesera am Kaninchen. Von Seigo KONDO.
(document C.H.213.1924.)
- Rapport de la Commission permanente de Standardisation biologique. Paris, 1924 (document C.H. /S.S. /1^{re} session P.V.).
- Second International Conference on the Biological Standardisation of Certain Remedies. Geneva, 1925 (document C.532.M.183.1925.III).
- Memorandum on the Present Position with regard to the Testing of Salvarsan and its Allied Compounds in Different Countries, by H. H. DALE (document C.H. /C.P.S. /2.1925).
- Memorandum on the Determination of Vitamins, by Professor P. E. POULSSON (document C.H. /C.P.S. /3.1925).
- Memorandum on the Biological Standardisation of Pituitary Extracts, by Professor Carl VOEGTLIN (document C.H. /C.P.S. /4.1925).
- Beitrag zur Eichung von Digitalis mit besonderer Berücksichtigung der Warmblütermethode, von Prof. R. MAGNUS (document C.H. /C.P.S. /5.1925).
- Beitrag zur pharmakologischen Auswertung von Secale Cornutum und von Secalepräparationen, von Prof. Paul TRENDELENBURG (document C.H. /C.P.S. /6.1925).
- The Biological Standardisation of Insulin, including Reports on the Preparation of the International Standard and the Definition of the Unit (document C.H.398.1925).
- Rapport sur le titrage (standardisation) des tuberculines, par le professeur A. CALMETTE et le Dr DE POTTER (document C.H.429.1926).

- Report of the Permanent Commission on Biological Standardisation. Geneva, 1926 (document C.H.517).
- Mémoires sur le titrage du sérum antidysentérique :
1. Sur le titrage de la toxine et du sérum antidysentériques, par C. IONESCU-MIHAESTI et D. COMBIESCU.
 2. Recherches sur le titrage du sérum antidysentérique, par P. CONDREA. (document C.H.483.1926.)
- Memoranda on Cardiac Drugs, Thyroid Preparations, Ergot Preparations, *Filix Mas*, Suprarenal Preparations, Vitamins, Pituitary, Salvarsan, Oil of Chenopodium, Insulin, by Professor E. KNAFFL-LENZ (document C.H.734.1928).
- Report of the Permanent Commission on Biological Standardisation. Frankfort-on-Main, 1928 (document C.H.717).
- Memoranda on the International Standardisation of Therapeutic Sera and Bacterial Products, by Professor C. PRAUSNITZ (document C.H.832.1929).
- Report on the Work of the Laboratory Conference on Blood Groups. Paris, 1930 (document C.H.885).
- Report of the Permanent Commission on Biological Standardisation. Geneva, 1930 (document C.H.945).
- Report of the Conference on Vitamin Standards. London, 1931 (document C.H.1055(1)).
- Report of the Permanent Commission on Biological Standardisation. London, 1931 (document C.H.1056(1)).
- Report of the Conference on the Standardisation of Sex Hormones. London, 1932 (Special Number, January 1935, of the *Quarterly Bulletin of the Health Organisation*).
- Report of the Second International Conference on Vitamin Standardisation. London, 1934 (Extract No. 15 from Volume III of the *Quarterly Bulletin of the Health Organisation*).
- Report of the Permanent Commission on Biological Standardisation. Copenhagen, 1934 (Special Number, January 1935, of the *Quarterly Bulletin of the Health Organisation*).
- Report of the Second Conference on the Standardisation of Sex Hormones. London, 1935 (*Quarterly Bulletin of the Health Organisation*, Vol. IV, No. 3).

ANNEX 2.

LIST OF INSTITUTES WHICH PARTICIPATED IN THE RESEARCHES.

DIPHThERIA ANTITOXIN.

- Copenhagen : Statens Serum Institut ;
 Frankfort-on-Main : Staatliches Institut für experimentelle Therapie ;
 Hampstead : National Institute for Medical Research ;
 Paris : Institut Pasteur ;

Rome : Laboratorio di batteriologia della Direzione Generale della Sanità Pubblica ;
 Washington : Hygienic Laboratory of the United States Public Health Service.

TETANUS ANTITOXIN.

Copenhagen : Statens Serum Institut ;
 Frankfort-on-Main : Staatliches Institut für experimentelle Therapie ;
 Hampstead : National Institute for Medical Research ;
 Paris : Institut Pasteur ;
 Rome : Laboratorio di batteriologia della Direzione Generale delle Sanità Pubblica ;
 Washington : Hygienic Laboratory of the United States Public Health Service.

ANTI-DYSENTERY SERUM (SHIGA).

Basle : Hygienisches Institut der Universität ;
 Beckenham : Wellcome Physiological Research Laboratories ;
 Berlin : Institut für Infektionskrankheiten "Robert Koch" ;
 Bucharest : Institut de Médecine expérimentale ;
 Copenhagen : Statens Serum Institut ;
 Cracow : Branch of the State Epidemiological Institute ;
 Elstree : Lister Institute of Preventive Medicine ;
 Frankfort-on-Main : Staatliches Institut für experimentelle Therapie ;
 Hampstead : National Institute for Medical Research ;
 London : Medical Research Council ;
 Paris : Institut Pasteur ;
 Tokio : Kitasato Institute for Infectious Diseases ;
 Warsaw : State Epidemiological Institute.

GAS-GANGRENE ANTITOXINS.

Beckenham : Wellcome Physiological Research Laboratories ;
 Berlin : Reichsgesundheitsamt ;
 Copenhagen : Statens Serum Institut ;
 Elstree : Lister Institute of Preventive Medicine ;
 Frankfort-on-Main : Staatliches Institut für experimentelle Therapie ;
 Hampstead : National Institute for Medical Research ;
 Paris : Institut Pasteur ;
 Washington : National Institute of Health.

ANTI-PNEUMOCOCCUS SERA.

Albany : Division of Laboratories and Research, Department of Health, New York State ;
 Beckenham : Wellcome Physiological Research Laboratories ;
 Berlin : Institut für Infektionskrankheiten "Robert Koch" ;
 Copenhagen : Statens Serum Institut ;
 Detroit : Parke Davis Laboratories ;
 Elstree : Lister Institute of Preventive Medicine ;
 Hampstead : National Institute for Medical Research ;

London : Laboratory of the Ministry of Health ;
 New York : Lederle Laboratories ;
 Paris : Institut Pasteur ;
 Toronto : Connaught Laboratories, University of Toronto ;
 Washington : National Institute of Health.

STAPHYLOCOCCUS ANTITOXIN.

Beckenham : Wellcome Physiological Research Laboratories ;
 Brussels : Laboratoire central de l'Administration de l'Hygiène ;
 Copenhagen : Statens Serum Institut ;
 Elstree : Lister Institute of Preventive Medicine ;
 Frankfort-on-Main : Staatliches Institut für experimentelle Therapie ;
 Hampstead : National Institute for Medical Research ;
 Marburg : Institut für experimentelle Therapie " Emil von Behring " ;
 Melbourne : Walter and Eliza Hall Institute for Research in Pathology and
 Medicine ;
 Paris : Institut Pasteur ;
 Toronto : Connaught Laboratories, University of Toronto ;
 Washington : National Institute of Health.

TUBERCULIN.

Beckenham : Wellcome Physiological Research Laboratories ;
 Copenhagen : Statens Serum Institut ;
 Frankfort-on-Main : Staatliches Institut für experimentelle Therapie ;
 Hampstead : National Institute for Medical Research ;
 Paris : Institut Pasteur.

DIPHTHERIA TOXINS.

Beckenham : Wellcome Physiological Research Laboratories ;
 Copenhagen : Statens Serum Institut ;
 Hampstead : National Institute for Medical Research ;
 Milan : Istituto Sieroterapico Milanese ;
 Prague : State Institute of Hygiene ;
 Toronto : Connaught Laboratories, University of Toronto ;
 Vienna : Staatliches serotherapeutisches Institut ;
 Warsaw : State School of Hygiene ;
 Washington : National Institute of Health.

STREPTOCOCCUS ANTITOXIN.

Beckenham : Wellcome Physiological Research Laboratories ;
 Berlin : Institut für Infektionskrankheiten " Robert Koch " ;
 Hampstead : National Institute for Medical Research ;
 Washington : Hygienic Laboratory of the United States Public Health Service.

ANTIMENINGOCOCCUS SERUM.

Albany : Division of Laboratories and Research, Department of Health, New
 York State ;

Berlin : Institut für Infektionskrankheiten " Robert Koch " ;
 Copenhagen : Statens Serum Institut ;
 Paris : Institut Pasteur.

DIPHTHERIA FORMOL-TOXOID.

Copenhagen : Statens Serum Institut ;
 Frankfort-on-Main : Staatliches Institut für experimentelle Therapie ;
 Garches : Institut Pasteur ;
 Hampstead : National Institute for Medical Research ;
 Toronto : Connaught Laboratories, University of Toronto ;
 Washington : National Institute of Health.

STAPHYLOCOCCUS FORMOL-TOXOID.

Toronto : Connaught Laboratories, University of Toronto.

SWINE ERYSIPELAS SERUM.

Cambridge : Institute of Animal Pathology ;
 Frankfort-on-Main : Staatliches Institut für experimentelle Therapie ;
 Zagreb : Institute and School of Hygiene.

DIGITALIS.

Ann Arbor : Medical School, University of Michigan ;
 Berlin : Reichsgesundheitsamt ;
 Copenhagen : Laboratory of Zoophysiology, University of Copenhagen ;
 Edinburgh : Department of Pharmacology, University of Edinburgh ;
 Ghent : Institut de Pharmacodynamie et de Thérapie ;
 Hampstead : National Institute for Medical Research ;
 Manila : Department of Pharmacology, College of Medicine, University of
 Philippines ;
 Munich : Pharmakologisches Institut der Universität ;
 Utrecht : Pharmacologisch Instituut der Rijks-Universiteit ;
 Vienna . Pharmakologisches Institut der Universität ;
 Washington : Hygienic Laboratory of the United States Public Health Service.

STROPHANTHUS (OUABAIN).

Paris : Laboratoire de Pharmacologie de la Faculté de Médecine.

INSULIN.

Beckenham : Wellcome Physiological Research Laboratories ;
 Copenhagen : Laboratory of Zoophysiology, University of Copenhagen ;
 Hampstead : National Institute for Medical Research ;
 Indianapolis : Lilly Research Laboratories ;
 New York : Squibb & Sons Research Laboratories ;
 Toronto : Insulin Committee of the University of Toronto.

ARSENOBENZENES.

Frankfort-on-Main : Staatliches Institut für experimentelle Therapie ;
 Hampstead : National Institute for Medical Research ;
 Washington : Hygienic Laboratory of the United States Public Health Service.

PITUITARY EXTRACT (POSTERIOR LOBE).

Freiburg-in-Brisgau : Pharmakologisches Institut der Universität ;
 Ghent : Institut de Pharmacodynamie et de Thérapie ;
 Hampstead : National Institute for Medical Research ;
 Utrecht : Pharmacologisch Instituut der Rijks-Universiteit ;
 Washington : Hygienic Laboratory of the United States Public Health Service.

ERGOT OF RYE.

Edinburgh : Department of Pharmacology, University of Edinburgh ;
 Freiburg-in-Brisgau : Pharmakologisches Institut der Universität ;
 Hampstead : National Institute for Medical Research ;
 Munich : Pharmakologisches Institut der Universität ;
 Utrecht : Pharmacologisch Instituut der Rijks-Universiteit.

THYROID EXTRACT.

Boston : Department of Pharmacology, Medical School of the Harvard University ;
 Munich : Pharmakologisches Institut der Universität.

ANTHELMINTHICS.

Munich : Pharmakologisches Institut der Universität ;
 Vienna : Pharmakologisches Institut der Universität ;
 Washington : Hygienic Laboratory of the United States Public Health Service.

VITAMINS.*Vitamin A.*

Amsterdam : Institute of Physiological Chemistry, University of Amsterdam ;
 Baltimore : School of Hygiene and Public Health, Johns Hopkins University ;
 Hampstead : National Institute for Medical Research ;
 Leipzig : Tierphysiologisches Institut der Universität ;
 Maddison : Department of Agricultural Chemistry, University of Wisconsin ;
 Paris : Laboratoire de physiologie de la nutrition, École des Hautes Études ;
 Stockholm : Institute for Bio-chemistry of the University ;
 Zurich : Institut für Organische Chemie der Universität.

Vitamin B₁.

Batavia : Geneeskundig Laboratorium, Dienst van de Volksgezondheid ;
 Hampstead : National Institute for Medical Research.

Vitamin C.

Hampstead : National Institute for Medical Research ;
 Szeged : Institute of Medical Chemistry, University of Szeged.

Vitamin D.

Baltimore : School of Hygiene and Public Health, Johns Hopkins University ;
 Göttingen : Allgemeines Chemisches Laboratorium der Universität ;
 Hampstead : National Institute for Medical Research ;
 Leipzig : Tierphysiologisches Institut der Universität ;

London : Pharmaceutical Society of Great Britain ;
Maddison : Department of Agricultural Chemistry, University of Wisconsin ;
Paris : Laboratoire de physiologie de la nutrition, École des Hautes Études ;
Stockholm : Institute for Bio-chemistry of the University ;
Washington : Food and Drugs Administration Laboratory, Department of
Agriculture.

ŒSTRUS-PRODUCING HORMONE.

Amsterdam : Pharmaco-Therapeutisch Laboratorium der Universiteit ;
Göttingen : Allgemeines Chemisches Laboratorium der Universität ;
Hampstead : National Institute for Medical Research ;
London : Courtauld Institute of Bio-chemistry, The Middlesex Hospital's Medical
School ;
 Department of Bio-chemistry, University College ;
 Pharmaceutical Society of Great Britain ;
Paris : Laboratoire du Dr. A. Girard ;
St. Louis : Department of Biological Chemistry, St. Louis University School of
Medicine.

AN ESSAY ON CHARLATANISM

by

Dr. I. WASSERBERG,

Member of the Health Section of the League of Nations Secretariat.

Among the many known definitions of quackery, the following two are noteworthy : (1) A quack is one who pretends to knowledge of which he is ignorant, particularly a medical impostor, and (2) a quack is a person who engages in the treatment of the sick without possessing the requisite State authorisation for the purpose.

One of these definitions thus hinges upon the abilities and the other upon the person of the quack. According to the first, knowledge and skill are the sole decisive factors, so that even a Government-licensed physician is to be classed as a quack if to that degree ignorant. According to the second, the issue is decided exclusively on the question of Government authorisation. The most incompetent doctor, if State authorised, is never a quack ; whilst, on the other hand, a layman with the most extensive medical knowledge is always a quack if he engages in the treatment of the sick.¹

For two reasons, we propose to adopt the second definition in the pages which follow. Firstly, because, with few exceptions, the right to treat the sick is in all civilised countries conditional upon a Government authorisation, and because, in such countries, laymen treating the sick are, in fact, everywhere regarded as quacks—quacks in the legal sense. Secondly, because the distinction between quackery in law and quackery in fact, which is apparent in both definitions, is of no great practical importance. It would,

¹ These two definitions are to be found : the first in the "Encyclopædia Britannica" (eleventh edition), the second in the "Handwörterbuch der Staatswissenschaften" (fourth edition).

of course, be wrong to assume, as a matter of course, that the medical layman is always ignorant of medicine and incompetent, just as it would be erroneous, on the other hand, to regard Government authorisation as an absolute guarantee of the skill and ability of approved doctors. There have been, there are, and there doubtless always will be incompetent doctors, side by side with medically competent laymen. Yet, although doctors who are incompetent despite their degree are by no means as rare as unqualified but medically competent laymen, it would be a mistake, on the whole, to consider State authorisation entirely without value. It is based, in all civilised countries, on a process of selection, the purpose of which is simply to secure the greatest degree of competence possible in the circumstances. The relation of the system of examination to competence is obviously not one of cause to effect. In other words, no individual candidate who succeeds in the examination can be pronounced competent in his subject on the mere strength of the examination results. It is, however, highly probable that, among a large number of authorised candidates, the majority is competent; and the degree of probability increases in measure as the quality of the training and of the examination system itself improves. *Mutatis mutandis*, this is also true of non-authorised laymen.

Consequently, we adhere to the second definition of quackery, to which we should add the almost ever-present characteristic accompaniment of commercial exploitation of treatment for gain. The question of the good or bad faith of the quack appears to us to be of no practical moment. In these matters we are not, after all, concerned with passing ethical judgment, but we have to consider the problem of quackery from the social utilitarian standpoint. Viewed from this angle, it would even seem plausible that the quack who carries on his business in good faith—who is therefore no swindler and who believes in his mission—is a greater danger socially than his fraudulent colleague. For psychological reasons which are easy to apprehend, he will be more sure of himself, adopt a more authoritative tone, will more quickly gain the confidence of his clients and be able to hold it longer.

The old adage, "*La médecine naquit avec un frère jumeau, le charlatanisme*", applies, if perhaps not to medicine generally, at

least to its modern phase since the tenth century, when it blossomed into new life after the confused early mediæval period. The first medical schools of Europe, the Arabian schools in Spain, and those of Salerno, Naples and Montpellier gave their graduates diplomas which, within a short time, carried with them the exclusive Government-guaranteed right to treat the sick. The fact that this medical monopoly was circumvented and that many sick persons sought the help of lay healers is to be ascribed to a series of reasons which, in part, are still operative to-day, and to which we shall revert later on. But one circumstance should be mentioned here because—though it has now ceased to exercise any influence—it is highly characteristic of the Middle Ages, and because it fostered among the broad masses of the population the habit of seeking treatment from non-medical healers.

We refer to the Church's negative attitude, on principle, against surgical intervention. For hundreds of years this exerted a retarding influence, still noticeable in the nineteenth century, upon surgery, including obstetrics and ophthalmology, thereby lowering the status of all those who engaged in surgical practice. To operate with the knife was regarded as rough manual labour, unworthy of a learned physician, and so it came about that such operative procedures as were still necessary or held to be necessary, despite this condemnation originating in religious motives, were carried out by people whose handicraft was related, however loosely, to the human body or to surgical instruments. Thus barbers, bath attendants and blacksmiths who were practised in the manipulation of the branding-iron, and, finally, even executioners, who might be supposed to have some general knowledge of anatomy, came into contact with the sick. The distinction between surgery and medicine proper was not always carefully observed, and gradually there arose, by the side of the legally authorised professional medical healers, an illegal competing class of lay healers.

Taken as a whole, these developments followed much the same course in all civilised countries of Europe. Up to the latter part of the nineteenth century, England was the only exception ; there, lay treatment had always been ranked on a par with medical treatment. Germany followed her example only in 1869. H. FISCHER, after examining 197 different legislations on the

subject of quackery, found only nineteen which did not prohibit its practice and, among these nineteen, only three of advanced countries—*i.e.*, England, Germany and the Swiss Canton of Appenzell Ausser Rhoden.¹

If the legislation of the vast majority of civilised countries has always prohibited lay treatment of the sick, this may be taken as a definite sign that charlatanism is regarded by the influential classes of such countries as a socially injurious and therefore undesirable phenomenon. This brings up with greater force than ever the question why the laws of England and Germany—two countries which are in the vanguard of progress, not only in purely scientific medical research, but also in the practical curative and social application of medical knowledge—appear to ignore the damage done by lay medicine.

An analysis of Germany's position will prove particularly instructive in this connection, for, whilst in England toleration of lay medicine is a tradition going back hundreds of years, and difficult to probe to its depths, Germany marched over into the camp of the charlatan-protectors scarcely more than sixty years ago. She may thus, in a sense, be said to have done so before our very eyes and with a full realisation of the impelling motives and of the objects sought. When her case has been considered, that of England will seem all the more comprehensible.

Up to 1869, in Germany, only authorised doctors were entitled to treat the sick. In the draft law on industries, occupations and professions (*Gewerbeordnung*), which came into force in that same year, this provision had been maintained, and, in the statement of reasons accompanying the draft, the Central Government expressed the view "that legislation would conflict seriously with popular feeling and with the demands that might justifiably be made of the State authorities with a view to safeguarding the life and health of the population, if the requirement of an attestation of competence were not upheld in this connection."²

¹ Among the remaining sixteen are to be numbered Uganda, Zanzibar, Morocco, Somaliland, Iran, Ethiopia, and a number of the smaller English colonies.

² *Veröffentlichungen aus dem Gebiete der Medizinalverwaltung*, 27, Berlin, 1928, page 701.

Suddenly, however, during the second reading in the Reichstag, there came a petition from the Berlin Medical Association, demanding that freedom be granted in the exercise of medicine. This was signed, among many others, by VIRCHOW, LANGENBECK, GRAEFE, and HIRSCH, the well-known author of the history of epidemics. Germany has thus mainly these celebrated medical authorities to thank for having, since 1870, gradually become the El Dorado of charlatanism. One may search the memorandum and the records of the subsequent discussion in vain for any statement of reasons based on the merits of the case. There was not even an attempt to furnish the not easily adducible proof that a regime of freedom in the exercise of medicine would provide better for the public health than a medical monopoly. At best, we find, here and there, an expression of opinion that anti-quackery laws were inoperative. The main considerations—understandably enough in this period of incipient liberalism in Germany—were arguments of a purely political and social character. The medical profession had always been regarded as particularly receptive to liberal ideas, and VIRCHOW was, in fact, one of the leaders of the Liberal Party of Germany. The right of the State to dry-nurse the medical profession was challenged. It was argued that the State was neither required nor entitled to grant any one class—not even the medical profession itself—the exclusive prerogative of the treatment of the sick, and that it had no right to limit the citizen's freedom to seek advice and help wherever he chose. Further, it was urged that laws against charlatanism were unworthy of a well-trained and well-educated people. The German's own sound common sense, it was said, would give him the best guidance, without advice imposed from above, as to whom he should trust and where he should look for assistance. Freedom was the best regulator here as elsewhere.

In a word, distrust of the Moloch State ; resistance to its all-engulfing tendencies, the freedom of the individual, his untrammelled right to dispose of his own property and, *a fortiori*, of his own life and health, that most personal of all forms of property ; the fight against class privileges ; romantic-democratic confidence in " the sound common sense ", and the reasonableness of the broad masses of the population, and a belief in that panacea : the open market and free competition ; all this, at the very time when the

watchwords of the struggle for life and of the survival of the fittest—that is to say, of the wisest—were just beginning to be popular.

This well-furnished arsenal of ideas of liberalism and “ progress ” contributed to the triumph of the principle of freedom of treatment in Germany. We fancy we shall not be wrong in saying that the state of affairs prevailing in England as regards charlatanism is attributable to much the same motives. The only thing is that, in that country, they no longer operate on the plane of reasoned controversy in which pros and cons are canvassed, as they do in Germany, but, as a precipitate of past experience, have already become part of the solid core of instinctive national reactions. As such, they operate in the dark, but all the more certainly. For this reason, we believe that we may expect any possible future endeavours to abolish or limit freedom of treatment to come up against much stronger resistance in England than they will in Germany.

When abstract principles clash with the exigencies of life, it is always the latter which prevail. In this question of freedom of treatment, we may observe, in the last few decades, both in England and in Germany, the slow but steady curtailment of the charlatan's rights relatively to those of the doctor. The Medical Act of 1858, like the German law on Industries, Occupations and Professions of 1900, both of which make it a punishable offence for lay healers to describe themselves as doctors or to adopt any other title which may induce the belief that its holder is an authorised physician, show which way the wind is blowing. Certificates which produce legal effects, such as death certificates, attestations of sickness, etc., are invalid, both in England and in Germany, unless they have been drawn up by a fully authorised doctor. In both countries, the recovery of charlatans' fees may not be sought by way of legal process (this circumstance not infrequently induces lay healers to supply the patient with drugs and instruments, which rank as sold merchandise, and can therefore give rise to a legally recoverable debt).

Under the terms of the Reich Vaccination Law, doctors are alone permitted to perform vaccination. In England, the same is true also for anæsthesia (Dangerous Drugs Act, 1920-1923 and 1932). Under the Midwives Act of 1902, only midwives and doctors may

engage in obstetrical practice, and, according to the Midwives and Maternity Homes Act, 1926, lay persons (including midwives) may only intervene in accouchements under the guidance and personal supervision of a fully qualified medical practitioner. The Venereal Disease Act, 1917, forbids any person who is not an authorised physician to treat venereal-disease patients, and a similar prohibition is enacted in Germany under the Reich Law of 1927 for the combating of venereal diseases, which, furthermore, prohibits any form of treatment of venereal disease by correspondence and the like. Finally, by virtue of the First Reich Insurance Code of 1884 and 1910, as well as by virtue of the National Insurance Act of 1912, only qualified doctors may be appointed by sickness insurance funds.

This last measure is by far the most important and the most severe in its effects upon the charlatan, since it tends to remove large portions of the population (in Germany some two-thirds) out of his reach in this very simple and practical manner.

It will thus be seen that the field of operation of the principle of freedom of treatment, as classically defined, has, in some directions, been distinctly narrowed in both these countries. The law in Germany and England has already had to reconcile itself to the fact that, in health questions, the "sound common sense" of the man in the street does not operate reliably on all occasions and in every way; that the risk of allowing him untrammelled freedom is sometimes too great from the standpoint of public health, and that a reasonable amount of benevolent guidance from above is to be preferred to the unlimited freedom of the individual whenever the latter is likely to bring public health dangers in its train.

Similar experience has also been gained in countries which, though against freedom of treatment on principle, have permitted lay treatment temporarily and under special circumstances—*i.e.*, France during the great revolution in 1792 and Russia in 1922.

In both countries we are dealing, of course, with one of these exceptional periods in which men are often tempted to do away summarily with all traditions in the name of freedom and equality. Both countries abolished the treatment monopoly of the medical profession, only to restore it at once—France in 1803 and Russia in 1925. The short experimental period of permitted lay treatment abundantly proved that the particular kind of freedom which it

was sought to protect merely leads to a state of anarchy, and, further, that the so-called monopoly of the medical profession safeguards in reality the vital interests of vast sections of the population and not those of the profession itself.

Another instance of a country in which the problem of charlatanism has developed in somewhat the same way as in France and Russia is the United States of America, where health legislation is enacted by the States and not by the Federal Government, and has, since 1840, been influenced in some States by motives similar to those which were operative in France and subsequently in Germany and Russia, and where freedom to treat was also introduced.

The evil consequences soon made themselves felt, however, and the legislative bodies of the various States were compelled sooner or later, in the interests of public health, to reintroduce the old prohibitions against charlatanism by the enactment of new laws; the last to take action were certain north-eastern States, which fell into line in the middle 'nineties.¹

American conditions display, however, one distinctive characteristic. Thus, whilst we in European countries are familiar only with doctors and with lay healers, we find in the United States a tripartite division. Between doctors and lay healers a third, intermediate, class intervenes, whose members have neither the status of lay healers nor that of fully qualified physicians, but are authorised by law to treat the sick. These are the so-called practitioners with limited licences, such as osteopaths and chiropractors, who in reality do not act as doctors or make out prescriptions and are not entitled to engage in instrumental surgery, but are none the less trained at special colleges and have special titles for which they qualify by passing examinations—*i.e.*, D.O. (Doctor of Osteopathy), D.C. (Doctor of Chiropractic), etc.—each being entitled to use his own special methods of treatment. These healers who, in European countries, would be classed without further ado as quacks, are legally recognised treaters of the sick in the United States—a circumstance which it is well to bear in mind.

¹ NEUBURGER: "Das Kurfuschertum in den Vereinigten Staaten", in *Veröffentlichungen aus dem Gebiete der Medizinalverwaltung*, 27, Berlin, 1928, page 657.

The anti-quackery legislation of various countries obviously diverges on many points. Such laws differ not only in detail but also in principle, nor is the current practice of enforcement uniform in all cases. To analyse all the minute details of the problems which arise would require a special legal treatise, which would no doubt be of extreme theoretical interest, but of little practical help in working out adequate methods of coping with charlatanism. Those who are familiar with these problems are aware that charlatanism is equally prevalent in countries of the most varied legislation ; that the problems which arise are independent, not only of detailed variations in the laws, but also whether the whole practice as such is prohibited by law or permitted. France suffers no less from charlatanism and its consequential effects, despite prohibitive laws, than England or Germany, where treatment by laymen is allowed. The Swiss Canton of Geneva "is swarming with quacks",¹ despite legal prohibitions. The same is true of Belgium, Spain, the United States, Norway,² etc.

This business of quack medicine seems to have great similarities with the question of alcohol. The demand for both articles is very great in all places, and the moral justification of the legal prohibition is, in both cases, not acknowledged by the broad masses of the population. Now prohibitive laws which are not in consonance with the feelings of the masses remain ineffectual. If we are to find effective methods of coping with quack medicine, we must first of all probe down to the real cause of the strong demand ; only thus shall we get the first glimmerings of an understanding why the question " doctor or quack " has so frequently been decided against the doctor by those in need of care.

In what numbers do quacks occur in the various countries ? It should be said in the first place that, with the exception of Germany, and to some extent the United States, countries have no data that are even approximately reliable on this subject. In countries in which charlatanism is prohibited, this absence of particulars is

¹ J. STEPHANI-CHEBULIEZ : "Pourquoi le succès des charlatans et des somnambules ?" *Revue médicale de la Suisse romande*, 52, 1932, page 560.

² Although Norway has laws against charlatanism, the position is the same, generally speaking, as in Germany. See W. A. HOYER : "Das öffentliche Gesundheitswesen in Norwegen", in *Veröffentlichungen aus dem Gebiete der Medizinalverwaltung*, 32, Berlin, 1930, page 98.

understandable enough. The little which is known does not go beyond more or less probable speculations and is based upon inferences from court proceedings, casual newspaper reports, advertisements of quacks and secret remedies, and, finally, upon the personal experience and general impression of medical and other circles that are in contact with the world of disease.

For Germany, we have the following official figures in respect of the period 1876-1930 :¹

| Year | Number of quacks | Number of women included in previous column | Number of quacks per 10,000 inhabitants | Number of quacks per ten doctors |
|------|------------------|---|---|----------------------------------|
| 1876 | 670 | 95 | 0.16 | 0.49 |
| 1887 | 1,713 | — | 0.36 | 1.08 |
| 1898 | 3,059 | — | 0.57 | 1.24 |
| 1909 | 4,468 | 1,322 | 0.7 | 1.46 |
| 1927 | 11,761 | 2,832 | 1.86 | 2.7 |
| 1928 | 12,098 | 2,803 | 1.9 | 2.63 |
| 1929 | 12,413 | 3,091 | 1.94 | 2.61 |
| 1930 | 12,942 | 3,094 | 2.01 | 2.74 |

This table shows that the absolute number of quacks in Germany has been growing continuously since 1876 and that their proportion in relation both to the total population and to the number of doctors has also steadily risen. In 1930, there were more than twenty-seven charlatans per hundred doctors. It will further be observed that the pace of increase in numbers has, in recent years, been growing more rapidly in the case of quacks than in that of doctors. Thus, whilst in 1928 the increase in the number of quacks relatively to the previous year was 2.8%, as against 5.6% increase in the number of doctors, the corresponding figures for 1929 and 1930 are 4.15% and 3.4%, and 4.3% and -0.7% respectively. In other words, in 1929, the number of quacks had grown much more than that of doctors relatively to the previous year. In 1930, the number of doctors even decreased, whereas the rate of increase of the quacks was still greater than in 1929.

In this connection it should be borne in mind that, whilst the figures for the medical profession cover all doctors without exception, those for quacks indicate far less than the real number, for, despite the compulsory registration which has been in force in Prussia since 1902, many charlatans prefer to have no contact with

¹ *Reichsgesundheitsblatt*, 1932 No. 9, page 140.

the Government departments. There are, indeed, very many—especially women—who carry on quack medicine as a side-line, under cover of some other occupation; such are fortune-tellers, astrologers, graphologists, etc. This class also includes many persons of both sexes who are drawn from the ranks of the medical auxiliary personnel, such as sick attendants, nurses, masseurs and masseuses, dentists' assistants, etc. There is always, in their career, a period of transition—of variable length, no doubt—during which they may still be regarded as belonging to the medical auxiliary personnel, though already engaged in quack medicine. Only after they have carried on their secret practice for some considerable time do they usually decide to abandon their old calling and register officially as lay healers. Finally, one should not forget in this connection the large number of commercial representatives who travel for manufacturers of secret remedies and who practise quack medicine whilst expatiating to their prospective clients on the merits of the secret remedies and medical appliances for self treatment they offer for sale.¹

In Prussia, which comprises about two-thirds of the total population of Germany, the conditions are in a general way similar to those for Germany as a whole. For the years 1927-1931, we have the following figures :

| Year | Number of quacks | Number of doctors | Number of quacks per ten doctors |
|------------|------------------|-------------------|----------------------------------|
| 1927 | 6,736 | 27,251 | 2.47 |
| 1928 | 7,081 | 28,427 | 2.49 |
| 1929 | 6,958 | 29,141 | 2.38 |
| 1930 | 7,544 | 29,589 | 2.55 |
| 1931 | 8,349 | 30,041 | 2.76 |

In Saxony, a highly industrialised area, we find, in 1929, 1,900 lay healers as against 2,800 doctors, this being a ratio of 1 : 1½; in Dresden, indeed, there are 607 lay healers as against 600 practising physicians.²

In the United States of America, accurate numerical particulars are available only for the intermediate group of "Practitioners

¹ In the *Journal of the American Medical Association* (99, No. 2, 1932, page 145), we read the following in a letter from Berlin dated May 30th, 1932 : "There is an immense army of pedlars with charlatanic tendencies, 700 of whom, according to court testimony, were employed by a single firm (the Fi-Sü G.m.b.H., Frankfurt-on-Main), which was recently dissolved".

² H. HABERER : "Das Kurpfuschertum im Freistaat Sachsen", *Veröffentlichungen aus dem Gebiete der Medizinalverwaltung*, 23, Berlin, 1927, page 418.

with Limited Licences". This class includes osteopaths, chiropractors, naturopaths, Christian Scientists, New Thought healers and the like. The number of such healers in 1930, in a total population of 120 millions with about 142,000 doctors, was as follows :

| | |
|--|--------|
| Osteopaths | 7,650 |
| Chiropractors | 16,000 |
| Naturopaths and the like | 2,500 |
| Christian Science and other Thought Healers..... | 10,000 |

Total of practitioners with limited licences .. 36,000¹

The ratio of quacks to doctors is thus seen to be 1 : 4, and tallies roughly with the proportion noted for Germany. The ratio to the population is higher, however, being 3 per 10,000 (in Germany, 2 per 10,000).

The number of real charlatans—*i.e.*, of persons who must be regarded as such even under the laws in force in the United States—is very high, probably far higher than the number of approved non-medical healers. All competent observers are agreed on that. Though in the last twenty years there has been a marked improvement, "the number of persons who are thus carrying on quack medicine in the worst sense of the term and to an extent rarely to be met with in our countries is enormous".²

"The army of swindlers", writes the same author a few pages further on, "who practise charlatanism by singing the praises of cures of all kinds is immeasurably vast." The numberless schools—institute, university, academy, are the terms usually employed—which spring up out of the ground like mushrooms and which, in a hand's turn—and frequently by correspondence—manufacture specialists in psychotherapy, radiotherapy, magnetotherapy, electrotherapy and what not, and the rich array of material which the American Medical Association has been publishing in a series of pamphlets since 1922, serve to show the considerable extension which lay treatment has now taken on in the United States of America.³

¹ Louis S. REED : "The Healing Cults", Chicago, 1932, page 131.

² NEUBURGER, *loc. cit.*, page 671.

³ The *Lancet* of January 31st, 1925, quotes the following from *Bruxelles Médical* : "An American writer to the *Dearborn Independent* states that there

Of the sixteen countries which took part in the international enquiry into illegal treatment of the sick, which was organised in 1928 by the *Revue internationale de Médecine professionnelle et sociale*, Belgium, Germany, Denmark, France,¹ Sweden and Yugoslavia reported that the number of quacks is fairly considerable and steadily increasing. England believes that a reduction is observable, which is attributed directly to the provisions of the National Health Insurance Act prohibiting the employment of quacks by insurance funds. Switzerland reports a decrease of charlatanism, which would seem to be at least doubtful, having regard to the evidence otherwise available. The small Canton of Appenzell, with its 55,000 inhabitants, has some eighty-four quacks, "and", says HUNZIKER,² "charlatan medicine has become a regular industry". This would probably be the highest known ratio to the population were it not for the fact that the Appenzell quacks also provide for the surrounding cantons. According to the same author, quacks play a not unimportant part in Basle-land Canton and in the cantons of French Switzerland. In Roumania, in a rural circumscription in Bucovina, in 1934, fifty-five lay healers (three-quarters of whom are peasants) have been found among a population of 14,500.³

Of Italy we know very little ; the fact, however, that, in the second quarter of 1929 alone, 631 persons were prosecuted for the illegal exercise of medicine shows that charlatanism is not unknown in that country.⁴ If the ratio of prosecutions to the total number of quacks is anything approaching what it is in other countries, the number of charlatans should be by no means small.

are about 2,000 Chinese charlatans at present practising in the United States, under such titles as 'Oriental healer' and 'Herbalist'. Their clientèle is composed entirely of white people . . ." The substances offered are "dried toads for kidney diseases, while the hair of a lion or a tiger is claimed as a specific for heart troubles. Unfortunately, however, the origin of the latter medicament can usually be traced to a defunct cat or dog."

¹ According to GILLES DE LA TOURETTE, "Hypnotisme et états analogues", Paris, 1889, there were already in those days some 500 quacks, in Paris alone, who treated the sick by hypnotism.

² "Der Kampf gegen das Kurpfuschertum in der Schweiz." *Veröffentlichungen aus dem Gebiete der Medizinalverwaltung*, 27, Berlin, 1928, page 648.

³ N. SOLONENCU : "Quackery in a Rural District of Roumania", *Revista de Igiene Sociala*, December 1934, page 736.

⁴ *Journal of the American Medical Association* of November 30th, 1929, page 1746.

When we come to consider the territorial distribution of quacks in various countries—and here again we have better information for Germany and the United States of America than for other countries—the most striking thing is the marked preference of the charlatan for towns—in particular, large cities—as distinct from rural areas. In ten towns of Prussia, for instance, with an aggregate population of 6.4 millions; there were, in 1928, 4,795 lay healers, or 7.5 per 10,000 inhabitants. In Munich, the ratio for the same year was somewhat over seven quacks per 10,000 inhabitants, whereas the corresponding figure for the Reich as a whole was only 1.9.

It is a well-known fact that the proportion of doctors to the population is very much greater in the town than in the country. If the two proportions are compared *inter se*, it will be found that the ratio of quacks to doctors in the towns is much higher than it would be if it were to correspond to the figure for the Reich as a whole. Whereas the latter is about 25 : 100, we find, in 1925, in four urban districts of Saxony¹ 797 charlatans for 1,331 doctors, which yields a ratio of 60 : 100 ; in Hamburg, in that same year, there were as many as 1,227 charlatans to 1,147 doctors—in other words, nearly 107 quacks per 100 doctors.²

These facts appear to us to be of importance for the reason that they enable us to clear away certain assumptions that have frequently been made in order to explain how quackery can get the upper hand—*i.e.*, the lack of medical practitioners and the comparatively low standard of education of the population. Now, in both these respects, towns are always far better off than country districts, and yet charlatanism is far more prevalent in urban centres. Nor is this true of Germany alone.

Thus, for instance, in the United States of America, during the years 1930-1931, 30% of the 7,650 osteopaths lived in towns of from 5,000 to 50,000 inhabitants, whereas only 17.2% of the medical profession were resident in towns of this size. In centres of less than 2,500 inhabitants, there live 12% of all osteopaths and 17% of all doctors. On the other hand, 48% of the medical

¹ Bautzen, Dresden, Zwickau, Chemnitz.

² F. RABE : "Das Kurpfuschertum im Freistaat Hamburg", *Veröffentlichungen auf dem Gebiete der Zentralverwaltung*, 23, Berlin, 1927, page 423.

profession live in towns of over 200,000 inhabitants, as against 37% of the osteopaths.¹

The group of some 16,000 chiropractors are even more heavily concentrated in the large cities. In four States—Colorado, Connecticut, Florida and Minnesota—14% of the chiropractors live in communities of less than 2,500 inhabitants, the corresponding figure for doctors being 18%. On the other hand, we find 39% of the chiropractors, as compared with only 26% of the doctors, in towns of more than 200,000 inhabitants.²

The same is true of the 10,000 Christian Science healers, of whom as high a proportion as 55% practise in towns of over 200,000 inhabitants, as against 48% of the total number of doctors. Only very few live in villages and small towns; 15% are resident in towns of up to 10,000 inhabitants, as against 26% of doctors.³

In France, too, the vigorous growth of charlatanism in the post-war period has been particularly noticeable in the towns. "Towns have illegal practitioners of both sexes whose numbers have doubled since the war . . .", we read in the French answer to the enquiry on the question of charlatanism.⁴

It has already been shown above that, in Switzerland, leaving aside Canton Appenzell, towns like Basle, Geneva, etc., are big centres of charlatanism. "In Geneva, where doctors abound—to say the least—illegal practitioners swarm and prosper."⁵

In Norway, also, where the towns are amply provided with doctors, the evil of charlatanism blossoms in the urban centres.⁶

Exact particulars of the sex, age-distribution, education, etc., of lay healers can only be found by pure chance here and there in newspaper reports, mostly in reports of legal proceedings against charlatans. Even Germany possesses no systematic statistical compilation of this kind covering any lengthy period, despite the compulsory registration introduced in Prussia since 1902. We have,

¹ Louis S. REED, *loc. cit.*, page 5.

² Louis S. REED, *loc. cit.*, page 35.

³ Louis S. REED, *loc. cit.*, page 73.

⁴ *Revue internationale de Médecine professionnelle et sociale*, No. 3, Paris, 1929, page 31.

⁵ J. STEPHANI-CHERBULIEZ, *loc. cit.*, page 560.

⁶ W. A. HOYER, *loc. cit.*, page 290.

however, some interesting figures for Berlin, where, on the occasion of the Police Exhibition in 1926, a circular enquiry was made among lay healers with the following result :

I. Among 1,301 lay healers, there were 851 men and 450 women.

II. The age sub-division was as follows :

| | |
|---------------------|-----|
| Under 21 years..... | 1 |
| 21-25 | 25 |
| 25-40 | 363 |
| 40-60 | 663 |
| Over 60 | 224 |
| Unknown | 25 |

III. Schooling :

| | |
|--|-----|
| Elementary schools | 316 |
| Middle-grade schools | 100 |
| Secondary school with leaving examination | 57 |
| Secondary school without leaving examination | 17 |

IV. University education :

| | |
|--|-----|
| Medical course uncompleted | 31 |
| Authorisation to practise medicine secured abroad | 114 |
| University course (non-medical) completed | 12 |
| Unknown | 277 |

Thus we find about twice as many men as women ; more than half between 40 and 60 years of age, and a considerable proportion with no more than an elementary-school education.

The age-distribution is, to this extent, remarkable that, of 1,276 quacks of known age, only 28% fall into the age-group 25-40 and 70% are over 40 years of age. Considering that charlatanism, so far from being a moribund profession, is one which attracts adepts in ever-growing numbers, and further that, as will be seen later, no very lengthy preparation is required, this peculiar age-distribution would seem to show—and the other evidence available in Germany and elsewhere brings confirmation of the fact—that most charlatans only pass from other occupations to their healing profession in middle life.

In this connection, three questions suggest themselves at once : What are the professions from which the major proportion of quacks is recruited ? Further, with what experience of treating the sick and from what motives do they take up this work ?

As regards the previous occupations of lay healers, we have the following figures for Prussia for the year 1909 :

Of 1,735 male charlatans :

| | | |
|-----|---------------------|---------------------------|
| 258 | had previously been | small farmers and pedlars |
| 587 | " | " |
| 300 | " | " |
| 76 | " | " |
| 287 | " | " |

Of 669 female healers :

| | | |
|-----|---------------------|----------|
| 49 | had previously been | midwives |
| 14 | " | " |
| 15 | " | " |
| 220 | " | " |
| 371 | " | " |

The Berlin statistics for 1926 give the following particulars on the same subject :

| | |
|--|-----|
| Teacher | 1 |
| Unskilled labourers | 58 |
| Artisans | 275 |
| Officials | 102 |
| Servant-girls | 24 |
| Work-girls in ready-made clothes factories | 18 |
| Midwives | 2 |
| Nurses | 38 |
| Sick attendants | 59 |
| Other medical auxiliary personnel | 73 |
| Unknown | 122 |
| No occupation | 3 |
| Commercial employees and the like | 70 |
| Pharmacists, druggists and chemists | 14 |
| Schoolmasters and writers | 9 |
| Hairdressers and barbers | 14 |
| Other occupations | 13 |
| Music-teacher | 1 |
| Engineers | 6 |
| Farmer | 1 |
| Artist | 1 |
| Police officials | 3 |
| Traders | 2 |
| Brewer | 1 |
| Widows and wives | 12 |
| Waiters and photographic chemists | 58 |
| Mission preacher | 1 |
| Total | 981 |

In 1930, every kind of profession and trade, from the unskilled labourer to the university scholar, was found to be represented among a group of 1,458 charlatans. Many are drawn from the ranks of the medical auxiliary personnel (masseurs, sick attendants, sick orderlies of the Army Medical Corps, midwives, pharmacists,

druggists). Here and there, we find medical students who did not complete their course.¹

The most striking feature of the Berlin figures for 1926 is the comparatively small proportion which is accounted for by the so-called para-medical occupations. Midwives, nurses, sick attendants, subordinate medical personnel, pharmacists, druggists and chemists taken together total less than 19%, whereas artisans, for instance, furnish 30% of the total. This circumstance is all the more noteworthy since in other countries,² not only has the considerable part played by para-medical occupations been recognised, but the noticeable increase of charlatanism during the post-war period has been ascribed precisely to the great development of these particular occupations. In France, for instance, where, as we have already seen, the number of charlatans in the towns is nearly twice what it was before the war, lay healing has been taken up by a large number of women who served as nurses during the war.³

In Yugoslavia, a similar phenomenon has been noted. There are large numbers of charlatans who served in the army medical corps during the war.⁴

A considerable extension of these various occupations has similarly been reported from England. This is ascribed to the growth of medical knowledge generally and, in particular, to the swift development of specialisation.⁴

Hospitals, sanatoria, practising physicians and, commensurately with rising standards of education, the public at large are feeling more and more the need for the services of an auxiliary medical

¹ "Das Gesundheitswesen des Preussischen Staates in 1930", *Veröffentlichungen aus dem Gebiete der Medizinalverwaltung*, 35, 1931, page 164.

² This has also been the case in Germany. ". . . Charlatans are usually persons who have at some time been connected with the treatment of the sick." *Vide RUBNER*, "Handwörterbuch der Staatswissenschaften", fourth edition, VI, page 116. Also *Münchener Medizinische Wochenschrift*, of November 15th, 1929: Among the 500 quacks existing in Munich in 1928, "many were or had been midwives, hydropathic attendants; 100 had been peasants and 100 masseurs and masseuses". In France, we can find some early evidence in P. BROUARDEL'S "L'exercice de la médecine et le charlatanisme", Paris, 1899, page 474. "Nowadays, pharmacists frequently practise illegal medicine, either treating the sick or giving them medicine without prescriptions." ; and on page 475: "The public is much too ready to turn to the chemist for advice. It fails to grasp fully the difference between medical and pharmaceutical training; it imagines that chemists have been through the same course of training as doctors, and have, in addition, studied the composition of drugs."

³ *Revue internationale de médecine professionnelle et sociale*, loc. cit.

⁴ *Ibid.*

personnel increasingly differentiated by functions. On the other hand, it is becoming more and more common a practice among the doctors, under whose supervision this auxiliary personnel should work, to entrust them, both in hospitals and in private practice, with duties which are far beyond their capacity to perform, thereby accustoming them to an irresponsible independence which may thereafter tempt them into seeking their own clientèle.

In this way, the responsibility for the gradual slipping-over of numerous sick attendants, electricians, masseurs, dentists' assistants and so on into the camp of the professional charlatans lies much too often at the doctors' own door.

In this matter, much, obviously, is attributable to conditions during the great war. Tens of thousands of men and women who served as medical auxiliaries during the war learnt the craft of handling the sick, and many of them resorted to charlatanism as a result of the persistent and increasing unemployment during the economically catastrophic post-war period. Statistical calculations such as the Berlin figures set forth above possibly fail to disclose the real circumstances of the case. A shoemaker, 30 years of age at the outbreak of war, for four years an Army Medical Corps orderly during the war, and a lay healer after the war, will, when questioned as to his previous occupation, probably give that of shoemaker. In reality, however, on the conclusion of peace, he had two callings, and the calling which induced him to turn to charlatanism was not his old civilian trade but the new para-medical occupation he had learnt during the war. What has been said above concerning the irresponsible independence of the auxiliary medical personnel applies even more strongly, of course, to this latter category, a circumstance which was, indeed, unavoidable under war conditions.

As regards the "specialised" training and the length of such training undergone by persons entering the profession of lay healer, the Berlin statistics for 1926 yield the following figures :

| | |
|---|------------|
| Kind of training : | |
| No training | 23 |
| Book study | 318 |
| Instruction by other quacks | 157 |
| Membership of associations | 45 |
| Attendance at special training institutions | 155 |
| Training from doctors or at hospitals..... | 21 |
| Unknown | 172 |
| Total | <u>891</u> |

| | |
|--------------------------------|----|
| Length of training : | |
| Less than one month | 87 |
| From two to three months | 67 |
| One year | 35 |
| Two years and over | 26 |
| Uncertain | 79 |

These figures are much too small to warrant any conclusions ; circumstances in most countries are, moreover, quite other than those prevailing in Germany. Special training colleges, associations and courses of instruction, such as exist in Germany for the benefit of would-be charlatans, are for obvious reasons impossible in countries where lay treatment is forbidden by law.

Furthermore, preparatory studies, considered from the purely formal standpoint, yield no indication as to the value of the charlatan judged on actual merit. Indeed, once we become better acquainted with the substantial content of the various systems of charlatanism, once we have probed the immense depths of prejudice and ignorance on which most of the charlatan doctrines are founded, we may perhaps come to the conclusion that scant preparation is in these cases preferable to more serious study. For the whole machinery of teaching and training of lay healers produces a subsidiary psychological effect which has its importance. The broad masses of the population, which are constantly hearing of academies for lay healers, training courses, congresses, etc., and are quite unable to judge whether really serious knowledge is inculcated there or not, ultimately begin to doubt whether charlatans are really as ignorant as is said ; whether the difference between so-called orthodox or classical medicine and some system of quackery or other really goes deeper than the difference between two separate, but equally scientific, theories. It is precisely because of these undesirable psychological effects that proposals to make a selection among charlatans by examination, such as have repeatedly been put forward in Germany¹ and England²—sometimes, indeed, from

¹ For instance, during the discussions on the Bill for combating the Abuses prevalent in the Healing Profession which took place in 1910 in the German Reichstag Committee. There was talk at that time of a "minor licence" for lay healers. *Vide Veröffentlichungen aus dem Gebiete der Medizinalverwaltung*, 25, 1927, page 321.

² Bill (ADAMSON) to regulate the Practice of Osteopathy and to prescribe the Qualifications of Osteopathic Practitioners, March 1931. *Vide*, also, LEONARD DE MARCHANT MINTY : "The Legal and Ethical Aspects of Medical Quackery", London, 1932, page 234, and, more recently, in February 1934, BOOTHBY's proposal in the House of Commons.

quarters friendly to the charlatans—should be rejected as nefarious. Though the purpose of all such proposals may be to weed out the most ignorant of the quacks, what they actually achieve is something quite different. To discriminate between great, greater and greatest ignorance is not easy and serves no very useful purpose. On the other hand, under this system, quacks who previously were—at best—tolerated receive the stamp of Government recognition, which, with their usual talent for publicity, they know full well how to turn to account.

The idea of a “minor licence” originated in the United States, where it has already to some extent been put into practice. We have already noted that in all States of the union certain classes of non-medical practitioners are authorised to treat the sick after passing a certain examination. These healers differ from fully qualified doctors in that each one of these sects may apply a particular method of treatment, which somehow is connected with the central dogma of the sect in question. Each sect has its particular schools and particular examination boards, which consist, naturally, of the high priests of the sect; for the various sects are at daggers drawn, and it is a common fact of experience that nobody can expect a just and impartial judgment from his antagonist. The special schools, even the best of them, lag far behind the medical faculties. Abraham FLEXNER¹ reported in 1910 that the training given in the eight existing schools of osteopathy was wholly valueless. Although the position was supposed to have much improved in the meanwhile, the Council on Medical Education and Hospitals of the American Medical Association still found, in 1927, that they were not even up to the standards of medical schools, Class C.²

For these reasons, various States³ have found it necessary to develop their system of examinations still further and to use a finer mesh on their sieve of selection. Under the so-called “basic science laws” of these States, all persons treating the sick are compelled, before they can be licensed, to satisfy a board of examiners that they possess an adequate knowledge of these sciences.

¹ “Medical Education in the United States of America and Canada”, New York, 1910, pages 163-166.

² L. S. REED, *loc. cit.*, page 21.

³ Wisconsin, Connecticut, Minnesota, Nebraska, Washington, Arkansas and District of Columbia.

They are : anatomy, physiology, pathology and bacteriology. Many States add thereto chemistry, hygiene and medical diagnosis. Only when they have been examined in these subjects by an impartial board of examiners are candidates of various kinds, such as osteopaths, chiropractors, etc., and, indeed, even orthodox medical men, entitled to appear before a special examining commission with a view to securing their special licence as approved healers of the sick.

The immediate consequences of these laws have been that, in Wisconsin, for instance, where, before 1925, some 200 non-medical healers had settled every year, the number establishing themselves since then has not exceeded three per annum. In the State of Washington, where previously only 27% of the sick healers approved every year were doctors, the proportion rose to 92% after the coming into force of the "basic science law". Since 1931, in the seven States concerned, a total number of 752 candidates have come forward for examination in "basic science", and, of these, 620 have passed. Among the 752 candidates there were 674 doctors, 33 osteopaths, 32 chiropractors and 13 "others". Of the doctors, 597, or 88% ; of the osteopaths, 18, or 55% ; of the chiropractors, 7, or 22% ; and of the 13 others, 5, or 38%, passed this examination.¹

The clean-up which this clearly reflects has, in fact, been even more drastic than the figures would suggest ; for those particular candidates whose preparatory medical training is most inadequate, but who, before 1925, could secure their licence without further ado, will now probably prefer not to expose themselves to the risk of the "basic science" examination at all. At the same time, some doubt may justifiably be felt whether the price paid for this clean-up has not been too heavy, seeing that the sectarian healers now have, in the eyes of the public, one more title to equality with scientifically trained doctors. It is no doubt true that the quality of doctors is not affected by the "basic science" examination, which, moreover, affords the guarantee of a minimum of scientific knowledge on the part of the sectarian healers. It is true, for instance, that an osteopath possessing the anatomical, physiological, pathological and diagnostic knowledge required to pass the "basic

¹ *Journal of the American Medical Association* of April 25th, 1931, page 1399.

science" examination will be better able to diagnose a case of syphilis accurately than he would without such knowledge. On the other hand, we must ask ourselves : What does it avail the patient that the osteopath should possess all this knowledge if, having thus accurately diagnosed syphilis, he tries to cure it by resetting the vertebrae? Again : How great is the social damage done if, impelled by the psychological effect described above, syphilitics resort in ever-increasing numbers to osteopaths in order to have their spinal columns manipulated this way and that ?

In all this we must not forget, however, that the institution of the so-called " limited licence " in the special conditions of America, as determined by her historical development, no doubt has its justification. For reasons which we cannot analyse in detail here, certain classes of non-medical healers are legally recognised as such in the United States. Now, if measures are taken in America to raise the scientific level of these healers, such action is no less justified than any endeavours that may be made to improve medical standards in countries such as England or Germany, where only doctors can be enrolled as State-recognised healers. If, however, an attempt were made in these latter countries, which tolerate charlatans but do not license them, to introduce a special kind of licence on American lines, this would obviously involve a lowering of the quality of approved healers taken together as a *single* class.

What remains to be said concerning the training of lay treaters may be summarised as follows :

The innumerable swindlers among the charlatans whose one purpose is to exploit the sick require no preliminary medical study. All they need is a little knowledge of human nature and cunning and the mastery of a certain technique of fraud. Either they bring these and similar talents fully developed into the fray or they are soon beaten in the struggle for life with their more " efficient " colleagues. Many a special school is far more concerned with developing this business ability in its disciples than with inculcating knowledge.

The founder of the chiropractors' sect declares unabashed : " Our school back at Davenport is established on a business and not on a professional basis. It is a business where we manufacture chiropractors. They have got to work like machinery. Of course,

salesmanship goes along with the training. We teach them the idea and then show them how to sell it."¹

Needless to say, there are also lay healers who are not frauds and whose work is even useful, and we shall have more to say about these in another connection. Suffice it to note at this point that the valuable achievements of such healers proceed in some way either from knowledge which they have acquired through book-study or contact with other lay healers, sometimes from a happy personal knack of observation, but mostly from the power of their own personality. Some of them hold it useful to relate their success to some family tradition which is kept a strict secret. This applies, in particular, to herbalists. Others are inclined to surround their own personality with an aura of mystery, claiming to possess special organs of sense or a kind of intuition, sometimes hereditary, to which they owe their success in a way incomprehensible even to themselves. A classical example of this kind of lay healer is the well-known bone-setter, Sir Herbert Barker, who is connected with the Huttons of Yorkshire—for centuries a family of bone-setters—and who says of himself that his technique is essentially not learnable by others.²

It is amusing to set opposite this man's somewhat mystical and self-confident judgment of his own abilities the following general pronouncement by one well versed in these matters: "The bone-setter is generally a person of inferior education, an athletic trainer, St. John Ambulance man, R.A.M.C. orderly who has lost his regular job and turns his amateur training into a means of getting a living."³

Why charlatanism is taken up as a career is a question easy to answer: supply, in this case as in others, is regulated by demand. As soon as there are prospects of earning more money in the treatment of the sick than in other occupations, the camp of charlatanism is immediately invaded by crowds of adepts. The individual's decision to abandon his old occupation and to become a quack is usually eased by an intervening period of transition during which charlatanism is exercised as a side-line. Matters are also facilitated by the fact that such qualifications as are needed for the

¹ *Journal of the American Medical Association* of November 6th, 1920, page 1276.

² H. BARKER, "Leaves from my Life", pages 29 and 203; Leonard DE MARCHANT MINTY, *op. cit.*, pages 81 and 82.

³ Leonard DE MARCHANT MINTY, *op. cit.*, page 88.

exercise of this new healing profession can usually be obtained at no great cost and with very little trouble.

A critical period such as we are now passing through is also calculated to accentuate the tendency in this direction, since the widespread unemployment reduces the risk of abandoning a previous calling to a minimum.¹

But, apart from the attraction of monetary gain, other, more subtle, motives come into play. The superior social status of a healer, the acknowledged respectability of his profession are far better calculated to satisfy the need for prominence of the ambitious than the modest calling of a manual worker or petty tradesman ; and, finally, we must not forget the small body of the " elect ", the founders of new dogmas, who are possessed of an intense belief in their mission, bordering at times on the religious, and of a fanatical will to minister to suffering mankind.

To gain some approximately correct idea of the extent of the profits of charlatanism is by no means easy. Figures on the subject are rare, attempts at verification mostly doomed to failure. The little we do know is culled from the reports of legal proceedings, in the course of which the fees and income of charlatans are not infrequently discussed. Where such direct sources of information are not available, it is sometimes possible to estimate profits approximately from the number of patients treated, when this is known. As in so many other aspects of this question, it is the United States which, thanks to the many organised special enquiries and studies, furnish the most definite information.

In *Veröffentlichungen aus dem Gebiete der Medizinalverwaltung*, Volumes 25 and 27, we find, scattered here and there, the following particulars in the records of court proceedings :

Schäfer Ast : annual income, 120,000 marks.

¹ In " Das Gesundheitswesen des Preussischen Staates im Jahre 1930 " (*Veröffentlichungen aus dem Gebiete der Medizinalverwaltung*, 35, 1931, page 164), we read : " Prevailing conditions tend to encourage the exercise of medicine by laymen and also by certain firms which produce more or less worthless remedies and seek to market their wares by advertising for representatives to whom the prospect of considerable gains is held out. As the exercise of medicine is free, many an unemployed is glad, in the prevailing economic distress, to seize this opportunity of earning money, after having, in the most favourable cases, acquired some rudiments of knowledge in the course of a few lessons received from a practitioner."

“ Hair-Diagnostician ” Buchholz¹ : received 200 patients a day (fee 2 marks).

Just, manufacturer of Luvos Curative Earth : annual income, 1,000,000 marks.

The Berliner K. Jacobi : registered 2,570 patients in eight months.

Nardenkötter (about 1901) : annual income, 160,000 marks.

The Breslau Institute for the Treatment of Venereal Diseases registered 220 patients in the first three weeks of its existence.

Fastenrath (Cologne), diagnosis by clairvoyance, received from 30 to 40 patients in his consulting hours.

A charlatan dealing with about 500 letters daily and advising from 150 to 200 patients.

The well-known quack Zeileis, at Gellspach (Austria), “ drew an income of 5,000-6,000 marks a day. Between 1,000 and 2,000 patients per day were treated.”²

What the position is in the United States with regard to the income of quacks we do not know. On the other hand, we have comparatively accurate data on the subject for the intermediate class of sectarian healers who, on European standards, would rank as quacks, despite the fact that, in the United States, they are recognised practitioners in the treatment of the sick.

Louis S. REED³ has ascertained the following figures :

| | Annual income \$ |
|---|---------------------|
| 7,650 osteopaths | 42,000,000 |
| 16,000 chiropractors | 63,000,000 |
| 2,500 naturopaths <i>et simil</i> | 10,000,000 |
| 10,000 Christian Science and New Thought practitioners | 10,000,000 |
| <hr/> 36,150 | <hr/> 125,000,000 |

¹ Of Buchholz, who practised in Hamburg, we even learn that the daily number of patients rose, within a short time, to four or five hundred. A doctor sent him, for examination, the hair of a corpse upon which a post-mortem had been performed, and communicated the resulting nonsense to the Press in so clever a form that Buchholz shortly after lost his practice and left Hamburg.— *Veröffentlichungen aus dem Gebiete der Medizinalverwaltung*, 23, Berlin, 1927, page 425.

² H. BURGER : “ The Doctor, the Quack and the Appetite of the Public for Magic in Medicine ”, in Proceedings of the Royal Society of Medicine, 1933, **XXVII**, page 173.

³ “ The Healing Cults ”, The University of Chicago Press, 1932.

That same figure of \$125,000,000 as the income of " non-medical practitioners ", healers and quacks is to be found in a report for the year 1930.¹

According to the calculations of Louis S. REED, the \$125,000,000 represent 12% of the aggregate annual expenditure of the total population of the United States on treatment fees, amounting to \$1,040,000,000. It would follow from this :

(1) That doctors' fees total somewhat more than \$900,000,000 ;

(2) That, whilst the ratio of sectarian healers to doctors in respect of their numbers is as 1 to 4, the ratio of the aggregate income of both classes is as 1 to 7.3 ;

(3) That the mean annual income of a doctor is thus about \$6,350, whilst the corresponding income of a sectarian healer barely amounts to \$3,500.

According to DAVIS's reports, the ratio is somewhat more unfavourable to the doctors, since, according to his calculations, the average income of the American doctor does not exceed \$4,500.²

A very important point has been stressed in England. Whereas medical fees are generally adjusted to the patient's financial standing, a charlatan has but one rule—that is to say, to squeeze out of the patient everything that can be got, and, the report goes on, to say that a poor man will always give everything he possesses for an assured cure.³

E. S. FLEMING,⁴ also writing about England, finds that " the sums spent on these cures (physical culture) must be enormous, for the fees charged are by no means small ". In another passage,

¹ M. M. DAVIS : " Doctors' Bills and Public Billions ", in the *Journal of the American Medical Association* of March 29th, 1930, page 1014.

² The figure of \$625,000,000 is the assumed aggregate annual income of the medical profession. It follows that the income of sectarian healers is lower than that of doctors and that the latter are thus, fortunately, exposed to no temptation in this direction. Similar facts are reported by most of the countries participating in the enquiry into the illegal practice of medicine. Hungary, Poland, Switzerland, Norway and Yugoslavia all agree that the fees of quacks are less than those of doctors. This, of course, tells us nothing as to their income.

³ The English Rapporteur is Dr. Cox, General Secretary of the British Medical Association.

⁴ E. S. FLEMING : " Quackery in Rural Districts ", *British Medical Journal* of May 27th, 1911.

the same author observes that the money spent on quack treatment would suffice to endow more than 40,000 hospital beds.

Though the motives which induce patients to seek medical help from laymen are deep-rooted in human nature, charlatanism would scarcely have become as all-pervasive as it is without intensive propaganda. On the other hand, intensive propaganda is scarcely conceivable without a sub-structure of organisation. And, indeed, we observe, especially—and for obvious reasons—in countries where the art of healing may be freely exercised and where open competition by the quack is accordingly subject to no legal restrictions, that numerous organisations gradually arise and develop with the object of converting as large sections of the public as possible to a belief in charlatanic systems whilst at the same time undermining their faith in scientific medicine. If such a system of recruiting adepts bears fruit, even in those countries in which charlatanism is forbidden by law, this is to be ascribed mainly to the character of modern propaganda work which can act powerfully even across political boundaries.

These methods include :

- (1) Associations of the charlatans themselves ; these being professional associations which are responsible for safeguarding the common interests of the charlatans and conducting propaganda by collective means ; and
- (2) Societies, whose members are followers of various charlatanic methods of treatment, people who are already sick or are candidates for sickness and who strengthen each other's faith in this or that system, or are, where necessary, confirmed in their faith by the quacks themselves, who obviously set the tone in organisations of that kind

Of such societies there are as many as there are systems of quackery ; for, although they all regard scientific medicine as the main enemy, their antagonism towards each other is only slightly less keen, and there is no question of making common cause against so-called academic medicine. To these should be added local organisations—that is to say, local groups of nationally organised quacks which occur in hundreds in the bigger countries. Even internationally co-ordinated organisations of lay healers are not

unknown. Such, for instance, is the Christian Science Movement. These associations are "usually supported by a very cleverly managed Press ; they are controlled by numbers of skilled business leaders and fight the medical profession by all available means. A great spirit of sacrifice on the part of their members makes them assured at all times of adequate reserves of money."¹

According to E. LIECK,² the charlatans in Germany have twenty Reich organisations and thousands of local groups. The German Biochemical Society³ comprises more than 400 associations and more than nineteen large State federations. The President of the Biochemical Union estimated some time ago that the supporters of the movement (registered and non-registered members) numbered about a million and a half.

In England we have, *inter alia*, the British Association of Naturopaths, the British Chiropractic Association, and the National Association of Medical Herbalists of Great Britain.

In the United States, we have mainly to consider the associations of sectarian lay healers. The American Osteopaths' Association (since 1901) numbers 4,350 of the 7,650 osteopaths among its members. Its objects are to provide its members with legal advice and raise the standard of education. It is a national association, but, on the model of the American Medical Association, it forms State osteopathic societies. Once a year there is a meeting of the House of Delegates, the osteopathic parliament of the United States, consisting of delegates of the State osteopathic societies—this, again, modelled on the American Medical Association. The Society for the Advancement of Osteopathy (since 1920) is concerned mainly with propaganda among the lay public.

The chiropractors, on the other hand, are a little less compactly organised. The National Chiropractic Association comprises no more than 3,000 of the 16,000 practising chiropractors. The main purpose of this organisation is also legal aid and the refund of any losses suffered by its members in respect of fines inflicted or compensation awarded against them. The chiropractors also have their

¹ DRESSLER, in the *Münchener medizinische Wochenschrift* of July 21st, 1933, page 1154.

² "Arzt und Kurpfuscher" in the *Wiener medizinische Wochenschrift*, Nos. 18, 19 and 20, 1933.

³ This refers, not to scientific biochemistry, but to a system of quackery, a degenerate form of homeopathy.

State Chiropractic Association and their International Chiropractic Congress consisting of delegates of the Boards of Chiropractic Examiners, the specialised schools, officers of the State Chiropractic Associations and representatives of followers in the faith. This organisation deals mainly with propaganda.

The Christian Science Church (since 1870) is organised around 1,265 churches. The followers of this religious movement are estimated in the United States at 700,000. The movement is, however, a pronouncedly international one, and there is hardly a moderately large-sized town in England, Germany, Switzerland or France without its Christian Science Church. The direction of the movement devolves upon the Mother Church at Boston, governed by a committee of five, which renews its membership by co-option.

Charlatan organisations make very extensive use of the Press. The quacks themselves distinguish strictly, it is true, between their so-called scientific publications and matter for popular consumption or pure propaganda ; though, in fact, it is nothing but propaganda in either case.

The German quacks have about 150 periodicals.¹ England has its *Health for All* with a circulation of 24,000 and the *Medical Herbalist* with a circulation of 3,000.

The scientific organ of the American osteopaths is the monthly *Journal of the American Osteopathic Association*. The Association issues four other periodicals as well.

The chiropractors publish a popular monthly journal, which had 100,000 subscribers in November 1930, and claims to add 3,000 more to its subscription list every week. The subscription is \$1 and the net profit is used for propaganda broadcasting.

The Christian Science Church spreads its influence over large sections of the population by means of the well-known daily paper *The Christian Science Monitor*, which is regarded by many as the best paper in the United States ; it operates mainly, however, through conferences and assemblies, which are organised in vast numbers. In the year 1930-31, 3,303,872 persons took part in such meetings.²

¹ E. LIECK, *oc. cit.*

² Alice E. PAULSEN : " Religious Healing ", *Journal of the American Medical Association*, 1926, 86, page 1519.

One of the most important features of the organisation of charlatanism is the special training schools, practically all of which carry on intensive propaganda in addition to discharging their main functions.

In Germany especially, "the growing fear of the law on industries, occupations and professions,¹ with the ultimate possibility of withdrawal of the unreliable charlatans' freedom to treat . . . has brought numerous courses of instruction into being".²

It will thus be observed that charlatans who feel that their livelihood is threatened begin to conceive doubts as to whether they possess a sufficiently complete mastery of the doctrines of their own system.

Purposes similar to those of the special schools are served by scientific institutes, societies and congresses, etc. (International Congress for Iris-Diagnosis at Dresden, Society for Iris Research, Pathological and Physiological Institute, Munich, and the like).

In London, we have the British School of Osteopathy with its clinic and the Nature Cure Hospital.

The best training machine is undoubtedly that of the United States quacks, more especially the osteopaths. In 1930, they had seven osteopathic colleges with 1,760 students. The curriculum covers four years. By way of preliminary training, candidates are required to have attended high school for four years. Hospitals and out-patient departments are attached to these osteopathic schools. The teaching staff of the seven schools comprises 251 professors, including fifteen doctors. According to the *Year-Book and Directory of the American Osteopathic Association*, there were, in 1930, 62 osteopathic hospitals, 57 of which had 1,727 beds and 33 out-patient departments. The A. T. Still Research Institute (California) has been established to promote the further development and elaboration of osteopathic theory.

The chiropractors had (in 1930) 21 special colleges with 1,400 students. The syllabus of what is admittedly the best of these³ covers a period of eighteen months. If this should appear too

¹ The reference here is to the introduction, proposed in various quarters, of an examination, in order to eliminate the unworthy from among the ranks of the healers.

² DRESSLER, *loc. cit.*

³ Palmer's school, Davenport, Iowa.

much to a would-be candidate, let him be immediately reassured : " Students may enroll and begin class work at any time during the year and graduate eighteen months from the date of such enrolment ". The preliminary study required is nil. There are no hospitals available for training. Anatomy is studied from atlases, and the prospectus, making a virtue of necessity, explains that " thus the student is given a clean and sanitary method to obtain a thorough knowledge of human anatomy without the necessity for dissection work on the human cadaver ".

The curriculum also contains a course of personal efficiency, which initiates the future chiropractor into the mysteries " of details of conducting office, the best methods of approaching the public, the important phases of advertising ". Should he prefer it, he can acquire a mastery of chiropractic wisdom by correspondence, as we learn from the prospectus of the American University in Chicago.

Of the numberless swindling undertakings which mass-produce doctors of various kinds or professors, we have spoken earlier on. These so-called " diploma mills " are not taken seriously by anyone in the United States. However, the various nice titles " often prove readily marketable as export wares for foreign consumption ".¹

We already know that the charlatan's clientèle is numerous and that everywhere the bulk of it is drawn from urban populations. We saw that the supporters of the Christian Science Church in the United States, for instance, are to be numbered by millions, that the biochemical sects alone have approximately a million and a half members or camp followers in Germany. An expert on quackery like LIECK² estimates, in common with other experienced writers, that about half of the German people turns its back upon orthodox medicine and runs to consult the ignorant quack ; he even believes that the number of " seceding patients would be even greater were it not for compulsory insurance, which covers some two-thirds of the German population and has given the doctors a monopoly ".

Now, who are the patients who seek medical advice from lay healers and entrust them with their health, nay, even their lives ? From what social strata do they come ? What is their level of education, their economic position ? We should like to clear up

¹ NEUBURGER, *loc. cit.*, page 672.

² *Loc. cit.*

these questions so far as is practicable before approaching, as a final point, the main question : What are the reasons why preference is so frequently given, not to the doctor, but to lay practitioners of whom numbers of their victims are fully aware that they are not acquainted even with the structure and normal functioning of the human body ? .

Just as lust of gain and trickery are usually ascribed to the quack as the main motives, if not *the* motives of his actions, so, on the other hand, there is a very widespread opinion that the great confidence that charlatans generally enjoy is due to sheer ignorance, dullness and stupidity on the part of their clients. Nothing is more directly at variance with the facts of everyday experience than this opinion, which is especially current in the medical profession ; for anyone at all capable of the unbiased recognition of facts cannot help acknowledging that believers in charlatanism occur in no less a proportion among the so-called educated classes than they do in the remainder of the population—in fact, that genuine charlatanic enthusiasm is encountered more frequently in these circles. In this connection, we should naturally bear in mind that educated people “ are often, to an exceptional degree, but half educated so far as the natural sciences are concerned ”.¹

The fact that, as already mentioned, the majority of charlatans earn their living in towns in itself raises doubts in the mind whether this predilection for the medical help of lay healers is in any way or to any appreciable degree dependent upon the advice-seeking patient's level of education, for it is a well-known fact that urban populations are usually better educated than country folk. We have, moreover, direct evidence to show that, within the population of the towns, the charlatans recruit a proportionately larger number of clients among the more prosperous and better educated classes than they do among the poorer and more ignorant. It appears, for instance, from the statistical compilation of E. J. G. BEARDSLEY² that 43% of the private patients he treated during a period of four years had been treated by quacks during the three months preceding their first consultation. The corresponding proportion for the same

¹ ASCHAFFENBURG in the *Münchener medizinische Wochenschrift* of June 16th, 1933, page 949.

² The therapeutic value of a complete physical examination, in the *Atlantic Medical Journal*, 1925, 28, page 647.

period among patients examined at a public consultation clinic was only 26%.

The Illinois Medical Society made a circular enquiry among 6,800 persons in Chicago, and found that "the semi-foreign communities out on the West Side of Chicago showed a smaller percentage experimenting with doubtful healing practices than the exclusive Hyde Park and North Shore residential districts".¹

The Committee on the Costs of Medical Care, after examining 16,000 representative American families, ascertained that, of the well-to-do families with an annual income of \$5,000 and over, 16% were under treatment by charlatans, whilst of those with incomes of \$2,000 and less only 6% were being so treated.²

These and similar facts will scarcely surprise anyone who has had an opportunity of attending the assemblies of the Christian Science Church. Among the thousands who take part in the well-known Wednesday meetings at the Mother Church at Boston, for instance, there is little likelihood of finding any representatives of the Boston proletariat. In Germany, according to LIECK, the people to be found in the charlatans' consulting-rooms are "precisely the upper strata of the population; not only the nobility, which is particularly well represented everywhere, but also statesmen, prominent lawyers, head masters, the leaders of the clergy of all denominations, forestry inspectors, engineers, great merchants, leading men of industry and banking and—not a few doctors".³

A. MOLL, in his varied experience, also found that, especially in the higher circles "of the Berlin and German aristocracy . . . superstition flourished appallingly".⁴

That matters are no different in France was observed by BROUARDEL even in his day: "Not only . . . among the poorer classes, but also among those who have been most carefully educated do we find the best clients of these charlatans, who take advantage of their truly inconceivable credulity."⁵

¹ B. C. KELLER: "The Latest Idea of the Physician", in *Illinois Medical Journal*, 1923, 44, page 13.

² L. S. REED, *loc. cit.*, page 117.

³ "Arzt und Kurpfuscher", *Wiener medizinische Wochenschrift*, Nos. 18, 19, 20, 1933.

⁴ A. MOLL: "Okkultismus und Magnetopathie", *Veröffentlichungen aus dem Gebiete der Medizinalverwaltung*, 23, Berlin, 1927, page 506.

⁵ B. BROUARDEL: "L'exercice de la médecine et le charlatanisme", Paris, 1899, page 474.

E. S. FLEMING, already quoted above, observes on the strength of his own observations and the experience of thirty-four other doctors of his district that "quackery is distributed pretty equally among all classes of society and in town and country"; that "rich and poor, educated and uneducated", turn alike to the lay healer for medical help; that "the town patient, though quicker in thought than his country cousin, is probably no less superstitious in regard to the treatment of his many ailments".¹ Some interest attaches also to the remark of OSLER: "I suppose, as a body, clergymen are better educated than any other, yet they are notorious supporters of the nostrums and humbuggery with which the daily and religious papers abound"²

We have already seen that the popularity of lay healers in countries which prohibit charlatanism is not noticeably less than in those in which the treatment of the sick is a profession that may be taken up and followed by any who care to do so. If the statutory prohibition is in any degree effective as a general hindrance to the exercise by such lay healers of their illegal profession, it follows that the explanation of their large numbers and extensive practice must be sought in the operation of some positive factors which, overriding all legal prohibitions, bring patients and lay healers together into one common anti-medical camp. These various factors can—at least *in abstracto*—be easily assigned to three classes, according to whether the living centre from which they radiate their force—of repulsion away from the doctor or of attraction to the quack—lies in the doctor, the relief-seeking patient or the lay healer himself.

Considering the great advances of medical knowledge, we should ask ourselves how it is possible that the rush of patients to the quack should increase year by year. It is, as a matter of fact, not upon the great achievements of medicine, but upon its all too many imperfections, the inadequacies of theory and especially its practical application that the issue turns whenever patients, after a vain appeal to science, turn their backs upon it in the hope of finding salvation elsewhere. It is true, of course, that they

¹ E. S. FLEMING, *loc. cit.*, pages 1247 and 1248

² William OSLER: "Address on Feeling and Thinking *Æquanimitas*". Second Edition, London, 1906, page 131.

obtain the desired relief even less often from charlatans than from scientifically trained physicians, but this does not help matters in the least ; that which carries thousands into the arms of charlatanism is not the actual finding of the relief sought but the hope of finding it there.

The conflict of learned opinions, the succeeding changes in theory and in the branches of practical learning that are founded upon it—all these, again, act very much like those blind spots of scientific medicine upon a public which is utterly devoid of any conception or appreciation of scientific method. The average man finds it difficult to realise that doctrines which are in a state of constant flux can be serious science ; the expression "immutable truth" is to him a pleonasm, for evolving truth strikes him simply as no truth at all. This instinctive belief of large masses is elaborately exploited against the medical profession by clever propaganda.¹

That impersonal abstraction "medicine" is for the patient a thing remote and unknown ; he comes into direct contact only with its representatives, the doctors, and, understandably enough, their imperfections are sometimes much greater and more perceptible than those of medicine itself. True, they are not greater than the ignorance of the quack, but the lay healer finds it much easier than the scientifically trained doctor to mask his ignorance and simulate knowledge when, in fact, he knows nothing.

Furthermore, the doctor suffers, not only from his lack of knowledge, but also from the consequences of the knowledge he possesses. Like all those who have been through the stern discipline of scientific training, he habitually weighs his opinion with accuracy and caution ; is inclined to undue modesty rather than excessive self-confidence ; and, owing to his unassuming manner and sceptical attitude, is much too apt to create an impression of indecision and to be ousted from popular favour by the utterly unrestrained and unblushing self-assertion of the lay healer.

¹ Dr. SCHÜSSLER, the founder of the "Biochemical Healing Method", which is very widespread in Germany, writes, for instance, as follows : "A science which is at all times ready to discard the old and adopt the new is no science. Science needs fixed and invariable laws." (Quoted from HISS in *Veröffentlichungen aus dem Gebiete der Medizinalverwaltung*, 25, 1927, page 213.)

Similarly, a doctor's scientific outlook exerts a negative influence on his own attitude of mind towards disease and the patient. The natural effect of self-criticism and prudence is to damp that optimism which is frequently his most powerful weapon in the fight against disease and which, in hopeless cases, is, indeed, his only means of helping his patient. The handicap under which the doctor and the patient labour in consequence has been realised by none better than BURGER :

"The optimism of the doctor is transmuted in the heart of the patient into a steadfast faith which in many a sick-room is a powerful factor for good. Thus the quack has really a much firmer position than the honest doctor. He can play the optimist under all circumstances. He can prophesy a cure of even the most grievous diseases. Doubt never assails him. If in the promised time the cure be not established, then it is an exceptionally stubborn case and a second and third treatment is clearly needed. When in the end failure can no longer be glossed over, then the fault lies with the bungling of his predecessors the doctors—and the cheated sufferer is reproached with having waited too long to come for treatment."¹

In addition to these two undesirable by-products of scientific training—scepticism and an inclination towards cautious pessimism rather than towards risk-fraught and responsibility-laden optimism in the judging of a condition—there arises a third disturbing factor—the impersonal and objective element in the doctor's attitude towards the object of his investigations or treatment, towards the "case".

It would no doubt be an exaggeration to say that the doctor's scientific approach to his subject destroys the personal relation between his patient and himself; but that it does incline him *cæteris paribus* to magnify the objective realities of the doctor-to-patient relation at the expense of its personal aspects, and that this tendency increases commensurately with the progression of scientific method in the field of medical studies, is hardly open to doubt. The type

¹ H. BURGER : "The Doctor, the Quack and the Appetite of the Public for Magic in Medicine", in *Proceedings of the Royal Society of Medicine*, 27, No. 2, 1933, page 172.

of "guinea-pig doctor" or "test-tube doctor" does not grow rarer with the passing of time, but more frequent, both in private practice and in public medicine ; and the complaint that medicine trains too many medical scientists and too few doctors grows ever more insistent.¹ This is undoubtedly one of the many factors which operate in the direction "away from the scientific doctor".²

There are two other tendencies just as characteristic and just as liable to estrange this type of doctor from his patient. They are the familiar tendency to take so-called "minor ailments" lightly and the even more dangerous tendency to see in the patient only the sick body and to leave his mind more or less out of the reckoning. Clearly these two tendencies stand towards each other in the relation of the particular to the general, since the minor ailments are regarded as such and taken less seriously, for the very reason that they centre, or are supposed to centre, mostly, if not exclusively, in the patient's mind.

Now, this minimising of subjective phenomena is in no sense an inevitable consequence of the scientific methods followed in modern medicine. True, it is appropriate to the mechanistic view of the universe which has gradually developed since the seventeenth century, and in line with the general endeavour to thrust the mental element as a "secondary quality" (JOHN LOCKE) or, in more modern parlance, as an "epiphenomenon" (WILLIAM JAMES) out of the field of reality. Such an endeavour is, however, the product less of modern scientific research than of one of its philosophical dogmas which has failed to stand the test of unbiased research. After DESCARTES developed the theory of the animal automaton, after HARVEY'S great discovery and his physical explanation of the circulation of the blood, and after LAMETTRIE coined the popular catch-phrase "l'homme machine", biology generally, and human pathology in particular, came completely under the spell of so-called "mechanistic principles". The youthful period of scientific clinical medicine was devoted exclusively to the investigation of

¹ J. H. SALOMON: *Münchener Medizinische Wochenschrift*, February 28th, 1930, page 366.

² "The exactitudes of science are utterly antipathetic to the sick person, who resents being regarded as a 'case' for whom the chances of recovery are so many per thousand." (A. J. CLARK: "The Historical Aspect of Quackery", in *British Medical Journal*, October 1st, 1927, page 590.)

organic alterations, the causal connection of which with factors of the external and internal, physical and physiological environment appeared to exhaust the scope of clinical research. Pathological anatomy had become the fundamental medical science. No one in those days of great clinical triumphs had much time for "epiphenomena".

Gradually, disease was identified with organic alterations, and its cure with the retrogression of morbid organic alterations. A pessimistic bedside tone was the immediate consequence of this. For nothing seemed more certain than that morbid organic alterations—especially those which were of long standing or had reached a given stage of progress—could be made to retrogress only with difficulty and never with complete success. No wonder, then, that, in the circumstances, the prospects of success with any therapeutic measure should have appeared poor from the start.

The point which was, however, either completely overlooked or given too little importance is that most organic diseases are largely overlaid with mental symptoms which are accessible to effective treatment, and that the mental symptoms thus superimposed on organic disease are frequently, in the patient's eyes, the most important part of his whole trouble. In most cases, the patient, unless instructed by the doctor, has no idea of the changes proceeding in his tissues ; that which makes him—in his own consciousness—a sick man, that from which he is really *suffering*, is not those objectively ascertainable organic alterations, but the concomitant mental effects : the pain experienced, the sensation of weakness, the depressed mood, the feeling of discouragement, the inward agitation, dread and despair, etc.—conditions which it is within the power of a competent physician to influence in the right direction, even if the subjacent organic alteration—the disease objectively considered—is entirely beyond his control and relentlessly following its natural course.

Unfortunately, however, the abilities required for this purpose are but rarely encountered—a circumstance which is partly due to the modern doctor's general approach to his subject and his habit of thinking in organic terms. The lay healer is helped over many a difficulty by his very ignorance and unscrupulousness ; by the former inasmuch as it blinds him to the inescapable organic progression of the disease, and by the latter inasmuch as it enables

him to promise the patient light-heartedly anything he may wish. In such a case, only the really skilled physician—that is, the learned artist who combines medical knowledge with the needful psychological tact—could work marvels. But such a blend of qualities is exceedingly rare. If psychological knowledge of a kind that could be acquired—and acquired in the same way as medical knowledge—should one day become available to replace that intuitive tact which is still a mystery to us, that day will witness a notable reduction in the sum of human suffering prevalent in the world.

For, how often—where the trouble is either an incurable organic disease or one for which, owing to other considerations, nothing can be done—is not a change in the patient's own mental attitude towards his condition sufficient to produce considerable improvement?¹ In bringing this about, the personality of the healer, no matter whether he be a doctor or a lay healer, plays a great part. We may quote a particularly instructive instance recorded by an experienced doctor :

“Some sixty years ago, it was discovered that ptosis of the kidney was a very serious pathological condition ; it was cured by excision of the kidney. WAGNER described, in 1878, 42 such cases, 11 of them with a fatal issue. Later, it was the practice to sew the kidney into position. Then I began to have doubts, and I said to the patients—most of them women—who came to me : ‘Ptosis of the kidney is a matter of no consequence, there can be no question of operating, *and, in any case, kidneys are now being worn a little lower again. . .*’. A wholly unscientific proceeding, but . . . unquestionably effective. The patients ceased to feel any discomfort, put on weight and became and remained quite fit for work.”¹

The neglect of physico-therapeutic methods, both in the medical student's curriculum and in the practice of the average doctor, also tends to give many patients confidence in the lay healer rather than in the doctor. That, in academic medicine, physical therapy is but rarely placed on a footing of complete equality with other methods of treatment is a state of affairs that may be attributed

¹ E. LIEK : “Arzt und Kurpfuscher”, *Wiener Medizinische Wochenschrift*, 18, 19 and 20, of 1933.

to the centuries-old pharmaco-therapeutic tradition, but is due principally to the fact that most physico-therapeutic methods were first introduced and used by laymen. This is rightly adduced by REED¹ as the reason for the remarkable circumstance that, although scientific medicine has had the major share in its development and in the definition of the conditions for its use, physical therapy has never managed to become truly popular in the medical profession. That these methods, introduced by laymen, were in so many instances exploited by swindlers before their value could be established is a distasteful reflection which makes doctors hesitate, even in after-times, as soon as they contemplate using them.

On the other hand, physical methods of treatment constitute the main treasure of so-called "popular medicine". Traditionally, the latter lays its principal stress just as much on water, light, air, sunlight, plants, food and similar "natural" factors as does academic medicine on chemical—that is, "artificial"—substances. And it should not be forgotten that the medical thought-equipment of large sections of the population is taken from the arsenal of popular medicine ; that, in fact, popular medicine is, in the last analysis, nothing else than this same set of ideas. No wonder, then, that nature-healing should make a much more ready appeal to the broad masses and that its representatives, mostly lay healers, should stand much higher in popular favour than the doctors. Besides, nature healing, like homœopathy, is merely a reaction against the abuse of drugs, against the so-called "polypharmacy" in the pre-scientific era of medicine. That this heroic period of endless purgative, sudorific and emetic draughts is long since over, that modern pharmacological research is working along strictly scientific lines, and what that entails—realisation of this fact is not likely to penetrate very quickly among broad sections of the population, not excluding, indeed, a large number of educated people.² In such circumstances, it is bound to be easy for nature

¹ See REED, *loc. cit.*, page 113.

² "How could I accept as scientific, so long as disease did not obfuscate my mind, all this empirical jumble which is taught under the deserved name of *materia medica* ? For is it not matter indeed, and matter without a trace of mind, this catalogue of prescriptions, lacking the slightest causal connection, the slightest regard for the incidences of the drug, and the slightest respect for the eminently synthetic nature of man ?" (S. DE MADARIAGA : "Reflections on Homœopathy", in the *Revue mensuelle de l'Union médicale latine*, 82, December 1933, pages 621-622.)

healers to exploit the natural distrust of the public by propaganda and to represent doctors as more or less dangerous poison-mixers.

Apart from these factors propitious to charlatanism, which arise out of the very nature of scientific medicine as such or out of certain accidental aspects of its development, like effects are produced by the new trend of modern medicine, which looks beyond the sick individual and his fortuitous environment to the social causes of disease and its social prevention. It is scarcely necessary to prove that the preventive tendency of medicine never meant abandoning the sick because they are already sick, and merely ensuring by social measures that no further cases shall occur in future. It stands to reason that preventive or social medicine should not supplant curative medicine, but that the latter should be supplemented by the former. Nevertheless, the natural effect of the preventive tendency in medicine among broad sections of the population was to engender a vague, possibly but semi-conscious, feeling that modern medical ideas meant better provision for future patients than for those at present suffering. The origin of this emotional fallacy—for a fallacy it is—is clear. It was supposed that the unquestionably greater importance of providing for the future—since the future means the whole future with all later generations whatsoever, whereas curative medicine deals only with the brief span of the present—was being pleaded to justify the disregard of any provision for the present. A fuller understanding of the position and a consequential greater confidence in the medical profession and modern medicine should not be too difficult to achieve on this point.

A much more weighty consideration for us than the general nature of social medicine would seem to arise out of the practice of sickness-insurance funds and the ever more numerous social functions of doctors.

So far as sickness-insurance funds are concerned, a first point to be noted is that, in many if not in most cases, the insured person has no free choice of medical attendant. This circumstance in itself is hardly favourable to the establishment of confident relations. An imposed and frequently changing medical attendant will gain the patient's confidence less easily than a doctor who is freely

selected, who is consulted on successive occasions, and who, like the dwindling number of family doctors, can take not only a professional but a personal interest in his patient. Another difficulty is the almost universal overburdening of fund doctors and the comparatively limited time that they can devote to the examination and treatment of their cases. This is perhaps the weakest point of the present-day sick-insurance organisation, and complaints about it are general. The contention that this lamentable state of affairs is at present inevitable, circumstances being what they are, and that the whole position is governed by financial considerations, may or may not be right, but this does not make the evil consequences any better. Confidence in the doctor wanes or disappears, and the medical profession and medicine as a whole are made responsible therefor. The unsatisfactory nature of the situation is, of course, also acknowledged by the doctors, who suffer from it no less than the insured patients themselves.

At the same time—thus the frequently heard vindictory argument runs—with all their inadequacies of organisation, the sickness-insurance funds have done wonderful work, and it is through their instrumentality that hundreds of thousands are now receiving incomparably better medical care than ever before. This, too, is true. When the matter is viewed from the standpoint of sheer utility, it cannot be denied that sickness-insurance funds have brought about a tremendous advance in the medical care of the large masses. That, however, is irrelevant to the issue here under consideration. Out of the complex whole of the sickness-insurance-fund system we have extracted a single component for examination, the patient's confidence in his doctor, and have demonstrated that this confidence has been impaired, and why.

The final point in connection with this question of confidence is "the association of the medical practitioner with the application of social hygienic measures compulsorily enforced by the Government" (compulsory notification, vaccination, etc.), as well as such functions as the doctor performs on military medical boards, especially in war-time; and in the assessment of working and earning capacity, etc.—functions which too frequently present him to the general public in the guise of a representative of the State, or—what is even worse—of class medicine. Tireless propaganda by

the lay healers represents the medical profession as partly responsible for all the attendant unpleasantness, and wide circles are thus inwardly estranged from the medical profession.¹

The factors which reside in the sick person himself or in the potentially sick person, and whose influence, like that of the factors in the first group, is also exerted both "away from the doctor" or "towards the lay healer", are, first, their faculty of reasoning, and, secondly, more or less conscious instinctive impulses, the driving force of which, as we know, is far greater than that of the dictates of reason.

The first factor for consideration is obviously the layman's manifold ignorance of medical questions. Of the difficulty of making a correct diagnosis, prescribing an appropriate method of treatment, of the responsibility entailed by venturing on a prognosis, he has scarcely an inkling; and, being unaccustomed to think in causal terms, he is equally ignorant of the ambiguity of symptoms.² Furthermore, he is either completely unaware of the distinction between subjective conditions and the objective state of affairs, or imagines that he can expect unbroken parallelism of the two sets of phenomena. He will be just as quick to interpret any feeling of well-being as the effect of a remedy, as a sign of improvement or recovery, as he will be to regard the slightest pain or any mild discomfort as a sign of serious illness, if not as a forerunner of approaching death.

It is the fullness of his ignorance which establishes such close bonds of sympathy between the sick layman and the lay healer: the lay healer, whose ignorance is not less, who is just as incapable as his patient of thinking in terms of cause and effect and just as wedded to subjective symptoms whenever—as is usually the case—he is incapable of ascertaining and judging the objective state.

"The patient wants his symptoms treated... he is satisfied if he can help himself from the bottle labelled 'headache', whether he has Bright's disease, eyestrain or a cerebral tumour", writes

¹ Vide C. WACHTEL: "Warum haben Kurpfuscher Erfolge?" Munich, 1925, page 33.

² Vide A. HELLWIG: "Die Einstellung des Volkes zur Kurpfuscherei", in *Veröffentlichungen aus dem Gebiete der Medizinalverwaltung*, 27, 1928, page 727.

a doctor who knows his patients and is well acquainted with their psychology.¹ The lay healer's object, on the other hand—supposing that he has any object beyond money-making—is obviously to produce a good effect by his treatment ; whether, however, a real effect or merely an apparent effect is a question about which the lay healer does not bother his head. In fact, he simply does not distinguish between a real and an apparent improvement and recovery, since he has not the necessary medical training to be able to think in terms of causation ; symptoms and disease are the same thing to him, and he is not to be shaken in his conviction that he has cured the disease once the symptom has abated or disappeared.

The sick layman and the lay healer are thus seen to have the same lack of understanding of the distinction between symptoms and essential sickness. At the same time, this inability to judge is not in itself the main practical question for our purpose, but rather the resulting erroneous inferences as to the value or uselessness of the therapeutic methods which are applied.

There is hardly any other single question in the whole field of medicine in which laymen—and not seldom scientifically trained laymen—are so ready to take absolutely for granted their ability to judge competently as that of the efficacy of any method of treatment, and yet hardly any question is more intricate and difficult to answer for the highly trained specialist. Of course, a certain amount of training is necessary even to realise its intricacy and to gauge accurately both the number and the kind of factors which intervene. No less a man than LAVOISIER thought it important, in his famous report to the French Academy on Mesmer's method of treatment, to deal at some length with this general question and, in particular, to draw attention to the way in which charlatans of all kinds contrive to turn this state of affairs to account.

“The art of drawing conclusions”, we read in the report, “from experiments and observations consists in estimating probabilities and in gauging whether they are sufficiently great and numerous to constitute proof. This kind of calculation is much more intricate and difficult than is thought ; it calls for great sagacity and is

¹ C. R. S. FLEMING : “Quackery in Rural Districts”, *British Medical Journal*, May 27th, 1911, page 1247.

generally beyond the powers of the ordinary man. It is mistakes in this kind of calculation that give an opening for the success of charlatans, sorcerers and alchemists, and, in the past, of magicians and enchanters and generally all those who labour under illusions themselves or seek to exploit the credulity of the public.

“In medicine, the difficulty of gauging probabilities is particularly great. Since the principle of life in animals is a force which is ever active, which is constantly endeavouring to overcome obstacles, and since nature, when left to its own devices, cures many diseases by itself, it follows that, when a remedy is applied, it is infinitely difficult to determine what effects are due to nature and what to the remedy. And so, whilst the multitude looks upon the cure of a disease as proof of the efficacy of the remedy, the result presents itself to the wise man as merely a greater or lesser degree of probability, and that probability can be converted into certainty only by a large number of facts of the same kind.”¹

The idea that so-called “academic medicine” is one system, just like all the other—unorthodox—doctrines of disease and treatment, a system possibly inferior, and certainly not superior, to the latter, is a widespread belief among the lay population, which does not accord the scientifically trained doctor the precedence to the lay healer to which he feels entitled.

The belief of academic medicine in specific serotherapy, in preventive vaccination, or in the diagnostic value of some microscopical or chemical analysis is simply ranked on a level with the belief in the healing virtue of “blue electricity”, telluric rays, diagnosis by means of the sidereal pendulum and what not, and the idea that science is not mere “belief” but knowledge methodically acquired on systematic lines does not even suggest itself. The difference between crude empiricism and methodical observation, between observation and experiment, between scientific generalisation verified step by step and pure flights of imagination is not realised, and any criticism of unfounded assertions is simply put down to the “well-known medical intolerance”. Whether higher standards of schooling will ever make things better in this respect is doubted

¹ *Vide* LAVOISIER: “Mémoire sur le magnétisme animal” (1784), in “Œuvres de Lavoisier”. Paris, 1865, Vol. III, page 509.

in many quarters ; certain it is, however, that matters will not improve until large sections of the population have been brought to a better understanding of what science is and of the way in which well substantiated or even conjectural knowledge is to be distinguished from superstition.

The charge of intolerance against the medical profession, just mentioned, itself shows the confusion of thought which prevails in this field. Where belief confronts belief, and dogma dogma, tolerance is possibly appropriate. Factors of equal logical status, such as two religious beliefs, can and should do each other the honour of tolerance. In the field of science, however, where dogma has no meaning, where, apart from proved facts, only provable facts arise for consideration, conflicting and so far unproven beliefs can only tolerate each other in so far as their probability has some scientific foundation. The tolerance thus shown is, in such a case, commensurate with that probability and lasts only until such time as a provable proposition has become a proved one.

In this sense, the scientific doctor is indeed intolerant towards every unprovable medical opinion as towards every assertion whose probability cannot be substantiated in accordance with the requirements of scientific method. Anything which evades the methods of scientific research and is represented as unorthodox medical knowledge is for him mere superstition and he has no reason to concern himself with it any further.

Now it is a strange thing that this "intolerant" attitude of the scientist towards superstitious stuff is accepted as natural in all other branches of science, even by people for whom, in the medical field, even the craziest notions do not seem crazy enough. It would never occur to any sensible man to look upon astrology as unorthodox astronomy and to ask serious astronomers to show tolerance towards their "irregular" colleagues who can read the future in the stars. Very few people would surely be found to regard a certain theory that potatoes planted on a moonless night do not flourish as unorthodox agricultural science, although such an "agronomical school" does exist, and numbers its adherents by millions. ¹

¹ On this point and on tolerance of doctors generally, *vide* some interesting statements by Chester ROWELL in the *Journal of the American Medical Association* of February 1st, 1930, page 342.

Medicine, however, is in a different position from all other sciences. Everything connected with health and life makes such a direct appeal to the instinctive forces in man, especially sick man, is so closely interwoven with the inmost core of his emotional being, that reason, nay even the plainest common sense, frequently fails, and magical procedures and formulæ and trumped-up miracles elicit a much readier response—because more keenly desired—among large circles of the lay population than many a sober, modest, scientific fact.

Closely bound up with this mistaken idea that scientific medicine is nothing more than one dogmatic system competing with others which are, in principle, of equal value, even though unorthodox, is the widespread fear among the population that consultation of an orthodox doctor entails foregoing the possibility of relief from all those methods of healing which are regarded as unorthodox. The general belief is that the orthodox doctor is slavishly tied down to certain particular methods of treatment and may not resort to those which are held to be unorthodox, no matter how convinced he may personally be of their therapeutic value ; and it is explained that, if the doctor's hands are thus tied, this is but the natural consequence of his belonging to a sect which competes with unorthodox healing sects and condemns their methods of treatment as a matter of course. What the lay world has mainly, if not exclusively, in mind, in this connection, are the methods of nature healing; for it is these which it regards as particularly valuable and it is towards these that it imagines it can detect an antagonistic attitude throughout the medical profession.

This deep-rooted belief, the importance of which in the struggle between doctor and charlatan for the confidence of the sick cannot be over-estimated, and which the charlatan hence keeps constantly alive by tireless propaganda, does not in the least prevent that same propaganda from adducing, when necessary, the contrary argument that official medicine has to thank the layman for, most of its teachings, and, in any case, for anything it possesses of value. Envy, dogmatic narrow-mindedness and intolerance are forgotten in a trice. The charge now levelled at the doctors is, on the contrary, their lack of originality, their being compelled to wait passively until they can learn and copy something valuable devised

by their unorthodox professional colleagues. The tale of the old female charlatan specialist for dropsy, among whose herbs WHITHERING found digitalis in 1775, the tale of smallpox vaccination, the first use of quinine and the discovery of hydropathic treatment, dietetic treatment, etc., all this and much more is impressed upon the lay public as proof that the real healers of mankind were always laymen. And it is all done with the transparent motive of convincing them how much more sensible it is in case of need to apply direct to the masters instead of seeking advice from the officially recognised doctors who are, at best, their unwilling disciples.

The medical profession has obviously no reason to contest substantiated facts. On the contrary, scientific medicine must, if it is to avoid falling into decay, insist upon its right to seek inspiration wherever it is to be found, and to endorse truths, no matter by whom discovered. That many things of importance to medicine have been discovered by laymen is a fact that has never been challenged by any serious-minded person and the ready acknowledgment and adoption by academic medicine of many valuable observations and inventions by laymen hardly suggests intolerance on the part of medical science. It is a fact, of course, that the manner of this recognition has varied from case to case; it is common knowledge that many a truth had to wait, and wait long for acceptance. This, however, is but the normal fate of every new truth, quite independently of whether or not its discoverer should happen to be a layman so far as the particular branch of knowledge is concerned. It is quite true that JENNER, in England, and SEMMELWEISS, in Austria, were opposed by medical societies. Such struggles are not, however, evidence of intolerance; they prove again that every truth has to fight for its right to existence. The struggle which precedes acknowledgment is, however, whilst it lasts, directed against what is supposed to be a fallacy of the opposing party.

Whilst the claims of lay healers, regarding their services to scientific medicine, are thus willingly recognised by the latter, it is necessary to utter a warning against exaggeration and, in all fairness, to qualify the recognition thus extended in three different ways. (1) Really important medical observations by laymen have always been comparatively rare; (2) they relate almost without exception to the past and have grown more and more infrequent in the course of time, as medicine has passed more and

more on to the scientific plane ; so that, medicine being now closely linked up with all branches of exact natural science, they have become so improbable that they may for the future be practically left out of the reckoning ; (3) finally, it is important to bear in mind the difference between the layman's original contribution, based in most cases upon crude observation, and the modern final product into which it has been converted in the course of time by the mills of scientific medicine. Modern digitalis therapy, just like modern hydrotherapy, has little more in common with the proceedings of WHITHERING's herb-woman or the first water-cure pioneers than the fact that both use the foxglove and water. All the new knowledge that has been brought to light by chemical analysis, modern pharmacology, physical and physiological experiments and accurate clinical measurement, concerning action, manner of administration and therapeutic indications, represents just the difference between crude empiricism and exact research. To bring this difference home to the intelligent layman, not indeed in order to detract from the achievements of lay pioneers and leaders, but merely in order to convey by a concrete example an idea of the methods of work of scientific medicine, seems to us a sounder way of removing the evil of charlatanism than any legislative prohibitions, which usually fall upon deaf ears.

A further important factor should be mentioned here which is also partly responsible for the handicap under which a doctor labours, compared with the lay healer, in his attempts to gain his patient's confidence. We refer to the system of ideas and mode of expression of the three parties concerned.

The sick layman and the lay healer understand each other better because their conceptions of disease are similar and they consequently use the same, or much the same, language. The scientific doctor, on the other hand, thinks and expresses himself in categories which are more or less foreign to the average man, convey little or nothing to his mind and call forth in him no intellectual or emotional response. Again, the scientific doctor is too apt to forget that his sick layman has conceptions of disease of his own ; he should have none—so he thinks—since he knows nothing of medicine ; therefore—he concludes—he has none. As a result of this fallacy—whether thus explicitly reasoned out or not is immaterial—

the doctor misses at a stroke the most favourable opportunity of establishing those bonds of sympathy which are so important for the patient's future reliance in him—a mistake of which his unorthodox rival is but seldom guilty.

Nothing could be clearer than the utterly fallacious character of such a conclusion. Even the intelligent layman, to whom it would never occur to advance personal views on θ —functions for instance, or upon the structure of the hydrogen atom if he is not a mathematician or physicist, can hardly refrain from entertaining ideas of his own as soon as the life and health of himself or of his next of kin are at stake—and that even though he knows as little of medicine as he does of mathematics. Life is, after all, too important a question for “human nature” to rest content with the stark alternative of either exact knowledge or abstention from judgment. In matters of health and sickness, a vacuum of thought is not to be borne. Failing any clearly defined notions, whatever comes to hand is substituted : venerable prejudices, magic formulæ, belief in miracles, legends, empty words, but also many a piece of sound knowledge distilled from the long experience of successive generations ; in a word, so-called popular medicine, a mixture of a little that is right and a great deal that is wrong, of every-day knowledge and abstruse thought, a system of ideas which, despite its logical inferiority, is of psychological importance to the extent that it reveals and apparently assuages the great hunger of large sections of the population for a knowledge and understanding of vital processes.

Now the processes of thought of popular medicine are the ideal sphere in which the lay healer and the lay patient meet on a footing of good understanding ; and the language of popular medicine is their common tongue.

Among the many circumstances which explain how the charlatan can thrive, one of the most important is the lay healer's therapeutic successes.

In order to judge these successes aright, we will first of all discuss the group of the so-called apparent cures. These are (1) cures of diseases diagnosed by the charlatans but in reality non-existent, or (2) apparent cures of real diseases in which a transient improvement in the patient's condition, the abatement or disappearance

of a symptom is quickly hailed as a cure, before the subsequent course of the disease makes it plain that the method of treatment adopted has had not the slightest effect upon the trouble.

Cases of cures coming within both the above-mentioned categories account for the majority of therapeutic successes by charlatans. The first sub-category, that of diseases invented by the lay healers, is a particularly numerous one, a circumstance which finds its natural explanation in the fact that lay healers usually lack the slightest qualification for the establishment of an even approximately correct diagnosis. This completely explains the frequent miraculous cures achieved by the use of ointments, plasters or dietetic courses in cases, for instance, of cancer, which are usually diagnosed as such with the one object of justifying a costly form of treatment and of affording a fresh demonstration of the author's marvellous powers. If account is also taken of their diagnostic methods—the sidereal pendulum, iris-diagnosis, the electrical appliances (*e.g.*, ABRAM'S) which automatically record diagnoses as a weighing-machine shows the weight—our understanding of so many wonderful cures becomes more thorough. The lay healer is, moreover, seldom content to establish the existence of but a *single* ailment. Usually the relief-seeking patient is apprised of a long list of diseases that have been “detected”, and will naturally require a lengthy course of treatment involving the use of numerous secret remedies, whilst, at the same time, the odds on success in treatment are thus rendered more favourable from the start. A diagnosis made by a Swiss herbalist as a result of a simple urine examination contains the following seven points: ¹ (1) Impureté du sang; (2) troubles gastro-organiques; (3) rhumatisme névralgique; (4) irritation des membranes ovariennes; (5) forte anémie; (6) catarrh bronchique; (7) engorgement lombaire compliqué d'inflammation des canaliculaires rénales [*sic!*].

By making such a “blunderbuss” diagnosis, the layman is clearly trying to kill two birds with one stone—viz., to secure a minimum of correct diagnosis as well as a maximum of success in treatment. The author mentioned also quotes in the same paper another such telediagnosis, made by an examination of the urine, which, by reason of its purely fictitious character, affords a truly classical

¹ André GUIAN : “Charlatanisme ancien et moderne en médecine”, in the *Revue médicale de la Suisse romande*, 1932, page 302.

example of a procedure designed to play for safety to the extent of one hundred per cent. "This person . . . is suffering from a complete reversal of the electric rotation of the blood, and the brain is thereby affected", after which, somewhat surprisingly—for the charlatan's processes of thought can never be completely fathomed—comes the following conclusion : "I regret, but I can do nothing for that". A very rare instance of exaggerated charlatanic modesty !

Another group of diseases whose successful treatment charlatan propaganda is particularly fond of hailing as a personal success is that type of affection which may disappear through so-called self-healing. It is common experience that many diseases—and the list is not limited to minor ailments—may finally disappear, not only without any treatment, but in spite of all treatment. This happy tendency operates, of course, equally in the practice of the physician and of the quack, but is exploited by charlatans with peculiar thoroughness. Whilst there are doubtless doctors who yield nothing to the charlatans on this point, such a thing could not be said in fairness to the majority of practitioners. In any case, since medicine has become an exact science, there has always been a strong tendency against polypharmacy and polypragmatism ; similarly, the principle of so-called "expectative therapy" has everywhere come to the fore and *primum non nocere* and trusting to the *vis medicatrix naturæ* are the precepts nowadays proclaimed in medical schools throughout the world.

So much by way of reminder of the essential modesty to which the modern medical profession has attained in its claims to personal success in the art of healing. A sect of charlatans with the slogan of *vis medicatrix naturæ* blazoned on its banner is, however, scarcely conceivable.

Lastly, we have the large group of *malades imaginaires*, patients who have "nothing wrong with them" save for the trifling fact that they feel ill, although they "ought" to feel well ; and the equally numerous group of nervous patients, whose trouble either is purely functional or consists of some neurotic reaction proceeding from organic causes. Both groups are easily accessible to mental influences and represent the real field of psycho-therapeutic treatment. Every experienced doctor knows the type of the *malade*

au petit papier (CHARCOT), an inexhaustible object of self-observation ; dyspeptics and neurasthenics with all their stomachic, intestinal and cardiac disturbances, their skin affections, cramp, paralysis, reflecting the powerful intervention of the psychological factor, which is capable, according to the way in which it operates, of bringing about either sickness or recovery. "Most patients are capable of recovering without any active treatment, through the sole action of nature ; hence the usurped reputation of numberless ineffectual remedies and of a host of utterly untrained medicasters" wrote a famous French clinician as far back as 1841.¹ William OSLER, discussing the method of treating this same category of patients, observes : "Without any special school in these cases, or special methods, our results at the Johns Hopkins Hospital were most gratifying. Faith in St. Johns Hopkins, as we used to call him, an atmosphere of optimism and cheerful nurses, worked just the same sort of cures as did Æsculapius at Epidaurus."²

The most convincing evidence of the importance of the psychological factor is afforded, however, by the annals of medical history. Generations of doctors have, in their practice, resorted, "with the best of results", to remedies whose absolute pharmaco-dynamic valuelessness has now been established. For centuries it was believed, for instance, that precious stones possessed great therapeutic properties. The book of MARBOT, Bishop of Rennes (1067-1123), concerning the curative potency of some sixty precious stones, was one of the best known of the Middle Ages and was translated into French, Italian, Hebrew and Danish.³ Just before his death, in 1534, Pope Clement VII was doctored with a diamond powder costing 3,000 ducats. In 1665, Louis XIV, acting on the advice of his physician, Vallot, took tablets containing gold and pearls, whilst, in 1664, a remedy compounded of pearls and coral had been prescribed for him.⁴ This belief in pearls and sapphires, corals and emeralds was not just a mere element of mediæval

¹ A. F. CHOMEL, "Éléments de pathologie générale", third edition. Paris, 1841.

² William OSLER, "The Faith that heals", *British Medical Journal*, June 18th, 1910, page 1470.

³ M. NEUBURGER and J. PAGEL : "Handbuch der Geschichte der Medizin", Jena, 1902, Vol. I, page 633.

⁴ O. HOVORKA and A. KRONFELD : "Vergleichende Volksmedizin", Stuttgart, 1908, Vol. I, pages 106 and 107.

popular medicine, but formed part of the official pharmacological science of the day and was accepted for centuries by the leaders of the medical profession. We have a recipe of Nicolas Copernicus which proves this,¹ and the great importance he attached to this prescription was perhaps best expressed by the fact that he copied it twice with his own hand into his copy of "Euclid's Elements".²

Charlatans are commonly reputed to take the correct psychological line in turning the patient's instincts to account. It can, however, only be termed correct if the quack's profit rather than the patient's advantage is selected as the criterion of correctness. For those of the patient's primitive instincts which are here involved have long since lost their usefulness and, under the conditions of modern civilised life, militate on most occasions against the patient's best interests.

The widespread and natural fear among the public of the "knife" and of "poisons" is rightly considered the best point of attack in the quacks' war against the medical profession. They conduct this campaign against the knife and poison with all the greater eagerness, since—even in countries permitting the free practice

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| ¹ Armenian bolus (<i>bolus rubra</i>) | 2 ounces |
| cinnamon | ‡ ounce |
| zedoary | 2 drachms |
| tormentil root | } āā 2 drachms |
| fraxinella root | |
| red sandalwood | |
| charred ivory powder | } āā 1 drachm |
| crocus | |
| animal carbon | } āā 2 scruples |
| camomile | |
| lemon peel | } āā 1 drachm |
| pearls | |
| emerald | } āā 1 scruple |
| red hyacinth | |
| sapphire | |
| stag's horn | 1 drachm |
| carob bean | } āā 1 scruple |
| unicorn's horn | |
| red coral | |
| gold | |
| silver | |

Zuccaris 1 lb. s. *vel quantum*
sufficit
Fiat pulvis.

Preserved in the Upsala University Library.

of medicine—they are forbidden to use either the one or the other. The harm that is done by the unscrupulous propaganda in favour of numberless methods of treating cancer “without recourse to the knife” is universally known. Despite this fact, the appeal to primitive fear often proves more powerful than all medical instruction ; for reason is simply unable to resist the driving force of an instinct that has now lost its significance.

To this should be added the patient's comprehensible desire for a cure, the inability of chronic sufferers to reconcile themselves to the fact that medical science can frequently help them but little, and the despair of the incurable. It is the sheer instinct of self-preservation that drives this class of patients into the arms of those whose promises are their last hope. Whether these hopes are aroused in good faith or—as is no doubt most frequent—with fraudulent intent does not alter the fact that, sooner or later—usually too late—the patient becomes aware of his true condition. But how often is not conscious fraud associated with self-deception. “The primary cause of quackery is our own readiness to deceive ourselves”, writes an anonymous author in a paper on the origins of charlatanism which is well worth reading.¹ “It must be confessed (with sorrow) that man has a natural tendency to self-deceit, and that, if there were no impostors to cozen him, he would delude himself, . . . the will to believe, of which we hear so much in the domain of theology, is so powerful a force in that of medicine.”²

Distrust of the specialist is a further natural mental factor which frequently decides in favour of the charlatan. Such distrust seems to conflict with every-day experience. Nobody would prefer to give his watch to an unqualified man for repair, and even “the most stupid person would not dream, in this age of railways and aeroplanes, of resorting to stage coaches”.³

Disease, especially when—as is usually the case—its causes are not patent, is not, however, to be placed on the same footing as any other occurrence ; it occupies an exceptional position in the

¹ “Causes of Quackery”, *British Medical Journal*, May 27th, 1911, page 1290.

² *Ibid.*

³ James FRAZER: “The Golden Bough”, abridged edition, London, 1935, page 55.

field of human experience, and even to-day millions react in a quite special way to anything which is connected with it.

For thousands of years, disease was thought to be produced by quite different forces than the common phenomena of nature, wherefore the means of dealing with it had similarly to be different. Whether termed magic or divine, the forces at work were either revengeful or punitive influences, and only those could overcome disease who knew how to circumvent them and find favour with them. For this, quite special aptitudes were needed which the ordinary mortal could not hope to acquire by schooling. It needed a special grace, in virtue of which the healer, as magician or priest, was made to appear as a supernatural being of like essence to the supernatural disease it was his business to heal.

This set of ideas, strongly tinged with emotion, embracing disease, cure and the healer alike, and deep-rooted in the popular mind, has persisted for thousands of years comparatively untouched by all scientific progress.

The belief in magic forces, "this universal faith, this truly catholic creed", is, "among the ignorant and superstitious classes of modern Europe, very much what it was thousands of years ago in Egypt and India and what it now is among the lowest savages surviving in the remotest corners of the world";¹ this belief is also the soil on which charlatanism best flourishes.²

In the paper just quoted, A. J. CLARK expresses the undoubtedly sound opinion that the idea of magic frequently remains alive under a top-layer of education and that it always comes to the surface "as soon as any strong emotion is aroused ; and both pain and fear are potent causes for arousing such emotions".³

This is why, in the public mind, the healing profession is never ranked on the same level as all the others ; why the manner and the nature of the healer's proceedings are held to derive in some sense from a miraculous endowment and cannot be simply learnt. Hence the distrust for the learned doctor and the credulous and trusting attitude towards healers "by the grace of God".

¹ James FRAZER : "The Golden Bough", abridged edition, London, 1935, page 55.

² A. J. CLARK : *loc. cit.*, page 590 : "It is in this universal and eternal creed that the charlatan finds his support".

"Deep in the soul of the people lies the belief that the medical art is a divine gift which may be exercised without science or study", observes BURGER in his previously quoted paper,¹ and the healer contributes as far as he can by the suggestive power of his personality to strengthen this conviction, which he shares himself.²

The charlatan is also an adept in the art of striking the patient's imagination by suitably stage-managing the examination and by the choice of impressive remedies. BURGER's graphic description of the Zeileis Institute at Gallspach (Austria), with its "Preparatorium" and its "Mysterium" and its strongly ozonised air, the array of electrical appliances, light signals, Röntgen tubes and "helium lamps, etc.", is a good example of the dramatic producer's art on a very high level.

Forms of treatment like that quoted by BROUARDEL are also familiar: "Urine of a six-year-old child; one dessertspoonful three times a day"; or this: "...the bones of a priest shot during the Commune were placed in the girl's bed"³ (the case was one of a girl of 18 with contracture in the hip joint). The charlatans of the Silesian highlands, who are frequently the local gravediggers, dose their patients with corpse fat suspended in wine in the belief that it is an excellent diaphoretic.⁴

To give a detailed account of the harm which is done by charlatanism in the field both of public and of private health would perhaps be superfluous. Full descriptions of this kind are both useful and desirable in their proper place: in educational papers, written for the general public. For our present purpose, it will suffice to make the following brief summary statement.

¹ H. BURGER: "The Doctor, the Quack and the Appetite of the Public for Magic in Medicine", *Proceedings of the Royal Society of Medicine*, 27, No. 2 (December 1933), page 171.

² "The common type (of the charlatan) is that of a man of unusual force of personality, who, in virtue of an imperfect education and ill-balanced judgment, has acquired a profound belief that some direct inspiration has made him independent of the slow advance of science, and has endowed him with semi-miraculous powers of healing." *Vide* A. J. CLARK, *loc. cit.*, page 589.

³ P. BROUARDEL: "L'exercice de la médecine et le charlatanisme." Paris, 1899, page 473.

⁴ O. HOVORKA and A. KRONFELD: "Vergleichende Volksmedizin." Stuttgart, 1898, Vol. I, page 133.

The harm which is done to the individual patient by the quack consists in the fact that (1) he frequently has to suffer longer than he need ; (2) he misses the most favourable opportunity, in the early stages of the disease, for the starting of rational treatment ; and (3) in many cases, not only is his health impaired owing to the irretrievable loss of time, but it is also directly injured by the type of drug administered or the treatment otherwise given ; (4) he is financially exploited without receiving any advantage in return.

However serious these evils may be, the damage to the community to the body social as a whole weighs far more heavily in the balance than any injury inflicted on the individual. In England, in 1910, the General Medical Council felt compelled to draw attention to the dangers entailed by lay treatment in the field of infectious diseases. Scarlet fever, typhus, diphtheria, etc., it was pointed out, were not always easy to diagnose, and "it appears unlikely that such diseases are recognised by lay healers". If, on the other hand, they are recognised, then they are not notified. This, however, enables the disease to spread, and hampers the public health authorities in their endeavours to trace the actual focus of the epidemics. Such dangers also arise, of course, in the field of venereal disease, and, as we have already seen, this has led, in Germany, for instance, to the statutory prohibition of treatment by laymen, despite the recognition of the lay healer in principle.

Finally, it must be pointed out that the quack frequently begins by himself creating the patients he needs. He owes his ability to do so alike to his own psychological astuteness and to the efficiency of the latest technical methods for influencing the public—viz., newspaper advertisement. "The refined and dangerous purposes of present-day advertisement (of fraudulent pharmaceutical products of all kinds) . . . is to arouse the fear of the public and set its imagination working. The marketer of kidney pills is intent, not only upon selling his products to those who are already convinced that they have kidney disease, but also upon bringing all those who merely feel something in their lower back to the point of purchasing his stuff"—thus an author who studied charlatanism in the United States,¹ and a few pages further on : "Proprietary

¹ NEUBURGER : *loc. cit.*, page 676.

medicine advertisements are intended for hypochondriacs who are not ill but who imagine they are as soon as they read the symptoms."¹

Not long ago, the following appeared in an English newspaper : "One soap manufacturer is covering the hoardings with pictures intended to persuade us that unawares we smell. 'B.O.' (body odour) is the refined term he uses to terrorise us. I do not know how a law could be drafted to prevent such methods of advertisement, but to try to increase unnecessary anxiety seems to me violently anti-social."²

The method followed always remains true to type, whether the subject is harmless body odour or the more serious arterio-sclerosis, dilation of the aorta or increased blood pressure. "He (the quack) sets forth under the eyes of the reader the most common symptoms, which he connects with the most formidable diseases. Thus, he makes him anxious, takes him captive and expects his ransom. Credulous people lose for ever the certainty of being quite well. Old age has no longer any natural sense. The smallest pathological incident is made to bear the aspect of a cataclysm, and it is in this way that the modern quack—the quack of the newspapers—has suddenly become a social danger", observes a correspondent of the *British Medical Journal*,³ and, logically, he concludes that charlatanism has thereby ceased to have any justification whatsoever, for "its primary mission . . . was at all costs to reassure, and to bring to the patient the consolation that science was incapable of giving him ; at certain moments the quack has been, with a certain semblance of legitimacy, the last resource for the hopeless. Since he has made himself an *agent provocateur* of disease, since he is no more of any use, except to disturb the minds of the healthy, he has lost his last excuse . . ."

We have already seen that the number of charlatans has notably increased during the last decades in all civilised countries. The same can also be said of systems of charlatanism. Doctrines are constantly changing, and the number of systems grows from year to year. In the light of experience, a valueless mode of treatment,

¹ NEUBURGER : *loc. cit.*, page 681.

² *New Statesman* of August 18th, 1934.

³ "Quackery in France", *British Medical Journal* of May 27th, 1911, page 1288.

an ineffectual remedy, finally lose their power of attraction, despite the ignorance and gullability of the masses, and have then to make way for new therapeutic doctrines which are constantly being devised.

The doctrines which are offered to the public vary according to the stratum of the population for which they are intended. Those which remain most conservative are the doctrines intended for those broad, uneducated masses whose concept of the world has not advanced beyond that of our oldest ancestors. Among them, disease is still held to be the work of a dæmonic will and is fought, now, as thousands of years ago, with spells, exorcism, symbolic casting out or magic transplantation. Among them, the oldest form of prophylaxis is to be found: the wearing of amulets.

The needs of the more educated portion of the public, which has some contact with scientific life through the schools, the Press, etc., are met by doctrines which are prone to flaunt the outward trappings of science itself.

“To-day, some travesty of physical science appears to be the most popular form of incantation”, observes CLARK.¹ Hence, the flood of electrical appliances, magnetic belts and radium plasters which “work”, even if the electric current is practically undetectable or the radium content less than one-thousandth of a milligramme. The efficient principle remains, as usual, “the mystery attaching to (the quack’s) method of treatment and the pseudo-scientific language he employs”.²

In the same way, the modern quack keeps pace with every advance of the biological sciences. PASTEUR’s ideas have, after all, penetrated very deeply into the popular mind, and millions go in fear of the bacillus. “Hence it comes about that the present-day quack is either an electrician or a pharmacist. The old platform is too narrow for his new pattern. He borrows the innumerable and incessant voices of the Press. He is up to date.”³ He is even beginning to take an interest in prevention. “There has been, among lay healers, a great increase in the popularity of so-called ‘de-radiation appliances’, which are built in under dwelling-houses and cattle-sheds, and are supposed to protect man and

¹ A. J. CLARK, *loc. cit.*

² *Encyclopædia Britannica*, fourteenth edition (“Quackery”).

³ “Quackery in France”, *British Medical Journal*, May 27th, 1911, page 1288.

beast against the effects of the allegedly highly dangerous telluric rays, and the diseases they cause, especially cancer", so we read in an official report.¹

Now there are many who think that the phenomena just described may be interpreted in a favourable sense as very promising symptoms for the shaping of future relations between the lay healer and medical science. Unfortunately, it seems to us very unlikely that lay medicine will gradually develop into a scientific system under the pressure of the public demand for "scientificity". For what the general public wants has very little to do with science ; only the external accessories of science are discernible to them, and any pseudo-scientific jargon that comes to hand will satisfy their "scientific" hunger.

It is no doubt true that the modern educated man knows more and is better informed about many processes of nature than his mediæval ancestor ; it would be wrong, however, to conclude that his mode of thought has become more scientific. Side by side with the new knowledge, the old superstition, which has merely changed its dress and donned the garb of science, is still alive. An American author is quite right in uttering the following warning : "For a large portion of the public, science is in danger of becoming a new kind of magic. . . Its facts may easily become as pretty and meaningless as so many seashells picked up by someone who knows nothing about the life of the sea. They may even lack the kind of system and logic that a traditional set of superstitions has."²

At the beginning of our paper, we felt forced to the conclusion that there was no coping with charlatans by prohibitive legislation. At the end, we reach the conviction that there is little prospect of entering upon the "promised land", within a measurable time, through the advent of rational insight among the lay public. Nevertheless, our outlook into the future is not without hope. We hold, indeed, that the final collapse of charlatanism is probable,

¹ "Das Gesundheitswesen des Preussischen Staates im Jahre 1932". Berlin, 1934, page 109.

² Robert L. DUFFUS : "This Unscientific Age", in *Harper's Magazine*, December 1934.

the more so as the weapons which can—and it is to be hoped will—destroy it are in the hands of the medical profession itself.

The lay public's confidence in the doctor will be gained and consolidated by the positive results of his treatment. In the long run, the layman cannot shut his eyes to therapeutic successes. These do not merely appeal to that higher insight which is mostly a delusion ; they also speak direct to the senses ; they "leap to the eye", they are visible and tangible ; and for their attainment, the following three conditions are both necessary and sufficient :

- (1) Progress in medical science, which comprises the whole of man, body and mind ;
- (2) Good doctors with up-to-date scientific training ;
- (3) Social measures securing the services of good doctors for the largest possible number of people by means of the best possible organisation.

In measure as these three postulates are in future satisfied, so will the patient's belief in the charlatan gradually wane ; and the doctor, fighting him back and repudiating any suggestion that he does so out of mere professional self-interest, will be able to point, comparatively, to his own and to the quack's successes and with calm self-confidence recall the words of BROUARDEL : "The doctors may suffer (from charlatanism), but the sick, they die of it."¹

¹ P. BROUARDEL, *loc. cit.*, page 536.

REPORT OF THE SECOND CONFERENCE ON THE STANDARDISATION OF SEX HORMONES

Held in London, July 15th to 17th, 1935.¹

PRELIMINARY NOTE.

In 1932, a Conference appointed by the Health Organisation was able to report² that work on the œstrus-producing hormone had reached a stage when an international standard preparation could be established. This was accordingly done. In the next two years progress in the study of gonad hormones was phenomenally rapid. Thus, the di-hydro derivative of the œstrus-producing hormone as well as various benzoylated preparations have come into common use, and by the middle of 1934 there was good evidence

¹ The following members were present :

Sir Henry H. DALE, London (*Chairman*) ;
Dr. A. S. PARKES, London } (*Secretaries*) ;
Dr. R. GAUTIER, Geneva }
Dr. W. M. ALLEN, Rochester, N.Y. ;
Professor A. BUTENANDT, Danzig ;
Professor E. C. DODDS, London ;
Professor E. A. DOISY, St. Louis, Missouri ;
Dr. A. GIRARD, Paris ;
Dr. A. W. GREENWOOD, Edinburgh ;
Professor F. C. KOCH, Chicago ;
Professor E. LAQUEUR, Amsterdam ;
Dr. G. F. MARRIAN, Toronto ;
Dr. C. MIESCHER, Basle.

The following also attended as experts :

Professor J. H. BURN, London ;
Dr. R. K. CALLOW, London ;
Professor V. KORENCHEVSKY, Elstree ;
Dr. Ch. LORMAND, Paris ;
Dr. K. H. SLOTTA, Breslau.

² *Quarterly Bulletin of the Health Organisation*, 1935, Vol. IV, Special Number, page 121.

that the existing standard of the hydroxy-ketonic substance was proving quite inadequate as a standard of comparison for the various preparations in use. The views of members of the 1932 Conference were therefore ascertained ; without exception they agreed that the present situation was unsatisfactory and that no useful discussion could take place by correspondence.

In the meantime, the situation with regard to the male hormone, about which only the most tentative conclusions could be reached in 1932, had advanced sufficiently to justify some international discussion. In 1927, MCGEE, working in Chicago, was able to show that the atrophic comb of the capon could be made to grow by the administration of lipid fractions of extracts of bull testes. The work was continued and extended by MOORE, KOCH and GALLAGHER and it was demonstrated that the various disabilities caused by castration in rodents could be wholly or partially repaired by administration of similar extracts. These experiments gave an experimental basis to the long-held theory that the testis produces an internal secretion regulating the growth and activity of the male accessory organs.

Shortly after, LOEWE and his co-workers were able to show that similar biological activity was shown by the lipid fractions of male urine extracts. This finding suggested that the testis hormone, or some other substance with a similar biological action, is excreted in appreciable amounts. In 1931, BUTENANDT prepared from male urine a small amount of crystalline material which caused the typical reaction of the capon comb. Further work by BUTENANDT showed that the active substance, now known as androsterone, had an empirical formula of $C_{19}H_{30}O_2$, and later, again, BUTENANDT was able to suggest that the active substance was a fully hydrogenated cyclo-pentenophenanthrene derivative containing a hydroxyl group in position 3 and a carbonyl group in position 17. This constitution has been fully confirmed by RUZICKA's preparation of the active substance from epi-cholestanol. It was not certain that androsterone was the primary male hormone as produced by the testis, but it seemed that it might be a suitable standard of reference for male-hormone activity.

With these various considerations in mind, a conference was planned for 1935 to deal with the problems arising out of the inadequacy of the present standard for the œstrus-producing hormone.

and to consider the establishment of a standard for male-hormone activity.

At the time when these plans were made, the progestational hormone of the corpus luteum, first obtained by CORNER and ALLEN, had been prepared in well-characterised crystalline form from natural sources by SLOTTA and by BUTENANDT, but it seemed unlikely that the situation would be sufficiently advanced to make it possible to deal with this hormone at the same conference. Shortly afterwards, however, the artificial preparation of this hormone from pregnandiol, and also from stigmaterol, so altered the situation that it was decided to extend the personnel of the conference slightly and to deal with the progestational hormone as well.

From time to time in the proceedings of the different technical conferences convened by the Health Organisation of the League of Nations to discuss the biological standardisation of various therapeutic substances, the question has arisen as to whether standard preparations and notations in units of activity are necessary and desirable, when once the active principles of the remedial agents in question have been isolated and identified in a state of chemical purity.

An earlier Conference (Geneva 1925), for example, considered the standardisation of preparations of the suprarenal medulla. It was easily agreed that such preparations should be standardised, whether by a biological or a chemical, colorimetric method, against a pure preparation of l-epinephrine (l-adrenaline). It was not found necessary, however, to provide an international standard preparation of that readily accessible substance, or to define units of biological activity. It was assumed that the activity of any preparation, even if determined by a comparative biological test, would be indicated in weight of l-epinephrine. As suggested in the report of the second International Conference on Vitamin Standardisation (1934), the same considerations may ultimately apply to the indication of some of the vitamin activities of various preparations and foodstuffs, in actual weights of the pure vitamins concerned.

This question was the subject of more explicit discussion, resulting in definite recommendations, at this Conference dealing with the hormones of the gonads. Pure crystalline substances were considered, and eventually adopted, as standards in several instances.

There was obviously much to be said for the view that, although the method of comparative assay was biological, there was no really logical reason for defining a unit of biological activity as that of a chosen weight of a chemically pure standard, instead of stating the equivalent of that standard in milligrammes or microgrammes. It will be seen that, in several cases, and especially in those in which the active substances are already themselves available in approximately pure form for practical use, the Conference have recommended the supersession of units of activity by ordinary gravimetric dosage, as rapidly and as far as this can be achieved. They had to bear in mind, however, the fact that the original reason for their convention, and the aim of their decisions, was the replacement of the competing and variable units defined in terms of animal reactions, and already current in different laboratories, by a uniform notation in units based on stable standard preparations. The Conference accordingly reached the conclusion that it was necessary, especially in the case of imperfectly purified preparations from natural sources, to retain the notation in international units of activity, at least until the former confusion of animal units had been superseded and forgotten. Even in such cases, however, they endeavoured to provide for the gradual replacement of uniform international units by indications in weights of pure hormones.

This appears to be the first occasion on which an international conference of this kind has given clear expression to an aim and a policy, which appears to have yet a further implication. If it is accepted as desirable that notation in units of activity should be replaced eventually by indications in equivalent weights of pure principles, it may further be recognised that biological methods of comparative assay, with their inherent limitations of accuracy and their heavy cost in material and skill, should be replaced by chemical determinations, whenever these can be made with as great accuracy and specificity as those based on animal tests. It may be hoped that, as chemical knowledge of the biologically important principles increases, remedies which still, with our present knowledge, can only be standardised by biological methods may pass, one by one, into the class in which chemical analysis, of an accuracy comparable to that of many vegetable drugs for their active alkaloids, will supersede biological standardisation. In that sense,

the ultimate aim of all progressive work on biological standardisation, as of all preventive medicine, may be regarded as self-extinction.

I. ŒSTRUS-PRODUCING HORMONES.

At the earlier Conference on Sex Hormones, held at London in 1932, it was decided that, "in view of the evidence before them as to the varying ratios between the activity of other forms of the hormone and that of the hydroxy-ketonic form, as measured by different biological tests, the members of the Conference are unable to recommend the determination of the activity of such other forms in the units here proposed".

In the period intervening, the position had been further complicated by the artificial production of the two dihydro-derivatives of the hydroxy-ketonic form (di-hydroxy forms), one of which had been proved by Professor DOISY to occur naturally in the ovary, and by the formation of their mono-benzoyl esters, as well as that from the hydroxy-ketonic form.

These new forms and derivatives of the hormone had acquired a practical importance as great as that of the originally isolated hydroxy-ketonic form ; and the standard of the latter, adopted at the previous Conference, had proved to be unsuitable for the comparative testing of these. The main problem before the Conference, therefore, with reference to the œstrus-producing hormones, was to consider the possibility of providing suitable standards for the testing of other forms than the hydroxy-ketonic, of their esters, and of preparations containing one or more of them in a state of incomplete purification.

After a full discussion of different proposals and possibilities, the Conference adopted the following resolutions :

1. That in the opinion of this Conference it is desirable that, as rapidly and as far as possible, the production of preparations of the œstrus-producing hormones should be limited to pure preparations of the different forms of the hormone and its chemically defined derivatives or of mixtures thereof, so that the activity may be indicated in exact weights, and indications in biological units may be abandoned.

2. That, in the case of preparations of pure chemical substances of this group, the exact weight and chemical nature of the substance present should in any case be indicated. In the case of pure preparations of the two substances accepted as international standards for biological assay (viz., the hydroxy-ketonic form of the hormone and the benzoate of its dihydroxy form, [vide 4]), the activity should for the present also be indicated in international units, and the activity of an incompletely purified preparation should be indicated in the equivalent weight of the appropriate standard and also in international units. In any case, incompletely purified preparations or extracts should be so labelled that they will not be confused with preparations of the pure substances.

3. That for the information of the practical user it is necessary to have the activity of incompletely purified preparations, or extracts, containing forms of the hormone other than those constituting the standard, indicated in international units on the label of the bottle or other container of the preparation. Such indications, however, may have a varying value, in accordance with the choice of mice or rats for the tests, with the method of solution, division and spacing of dosage, etc. It is accordingly recommended that, with a view to greater uniformity of dosage in practice and to more accurate interpretation of effects recorded in the literature, such additional data concerning the details of the test determining the indicated unitage should be given in some document accompanying each package of such preparations.

4. That, in addition to the existing international standard (in the form of the hydroxy-ketonic substance), a second international standard shall be established of the mono-benzoate of the di-hydroxy form prepared by benzylation on the phenolic hydroxyl group, M.P.194°-195° C. (uncorrected).

5. That the international unit for benzyolated forms of the hormones shall be the specific œstrus-producing activity contained in 0.1 gamma of the standard preparation described under 4.

Though the Conference thus adopt, as the unit for benzyolated preparations of the hormones, the same actual weight (0.1 gamma) of the benzyolated standard as that previously adopted for the unit based on the hydroxy-ketonic form of the hormone, they wish to avoid any suggestion that these two units are equivalent in biological activity.

6. That the National Institute for Medical Research, London, shall keep the standard, and shall prepare it by uniform admixture of quantities of the pure mono-benzoate of the dihydro form of the hormone as defined under 4, offered for this purpose by Professor BUTENANDT, Dr. GIRARD, Professor LAQUEUR and Dr. MARRIAN.

7. That benzoylated preparations of the hormone should be tested in comparison with the new mono-benzoate standard, and that the units determined in terms of this standard should be distinguished from units determined in terms of the hydroxy-ketonic standard by describing them as "units (benzoate standard)".

8. That by the term "specific œstrus-producing activity" is to be understood the power of producing, in the adult female animal completely deprived of its ovaries, an accurately recognisable degree of the changes characteristic of normal œstrus. For the present, the only such change regarded by the Conference as providing a suitable basis for quantitative determination of activity in comparison with the standard preparation is the series of changes in the cellular contents of the vaginal secretion of the rat or mouse.

9. That the comparison of an unknown preparation with the standard for such specific activity can only be accurately made if the conditions of administration of both, and of observing the results produced in each case, are completely identical, particularly in the following respects :

(a) The standard and the preparation under test must be administered in identical solvents.

(b) Administration should be by truly subcutaneous and not intramuscular injection.

(c) The standard preparation and the preparation under test should both be administered by a method ensuring slow absorption at identical rates. This can be attained by administering both dissolved in the same oily solvent, in which case single injections may be used, or by preparing both in watery solution, and administering in an equal number of fractions, not less than three, the injections being spaced in an identical manner in both cases, over a total time of not less than nine hours.

(d) The vaginal smears should be taken at the same intervals after the injection from the animals injected with the standard and from those injected with the preparation under test, but should be continued at least once daily until the animals have returned to the dioestrous condition. On the day on which the maximum response is expected, at least two smears should be taken. If the maximum occurs in the animals receiving the standard and in those receiving the preparation under test, at intervals after the injection differing by more than twenty-four hours, the comparison cannot be regarded as valid.

(e) In comparing the activity of a preparation with the standard, the procedure should aim at finding a dose of the unknown preparation producing the chosen limiting reaction in the same proportion of animals as that in which it is produced by a known dose of the standard. A method should be chosen which has been proved, in the hands of the particular investigator, to be capable of determining such equality of activity with an error not greater than plus or minus 20%. According to the experience of the members of the Conference, an accuracy of this degree is not attainable, by any method, with the use of less than twenty animals for each dose.

10. That the preparation be preserved as dry crystals at a temperature of 0° C. or less, and protected from light and from contact with traces of oxygen.

11. That, when thus adopted, the standard preparation will be distributed into sealed ampoules filled with dry nitrogen, each containing about 20 milligrammes. A suitable number of these ampoules will be placed at the disposal of each country requiring to use the standard, for local distribution.

12. That standards or units for other forms of the œstrus-producing hormones, or other derivatives thereof, be not at present established.

13. The European representatives agreed to use for scientific purposes the following nomenclature for œstrogenic compounds :

Hydroxy-ketonic form—œstrone.

Tri-hydroxy form—œstriol.

Di-hydroxy form—œstradiol.

II. MALE HORMONES.

The Conference proceeded to consider the possibility of setting up a standard and defining a unit for the indication of the specific activity of substances having male-hormone action. After full discussion they adopted the following resolutions :

1. That, for the male hormones at present obtainable and susceptible of quantitative biological measurement, the substance known as androsterone will form a suitable standard.

2. The standard shall consist of a pure crystalline preparation of artificially prepared androsterone with the following characters :

M.P. 183.5°-184.5° C. (corrected).

$[\alpha]_D^{20} + 97.3^\circ$ in absolute alcohol.

3. That the National Institute for Medical Research, Hampstead, shall keep the standard, and shall prepare it by uniform mixture of quantities of pure androsterone offered by Professor BUTENANDT, Professor LAQUEUR and Dr. MIESCHER (a quantity of 5 grammes having already been presented by Dr. MIESCHER on behalf of CIBA, Basle). The standard preparation will be preserved as dry crystals at a temperature of 0° C. or less, and protected from light and from contact with oxygen. It will be distributed into sealed ampoules filled with dry nitrogen, each containing about 250 milligrammes. A suitable number of these ampoules will be supplied to the appointed national centres, for national distribution to institutions and manufacturers in different countries requiring the standard for purposes of standardisation.

4. The unit of activity shall be defined as the activity of 0.1 mgrm. of this standard as measured by a specific biological reaction ; this weight is approximately the daily dose required to give an easily measurable response in the comb after five days.

5. That, on information before the Conference, the test based on the induction of growth in the comb of the capon is, at present, the only one sufficiently specific for the quantitative determination of activity in comparison with the standard preparation (GALLAGHER and KOCH). The Conference recognises, however,

that a method of biological assay on mammals is also desirable and recommends further comparative investigation of the value and specificity of such methods.

6. That for the information of the practical user it is necessary to have the activity of incompletely purified preparations, or extracts, containing forms of the hormone other than that constituting the standard, indicated in international units on the label of the bottle or other container of the preparation. These units, however, may have a varying value in accordance with details of application of the test. It is accordingly recommended that, with a view to greater uniformity of dosage in practice and to the more accurate interpretation of effects recorded in the literature, the details of the method used in determining the indicated unitage should be given in some document accompanying each package of such preparations.

7. That, in the case of preparations of pure substances of this group, the exact weight and chemical nature of the substance present should be indicated, in addition to a statement of the activity in international units ; and that the activity of a preparation or an extract consisting of incompletely purified substances should be indicated in the equivalent weight of the standard, as well as in units of activity. In the case of such incompletely purified preparations or extracts, it should be stated whether they are prepared from urine or from testes, or from both, and in the last case in what proportion.

8. That the comparison of an unknown preparation with the standard, for specific activity as defined above, can only be accurately made if the conditions of administration of both, and of measuring the results produced in each case, are completely identical, particularly in the following respects :

(a) The standard and the preparation under test must be administered in identical solvents. The method of administration must be identical for standard and for substance under test.

(b) The only method of administration which can be recommended on evidence before the Conference is that of injection into the pectoral muscles. It is suggested that the accuracy of methods based on injection into or superficial application to the comb should be further investigated.

(c) If, as is customary, the total dose is divided into portions for injection on several days, the division and the spacing of the doses must be identical for the standard and for the substance under test.

(d) In comparing the activity of a preparation with the standard, the procedure should aim at finding a dose of the unknown preparation producing a reaction quantitatively identical with that produced by a known dose of the standard, as determined either directly in the test or by reference to a standard curve drawn from results obtained on the same stock of birds.

9. That no sufficient information is yet available concerning the biological activity of artificially esterified preparations of male hormones to justify any detailed recommendation with regard to their standardisation. The androsterone standard, now adopted, does not afford a suitable basis for their comparative assay in units, by simultaneous observation of their effects.

III. PROGESTATIONAL HORMONE OF THE CORPUS LUTEUM.

The Conference proceeded to consider the possibility of setting up a standard for the progestational hormone of the corpus luteum, and of defining a unit in terms of it. After discussion they adopted the following resolutions :

1. That the Conference recommend the adoption, for common use in scientific literature, of the name progesterone for the pure, crystalline progestational hormone.

2. That an international standard preparation of the progestational hormone be accepted, and that this standard shall consist of the pure, crystalline progesterone, crystallised entirely in the form of needles :

M.P. 121° C. (uncorrected).

$[\alpha]_D^{20} + 200^\circ$ in CHCl_3 .

3. That the international unit for the progestational hormone shall be the specific progestational activity of 1 milligramme of the international standard preparation.

4. That the test for activity in international units must, according to present information, be based on the production of a progestational reaction.

5. That the only method of applying this progestational reaction in practical testing, concerning which sufficient information is available to justify a recommendation, is that based on the degree of proliferation produced in the endometrium of the rabbit. This can be applied to the adult female rabbit deprived of the ovaries after coitus (CORNER and ALLEN), or to the immature female rabbit after treatment with the oestrus-producing hormone (CLAUBERG).

6. That the comparison of an unknown preparation with the standard for such specific activity can only be accurately made if the conditions of administration of both, and of observing the results produced in each case, are completely identical; in particular, the standard and the preparation under test must be administered in identical solvents.

7. That the preparation be preserved as dry crystals at a temperature of 0° C. or less, and protected from light and from contact with traces of oxygen.

8. That, when thus adopted, the standard preparation will be distributed into sealed ampoules filled with dry nitrogen, each containing about 100 milligrammes. A suitable number of these ampoules will be placed at the disposal of each country requiring to use the standard, for local distribution.

9. That, in the case of preparations of pure substances of this group, the exact weight and chemical nature of the substance present should be indicated, in addition to a statement of the activity in international units; and that the activity of a preparation or an extract consisting of incompletely purified substances should be indicated in the equivalent weight of the standard, as well as in units of activity.

IV. GONADOTROPIC HORMONES.

The Conference regards the question of the gonadotropic hormones of the anterior pituitary lobe and of urine as so closely connected with those of other anterior pituitary hormones as to be unsuitable for detailed discussion at this meeting.

LEAGUE OF NATIONS
QUARTERLY BULLETIN
OF THE HEALTH ORGANISATION

VOL. IV, No. 4.

December 1935.

Authors are alone responsible for views expressed in signed articles.

**REPORT OF THE INTER-GOVERNMENTAL
CONFERENCE ON
BIOLOGICAL STANDARDISATION**

Held at Geneva from October 1st to 4th, 1935.

In a Circular Letter, dated March 23rd, 1935,¹ the Secretary-General of the League of Nations drew the attention of the Governments of the States Members and of the United States of America, Brazil, Egypt and Japan, the Office international d'Hygiène publique and the Office international des Épizooties to the fact that the work carried out by the Permanent Commission on Biological Standardisation under the auspices of the Health Committee had enabled the latter to adopt international standards for a series of products, the assay of which can only be effected by biological methods. The following is a list of these products :

1. *Sera and bacterial products :*

Diphtheria antitoxin.

Tetanus antitoxin.

Anti-dysentery serum (Shiga).

¹ Circular Letter 45.1935.III.

Anti-pneumococcus serum { Type I.
Type II.

Staphylococcus antitoxin.

Gas-gangrene antitoxin (*B. œdematiens*).

Gas-gangrene antitoxin (*Vibrion septique*).

Gas-gangrene antitoxin (*B. perfringens*).

Gas-gangrene antitoxin (*B. histolyticus*).

Diphtheria antitoxin for the flocculation test.

Old tuberculin.

2. *Hormones* :

Insulin.

Pituitary extract (posterior lobe).

Æstrus-producing hormone.

Male hormone.

Progestational hormone of the corpus luteum.

3. *Vitamins* :

Vitamin A.

Vitamin B₁.

Vitamin C.

Vitamin D.

4. *Other remedies* :

Digitalis.

Strophanthus (ouabain).

Salvarsan.

Neosalvarsan.

Sulpharsphenamine.

The Governments had also been asked to send representatives to an Inter-governmental Conference which would be called upon to review the results obtained in the field of biological standardisation and to discuss the steps that should be taken to ensure the wider utilisation and, if possible, the adoption into national pharmacopœias of the standards and units recommended by the Permanent Commission on Biological Standardisation.

On August 12th, 1935, the Secretary-General informed the Governments and institutions mentioned above that the Inter-

governmental Conference would open at Geneva on October 1st, 1935, and communicated to them the agenda of this Conference (Annex 1).

The following countries agreed to send representatives to the Conference :

| | |
|------------------------------|--------------------------|
| Australia | India |
| Austria | Irish Free State |
| Belgium | Japan |
| United Kingdom of Great Bri- | Latvia |
| tain and Northern Ireland | Netherlands |
| China | Norway |
| Czechoslovakia | Poland |
| Denmark | Roumania |
| Ecuador | Sweden |
| Estonia | Switzerland |
| France | United States of America |
| Guatemala | Yugoslavia. |
| Hungary | |

The Office international d'Hygiène publique and the Office international des Épizooties also consented to take part.

* * *

1. The Conference sat at Geneva from October 1st to 4th, 1935, and, at its first meeting, appointed its officers as follows :

President :

Dr. Th. MADSEN, Director of the Danish State Serum Institute, Copenhagen ;

Vice-Presidents :

Professor Louis MARTIN, Director of the Pasteur Institute at Paris ;

Dr. G. W. MCCOY, Director of the National Health Institute, Washington ;

Dr. E. ZUNZ, Professor of Pharmacology at Brussels University.

A list of delegates will be found in Annex 2.

2. In his opening statement, Dr. MADSEN, speaking in the twofold capacity of President of the Conference and Chairman of the Permanent Commission on Biological Standardisation of the Health Organisation, set forth the objects of the Conference. Its main purpose was to induce all those who deal with biological assays—health administrations, pharmacopœia commissions, research laboratories and manufacturers—to express the results of titrations in terms of the international standards and units established by the Permanent Commission on Biological Standardisation.

Furthermore, the method so far followed in distributing these standards to those requiring them needed some modification in order to relieve somewhat the two institutes which distribute these standards on behalf of the Health Organisation—namely, the National Institute for Medical Research at Hampstead, London, as regards certain drugs, vitamins and hormones ; and the Danish State Serum Institute at Copenhagen, as regards sera and bacterial products. It appeared that the most suitable solution would be to set up in each country a national centre or centres which would take charge of the distribution of all the international standards to the laboratories and manufacturers concerned.

The President emphasised that the work done in the field of standardisation, despite its magnitude and the great number of experimenters associated with it, had been carried on in the silence of the laboratory and was hence insufficiently known even to the medical profession. Now that twenty-six international standards had been established, the time seemed to have come to consider, from an international standpoint, what steps could be taken to ensure that they might be much more generally used.

Dr. P. HARTLEY and Dr. Claus JENSEN then outlined the methods of preparing, preserving and distributing the standards at the Hampstead and Copenhagen Institutes, whose Biological Standards Departments they respectively control.

3. The Conference next proceeded to consider the reports sent in by the various countries.

In a letter dated July 9th, 1935,¹ the Director of the Health Section asked the Health Administrations of the countries invited

¹ C.L.12.1935.VIII.

to the Conference for information on the following points, so as to complete the documentary material required for the Conference :

(1) For which of the preparations in the attached list (Annex 3) is an official control required in your country :

(a) When such preparations are manufactured in your country ;

(b) When they are imported from abroad ?

(2) Please give the names and addresses of the institutions entrusted with such official control :

(a) Of sera and bacterial products ;

(b) Of glandular products (insulin, pituitary extract, sex hormones) ;

(c) Of vitamin-containing products ;

(d) Of extracts of digitalis and of strophanthus, as well as the arsenobenzenes.

What standards and units are used for the assay of these products ?

(3) Does your legislation or pharmacopœia require that the activity of all or certain of these products should be assayed against international standards and expressed in international units ?

Thirty-five Health Administrations responded to this request, and their replies are set forth in a document¹ which was examined by the Conference. In addition, the delegates of certain countries which had not replied to the above questions gave verbal particulars on the various points.

These communications and reports proved to be of such interest that the Conference proposed that the material be kept up to date ; for this purpose, it advocated the periodical publication of the data furnished by the Governments.

4. The Conference set up two technical committees to consider separately the two groups of international standards ; the first, under

¹ C.H. /GPSB.28.

the chairmanship of Dr. Th. MADSEN, was to review the standards adopted for sera and bacterial products, while the second, under the chairmanship of Sir Henry DALE, Director of the National Institute for Medical Research, was to consider the standards established for certain remedies, vitamins and hormones. To facilitate this examination, the two committees were furnished with a pamphlet written by the Secretary of the Permanent Commission on Biological Standardisation entitled "The Health Organisation and Biological Standardisation".¹

These two committees, after making a detailed examination of the decisions taken by the Permanent Commission on Biological Standardisation in respect of each of the standards adopted by it, recorded their full concurrence in these decisions. They further adopted a series of recommendations which will be considered by the Permanent Commission on Biological Standardisation at its next session.

The First Committee proposed :

(a) That the study of the principles to be followed for the assay of tetanus antitoxin should be continued ;

(b) That consideration should be given to the possibility of distributing to the institutes concerned a dysentery toxin (Shiga) at the same time as the standard anti-dysentery serum, in order to render assay more accurate and easier to perform ;

(c) That work with a view to the standardisation of anti-meningococcus serum and anti-anthrax serum should be resumed ;

(d) That the standardisation of anti-swine-erysipelas serum should be studied in consultation with the Office international des Épizooties ;

(e) That documentary material should be collected on the best methods of ensuring the stability, sterility and innocuity of therapeutic sera in general ;

(f) That the possibility of standardising the anti-typhoid and anti-snake-venom sera be considered ;

¹ See *Quarterly Bulletin of the Health Organisation*, 1935, Volume IV, No. 3, page 496.

(g) That research regarding methods of controlling the antigens used for anti-diphtheria vaccination, including Ramon's formol toxoid (anatoxine), should be continued ;

(h) That the possibility of standardising Frey's antigen should be considered ;

(i) That comparative studies regarding the standardisation of the technique of the Widal test should be undertaken in different countries.

The First Committee also put forward a recommendation (No. IV) concerning the drawbacks of the patentability of streptococcus antitoxin. This recommendation was submitted to the Plenary Conference and adopted by it.

The Second Committee proposed :

(a) That the desirability of establishing a standard prepared from the leaves of *Digitalis lanata* should be considered ;

(b) That the unit of anti-diuretic activity of posterior lobe pituitary extracts should be the anti-diuretic action exercised by 0.5 mgrm. of the standard powder previously adopted to measure the oxytocic and pressor action of preparations of posterior lobe pituitary ;

(c) That the preparation of vitamin B₁ in crystalline form, proposed by Professor SUZUKI, of Tokio, be studied in various laboratories, and that the question of its possible adoption as the international standard of vitamin B₁ be submitted to the next Conference on Vitamin Standardisation ;

(d) That the establishment of a new male hormone standard consisting of crystallised testosterone be considered.

**RECOMMENDATIONS ADOPTED
BY THE CONFERENCE.**

I. The Conference expresses the hope that the use of the international standards adopted by the Permanent Commission on Biological Standardisation of the Health Organisation will be made effective by the competent authorities of all countries.

II. The Conference recommends :

That each country should have a national centre or centres, recognised by the competent authority, to take charge of the international standards and equivalent national standards ;

And that every such centre should have a qualified staff to control the application of the international standards in its own country and thus to serve as the recognised national scientific authority in this field.

III. The Conference,

Looking confidently to the Health Committee to maintain the principle of the free distribution of international standards :

Recommends that the League of Nations should place the necessary funds at the disposal of the Health Organisation for it to continue to meet the expense entailed by the free distribution of such standards.

IV. The Conference,

Having been informed that patents protecting the preparation of streptococcus antitoxin (anti-scarlatina serum) and of the toxin used for its assay have been granted in certain countries ;

Believing that this practice constitutes an obstacle to progress in the standardisation of this serum :

Draws the attention of the Health Committee of the League of Nations to this state of affairs, and suggests that the Committee might usefully consider what means could be employed to avoid the serious drawbacks which ensue.

V. The Conference recommends that, in view of the progress achieved in the field of biological standardisation, inter-governmental conferences on this subject be summoned periodically at intervals not exceeding three years.

ANNEX 1.

AGENDA.

1. Election of the President.
2. Address by Dr. Th. MADSEN, Chairman of the Permanent Commission on Biological Standardisation ; followed by Statements on the Methods of preparing and distributing the International Standards, by Dr. P. HARTLEY (Hampstead) and Dr. Claus JENSEN (Copenhagen).
3. Consideration of Reports submitted by Representatives of Different Countries as to the Arrangements by which the International Standards are applied and rendered available.
4. Appointment of Two Committees to review the International Standards established for :
 - (i) Sera and Bacterial Products ;
 - (ii) Drugs, Vitamins and Hormones.
5. Desirability of establishing in Each Country a National Distributing Centre for all International Standards.
6. Possibility of National Standards being set up for Certain Standardised Preparations.
7. Maintenance of Free Supply of International Standards by the Copenhagen and Hampstead Institutes to National Distributing Centres.
8. Adoption of Recommendations.
9. Miscellaneous.

ANNEX 2.

LIST OF DELEGATES.

- | | |
|---|---|
| <i>Australia :</i> | Dr. Frank TRAVIA WHEATLAND, M.B., B.S., Senior Medical Officer, Commonwealth Serum Laboratories, Parkville, Victoria. |
| <i>Austria :</i> | Dr. Bruno BUSSON, Professor in the University of Vienna, in charge of the State Control of the Serotherapeutic Institute of Vienna. |
| | Dr. Ernst PICK, Professor in the University of Vienna. |
| <i>Belgium :</i> | M. R. WILLEMS, Director of the State Laboratory for Veterinary Research and Diagnosis, Brussels. |
| | Dr. E. ZYNZ, Professor in the University of Brussels. |
| <i>United Kingdom of Great Britain and Northern Ireland :</i> | Dr. M. T. MORGAN, M.C., M.D., Medical Officer, Ministry of Health, London. |

- China* : Dr. Robert LIM, Professor in the Peiping Union Medical College, Peiping.
- Czechoslovakia* : Dr. O. SCHUBERT, Chief of the Department for the Biological Control of Drugs in the State Institute of Hygiene, Prague.
- Denmark* : Dr. Th. MADSEN, Director of the State Serum Institute, Copenhagen.
- Ecuador* : M. Alejandro GASTELÚ, Secretary of Legation, Consul-General for Switzerland of the Republic of Ecuador.
- Estonia* : Dr. H. PETERSON, Director of the State Serotherapeutic Institute, Tartu.
- France* : Dr. Louis MARTIN, Director of the Pasteur Institute, Paris.
Dr. M. TIFFENEAU, Professor of Pharmacology in the Faculty of Medicine, University of Paris.
- Guatemala* : M. Louis WILLEMEN, Consul for Guatemala, Geneva.
- Hungary* : Professor Joseph TOMCSIK, Director of the Institute of Hygiene, University of Szeged.
- India* : Lieut.-Colonel A. J. H. RUSSELL, C.B.E., V.H.S., I.M.S., Public Health Commissioner with the Government of India, Simla.
- Irish Free State* : Professor W. D. O'KELLY, Bacteriologist, Local Government Department of Public Health, Dublin.
- Japan* : Dr. M. TSURUMI, Central Sanitary Bureau, Tokio.
- Latvia* : M. Karlis KALNINŠ, Secretary to the Permanent Delegation of Latvia accredited to the League of Nations.
- Netherlands* : Dr. U. G. BIJLSMA, Professor in the University of Utrecht.
Dr. W. Aeg. TIMMERMAN, Director of the State Institute for Public Health, Utrecht.
- Norway* : Dr. Klaus HANSEN, Professor in the University of Oslo.
- Poland* : Dr. L. HIRSZFELD, State Institute of Hygiene, Warsaw.
- Roumania* : Professor G. IONESCO-MIHAESTI, Director of the Institute for Experimental Medicine, Bucharest.
- Sweden* : Dr. Hans von EULER-CHELPIN, Professor in the Faculty of Science, University of Stockholm.
Dr. Carl A. KLING, Professor in the Faculty of Medicine, University of Stockholm ; Director of the State Bacteriological Laboratory.
Dr. Göran LILJESTRAND, Professor in the Faculty of Medicine, University of Stockholm.
- Switzerland* : Dr. Otto STNER, Chief of the Department for the Control of Sera and Vaccines, Federal Public Health Service, Berne.
- United States of America* : Dr. G. W. MCCOY, Director, National Institute of Health, United States Public Health Service, Washington, D.C.
- Yugoslavia* : Dr. Marjan BANIĆ, State Institute of Hygiene, Zagreb.

Office internationale d'Hygiène publique : Dr. Carl A. KLING, Professor in the Faculty of Medicine, University of Stockholm.

Experts :

Sir Henry H. DALE, C.B.E., F.R.S., Director of the National Institute for Medical Research, Hampstead, London.

Dr. P. HARTLEY, Director, Department of Biological Standards, The National Institute for Medical Research, Hampstead, London.

Dr. Claus JENSEN, Director, Department of Biological Standards, State Serum Institute, Copenhagen.

ANNEX 3.

INTERNATIONAL STANDARD PREPARATIONS HELD AND DISTRIBUTED ON BEHALF OF THE HEALTH ORGANISATION OF THE LEAGUE OF NATIONS.

A. *By the Statens Serum Institut, Department of Biological Standards, Copenhagen S.*

| Standard | When adopted | International unit in milligrammes |
|--|--------------|------------------------------------|
| Diphtheria antitoxin | 1922 | 0.0628 |
| Tetanus antitoxin | 1928 | 0.1547 |
| Anti-dysentery serum (Shiga) | 1928 | 0.0500 |
| Gas-gangrene antitoxin (<i>B. perfringens</i>) | 1931 | 0.2660 |
| Gas-gangrene antitoxin (<i>Vibrion septique</i>) | 1934 | 0.2377 |
| Gas-gangrene antitoxin (<i>B. œdematiens</i>) | 1934 | 0.2681 |
| Gas-gangrene antitoxin (<i>B. histolyticus</i>) | 1935 | 0.3575 |
| Anti-pneumococcus serum, Type I | 1934 | 0.0886 |
| Anti-pneumococcus serum, Type II | 1934 | 0.0894 |
| Staphylococcus antitoxin | 1934 | 0.5000 |
| Diphtheria antitoxin for the flocculation test... | 1935 | . |
| Old tuberculin | 1931 | . |

B. *By the National Institute for Medical Research, Department of Biological Standards, Hampstead, London, N.W. 3.*

| Standard | Nature of the standard preparation | When adopted | International unit in milligrammes |
|----------------------------|---|--------------|------------------------------------|
| Insulin | Dry insulin hydrochloride | 1925 | 0.125 |
| | Dry insulin hydrochloride, pure | 1935 | 0.045 |
| Digitalis | Dry powdered leaves of <i>Digitalis purpurea</i> | 1926 | 100.0 |
| Sulpharsphenamine | Dry sample of sulpharsphenamine .. | 1928 | — |
| Pituitary (posterior lobe) | Dry powdered acetone-extracted posterior lobes of ox pituitaries .. | 1927 | 0.5 |
| Strophanthus | Pure crystalline ouabain | 1928 | — |
| | Carotene | 1931 | 0.001 |
| Vitamin A | Pure carotene | 1934 | 0.0006 |
| Vitamin B ₁ | Standard adsorption product of vitamin B ₁ | 1931 | 10.0 |

BIOLOGICAL STANDARDISATION

| Standard | Nature of the standard preparation | When adopted | International unit in milligrammes |
|---------------------------|--|--------------|------------------------------------|
| Vitamin C | Pure 1-ascorbic acid | 1934 | 0.05 |
| Vitamin D | Standard solution of irradiated ergosterol | 1931 | 1.0 |
| | Calciferol | 1934 | 0.000025 |
| Œstrus-producing hormones | Hydroxy-ketonic form | 1932 | 0.0001 |
| | Benzoate of the dihydroxy form | 1935 | 0.0001 |
| Male hormone | Pure crystalline androsterone | 1935 | 0.1 |
| Corpus luteum hormone | Pure crystalline progesterone | 1935 | 1.0 |

A DISCUSSION OF SOME POINTS CONTAINED IN THE "THIRD GENERAL REPORT OF THE MALARIA COMMISSION" ON "THE THERAPEUTICS OF MALARIA"

By

Lieut.-Colonel J. A. SINTON, M.D., D.Sc., I.M.S.,
Director, Malaria Survey of India, Kasauli (Indian Research Fund Association).

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I. INTRODUCTION.

The report of the Malaria Commission of the League of Nations upon "The Therapeutics of Malaria" has received very wide publicity and many varied opinions have been expressed on its contents. The deductions and recommendations made in the report are on many points contrary to the views held by myself and my colleagues in India, as the result of our experience and investigations into malarial therapeutics. Although this is so, I had no desire to publish any critical discussion of these disputed points. The present discussion of certain aspects of this Report was only prepared at the urgent request of the Director of the Health Section of the League of Nations, and under instructions from my superior officers in India.

II. GENERAL CONSIDERATION OF THE REPORT.

1. THE FORM AND TITLE OF THE REPORT.

When one reads on the first page of the preface that "clinical trials *in the field*¹ on quinine and other cinchona alkaloids as well as on plasmoquine, stovarsol and other synthetic remedies were conducted by research workers in several countries and the results were communicated to the Commission", and that, "in October 1932, the Commission decided to prepare a general report on the therapeutics of malaria based on *these*² communications², and it entrusted the task to a Reporting Committee", one expects to find information based on such reports, and deductions which have been made for the practical guidance of such field workers. Reading through the report, it is discovered that the bulk of the work to which prominence is given, or which appears to be considered of value, has been almost entirely that conducted under laboratory conditions in mental hospitals. After the clinician and the field worker have waded through the mass of information contained in the report to obtain guidance in the treatment of malarial cases, they are suddenly confronted on almost the last page with the statement that "it is inevitable that a report which pretends to review modern therapeutics of malaria must deal with the subject from the point of view of persons who are in a position to obtain expert medical advice and efficient care *rather than from that of the mass of the population of malarious countries*"¹ (page 277).

I had understood, perhaps wrongly, that one of the avowed objects of the Malaria Commission was to discover some means whereby the lot of those people who could not afford the more expensive measures of malaria control would be alleviated. Their previous therapeutic work on the cinchona alkaloids had as an object the discovery of a cheap form of treatment for such populations, and one expected that the present report would be compiled

¹ The italics are mine.

² A member of the Reporting Committee desires to draw the reader's attention to the fact that, in the Preface to the third general report, the communications on which the Reporting Committee based the drafting of its report clearly meant *all* the communications received since 1925 and not only the communications on clinical trials in the field which were communicated to the Commission while the work from 1925 to 1932 was proceeding [*Editor*].

with this object, or at least to aid it. On the other hand, it appears designed for that special and comparatively rare class of persons who are in a position to avail themselves of expensive measures of treatment.

The treatments advocated appear to have been compiled chiefly for the benefit of "travellers and settlers in malarious countries" (page 200), and of those very limited few who are in a position to obtain, or pay for, the medical and other care needed in carrying out the very elaborate systems of treatment recommended by the Commission.

As JAMES has so pertinently remarked: "No policy can be considered entirely satisfactory that aims at the protection of only a few, however important these few may be, while it leaves the bulk of the inhabitants of a place in the same condition".

The sub-heading of the report is the "Principles of Treatment based on the Results of Controlled Experiments". From a careful study of the text, such a title appears to me to be misleading. The report seems rather to be "Some general principles in malarial therapeutics suggested by the results of experimental work in induced malaria, and some recommendations upon the lines which future research should follow". While the report is most valuable to a certain class of research worker, it has come to my notice that, in many instances, a study of the report has confused the issue for the field worker and the clinician in the tropics.

2. MISCELLANEOUS.

The report is, in many places, made up of the views culled almost verbatim from the published writings of different workers; but, unfortunately, in many instances the context has not been given, or at least clearly indicated. This has resulted in the inclusion of certain statements which I am sure the Commission did not wish to make, and which may be very misleading to the worker who is not thoroughly familiar with the original literature of the subject.

Thus we are told one of the defects of quinine is that "it has only a slight action on the sexual stage" (page 187) and that "quinine has no action, or in any case only an incomplete action, on gametocytes" (page 246). Yet, on the other hand, it is stated that "the gametocytes of *P. vivax* and *P. malarix* are almost as susceptible

to the action of quinine as are the asexual parasites of those species of parasite" (page 241).

In some other instances, generalisations and dogmatic statements are made, which, while almost certainly true about one species or strain of parasite, do not seem applicable justifiably to *all* other species or strains on the evidence at present available. The Commission¹ itself emphasises in many places the importance of recognising that there may be marked differences in both the biological and chemo-therapeutical reactions, not only of different species, but also of different strains of the same species of *Plasmodium*. The worker who has some familiarity with the literature of the subject assumes that, through an oversight, the necessary qualifying sentence has been omitted in most cases, and that no such dogmatic generalisation is intended, but to the field worker and the clinician these statements may be very misleading.

III. SPECIAL DISCUSSION OF THE CONTENTS OF THE REPORT.

The Director of the Health Organisation has asked me to state the technical reasons *for my disagreement*² with certain parts of the report, and I have, as requested, endeavoured to quote chapter and verse for these reasons. The fact that my note is, therefore, confined mainly to a discussion of those points with which I am not in agreement does not mean that I do not consider the report to contain most valuable information upon the subject of malarial therapeutics, both with regard to suggested future lines of research and on the practical application of the results of our present knowledge.

The points which I deal with are mainly those concerned with the work in India prior to the publication of the report, and upon the validity of which the Commission casts so much doubt.

¹ Throughout this note I have used the word "Commission" in the sense used in the text of the report, although I do not know exactly to whom it refers.

² The italics are mine.

A. THE COMBINED OR ADJUVANT ACTION OF DIFFERENT DRUGS.

The report states that "there would be a scientific reason for the practice (of using quinine and plasmquine together), if it were the case that, by giving 1 grm. of quinine mixed with 0.03 grm. of plasmquine, the mixture, when it reached the stomach, produced a new anti-malarial compound more effective than either drug separately. But this does not happen ; the two drugs do not combine, and each exerts only its own action" (page 226). Again, it is said : "It was pointed out that, as this mixture does not produce a new compound in the stomach, each drug exerts its own specific action, and that the doses of plasmquine which are given with quinine in this method are smaller than those which exert a specific action on sporozoites and trophozoites during the developed attack". "This being the case, and it being also known that quinine does not prevent relapses, the proposition that relapses can be reduced by giving ineffective doses of both drugs is paradoxical" (page 275). This is reiterated : "It may, in fact, be true that a mixture of a non-effective quantity of plasmquine (or of bicarbonate of soda or of an arsenical preparation) with a therapeutic dose of quinine gives better results in preventing relapses than can be obtained with quinine alone, but at the moment the proposition can only be described as being paradoxical" (page 227).

The so-called paradoxical element would appear to be based mainly on the report that quinine and plasmquine do not form a new compound *in the stomach*, and that each drug exerts its own specific action. Surely it is not what happens in the stomach that is the important factor, but what takes place in the fluid and solid tissues of the body, where the parasite resides. So far as I know, we have no conclusive evidence that quinine and plasmquine do not form a new compound *after absorption*, which combines the therapeutic action of each drug and possibly is more effective than either singly.

Although it is stated that "the manner in which quinine acts in bringing about the disappearance of fever and parasites is not known and this seems to be true also for the new synthetic remedies" (page 213), yet the reason put forward above would seem to assume that the mode of action of all anti-malarial drugs is identical, and therefore the combined effects of two different drugs will have no more action than an equal therapeutic dose of one of them.

The following are among the many theories which have been put forward to explain the parasitocidal action of different anti-malarial drugs :

- (1) By the direct toxic action of the drug after being absorbed into the blood stream ; or
- (2) By the conversion into a more powerful parasiticide after absorption ; or
- (3) By the stimulation of certain cells of the body to produce parasitocidal substances or "antibodies" ; or
- (4) By stimulation of the parasitocidal mechanism of the body cells ; or
- (5) By rendering the red cells resistant to the attack of the parasites ; or
- (6) By a combination of two or more of these factors (*vide* also page 244).

Even if we knew the mode of action of one of the recognised anti-malarial drugs, we have no evidence to prove that one or more of the others has the same *modus operandi*. Indeed, on page 275, a difference in the specific action of quinine as compared with plasmoquine seems to be put forward as proof that no new anti-malarial compound is formed in the stomach when these two drugs are given together.

It appears to me, therefore, to be much more paradoxical to assume that drugs of such widely different chemical compositions as quinine, plasmoquine, atebirin and the arsenical preparations should produce their results in identical fashions. That their actions are probably different is suggested by the facts that (a) plasmoquine has little or no effect on the schizonts of malignant tertian malaria, while quinine and atebirin have ; (b) that plasmoquine is acknowledged to have a marked effect on crescents, while none of the other drugs has ; (c) that differences are reported between the effects of quinine and atebirin on the morphology of *P. vivax* (page 272) ; and (d) that stovarsol has a much greater action upon some forms of *P. vivax* than on those of *P. falciparum*.

It is quite possible that some drugs have a direct, and some an indirect, toxic action on the parasites, or even on different parts of the same parasite. Other drugs may act more indirectly by their effects in stimulating the body to a more rapid development of that "tolerance" upon which the report has laid so much stress

in the production of clinical cures. If all these drugs and their "adjuvants" do not act in the same way in producing their results, it would appear to me to be most scientific to combine their different actions when necessary and possible. The clinical evidence available supports the view that, in some cases at least, one drug may reinforce the action of another, even when smaller doses are given than those which *some persons* believe to be therapeutically active.

" Present practice is to use it (plasmoquine) in those small doses (not more than 0.03 gm. per diem) along with quinine or along with atabrin. The Commission is of opinion that, when the object in view is solely the prevention of relapses, this practice is of doubtful value and is likely to bring further confusion into a problem which is already immensely complex " (page 226).

If clinicians in many parts of the world have already found that, under their local conditions, such a combination of drugs is of practical benefit, is the afflicted population to be deprived of such benefits until the *modus operandi* of such drugs is discovered, in order to avoid confusion in the scientific side of the problem? If this be the line of malarial therapeutics which is to be advocated, it would seem to me that, logically, the use of anti-malarial drugs of any description should be prohibited, except for experimental purposes and under the very strict scientific conditions laid down in the report, until the exact mode of action of the drugs is determined!

From the evidence available, it seems probable that the same combination of drugs may not be equally effective in different areas in different kinds of infections. It appears likely, however, from the recorded differences in the actions of single drugs on different species and strains of parasites, that certain combinations should prove more effective than any one singly, at least in producing radical cures in a larger percentage of cases.

1. *The Treatment of Benign Tertian Malaria with Plasmoquine plus Quinine.*

The opinion of the Commission is that a combination of quinine and plasmoquine for the prevention of relapses " is of doubtful value " (page 226). The Commission has discussed in the report the problem whether a lower percentage of relapses can be brought

about by plasmoquine *plus* quinine than by quinine alone. Because of the finding, discussed above, that no new compound is formed in the stomach, and that the doses given are *said* to be smaller than those of either drug which is therapeutically active alone, the Commission considers that, this being so, "the proposition that relapses can be reduced by giving ineffective doses of both drugs is paradoxical" (page 275).

I do not know upon what evidence other than theoretical considerations, such as I have already dealt with, the Commission bases its damning indictment of the combined quinine and plasmoquine treatment of malaria. If it be upon the effects seen in therapeutic malaria, in the light of our present knowledge it seems to me that one is not warranted in drawing general conclusions from the results obtained with only the few strains of *P. vivax* which have been used in such work. There is much evidence to support the view that different strains of parasites may react very differently to the same agent—for example, the differences between the effects of plasmoquine upon the Madagascar and Dutch strains of *P. vivax* (page 227), and between the action of neosalvarsan on these strains (KORTWEG). JAMES (1932) has already pointed out that "the remarkable contrast brought out by therapeutic tests raises the question whether, from the chemo-therapeutic point of view, the biological susceptibility of a parasite to the action of drugs may not be more important than its morphological characters—strains may be more important than species". The Commission itself states that "the percentage of relapses following any system of specific treatment (and even the percentage following no specific treatment) varies greatly in different countries, in different localities of the same country, and in different individuals" (page 276). If this be so, how, then, can the Commission make such dogmatic statements as to the value or inefficacy of any system of treatment from the results of the study of infections due to a very few strains of parasite, and observed under artificial conditions?

The Commission gives a statement of some of the earlier work done by SINTON and BIRD (1928) and says from this:

"It is evident that neither plasmoquine alone nor plasmoquine plus quinine brings about sterilisation of the parasite in the human host. The same conclusion has to be drawn from the results of trials on induced malaria" (page 223).

The Commission, in making these deductions, appears to have taken no notice of the later work on this treatment of benign tertian malaria carried out by the Malaria Treatment Centre, Kasauli, and recorded by SINTON, SMITH and POTTINGER (1930) and by JARVIS (1932, 1932a).¹ SINTON *et al.* (1930) report a further series of seventeen cases treated with 0.06 gm. plasmoquine for four to twenty-one days combined with 1.3 gm. quinine sulphate in solution for twenty-one days, which showed a maximum relapse rate of 11.3% (average 8.4%). In another series of forty-four cases given 0.04 gm. plasmoquine and 1.3 gm. quinine daily for twenty-one days, the average relapse rate was 5.9%.

This work was continued by JARVIS (1932, 1932a), who reports that, in one series of seventy-five cases treated with 0.3 gm. plasmoquine plus 1.3 gm. quinine daily for twenty-one days, the relapse rate was 8%, while in another series of thirty-one cases receiving a similar course of treatment, but kept in bed for the first fourteen days of the treatment, there were no relapses during an observation period extending up to an average of 12.7 weeks (nine to twenty weeks) after the cessation of treatment.

The treatment of 0.04 gm. plasmoquine plus 1.3 gm. quinine daily for twenty-one days was tried out in the British Army in India on a large scale. MANIFOLD (1932) has collected the reports upon the results of this work. He states that the recorded relapse rate in over 3,000 cases, observed during an average period of four and a-half to five months, was only 5.2%. DIXON (1933) has more recently carried out a careful investigation of the treatment of benign tertian malaria by plasmoquine and quinine. His cases were British soldiers whose histories after treatment were "carefully observed over a period of from three and a-quarter years to a minimum of ten months". He reports, "In 215 cases of *P. vivax*, primary infections were observed over an average period of two years; the relapse rate was 4.1%. In 141 cases of *P. vivax* relapse cases the relapse rate was 4.7%".

It is pointed out in the report (page 227) that the relapse rate under the controlled conditions of the Malaria Treatment Centre

¹ The type of patient and the conditions under which they were treated and observed will be discussed in the section on "Investigations of the Radical Cure of Malarial Infections".

was higher than in the "mass treatment" experiment recorded by MANIFOLD (1932). As is noted in the articles of SINTON *et al.* (1928, 1930), the patients treated at Kasauli were all chronic relapsing cases of benign tertian malaria, which had proved resistant to anti-relapse treatment with the cinchona alkaloids on very many occasions. Such a population is, therefore, quite different from the usual army one, which contained a considerable proportion of primary infections, many of which were probably with those strains of *P. vivax*, or in those individuals, among which, if "treated with quinine in the primary attack, only about 50% have any further manifestations of the disease" (page 192).

Moreover, the later blood examinations of the cases recorded by MANIFOLD were usually made only when some suspicious clinical manifestation suggested that a relapse was imminent, and not by weekly thick-film blood examinations, as in the case of the patients at the Malaria Treatment Centre. The recorded "relapses" in the latter instances were, therefore, "parasitic" ones, in which clinical manifestations were often absent, while in MANIFOLD's cases the parasitic relapses were only discovered because of the clinical ones. These are two entirely different conditions.

In the early days of the Malaria Treatment Centre, when intractable chronic relapsing cases of malaria were sent to Kasauli from all over India, these were mainly benign tertian infections. In those days when the value of different cinchona alkaloids was being tested, the centre had usually about 200 patients and a waiting-list of many others requiring admission. Since the introduction of the combined quinine and plasmoquine treatment as a routine in the army, more especially for the treatment of such quinine-intractable cases,¹ the numbers fell so low that the centre had to be closed. This closure was not due, as stated by SCHULEMANN (1935), to the absence of cases of malaria, but to the elimination of that intractable and constant relapsing type of benign tertian infection previously so common among British troops, and from which the vast majority of the patients sent to Kasauli were suffering.

¹ By "quinine-intractable" I mean that any course of treatment of this population with the cinchona alkaloids cured *radically* but a small number (about 35%). In so far as the clinical manifestations of the attack were concerned, these were very easily controlled by such alkaloids.

As the result of the introduction of a "local standard treatment", the army has been able to cut down to a minimum those chronic relapsing cases of benign tertian malaria on which the cinchona alkaloids had proved of little value in the production of a radical cure of the infections. This has resulted in a great saving in hospitalisation, chronic sickness, diminished efficiency and invaliding.

The army medical authorities state in the "Annual Report of the Public Health Commissioner with the Government of India for 1932, Part II, The Health of the British Army in India"¹ that, "partly by a process of exclusion and partly from slowly accumulating clinical and statistical evidence, the tentative opinion is now expressed that the more extensive and intelligent use of plasmoquine is mainly responsible for the fact that 1932 was a record year" (from the point of view of low malarial incidence). I understand that, from more recent trials, the conclusions as to the value of this drug in army practice are even more enthusiastic.

With regard to the so-called confirmatory observations in induced malaria on the inefficacy of the combined quinine and plasmoquine treatment in preventing relapse, the work of CIUCA, BALLIF and VIERU, and that of SWELLENGREBEL and DE BUCK, is quoted. If one considers the observations of these two sets of observers it will be seen that the amount of quinine given daily was in no case more than 1 gm., which, while it may be an effective curative dose for clinical symptoms, is not in my opinion sufficient to have, in courses of such short duration, any marked permanent or anti-relapse result on the type of benign tertian malaria with which our Indian work was carried out (*vide* SINTON 1930, 1931). Again, the results recorded by SWELLENGREBEL and DE BUCK were conducted with the Madagascar strain of *P. vivax*, which is known to show more resistance to treatment than are some other strains (*vide* PIEBENGA's work with the Dutch strains). Although it is laid down that experimental work should be conducted with individuals who were "infected by the bites of approximately the same number of mosquitoes infected with the same strain of the specific parasite on which the tests are made" (page 265), and "it

¹ These annual reports contain additional data as to the results obtained and methods used to "follow up" the cases after the cessation of treatment. This is especially the case in the report for 1933 (in the press).

is understood, of course, that, in all therapeutic tests on induced malaria, every endeavour should be made to imitate natural conditions as closely as possible " (page 263), yet the infections studied by SWELLENGREBEL and DE BUCK were produced by multiple bites—in fact, a condition which would probably not be a very common happening in nature.

That this experiment cannot be taken as a confirmation of the doubtful value of quinine *plus* plasmoquine treatment appears to be admitted by the authors (SWELLENGREBEL and DE BUCK, 1932), who say : " It only shows that a system of prophylaxis and treatment which has definitely proved its great practical value may occasionally break down under the stress of an unusually great number of infected mosquitoes or the prevalence of some strain of parasites of particular vitality ".

One possible fallacy in the work of CIUCA, BALLIF and VIERU have already been discussed.¹ I am unable to understand how the Commission is able to make such dogmatic statements upon the evidence available, in view of the opinions it has expressed in other parts of the report.

The Commission states that :

" It is evident that neither plasmoquine alone nor plasmoquine *plus* quinine brings about sterilisation of the parasites in the human host " (page 223).

Surely this is a very sweeping statement, for it is known and admitted (page 192) that quinine treatment will free the patient of parasites in a very large number of cases. I do not think that I or any other worker have claimed that such a combined treatment was a *therapia magna sterilisans*. All that has been claimed is that by this means a much higher percentage of permanent cures can be obtained under certain conditions than with quinine therapy or with plasmoquine alone in non-toxic doses.

Even if one does not admit that the greater value of such a combined treatment in the radical cure of benign tertian infections is proven, I think it must be admitted that such a line of treatment has been found of the greatest practical value by the clinician and the patient in many parts of the world.

¹ Other points on this work are discussed on page 679.

In the work of the Malaria Treatment Centre it was shown that the combined treatment with plasmoquine reduced the number of parasitic and clinical relapses in chronic benign tertian infections to about 10%, during an observation period by blood examination of at least eight weeks after the termination of treatment. On the other hand, with any course of treatment with the cinchona alkaloids alone, the relapse rate in this type of case averaged about 65% in the same period.

MANIFOLD'S records seem to indicate that such treatment kept off clinical relapses in about 95% of his cases for an average period of four and a-half to five months. In both these investigations the men were undergoing, during the period of observation, the ordinary hard physical labour and exposure to severe climatic conditions of army life in India. These are among the circumstances mentioned by the Commission (page 231) as likely to cause relapses, even while the patient is receiving a course of "clinical prophylaxis".

"Plasmoquine, when used for the treatment of the human subject, is known to have a marked action in preventing or delaying the onset of a primary attack of benign tertian malaria" (page 261).

If this be so, why should it not have a similar effect in preventing or delaying secondary attacks, more especially when its action is reinforced by the "tolerance" which the Commission states is developed during chronic infections? It seems to me that any course of treatment which keeps the majority of patients free from either clinical or parasitic relapses for long periods under the natural conditions of life, apart from any questions of radical cure, is one to be encouraged rather than deprecated. The reports from clinicians in many parts of the world strongly support the view that such a *practical* benefit is obtained by the combined quinine and plasmoquine treatment.

The Commission states that :

"It is not good practice to treat attacks of malaria *in the acute* stage with a combination of two of the specific drugs mentioned, in the hope that one of them will be effective in curing the attack, the other in preventing relapses. Particularly with regard to the growing practice of treating acute

attacks with a combination of quinine and plasmoquine, the Commission's attention has been drawn to observations indicating that the toxic effects of plasmoquine seem to be enhanced by a condition of fever and anæmia" (page 215). "*They desire also to state without any qualification that, in their view, plasmoquine should not be used in the treatment of acute attacks in any form of malaria*" (page 274).

The majority of the observations of which the Commission appears to have taken any cognisance are those in which the daily dosage of plasmoquine was 0.06 gm. or over, in which it is admitted that toxic symptoms are a common occurrence. With the smaller doses which are in common use for the routine treatment of malaria (*vide* SINTON *et al.*, 1930 ; MANIFOLD, 1931 ; JARVIS, 1932 ; DIXON, 1933), severe toxic complications are of a comparatively rare occurrence. As pointed out by SINTON *et al.* (1930), and numerous other workers, there are certain physical and pathological conditions in which plasmoquine is to be used with caution, if at all. SINTON (1930) in his "standard treatment" has pointed out the necessity for medical supervision in the use of plasmoquine, and I gather that the recommendations of the report are intended to apply almost entirely to this type of patient—*i.e.*, "persons who are in a position to obtain expert medical advice and efficient care" (page 277). SINTON has also indicated the type of patient to whom plasmoquine may be dangerous. It should also be noted that, in this treatment, the daily dosage of plasmoquine recommended by him for acute primary attacks is only 0.015 gm. This should satisfy the objections of the Commission, and at the same time it means that it is only in the residue of relapsing patients that larger amounts of this more expensive drug are needed.

The report lays stress upon the point that "the great advantage of possessing two curative drugs is that, in cases which seem resistant to treatment with one of them, trial of the other can be made" (page 274).

The Commission, in its treatment of malignant tertian malaria, also recommends that, if treatment of the primary attack by one drug be followed by a relapse, the practitioner should try another drug for the treatment of the relapse. Except in so far as the two drugs are not given together in the primary attack, this recommendation does not seem to me to be very different from the practice

of using two drugs combined in attempts to produce a permanent cure in benign tertian malaria.

From the evidence available, it would seem probable that there are certain strains of *P. vivax* which show a considerable resistance to permanent cure by ordinary therapeutic courses of the cinchona alkaloids, but which may be amenable to plasmoquine. In natural infections it is impossible under most circumstances to tell either clinically or microscopically with which type of *P. vivax* the patient is infected, or whether he is infected with more than one type. Under these conditions, it would seem to me to be *practical*, though *perhaps not research, science* to use the two drugs together.

While, *from research considerations*, it may be advisable to give two separate courses of treatment (*i.e.*, one for the attack and one for the relapse), such a procedure would not, I think, recommend itself either to the ordinary general practitioner or to his patient. One of the aims of malarial treatment should be to make its duration as brief as possible, consistent with efficacy. In my experience, the patient will not thank you if you give him a course of treatment from which he may be expected to relapse in a very short period. This is more especially the case if he thinks that by other methods, such as by combined quinine and plasmoquine treatment, or by other drugs, the infection can be cured, or at least the intervals between attacks very much prolonged. Such continued and frequent relapses may interfere very seriously with the ordinary affairs of the patient's life.

From the results which have been obtained in India and elsewhere by the use of the combined quinine and plasmoquine treatment for benign tertian infections, I am unable to agree, for the reason given, with the conclusions of the Commission that, as a practical measure, such a system of treatment is "of doubtful value". While the separation of the treatment of the attack from that of the relapse may be necessary in scientific investigations into various factors influencing the action of different drugs, I think that it is called for on very few occasions when one wishes to obtain a radical cure of the infection.

While I am prepared to admit that it *may* be proved, in the light of more advanced knowledge, that there are many and even serious fallacies in our work on the therapeutic effects of different drugs on Indian malaria, yet I am not prepared to admit that, on the

evidence put forward in the report, the Commission is justified in its sweeping condemnation of this work.

2. *The Dosage of Plasmoquine and Quinine in Combined Treatment.*

The Commission says that :

“ It may, in fact, be true that a mixture of a non-effective quantity of plasmoquine (or of bicarbonate of soda or of an arsenical preparation) with a therapeutic dose of quinine gives better results in preventing relapses than can be obtained with quinine alone, but at the moment the proposition can only be described as being paradoxical ” (page 227).

The statement would be clearer if the Commission had given some more lucid definition of what it means by “ non-effective ” doses of plasmoquine and “ therapeutic ” doses of quinine. Neither does the Commission, when it states, “ as regards quinine, it has been proved that large doses are not more effective than moderate ones ” (page 213), define these doses.

When the Commission discusses the use of plasmoquine in primary attacks of malaria, it deals almost entirely with doses of 0.06 and 0.1 gm. of this drug daily. This dosage was condemned by most workers some years before the Commission's report appeared. When mention is made of doses of 0.04 and 0.02 gm. daily, it is said that, “ in these small doses, it has little or no curative action on the asexual (fever-producing) stages of the malaria parasite, and for this reason its use in the acute stage of a primary attack is difficult to justify ” (page 220). Has the Commission scientific evidence that such small doses are ineffective in all strains of *P. vivax*, or is it again arguing from the particular to the general ?

One of the objections which has been raised to the use of plasmoquine is that it does not conform with “ the strict rule applicable to all chemo-therapeutic remedies that they should not be used *for general purposes* unless they comply with the requirement that the dose which killed the parasites must be very much smaller than the dose which the human host will tolerate without suffering any injury ” (page 253). This was one of the objections raised to plasmoquine when given in the larger doses mentioned above, and was quite a legitimate one ; but, since the dosage was reduced to what the Commission calls “ ineffective ” limits, the dangers from this

cause have been very much lessened, and probably abolished almost completely, if proper medical supervision and choice of cases is carried out. If one is to condemn this valuable drug, plasmoquine, because of a relatively small number of cases of serious results due often to improper individual dosage or improper supervision,¹ one should equally condemn many of the new arsenical preparations which are used in the treatment of syphilis and other diseases, because of the accidents which occasionally occur. Indeed, it seems to me that, probably in proportion to the number of doses of plasmoquine given, the serious results are much more numerous in the latter instance.

The statement is made that :

“ It has been shown definitely, for example, by comparative therapeutic tests under experimental conditions, that, in benign tertian malaria, no better effect can be detected when a dose of 2 grm. quinine (30 grains) is administered than when the dose is only 1.2 grm. (20 grains) ” (page 218).

I presume that 20 grains of quinine is what the Commission considers to be a therapeutic dose ; yet, in the work of SWELLEN-GREBEL and DE BUCK, and of CIUCA *et al.*, which it quotes as confirmatory of the uselessness of the quinine and plasmoquine treatment, the daily dosage was 15 grains or less. The “ treatment ” recommended by SINTON (1930) has a minimal daily dosage of 20 grains of quinine combined with plasmoquine for the radical cure of chronic relapsing infections of *P. vivax*, in India at least.

The question of the optimum dosage for a standard treatment designed to produce a *radical cure* of malarial infections is discussed by SINTON (1930, 1931). SINTON (1930) says :

“ These observations show that doses of 10 to 15 grains of quinine daily, when properly administered, will control the febrile manifestations of malarial infection in most, if not all,

¹ While it is very probable that plasmoquine in the small doses at present advocated can be used with complete safety under medical supervision, still there are three factors which may *possibly* be responsible for some of the toxic symptoms reported in the past : (i) the individual idiosyncrasy of the patient to the drug, (ii) the possibility of an increased toxicity when two of the synthetic drugs are given together, and (iii) the possibility that plasmoquine may undergo deterioration under certain conditions of storage. It is chiefly for these reasons that I think careful medical supervision is needed with the dosage advocated at present.

cases ; but many of these cases relapse as soon as such daily treatment is discontinued. Such a dosage is therefore below the therapeutic optimum (*i.e.*, for radical cure).

“ In some European countries, the maximum daily dosage of quinine recommended seems to be 20 grains, but it must be remembered that in these countries benign tertian is the predominant infection and such doses can be given with safety. In the tropics, however, where malignant tertian infections are much more common, most authorities recommend a daily dosage of at least 30 grains, on account of the dangers of the development of pernicious symptoms. Although in our investigations it was found that doses of less than 30 grains daily would have a considerable curative effect in at least as far as clinical manifestations are concerned, a daily dosage of 30 grains is considered to be the optimum, consistent with (radical) curative action and the avoidance of harm and excessive discomfort to the patient. This dose seems to be that most usually recommended for the treatment of acute attacks in the tropics irrespective of the kind of infection. In our work, the cure rate in malignant tertian malaria treated with quinine in doses of 20 grains daily was less than half that with 30 grains doses ”, given over an equal period.

The Commission itself notes the larger amounts of quinine needed to control primary attacks of the Rome strain of *P. falciparum* than the India ones. JAMES (1932*a*), whose work is quoted, says :

“ We were equally surprised to find in our third and fourth series (infected with Rome I and Sardinia strains) that full curative doses of quinine given intravenously and by the mouth at frequent intervals were required in order to control fever and to cause the parasites to disappear from the peripheral blood . . . We have indicated . . . how much more difficult it is to cure with quinine the primary attack of some infections with *P. falciparum* than it is to cure the primary attack of any infection of *P. vivax*. ”

It is clear from this that the “ clinically curative ” doses of quinine varies, not only with species of parasites, but also with strains of the same parasite. JAMES (1932*a*) points out that infections with his Indian strains of *P. falciparum* were much more easily cured

radically with quinine than were those with his Italian strains of this parasite. It is therefore evident that dosage has a relationship to radical cure, and that one cannot expect to obtain the same number of such cures with an ineffective dosage of the drug than with an effective one. It cannot be assumed that what is the minimum or the optimum dosage to produce a "clinical cure" is also the optimum for a "radical" one.

It is seen from the above discussion that the Commission has made statements about "large", "small", "therapeutic" and "ineffective" doses of drugs, without giving any exact idea as to what they mean by such generalisations, nor in most cases have they produced any evidence to support these *ex cathedra* statements.

The Commission, when it talks about the dosage of quinine, also fails to state either the salt of the drug or the form in which it was administered. These factors are of very considerable importance in relation to the amount of alkaloidal base absorbed into the body and therefore to that which is potentially active as a therapeutic agent (*vide* SINTON, 1930).

B. INVESTIGATION OF THE RADICAL CURE OF MALARIAL INFECTIONS.

The report contains such general statements as the following :

(i) "Neither treatment with quinine nor any of the new synthetic drugs, however intensive the treatment may be, is a *therapia magna sterilisans*" (page 213).

(ii) "For, although quinine and other specific remedies will cure temporarily each attack of malaria from which a person suffers, no drug, or combination of drugs, is yet available which will sterilise all the parasites in the human host and thus prevent the possibility of relapse. That quinine will not do so is universally admitted" (page 221).

(iii) "Clinicians should try to throw off the belief that by one or other form of 'intensive drug treatment' during the primary attack they can sterilise all the parasites in infected persons" (page 228).

(iv) "It being known that quinine does not prevent relapses" (pages 275-276).

Such dicta give one the impression that it is useless to attempt to produce a complete cure in any malarial infection by drug therapy alone. Such an impression is only very slightly modified by such statements as :

(v) " Its (quinine) curative effect is not always permanent, for the disease is liable to recur within a short period after cessation of treatment " (page 187).

(vi) "No drug or combination of drugs seems yet to be available which will sterilise all the parasites in the human host and thus prevent the possibility of relapse. Neither treatment with quinine alone nor with atebirin alone, nor treatment with either of these in combination with plasmoquine, however intensive or prolonged the treatment be, can be guaranteed to do this " (page 275).

I do not for a moment think that the Commission wishes to convey such an impression, but merely desires to emphasise the fact that we have as yet found no drug, or system of treatment, which can be guaranteed to produce a radical cure " in all cases ". But to the clinician who has no intimate knowledge of the recent work on malarial therapeutics which the report purports to place before him, such an apparent defeatist attitude is very discouraging.

I do not think it has ever been claimed that any of the treatments disparaged by the Commission were a *therapia magna sterilisans* for all types of malaria. All that is claimed appears to be that, with certain forms of treatment, a larger number of permanent cures can be obtained than with quinine alone. It is admitted in the report of the Commission that, in induced malaria, a short course of quinine therapy will, in many instances, cure permanently a considerable percentage of individuals infected with certain strains of parasite. Thus, JAMES (1932a) tells us that "quinine treatment of the primary attack brings about a permanent cure in less than 20% of cases of malignant tertian malaria as compared with 50% of cases of benign tertian disease ". Are we therefore to discard quinine, and, indeed, other anti-malarial drugs, in our efforts to produce permanent cures of the disease because we do not obtain 100% of such cures after the treatment of the primary attack ?

Many other workers have reported that, under their conditions of investigation, they have been able to obtain a much higher

percentage of permanent cures by certain therapeutic measures than they do with quinine alone. Does the Commission advocate that these measures should be stopped because the results do not agree with those obtained with only a few strains of parasites studied under artificial conditions ?

The Commission lays down that :

“ The percentage of relapses following any system of specific treatment (and even the percentage following no specific treatment) varies greatly in different countries, in different localities of the same country, and in different individuals ” (page 276).

“ On one of the problems, the prevention of relapses, it has only recently become known that *the results of all clinical tests conducted prior to 1931 were quite misleading*,¹ in that, from lack of knowledge of the natural course of benign tertian malaria,² the tests failed to take account of the most important type of relapse—namely, the type which occurs (after what appears to be complete clinical and parasitological recovery) about eight months after the primary attack ” (page 192).

Even if one agrees with this statement, in so far as benign tertian malaria is concerned, I am unable to understand how such a general statement can be applied to malarial “ relapses ” in other types of malarial infection, such as those of malignant tertian and quartan. JAMES (1932a) states specifically that “ there has been no example of this phenomenon (late relapses) among our twenty-three mosquito-infected cases of malignant tertian malaria ”. The report also bears out such a view (*vide* page 232).

The report states that, “ in hospitals where there is insufficient watchfulness and attention to the blood condition, the fatality rate due to this strain of benign tertian malaria is not less than between 10 to 14% ” (page 217).

¹ The italics are mine.

² The Commission states that “ the factors which influence the occurrence and frequency of relapses in malaria are so numerous and so little is known about them that it is believed to be beyond the wit of man to devise for this purpose a field test which will bear examination by modern statistical methods ” (page 269). If these factors are so unknown, I am unable to understand how one can lay down any precise or general statements about the “ natural course ” of any type of malarial infection.

This observation confirms the view that what is described as the "natural course" of benign tertian malaria may be different from that seen "in nature", where such a high case mortality is probably unknown among adults. This mortality indicates either that a strain of *P. vivax* more virulent than the average is being used, or that the condition of the patients is so abnormal that the course of the disease in them cannot be compared to infections in an otherwise normal population, or to both causes.

Apart from any question of variations in the "natural course" of infections produced by different strains of the name species of parasite, which is discussed elsewhere, it appears necessary to consider the above *ex cathedra* statements in relation to species infection only. In doing this I will deal mainly with the results obtained by myself and my collaborators in India, as these are those upon which I am most competent to speak, and which were obtained almost entirely before 1931.

Both I and my colleagues welcome legitimate criticism of our work, but we do not consider that such criticism should be based upon what would appear to be an incomplete study of both our results and our methods.

In attempting to defend the value of the experimental work carried out in India, on the effects of different forms of treatment in the production of radical cures of malarial infections, I have in many instances used the arguments upon which the Commission appears to base its deductions. This does not mean, however, that I am completely satisfied that the arguments put forward by it are in every case correct, nor that I interpret the observations reported in the same manner as the Commission does.

In considering the Indian work, it is necessary to divide it into that done in connection with malignant tertian infections and that done with benign tertian ones. In many cases the same arguments apply in both instances and have not, therefore, been repeated.

1. *The Relapse Rate in Malignant Tertian Malaria.*

The report mentions several factors which the Commission considers to introduce fallacies into the older records of investigations into the comparative value of different drugs in preventing relapses (*i.e.*, radical cure of infection) in malignant tertian infections.

(a) *Methods for the Determination of Radical Cure.*

The report lays down that " a period of observation of eight weeks no longer suffices to ascertain whether one form of treatment has more effect in reducing relapses than another " (page 269).

In discussing the validity of this period of observation in malignant tertian infections, various factors must be considered :

(i) The duration of observation *after the cessation* of all treatment, and

(ii) The criterion of " relapse " and the methods employed to determine it.

(i) *Duration of Observation after the Cessation of Treatment.*—
" It is not justifiable to compare the results of a course of treatment lasting forty days with the results of a course lasting seven days. But this is frequently done. The long course is really a method of ' clinical prophylaxis ' during the period covered by it, and, *unless the subsequent period of observation is much longer*¹ than the period of observation *following*¹ the short course, the results expressed ' as percentage of relapses ' are not comparable " (page 271).

I am unable to understand why a much longer period of observation is needed *after the cessation of treatment of any kind.*

In the cases of malignant tertian malaria studied in our work, the period of observation by blood examination *after the cessation* of all specific treatment was fixed at a minimum of eight weeks. As the cases observed by us had a duration of treatment of four to seven days only, they are comparable as being " short courses " (SINTON, 1926). Under these conditions, the objections raised above appear to be satisfied.

We are told that an observation period of eight weeks is no longer sufficient to ascertain whether one form of treatment is better than another in reducing the percentage of relapses, because of lack of knowledge of the " natural course " of benign tertian malaria. Let us consider this argument in relation to what *we are told*² is the natural course in malignant tertian malaria.

¹ The italics are mine.

² This description of the " natural course " of the disease appears to be based on the study of comparatively few strains of parasite, as is also the case with benign tertian malaria. While it may be correct, it does not appear to me that the evidence is sufficient upon which to make any general statement, in view of the probability that a very great multiplicity of strains of *P. falciparum* exists, and that infections with all these may not follow a similar course.

The report states that, " in malignant tertian malaria, the usual interval between recrudescences is about ten days . . . The duration of the disease as manifested by febrile attacks is seldom less than a month and seldom longer than six months " (page 232) (*vide* also JAMES, 1932*a*). By recrudescences are apparently meant febrile attacks. In our work, the patients were examined once weekly by the thick-film method of blood examination, and *in addition* whenever there was any evidence of febrile manifestations. This being so, I am unable to understand why such examinations would not detect at some time during a period of eight weeks the vast majority if not all, of the infections which had not been cured by the primary course of treatment, if " the usual interval between recrudescences is about ten days ".

The reasoning with regard to the " natural course " of malignant tertian malaria appears to be based mainly, if not entirely, upon the work of JAMES (1932*a*). Let us consider the findings of this worker in relation to the so-called " natural course " of this disease.

JAMES (1932*a*) states that " about 20% of patients who contract a malignant tertian infection for the first time continue to harbour parasites for a longer or shorter period after apparently complete clinical recovery ". The cases reported as " cures " in our work with malignant tertian malaria had all complete clinical recovery from the effects of their infection, so our results would only appear to vary by a maximum of 20%, which would have little effect on the validity of our findings. If it be argued that our cases were not first infections, and, therefore, such a rule is not applicable, I should have thought that, on the theory that the development of immunity helps permanent cure, most of our cases would have been more favourably situated as regards cure than primary infections, and that the good results of our treatment would be more easily understood.

" Clinically, as has just been said, malignant tertian malaria, in its general course, is an acute disease consisting of a severe primary attack followed by several less severe recrudescences occurring at relatively short intervals " (JAMES, 1932*a*).

If we consider the table given by JAMES (1932*a*) of the " period during which parasites were still found in thin-films after recovery from the last febrile recrudescence ", it is seen that in only three

out of the ten cases cited could parasites be found after eight weeks by the thin-film method. In addition, all the charts given by this author suggest that parasitic relapses can be detected, even by the thin-film method, within a period of one or two weeks after any course of treatment has ceased.

Apart from the fact that our patients were examined for at least eight weeks after the cessation of all treatment, the great majority of them were under clinical observation for a much longer period. These patients were mainly prisoners, and, as a routine measure, our enquiry carried out blood examinations of all individuals in the jail who reported sick with "fever". In this way we were able to detect any of our old patients who might have clinical attacks after the termination of the period of blood observation. The numbers thus found were very small, and were insufficient to affect to any marked extent the comparative validity of our figures.

Among our European patients, most of whom had infections with malignant tertian malaria for the first time, the period of clinical observation after the cessation of blood examinations was in many cases very prolonged (*vide* SINTON, 1926*a*). The results of this longer observation period did not appear to affect materially the validity of the general principles of the eight-week observation period in malignant tertian malaria, for which we have only claimed that it "will reveal most, if not all, the uncured infections of *P. falciparum*".

From the evidence available, it appears to me that the Commission has very insufficient and unsatisfactory data upon which to condemn the results of our experiments on the relapse rate in malignant tertian malaria. Indeed, it seems to me that what it has defined as the "natural course" of this fever is rather in favour of the validity and value of the eight-week observation period used in our work.

(ii) *The Criterion of Relapse and the Methods employed to determine it.*—In the report of the Commission, the criterion of "relapse" appears to be the occurrence of a febrile attack accompanied by the presence of detectable parasites in the peripheral blood. JAMES (1932*a*) admits that, under the conditions of his experiments, 20% of his cases of induced malignant tertian malaria continued "to harbour parasites for a longer or shorter period after apparently

complete clinical recovery". In our work, the detection of parasites in the peripheral blood was considered to constitute a "relapse" of the infection, for the purposes of our investigation, irrespective of the presence or absence of fever or other symptoms. While a state of "premunition" may control the presence of clinical manifestations over long periods, the presence of parasites in the peripheral blood is a sure indication that such infections are not yet radically cured. It is seen, therefore, that our criterion of "relapse" is a much stricter and truer one than that which appears to satisfy the Commission.

With regard to the detection of parasites in the blood, as far as I can gather from a study of the literature, and from what I have seen of the methods employed in induced malaria, workers in this sphere of research would appear to rely, in the majority of instances, mainly upon the obsolete method of the thin-film for detecting malarial parasites in the peripheral blood. It has been shown by many workers in the tropics that, if properly used, the thick-film method is much more reliable for this purpose than is the thin one.

It has been pointed out by SINTON and BANERJEA (1925) that, in the case of malignant tertian malaria, the thick-film method is probably about twenty times better than the thin one for routine diagnosis in malarial infections. This was the method employed by us, and it would seem, therefore, that our blood examinations were probably more searching than those used by many investigators in therapeutic malarial infections.

(b) *Factors in the Human Host influencing the Occurrence of Relapses.*

"It is no longer permissible to omit from consideration (of the effects of treatment on relapses) various factors relating to the human host" (pages 269-270).

"The reason (why the Commission has not included an enquiry into the effects of drugs in preventing relapses) is that it is exceeding difficult (if not impossible) in clinical trials conducted on natural cases of malaria to make satisfactory arrangements for ensuring that the results, as represented by the 'percentage of relapses', are really due to the remedies administered and not to some other circumstances which cannot be controlled" (page 269).

In the light of our present knowledge, some of the chief factors suggested as likely to influence the occurrence of relapses, in so far as the human host is concerned, are :

- (i) The degree of natural susceptibility possessed by the host ;
- (ii) The degree of immunity which he has acquired to the strain infecting him, and
- (iii) The conditions under which he lived during the period of observation, if he be not cured of his infection by the course of treatment being studied.

(i) *Susceptibility of the Human Host to Infection.*—It has been found that normal individuals can be classified into those who are “ very susceptible ”, those who are “ quite refractory ”, and those who are “ normally susceptible ” to the results of inoculation, by blood or mosquito-bite, with the same strain of *P. vivax*. JAMES (1932a), from his experience with *P. falciparum*, quotes several examples which he considers to support the view that a similar variation among individuals occurs to infection with this parasite also.

If one considers the Indian patients treated by us, their infections were only discovered originally because of the occurrence of febrile manifestations. This being so, it appears probable that the majority of them would not come under the heading “ quite refractory ”. In the case of our European patients, the infections were chronic relapsing ones, so it is also probable that here, again, the “ quite refractory ” and some of the “ normally susceptible ” individuals had been weeded out by previous courses of treatment.

If one compares our position with regard to the natural susceptibility of the patients with those used in induced malaria, we would appear to be in a more favourable position, in that we were probably dealing mainly with two classes of patients and not with three.

(ii) *The Degree of Acquired Immunity present.*—All our Indian patients had probably some degree of residual acquired immunity, present as the result of previous infection in childhood, adolescence or manhood. The majority of the infections treated were, however, probably reinfections, as they were discovered on account of febrile

attacks during the period of the year when the incidence of malignant tertian malaria was at its height. As the prisoners were drawn to Lahore from all parts of India, mainly the Punjab, there is no evidence to show that these reinfections were not due to heterologous local strains in many cases. It appears to me, perhaps wrongly, that, under these conditions, the "alternative case" method used in the large number of infections observed by us should give evidence of the comparative benefits of the different treatments tested.

With regard to the European patients, they all had chronic relapsing infections, and under these conditions any slight degree of variation in acquired immunity would probably be balanced by the "alternative case" method used in both investigations.

There is also no evidence to show that the differences in the degree of acquired immunity between individuals in our series were any greater than the natural tolerance variations recorded in non-immune populations, upon which the Commission places so much stress.

(iii) *The Conditions under which the Patient lives during the Period of Observation after Treatment.*—In speaking of clinical prophylaxis, the Commission states that :

"Often, alas ! he goes down with an attack when exposed to unusual climatic conditions or has to undertake heavy labour, long marches, or other fatiguing tasks" (page 231).

It also quotes the opinion of one member of the Reporting Committee (Professor NOCHT) :

"The interruption of quinine prophylaxis, climate—in particular, variations of temperature—defective nutrition, over-fatigue, etc., may cause this latent state to develop into acute infection" (page 248).

The mental patients, who have been studied in relation to relapse and the so-called "natural course" of malaria, were all leading sheltered lives, in many cases bed-ridden for months, and protected for long periods after the last febrile attack from the harmful factors mentioned as likely to produce an acute attack of the disease. On the other hand, the Indian patients observed by us returned to

their normal duties, in almost all cases, within about a week after the completion of treatment. They were also subject to the variations in climate which occur in Lahore between the hot æstivo-autumnal months and the colder weather of winter and spring.

After the cessation of treatment, the European cases returned to their duties as soldiers on guard, parade and fatigue duties as Kasauli. The majority of them played their games of football and hockey there, under the trying conditions of an altitude of 6,000 feet ; indeed, the team of " convalescents " on one occasion won the local football competition ! These patients were also exposed to the more extreme variations in climate which occur at this height.

Under these conditions, one would expect that, in a larger number of the patients, febrile relapses would have been induced inside eight weeks than among those leading sheltered and invalid lives in hospital, *if* there had not been a radical cure of most of the infections. Yet, under the latter conditions in uncured infections, we are given to understand that relapses occur on an average of every ten days.

(c) *Factors in the Parasite influencing the Occurrence of Relapses.*

" It is no longer permissible to omit from consideration various factors relating to . . . the parasite about which information has only recently become available " (pages 269 and 270).

The Commission has in several places pointed out that different strains of parasite react differently to therapeutic reagents. JAMES (1932a) states that his work " demonstrates plainly that the cases in the Rome and Sardinia groups (of malignant tertian infection) continued to relapse for a much longer time than those in the Indian group ", while, of sixteen cases in the latter group, the infection in none lasted more than eleven weeks. The Commission itself points out that " it has been found, for example, that, to control the primary attacks of malignant tertian malaria infected with a Rome strain of *P. falciparum*, it required eight times as much quinine as was required to control cases infected under precisely the same conditions with an Indian strain " (page 209), and also that certain strains of this parasite exist which react better to atebryn than to quinine (pages 216-217).

In condemning or depreciating the results recorded with the "quinine and alkali" treatment of malignant tertian malaria, the Commission appears to have overlooked its own statements—that different drugs may react differently on different strains, and to have allowed its judgment to be biased by the results of experiments with a few very virulent strains of *P. falciparum*.

In view of the great differences in the reaction of different strains to therapeutic agents, I cannot understand why the Commission is unable to accept the results of our Indian work. This is more especially so when they admit that "experimental studies of cases infected intentionally with a strain from the area to which those observers referred (*i.e.*, India) have shown that, on an average of the amounts of quinine used in twenty cases, only 3 grm. of quinine given by the mouth and spread over a few days were required to cure the primary attack and to prevent, in 25% of cases, any subsequent relapse" (page 216).

(d) *Statistical Considerations.*

"To obtain statistically significant results it is essential that the groups of patients treated with different drugs must contain an equal number of patients each possessing all the known and unknown factors which influence the course of the disease" (page 270).

The question of the known and unknown factors influencing the course of the disease have already been discussed. In the majority of our experiments with malignant tertian malaria, the numbers of patients observed were approximately equal, slight differences being due to uncontrollable factors, such as the transfer or release of a prisoner, etc.

"They are informed also that, if there are only 100 cases in each group, a small difference between the percentages of relapses in the two groups might easily arise by chance" (page 270).

In one series of experiments in which four different kinds of treatment were used by us, there were over 100 patients in each group. This is, I think, the largest *controlled* experiment of this

kind reported with malignant tertian malaria. Whether the results are statistically significant, or merely due to chance, I am not prepared to state, but the observed parasitic relapses in infections with *P. falciparum*, following upon the "quinine and alkali" treatment, were less than half those observed by any other method tried.

While the Commission emphasises the statistical importance of this equality in numbers and other factors, and the need for large numbers of observations, it does not seem to me that all the findings upon which they place so much reliance comply with these conditions.

(e) *Conclusions.*

I have discussed in some detail the points upon which the Commission appears to base its view that "the results of all clinical tests conducted prior to 1931 were quite misleading" with regard to the effects recorded in the prevention of relapse (*i.e.*, the radical cure of infections). It appears to me, perhaps wrongly, that, at least in the case of the malignant tertian infections studied by us, the evidence which they give adds considerable support to the validity of our results, as compared with those obtained in inoculation malaria.

Even if one admits that the method of observation is wrong, the mere fact that the treatment kept the patients free from clinical and parasitic relapses for a much longer period than did quinine or cinchona febrifuge alone establishes the value of the "quinine and alkali" treatment to the clinician, in the type of patient studied and under the conditions recorded. It is at such a diminution in the number of clinical relapses that the Commission appears to aim in their suggested lines of treatment.

2. *The Relapse Rate in Benign Tertian Malaria.*

We must consider in detail the dictum that :

"On one of the problems, the prevention of relapses, it has only recently become known that the results of all clinical tests conducted prior to 1931 were quite misleading, in that, for lack of knowledge of the natural course of benign tertian

malaria, the tests failed to take account of that important type of relapse which occurs (after what appears to be complete clinical and parasitological recovery) about eight months after the primary attack " (page 192).

(a) *Late Relapses in the " Natural Course " of Benign Tertian Malaria.*

We are told about " the natural course of relapsing cases of benign tertian malaria " that, " at a period which is usually seven to ten months after the primary disease, the liability to a return of fever and parasites is about twice as great as at any earlier period " (page 229).

This statement is apparently based upon the study of one or two strains of *P. vivax* only, and from this a generalisation has been evolved to cover the multitudinous strains of this parasite. The patients observed were leading an unnatural existence in many instances—sheltered lives, often bed-ridden for considerable periods, and protected for a long time after the last febrile attack from those harmful influences mentioned as likely to stimulate clinical relapses (page 231 ; page 248).

My experience, and probably that of many other workers, has been that, if patients suffering from chronic benign tertian malaria are merely put to bed, and given no specific treatment, any febrile manifestations present will disappear rapidly, in the great majority of cases. While such late relapses between the seventh and tenth months are, perhaps, a feature of infections with certain strains of *P. vivax*, yet one is tempted to ask whether such relapses may not coincide more closely, in many instances, with the time when the patient leaves his sheltered existence and takes up a more normal mode of life, with consequent re-exposure to those vicissitudes which are likely to cause relapse.

Even if we admit that such late relapses are a normal event, what evidence have we that the uncured infection which produces them would not have been detected by regular routine thick-film blood examinations made during the first eight weeks after the cessation of treatment? The patients we studied with chronic relapsing infection lead no such sheltered lives, and, as pointed out in speaking of malignant tertian infections, were exposed to

various conditions which should have been conducive to relapse, parasitic if not clinical, if there has been no radical cure of the infection.

SINTON and BIRD (1929) found that, among this type of chronic relapsing infection with *P. vivax*, about 65% of over 1,000 cases treated with different cinchona alkaloids showed at least parasitic, if not febrile, relapses inside eight weeks after the cessation of all specific treatment. Even if we assume that *none* of the infections we treated were cured radically, these results would appear to indicate that, under the conditions of our eight-week observation scheme, one would expect to detect at least 65% of uncured infections.

In so far as this method of observation affects the results of our quinine plus plasmoquine experiments, it has been pointed out in another part of this note that the periods of observation were in many cases much longer than eight weeks, and the latter period was regarded as a minimum.

Other factors in relation to the duration of observation have already been discussed in dealing with relapses of malignant tertian infections. Most of these are equally applicable to benign tertian ones.

With regard to relapsing cases, the Commission lays down that :

“ In a scientific system for the prevention of relapses, no attempt is made to give ‘ treatment for the prevention of relapses ’ during the primary attack. One waits until the first recrudescence and then uses the specific remedies in such a way that they assist, rather than hinder, the development of the patient’s natural defensive forces. By repeating this plan with the same watchfulness during the second recrudescence (using the specific drug at a later period and more sparingly than in the first recrudescence) and again, if necessary, during the third recrudescence, it happens, in most cases, that the patient becomes fortified or premunised against the disease to the extent that he not only ceases to suffer from relapses but fails to have an attack when he is reinfected ” (page 234).

In its discussion of “ Treatment to prevent Relapses ”, the Commission says :

“ It is known that quinine and atebirin are very effective in benign tertian malaria when parasites can be found without

difficulty in the peripheral circulation, and particularly so when the patient has already passed through one or more febrile paroxysms. Moreover, it is known that they are more effective in relapses than in the primary attack " (page 230).

From these and other observations in the report, the impression one gets, perhaps wrongly, is that chronic relapsing infections of benign tertian malaria should be, and are, more easily cured radically than primary attacks, because the specific effect of treatment will be reinforced by the natural and acquired defensive forces of the body of the host. Indeed, this appears to form a large part of the basis upon which the delayed relapse treatment advocated by the Commission for benign tertian infections is founded (pages 233-234).

That the natural or acquired "resistance" of the host may play a very important part in the production of a radical cure of a malarial infection is not disputed, but there are certain factors which must be considered in this connection.

If acquired immunity combined with quinine treatment was the whole story in our chronic relapsing cases, we should have expected to obtain at least an equal, and probably a higher, rate of radical cure than in primary infections (*vide* pages 233-234), for our cases had all had an average of about four febrile relapses before they were placed on special treatment by us. On the contrary, when quinine or other cinchona alkaloids were used, the observed parasitic relapse rate inside eight weeks was about 65%—*i.e.*, appreciably higher than the 50% mentioned by the Commission in primary infections receiving much less treatment (page 192), or than that reported by SINTON and BIRD (1929). Under these circumstances, it appears necessary to look for some other factors, either in the parasite or in the host, to account for this.

(b) *The Influence of Strains of Parasite upon the Occurrence of Relapses after Treatment.*

As was found by JAMES (1932) in the case of atebtrin and quinine in malignant tertian malaria, and as recorded by PIEBENGA and SWELLENGREBEL (page 227) in the case of plasmoquine and quinine, and by KORTWEG with neosalvarsan in the treatment of the Madagascar and Dutch strains of *P. vivax*, the permanent curative effects

of different drugs would appear to vary greatly with different strains of the same parasite. Under these conditions, it seems to me quite possible that, even although certain drugs have little action against the Madagascar strain of *P. vivax*, this is not a sufficient basis upon which to disparage the results obtained by other workers with different strains.

It would seem probable from these observations that some drugs are more active in producing a permanent cure with certain strains of parasite than with others. As all our cases had previously received many courses of quinine treatment, it is possible that patients infected with those strains which were specially susceptible to the permanent curative action of quinine had been eliminated previously. Such a view would be in keeping with the difficulty which was experienced after the war at Liverpool, Dagshai, etc., in curing with the cinchona alkaloids the chronic cases of benign tertian malaria which finally reached these centres after many courses of treatment in the areas of military operations.

There is no means of proving such a suggestion, and, as will be seen from the next section, the failure of quinine in such cases may have been due also to individual idiosyncrasies of the patients.

(c) *The Influence of the Natural Susceptibility of the Human Host on the Eradication of Malarial Infections.*

As previously mentioned, it has been found, and appears to be generally accepted, that normal individuals may be classified into those who are "very susceptible", those who are "quite refractory" and those who are "normally susceptible" to the results of infection with the same strain of *P. vivax*. The persons in the latter two classes appear to be able to eliminate the infection comparatively rapidly, either naturally or when assisted by quinine therapy. It is, therefore, possible that the type of chronic relapsing case studied by us may have consisted mainly of the "very susceptible" class.

Whether the chronic relapsing character of the infections studied by us were due to some defect in the degree of natural resistance of the host, or his power to develop such resistance, or whether it was due to a peculiarity of the strains of *P. vivax* with which the patients were infected is impossible to say.

The Commission states that, in investigations into the prevention of relapses, such as those carried out by us :

“ It is no longer permissible to omit from consideration various factors relating to the human host and to the parasite about which information has only recently become available ” (pages 269-270).

By these factors I presume it means those mentioned above—*i.e.*, the strain of parasite and the degree of natural or acquired tolerance in the patient.

It is admitted that, in induced malaria, one can make certain of the strain of parasite used, which is not the case in natural infections. With regard to the host, the question of a previously acquired immunity will always arise in patients who are, or have been, inhabitants of a malarious country, so in this respect experiments under these conditions should be no more satisfactory from the point of view of the Commission than natural ones.

In discussing the value of plasmoquine in the prevention of relapses the Commission says that, from the records of natural infections :

“ It is evident that neither plasmoquine alone nor plasmoquine *plus* quinine brings about sterilisation of the parasite in the human host. The same conclusion has to be drawn from the results of trials in induced malaria ” (page 223).

In support of this contention, the Commission quotes the work of CIUCA, BALLIF and VIERU, who were working in a malarious country—Roumania. *A priori*, the fact that the patients studied by these workers were inhabitants of a malarious country would lead one to believe that a greater or less proportion of them had previously suffered from the disease and had thus acquired some tolerance. That this is so is shown by the later report of these Roumanian workers (CIUCA, BALLIF and VIERU, 1933), in which it is stated, that, following blood inoculation experiments, (a) of 873 individuals inoculated with *P. vivax*, only 50% contracted the infection (fever *plus* parasites), 16% only showed parasites temporarily, and 33% resisted infection ; (b) with *P. malarix*, of 109 persons only 53% were positive after primary inoculation ; while (c) with *P. falciparum*, in 258 individuals, 85% became infected, 7% only showed parasites temporarily, and 8% resisted

one or more blood inoculations. As Professor CIUCA was for many years the Secretary of the Malaria Commission, I must assume that the Commission was familiar with these findings.

Yet the Commission states :

“ The reason that it is exceedingly difficult (if not impossible) in clinical trials conducted on natural cases of malaria to make satisfactory arrangements for ensuring that the results, as represented by the ‘ percentage of relapses ’, are really due to the remedies administered and not to some other circumstances which cannot be controlled ” (page 269).

It is also said that :

“ It is known that in untreated persons in nature the frequency, duration and severity of their relapses depend chiefly on the amount of defensive power which they have been able to acquire as a result of preceding attacks ” (page 228).

As the Commission emphasises the importance of the tolerance of the patient in evaluating the relative benefits of any form of treatment, I am unable to see how they can logically quote the Roumanian work in support of their contention as to the uselessness of plasmoguinine and quinine in preventing relapses.

If experiments are conducted with persons in a non-malarious country, the question of acquired immunity is eliminated, but one does not get away from the great variations in natural susceptibility which appear to occur in such individuals. Taking these facts into consideration, it seems to me that, if we are to believe the statistical information given (page 270), a very large number of cases will need to be observed before one can make any precise statement about either the natural course of infection or the effects of therapy upon any one strain of malarial parasite, and that it would be impossible to make any generalisations from such information, unless backed by similar statistically sound data about a very large variety of strains.

Let us consider to what degree the patients studied by us formed a homogeneous population, in so far as the virulence of the strain and the susceptibility of the human host were concerned. The pyrogenic threshold in a number of these cases was determined by SINTON, HARBHAGWAN and JASWANT SINGH (1931). The results

showed that there was a most extraordinary similarity between the number of parasites which produced pyrexia in these cases. Whether this was due to the strain or the host factor it would appear to prove that, in our population, there was a remarkable uniformity between the effects of the infection in the different individuals. This being so, it would seem to indicate that our population was in this respect a much more homogeneous one than could be expected from inoculation of a normal population, consisting of individuals of very varying degree of natural susceptibility.

(d) *Conclusions.*

The dictum that "the results of *all*¹ clinical tests conducted prior to 1931 were *quite*¹ misleading" has been discussed in relation to the prevention of relapses in chronic relapsing infections of benign tertian malaria.

From a consideration of the objections raised by the Commission in its report, it does not appear to me that such a sweeping statement is justified in the case of the infections studied at the Malaria Treatment Centre, Kasauli, before 1931.

There is considerable evidence to show :

(1) That the population treated at Kasauli was a much more homogeneous one than that used in most inoculation experiments with *P. vivax* ;

(2) That the patients were observed under much more natural conditions than in mental hospitals ;

(3) That, with the method of observation used, the occurrence of "late" relapses in the "natural course" of benign tertian malaria does not invalidate the results obtained to any marked degree ; and

(4) That the findings recorded have proved of much practical value to workers in India.

3. *Standard Treatments for the Radical Cure of Infections.*

"It has been shown, further, that, even as regards the use of quinine by the practising physician for the cure of malarial

¹ The italics are mine.

attacks, the time has passed when it can be considered satisfactory or sufficient to make a diagnosis of 'malaria' and to begin at once a 'standard quinine treatment'. Nor is it sufficient to know the species of parasite concerned and to prescribe the particular system of quinine treatment which, up to now, has been considered most appropriate for an infection of this type. What has to be done now is to endeavour to learn much more about the case than has been customary hitherto" (page 187).

"A 'standard form of treatment' can no longer be recommended, for it has been proved that, although such a scheme may suffice for curing most cases of malaria in the country where the routine was devised, it may be quite ineffective in another part of the world" (page 191).

If the Commission had used the term "universal standard treatment", which seems to be what is meant, such statements would have been more acceptable. Even in spite of its recognition that the problem may vary from country to country, the Commission has made very definite statements about the value of certain drugs and lines of treatment, which would not appear to be justifiable if it is to be consistent in its arguments.

The Commission lays down that :

"It has become all important to know what is, in general, the clinical virulence of the particular strain of the parasite with which the patient is infected, what is the usual course of the disease in treated and untreated infections with that strain, and what is the patient's status as regards tolerance or immunity to its clinical effects. For, to existing knowledge that some species of the malaria parasite are much more virulent to the human host than others has been added the information that there is a difference between the clinical virulence of different geographical races or strains of the same morphological species. This finding has an important bearing on treatment" (page 187).

"Again, it has been found in the Netherlands that various geographical races of *P. vivax* react differently to the same remedy. These and other results afford a reasonable explanation of contradictory observations on the therapeutic efficacy

of the same plan of treatment conducted in different countries and indicate the importance of *local* therapeutic investigation " (page 209).

" The percentages of relapses following any system of specific treatment (and even the percentage following no specific treatment) varies greatly in different countries, in different localities of the same country, and in different individuals " (page 276).

" The desirability of investigating separately the therapeutic effect of antimalarial remedies on each of the different species of parasite is everywhere recognised, and modern practice endeavours, as far as possible, to apply the results in practice " (page 208).

" In connection with this (the value of atebirin) and several other therapeutic questions, the Commission has drawn particular attention to the discovery that the therapeutics of malaria, like every other aspect of the disease, is much more a local or individual problem than has hitherto been thought, and has suggested that workers in different countries throughout the world should endeavour, as soon as possible, to ascertain by carefully controlled experiments what is the comparative susceptibility to quinine and atebirin of the particular strains of parasite locally prevalent " (page 275).

" Field workers and hospital physicians in all malarious parts of the world should endeavour as soon as possible to add to existing information on the clinical virulence and amenability to quinine of the particular strains of *P. falciparum* and of other species prevalent in the countries where they work" (page 209).

It would appear to me that the logical outcome of these recommendations of the Commission, if they are to be of practical apart from scientific value, would be the formulation of " local standard treatments " suitable to different areas or countries.

The work of the Malaria Treatment Centre, Kasauli, and of the Quinine and Malaria Enquiry of the Indian Research Fund Association, may be considered as attempts to determine the relative values of different drugs on the local Indian species and strains of parasite, although, when the work was commenced, the importance

of strains was not so evident. The local "standard treatment" suggested by SINTON (1930) was based on these findings. Although, from my interpretation of the text, this is what the Commission now advocated, yet because such treatments do not prove so effective against the few strains studied by certain members of the Commission they are to be considered as "of doubtful value". This does not appear to me to be a logical attitude, when one considers the stress which the Commission has placed upon the great variations in the therapeutic reactions of strains of parasites from different geographical areas, and the varied reactions of different individuals to treatment.

Apart from the use of certain forms of treatment for different specific infections, the Commission would seem to advocate that each individual case should be treated on its merits, having taken into consideration the virulence of the strain of parasite, the degree of immunity, whether individual or acquired, possessed by the host, and the stage of the disease. I agree that it would be a great help in formulating special treatments for individual patients *if* one could determine the factors suggested. Unfortunately, I am unaware of any methods by which this can be done either clinically or microscopically under natural conditions. It may be quite simple under the very specialised conditions of induced malaria, where a single strain of parasite is being passed through large numbers of non-immune patients, and where facilities are present which allow of continued and detailed clinical and laboratory observations under both treated and untreated conditions in individual patients.

In my opinion, there are very few places in the tropics or other malarious countries where it would be possible to carry out with any degree of scientific accuracy, in our present state of knowledge, the lines of investigation recommended by the Commission, because :

(i) One would have to assume that *all the strains* of one species of *Plasmodium* were identical in a given area, for there is no known method of differentiating these strains by their morphological characters. Such an assumption does not seem justifiable, if one would believe the work of BOYD and STRATMAN-THOMAS (1933), who report the presence of at least three immunologically heterologous strains of *P. vivax* within

a radius of 25 miles. The presence of such a multiplicity of strains in certain localities is supported by the findings of MULLIGAN and SINTON (1933, 1933a), who record seven strains of *P. Knowlesi* differing in their immunological reactions in the Malayan monkey *Silenus irus*. Such strains would appear to be capable of differentiation by cross-immunity experiments, a method which, apart from the other factors involved, would not be applicable in general practice, nor would such experiments in natural infections appear likely to give results which would further our knowledge of the practical treatment of malaria.

It may be, however, that all or most of the strains of a species of parasite in a given area have more or less the same reaction to individual therapeutic agents, but as yet we have no precise evidence to confirm this view. Indeed, in northern India we appear to have at least one strain of *P. vivax* which is susceptible to quinine therapy, and another which is more resistant to this drug but which is acted upon by plasmoquine plus quinine.

(ii) Attempts at the determination of the clinical characters of one strain in each naturally infected patient have many pitfalls:

(a) The patient may be infected with multiple strains of the same species of parasite, each producing different degrees or kinds of clinical manifestations.

(b) The patient may have acquired a considerable degree of immunity, as the result of infection with malaria; but it is, at present, impossible under natural conditions, or in the laboratory, to determine with any scientific accuracy whether the attack being studied is a relapse, a reinfection with a homologous strain, or a superinfection with a heterologous one. All these conditions may have different effects on the reaction of the host to the infection, and of the infection to therapeutic agents.¹

¹ In malarious countries, the only population which might be considered as unaffected by acquired immunity, with any degree of scientific accuracy, would be the infant one. Here, again, such a population would almost certainly have to be divided into those of different racial origin, if the question of "natural tolerance" were to be taken into account. I do not think the Commission would advocate that infected infants should be left untreated for the purposes of a scientific investigation.

(c) As pointed out by Colonel JAMES and other workers, individuals in a presumably non-infected community may vary considerably in their tolerance to the effects of the same strain parasite, some being hypersusceptible and others relatively immune. There is also considerable evidence to suggest that individuals of certain races possess a greater degree of natural tolerance, or power to develop such tolerance more rapidly, than do those of other races. Under these conditions, there may be great *apparent* differences in the virulence of the same strain, unless a sufficient number of persons infected with this strain can be studied, a method which is not possible in ordinary practice. Indeed, in any such attempts in a malarious country natural or acquired tolerance may be very important factors (*vide* the experiments of CIUCA *et al.* (1933) with induced malaria in Roumania).

(d) In view of the large number of undetected mixed infections which occur in very malarious parts of the tropics, I consider that, even if there were not the objections mentioned above, it is not a justifiable procedure to leave patients untreated, unless under *very strict* conditions of nursing, medical supervision and laboratory control, such as are available in very few places.

“ From the point of view of economy in the consumption of *quinine*,¹ the importance of prescribing a plan of treatment applicable to each parasite instead of a ‘ standard plan applicable to all ’ has become greater since the discovery of *P. ovale*. As a general rule, this parasite is so ‘ benign ’ that one or two doses of quinine suffice to cure the attack ” (page 208).

I presume this economy in the consumption of quinine is meant for the benefit of the millions of poor who suffer from malaria, and not merely a saving under experimental conditions.

In the tropics and in other poor countries where malaria is prevalent, it is impossible under present conditions to prescribe for the vast majority of patients a separate plan of treatment applicable to each species of parasite, apart from any question of treatment

¹ The italics are mine.

specially adapted to individual cases. A standard treatment for each type of infection might result in an economy of quinine, which I admit is an object to be aimed at. But is such an ideal practicable for even a very small minority of the malarious population of the world ?

I agree that, from the point of view of science and research work, one should aim at determining the best treatment from a purely therapeutic point of view, and then consider in how far such a form of treatment is applicable in practice. However, from the point of view of the administrations of malarious countries, the object to be aimed at is to give the greatest benefit to the greatest number of persons for the money available.

It appears to me that, if one is to employ the skilled personnel necessary to diagnose the type of infection, is to determine the individual peculiarities of the infection in the patient, and is to provide the hospital and laboratory facilities necessary for such study, the cost would be very much greater than any saving which would be obtained from giving a few extra doses of quinine to a patient who might be cured by a smaller amount of the drug.

Under these conditions, it seems to me that, for practical purposes, it is necessary to have some *local* form of standard treatment which will have the desired therapeutic action in the majority of cases, irrespective of the species of parasite. Such a treatment would enable the physician to give more individual attention to those patients who, for any reason, do not react favourably to routine measures.

It was upon such principles that the Indian " standard treatment " ¹ *for the production of radical cures* was based by SINTON (1930).

In this treatment, patients suffering from attacks, which are probably primary, are given quinine in those doses which it was considered necessary to cure radically within a week the majority of the strains of parasite which are susceptible to this action of the drug.

If the patient developed a relapse at a later date, he is given a treatment which contains larger, and relatively non-toxic, doses

¹ In the light of our present knowledge of strains, which has been gained mainly since this treatment was published, it would appear that this should be regarded as a " *local standard treatment* ".

of plasmoquine in combination with quinine. In this way it was hoped to cure radically most of those infections which had shown a tolerance to the permanent curative action of quinine alone, and which would probably be acted upon by therapeutic doses of plasmoquine, especially when it was combined with quinine.

Such a routine method of treatment appears to me to be both scientific and economical, under conditions where the very elaborate schemes advocated by the Commission cannot be put into force. From the scientific point of view, the treatment is very similar to the alternate use of different drugs which the Commission recommends for relapsing cases of malignant tertian malaria. From the economical standpoint, the cost of the more prolonged treatments advocated in the past is avoided, larger amounts of the expensive drug, plasmoquine, are needed only for those patients who relapse after the ordinary course of treatment (a great saving), and very much of the great expense of special hospital and laboratory facilities is avoided.

It appears to me, therefore, that, for the treatment of large numbers of patients under those conditions where radical cures of the infection are aimed at, some "standard treatment", suitable to the local circumstances, is an essential measure, if one is to obtain the greatest benefit of the greatest number of patients for the money available.

As is discussed in another section, it may not always be in the best interests of the population, or the individual, to attempt to obtain a *radical cure* of the infection in all cases.

C. GENERAL PRINCIPLES FOR THE TREATMENT OF MALARIAL INFECTIONS.

1. *Treatment of Primary Attacks.*

The Commission, "in selecting the best treatment" for an attack of malaria, says that :

"Quinine has no appreciable effect when given during the incubation period, and it has little effect when given on the first or even the second day of the 'initial fever'. It is much more effective after the patient has had several paroxysms

of fever than at an earlier stage, and its effect is greatest when fever and parasites are beginning to decline as a result of the natural defensive mechanism which normal human beings possess " (page 209).

This and other statements lead one to believe that the Commission advocates that the patient in his primary febrile attack should be left untreated for some days. This may be all right under the experimental conditions found in mental hospitals, where the greatest individual attention can be given to the natural development and course of the infection in each case. Such meticulous and searching study of each case is very seldom possible under ordinary hospital conditions in malarious countries, where very large numbers of patients have to be treated by physicians who have many other duties. Nor would it be possible for the ordinary practising physician in the tropics, and probably very seldom even in Europe. Even in induced-malarial practice, we are told that, " in hospitals where there is insufficient watchfulness and attention to the blood condition, the fatality due to this strain of benign tertian malaria is not less than between 10% and 14% " (page 217). If delayed treatment in benign tertian infections can cause such an excessive mortality, even among patients receiving ordinary care in hospital, how much more dangerous is such a plan of treatment likely to be in general practice ? In general practice one has at first usually no indication of the virulence of the infecting strain, nor can one determine with certainty that a mixed infection is not present.

This question has been discussed by SINTON and MULLIGAN (1933), who state :

" JAMES (1931) reports that the therapeutic action of quinine in benign tertian malaria is considerably enhanced if the patient be allowed to develop a certain degree of tolerance to the infection before treatment is commenced. He, however, remarks that it ' would be unjustifiable at present to withhold quinine from a case of malignant tertian malaria later than the first discovery of parasites in the blood '.

" It appears to us that, in view of the not uncommon occurrence of unsuspected mixed infections in malarial patients in the tropics, one is seldom or never justified in allowing any malarial

infection to remain untreated in the hope of obtaining this degree of acquired immunity. It was found by ANTIC (1925) that, in experimental mixed infections with *P. vivax* and *P. falciparum*, the former parasite could be detected at a very early stage of the infection, but that the latter quickly predominated. The more conspicuous morphology of *P. vivax* and its presence in the peripheral blood during the whole of its schizogony cycle make it much more easily detectable¹ than the small rings of *P. falciparum* which are usually present in the circulating blood for a much shorter period of each cycle. The latter parasite might, therefore, be overlooked during the first few paroxysms of an acute attack. The difficulty which is *sometimes* experienced in detecting *P. falciparum* in some early acute cases has been noted by many workers, even when there has been no mixed infection to obscure the issue. If the patient remains untreated, in the hope that the more benign parasite may produce some tolerance to aid the effect of treatment, the unsuspected infection with *P. falciparum* may quickly predominate. Daily blood examinations are usually impossible under the conditions of general practice in the tropics. If treatment be withheld on the assumption that the primary diagnosis of *P. vivax* is correct, the rapid development of *P. falciparum* may remain undetected until therapeutic measures are too late to save the life of the patient, or at least to avert a pernicious attack.

“ Many of the older physicians recognised the occurrence of spontaneous recovery in the intermittent fevers of the spring and winter, and TORTI recommended that these should often be left *viribus naturæ et imminenti naturæ*. In the case of the autumnal fevers, however, the necessity for immediate treatment with cinchona was emphasised.

“ While believing that some degree of acquired tolerance probably augments the action of quinine, we do not think that

¹ The difficulty of detecting small forms of *P. falciparum* in the peripheral blood is much enhanced by (a) the fact that many workers use the thin and not the thick film method of blood examination, and (b) that many workers who have not considerable experience of blood examination may confuse some rings of *P. falciparum* (*sens. lat.*) with those of *P. vivax* (e.g., the large rings of the “*tenue*” parasite, which is more common in eastern and southern India, as compared with the northern form of malignant tertian parasite).

patients can be left, as a routine measure, untreated so that such tolerance will develop. At least, it does not seem a wise procedure in areas where *P. falciparum* is common. The shortage of hospital accommodation and expert medical supervision in many tropical areas also precludes this method as a routine step, however desirable it may be under the more carefully controlled conditions of therapeutic malaria.

“ The work summarised by MULLIGAN and SINTON (1933) also suggests very strongly that any immunity, thus acquired, may only be effective against the same strain of parasite, and will have no very marked effect if the patient be reinfected with another strain. Now that several of the new synthetic drugs have been found to have a marked curative action in chronic infections with *P. vivax*, the necessity for leaving malarial patients untreated in this fever seems to have disappeared to a very large extent.”

However desirable such “ delayed treatments ” may be for the purposes of researches into the value of certain therapeutic agents, into the mechanism of the development of immunity, or into various problems connected with the therapeutic use of malarial infections, I do not consider that it is a measure which can justifiably be recommended for use in the majority of hospitals in the tropics, nor for the practising physician of any country, in our present state of knowledge.

2. *Treatment to prevent Relapses.*

“ An endeavour has been made [by the Commission] to indicate the principles by which, in the present state of knowledge, the physician should be guided in selecting a system for preventing relapses ” (page 233).

The main points given are as follows :

“ The frequency and severity of relapses are dependent chiefly on the amount of defensive power which the infected person possesses naturally or acquires as a result of previous attacks. A scientific method of preventing relapses should be based on this knowledge or should take this knowledge into

account by allowing an infected person to acquire as much defensive power as possible. Persons who are treated with large doses of quinine or other specific drug at the first onset of fever in their primary attack and in each relapse get no opportunity of acquiring defensive power to prevent relapses. Persons who are so treated usually relapse every month for a very long period. During the primary attack, it may not be safe to abstain for a day or two from giving a specific drug, but it is quite safe to do so in the first and any subsequent relapse.

“ In a scientific system for the prevention of relapses, no attempt is made to give ‘treatment for the prevention of relapses’ during the primary attack. One waits until the first recrudescence and then uses the specific remedies in such a way that they will assist, rather than hinder, the development of the patient’s natural defensive forces. By repeating this plan with the same watchfulness during the second recrudescence (using the specific drug at a later period and more sparingly than in the first recrudescence), and again, if necessary, during the third recrudescence, it happens, in most cases, that the patient becomes fortified or premunised against the disease to the extent that he not only ceases to suffer from relapses but fails to have an attack when he is ‘reinfected’. In the Commission’s view, an endeavour to follow that plan should be made for the prevention of relapses of benign tertian and quartan fever. But they consider that, for preventing relapses of malignant tertian fever, it is justifiable to endeavour to sterilise all the parasites by specific drug therapy during the first recrudescence . . . The Commission believes that, when it is not considered justifiable or practicable to prescribe a system for the prevention of relapses which is based on the above principles, the best practice is to adopt a system of ‘clinical prophylaxis’ consisting of the administration of a small dose of quinine (0.4 grm.) daily throughout the period of residence in the malarious country and for several months after leaving ” (pages 233-234).

There are several points which require discussion in this statement of the scientific principles advocated by the Commission for the

prevention of relapses, if one is to apply these to the treatment of malaria outside mental hospitals, or similar institutions, where expert facilities and time are available for the work.

(a) *The Value of Acquired Immunity in the Prevention of Relapses.*

That some degree of acquired immunity is of great importance in the control of the clinical manifestations of a malarial attack is probably not disputed by most workers. Such an acquired immunity also assists materially in the radical cure of the disease, especially when augmented by the effects of appropriate specific therapy. In certain infections, however, even in the presence of opportunity for developing a high degree of acquired tolerance, and of specific therapy of a certain nature, relapses may continue to occur over long periods, and radical cure of the disease may be delayed for months, if not years. In many such cases, it seems to me that, in so far as a radical cure of the infection is concerned, the failure is not due so much to a low degree of immunity as to a special resistance of the parasite to the destructive action of the specific drug used. Under these conditions, it would appear to be the obvious thing, if one aims at a radical cure, to change the specific drug rather than allow the patient to continue relapsing for months in the hope of obtaining a higher degree of resistance, and so a "tolerance", which may be broken down at any time by adverse conditions.

We are told that by this procedure "the patient becomes fortified or premunised against the disease to the extent that he not only ceases to suffer from relapses but *fails to have an attack when he is reinfected*"¹ (page 234).

It is now generally recognised that, in human, simian and avian malaria, an immunity such as has been described to one strain of a species of *Plasmodium*, may have little or no effect in preventing acute attacks when the host is reinfected by either heterologous strains or species of parasite. If the patient be living under natural conditions in a malarious country, the elaborate procedure which the Commission has evolved to premunise him will only have a marked effect, in the majority of instances, if he is reinfected with the same

¹ The italics are mine.

strain of *Plasmodium*. As will be discussed later, such a procedure may be very suitable under certain conditions, but it is not what the average patient, for whom the Commission appears to cater¹ and who resides in the tropics for only a relatively short period of his life, asks for. If this procedure is to be effective in his case, he would have to acquire an immunity to *all* the local strains of parasite, a process which would probably take him some years, during which he would be in a continual state of ill-health. It also appears probable that such premunition might also fail when the patient is subjected to adverse conditions, to a large dose of sporozoites, or to infection with new strains if he moves to another locality.

I do not think, therefore, that such an attempt to develop premunition is to be advised for patients whose period of residence in malarious countries is short, or who are living under conditions in which the chances of reinfection can be avoided to a large extent.

(b) *Delayed Treatment during the Recrudescence or Relapse.*

Upon the occurrence of a recrudescence or a relapse of a primary infection, the Commission considers that there is little danger to the patient's life. It is suggested, therefore, that the patient should be allowed to have several febrile paroxysms, and that the amount and duration of specific treatment should be small, so that the natural process of premunition may not be interfered with.

As has been pointed out elsewhere in this note, it is agreed that a very considerable percentage of malarial infections are radically cured by the treatment given in the primary attack. In induced malaria, the reappearance of fever and parasites is, of course, a recrudescence or relapse. It is not always so, however, under natural conditions in malarious countries. In very malarious localities, a patient who returns with a malarial attack some time after the termination of treatment for the primary attack is not necessarily a relapse. It may be that the primary treatment has cured his infection, and that what he now suffers from is a reinfection or a superinfection with a heterologous strain or species of parasite. Such an infection may give quite as severe clinical manifestations

¹ That is from the point of view of "persons who are in a position to obtain expert medical advice and efficient care rather than from that of the mass of the population of malarious countries" (page 277).

as, or even more severe ones than, the primary infection which was originally treated. If such a case be treated by the method which is recommended by the Commission as suitable for a recrudescence or a relapse of a primary infection, the small dosage and the delayed administration of the specific drug may allow of such serious developments in the infection that it may be too late to save the patient's life when proper treatment is instituted.

Apart from the greater severity of attacks of malignant tertian malaria, the report states that, "in hospitals where there is insufficient watchfulness and attention to the blood condition, the fatality rate due to this strain (the Madagascar) of benign tertian malaria is not less than 10% to 14%". Surely when a mortality like this may occur in infections with the "*benign*" parasite treated in hospital, one is not justified in recommending delayed treatment in general practice, nor, indeed, except under *very special* conditions of hospitalisation.

(c) *A Separate Treatment for Acute Attacks and for Relapses.*

The Commission gives its opinion that :

"It is seldom or never in the best interests of patients to endeavour to combine a plan of treatment designed for the prevention of relapses with a plan having for its object the rapid clinical cure of an acute attack" (page 214).

"The two problems (cure of primary attack and prevention of relapses) are so entirely different that, in the opinion of the Commission, it is incorrect to endeavour to accomplish them both at the same time" (page 215).

Such a dissociation of the two treatments may be practicable and advisable under the conditions of therapeutic malaria, or where there is an adequate staff of expert medical, laboratory and nursing personnel to carry it out. Such conditions are, unfortunately, very seldom available in the tropics, or in most malarious countries, nor could such countries provide the hospital accommodation which would be necessary for the observation of patients over the long periods required by such separate treatments.

As the Commission apparently recognises, or countenances, the use of two drugs only (atebrin and quinine) in the treatment of

malarial attacks (page 274), such an opinion appears an obvious outcome of this. As the clinical effects of these two drugs are apparently very similar, there does not seem to be much advantage to be gained by administering them at the same time to produce a greater effect in the production of a radical cure. Many workers, however, consider that, in the prevention of relapses, plasmoquine is also an anti-malarial drug of the greatest importance in benign tertian malaria. The reasons for this opinion have been discussed elsewhere in this note, and for these reasons alone I consider that it is not incompatible to combine the latter drug with quinine, so that the treatment for an attack and for the radical cure of an infection should run concurrently.

The difference between the treatments advocated by the Commission for benign tertian and malignant tertian infections appears to depend upon these factors. It seems probable that some strains of malignant tertian parasites are more easily eradicated by the therapeutic agents advocated by the Commission (quinine and atabrin) than are some strains of benign tertian by the same agents. The dosage of these drugs needed to produce a clinical cure of the acute attack of malignant tertian malaria is usually greater than that needed for benign tertian infections. Under these conditions, without the administration of excessive doses of the drugs, the chances of obtaining a radical cure in the latter (and what some people believe to be the more easily cured) infection are greater. I think it is probable that, if the Commission had been convinced of the value of plasmoquine in the treatment of certain benign tertian infections, it would not have made any essential differences between the principles of the systems of treatment advocated for these two kinds of malarial infection.

(d) *Clinical Prophylaxis.*

“ Clinical prophylaxis is correctly defined as being a procedure for curing slight clinical attacks of malarial fevers—it is a curative, not a prophylactic measure ” (page 204).

“ The Commission is of opinion that quinine is effective for this purpose and that it is the best drug to use. The correct plan is to take a daily dose of 0.4 grm. (6 grains) ” (page 274).

I am in complete agreement that beneficial results, with regard to morbidity and mortality, may be obtained in malarious areas by the plan advocated. However, I do not consider that such a plan can be carried out on any large scale, except under very special circumstances, among the undisciplined and uncontrolled populations who form the bulk of the malarious people of the world. Apart from the trouble of inducing an uneducated population to take such a drug in the absence of clinical symptoms, the expense of the drug and the cost of distribution would be so prohibitive that the scheme appears to me to be an ideal which few Governments can hope to aspire to under the present financial conditions.

In Army practice, I have had very good results in lowering the malarial morbidity and inefficiency among troops by this measure, but I am unable to understand how the Commission can reconcile such a continuous use of quinine with its theories of the action of quinine, and its desire to avoid a waste of this drug.

We are told that :

Quinine has little or no action *until a febrile attack is imminent or has already occurred* . . . Quinine exhibits precisely the same lack of therapeutic action when it is given during the fever-free and parasite-free period just before the onset of the type of relapse known in England as a 'recurrence' (the type in benign tertian malaria which occurs usually about eight months after infection) " (page 203).

These statements appear to be based mainly upon the study of benign tertian infections only, and that of one or two strains of this parasite, in so far as I can judge from the data given by the Commission. No evidence appears to be produced that such is the case in infections with other species of *Plasmodium*. The Commission seems to have forgotten, as in many other instances where such general statements are made, that *P. vivax* is not the only species of human malaria parasite, and that different strains of even the same species of parasite may not react in a similar manner to the same drug.

Again, it is stated that " quinine has no appreciable effect when given during the incubation period, and it has little effect when given on the first or even the second day of the initial fever " (page 209) ; and that, when the primary attack has been cured by a short course

of treatment, "no advantage whatever is derived from continuing to give the specific drug during that fever-free and parasite-free period" (page 213).

If such be the case in infections of all kinds, the administration of quinine daily seems to be paradoxical from a scientific point of view, and suggests that the observations quoted on the effects of quinine may only apply to special strains of *P. vivax*.

If we admit these statements of the Commission, it seems to me that such clinical prophylaxis must be a deplorable waste of an expensive drug like quinine, economy in the use of which is advocated. If, however, one would follow out the *theoretical* argument to its logical conclusion, it seems to me that the rational form of clinical prophylaxis to be recommended would be to give every person in a malarious area a supply of quinine which he would take when he felt fever to be imminent—*i.e.*, to catch the infection at the time when the Commission states that this drug has its greatest effect. It is, however, such an irregular use of "prophylactic quinine" which many workers in blackwater fever areas condemn.

One of the reasons given by the Commission for its advocacy of this method of clinical prophylaxis is that "it does not entirely eradicate the infection, the defensive mechanism of the body is continuously at work and becomes increasingly powerful as time goes on ('acclimatisation without risk')" (page 235). If, as one is led to believe, the defensive mechanism of the body is stimulated by the parasites, one would argue that a much more powerful stimulus would be given if they were destroyed only when they were sufficiently numerous to produce fever (*i.e.*, when fever is imminent) rather than being continually kept at a very low level. It may be, however, that the Commission believes that quinine *per se*, in the doses advocated, increases the defensive action of the body, but we have no conclusive evidence that it does so. Again, the Commission may believe that parasites killed by quinine are a much more active stimulus to defence than those which are destroyed by the natural body mechanism. If the latter be so, it would seem rational to stimulate this action as early as possible by giving quinine when parasites are found, irrespective of whether the clinical condition of the patient indicates such treatment as a necessity or not. The Commission, however, appears to recommend that, *as far as possible*, such acute attacks should be left untreated.

If the benefits of clinical prophylaxis after a single infection are thought to depend mainly upon an increased defensive action of the body, its benefits would, theoretically, be applicable to one strain of one species of parasite only, for the defensive action against a single strain should have little or no effect upon superinfection with a heterologous strain of species *Plasmodium*. According to the statements of the Commission, clinical prophylaxis should have no action in the prevention of superinfections, because it says that "quinine, even in curative doses, has no true causal prophylactic action" (page 197).

If, however, as would appear to be indicated, one of the advantages claimed for this method is that "it enables troops and agricultural and other workers to carry out their daily task" (page 235), I am unable to reconcile this with the statements of the Commission. The latter tells us that quinine has :

- (a) No true "causal prophylactic" effect ;
- (b) No appreciable effect during the incubation period, and has little effect when given on the first and even the second day of the initial fever ;
- (c) Little or no action until the febrile attack is imminent or has already occurred ; and
- (d) Has the same lack of therapeutic action when given during the fever-free and parasite-free period just before relapse.

As I presume the object of "clinical prophylaxis" is to prevent the occurrence of clinical attacks of the disease, I do not understand how it can do so *if* we are to accept the statements of the Commission. The theories mentioned suggest that its effects will only come into action when an attack has already developed, and has possibly been in progress for some time.

If such populations or single individuals are not liable to reinfection and superinfection (either because of their local environment or because of protective measures against infection), in my opinion, *if* one accepts the statements of the Commission, the obvious course would not be to give clinical prophylaxis, but to attempt to cure radically each infection as it is discovered. This would probably be a much less expensive measure than daily clinical prophylaxis carried out over long periods, with a great chance that a relapse will occur when it is discontinued.

Although I am unable to reconcile with its advocacy of " clinical prophylaxis " the dogmatic statements of the Commission upon the action of quinine upon certain stages of the malarial infection, yet I am in complete agreement with the Commission that this measure may be of the greatest practical value under those conditions where it can be properly carried out.

IV. CONCLUSIONS AS TO THE GENERAL PRINCIPLES OF THE THERAPEUTICS OF MALARIA, BASED ON A STUDY OF THE REPORT AND OF THE WORK IN INDIA.

The Commission, in its report, has dealt with modern therapeutics of malaria from " the point of view of persons who are in a position to obtain medical advice and efficient care rather than from that of the mass of the population of malarious countries " (page 277). Unfortunately, the vast majority of our millions of malarious sick in India are not in a position to obtain such advice and care, and it is probable that the same holds good for many other malarious countries.

Although in writing this article I have been asked to indicate *those points upon which I disagree* with the findings of the Commission, yet I would like to point out that the report is a mine of valuable information to the worker who is familiar with modern studies on the therapeutics of this disease. The investigations which have been carried out by workers under the auspices of the Malaria Commission have shed much new light upon the problems of immunity and therapy in malaria. In the light of this information and our Indian experiences, I would like to suggest what I consider, *in our present state of knowledge*, to be the principles upon which malarial therapy should be applied by the clinician and field worker, as distinct from the research or laboratory worker. It is the last for whom the Commission's report appears to cater mainly.

For the application of such therapy, infected populations may be divided into two main groups, in which, as judged in the light of our present knowledge, the object of treatment is distinctly different. These groups are :

- (a) Those individuals in whom the risk of reinfection is relatively slight or absent, because of environmental factors, or of anti-malarial measures of various kinds ; and

(b) Individuals who are liable to reinfection or superinfection within a very short time after the termination of treatment.

1. AMONG INDIVIDUALS LITTLE LIABLE TO REINFECTION.

In individuals situated under these conditions, one should aim at the production of a radical cure of the infection at the earliest opportunity, and by such methods as have been discussed above, or by such new methods as may be considered suitable.

If such persons are not liable to reinfection at frequent intervals, there appears to be no object in allowing them to acquire, by prolonged latent infection, an immunity which would be of value only against the infecting strain. The chances are that they may be infected on the next occasion by a heterologous strain or species, against the clinical effects of which their hard-won immunity may have little protective power. Under such conditions, the patient will have suffered, to little advantage, the long series of relapses and recrudescences advocated by the Commission.

In the production of radical cures in such individuals, I consider that, wherever possible, the treatment for clinical cure and that for radical cure should be combined. In this way the period of morbidity and inefficiency would be cut down as much as possible—very important points economically and from the patient's standpoint.

As the meticulous individual attention recommended by the Commission is very seldom possible in practice, the greatest benefit for the greatest number of persons will probably be obtained by some form of "local standard treatment". Where satisfactory treatments of this nature do not already exist, they will need to be devised to suit local conditions, after careful study. While such "local standard treatments" will probably be found efficacious in the majority of cases, the therapy of certain patients will require more detailed attention; but, by the exclusion of the patients who have reacted, the clinician will be able to devote more time to the cure and treatment of these refractory ones.

In our present state of knowledge, it seems to me that, both from the point of view of economy and because of their marked action on malarial infections, quinine or some of the other cinchona alkaloids should form the basis of all such "standard treatments". The newer drugs have in some cases advantages which the cinchona

alkaloids do not possess, but they have also disadvantages not shared by those alkaloids. In my opinion, such new drugs can only be considered as adjuvants to the action of the cinchona alkaloids, more especially because of their relatively high cost, which places them beyond the reach of the majority of patients.

Under these conditions, *where possible*, the "adjuvant" action of these and other drugs should be taken advantage of in treatments which aim at a rapid clinical cure. Certain drugs can with advantage be used in combination with the cinchona alkaloids, while others may be substituted for them in those infections which for any reason have proved refractory to the radically curative effects of quinine, alone or in combination with certain adjuvants.

2. AMONG INDIVIDUALS LIABLE TO CONSTANT AND FREQUENT REINFECTION.

There is much evidence to support the view that, when, by natural or therapeutic means, an individual is radically cured of an infection with one strain of parasite, irrespective of its species, he rapidly loses most of any acquired immunity or premunition which he has developed to this strain as the result of his infection. The evidence available suggests very strongly that, to maintain any high degree of such "tolerance" to the clinical effects of infection, it is necessary that the individual should continue to harbour the parasites of this strain—*i.e.*, that his defensive mechanism should be continually stimulated either by the parasites of a latent infection of the strain or by continued reinoculation with the same strain.

If these facts be correct, and they appear to be so, it would seem that the production of a radical cure under conditions where reinfections are frequent is contra-indicated. Such cures of the infection would, theoretically at least, leave the patient more liable to severe clinical attacks, if the intervals between the reinfections *with the same strain* of parasite were greater than the duration of his immunity after radical cure.

An almost identical suggestion is also put forward by the Commission in its report :

- (i) " A therapeutic policy designed to reduce the severity and fatality of the disease rather than to eliminate the parasites radically and completely is one that, in existing circumstances

in some severely affected countries, can be justified on scientific grounds. It is known, for example, that, in some localities in Africa and other tropical countries, the entire native population above one year of age harbour malaria parasites in their blood continuously, although no one above a few years of age suffers any appreciable illness attributable to the parasitic infestation. The latter result is due—as has been proved by laboratory investigations made in connection with the practice of malaria-therapy—to the fact that many persons who are repeatedly infected and reinfected with malaria quickly become immune to the clinical effects of the infecting organisms, although the parasites themselves survive and continue their life cycle in the human host. This condition of acquired immunity resulting in freedom from malarial disease after childhood is advantageous to the populations concerned, and radical interference with the process by which it comes about might be most unwise ” (page 189).

(ii) “ It might be most unwise *in some malarious countries . . .* to interfere too radically with the natural process by which the indigenous inhabitants acquire immunity to the disease ” (page 278).

The evidence available suggests, therefore, that, in certain communities liable to constant reinfection, it would be inadvisable, or even harmful, to attempt to produce a *radical* cure of any infections detected. During the process of development of the tolerance which protects the individual from clinical manifestations, he has probably gone through many acute attacks as he became infected and superinfected with the different local strains and species of *Plasmodium*. In this prolonged process, it is probable that, in the absence of treatment, many of the sufferers succumb to these infections before they attain the necessary degree of tolerance. In such populations the object to be aimed at would appear to be to provide treatment for those clinical attacks of the disease which cause so much morbidity, mortality and labour inefficiency, and not to attempt treatments which aim at radical cures of the infection.

In so far as Indian conditions are concerned, SINTON (1935) says :

“ Most of the uncontrolled rural population of India have (a) no wish to continue treatment after the fever and clinical manifestations of malaria have disappeared and (b) have

not the financial means to pay for the cost of a treatment which might produce a permanent cure of the infection that is troubling them at the time. Even if they could be cured, the chances of reinfection at a comparatively early date are great in many places. Under such conditions of liability to reinfection, the attempt to produce a permanent cure seems futile and, indeed, may have unfortunate effects. As pointed out in our monkey experiments and as noted in malarial investigations in Europe, the patient who survives an attack may develop an immunity to the strain of parasite which infects him, and this immunity may act as a considerable protection against another infection with the same strain. Such latent infections under ordinary conditions do not produce very severe clinical effects, and such as are produced are usually easily controlled by a little treatment. As we have not solved the problem of the prevention of reinfection among the rural population—*i.e.*, the destruction of the infected insect host—or means for preventing the transmission of the disease by it, attempts to produce a permanent cure of the infection appear to be a waste of money in most cases.

“ Under these conditions, in my opinion and in our present state of knowledge, the objects to be aimed at are (a) to make available suitable treatment which every sufferer can obtain, either free or within his financial means, and (b) to ensure that such treatment can be obtained by the patient with ease in whatever place he may be. The result of such provision would be that a sufferer from a malarial attack would have treatment available, and thus (i) diminish the risk of a fatal result, (ii) diminish the intensity and duration of the attack, and (iii) curtail the period of physical disability. ”

Such a system of clinical cure among populations liable to reinfection should not interfere radically with the development of their “ tolerance ” to the clinical manifestations with infections of the local strains, nor in the presence of continual reinfection should it interfere seriously with any immunity already acquired.

This would seem to me to be in line with the aim of the Commission to

“ replace present schemes of ‘ mass treatment ’ by a rational scheme designed to stop malaria from being fatal and to

mitigate its severity without at the same time interfering unduly with the process of acquiring immunity which is so advantageous to the populations concerned when their childhood is passed " (page 279).

Because the majority of rural populations are comparatively stationary, as they advance in age they should gradually acquire, through a process of infection, reinfection and superinfection, a " tolerance " to the clinical manifestations of infection with the local strains under most circumstances. Such a tolerance might be broken down temporarily by certain factors especially affecting the individual. Apart from individual failure of tolerance, we may also have such a failure on a larger scale in a community. Such a failure may occur as the result of an excessive dose of infection, or from infection with foreign strains or species of parasites. The latter condition is usually most evident under conditions of emigration to a new area, or where " tropical aggregation of labour " occurs (*vide* SINTON, 1932).

This power of developing tolerance appears to be present to a different degree in different races. As has been proved by experiments with induced malaria, the degree of individual susceptibility to the clinical effects of malarial infection in previously uninfected persons may vary very considerably. It would also appear from field observations in various parts of the world that certain races may possess a considerable degree of so-called " natural immunity " to malarial disease as compared with other races. It is possible that, through very many centuries of exposure to intensive, untreated malaria, persons with a greater susceptibility to the disease would be more liable to death in childhood, and would be weeded out. So the race would be continued by survivors (the adults) having a more marked degree of tolerance or power to develop such tolerance rapidly. Such a trait might possibly be transmitted as a dominant Mendelian character, and so, after ages of residence in a highly malarious country, a race was evolved in whom the majority of the individuals possessed this character of diminished susceptibility or increased power to develop tolerance to the disease, at least in so far as the local strains and species of parasite are concerned.

The difference between the " naturally tolerant " and the " susceptible " populations would appear to be mainly one of degree,

in so far as the principles of treatment are concerned. In the former case the individual probably acquires more rapidly and more strongly a "tolerance" to the local strains or species of parasites than does the latter. Under the same conditions in a "susceptible" population, the clinical attacks of the disease would be severer, the amount of morbidity and mortality would be greater, and the time taken to acquire immunity would be longer, than in a "naturally tolerant" population. The former population would probably need much more frequent treatment and a larger dosage of specific drugs to cure their symptoms. Such a system of treatment would probably be necessary until the patient reached a greater age than in the case of the "immune" population.

3. CLINICAL PROPHYLAXIS.

This has already been discussed. Such a system of treatment appears to me to be recommended chiefly when large bodies of people are sent into areas in which they have little or no immunity against the local strains of parasite, and it is desired that as few persons as possible will develop clinical manifestations of malaria during their stay in the area. The good effects of this method would appear to depend upon the fact that the number of parasites in the patient's body, as the result of infection and reinfection, are kept below pyrogenic limits by continual small doses of quinine. It is really an early "clinical curative" treatment.

This method may help the individual to develop a considerable degree of immunity to reinfection or superinfection with local strains or species of parasite. The cost of such a daily dosage of the specific drug is too great to enable such a method to be employed except under very special conditions.

4. SUMMARY OF THE SUGGESTED PRINCIPLES OF MALARIAL TREATMENT.

(i) In populations of individuals in whom the chances of reinfection are comparatively slight, the treatment adopted should aim at a radical cure of the infection.

(ii) In populations liable to constant infection and reinfection with multiple strains and species of parasite, such a radical cure should not be attempted, but the treatment should aim at the production of a rapid clinical cure of attacks of the disease.

(iii) Under special conditions, where it is advisable to reduce the malarial morbidity and inefficiency in any population to the lowest limits for a relatively short period, clinical prophylaxis should be employed, if financially sound.

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SCHOOL MEDICAL INSPECTION IN THE UNITED STATES OF AMERICA

by

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INTRODUCTION.

“We have many doubts whether our common schools will ever become what they ought to be as places for the promotion of health, as well as of knowledge and piety, until they are brought under the care—more or less—of judicious medical men, and until the latter make it their constant duty to watch over their physical education and management. Until the teachers of these schools can be trained to a thorough and practical knowledge of the science of human life and health, there will be a thousand things of frequent, if not daily, recurrence in every school which will require medical attention. Or, to say the least, there will be daily or hourly recurring cases which will raise these enquiries in the minds of the honest, faithful, enquiring teachers who have had their minds turned to the subject of health, and a desire implanted in their bosoms to obey its laws, which they will remember or note down, and be glad to present to the medical man at his semi-weekly, weekly or monthly visits. For, say what we will of the novelty of such a plan or proposal, our schools ought to have their regular physicians, as much as our houses of industry, our almshouses or our penitentiaries.”¹

¹ ALCOTT, W. A., “Health in Common Schools”; Boston, 1840.

So wrote Dr. William A. ALCOTT, of Boston, in 1840 ; but it was not until half a century later (in 1894) that this city became the pioneer in methodical medical inspection of schools in this country. In doing so, however, it followed an example which had been set abroad for many years.

Doubtless, enthusiastic physicians, like ALCOTT, had previously lent their services occasionally to the improvement of school conditions in various parts of the country ; but in 1894, after four years of effort on the part of the Commissioner of Health of Boston, fifty "medical visitors" (one for each school district) were appointed in that city. These physicians visited the schools daily and examined "all children thought by their teachers to be ailing". The teachers and doctors both proved efficient, for, in four months, over 9,000 children were examined, of whom 5,825 were found to be ailing and 1,033 were sent home. Among these were 58 cases of diphtheria, 19 of scarlet fever, 42 of measles, 17 of whooping-cough, 35 of mumps, 22 of chickenpox and 7 of congenital syphilis. The superintendent of schools commented, "I believe the importance of this work can hardly be overestimated". New York City followed the example of Boston in 1897 by the appointment of 134 medical inspectors.

As might have been expected, the findings of these earlier examiners were largely skin diseases, and the exclusion of the infected children from school removed them from the source of instruction, but did not always result in their treatment or cure. Experiments in New York City with nurses who either treated such children in school or secured their treatment by the parents solved the difficulty, and in 1902 the first staff of school nurses was appointed.

STATE LEGISLATION.

In 1899, the State of Connecticut passed a law requiring the examination of all schoolchildren by teachers, every three years, for faults of vision, and by 1905 many school physicians had taken up the examination of children for these and other defects. Statistics of diseases or defectiveness were accumulated in large and "startling" figures, but the results in "correction" or treatment were comparatively small until, as for skin diseases, the nurse was made a home visitor and educator concerning the meaning and intent of the child's examination.

By 1910, over 400 cities had made a beginning in medical inspection, and there has been a rapid development of such work since that time. Nevertheless, medical inspection is by no means universal, and only recently we saw an account of its introduction into the schools of a community of considerable size, which account read, with its enumeration of the "defects discovered", very much like such reports of a quarter of a century ago.

In the United States we have no national administration of education, nor have we a central directing officer in matters of health. The powers of the Public Health Service for protecting the country at large from the importation of disease and defectiveness from without its borders are unlimited, but within those borders its work (in the States and in inter-State matters) is advisory and co-operative. The United States Office of Education has no general administrative functions, its prescribed purposes and duties being the collection and diffusing of information in the various educational fields. In educational matters, including school health conditions and health activities, each State is a law unto itself and (if local interest is sufficiently developed) sets up its collective ideas of what should be done in its statutes. Forty of our States have reached the legislative stage with reference to the medical examination of schoolchildren, and, since few of these laws are alike, the subject, even from the standpoint of what is prescribed or permitted in each of the States, presents a varied picture. Under these laws, the State Department of Education is not expected to offer more than information and general direction, nor, except in two States, does the State Department of Health exercise active control. What happens in the schools (if anything takes place) is left chiefly to local boards of education or of health. We mention education first, because the local development of medical inspection is usually left, by law, to its initiative.

As a consequence of this lack of central direction and the variety of State laws, we have medical inspection in every conceivable form and degree of evolution, or it may be without form and void. A summary of the main features of the State laws will indicate what is required or permitted.

In 27 States the law is more or less mandatory in its wording ; in 13 it is permissive. In 3 the examiner is to be the county health officer ; in 5, a physician ; in 3, a nurse ; in 7, the teacher ; in 9,

a physician or nurse ; in 6, a physician or teacher ; in 5, a physician, teacher or nurse ; in 2, a dentist (in these States the law refers only to dental examination).

As to frequency of examinations, 20 States require or permit an annual, 2 a biennial and 3 a triennial examination. This item is omitted in other laws.

Examination of vision only is specified in 1 State ; of sight and hearing in 3 ; sight, hearing and breathing in 1 ; sight, hearing, breathing and teeth in 1 ; sight, hearing, nose and throat, 1 ; teeth, 2 ; growth and development, 1 ; and a more general examination in 14. The nature of the examination is not mentioned in the remaining laws. The specifications given do not prohibit examinations of other organs, but were doubtless intended to emphasise the importance of certain readily observed defects. (It should be stated here that, in States with no medical inspection laws, excellent systems of examination have been developed in some school systems.)

In some States the parent may refuse to have his child examined by the school physician (which is rarely the case), or the physician is legally restricted from removing the child's clothing without permission of parent or guardian (a law which is usually ignored). In 1 State the parent may be fined for refusing examination. One law limits the number of children to be assigned to a physician at 2,500, and in 2 States it is required that teachers in training be instructed in methods of examination for diseases and defects.

Where a State administrative authority is specified by the law, this, in 13 States, is the Department of Education, in 11 it is the Department of Health, and in 9 there is to be joint management. Save in half a dozen States, the State " authority ", whether of education or health, is confined chiefly to the preparing of examination blanks. The exceptions will be mentioned later.

Locally, the matter of administration is conferred in 30 States on the educational authorities, in 6 on the health authorities, and in 1 there is to be joint control.

SUMMARY OF STATE LEGISLATION FOR MEDICAL INSPECTION.

| State | Law | State authority ¹ | Local authority | Mandatory or permissive | Examiner | How often | Extent of examination, etc. |
|-----------------------|------------------|------------------------------|-----------------|-------------------------|--|-----------|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| Alabama | Yes | Joint | Joint | *M | County health officer | Annual | Any defect and deformity. Physical and mental. |
| Arizona | Yes | — | Education | P | Physician, nurse and dentist | — | Not stated. |
| Arkansas | Yes | Education | — | P | Physician, nurse and teacher | Annual | Contagious disease and defects. |
| California | Yes | — | Education | P | "Physical inspector" certified by State | — | |
| Colorado | Yes | Education | Education | M | Teacher | Annual | Sight, hearing, breathing. |
| Connecticut | Yes | Education | Education | *M | Physician, nurse, teacher, optometrist | Annual | Vision for all. Other defects where physician is employed. |
| Delaware | Yes | Education | Education | P | Physician and nurse | — | |
| Florida | Yes | Health | Health | M | County medical inspector | Annual | (No physician shall be assigned more than 2,500 children.) |
| Georgia | Yes | Health | Health | *M | Commissioner of health | Annual | General examination. |
| Idaho | No | — | — | — | — | — | |
| Illinois | No | — | — | — | — | — | |
| Indiana | Yes | Joint | Education | P | Physician | — | General. |
| Iowa | Yes ⁴ | — | Education | — | — | — | Dental. |
| Kansas | Yes | — | Education | *P | Dentist | Annual | Dental. |
| Kentucky | Yes | Health | Health | M | County health officer and public health nurse. | — | |
| Louisiana | Yes | Joint | Education | M | Teacher | Annual | Sight, hearing, and diseases of eyes and ears. |
| Maine | Yes | Education | Education | M | Teacher or physician | Annual | Sight, hearing, and any other defects interfering with school progress. |

| | | | | | | | |
|-------------------|-----------------|-----------|-----------|---|--|----------------------------|--|
| Maryland | Yes | Joint | Education | P | Physician | At least every two years | Sight, hearing, and any other defects interfering with school progress. |
| Massachusetts .. | Yes | Joint | Education | M | Physician ; teacher for sight and hearing | Annual | Sight, hearing, and any other defects interfering with school progress. (Teachers to be instructed in normal schools.) |
| Michigan | No | — | — | — | — | — | — |
| Minnesota | Yes | Joint | Education | M | Physician, nurse and teacher | — | — |
| Mississippi | Yes | Education | Education | M | Available agencies | Periodic | — |
| Missouri | Yes | Health | Education | P | Physician, nurse, supervisor of physical education | Periodic | — |
| Montana | Yes | — | Education | M | Physician | — | General health conditions. |
| Nebraska | Yes | Health | Education | M | Teacher | Annual | Sight, hearing, teeth, mouth breathing, and communicable disease. |
| Nevada | Yes | Health | Education | M | Teacher | Annual | — |
| New Hampshire .. | Yes | Education | Education | M | Physician ; teacher for eyes and ears | Annual | Sight and hearing ; defects and diseases. |
| New Jersey | Yes | Education | Education | M | Physician or nurse | — | Any defects, also growth and development (annually). |
| New Mexico | No | — | — | — | — | — | — |
| New York | Yes | Education | Education | M | Physician ; teacher for eyes and ears | Annual | Vision and hearing by teachers (Teachers to be trained.) |
| North Carolina .. | Yes | Health | None | M | Teacher | At least every three years | (Parents notified of serious defects by State board of health.) |
| North Dakota .. | Yes | Health | Health | P | Physician or nurse | Annual | — |
| Ohio | Yes | Joint | Health | P | Physician or nurse | — | — |
| Oklahoma | No ^a | — | — | — | — | — | — |
| Oregon | Yes | Education | Education | M | Teacher | Annual | Obvious physical defects. |
| Pennsylvania ... | Yes | Health | Health | M | Physician | Annual | All defects. |
| Rhode Island ... | Yes | Education | Education | M | Physician ; teacher for eyes and ears | — | — |

See notes at end of table.

SUMMARY OF STATE LEGISLATION FOR MEDICAL INSPECTION (continuation).

| State | Law | State authority ¹ | Local authority | Mandatory or permissive | Examiner | How often | Extent of examination, etc. |
|----------------|-----|------------------------------|-----------------|-------------------------|------------------------------|-----------|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| South Carolina | Yes | Health | Education | M | Physician, dentist, nurse | Annual | Medical and dental. |
| South Dakota | Yes | — | Health | P | Public health nurse | — | Eyes, ears, nose, throat, teeth, and communicable diseases. |
| Tennessee | No | — | — | — | — | — | — |
| Texas | Yes | — | County court | P | Nurse | — | — |
| Utah | Yes | Joint | Education | M | Physician or teacher | Annual | Sight, hearing, teeth, and mouth breathing. |
| Vermont | Yes | Health | Education | *M | Teacher, physician and nurse | Biennial | Sight and hearing by teacher. |
| Virginia | Yes | Joint | Education | M | Teacher, physician and nurse | Annual | Sight and hearing, weight and nutrition, throat and nasal obstruction. |
| Washington | Yes | — | Education | P | Physician or nurse | — | May be established in cities of first class and no objection to work by volunteer nurses elsewhere. |
| West Virginia | Yes | — | Education | *M,P | Physician or nurse | — | — |
| Wisconsin | No | — | — | — | — | — | — |
| Wyoming | Yes | Education | Education | *M | Teacher | Annual | Sight, hearing, nose, throat. (Specific tests provided by law.) |

¹ State "authority", especially as regards the Department of Health, is seldom more than that of preparing blanks for examinations.

² Where there is a county health officer.

³ For vision.

⁴ Power to establish dental clinics.

⁵ Free dental examination required. First and second class cities and "in school districts".

⁶ Has some local ordinances.

⁷ Sight and hearing.

⁸ Mandatory for independent, permissive for other districts.

⁹ For incorporated cities and towns. More or less mandatory, 27; permissive, 13.

In 1930, a committee on legislation of the White House Conference requested the opinions of representative medical inspectors throughout the country as to the desirable content of State laws. In general, they agreed that :

1. Legislation should not be too specific in its requirements.
2. The law should be mandatory.
3. The State Department of Education should be made responsible for carrying out the provisions of the law.
4. There should be a State Director of Medical Inspection.
5. The local Board of Education should be made responsible for the local administration of the law.
6. There should be nothing in the law to limit the thoroughness of examination.
7. The examiner or examiners should be specified, or, at any rate, the official in charge of examination.
8. The training of teachers for the detection of signs of communicable disease and of gross physical defects should be required.
9. The securing of the consent of parents for examination of children should not be mentioned.
10. Permission for the setting up of dental or medical clinics should be granted by the law if it seems needful to have them.
11. Provision for mental examinations of schoolchildren should be included.

One condition which inclined some of the correspondents to prefer control and direction by the Department of Education rather than by the Department of Health is that there is less of politics in the former and, hence, likelihood of better tenure of office and better personnel. Another reason for such direction is that, aside from the control of communicable disease, the work of medical inspection is chiefly educational and should be correlated with the general health educational work of the school.

The work of the modern Department of Health is largely educational, and there is much to be said for the administration of school medical inspection by that department. This view of the subject has been admirably stated by Professor HiscocK, of Yale University,

as editor of the report of the Committee on Administrative Practice of the American Public Health Association :¹

“ Broadly speaking, for economy of service and simplicity of organisation, health supervision should be exercised through one administrative department. Whether this be the Health Department or the Department of Education is of less importance than the assurance that the work is done effectively . . .

“ The health examination is primarily an educational experience for parent, teacher, nurse and child. It is most desirable that the parents be present, and this will often provide the first opportunity for the parent to understand the nature and significance of a health examination by a physician. It should reveal the physician to the child in the new rôle of an understanding friend, and the child to the physician as a distinctive personality requiring his best wisdom and understanding to comprehend and advise. Teacher and nurse should add their knowledge of the child, and in turn profit by the physician's advice regarding the child. In so far as is administrative-ly practicable, the teacher should be present at the examination to add still greater significance to it, to help interpret the child to the physician, and to benefit by the first-hand advice of the physician regarding the child.”

STATE-WIDE ACTIVITIES.

A few States stand out as deserving mention of State-wide work under the administration of the State Department of Health or of Education.

In New York State, the Commissioner of Education is requested to appoint a “ competent physician as State medical inspector of schools whose duty it is to carry out the provisions of the medical inspection law”.

In the course of twenty years the State director has developed a considerable staff, consisting, at the present time, besides himself, of :

A general supervisor of medical inspection ;

A supervisor of sight and hearing ;

¹ Hiscock, Ira V., “ Community Health Organisation ”. The Commonwealth Fund, New York, 1932.

- A supervisor of oral hygiene ;
- A supervisor of heart and lungs ;
- A supervisor of psychiatry ;
- Two supervisors of school-nursing ;
- A supervisor of health for teacher-education institutions.

The State law has undergone a number of revisions since its passage in 1913 and is supplemented by regulations of the State Department of Education.

Under a regulation of the State Board of Education (or " Regents", as the members of the board are known in that State), the full-time medical inspector is now known as a " school medical supervisor ", and physicians who aspire to this position must possess the following qualifications :

(1) Graduation from a medical school registered by the State Education Department and licensed to practise medicine in New York State.

(2) One year of acceptable internship. Five years of successful practice in medicine may be accepted in lieu of one year of internship.

(3) Six semester hours of post-graduate work in a school or schools of medicine in such subjects and in such institutions as may be approved by the State Commissioner of Education. The following subjects indicate the type of instruction that should be included in such post-graduate courses :

- (a) Medical examination of school-children ;
- (b) Psychiatric problems of school-age ;
- (c) Problems of growth and nutrition ;
- (d) Preventable defects of eyes, ears, teeth, posture ;
- (e) School sanitation ;
- (f) Communicable disease control.

(4) Six semester hours of post-graduate work in a school or schools of education in such subjects and in such institutions as may be approved by the State Commissioner of Education.

The following subjects indicate the type of instruction that should be included in such post-graduate courses :

- (a) Principles of health education ;
- (b) Organisation and administration of health education in public schools.

The State Commissioner of Education may grant a temporary certificate to physicians who present satisfactory evidence of successful experience for three or more years in medical inspection and health service.

(5) Where undergraduate medical instruction and training have included special preparation in the field of health service equal to the qualifications set up for post-graduate work, such undergraduate preparation may be accepted for the certification of medical supervisors.

A nurse certified by the Teacher Training Division of the State Department of Education as qualified for working in the schools is known as a " nurse-teacher " and she must meet the following requirements :

- (1) Graduation from an approved four-year high-school course or its equivalent ;
- (2) Graduation from a training-school for nurses registered by the Regents of the University ;
- (3) Certification as a registered nurse in New York State ;
- (4) Completion of at least six semester hours in approved professional courses in health education.

Dental hygienists, who work always under the direction of a school dentist, are required to meet the following conditions :

- (1) Annual registration as a dental hygienist in New York State ;
- (2) Graduation from an approved four-year high-school course or its equivalent ;
- (3) Credentials showing completion of at least twelve semester hours' work in approved professional courses in health education ;
- (4) Limited certificates valid for three years may be issued to those who qualify under (1) and (2) and complete not less

than six semester hours in approved professional courses in health education, on the recommendation of an employing superintendent of schools ;

- (5) Permanent certificates may be issued upon completion of qualifications under (1), (2) and (3) and at least two years' successful experience as a dental hygiene teacher.

The State Department has prescribed a " health record " form.

The local boards are requested to report the number of pupils to be examined, the percentage examined, the number of defects found and the number and percentage of defects treated. In a recent report a considerable number of boards reported 100 % of pupils examined.

In a recent year the State had about 1,300 school medical inspectors, exclusive of those in New York City, Buffalo and Rochester, which would average one physician to about 850 pupils enrolled. There were 600 nurses—about one to 1,800 scholars. Of these, 450 are employed by Boards of Education and are certificated as " school nurse-teachers ". The remaining 150 are employed jointly by school and by other health authorities and divide their work accordingly.

In Pennsylvania, the State Department of Health is responsible for the medical inspection of children in school districts of the fourth class (under 5,000 population). The inspectors are appointed by, paid by and work directly under the State department. In 1930, the personnel of the school hygiene section of the department included a medical director, who was deputy supervisor of health, a supervisor and an assistant supervisor of school sanitation, a full-time and four part-time medical supervisors, 415 part-time medical inspectors of schools and eighteen clerks and stenographers. Some of the fourth-class school districts employ their own nurses, but the majority make use of nurses available through State clinics. In these districts there was one inspector for about 1,750 pupils enrolled.

The minimum requirements of the school nurse in Pennsylvania are :

- (a) Graduation from an approved high school ;
- (b) Graduation from an approved school of nursing ; and
- (c) State registration in nursing.

In addition, a permanent standard certificate is offered to those nurses with :

- (a) An average or better than average rating ;
- (b) Evidence of four years' successful school nursing ; and
- (c) Not fewer than twelve semester hours of professional work in the following subjects : principles of public health nursing, psychology, education, technique of teaching, sociology and public speaking.

In North Carolina the triennial examination of children is carried on under the direction of the State Department of Health with the assistance of county health officers and teachers. In 1930, the staff in the Bureau of Medical Inspection of Schools consisted of a director, seven dentists, seven school nurses, three clinic nurses and an anæsthetist. Dental clinics and tonsil and adenoid clinics are conducted throughout the State.

Besides laws requiring the medical examination of schoolchildren, we have, in thirty-six States, laws requiring provision in public schools for the teaching and supervision of physical activities (physical education) ; and in the Departments of Education of thirteen States we have, as a member of the staff, a State Director of Physical Education or Health and Physical Education. In two of these States, Connecticut and New Jersey, this official is a physician, and one of his functions is that of the promotion of the medical and nursing service of the schools throughout the State. Thus, in three States (including New York, which has already been mentioned) we have a centralisation and co-ordination of the sources of inspiration and information for all the health activities of the schools under one head in the Department of Education.

The State Department of Education of New Hampshire employs a " supervisor of health ", who assists local schools in the development of their health service. About half the school districts of the State now employ a part-time physician and most of them a full- or part-time nurse.

In Virginia, the State Departments of Health and of Education work jointly in carrying out a law which requires the training of teachers in the weighing and measuring of pupils, the examination of their vision, hearing, teeth and throat and the annual application of this knowledge in the schoolroom. The parents are notified of

the results of the examination. With the parent absent at the time of inspection and with no go-between in the shape of a nurse, the results were, at first, negligible. In 1926, the plan of offering a reward to each child who had all his defects corrected was adopted. This consists of a "Five Point" certificate signed by the State Commissioner of Health and the State Commissioner of Education. Those receiving the certificate are known as "Five Pointers", from the fact that only eyes, ears, teeth, throat and weight are considered in the examination. In a recent year the percentage of children to whom certificates were awarded ranged from 4 to 64 %, with an average for all counties of the State of 23 %. It is evident from the wide range of results that the mere awarding of this certificate does not, in itself, create an interest in the correction of defects.

The award of pins, buttons, ribbons or other stimuli have been tried locally in other States for five or more "points" made as the result of securing the treatment of defects. Such a method of arousing interest in bodily condition does not work automatically and has been largely abandoned for more direct methods of approach.

In Massachusetts, the State law lays no responsibility for medical inspection upon the State departments, save that the Department of Health is to prescribe directions for tests of sight and hearing (to be made by teachers), while the Department of Education issues rules and materials for the tests. The law orders that the local school committee "shall appoint one or more school physicians and nurses". "Towns may appoint school nurses to work under the board of health of the town."

While in 286 out of 317 cities and towns the physician, and in 293 the nurse, works under the local school committee rather than the Board of Health, the State Department of Health does a great deal to promote all forms of school health work and employs on its staff a pediatrician as "Consultant in School Hygiene". The following (1932-1933) statistics show the extent of this work: In cities (a) with a population over 25,000 the average number of pupils per physician was 2,500; (b) in cities of 10,000 to 25,000, 2,500; (c) in places of 5,000 to 10,000, 1,229; and (d) in smaller communities, 309. The average number of pupils per nurse in cities of group (a) is 2,100; in (b), 2,250; in (c), 1,600; and in (d), 325. In most of the smallest communities, group (d), the nurses are on part-time.

In medical examinations, about 50 % of the children are stripped to the waist and the average time spent in examinations is five minutes. In about half the communities (172), examinations are made of children about to enter school (the "summer round-up"), and these examinations are usually conducted by the school department.

About half (149) of the communities have a dental clinic and in 50 % of these (77) this is conducted by the Board of Health. Eight travelling clinics supply schools in sixty-eight towns.

In other States besides Massachusetts, the Department of Health is doing much, without specific legal sanction, to assist in the development of school health work.

MEDICAL INSPECTION IN CITIES.

All of our cities with a population of 100,000 or more have highly organised systems of medical inspection. About 90 % of cities of 30,000 to 100,000, and about 80 % with a population of 10,000 to 30,000, employ school physicians and nurses and sometimes dentists. In smaller cities, unless inspection is required by the State law, the percentage conducting general medical examinations is still smaller, though partial examinations (as of vision) may be made in most of them.

The search for communicable disease, which was the first function of medical inspection, was naturally instituted by Departments of Health and, since such work was begun in our largest cities, the administration of such work devolved upon that department. The search for defects of vision instituted as a function of the teacher by the law of Connecticut in 1899 was placed by the Legislature in the hands of the State Department of Education. Whether or not this served as a precedent, the administration of medical inspection in cities is usually found in the hands of the Department of Education and, in at least two of our larger cities (Boston and Providence), this work has been shifted since its origin from the Department of Health to that of the Department of Education, and we have no record of changes in the opposite direction. In 1930, 60 % of cities with a total population of 100,000 or more reported their medical inspection as administered by the Department of

Education, in 25 % by the Department of Health and in the remainder it was managed jointly. In 78 % of cities with 30,000 to 100,000 people it is placed under the Department of Education ; in fourteen, under the Department of Health; and in the remainder this responsibility is divided. In cities of from 10,000 to 30,000 population, the percentage runs about the same.

The development of medical inspection came, as a rule, later in small cities than in large ones, and the above figures indicate a trend in administration from the Department of Health to that of Education. Where changes have been made in the larger cities (as in Boston and Providence) it has been in this direction. That in at least a third of our larger cities the officer in charge of medical inspection is given the title of " Director of Health " or " Director of Hygiene " indicates the movement toward a unified direction of school sanitation, medical inspection, health instruction, physical education and mental hygiene.

While most cities with a population over 100,000 have a full-time medical officer, the percentage employing such an official diminishes rapidly as we descend the scale of population, and in cities with ten to thirty thousand people only about 10 % can boast a physician in charge of the school health activities.

Where the health work of the school is headed by a physician, it is rarely the case that he has had any special schooling in the fields he covers (except in New York State, as previously mentioned). Within the past ten years many of our medical schools have furnished to all students a general course in public health, in which school work may be touched upon ; but the school medical officer who is also a graduate in public health is nearly non-existent. The lack of supply hints at a lack of demand for specially trained workers, and along with this goes an insufficiency of salary, although full-time physicians are much better paid than formerly, and up to \$6,000 in 1930. In that year at least twenty-five cities paid their chief medical inspectors \$4,000 or more, and one city of less than 30,000 people reported a salary of \$5,500. Figures for salaries and other expenditures will probably mean little to a reader in another country and there will be little mention of this side of the subject hereafter.

PERSONNEL.

In our larger cities (over 30,000 inhabitants), the staff of the school health service usually includes physicians, dentists, nurses, and sometimes dental hygienists. In cities with fewer inhabitants, the dentist is likely to be missing, as well as the dental hygienist, or the latter may serve as a substitute for the former. In still smaller communities, the physician may also be absent from the picture, and only (if anyone) a nurse remains.

Except for the chief medical officers in the large school systems, medical inspectors of city schools are almost always part-time workers, spending from one to three hours per day in the schools. Dentists are usually part-time employees, the number of hours of service per week ranging from four to forty-four.

Nurses and dental hygienists are employed for full time and often for twelve months, although schools are not in session more than ten months. Nurses employed during the vacation continue their work of securing treatment for children found defective, or they may take part in other public health service. In most school systems, the nurses are not expected to work more than forty hours per week, and in many only thirty hours are required.

TRAINING OF PERSONNEL.

School physicians in city schools must be persons of good standing in the profession. Some cities require a certain number of years' experience. Competitive civil service examinations are given in some communities, in which case special knowledge or experience counts for the applicant. In a few large cities, the medical inspectors are given some training for their work by the chief inspector, and their advancement in salary is based on their theoretical, as well as practical, knowledge.

A few of our large school systems employ one or more physicians with special training in a limited field of medicine—as in diseases of children, of the eye, ear, heart, lungs, speech or of orthopædics. These specialists serve as consultants or as special examiners of pupils found defective along their lines of practice. They may also, in some instances, supervise the treatment of these cases.

The school dentist is a licensed practitioner who has had the usual training.

School nurses have, in the past, received little or no special training. The nurse without the usual three years of general training is, however, not now acceptable, and, thanks to the effort of the National Association for Public Health Nursing, the curricula of training in this graduate field, given in fifteen universities and colleges, include courses in school nursing. Through the monthly journal of this association, outlines and material are offered for the self-improvement of nurses already in service.

Dental hygienists receive a special training usually of two years in methods of examination and in the cleaning of teeth. They do no other instrumental work.

FREQUENCY OF EXAMINATION.

It will be noted that, in twenty States, an annual examination of all children is required by law, in two it must be made every two years, and in one at least every three years. This, of course, refers to routine examinations. Where more than the letter of the law is carried out, pupils may be sent by the teacher for a looking-over at any appointed time of visit of the school by the examiner, and children recommended for treatment are kept under observation. The variety of practice with regard to periodicity of examination is illustrated by the example of ten representative cities with well-organised systems of medical inspection which range in school population from 15,000 to 275,000 children. In one, the regular examinations are made in the kindergarten, 3rd grade, 7th grade, 10th and 12th grades. (There are twelve grades in our public schools above the kindergarten, the average of ages in the grades being from 6 to 17 years.) In two cities, examinations are made in the kindergarten, 3rd, 5th, 9th and 12th grades ; in one, in the kindergarten, 2nd, 4th, 5th, 6th and 8th grades ; in one, in the kindergarten, 2nd, 4th, 6th and 9th ; in one, in the 1st, 4th and 8th grades ; in one, in the kindergarten, 1st, 4th and 7th ; in two, in the 1st to the 9th grades inclusive ; and in one, from the 1st to the 12th grades inclusive. It happens that in four of these ten cities examinations are made of children in the twelfth or last year of school ; but, taking the country over, it is unusual for children beyond the eighth

grade to receive an examination unless it happens that they are spending part of their time in industry or unless they are candidates for strenuous interschool athletics, in which case the examination is likely to be limited to the heart. Notwithstanding that twenty out of twenty-three States recommend or require an annual examination, there is a tendency in this country to extend the interval between " routine " or " regular " examinations, although, of course, pupils referred by teachers or nurses will be studied at any time.

THE EXAMINERS.

We have noted that, in its beginnings in Boston, pupils were sent by teachers for examination by the school physician, and that, later, the school nurse served as the first-line inspector. This was before defects of eyes, ears, etc., were looked for. When it came to such examinations, only a physician was supposed to be competent, although at that time (a quarter of a century ago) it was rare indeed that an unspecialised physician had experience in the examination of any part of the body save the heart and lungs. The State of Connecticut went a long way in requiring the examination of vision by teachers, and this was to be done without previous training in such work.

In some States, as in Colorado and Wyoming, the teacher is expected to make examinations of the eyes, ears, nose, throat and teeth. This was required in States where it was not be expected to that examinations by physicians were likely to be secured.

In most schools to-day, the regular examination of children is made by a school physician without assistance, unless the clothing is to be removed to the waist ; but in many city schools the nurse makes the usual tests of vision and may examine the teeth or test the hearing. In a few cities, practically all examinations are made by nurses, the physician serving as consultant in special cases.

The possibilities of the teacher as examiner have been tried out on a large scale for the past thirteen years in Detroit. Having eyes and ears and more than average intelligence, the teacher with some instruction and experience makes an excellent examiner. The pupils found defective by the teachers are referred to the school physicians (of which there are seventy-five on part time) for re-examination before parents are notified of defects.

There is a wide range in findings of defects by school physicians—a variation amounting in one city, for example, of from 1.5 to 24 % for defective vision ; of 2 to 35 % for diseased tonsils ; 8 to 49 % for decayed teeth, and 0.5 to 25 % for anæmia.

In Detroit, there is an agreement between the findings by teachers and school physicians in 90 % of cases. Examinations of the heart and lungs are not made by teachers, although symptoms of serious cases might as readily be detected by an informed teacher as by a school physician.

In Virginia, all teachers are by law given training in the knowledge of, and examination for, certain physical defects and, in city schools, they are at least prepared for this service, should the physician expect it of them.

Although in fifteen States the teacher is specified as the examiner, or an examiner, the laws, except in Virginia, are silent as to her training for this important work. However, teacher-preparation institutions in a number of States are educating along this line as a part of their curricula in school hygiene.

As previously noted, physicians with training in certain specialities form a part of the school medical staff of some cities. In the ten selected cities already referred to, one employs on part time specialists for the eye, ear, nose and throat, and an orthopædist ; another employs specialists for the eye, ear, heart, lungs and an orthopædist ; one a paediatrist, a psychiatrist and a roentgenologist ; one a psychiatrist, orthopædist and cardiologist.

At one time a few city systems employed as examiners a group of specialists who worked together, the pupils under inspection being passed from one to the other. A city conspicuous for its use of this method has recently abandoned the plan, and we believe it is not the custom elsewhere. These special workers serve as referees or consultants for pupils found in the regular examinations by teachers, nurses or physicians. The oculist may do refractions, and the care of pupils assigned to special schools (see page 735) may be under the supervision of these specialists.

DENTAL EXAMINATIONS.

In city schools, the physician or nurse or teacher making the regular examinations often includes the condition of the teeth ; but, if

a dentist or dental hygienist are employed, the much wiser practice is usually followed of leaving mouth conditions to their more skilful observation. It is of most importance to find and repair beginning caries, and this is likely to be undiscovered by untrained examiners. Where teeth are cleaned in school by the hygienist or dentist, the examination may be done at the same sitting.

NUMBER OF PUPILS PER EXAMINER.

In 1930, the number of pupils per physician reported from large cities ranged from 1,240 to 38,670, with an average of 5,320. The figures suggest that the supply of examiners might be altogether too small if it were not for the fact that much of the examining may be done by nurses or teachers. In the ten representative cities previously mentioned, the range in pupils per physician in the present year is from 2,200 to 15,500. In the latter city, the routine examinations are all made by nurses. In the former, regular examinations are made in every other grade. One city in which examinations are made yearly in all grades has an average of about 2,900 pupils per part-time physician.

There is a large range in pupils per dentist, depending on what the dentist does, with an average in 1930 of about 10,000. In two of the small group of cities mentioned, no dentist is employed ; in another, the dental service is voluntary ; in one there is a dentist for 5,000 of the school population ; and in the remainder only one dentist is employed.

Only four out of these ten cities employ a dental hygienist, and in these there are about 10,000 pupils per hygienist. Dental hygienists are comparatively infrequent in our schools.

TIME OF EXAMINATIONS.

The time devoted to examinations is reported by one city as five minutes ; by one, six minutes ; by two, eight to ten ; by three, ten ; and by two, as twelve minutes.

The clerical work, which may consume endless time if the records are detailed, is usually taken care of by a nurse, and in a few cities a record blank for a detailed history is sent to the home.

THE COSTS OF EXAMINATIONS.

Where such wide variations in organisation and practices prevail, one would expect large variation in costs, and, where reported by the ten cities, the range is from 70 cents to \$4 per pupil. However, this includes all work done and not merely the routine examinations.

RELATION OF TEACHERS.

Except where the teacher is the original examiner, or one of the examiners, she is not often present at the examination, although in some cities she may be asked to attend, or, from interest, asks to attend.

RELATION OF PARENTS.

In the beginning of medical inspection in this country, the parent was informed of the fact that his child was considered defective by means of a form signed by the school official or by the school physician. This distant way of handling the situation produced little result, and, in case of no results, the school nurse was sent to follow up the case. The more direct and personal approach of having the parents attend the examination has not developed on a wide scale in this country, although a few cities report as high as 100 % of children attended by one or more parents at their first examination. Probably the conglomerate population of most of our large cities, making the use of an interpreter needful for conversation with a considerable proportion of parents, has had something to do with the indirect mode of approach in so important a matter.

AFTER EXAMINATION.

In the United States, the medical examination of schoolchildren is looked upon as an "educational" procedure. The child is given evidence that he is a mechanism which may get out of order and which needs a periodical looking over if it would be kept at its best. The parent is also educated by the fact that he is informed if his child is defective (sometimes a copy of the examination blank

is sent to the parent, whether or not defects are found). Following this lesson, the parent is expected to visit his own physician or a specialist and ask his opinion whether the findings of the school physician are correct and the defect or disease needs to be treated. If the parent feels unable to pay for a visit to a physician or for treatment, the school nurse lends her services in securing diagnosis and treatment at public expense. This may be secured at a public clinic or, where this does not exist, by special arrangement with physicians for advice and treatment at reduced charges or without cost.

About half our cities have dental clinics for schoolchildren, these being relatively more numerous in cities of larger size. Treatment is furnished free or at small cost to those who cannot afford private treatment. In a few cities, refraction work is done by the Department of Medical Inspection, but this is about as far as we have gone in the way of furnishing free service as a part of the scheme of remedial work.

THE OUTCOME OF MEDICAL INSPECTION.

It must be evident that, while the mere finding of disease and defects and the notification of the parent to this effect may be educational, the work of examining is valuable in proportion to the percentage of defects or diseases corrected or treated. If the end results of examination are a test of effectiveness of the system of examinations and follow-up employed, there are all degrees of efficiency : in cities of New York State reporting to the State department of education in a recent year the percentage of defects treated ranged from 15 to 95 %.

FORMS AND RECORDS.

Those interested in the printed forms used in connection with medical inspection are referred to the work by WOOD and ROWELL.¹

¹ WOOD, T. D., and ROWELL, H. G., "Health Supervision and Medical Inspection of Schools". W. B. Saunders Company, Philadelphia, Pennsylvania.

Examination forms for the examination of children before entrance (the "summer round-up") have been published by the American Medical Association, and record blanks for schoolchildren have been issued by the American Public Health Association and the National Organisation for Public Health Nursing. Record cards are kept in the school and accompany the child from grade to grade.

RURAL SCHOOLS.

The subject of medical inspection in rural schools has already been touched upon in connection with State-wide programmes. Except where the State department is active in promoting such work, the rural schools lag behind the cities, and it is probable that, the country over, not more than half of the former employ either a nurse or physician, and, of the two, the nurse is much more frequently present and more useful. In fact, the entire school health programme may be placed in her hands.

Consolidation of country schools, which has been going on to a large extent, makes it easier to handle the school health service, and, at the same time, the bringing together of larger numbers of children makes it more imperative to prevent the spread of communicable diseases of all kinds.

County organisation of schools also makes for organisation and specialisation in school health work. In 1924, a law was passed by New York State permitting the establishment in any county of a "school hygiene district", and a "district director of school hygiene" can be appointed, whose duty it is :

" . . . to advise, assist and exercise general supervision over medical inspectors, dentists and school nurses in the public schools in such school hygiene district ; to keep informed as to their work and require such reports from them as he may deem necessary ; to see that suitable recommendations based on the findings of the medical inspectors in their examinations of pupils are brought to the attention of their teachers and of those in parental relation to such pupils ; to aid, and keep informed as to the work of, oral hygienists, nutrition workers and other school employees engaged in health work in such schools ; to inspect, and report to the proper authorities on,

the sanitary conditions of school buildings, and in other ways to promote the physical welfare and health education of pupils.”

To date, only two of such districts have been established. That in Ontario County seems very successful. The district includes 171 schools with, in 1932-33, a total of 5,901 pupils. Two nurses are employed. In 1932-33, 5,681 children were examined ; 5,322 defects were found and 2,358 defects treated, or 45 %. The total expense of the department for the year was \$10,000, of which the county paid \$5,000. The cost per pupil was \$1.70.

In some rural sections the examination of children is done at a *per capita* cost, and in New York State the charge for such an examination is fixed at \$1. This does not include the cost of the work of the school nurse.

In most, if not all, counties throughout the country in which there is a public health unit (about 557 counties in 1931, including about 28 % of the rural population), the nurses do more or less work in public schools, depending on the time they can spare from other duties.

THE SUMMER ROUND-UP.

The medical examination of persons in institutions for education in this country began three-quarters of a century ago in the quite thorough work which was done in Amherst, Yale and a few other colleges. Such examinations filtered into the public schools in the beginning of this century, but there was no examination of children before entrance to school or attempt to remove their defects until 1925, when the “summer round-up” of children about to enter school was started by the National Congress of Parents and Teachers. The scheme of pre-school examinations has been promoted on a nation-wide scale, with the use of awards by the Congress to the local units and to States making the best showing. Public health and school nurses have been utilised where these were employed locally and most of the examining is done by volunteer physicians. The movement has had the effect of causing the local school health authorities to take over the examination of these children.

For 1933, the Parent-Teacher Association reported the examination of 87,797 children out of a total of 161,587 in the districts

where the "summer round-up" was carried on. The total number of children entering school was over 2,000,000, so that about 4 % were examined who would not otherwise have had their physical condition looked into. Of the children examined, about 80 % were attended by a parent or guardian. Roughly 35 % of the children were immunised for smallpox and 25 % for diphtheria.

IMMUNISATION.

It will be noted that many children are immunised as a part of the "summer round-up". Such work is also a part of the work of medical inspection. In some States and in some cities (without reference to State), vaccination for smallpox is a requirement for school attendance, and where this has not been done before entrance, it is carried out in the early weeks of school by the school physician assisted by the nurse. While not required, protective inoculation against diphtheria is done in some communities, the consent of parents being first obtained. Inoculation against typhoid is also sometimes offered and, in emergency, protection against scarlet fever.

TUBERCULOSIS.

Until within recent years, cases of tuberculosis were considered rare in schoolchildren and, by the methods of examination available, a rough rate of 1 per 25,000 children was mentioned for pupils with active disease. The tuberculin test and X-ray shadows have changed our views of the disease by making manifest its early signs. From a special examination of 50,000 children in the elementary schools of Massachusetts,¹ CHADWICK concluded that 1.5 % of elementary children had the childhood type of the disease and RATHBUN,² from studies of high-school students, reported 1 % as having pulmonary tuberculosis of the adult form. More recently, special surveys have been made by health and school

¹ CHADWICK, Henry D., "Childhood Types of Tuberculosis". National Tuberculosis Association, 1930.

² RATHBUN, Walter F., "Report to the Board of Education, Jamestown, New York, 1930."

authorities of 56,942 children in the schools of Connecticut and in a few large cities elsewhere.

The examination of schoolchildren by these special tools, while evidently belonging to the realm of the specialist in this field, comes under the supervision of the Director of Medical Inspection, as does also the provision for children selected as needing special care while attending school. It has already been noted that a specialist in tuberculosis is employed on the staff of the New York State Department of Education to assist local schools in their efforts to find and care for the tuberculous.

EXAMINATIONS FOR WORK CERTIFICATES.

Besides the making of routine examinations, the examination of pupils referred by teacher or nurse and the work of immunisation, the medical inspector examines all children of school age who apply for a certificate to enter upon part-time industrial occupation. In 1923, the United States Department of Labour recommended certain minimum standards of physical fitness for children entering and working in industry.¹ However, the adoption of these or other standards and their application is left to the individual States. The compulsory attendance law lays the burden for examination and physical supervision of children of school age upon the school authorities. As carried out in some States, those applying for work certificates are not only examined and their physical defects pointed out, but certificates are refused if defects are not corrected, restrictions are made as to the nature of the employment which may be entered into, and re-examinations are required as seems advisable. For details, the reader is referred to the chapter on this subject in "Health Supervision and Medical Inspection of Schools", by WOOD and ROWELL.

EXAMINATION OF TEACHERS AND OTHER EMPLOYEES.

In some States, a health certificate is required of applicants for teaching positions and a few States require periodic examinations.

¹ "Physical Standards for Working Children". Bureau Publication No. 79, Children's Bureau, Department of Labour, Washington, D.C., 1923.

While the examinations for such a certificate are usually made by any physician selected by the applicant, a number of cities require the applicant to undergo an examination by their own medical staff. Would-be teachers are sometimes rejected for physical causes, and in some instances placed on probation until certain defects are remedied. Not only may teachers be required to undergo an examination, but also other school employees. In eighty cities an annual examination is offered free by the school health service. Details concerning such activities have recently been published by the United States Office of Education.¹

OTHER ACTIVITIES OF THE MEDICAL INSPECTOR.

Besides the duties referred to above, examinations are made of pupils referred at any time by teacher or nurse as in need of special attention. In some schools, all pupils returning after an illness are examined by the school physician. There are also examinations to be made of candidates for strenuous sports. These latter examinations have hitherto been confined to the heart, but it is not unlikely that the healthfulness of the lungs will be considered of first importance. In addition, a periodic examination of the sanitary condition of schools may fall within the province of the medical inspector.

SPECIAL SCHOOLS AND CLASSES.

The school medical service is, of course, the source of supply of students for the special schools for the physically defective—the hard-of-hearing, partially seeing, tuberculous or otherwise delicate, the heart defective, the speech defective, and those crippled in body or limb. Whether handled in separate schools or classes, or specially controlled as individual cases, these pupils come under the supervision of the school physicians and nurses, and it is in the selection and care of such children that specialised members of the school staff are chiefly employed.

¹ "The Welfare of the Teacher" ; *Bulletin*, 1934, 4.

Hard-of-hearing children are usually placed under the tutelage of special teachers of "lip-reading" or "speech reading" for certain hours until this feat is acquired, when they spend the full time in regular classes. The same is the case for children with speech defects. Partially seeing children are given a special equipment of large-type books, a typewriter, etc., and in large cities they may be brought together in special rooms. Seriously crippled children, especially those needing treatment, are handled in special classes or in special schools and are transported to and from the schools. The actively tuberculous are, of course, isolated in twenty-four-hour "preventoriums" or are taught in sanatoria. The handling of children with juvenile tuberculosis, those exposed to this disease in the home, the evidently malnourished, anæmic or otherwise delicate, has undergone considerable change in recent years. Special schools are not considered essential for such children, and even special "open-air" rooms or classes have been largely abandoned for comfortably warmed, well-ventilated and not overfilled class-rooms, with cots for use in rest periods. More recently, there is a drift to the setting apart of a special rest-room to which selected pupils are sent from their regular class-rooms at convenient times for periods of rest. Cases of cardiac lesions may be similarly handled. Special lunches may be supplied for these or for other children as is deemed advisable.¹

FACILITIES FOR EXAMINATIONS.

In the beginning of school medical work, examinations were made in class-rooms, vacant rooms or in halls. In at least one large city a room is now set apart for this purpose in every building. In new buildings, a special suite is often included in the plans. This consists of an examining-room and at least one waiting-room, with

¹ The following publications of the United States Office of Education furnish details concerning the management of specially defective children :

- "Education of Crippled Children", *Bulletin*, 1930, 11 ;
- "Schools and Classes for Delicate Children", *Bulletin*, 1930, 22 ;
- "The Speech-defective Schoolchild," *Bulletin*, 1931, 7 ;
- "Blind and Partially Seeing Children", Pamphlet No. 40, 1933 ;
- "Deaf and Hard-of-hearing Children", Pamphlet No. 54, 1934 ;
- "Crippled Children", Pamphlet No. 55, 1934.

washing facilities, closets, etc. The examining-rooms are, or should be, located centrally and where there will be least noise. Special rooms are set apart for dental work. For dental work in rural schools, a travelling outfit is used which can be set up in each school. In at least one county, a specially built automobile with rooms and equipment for eye examination, dental work and tonsillectomies is in service.

MAKING THE MEDICAL EXAMINATION EDUCATIONAL.

It has already been mentioned that, in this country, the aim of medical inspection is "educational". The man-in-the-street would expect it to be for purpose of producing better health and better physique through the finding and treatment of conditions adverse to such ends. However, the parent stands between the school medical authorities and this result. Both he and the child may be brought to feel the need for treatment and to seek it. The mere examination is, in a way, educational to the child and may tend to the formation of a habit of periodic examination later in life. The parent, when notified of defects or diseases, may be said to be educated. The presence of the parent at the examination is much more to the point, for the parent feels that he is being taken into the confidence of the school authorities and, at the same time, is interested in the general process of a medical and dental overhauling. Whether or not the child needs attention, the parent observes the process.

A few examiners who are especially interested in the health instruction of the classroom¹ have prepared the pupils, in a grade of appropriate age, by demonstrating the methods and instruments used and by explaining briefly the purposes of the examination. The lesson is introduced by the class-teacher with such leading questions as, "What is a health examination?", "Why have a health examination?", "How can the doctor tell when we are in good condition?", etc.

It will be observed that the term "health examination" is used above instead of "medical examination". This is in line with the

¹ KLEINSCHMIDT, E. E., "Health Examinations in Schools". *School Physicians' Bulletin*, 1933, 3, 6-8.

trend toward emphasis on the maintenance of health, rather than escape from disease. In fact, the medical inspection activities are more and more spoken of as the "school health service".

More positively educational in its procedures has been an enquiry before or at the time of the examination into the habits of the child of sleeping, eating, etc., the hygiene of the home, and the prejudices of parents which may affect the child's physical well-being. In particular, the child's food habits are looked into in connection with dental disease. It is evident that the presence of the parent not only furnishes the examiners with first-hand information, but renders it directly possible to advise with them as to the bringing about of needed changes.

The school health programme consists of (a) the sanitary and safety supervision of buildings, (b) the dispensing of school meals, (c) medical and dental (or health) examinations, (d) the general direction of special schools, (e) instruction in hygiene, (f) physical education and (g) the general hygienic planning of the mental activities. These various fields interlock with the need of a co-ordinating head with adequate training. Such a head would seem to need medical and public health training; but, since our medical inspectors, as a rule, are part-time workers without other preparation than that for the practice of medicine, the general direction of the school programme (where there is such direction) seldom falls into their hands, although perhaps the supply of such fully equipped persons is equal to the present demand.

PREPARATION OF SCHOOL PHYSICIANS.

Some mention has already been made of the training—or lack of training—of school physicians. Since the vast majority of them are part-time workers, it is not to be expected that more than a few will even have read books or articles on their special work. Rarely, the school physician is a full-time physician in the Department of Public Health of a city, but this does not add to his preparation for school work. Even health officers have seldom been specially trained for their work, although in only a small percentage of communities is the school medical work in their hands.

Fortunately, in many schools students of medicine now take a brief course in public health, which includes at least some reference to the general principles of school medical work. Also, in a few larger cities, the chief medical inspector furnishes instruction to his staff and bases advancement in salary partly on their reaction to such teaching.

The publication of a monthly bulletin by the American Association of School Physicians serves as a stimulus to knowledge in this field for its members.

THE SCHOOL NURSE.

Except in rural districts and, very rarely, in cities, the school nurse is a school nurse and not a district nurse. Where the district system has been tried in cities, there is no evidence that better results are obtained than where the nurse can concentrate on the specialised work of the school. In rural sections and where there are comparatively few schoolchildren to look after, the situation is different. The school work fits into the scheme of general nursing which is made necessary from the financial standpoint.

We have already mentioned that a nurse may direct and carry out the whole school health programme, including sanitation, school feeding, physical examinations, health instruction, etc. In more limited fields she may do all or most of the examining under the direction of the physician, or she may do some of the examining (as of eyes, ears and teeth) and assist the physician with his records.

It was as a go-between for school and home that the nurse made her early reputation. She also, in the earlier days, did much in the way of treatment of skin diseases and chronic lesions, such as running ears. This latter work has been shifted to the home as far as possible, with double effect, since the home is the chief source of skin infections and other members of the family than those in school may need attention. Where parents have been invited to attend the examination of the child, the necessity of home visitation has been reduced and much time and shoe-leather saved. In some instances, the nurse has set aside certain hours at school when the parent may consult her with regard to the physical welfare of the child.

It is, of course, a function of the nurse to aid ill-to-do parents in obtaining treatment for their children and to see that such treatment is carried out for maximum results. She keeps in touch with the records of children accordingly.

The nurse, when present, is expected to render first aid to the injured or ill and may furnish instruction in such work to teachers or to pupils of suitable age. In large secondary schools, her time may be fully occupied with this work and with consultations with pupils. In all schools, she is expected to examine pupils referred by the teacher as having symptoms of a communicable disease, and she may be called upon to examine children returning to school after an absence of a few days.

MENTAL HYGIENE.

Mental hygiene is a somewhat hazy branch of school health work. Sometimes the school physician is expected to serve as the mental hygienist and a psychiatrist, if employed, may be placed on the medical inspection staff. Besides fitting the work of the school to the capacities of the child, there are always the cases of mental twists and peculiarities for which the best knowledge of mental behaviour is none too helpful.

RESEARCH.

When school medical work is largely done by part-time workers and where the "full-time" worker, so called, usually engages in some sort of medical practice out of school hours, one cannot expect much in the way of study of the mine of valuable material which lies in the records of every large school system. There are notable exceptions to the rule, however, as the Department of Medical Inspection of Philadelphia, Pennsylvania,¹ and in the studies with regard to the results of tonsillectomies made from the school records of Rochester, New York.²

¹ See annual reports of the Division of Medical Inspection.

² KAISER, A. D., "Children's tonsils, in and out". J. B. Lippincott, Philadelphia, Pa.

General organisations have contributed much through studies of schoolchildren. The Henry Phipps Institute of the University of Pennsylvania, under a grant from the Metropolitan Life Insurance Company, has recently contributed a study of tuberculosis in public-school children.¹

The American Child Health Association contributed in 1929 to a study of the "Public Health Aspects of Dental Decay in Children"; in 1933, "An Evaluation of School Health Procedures"; and, in 1934, "Physical Defects—The Pathway to Correction," a critical investigation of medical inspection procedures in New York City.

The United States Public Health Service has, over a number of years, conducted studies of the incidence of defects and of illness in schoolchildren. The results of these studies have appeared from time to time in the public health reports.

The studies of the Office of Education so far published have been of a statistical nature rather than direct studies of children. In its bulletins (especially its biennial surveys), it has published the results of studies made by other agencies throughout the world.

HEALTH SERVICE IN COLLEGES.

The medical examination of scholars really began in this country in colleges and universities in the 'seventies of last century and has only recently filtered down through the schools to the child before entrance.

Amherst College was the pioneer in this field under Dr. Edward HITCHCOCK, followed soon by Harvard and Yale. The physical examinations were begun in connection with physical training, but have become highly specialised in what is now generally known as the Student Health Service, often with a large medical staff, including a number of specialists, nurses, laboratory workers, and physiotherapists. Elaborate routine (usually annual) examinations are made occupying five or ten times the period devoted to the school-child, with X-ray examinations (sometimes made of all students), urine analyses, and, if advisable, sputum or blood examinations.

¹ Reprinted in book form under the above title from the *American Review of Tuberculosis*, October 1929, by the Metropolitan Life Insurance Company, New York City.

Refraction service may be furnished for all, or at least for a part, of the student body. There may be a dental department, also dispensary and hospital or dormitory service for those who are ill. Both the well and the ill are looked after.

Yale University, for example, with a student body of about 5,300 in a recent year, had a staff of twenty-six physicians or dentists, twelve nurses and technical workers, and thirty stenographers and other employees. This is without consideration of the infirmary or hospital service.¹

ORGANISATIONS.

The American Association of School Physicians was organised in 1927 ; it has now a membership of about 1,000, and publishes a monthly *Bulletin*. There are State associations in Michigan and New York, and that of Michigan issues a monthly publication.

The school nurses are organised as a section of the National Organisation for Public Health Nursing. The journal *Public Health Nursing* serves as the organ of this body.

Other national organisations which have been helpful in promoting the development of medical inspection are : The American Public Health Association, the National Tuberculosis Association, the American Red Cross, the American Child Health Association, the American Medical Association, and the National Congress of Parents and Teachers.

SUMMARY.

It must be evident from the preceding sketch that, in the United States, we have medical inspection of schools in all stages of development and in every conceivable form of organisation and method of procedure. Of more concern is the fact that we have every degree of result from the nearly negative one of finding " defects "

¹ Those who are interested will find an account of the health services of Cornell University, Yale University, University of California and Oregon State College of Agriculture in Publication No. 19 of the Committee on Costs of Medical Care, published in 1932 by the University of Chicago Press.

These health departments support a national organisation, the American Student Health Association, with some 125 member institutions.

to a conservative appraisalment of the child and his hygiene with a high degree of effectiveness in treatment of his physical and functional deficiencies.

DRIFT AND DIFFICULTIES.

Perhaps the above heading would be more appropriate if the wording were reversed, for drift is usually a consequence of difficulty. And yet it is characteristic of the human that he often attempts and succeeds in overcoming obstacles. From the beginning, the most troublesome feature of school medical work has been the securing of treatment for the diseases and defects found on examination. The examination does not lead immediately to treatment, but there is an intermediary reference to the parent of the knowledge that (as usually worded) the child "seems to be suffering from" certain abnormal conditions. There lies between the discovery and the desired result the indifference (or seeming indifference) of many parents and often their real inability to pay for treatment. We are inclined to think that, if parents seem indifferent to the welfare of their children, it is because they are treated, or think they are treated, with comparative indifference by school authorities. In the reports to the cities of New York State, the percentage of defects ranged (in a recent year) from 15 to 95. Ten cities reported the treatment of more than 80 % of defects, which indicates that, by the right procedures, there need not be the waste of time and of public funds which is the consequence of failure of treatment. A comparison of the ten cities reporting the highest percentages of treatments with the ten reporting the lowest percentages shows that in all the former the chief medical inspector is on full time (which means that he has had special training for his work), while, in the latter, none are on full time, and that in the former group of cities there were better public facilities for treatment.

With uncertainty as to whether anything will be done concerning the defects found, there goes a certain degree of carelessness in examinations. It is easy to find defects, but not so easy to decide what conditions are especially deserving of treatment.

A school clinic would facilitate treatment, but, aside from dental clinics and, in a few instances, refraction clinics, not many such

treatment centres have been set up by the schools themselves. Certain cases, as the crippled, the tuberculous and the malnourished, sometimes receive treatment in school and under the direction of physicians employed by the Department of Education ; but in these cases it has become recognised that it is impossible for the parent to pay for treatment, and that, the more adequate the treatment, the less likely is the child to become a burden to the State.

In this connection it is interesting to note that a law was passed recently in the State of Vermont which authorises school-boards to expend annually not more than 3 % of the school budget for such health service activities as may be necessary to provide for the improvement of the physical efficiency of schoolchildren of indigent parents. Expenditures for this purpose may include purchase of milk for under-nourished children, ingredients for hot lunches, glasses, dental service, the removal of tonsils and other health services which are approved by the town health officer and the teacher or public health nurse.

It will be noted that special preparation of physicians for the work of medical inspection, even in supervisory positions, is infrequent. However, there is a slow drift in a more desirable direction. This is being hastened by the payment of better salaries for full-time work.

The grade teacher is always the central figure in the health service programme, and in not a few training-schools she is being better prepared to recognise the presence of gross defects and signs of communicable disease in the children who face her daily and whose condition does not await the annual visit of a physician or the weekly appearance of a nurse.

From time to time the thoroughness of the school medical examination is questioned, and in a few instances very elaborate examination blanks have been prepared and much time is spent on each child. However, now that an X-ray picture of the chest disposes of the examination of the lungs, five or six minutes per child seems, on the average, an ample allotment for school purposes.

The drift in routine work is from annual to biennial and even triennial examinations, with some tendency to lengthen the interval still further. This does not, of course, extend to dental examinations, the periods between which should be shortened rather than lengthened, and such examinations are more often made by dentists or their trained assistants rather than by physicians, nurses or teachers.

Except in small school districts where nurses cannot be used for full time, the district nurse is nearly non-existent. Save where she has comparatively few pupils in her care, the work of the school nurse would seem to be better done where she can devote her whole time to school work undisturbed by manifold other duties.

Present economic conditions limit expenditures on personnel ; but, on the whole, school health work has held its own, except where such work had not made a very favourable impression and perhaps deserved to be curtailed.

From time to time, especially where the personnel of the school health service is wholly inadequate, there has been agitation to have pupils examined by private physicians. Since, by our methods, a physician not connected with the school (the " family doctor " or the doctor serving a free clinic) must be consulted before anything is accomplished in the way of treatment, the school physician might seem a superfluous go-between, but family physicians, if they exist, are often considered a luxury, their fees for school examinations would need to be reduced in a certain percentage of cases and omitted in others, and, after examination, there still remains the problem of treatment to be arranged according to the circumstances of the parents. The matter of follow-up is likely to be far less effective where there is no school physician or nurse who make this their business. That the drift, at present, is not in the direction of examinations out of school is indicated by the fact that, in New York State, where the annual presentation of a health certificate is required by law (the alternative being an examination by the school physician), the number of children examined out of school is not over 5 %.

Nevertheless, if school medical inspection is to be truly " educative ", it should point out to parents, not merely the presence of defects in their children and the need of treatment, but the importance of availing themselves, first hand, of professional services in the preservation of the child at his best from infancy onward. With this ideal end in view, it would seem essential that the parents should be present at the school examination, and that they be encouraged to take this phase of child care into their own hands as far as possible.

Logically, the health supervision should begin in infancy and continue upward, and doubtless, in time, there will be no sudden

searching for defects and diseases at 5 or 6 years of age (the time of school entrance), but a continuous care through private or public service extending from infancy upward. This service will be more preventive and supervisory of the child's development and well-being than that which at present exists, and it goes without saying that it will include measures for adequate medical and dental treatment for all children.

ANNEX 1.

FREQUENCY AND EXTENT OF MEDICAL EXAMINATIONS.

RECOMMENDATIONS OF THE AMERICAN PUBLIC HEALTH ASSOCIATION AND THE
WHITE HOUSE CONFERENCE ON CHILD HEALTH AND PROTECTION.

The Committee on Administrative Practice of the American Public Health Association says :

"An important function of school health supervision is the health examination of children for the discovery of physical defects. If this can be done by the family's attending physician and essential facts transmitted to the school, so much the better ; otherwise, these examinations, sufficiently complete to include vision, hearing, throat, heart, lungs, cervical glands and nutrition, should be made by school physicians assisted by nurses. One examination should be made at entrance and at least one thereafter (preferably two if medical personnel is adequate), with children's outer clothing removed to the waist and shoes and stockings off. Parents are urged to be present, at least for the first examination, in order to enlist their interest in and understanding of the findings. The length of time devoted to each individual is one indication of the thoroughness of the examination. Analysis of the school medical work in a large number of cities reveals that the practice which is common is a rapid physical inspection which results in the detection of only the most apparent physical defects. While recognising that even so coarse a method of inspection is not without some value, the development of the thorough health examination with educational emphasis has revealed the limitation and inadequacy of this more superficial method, which is sometimes mentioned as a 'screening process'. At least five minutes per child, on the average, should be allowed for the group of examinations indicated. For many children, fifteen minutes or longer is necessary. The second examination may occur in the fifth or sixth grade ; while, if possible, a third examination should be made in the eighth or ninth grade. Provision should also be made for the examination of selected children referred by the principal for special reasons, as those failing in grade, of new pupils admitted to the school system from other communities, and of cases suspected by the nurse through her inspections to need such examination. In the high schools, provision should be made for the careful examination of pupils who are to engage in competitive athletics and, wherever possible, of all pupils at least in the entering class. Examination should be urged when the child leaves the school system at whatever grade."

On this subject the report of the White House Conference reads :

"The optimum programme involves a thorough pre-school examination of every child, followed by an examination once a year thereafter. Some

administrators contend that an annual examination by a physician is unnecessary, and advocate the following plan as making possible a more thorough examination at reasonable cost : an examination of all pupils before entrance or in the first year of school, and in grades 3, 7, and 10, and of those entering the school system from other districts who do not show evidence of recent examination ; health inspections and screenings by nurses, class-room teachers, or others during intermediate years, and more frequent examinations only for those showing defects or chronic ailments of a more serious nature. The annual examination is undoubtedly preferable if it does not result in superficial diagnosis. A thorough health examination, one that affords opportunity for real education at the time it is made, is fundamental to the whole health programme. It is doubtful whether, on the average, more than four thorough examinations can be made in an hour by one physician, although many systems, inadequately equipped with staff, attempt as many as six to eight.

“A complete examination should include consideration of all aspects of physical, mental and emotional health. It should involve the services of some or all of the following specialists : physician, dentist, otologist, oculist, orthopædist, pediatrician and psychologist. Certain facts pertinent to the examination, such as height, weight and age, can be supplied by the nurse or teacher. The nurse might conduct some of the non-technical phases of the examination, under the direction of the specialists, although all features involving technical knowledge of health conditions should be examined directly by a physician, if possible. When the service of a physician is not available for a yearly health examination, a health-screening or inspection can be made by the class-room teacher or the nurse, if adequately trained, to detect those pupils most obviously having health defects who should be referred to family or school physicians for complete examination and technical diagnosis. Individual and cumulative health records should be kept, following each child throughout his school career.

“If possible, the examination by the physician should be made with the child stripped or clothed only with a slip cover. One or both parents should be present, especially during the examination in the early years of school life when the child is too young to profit much from instruction by the physicians or nurses, and the parent must receive the instruction for him. The programme following the examination is usually more effective if one of the parents has been present.

“The examination should include eyes, ears, nose, throat, teeth, heart, lungs, feet, abdomen, back, extremities, skin, orthopædic conditions, nutritional conditions, nervous condition, mental and emotional state, glandular condition and general health tone.

“The permanent health card should also give salient facts concerning mental ability and scholastic attainment as shown by standard tests, together with the health history of the pupil, the family and social background that may have significant relation to mental, emotional, physical and social conditions discovered through the periodic examinations. For

educational purposes, the weight should be recorded monthly during the early school years, including the junior high school, even if this detail is not needed as frequently for health diagnosis. The weight should also be recorded semi-annually, if not more often, in the senior high school. Although weight is no longer regarded as a direct measure of nutrition, or as a dependable index of health, every child should gain in weight. Height should be recorded semi-annually throughout the child's school life.

"Because of the universal need of dental care for children, school dental work is assigned a prominent place in the school health programme. Each child should have a complete dental examination twice annually. Such a programme is rather heavy for the school to finance. However, the school can promote this programme by education of the parents. The following adjustment in a school dental programme has proved satisfactory : a complete dental examination for each child in the kindergarten or first grade, and again in the fourth grade ; careful inspection should be made during the intermediate and following years by dental attendants or dental hygienists, all cases needing special attention being referred to the family dentist, or to a dental clinic if the family is unable to provide the necessary care. All work done by the school should be preventive and educational in nature, and should have the consent of the parents."

ANNEX 2.

SCHOOL NURSING SERVICES.

RECOMMENDATIONS AS GIVEN BY THE COMMITTEE OF THE AMERICAN PUBLIC HEALTH ASSOCIATION.

"In school health service, the nurse works with the teacher, physician, and parents for the health of the child and is a connecting-link between the community health resources and the home . . . The ultimate purpose of the health examination is the well-being of the child, which will be promoted by the correction or alleviation of defects thus revealed ; hence, careful follow-up work by nurses should be done in the home to ensure that the parents assume responsibility for the correction of physical defects and the formation of correct health habits. The nurse should participate in the promotion of hygiene and sanitation of the school plant, assist in securing proper instruction of pupils and parents in the principles of healthy living, and assure herself that adequate nursing care is provided to sick children in their homes when necessary. The nurse-parent-teacher conferences are valuable because they familiarise the parent with the school health programme and environment. In the past, the school nurse has frequently carried on a part of the formal health instruction. With the better training of teachers for teaching health subjects and the development of sound courses of study, the time of the nurse can be spent on services for which she is better fitted.

“Present objectives call for the time of approximately eight nurses to 20,000 schoolchildren, thereby providing for about 400 home visits per 1,000 school population each year. In a city of 100,000 population, this would call for 8,000 home visits, assuming that there are 20,000 schoolchildren. To make these visits would consume 6,133 nurse-hours (forty-six minutes per visit, including travel, etc.), or about two-fifths of the nurses' time, while the remainder (9,200 nurse-hours) would be spent in schools and clinics. Records of defects corrected either by private physicians or dentists or in clinics should be secured and entered as promptly as possible on the individual pupil's card, which should be combined with the scholastic record.

“Nursing service should be provided to assist in the school examinations and inspections, vaccination and special clinics, the follow-up work in the homes, and the conduct of child-care classes. As rapidly as personnel and funds permit, school nursing work should be extended to the high schools, where increasing emphasis may be given to the educational phases of the health programme. In most cities, the school nurses specialise in work for schoolchildren, but it is believed that the advantages of generalised district service hold good here, as in other fields of public-health nursing. It is important, however the school nursing work is organised, that the community nursing problem be visualised and that a proper relationship and division of responsibility be worked out. With a ratio of one generalised nurse serving a district of 2,000 or 2,500 population, each nurse would have an average of 350 to 400 schoolchildren under her charge, so that her district work need not be seriously hampered. While there are difficulties presented by the lack of coincidence between residence districts and grades, or even schools, the experience of a number of cities shows that such difficulties may be overcome with substantial gains in efficiency over the specialised plan.”

ANNEX 3.

SUPERVISION OF CHILDREN DURING AND AFTER TREATMENT.

WHITE HOUSE CONFERENCE ON CHILD HEALTH AND PROTECTION WITH REFERENCE TO FOLLOW-UP PROGRAMME.

“A report of the examinations should be made to all teachers and other school workers who come in contact with the child. If the parents are not present, as soon as possible after the examination they should be informed of the conditions, discovered in the school health examination, which seem to need attention. It is not the function of the school to correct defects, but it is its function to recommend to the home that attention be given the child by the family physician. Where there is no family physician, it is the legitimate function of the school to advise the home regarding available clinical facilities.

“After the report has been made to the parents, either through home visitation or by inviting the parents to come to the school for a conference, the nurse

or visiting teacher should follow the case in the home to learn what has been done to remedy defects. Through conference with the parents, every effort should be made to secure adequate treatment. It may be necessary at times to exercise pressure to secure action, but this should be only as a last resort. Persuasion is usually more effective in producing desirable educational results . . .

"Owing to financial limitations, it is not always possible for parents to have family physicians to give treatment for correction of defects. Under such circumstances, the nurse should endeavour to have the work done through some other agency, preferably a community health clinic. If no clinical facilities are provided by the community, rather than allow the health of the children to suffer, the school may make temporary and emergency provisions for treatment, until the community can be led to provide proper facilities. The permission of parents should, of course, be secured before any action is taken affecting the child."

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A SIXTH ANALYTICAL REVIEW 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 1933. A few reports relating to the previous year, received since the publication of the fifth review, are included.

Schedules which reached Geneva later than May 31st, 1935, will be dealt with in the next review, together with the bulk of the statistics for 1934.

The present analysis deals with a total of 118,062 treated persons, as compared with 115,859 in the fifth, 119,433 in the fourth, 69,541 in the third, 69,707 in the second and 31,656 in the first review. The response in the submission of schedules is gratifying, and the reviewer again desires to express his thanks to the directors of the various institutes for their careful and willing co-operation. The total number of treated persons dealt with in the six reviews is 524,258.

The general characteristics of each schedule are given below.

¹ For previous reviews, see document C.H.844, and the *Quarterly Bulletin*, I, pages 110 and 725 ; II, page 553 ; III, page 613.

METHODS USED AND RESULTS OBTAINED.

| Institute | Year | Vaccine | Days of treatment | Number treated | Deaths | Mortality % | Paralytic accidents |
|---|------|-------------------------------|-------------------|----------------|--------|-------------|---------------------|
| (1) <i>Dried or glycerinated cords.</i> | | | | | | | |
| 1. Algiers | 1933 | Dried 5-2 days : glyc. | 15-25 | 2,518 | 5 | 0.19 | 0 |
| 2. Antananarivo | 1933 | Dried 5-1 days : glyc. | 14-18 | 159 | 1 | 0.62 | 0 |
| 3. Bangkok | 1933 | Dried — : glyc. | 18-25 | 368 | 0 | 0 | 0 |
| 4. Bari | 1933 | Dried 6-2 days : — | 18-25 | 171 | 0 | 0 | 0 |
| 5. Berne | 1933 | Dried 10-2 days : glyc. | 18-21 | 2 | 0 | 0 | 0 |
| 6. Beirut | 1933 | Glyc. 11-20 days. 300-620 mg. | 8-15 | 195 | 3 | 1.5 | 0 |
| 7. Bologna | 1933 | Dried 10-2 days : — | 15-20 | 123 | 0 | 0 | 0 |
| 8. Brussels | 1933 | Dried 9-2 days : glyc. | 18-23 | 30 | 0 | 0 | 0 |
| 9. Buenos Aires | 1933 | Dried 8-1 days | 16-21 | 1,676 | 7 | 0.41 | 2 (both recovered) |
| 10. Ceará (Brazil) | 1933 | Dried 7-2 days : glyc. | ? | 408 | 2 | 0.49 | 0 |
| 11. Dakar (Europeans) | 1933 | Dried 4-2 days : glyc. | 8-16 | 9 | 0 | 0 | 0 |
| 12. Dakar (non-Europeans) | 1933 | Dried — : glyc. | 8-16 | 17 | 0 | 0 | 0 |
| 13. Hanoi (Tonkin) | 1933 | Dried 6-0 days : glyc. | 15-20 | 1,328 | 10 | 0.74 | 0 |
| 14. Keijo (= Seoul, Chosen) | 1933 | Dried 5-1 days : glyc. | 18 | 2,000 | 22 | 1.10 | 0 |
| 15. Lille | 1933 | Dried 5-2 days : glyc. | 14-24 | 95 | 0 | 0 | 0 |
| 16. Lyons | 1933 | Dried 4-2 days : glyc. | 15-25 | 154 | 0 | 0 | 0 |
| 17. Marseilles | 1933 | Dried 5-2 days : glyc. | 15-25 | 294 | 0 | 0 | 0 |
| 18. Montevideo | 1933 | Dried 8-2 days : — | 16-20 | 615 | 0 | 0 | 0 |
| 19. Montpellier | 1933 | Dried 5-2 days : glyc. | 13-24 | 252 | 0 | 0 | 0 |
| 20. Palermo | 1933 | Dried 8-2 days | 27-39 | 387 | 0 | 0 | 0 |
| 21. Paris | 1933 | Dried 5-2 days : glyc. | 15-25 | 443 | 0 | 0 | 0 |
| 22. Saigon (Europeans) | 1933 | Dried 6-1 days : glyc. | 15-21 | 175 | 0 | 0 | 0 |
| 23. Saigon (non-Europeans) | 1933 | Dried — : glyc. | 15-21 | 1,220 | 3 | 0.24 | 0 |
| 24. Tartu (Estonia) | 1933 | Dried 4-2 days : glyc. | 21 | 163 | 0 | 0 | 0 |
| 25. Tokio | 1933 | Dried 5-1 days : — | 18 | 81 | 0 | 0 | 0 |
| 26. Tunis | 1933 | Dried 4-1 days : glyc. | 18-23 | 1,849 | 5 | 0.27 | 0 |
| 27. Vilno | 1933 | Dried 8-2 days : glyc. | 14-20 | 15 | 0 | 0 | 0 |
| | | | | 14,747 | 58 | 0.39 | 2 (0.00014 %) |

| Institute | Year | Vaccine | Days of treatment | Number treated | Deaths | Mortality % | Paralytic accidents |
|---|------|-------------------------------------|-------------------|----------------|--------|-------------|---------------------|
| (2) <i>Modified dilution methods.</i> | | | | | | | |
| 1. Barcelona | 1933 | Högyes modified : 1/5000-1/100 | 20 | 1,053 | 1 | 0.09 | 0 |
| 2. Budapest | 1933 | Högyes modified : 60-240 mg. | 6-10 | 4,844 | 3 | 0.06 | 3 (all fatal) |
| 3. Certain Bulgarian Institutes . | 1933 | Boecker's vaccine : 90 mg. | 20 | 3,654 | 8 | 0.22 | 0 |
| 4. Cernauti (Roumania) | 1933 | Högyes modified | 15-23 | 46 | 0 | 0 | 3 (all fatal) |
| 5. Cernauti (Roumania) | 1933 | Högyes original | 15-21 | 959 | 0 | 0 | 0 |
| 6. Diyarbekir (Turkey) | 1932 | Högyes modified : 122.5-195 mg. | 21 | 70 | 0 | 0 | 0 |
| 7. Diyarbekir (Turkey) | 1933 | Högyes modified : 122.5-195 mg. | 21 | 81 | 1 | 1.23 | 0 |
| 8. Helsinki (Finland) | 1932 | Dried 1 day | 12-21 | 14 | 0 | 0 | 0 |
| 9. Helsinki (Finland) | 1933 | Dried 1 day | 12-21 | 14 | 0 | 0 | 0 |
| 10. Istanbul (Turkey) | 1932 | Högyes modified : 122.5-195 mg. | 21 | 2,020 | 8 | 0.40 | 0 |
| 11. Istanbul (Turkey) | 1933 | Högyes modified : 122.5-195 mg. | 21 | 1,741 | 17 | 0.97 | 0 |
| 12. Madrid | 1933 | Högyes modified : 1/5000-1/100 | 17-20 | 1,714 | 3 | 0.18 | 0 |
| 13. Riga (at institute) | 1933 | Dilution | 14-21 | 29 | 0 | 0 | 0 |
| 14. Riga (outside) | 1933 | Dilution | 14-21 | 171 | 0 | 0 | 0 |
| 15. Utrecht | 1933 | Högyes : 72-212 mg. | 15-21 | 0 | 0 | 0 | 0 |
| 16. Sivas (Turkey) | 1932 | Högyes modified : 122.5-195 mg. | 21 | 153 | 5 | 3.27 | 0 |
| 17. Sivas (Turkey) | 1933 | Högyes modified : 122.5-195 mg. | 21 | 167 | 1 | 0.59 | 0 |
| | | | | 16,730 | 47 | 0.28 | 6 (0.00036 %) |
| (3-5) <i>Phenol vaccines : modifications of fermi's method.</i> | | | | | | | |
| (3) <i>Killed phenol vaccines : Semple and Mulford's modifications.</i> | | | | | | | |
| 1. Baghdad (Europeans) | 1933 | 700-3500 mg. : Semple | 7-14 | 13 | 0 | 0 | 0 |
| 2. Baghdad (non-Europeans) ... | 1933 | 700-3500 mg. : Semple | 7-14 | 266 | 0 | 0 | 0 |
| 3. Bangkok (at institute) | 1933 | Carbolised | 14 | 909 | 5 | 0.55 | 0 |
| 4. Bangkok (outside) | 1933 | Carbolised | 14 | 617 | 5 | 0.81 | 0 |
| 5. Bombay (Europeans) | 1933 | 700-7000 mg. : Semple | 7-14 | 357 | 0 | 0 | 0 |
| 6. Bombay (non-Europeans) | 1933 | 700-7000 mg. : Semple | 7-14 | 7,674 | 33 | 0.43 | 0 |
| 7. Cairo (Europeans) | 1933 | 1400-2100 mg. : Semple | 14-20 | 96 | 0 | 0 | 0 |
| 8. Cairo (non-Europeans) | 1933 | 1400-2100 mg. : Semple ¹ | 14-20 | 2,879 | 24 | 0.38 | 0 |

¹ A few severe cases treated with a 5% emulsion according to Allivisatos' method.

| | | | | | | | |
|--|------|------------------------|-------|--------|-----|--------------|--------------------|
| 9. Calcutta | 1933 | 350-700 mg. : Semple | 7-14 | 7,532 | 38 | 0.50 | 0 |
| 10. Cernauti (Roumania) | 1933 | 600-900 mg. : Semple | 12-18 | 503 | 3 | 0.59 | 0 |
| 11. Colombo | 1933 | | 14 | 990 | 7 | 0.71 | 1 (recovered) |
| 12. Coonoor (Europeans) | 1933 | 700-7000 mg. : Semple | 7-14 | 281 | 0 | 0 | 0 |
| 13. Coonoor (non-Europeans) | 1933 | 700-7000 mg. : Semple | 7-14 | 9,192 | 33 | 0.36 | 0 |
| 14. Cracow | 1933 | — : Semple | 20 | 111 | 1 | 0.90 | 0 |
| 15. Hong-Kong | 1933 | 1400 mg. : Semple | 14 | 208 | 0 | 0 | 0 |
| 16. Jerusalem | 1933 | 700-2000 mg. : Semple | 14-20 | 760 | 1 | 0.13 | 0 |
| 17. Kasauli : Class II (at institute) | 1933 | 1400 mg. : Semple | 14 | 454 | 0 | 0 | 0 |
| 18. Kasauli : Class II (out-centres) | 1933 | 1400 mg. : Semple | 14 | 4,229 | 11 | 0.26 | 0 |
| 19. Kasauli : Class III (at institute) | 1933 | 3500 mg. : Semple | 14 | 1,062 | 1 | 0.09 | 0 |
| 20. Kasauli : Class III (out-centres) | 1933 | 3500 mg. : Semple | 14 | 5,099 | 15 | 0.29 | 1 (fate unknown) |
| 21. Kasauli : Class IV (at institute) | 1933 | 7000 mg. : Semple | 14 | 992 | 20 | 2.02 | 1 (recovered) |
| 22. Kasauli : Class IV (out-centres) | 1933 | 7000 mg. : Semple | 14 | 1,722 | 37 | 2.15 | 2 (both recovered) |
| 23. Kuala Lumpur | 1933 | 1400-2100 mg. : Semple | 14-21 | 46 | 0 | 0 | 0 |
| 24. Lisbon | 1933 | 2500-7500 mg. : Semple | 10-40 | 265 | 0 | 0 | 0 |
| 25. Lwow (at institute) | 1933 | Mulford's vaccine | 20 | 221 | 0 | 0 | 0 |
| 26. Lwow (outside) | 1933 | — : Semple | 20 | 637 | 3 | 0.47 | 0 |
| 27. Milan | 1933 | 4500-7500 mg. : Semple | 15-25 | 41 | 0 | 0 | 0 |
| 28. Mexico | 1932 | 2240-4960 mg. : Semple | 14-16 | 3,469 | 0 | 0 | 0 |
| 29. Mexico | 1933 | 2240-4960 mg. : Semple | 14-16 | 3,241 | 0 | 0 | 0 |
| 30. New York | 1933 | — : Semple | 14-21 | 1,244 | 0 | 0 | 0 |
| 31. Rangoon (Europeans) | 1933 | 700-7000 mg. : Semple | 7-14 | 170 | 0 | 0 | 0 |
| 32. Rangoon (non-Europeans) | 1933 | 700-7000 mg. : Semple | 7-14 | 1,366 | 7 | 0.51 | 1 (fatal) |
| 33. Santa Clara (Cuba) | 1933 | 1920-3360 mg. : Semple | 15-21 | 451 | 0 | 0 | 0 |
| 34. Santiago (Chile) | 1933 | 2240-3200 mg. : Semple | 14-20 | 184 | 0 | 0 | 0 |
| 35. Shanghai (Europeans) | 1933 | 675-1800 mg. : Semple | 15-24 | 138 | 0 | 0 | 0 |
| 36. Shanghai (non-Europeans) | 1933 | 675-1800 mg. : Semple | 15-24 | 259 | 2 | 0.76 | 0 |
| 37. Toronto | 1932 | — : Semple | 14-21 | 15 | 0 | 0 | 0 |
| 38. Toronto | 1933 | — : Semple | 14-21 | 62 | 1 | 1.61 | 0 |
| 39. Warsaw (at institute) | 1933 | 800 mg. : Semple | 20 | 146 | 0 | 0 | 0 |
| 40. Warsaw (outside) | 1933 | 800 mg. : Semple | 20 | 1,903 | 12 | 0.63 | 0 |
| | | | | 59,804 | 259 | 6 (0.0001 %) | |

| Institute | Year | Vaccine | Days of treatment | Number treated | Deaths | Mortality % | Paralytic accidents |
|---|------|---|------------------------------------|----------------|--------|-------------|---------------------|
| (4) <i>Live phenol vaccines : Puntoni's modification.</i> | | | | | | | |
| 1. Ancona | 1933 | Puntoni's modification | 16-24 | 16 | 0 | 0 | 0 |
| 2. Catania | 1933 | Puntoni's modification | 15-25 | 58 | 1 | 1.72 | 0 |
| 3. Rome | 1933 | Puntoni's modification | 15-25 | 166 | 0 | 0 | 0 |
| 4. Trapani | 1933 | Puntoni's modification | 15-25 | 26 | 0 | 0 | 0 |
| 5. Turin | 1933 | Puntoni's modification | 20-27 | 35 | 0 | 0 | 0 |
| | | | | 301 | 1 | 0.33 | 0 |
| (5) <i>Fermi's original method.</i> | | | | | | | |
| 1. Genoa | 1933 | Fermi | 15-25 | 13 | 0 | 0 | 0 |
| 2. Košice (Czechoslovakia) | 1933 | Fermi | 14-21 | 338 | 0 | 0 | 0 |
| | | | | 351 | 0 | 0 | 0 |
| (7) <i>Heated vaccines : Babeş method.</i> | | | | | | | |
| 1. Bucharest | 1933 | Dried 6-0 days + heated 50°-60° C. | 10-24 | 8,256 | 22 | 0.27 | 0 |
| 2. Jassy | 1933 | Heated 45°-65° C. + unheated | 15-23 | 4,364 | 1 | 0.02 | 4 (one fatal) |
| | | | | 12,620 | 23 | 0.18 | 4 (0.00031 %) |
| (8) <i>Killed ether vaccines : Hempt's method.</i> | | | | | | | |
| 1. Yugoslav institutes | 1933 | Hempt's standard vaccine : 2000-3000 mg. | 4-6 | 8,248 | 13 | 0.16 | 0 |
| (9) <i>Mixed treatments.</i> | | | | | | | |
| 1. Athens | 1933 | } Slight cases, Boecker's method Severe cases, same + Alivisatos | 20-? | 1,776 | 1 | 0.06 | 1 (recovered) |
| 2. Certain Bulgarian institutes .. | 1933 | | Högyes + Alivisatos ; 275-3700 mg. | 13-15 | 3,202 | 5 | 0.15 |
| 3. Vienna | 1933 | Högyes + Alivisatos | 13-21 | 283 | 1 | 0.35 | 2 (both recovered) |
| | | | | 5,261 | 7 | 0.13 | 3 (0.057 %) |

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, as in previous reviews, under the following heads :

1. *Dried or glycerinated cords* (Pasteur's original and Calmette).
2. *Modified dilution methods* (Högyes).
- 3-5. *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 treatment* (dilutions plus, in severe cases, Alivisatos).
10. *Yalren vaccine.*

It will be noted that Nos. 3-6 above comprise Fermi's original method and its modifications.

In certain instances, the following shortened scheme of classification has been followed :

- (a) Killed vaccines : comprising 3 and 8 above.
- (b) Live vaccines : comprising 1, 2, 4 and 9 above.
- (c) Heated vaccine : 7 above.
- (d) Other : comprising 5, 6 and 10 above.

III. NUMBERS OF PERSONS TREATED.

The total number of treated persons regarding whom information has been submitted was 118,062. The adjoining table gives the distribution of these according to the method of treatment, the number of institutes concerned, the number of annual returns submitted, and the average number of patients per annual return. The object of this table is to show the average annual number treated during a single year according to each particular method

of treatment. When the statistics of a group of institutes are submitted in combined form in a single schedule—viz., Yugoslav institutes, treatment Hempt's method ; and Bulgarian institutes, treatment either modified Högyes method or the same reinforced by Alivisatos vaccine, and classified above in the group 9, Mixed—the table cannot be entered. Where no entry is made, the detail will be found in the table on pages 753-756.

| | Patients | Institutes | Annual returns | Average per annual return |
|---------------------------|----------|------------|----------------|---------------------------|
| 1. Cords | 14,747 | 25 | 25 | 590 |
| 2. Dilutions | 16,730 | — | — | — |
| 3. Killed phenol | 59,804 | 24 | 26 | 2,300 |
| 4. Live phenol | 301 | 5 | 5 | 60 |
| 5. Fermi's original | 351 | 2 | 2 | 175 |
| 7. Heated | 12,620 | 2 | 2 | 6,310 |
| 8. Killed ether | 8,248 | — | — | — |
| 9. Mixed | 5,261 | — | — | — |
| Total | 118,062 | | | |

IV. MORTALITIES FOR ALL PATIENTS.

Of the total of 118,062 treated persons, 408 died of rabies. The percentage mortality was thus 0.35, 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, and 0.40 over the whole period covered by the six reviews.

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

| | Sixth review | | | All six reviews | | | |
|------------------------------|----------------|--------|-------------|-----------------|----------|-------------------------|-------------|
| | Number treated | Deaths | Mortality % | Number treated | Deaths | | Mortality % |
| | | | | | Observed | Calculated ¹ | |
| 1. Cords | 14,747 | 58 | 0.39 | 78,400 | 300 | 310 | 0.38 |
| 2. Dilutions ... | 16,730 | 47 | 0.28 | 43,770 | 95 | 173 | 0.22 |
| 3. Killed phenol | 59,804 | 259 | 0.42 | 233,488 | 1,415 | 925 | 0.61 |
| 4. Live phenol. | 301 | 1 | 0.33 | 2,268 | 5 | 9 | 0.22 |
| 5. Fermi's orig. | 351 | 0 | 0 | 5,124 | 12 | 20 | 0.23 |
| 6. Fermi's sero-vaccine | — | — | — | 255 | 0 | 1 | 0 |
| 7. Heated | 12,620 | 23 | 0.18 | 67,664 | 120 | 268 | 0.18 |
| 8. Killed ether. | 8,248 | 13 | 0.16 | 46,547 | 65 | 184 | 0.14 |
| 9. Mixed | 5,261 | 7 | 0.13 | 41,358 | 51 | 164 | 0.12 |
| 10. Yatren | — | — | — | 5,384 | 13 | 21 | 0.24 |
| Total | 118,062 | 408 | 0.35 | 524,258 | 2,076 | 2,075 | 0.40 |

$P < 1$ in a million

¹ "Calculated" from the mortality of the total of the ten groups (i.e., from 0.40): for example, $310 = 0.396 \times 78,400 \cdot 100$. In the above table the rate 0.396 has been rounded to 0.40.

According to the shortened system of classification the figures are :

| | Sixth review | | | Number treated | All six reviews | | Mortality % |
|----------------------|----------------|--------|-------------|----------------|-----------------|------------|-------------|
| | Number treated | Deaths | Mortality % | | Observed | Calculated | |
| (a) Killed | 68,052 | 272 | 0.40 | 280,035 | 1,480 | 1,109 | 0.53 |
| (b) Live | 37,039 | 113 | 0.31 | 165,796 | 451 | 657 | 0.27 |
| (c) Heated | 12,620 | 23 | 0.18 | 67,664 | 120 | 268 | 0.18 |
| (d) Other | 351 | 0 | 0 | 10,763 | 25 | 43 | 0.23 |
| Total | 118,062 | 408 | 0.35 | 524,258 | 2,076 | 2,077 | 0.40 |

P < 1 in a million

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

| | First | Second | Third | Fourth | Fifth | Sixth | All six |
|----------------------|-------|--------|-------|--------|-------|-------|---------|
| (a) Killed | 0.65 | 0.80 | 0.28 | 0.66 | 0.51 | 0.40 | 0.53 |
| (b) Live | 0.27 | 0.26 | 0.21 | 0.26 | 0.23 | 0.31 | 0.27 |
| (c) Heated | — | 0.15 | 0.08 | 0.04 | 0.24 | 0.18 | 0.18 |
| (d) Other | — | — | — | 0.22 | 0.27 | 0 | 0.23 |
| Total | 0.49 | 0.48 | 0.23 | 0.48 | 0.34 | 0.35 | 0.40 |

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 conventionally be taken as being defined by $P = 0.05$, any lesser value indicating a real discrepancy.¹

V. RACIAL STATISTICS.

Information regarding race-type was lacking in the case of 7,345 persons, none of whom died of rabies. These relate to the institutes

¹ . . . and in the present comparison significant differences in the efficacy of the various vaccination methods employed. [EDITOR.]

at Santiago (Chile), Santa Clara (Cuba), and Mexico. Of the remaining, 57,577 were Europeans (52 %) and 53,140 were of non-European birth (48 %).

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

| | First | Second | Third | Fourth | Fifth | Sixth | All six |
|---------------------------------------|-------|--------|-------|--------|-------|-------|---------|
| 1. Cords | 57.6 | 52.7 | 50.2 | 62.5 | 56.1 | 49.5 | 54.4 |
| 2. Dilutions . . . | 100 | 100 | 100 | 94.8 | 96.6 | 100 | 98.7 |
| 3. Killed phenol | 19.7 | 11.9 | 62.1 | 10.3 | 15.6 | 12.9 | 15.5 |
| 4. Live phenol . | — | 100 | 100 | 100 | 100 | 100 | 100 |
| 5. Fermi's vacc. | — | — | — | 100 | 100 | 100 | 100 |
| 6. Fermi's sero- vaccine | — | — | — | 100 | 100 | — | 100 |
| 7. Heated | — | 100 | 100 | 100 | 100 | 100 | 100 |
| 8. Killed ether. | 99.7 | — | 100 | 100 | 100 | 100 | 100 |
| 9. Mixed | 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 | 56.6 |

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

| | Number treated | Sixth review | | | Mortality % | All six reviews | | | |
|---------------------------------------|-------------------|--------------|------------|----------------|----------------|-------------------|----------|------------|----------------|
| | | Deaths | | Mortality % | | Number treated | Deaths | | Mortality % |
| | | Observed | Calculated | | | | Observed | Calculated | |
| <i>Europeans.</i> | | | | | | | | | |
| 1. Cords | 7,309 | 10 | 15 | 0.14 | 40,522 | 66 | 66 | 0.16 | |
| 2. Dilutions . . . | 16,730 | 47 | 35 | 0.28 | 43,218 | 85 | 71 | 0.20 | |
| 3. Killed phenol | 6,757 | 20 | 14 | 0.30 | 34,034 | 51 | 56 | 0.15 | |
| 4. Live phenol. | 301 | 1 | 0.6 | 0.33 | 2,268 | 5 | 4 | 0.22 | |
| 5. Fermi's vacc. | 351 | 0 | 0.7 | 0 | 5,123 | 12 | 8 | 0.23 | |
| 6. Fermi's sero- vaccine | — | — | — | — | 255 | 0 | 0.4 | 0 | |
| 7. Heated | 12,620 | 23 | 27 | 0.18 | 67,664 | 120 | 111 | 0.18 | |
| 8. Killed ether. | 8,248 | 13 | 17 | 0.16 | 46,547 | 65 | 76 | 0.14 | |
| 9. Mixed | 5,261 | 7 | 11 | 0.13 | 41,358 | 51 | 68 | 0.12 | |
| 10. Yatren | — | — | — | — | 5,384 | 13 | 9 | 0.24 | |
| Total | 57,577 | 121 | 120 | 0.21 | 286,373 | 468 | 469 | 0.16 | |
| | | P = 0.07 | | | | P = 0.15 | | | |
| <i>Non-Europeans.</i> | | | | | | | | | |
| 1. Cords | 7,438 | 48 | 40 | 0.65 | 33,915 | 225 | 244 | 0.66 | |
| 3. Killed phenol. | 45,702 | 239 | 246 | 0.52 | 185,766 | 1,353 | 1,334 | 0.73 | |
| Total | 53,140 | 287 | 286 | 0.54 | 219,681 | 1,578 | 1,578 | 0.72 | |
| | | P = 0.17 | | | | P = 0.18 | | | |

Or, using the shortened system of classification :

| | Number treated | Sixth review | | | Mortality % | Number treated | All six reviews | | Mortality % |
|-----------------------|----------------|--------------|------------|-------------|-------------|----------------|-----------------|------------|-------------|
| | | Deaths | | Mortality % | | | Deaths | | |
| | | Observed | Calculated | | | | Observed | Calculated | |
| <i>Europeans.</i> | | | | | | | | | |
| (a) Killed | 15,005 | 33 | 32 | 0.22 | 80,581 | 116 | 132 | 0.14 | |
| (b) Live | 29,601 | 65 | 62 | 0.22 | 127,366 | 207 | 208 | 0.16 | |
| (c) Heated | 12,620 | 23 | 27 | 0.18 | 67,664 | 120 | 111 | 0.18 | |
| (d) Other | 351 | 0 | 0.7 | 0 | 10,762 | 25 | 18 | 0.23 | |
| Total | 57,577 | 121 | 121.7 | 0.21 | 286,373 | 468 | 469 | 0.16 | |
| | | P = 0.60 | | | | P = 0.16 | | | |
| <i>Non-Europeans.</i> | | | | | | | | | |
| (a) Killed | 45,702 | 239 | 246 | 0.52 | 185,766 | 1,353 | 1,334 | 0.73 | |
| (b) Live | 7,438 | 48 | 40 | 0.65 | 33,915 | 225 | 244 | 0.66 | |
| Total | 53,140 | 287 | 286 | 0.54 | 219,681 | 1,578 | 1,578 | 0.72 | |
| | | P = 0.17 | | | | P = 0.18 | | | |

The mortalities as compared with previous reviews are as under :

| <i>Europeans.</i> | First | Second | Third | Fourth | Fifth | Sixth | All six |
|-----------------------|-------|--------|-------|--------|-------|-------|---------|
| (a) Killed | 0.10 | 0.14 | 0.10 | 0.12 | 0.19 | 0.22 | 0.14 |
| (b) Live | 0.20 | 0.11 | 0.13 | 0.15 | 0.17 | 0.22 | 0.16 |
| (c) Heated | — | 0.15 | 0.08 | 0.04 | 0.24 | 0.18 | 0.18 |
| (d) Other | — | — | — | 0.19 | 0.27 | 0 | 0.23 |
| Total | 0.17 | 0.13 | 0.10 | 0.14 | 0.21 | 0.21 | 0.16 |
| <i>Non-Europeans.</i> | | | | | | | |
| (a) Killed | 0.83 | 0.89 | 0.93 | 0.85 | 0.65 | 0.52 | 0.73 |
| (b) Live | 1.02 | 0.82 | 0.71 | 0.74 | 0.46 | 0.65 | 0.66 |
| Total | 0.84 | 0.88 | 0.78 | 0.83 | 0.62 | 0.54 | 0.72 |

Each of the values of P, in the figures relating to the sixth review and in those relating to all six reviews, is greater than 0.05, and consequently there is no evidence of heterogeneity arising from method of treatment.¹

It should be noted that, as indicated in the above table of comparative mortalities, there appears to be a distinct tendency for the mortalities of non-Europeans treated by killed vaccines to fall. From a level of approximately 0.85 % over the period of the first four reviews, it has fallen to 0.65 in 1932 and 0.52 in 1933.

Finally, it appears from the combined figures that the mortality amongst non-Europeans is 4.5 times as great as that amongst Europeans. This difference is, as previously, highly significant.

¹ *I.e.*, no evidence of significant differences in the efficacy of the various methods. [EDITOR.]

VI. SPECIES OF BITING ANIMAL.

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

| | Dog | Cat | Wolf | Jackal | Solipeds | Ruminants | Other | Human |
|-------------------------|------|------|------|--------|----------|-----------|-------|-------|
| 1. Cords | 88.0 | 8.4 | 0.1 | 0.3 | 0.7 | 0.5 | 1.5 | 0.5 |
| 2. Dilutions | 79.4 | 10.4 | 0.2 | 0.2 | 0.9 | 5.2 | 1.7 | 2.1 |
| 3. Killed phenol | 89.2 | 1.7 | 0.1 | 6.4 | 0.4 | 0.6 | 1.1 | 0.5 |
| 4. Live phenol | 80.1 | 18.3 | 0 | 0 | 0.3 | 0 | 1.3 | 0 |
| 5. Fermi's vaccine | 81.2 | 12.0 | 0 | 0 | 0 | 4.0 | 2.8 | 0 |
| 7. Heated | 87.4 | 7.1 | 0.2 | 0 | 0.4 | 3.2 | 0.8 | 0.8 |
| 8. Killed ether | 79.1 | 5.8 | 0.2 | 0.05 | 0.9 | 4.6 | 1.7 | 7.7 |
| 9. Mixed | 84.7 | 8.4 | 0.1 | 0.1 | 1.7 | 4.0 | 0.4 | 0.5 |
| Total | 86.5 | 5.0 | 0.1 | 3.3 | 0.6 | 1.9 | 1.2 | 1.3 |

The figures relating to mortality are as follows :

| | (a) Dog | | | (b) Cat | | |
|-------------------------|----------------|--------|-------------|----------------|--------|-------------|
| | Number treated | Deaths | Mortality % | Number treated | Deaths | Mortality % |
| 1. Cords | 12,987 | 55 | 0.42 | 1,236 | 2 | 0.16 |
| 2. Dilutions | 13,255 | 39 | 0.29 | 1,730 | 0 | |
| 3. Killed phenol | 52,879 | 208 | 0.39 | 996 | 0 | |
| 4. Live phenol | 241 | 1 | 0.41 | 55 | 0 | |
| 5. Fermi's vaccine | 285 | 0 | 0 | 42 | 0 | |
| 7. Heated | 11,036 | 21 | 0.19 | 895 | 0 | |
| 8. Killed ether | 6,530 | 8 | 0.12 | 477 | 0 | |
| 9. Mixed | 4,456 | 7 | 0.16 | 440 | 0 | |
| Total | 101,669 | 339 | 0.33 | 5,871 | 2 | 0.03 |

(c) Wolf

| | Sixth review | | | All six reviews | | | |
|------------------|----------------|--------|-------------|------------------|----------|------------|-------------------|
| | Number treated | Deaths | Mortality % | Number treated | Deaths | | Mortality % |
| | | | | | Observed | Calculated | |
| 1. Cords | 20 | 0 | 0 | 43 | 4 | 4 | 9.30 |
| 2. Dilutions ... | 31 | 7 | 22.6 | 52 | 11 | 5 | 21.15 |
| 3. Killed phenol | 44 | 2 | 4.6 | 253 | 28 | 25 | 11.06 |
| 7. Heated | 25 | 2 | 8.0 | 72 | 6 | 7 | 8.33 |
| 8. Killed ether. | 17 | 5 | 29.4 | 152 ¹ | 11 | 15 | 7.24 ¹ |
| 9. Mixed | 6 | 0 | 0 | 66 | 5 | 6 | 7.58 |
| 10. Yatren | — | — | — | 23 | 0 | 2 | 0 |
| Total | 143 | 16 | 11.2 | 661 ¹ | 65 | 64 | 9.83 ¹ |

¹ These figures are correct. That they are not in exact agreement with those given in the fifth review arises from the fact that a correction was received from Yugoslavia.

(d) *Jackal*

| | Sixth review | | | All six reviews | | |
|------------------------|----------------|-----------|-------------|-----------------|------------|-------------|
| | Number treated | Deaths | Mortality % | Number treated | Deaths | Mortality % |
| 1. Cords | 50 | 0 | | 93 | 0 | |
| 2. Dilutions | 27 | 0 | | 29 | 0 | |
| 3. Killed phenol | 3,794 | 46 | 1.21 | 16,525 | 273 | 1.65 |
| 7. Heated | — | — | | 70 | 0 | |
| 8. Killed ether | 4 | 0 | | 4 | 0 | |
| 9. Mixed | 4 | 0 | | 29 | 1 | 3.44 |
| Total | 3,879 | 46 | 1.19 | 16,750 | 274 | 1.64 |

(e) *Solipeds, Ruminants, Human and Other*

| | Solipeds | Ruminants | Other | Human |
|--------------------------|------------|--------------------------|--------------------------|--------------------------|
| 1. Cords | 96 | 76 ¹ | 215 | 67 |
| 2. Dilutions | 155 | 864 | 281 ¹ | 359 |
| 3. Killed phenol | 254 | 332 | 656 ² | 322 ¹ |
| 4. Live phenol | 1 | — | 4 | — |
| 5. Fermi's vaccine | — | 14 | 10 | — |
| 7. Heated | 56 | 406 | 104 | 98 |
| 8. Killed ether | 71 | 377 | 138 | 634 |
| 9. Mixed | 91 | 210 | 23 | 27 |
| Total | 724 | 2,279¹ | 1,421² | 1,507¹ |

¹ One death.

² Two deaths.

³ Three deaths.

Information regarding the biting animal was lacking in the case of 569 persons.

One death was reported amongst persons bitten by ruminants. This case was reported from Keijo (Seoul, Chosen). The bite inflicted by a cow was deep and on the bare arm; the case belonged to category B. The patient was eighteen days late in commencing treatment, and died of rabies on the thirty-sixth day after the bite.

A case of human origin is reported from Kasauli; its features were as follows: Category A, superficial, on bare skin, on arm, seven days late in commencing treatment, interval between wounding and death doubtful.

Of the deaths amongst those bitten by other animals, one was of a person bitten by a hyena and treated by dilutions at Diyarbekir, two were bitten by leopards and treated by killed phenol vaccines at Coonor and Kasauli respectively.

From the combined figures for the six reviews, it appears that, of 12,007 persons bitten by solipeds and ruminants, only one case—that cited above from Chosen—has developed rabies. Of 3,692 persons who have been in contact with cases of human rabies, only

one person—that cited above from Kasauli—is reported as having developed rabies.

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 | 10.8 | 15.4 | 67.4 | 6.4 |
| 2. Dilutions | 19.1 | 21.4 | 50.5 | 9.0 |
| 3. Killed phenol | 5.6 | 6.3 | 87.1 | 0.9 |
| 4. Live phenol | 15.3 | 21.8 | 60.7 | 2.2 |
| 5. Fermi's original | 34.5 | 5.4 | 58.1 | 2.0 |
| 7. Heated | 6.3 | 32.3 | 53.4 | 8.0 |
| 8. Killed ether | 22.9 | 12.2 | 64.9 | 0 |
| 9. Mixed | 19.9 | 34.9 | 27.6 | 17.9 |
| Total | 10.0 | 14.0 | 71.8 | 4.2 |

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

Category A.

| | Sixth review | | | All six reviews | | |
|-------------------------|----------------|--------|-------------|-----------------|--------|-------------|
| | Number treated | Deaths | Mortality % | Number treated | Deaths | Mortality % |
| 1. Cords | 1,579 | 14 | 0.89 | 4,916 | 38 | 0.77 |
| 2. Dilutions | 2,768 | 4 | 0.14 | 4,096 | 9 | 0.22 |
| 3. Killed phenol | 3,332 | 17 | 0.53 | 10,155 | 64 | 0.63 |
| 4. Live phenol | 42 | 0 | 0 | 174 | 0 | 0 |
| 5. Fermi's original ... | 121 | 0 | 0 | 181 | 1 | 0.55 |
| 6. Fermi's sero-vaccine | — | — | — | 5 | 0 | 0 |
| 7. Heated | 790 | 2 | 0.25 | 5,138 | 18 | 0.35 |
| 8. Killed ether | 1,888 | 3 | 0.16 | 4,897 | 14 | 0.29 |
| 9. Mixed | 1,042 | 3 | 0.29 | 4,944 | 8 | 0.16 |
| 10. Yatren | — | — | — | 298 | 0 | 0 |
| Total | 11,562 | 43 | 0.37 | 34,804 | 152 | 0.44 |

Category B.

| | | | | | | |
|-------------------------|--------|----|------|--------|-----|------|
| 1. Cords | 2,262 | 12 | 0.53 | 13,700 | 87 | 0.64 |
| 2. Dilutions | 3,091 | 15 | 0.49 | 8,976 | 32 | 0.36 |
| 3. Killed phenol | 3,707 | 10 | 0.27 | 14,471 | 53 | 0.37 |
| 4. Live phenol | 60 | 1 | 1.67 | 488 | 2 | 0.41 |
| 5. Fermi's original ... | 19 | 0 | 0 | 879 | 2 | 0.23 |
| 6. Fermi's sero-vaccine | — | — | — | 23 | 0 | 0 |
| 7. Heated | 4,074 | 4 | 0.10 | 16,177 | 25 | 0.15 |
| 8. Killed phenol | 1,005 | 2 | 0.19 | 4,658 | 8 | 0.17 |
| 9. Mixed | 1,831 | 2 | 0.11 | 16,375 | 26 | 0.16 |
| 10. Yatren | — | — | — | 2,644 | 9 | 0.34 |
| Total | 16,049 | 46 | 0.29 | 78,391 | 244 | 0.31 |

¹ A = proved rabid by experiment ; B = certified rabid by medical or veterinary physician ; C = suspected to be rabid ; D = not suspected to be rabid.

Category C.

| | Sixth review | | | All six reviews | | |
|-------------------------|----------------|------------|-------------|-----------------|--------------|-------------|
| | Number treated | Deaths | Mortality % | Number treated | Deaths | Mortality % |
| 1. Cords | 9,898 | 32 | 0.32 | 47,435 | 147 | 0.31 |
| 2. Dilutions | 7,300 | 14 | 0.19 | 21,481 | 33 | 0.15 |
| 3. Killed phenol | 51,408 | 231 | 0.45 | 189,394 | 1,261 | 0.66 |
| 4. Live phenol | 167 | 0 | 0 | 1,119 | 2 | 0.18 |
| 5. Fermi's original ... | 204 | 0 | 0 | 1,058 | 3 | 0.28 |
| 6. Fermi's sero-vaccine | — | — | — | 5 | 0 | 0 |
| 7. Heated | 6,745 | 17 | 0.25 | 41,923 | 74 | 0.18 |
| 8. Killed ether | 5,355 | 8 | 0.15 | 21,272 | 36 | 0.17 |
| 9. Mixed | 1,448 | 1 | 0.07 | 10,959 | 9 | 0.08 |
| 10. Yatren | — | — | — | 1,486 | 4 | 0.27 |
| Total | 82,525 | 303 | 0.37 | 336,132 | 1,569 | 0.47 |

Category D.

| | | | | | | |
|-------------------------|--------------|----------|-------------|---------------|-----------|--------------|
| 1. Cords | 937 | 0 | 0 | 5,285 | 3 | 0.06 |
| 2. Dilutions | 1,300 | 1 | 0.08 | 4,642 | 5 | 0.11 |
| 3. Killed phenol | 557 | 1 | 0.18 | 6,874 | 7 | 0.10 |
| 4. Live phenol | 6 | 0 | 0 | 85 | 0 | 0 |
| 5. Fermi's original ... | 7 | 0 | 0 | 18 | 0 | 0 |
| 6. Fermi's sero-vaccine | — | — | — | — | — | — |
| 7. Heated | 1,011 | 0 | 0 | 2,993 | 0 | 0 |
| 8. Killed phenol | — | — | — | 12,722 | 0 | 0 |
| 9. Mixed | 940 | 1 | 0.11 | 5,516 | 3 | 0.05 |
| 10. Yatren | — | — | — | 956 | 0 | 0 |
| Total | 4,758 | 3 | 0.06 | 39,091 | 18 | 0.046 |

Details regarding 3,168 persons, of whom thirteen died of rabies, are lacking.

Three fatal cases are reported as having occurred from the bites of animals not suspected to be rabid (category D above). Two of these occurred at Bulgarian institutes, and one was reported from Kasauli out-centres.

As in former reviews, in this and in the succeeding sections the statistics of the two race-types—European and non-European—will be treated separately, as the degree of heterogeneity introduced when the two race-types are considered together is so great as to mask other effects. The reviewer is grateful to the directors of institutes who have acceded to the request that the figures relating to the two race-types should be submitted on separate schedules.

In the following table the statistics for categories A and B combined—that is, the statistics regarding those bitten by animals

proved or certified to be rabid—and those for category C, relating to those bitten by animals suspected to be rabid, are given for the sixth review and for the total of the six reviews.

Categories A and B (combined).

| | Sixth review | | | All six reviews | | | Mortality % |
|---------------------------------------|----------------|-----------|-------------|-----------------|------------|------------|-------------|
| | Number treated | Deaths | Mortality % | Number treated | Deaths | | |
| <i>Europeans.</i> | | | | | Observed | Calculated | |
| 1. Cords | 1,513 | 3 | 0.20 | 7,438 | 15 | 16 | 0.20 |
| 2. Dilutions . . . | 5,859 | 19 | 0.32 | 15,268 | 43 | 32 | 0.28 |
| 3. Killed phenol | 3,193 | 9 | 0.28 | 11,492 | 21 | 24 | 0.18 |
| 4. Live phenol. | 102 | 1 | 0.98 | 968 | 3 | 2 | 0.31 |
| 5. Fermi's orig. | 140 | 0 | 0 | 1,060 | 3 | 2 | 0.28 |
| 6. Fermi's sero- vaccine | — | — | — | 28 | 0 | (0.06) | 0 |
| 7. Heated | 4,864 | 6 | 0.12 | 22,325 | 46 | 47 | 0.21 |
| 8. Killed ether. | 2,893 | 5 | 0.17 | 12,553 | 29 | 27 | 0.23 |
| 9. Mixed | 2,873 | 5 | 0.17 | 23,647 | 38 | 50 | 0.16 |
| 10. Yatren | — | — | — | 2,942 | 9 | 6 | 0.31 |
| Total | 21,437 | 48 | 0.22 | 97,721 | 207 | 206 | 0.21 |
| <i>Non-Europeans.</i> | | | | | | | |
| 1. Cords | 780 | 13 | 1.67 | 1,779 | 24 | 13 | 1.35 |
| 3. Killed phenol. | 1,847 | 9 | 0.49 | 7,616 | 47 | 58 | 0.62 |
| Total | 2,627 | 22 | 0.84 | 9,395 | 71 | 71 | 0.76 |
| P = 0.27 | | | | | | | |
| P = 0.0007 | | | | | | | |

Category C.

| | | | | | | | Mortality % |
|---------------------------------------|----------------|------------|-------------|----------------|------------|------------|-------------|
| | Number treated | Deaths | Mortality % | Number treated | Deaths | | |
| <i>Europeans.</i> | | | | | Observed | Calculated | |
| 1. Cords | 2,877 | 4 | 0.14 | 10,351 | 14 | 16 | 0.14 |
| 2. Dilutions . . . | 7,300 | 14 | 0.19 | 20,954 | 24 | 32 | 0.11 |
| 3. Killed phenol | 2,677 | 11 | 0.41 | 14,548 | 25 | 22 | 0.17 |
| 4. Live phenol. | 167 | 0 | 0 | 1,119 | 2 | 2 | 0.18 |
| 5. Fermi's orig. | 204 | 0 | 0 | 1,058 | 3 | 2 | 0.28 |
| 6. Fermi's sero- vaccine | — | — | — | 5 | 0 | (0.008) | 0 |
| 7. Heated | 6,745 | 17 | 0.25 | 41,923 | 74 | 65 | 0.18 |
| 8. Killed ether. | 5,355 | 8 | 0.15 | 21,272 | 36 | 33 | 0.17 |
| 9. Mixed | 1,448 | 1 | 0.07 | 10,959 | 9 | 17 | 0.08 |
| 10. Yatren | — | — | — | 1,486 | 4 | 2 | 0.27 |
| Total | 26,773 | 55 | 0.21 | 123,675 | 191 | 191 | 0.15 |
| <i>Non-Europeans.</i> | | | | | | | |
| 1. Cords | 2,818 | 12 | 0.43 | 5,511 | 29 | 38 | 0.53 |
| 3. Killed phenol. | 33,607 | 178 | 0.53 | 97,260 | 680 | 671 | 0.70 |
| Total | 36,425 | 190 | 0.52 | 102,771 | 709 | 709 | 0.69 |
| P = 0.14 | | | | | | | |

It will be noted in the total figures that, with the exception of the group non-Europeans, categories A and B, there is no evidence of heterogeneity arising from differences in the methods of treatment. The evidence of heterogeneity in the group non-European, categories A and B, appears for the first time in this review. In the fifth review, the value of P was 0.24. This variation seems to arise from an increased mortality amongst those treated by cords (1.67 as compared with 1.11 in the previous review) and from the fall in mortality amongst non-Europeans treated by killed phenol vaccines which had occurred in the year 1933, to which attention has already been directed. For the increased mortality amongst those treated by cords, a high mortality rate reported from Keijo (Seoul, Chosen) is mainly responsible.

A final table combining the figures relating to the three categories A, B and C may be of interest. It relates to the whole figures for the six reviews. It may be compared with the table given in Section V for racial differences. The essential difference between the two tables is that persons belonging to category D have been excluded.

Categories A, B and C (combined).

| | Number treated | All six reviews Deaths | | Mortality % |
|-------------------------------|----------------|---------------------------|------------|-------------|
| | | Observed | Calculated | |
| <i>Europeans.</i> | | | | |
| 1. Cords | 17,789 | 29 | 32 | 0.16 |
| 2. Dilutions | 36,222 | 67 | 65 | 0.18 |
| 3. Killed phenol | 26,040 | 46 | 47 | 0.18 |
| 4. Live phenol | 2,087 | 5 | 4 | 0.24 |
| 5. Fermi's vaccine | 2,118 | 6 | 4 | 0.28 |
| 6. Fermi's sero-vaccine | 33 | 0 | (0.06) | 0 |
| 7. Heated | 64,248 | 120 | 115 | 0.19 |
| 8. Killed ether | 33,825 | 65 | 61 | 0.19 |
| 9. Mixed | 34,606 | 47 | 62 | 0.14 |
| 10. Yatren | 4,428 | 13 | 8 | 0.29 |
| Total | 221,396 | 398 | 398 | 0.18 |
| | | P = 0.34 | | |
| <i>Non-Europeans.</i> | | | | |
| 1. Cords | 7,290 | 53 | 51 | 0.73 |
| 3. Killed phenol | 104,876 | 727 | 729 | 0.69 |
| Total | 112,166 | 780 | 780 | 0.70 |
| | | P = 0.77 | | |

Also in the abbreviated form of classification :

| | Number treated | All six reviews | | Mortality % |
|-----------------------|----------------|-----------------|------------|-------------|
| | | Deaths | | |
| | | Observed | Calculated | |
| <i>Europeans.</i> | | | | |
| (a) Killed | 59,865 | 111 | 108 | 0.18 |
| (b) Live | 90,704 | 148 | 163 | 0.16 |
| (c) Heated | 64,248 | 120 | 115 | 0.19 |
| (d) Other | 6,579 | 19 | 12 | 0.29 |
| Total | 221,396 | 398 | 398 | 0.18 |
| | | P = 0.12 | | |
| <i>Non-Europeans.</i> | | | | |
| (a) Killed | 104,876 | 727 | 729 | 0.69 |
| (b) Live | 7,290 | 53 | 51 | 0.73 |
| Total | 112,166 | 780 | 780 | 0.70 |
| | | P = 0.77 | | |

These tables show no indication of heterogeneity.

From the above analysis it appears also that, in the A and B categories, the mortality amongst non-Europeans is 3.6 times as great as amongst Europeans, whilst in the C category the ratio is 4.6. These differences are both significant.

Again, in the case of Europeans, the mortality in the A and B categories is 1.4 times as great as in the C category, whilst in the case of non-Europeans the mortality in the A and B categories is 0.91 of that in category C. The first difference is significant ($P = 0.02$), the second is not. Thus, in the case of non-Europeans, it appears that those in the C category are practically at as high a degree of risk as those in the A and B categories.

VIII. SEVERITY OF BITING.

The percentage proportions in the several groups are as follows :

| | Deep | Superficial | No visible lesion |
|--------------------------|-------------|-------------|-------------------|
| 1. Cords | 24.5 | 61.4 | 14.1 |
| 2. Dilutions | 19.2 | 59.5 | 21.4 |
| 3. Killed phenol | 47.8 | 46.1 | 6.2 |
| 4. Live phenol | 37.9 | 50.8 | 11.3 |
| 5. Fermi's vaccine | 32.5 | 61.3 | 6.3 |
| 7. Heated | 17.9 | 77.0 | 5.1 |
| 8. Killed ether | 15.5 | 53.9 | 30.6 |
| 9. Mixed | 17.8 | 58.4 | 23.8 |
| Total | 34.1 | 54.3 | 11.6 |

The percentages with no visible lesion, and treated by dilutions, killed ether and mixed methods, are excessive.

The figures relating to mortality 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 | 3,573 | 40 | 1.12 | 8,935 | 17 | 0.19 | 2,053 | 0 |
| 2. Dilutions | 2,779 | 31 | 1.12 | 8,610 | 3 | 0.03 | 3,098 | 0 |
| 3. Killed phenol ... | 28,078 | 198 | 0.71 | 27,081 | 59 | 0.22 | 3,647 | 1 |
| 4. Live phenol | 114 | 1 | 0.88 | 153 | 0 | 0 | 34 | 0 |
| 5. Fermi's vaccine . | 114 | 0 | 0 | 215 | 0 | 0 | 22 | 0 |
| 7. Heated | 2,254 | 9 | 0.40 | 9,722 | 14 | 0.14 | 644 | 0 |
| 8. Killed ether | 1,276 | 7 | 0.55 | 4,451 | 6 | 0.13 | 2,521 | 0 |
| 9. Mixed | 935 | 6 | 0.64 | 3,073 | 1 | 0.03 | 1,253 | 0 |
| Total | 39,123 | 292 | 0.75 | 62,240 | 100 | 0.16 | 13,272 | 1 |

Information is not available regarding 3,427 treated persons, of whom fifteen died. One death is reported from Lwow amongst those who had "no visible lesion".

In the following table the statistics for the periods of the sixth review, and for all six reviews, are, as before, subdivided according to race-type :

| | (a) <i>Deep</i> | | | | All six reviews | | | |
|-------------------------------|-----------------|----------------|-------------|----------------|-----------------|------------|-------------|--|
| | Sixth review | | | Number treated | Deaths | | Mortality % | |
| | Europeans. | Number treated | Deaths | | Observed | Calculated | | |
| 1. Cords | 1,086 | 6 | 0.55 | 4,501 | 26 | 23 | 0.58 | |
| 2. Dilutions ... | 2,779 | 31 | 1.12 | 7,671 | 62 | 40 | 0.81 | |
| 3. Killed phenol | 940 | 16 | 1.70 | 3,335 | 35 | 17 | 1.05 | |
| 4. Live phenol. | 114 | 1 | 0.88 | 671 | 2 | 3 | 0.30 | |
| 5. Fermi's orig. | 114 | 0 | 0 | 642 | 6 | 3 | 0.93 | |
| 6. Fermi's sero-vaccine | — | — | — | 8 | 0 | (0.04) | 0 | |
| 7. Heated | 2,254 | 9 | 0.40 | 12,311 | 49 | 64 | 0.40 | |
| 8. Killed ether. | 1,276 | 7 | 0.55 | 9,822 | 44 | 51 | 0.45 | |
| 9. Mixed | 935 | 6 | 0.64 | 12,301 | 36 | 64 | 0.29 | |
| 10. Yatren | — | — | — | 187 | 7 | 1 | 3.74 | |
| Total | 9,498 | 76 | 0.80 | 51,449 | 267 | 266 | 0.52 | |
| P < 1 in a million | | | | | | | | |
| <i>Non-Europeans.</i> | | | | | | | | |
| 1. Cords | 687 | 18 | 2.62 | 1,355 | 35 | 14 | 2.58 | |
| 3. Killed phenol. | 20,819 | 143 | 0.69 | 61,816 | 608 | 629 | 0.98 | |
| Total | 21,506 | 161 | 0.77 | 63,171 | 643 | 643 | 1.02 | |
| P < 1 in a million | | | | | | | | |

STATISTICS ON RABIES

(b) *Superficial*

| <i>Europeans.</i> | Sixth review | | | Number treated | All six reviews | | Mortality % |
|-------------------------------------|----------------|-----------|--------------|----------------|-----------------|------------|-------------|
| | Number treated | Deaths | Mortality % | | Deaths | | |
| | | | | | Observed | Calculated | |
| 1. Cords | 2,909 | 1 | 0.03 | 14,837 | 7 | 13 | 0.05 |
| 2. Dilutions . . . | 8,610 | 3 | 0.04 | 21,473 | 14 | 19 | 0.07 |
| 3. Killed phenol | 3,270 | 2 | 0.06 | 16,552 | 11 | 15 | 0.07 |
| 4. Live phenol . | 153 | 0 | 0 | 1,284 | 3 | 1 | 0.23 |
| 5. Fermi's orig. | 215 | 0 | 0 | 1,437 | 0 | 1 | 0 |
| 6. Fermi's sero- vaccine | — | — | — | 218 | 0 | (0.2) | 0 |
| 7. Heated | 9,722 | 14 | 0.14 | 50,772 | 69 | 46 | 0.14 |
| 8. Killed ether. | 4,451 | 6 | 0.13 | 29,113 | 21 | 26 | 0.07 |
| 9. Mixed | 3,073 | 1 | 0.03 | 21,805 | 15 | 20 | 0.07 |
| 10. Yatren | — | — | — | 3,334 | 6 | 3 | 0.18 |
| Total | 32,403 | 27 | 0.083 | 160,825 | 146 | 144 | 0.09 |
| $P = 0.0007$ | | | | | | | |
| <i>Non-Europeans.</i> | | | | | | | |
| 1. Cords | 2,597 | 7 | 0.27 | 5,421 | 17 | 15 | 0.31 |
| 3. Killed phenol | 14,162 | 45 | 0.32 | 44,708 | 123 | 125 | 0.28 |
| Total | 16,759 | 52 | 0.31 | 50,129 | 140 | 140 | 0.28 |
| $P = 0.58$ | | | | | | | |

As in the previous review, the combined figures indicate definite heterogeneity in all groups, with the exception of superficially bitten non-Europeans. The mortality rates in the various groups appear to vary considerably from year to year, and it is suggested that there is considerable variation in the interpretation of the phrase "deeply bitten" at the various institutes.

An interesting fact comes to light when the figures for non-Europeans for this sixth review are compared with those collected in the previous five reviews—viz. :

| | Number treated | Deaths | Mortality % |
|---|----------------|--------|-------------|
| Deeply bitten non-Europeans : | | | |
| 1. Cords | 668 | 17 | 2.54 |
| 3. Killed phenol | 40,997 | 465 | 1.13 |
| Superficially bitten non-Europeans : | | | |
| 1. Cords | 2,824 | 10 | 0.36 |
| 3. Killed phenol | 30,546 | 78 | 0.26 |

When these figures are compared with the corresponding figures in the preceding table (for the sixth review), it is at once obvious

that there is a marked fall in the mortality rate for those deeply bitten and treated by killed phenol vaccines, the rate for the sixth review being 0.69 % as compared with 1.13 % during previous years. This difference is highly significant (P is of the order of 2 in a million). The other mortalities are not significantly altered.

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

Also amongst Europeans the mortality from deep bites is 5.8 times as great as from superficial, whilst amongst non-Europeans it is 3.6 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 | 64.3 | 35.7 |
| 2. Dilutions | 74.0 | 26.0 |
| 3. Killed phenol | 77.8 | 22.2 |
| 4. Live phenol | 67.8 | 32.2 |
| 5. Fermi's vaccine | 45.6 | 54.4 |
| 7. Heated | 64.6 | 35.3 |
| 8. Killed ether | 50.6 | 49.4 |
| 9. Mixed | 70.7 | 29.3 |
| Total | 72.4 | 27.6 |

The figures relating to mortality are :

| | (a) On bare skin | | | (b) Through clothing | | |
|-------------------------|------------------|------------|-------------|----------------------|-----------|-------------|
| | Number treated | Deaths | Mortality % | Number treated | Deaths | Mortality % |
| 1. Cords | 8,279 | 48 | 0.58 | 4,590 | 5 | 0.11 |
| 2. Dilutions | 10,715 | 31 | 0.29 | 3,772 | 3 | 0.08 |
| 3. Killed phenol | 45,441 | 243 | 0.53 | 12,981 | 15 | 0.12 |
| 4. Live phenol | 204 | 1 | 0.49 | 97 | 0 | 0 |
| 5. Fermi's original ... | 160 | 0 | 0 | 191 | 0 | 0 |
| 7. Heated | 7,745 | 22 | 0.28 | 4,231 | 1 | 0.02 |
| 8. Killed ether | 2,900 | 13 | 0.45 | 2,827 | 0 | 0 |
| 9. Mixed | 3,719 | 6 | 0.16 | 1,542 | 1 | 0.06 |
| Total | 79,163 | 364 | 0.46 | 30,231 | 25 | 0.08 |

Information regarding 8,668 treated persons, of whom nineteen contracted rabies, is lacking.

STATISTICS ON RABIES

The corresponding statistics subdivided according to race-type, for the sixth review and for all six reviews, are as under :

(a) *On bare skin.*

| <i>Europeans.</i> | Sixth review | | | Number treated | All six reviews Deaths | | Mortality % |
|---------------------------------|----------------|------------|-------------|----------------|---------------------------|------------|-------------|
| | Number treated | Deaths | Mortality % | | Observed | Calculated | |
| 1. Cords | 3,431 | 7 | 0.20 | 14,790 | 32 | 37 | 0.22 |
| 2. Dilutions . . . | 10,715 | 31 | 0.29 | 26,562 | 73 | 67 | 0.28 |
| 3. Killed phenol | 3,638 | 18 | 0.49 | 20,343 | 44 | 51 | 0.22 |
| 4. Live phenol. | 204 | 1 | 0.49 | 1,463 | 4 | 4 | 0.27 |
| 5. Fermi's vacc. | 160 | 0 | 0 | 1,244 | 5 | 3 | 0.40 |
| 6. Fermi's sero-vaccine | — | — | — | 98 | 0 | (0.24) | 0 |
| 7. Heated | 7,745 | 22 | 0.28 | 42,437 | 111 | 107 | 0.26 |
| 8. Killed ether. | 2,900 | 13 | 0.45 | 16,093 | 63 | 41 | 0.39 |
| 9. Mixed | 3,719 | 6 | 0.16 | 27,009 | 45 | 68 | 0.17 |
| 10. Yatren | — | — | — | 3,767 | 11 | 10 | 0.29 |
| Total | 32,512 | 98 | 0.30 | 153,806 | 388 | 388 | 0.25 |
| P = 0.003 | | | | | | | |
| <i>Non-Europeans.</i> | | | | | | | |
| 1. Cords | 1,918 | 21 | 1.09 | 4,136 | 44 | 33 | 1.06 |
| 3. Killed phenol. | 29,283 | 176 | 0.60 | 87,117 | 687 | 698 | 0.78 |
| Total | 31,201 | 197 | 0.63 | 91,253 | 731 | 731 | 0.80 |
| P = 0.048 | | | | | | | |

(b) *Through clothing.*

| <i>Europeans.</i> | Sixth review | | | Number treated | All six reviews Deaths | | Mortality % |
|---------------------------------|----------------|-----------|-------------|----------------|---------------------------|--------------|--------------|
| | Number treated | Deaths | Mortality % | | Observed | Calculated | |
| 1. Cords | 1,156 | 0 | 0 | 6,243 | 1 | 2.0 | 0.016 |
| 2. Dilutions . . . | 3,772 | 3 | 0.08 | 10,562 | 4 | 3.3 | 0.038 |
| 3. Killed phenol | 1,862 | 1 | 0.05 | 6,895 | 2 | 2.2 | 0.029 |
| 4. Live phenol. | 97 | 0 | 0 | 768 | 1 | 0.2 | 0.130 |
| 5. Fermi's vacc. | 191 | 0 | 0 | 892 | 1 | 0.3 | 0.112 |
| 6. Fermi's sero-vaccine | — | — | — | 157 | 0 | 0.05 | 0 |
| 7. Heated | 4,231 | 1 | 0.02 | 24,583 | 9 | 7.8 | 0.036 |
| 8. Killed ether. | 2,827 | 0 | 0 | 19,984 | 1 | 6.3 | 0.005 |
| 9. Mixed | 1,542 | 1 | 0.07 | 13,901 | 6 | 4.4 | 0.043 |
| 10. Yatren | — | — | — | 1,617 | 2 | 0.5 | 0.124 |
| Total | 15,678 | 6 | 0.04 | 85,602 | 27 | 27.05 | 0.031 |
| P = 0.30 | | | | | | | |
| <i>Non-Europeans.</i> | | | | | | | |
| 1. Cords | 1,756 | 4 | 0.20 | 3,297 | 9 | 6.8 | 0.27 |
| 3. Killed phenol. | 6,528 | 12 | 0.18 | 22,384 | 44 | 46.2 | 0.20 |
| Total | 8,284 | 16 | 0.19 | 25,681 | 53 | 53.0 | 0.21 |
| P = 0.40 | | | | | | | |

There is thus no evidence of heterogeneity amongst those bitten through clothing either in the case of Europeans or of non-Europeans. For those bitten on the bare skin, the value of P for non-Europeans is just on the margin of possible significance ($P = 0.048$); that for Europeans, $P = 0.003$, is chiefly affected by an excessive mortality in the case of those treated at Yugoslav institutes by killed ether vaccines.

The mortality amongst those bitten on the bare skin is, in the case of Europeans, eight times, and, in the case of non-Europeans, 3.8 times, as great as that observed amongst those bitten through clothing. As has been suggested before, the probable reason for this difference of degree is that the European bitten on the bare skin is usually bitten on the head or hands, whereas in the case of non-Europeans this is not so generally true.

The mortality amongst non-Europeans in the case of those bitten on the bare skin is 3.2 times, and in the case of those bitten through clothing is seven times, as great as amongst Europeans. It would thus appear that the clothing of the European is a greater safeguard than is that of the non-European.

If one compares the figures for the present review with those for the previous five reviews (published in the fifth review), it appears that the only significant variation is a fall in the mortality of non-Europeans treated by killed phenol vaccines and bitten on the bare skin from 0.88 % to 0.60 %. There is no corresponding fall amongst those bitten through clothing.

X. POSITION OF BITE.

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

| | Head | Arm | Trunk | Leg |
|-------------------------|------|------|-------|------|
| 1. Cords | 4.8 | 46.9 | 4.5 | 43.8 |
| 2. Dilutions | 5.9 | 59.5 | 2.2 | 32.4 |
| 3. Killed phenol | 5.9 | 35.5 | 3.8 | 54.8 |
| 4. Live phenol | 6.3 | 54.5 | 6.3 | 32.9 |
| 5. Fermi's original ... | 7.7 | 44.7 | 17.1 | 30.5 |
| 7. Heated | 5.1 | 56.5 | 5.0 | 33.4 |
| 8. Killed ether | 5.9 | 43.2 | 4.0 | 46.9 |
| 9. Mixed | 2.8 | 59.4 | 2.4 | 35.4 |
| Total | 5.5 | 44.3 | 3.7 | 46.5 |

STATISTICS ON RABIES

The figures relating to mortality are as follows :

| | (a) Head | | | (b) Arm | | |
|-------------------------|----------------|------------|-------------|----------------|------------|-------------|
| | Number treated | Deaths | Mortality % | Number treated | Deaths | Mortality % |
| 1. Cords | 674 | 24 | 3.56 | 6,638 | 18 | 0.27 |
| 2. Dilutions | 994 | 25 | 2.52 | 9,949 | 20 | 0.20 |
| 3. Killed phenol | 3,482 | 94 | 2.70 | 20,943 | 91 | 0.43 |
| 4. Live phenol | 19 | 1 | 5.26 | 164 | 0 | 0 |
| 5. Fermi's original ... | 27 | 0 | 0 | 157 | 0 | 0 |
| 7. Heated | 607 | 14 | 2.31 | 6,762 | 7 | 0.10 |
| 8. Killed ether | 338 | 6 | 1.78 | 2,473 | 6 | 0.24 |
| 9. Mixed | 147 | 2 | 1.36 | 3,127 | 4 | 0.13 |
| Total | 6,288 | 166 | 2.64 | 50,213 | 146 | 0.29 |

| | (c) Trunk | | | (d) Leg | | |
|-------------------------|----------------|----------|-------------|----------------|-----------|-------------|
| | Number treated | Deaths | Mortality % | Number treated | Deaths | Mortality % |
| 1. Cords | 635 | 3 | 0.47 | 6,201 | 13 | 0.21 |
| 2. Dilutions | 362 | 0 | 0 | 5,425 | 2 | 0.04 |
| 3. Killed phenol | 2,218 | 2 | 0.09 | 32,335 | 71 | 0.22 |
| 4. Live phenol | 19 | 0 | 0 | 99 | 0 | 0 |
| 5. Fermi's original ... | 60 | 0 | 0 | 107 | 0 | 0 |
| 7. Heated | 600 | 0 | 0 | 4,007 | 2 | 0.05 |
| 8. Killed ether | 231 | 0 | 0 | 2,685 | 1 | 0.04 |
| 9. Mixed | 127 | 1 | 0.79 | 1,860 | 0 | 0 |
| Total | 4,252 | 6 | 0.14 | 52,719 | 89 | 0.17 |

Information was lacking regarding 5,090 persons, of whom one died of rabies.

The statistics for the sixth review and for all six reviews subdivided according to race-type are as follows :

| | (a) Head | | | All six reviews | | | |
|-------------------------------|--------------|----------------|-------------|-----------------|------------|------------|-------------|
| | Sixth review | | | Number treated | Deaths | | Mortality % |
| | Europeans. | Number treated | Deaths | | Observed | Calculated | |
| 1. Cords | 276 | 2 | 0.73 | 1,344 | 11 | 19 | 0.82 |
| 2. Dilutions ... | 994 | 25 | 2.52 | 3,035 | 51 | 44 | 1.68 |
| 3. Killed phenol | 412 | 11 | 2.67 | 1,902 | 26 | 28 | 1.37 |
| 4. Live phenol. | 19 | 1 | 5.26 | 152 | 2 | 2 | 1.32 |
| 5. Fermi's orig. | 27 | 0 | 0 | 192 | 7 | 3 | 3.65 |
| 6. Fermi's sero-vaccine | — | — | — | 10 | 0 | (0.1) | 0 |
| 7. Heated | 607 | 14 | 2.31 | 3,247 | 56 | 47 | 1.72 |
| 8. Killed ether. | 338 | 6 | 1.78 | 2,407 | 37 | 35 | 1.54 |
| 9. Mixed | 147 | 2 | 1.36 | 2,238 | 17 | 32 | 0.76 |
| 10. Yatren | — | — | — | 180 | 6 | 3 | 3.33 |
| Total | 2,820 | 61 | 2.16 | 14,707 | 213 | 213 | 1.45 |

$$P = 0.003$$

Non-Europeans.

| | | | | | | | |
|--------------------|--------------|-----------|-------------|--------------|------------|------------|-------------|
| 1. Cords | 168 | 12 | 7.14 | 372 | 24 | 17 | 6.45 |
| 3. Killed phenol. | 1,825 | 71 | 3.89 | 5,472 | 240 | 248 | 4.39 |
| Total | 1,993 | 83 | 4.16 | 5,844 | 264 | 265 | 4.52 |

P = 0.07

(b) Arm

| <i>Europeans.</i> | Sixth review | | | Number treated | All six reviews Deaths | | Mortality % |
|----------------------------------|----------------|-----------|-------------|----------------|---------------------------|------------|-------------|
| | Number treated | Deaths | Mortality % | | Observed | Calculated | |
| 1. Cords | 2,943 | 4 | 0.14 | 12,944 | 18 | 18 | 0.14 |
| 2. Dilutions ... | 9,949 | 20 | 0.20 | 25,657 | 36 | 36 | 0.14 |
| 3. Killed phenol | 3,796 | 7 | 0.18 | 18,016 | 17 | 25 | 0.09 |
| 4. Live phenol . | 164 | 0 | 0 | 1,187 | 2 | 2 | 0.17 |
| 5. Fermi's orig. | 157 | 0 | 0 | 1,949 | 1 | 3 | 0.05 |
| 6. Fermi's sero- vaccine | — | — | — | 160 | 0 | (0.2) | 0 |
| 7. Heated | 6,762 | 7 | 0.10 | 24,056 | 46 | 34 | 0.19 |
| 8. Killed ether. | 2,473 | 6 | 0.24 | 13,955 | 27 | 20 | 0.19 |
| 9. Mixed | 3,127 | 4 | 0.13 | 21,678 | 22 | 31 | 0.10 |
| 10. Yatren | — | — | — | 3,393 | 5 | 5 | 0.15 |
| Total | 29,371 | 48 | 0.16 | 122,995 | 174 | 174 | 0.14 |

P = 0.10

Non-Europeans.

| | | | | | | | |
|--------------------|---------------|-----------|-------------|---------------|------------|------------|-------------|
| 1. Cords | 904 | 6 | 0.66 | 2,001 | 11 | 13* | 0.55 |
| 3. Killed phenol. | 10,987 | 68 | 0.62 | 32,074 | 212 | 210 | 0.66 |
| Total | 11,891 | 74 | 0.62 | 34,075 | 223 | 223 | 0.65 |

P = 0.57

(c) Trunk

| <i>Europeans.</i> | Sixth review | | | Number treated | All six reviews Deaths | | Mortality % |
|----------------------------------|----------------|----------|-------------|----------------|---------------------------|------------|-------------|
| | Number treated | Deaths | Mortality % | | Observed | Calculated | |
| 1. Cords | 99 | 0 | | 523 | 0 | | 0 |
| 2. Dilutions ... | 362 | 0 | | 972 | 0 | | 0 |
| 3. Killed phenol | 167 | 0 | | 807 | 0 | | 0 |
| 4. Live phenol . | 19 | 0 | | 108 | 0 | | 0 |
| 5. Fermi's orig. | 60 | 0 | | 198 | 0 | | 0 |
| 6. Fermi's sero- vaccine | — | — | | 6 | 0 | | 0 |
| 7. Heated | 600 | 0 | | 3,701 | 0 | | 0 |
| 8. Killed phenol | 231 | 0 | | 1,900 | 0 | | 0 |
| 9. Mixed | 127 | 1 | | 1,450 | 3 | | 0 |
| 10. Yatren | — | — | | 112 | — | | 0.21 |
| Total | 1,665 | 1 | 0.06 | 9,777 | 3 | | 0.03 |

Non-Europeans.

| | | | | | | | |
|------------------|--------------|----------|-------------|--------------|-----------|-----------|-------------|
| 1. Cords | 320 | 3 | 0.94 | 585 | 4 | 2 | 0.68 |
| 3. Killed phenol | 1,324 | 2 | 0.15 | 3,895 | 8 | 10 | 0.21 |
| Total ... | 1,644 | 5 | 0.30 | 4,480 | 12 | 12 | 0.27 |

P = 0.12

STATISTICS ON RABIES

(d) *Leg*

| <i>Europeans.</i> | Sixth review | | | Number treated | All six reviews Deaths | | Mortality % |
|-------------------------------------|----------------|----------|-------------|----------------|---------------------------|-------------|-------------|
| | Number treated | Deaths | Mortality % | | Observed | Calculated | |
| 1. Cords | 1,272 | 1 | 0.08 | 6,891 | 6 | 2.7 | 0.09 |
| 2. Dilutions . . . | 5,425 | 2 | 0.04 | 13,639 | 7 | 5.4 | 0.05 |
| 3. Killed phenol | 1,684 | 1 | 0.06 | 8,490 | 3 | 3.4 | 0.04 |
| 4. Live phenol. | 99 | 0 | 0 | 784 | 1 | 0.3 | 0.13 |
| 5. Fermi's orig. | 107 | 0 | 0 | 1,865 | 1 | 0.7 | 0.05 |
| 6. Fermi's sero- vaccine | — | — | — | 76 | 0 | (0.03) | 0 |
| 7. Heated | 4,007 | 2 | 0.05 | 18,534 | 5 | 7.3 | 0.03 |
| 8. Killed ether. | 2,685 | 1 | 0.04 | 20,837 | 1 | 8.3 | 0.005 |
| 9. Mixed | 1,860 | 0 | 0 | 15,544 | 9 | 6.2 | 0.06 |
| 10. Yatren | — | — | — | 1,699 | 2 | 0.7 | 0.12 |
| Total | 17,139 | 7 | 0.04 | 88,359 | 35 | 35.0 | 0.04 |

P = 0.014

| <i>Non-Europeans.</i> | | | | | | | |
|------------------------|----------------|-----------|-------------|----------------|------------|------------|-------------|
| | Number treated | Deaths | Mortality % | Number treated | Observed | Calculated | Mortality % |
| 1. Cords | 2,307 | 4 | 0.17 | 4,542 | 14 | 15 | 0.31 |
| 3. Killed phenol. | 21,675 | 47 | 0.22 | 65,366 | 215 | 214 | 0.33 |
| Total | 23,982 | 51 | 0.21 | 69,908 | 229 | 229 | 0.33 |

P = 0.79

As in the fourth and fifth reviews, the values of P indicate no evidence of heterogeneity amongst non-Europeans bitten in any of the four localities. With regard to Europeans, on the other hand, there is evidence of heterogeneity amongst those bitten on the head and on the leg. In the case of those bitten on the head, the disturbing factors arise mainly from the methods—Fermi's vaccine, where the observed mortality is too high, and mixed methods, where the observed mortality is unexpectedly low. In the case of those bitten on the leg, the discrepancy is almost entirely ascribable to the low mortality amongst those treated by Hempt's method in Yugoslavia. It will be remembered that, in the previous review, attention was drawn to the fact that no deaths had occurred amongst 14,997 persons bitten on the leg and treated at Yugoslav institutes. The figures for the year 1933 report one death amongst 2,685, and so, for the period covered by the six reviews, one death occurred out of 20,837, instead of an expected 8.3 as calculated from the average for all methods of treatment. This curious result remains unexplained.

The mortalities amongst those bitten in the various positions for the two race-types are as follows :

| | Europeans | Non-Europeans | Ratio | Non-European mortality |
|-------------|-----------|---------------|-------|------------------------|
| | | | | European mortality |
| Head | 1.45 | 4.52 | | 3.1 |
| Arm | 0.14 | 0.65 | | 4.6 |
| Trunk | 0.03 | 0.27 | | 9.0 |
| Leg | 0.04 | 0.33 | | 8.3 |

Each of these ratios indicates a significant difference. That the legs of Europeans are more usually and more efficiently clad than those of non-Europeans probably accounts for the higher ratio for those bitten on the leg, and similarly for the trunk.

XI. DELAY IN COMMENCEMENT OF TREATMENT.

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

| | 0 to 4 days | 5 to 7 days | 8 to 14 days | More than 14 days |
|-------------------------|-------------|-------------|--------------|-------------------|
| 1. Cords | 58.8 | 24.2 | 12.1 | 4.9 |
| 2. Dilutions | 51.0 | 25.3 | 16.6 | 7.1 |
| 3. Killed phenol | 63.1 | 17.5 | 12.5 | 6.9 |
| 4. Live phenol | 50.5 | 21.6 | 14.6 | 13.3 |
| 5. Fermi's original ... | 56.4 | 26.5 | 12.0 | 5.1 |
| 7. Heated | 68.2 | 20.2 | 8.5 | 3.2 |
| 8. Killed ether | 71.0 | 13.8 | 8.1 | 7.0 |
| 9. Mixed | 43.3 | 24.1 | 21.8 | 10.9 |
| Total | 60.9 | 19.8 | 12.7 | 6.5 |

The figures relating to mortality are as follows :

| | (a) 0 to 4 days | | | (b) 4 to 7 days | | |
|-------------------------|-----------------|--------|-------------|-----------------|--------|-------------|
| | Number treated | Deaths | Mortality % | Number treated | Deaths | Mortality % |
| 1. Cords | 8,590 | 35 | 0.41 | 3,533 | 9 | 0.25 |
| 2. Dilutions | 8,536 | 26 | 0.30 | 4,226 | 11 | 0.26 |
| 3. Killed phenol | 37,299 | 158 | 0.42 | 10,373 | 41 | 0.40 |
| 4. Live phenol | 152 | 1 | 0.66 | 65 | 0 | 0 |
| 5. Fermi's original ... | 198 | 0 | 0 | 93 | 0 | 0 |
| 7. Heated | 8,605 | 16 | 0.19 | 2,544 | 5 | 0.20 |
| 8. Killed ether | 5,862 | 12 | 0.20 | 1,142 | 0 | 0 |
| 9. Mixed | 2,276 | 5 | 0.22 | 1,268 | 1 | 0.08 |
| Total | 71,518 | 253 | 0.35 | 23,244 | 67 | 0.29 |

STATISTICS ON RABIES

| | (c) 8 to 14 days | | | (d) More than 14 days | | |
|-------------------------|------------------|-----------|-------------|-----------------------|-----------|-------------|
| | Number treated | Deaths | Mortality % | Number treated | Deaths | Mortality % |
| 1. Cords | 1,765 | 5 | 0.28 | 714 | 9 | 1.26 |
| 2. Dilutions | 2,779 | 5 | 0.18 | 1,189 | 5 | 0.42 |
| 3. Killed phenol | 7,370 | 28 | 0.38 | 4,094 | 32 | 0.78 |
| 4. Live phenol | 44 | 0 | 0 | 40 | 0 | 0 |
| 5. Fermi's original ... | 42 | 0 | 0 | 18 | 0 | 0 |
| 7. Heated | 1,068 | 1 | 0.09 | 403 | 1 | 0.25 |
| 8. Killed ether | 665 | 0 | 0 | 579 | 1 | 0.17 |
| 9. Mixed | 1,145 | 1 | 0.09 | 572 | 0 | 0 |
| Total | 14,878 | 40 | 0.27 | 7,609 | 48 | 0.63 |

Information was not available regarding 813 treated persons, none of whom died of rabies.

The figures subdivided according to race-type for the sixth review and for the whole set of six reviews are as follows :

| | (a) 0 to 4 days | | | | | | |
|-----------------------------------|-----------------|-----------|-------------|----------------|-----------------|------------|-------------|
| | Sixth review | | | Number treated | All six reviews | | Mortality % |
| | Number treated | Deaths | Mortality % | | Deaths | | |
| <i>Europeans.</i> | | | | Observed | Calculated | | |
| 1. Cords | 2,902 | 7 | 0.24 | 12,115 | 23 | 22 | 0.19 |
| 2. Dilutions ... | 8,536 | 26 | 0.30 | 25,132 | 59 | 46 | 0.23 |
| 3. Killed phenol | 4,048 | 17 | 0.42 | 18,372 | 38 | 33 | 0.21 |
| 4. Live phenol. | 152 | 1 | 0.66 | 1,174 | 4 | 1 | 0.34 |
| 5. Fermi's orig. | 198 | 0 | 0 | 1,895 | 6 | 2 | 0.32 |
| 6. Fermi's sero- vaccine | — | — | — | 150 | 0 | (0.3) | 0 |
| 7. Heated | 8,506 | 16 | 0.19 | 34,649 | 51 | 63 | 0.15 |
| 8. Killed ether. | 5,862 | 12 | 0.20 | 34,118 | 56 | 62 | 0.16 |
| 9. Mixed | 2,276 | 5 | 0.22 | 21,928 | 30 | 40 | 0.14 |
| 10. Yatren ... | — | — | — | 2,080 | 8 | 4 | 0.38 |
| Total | 32,480 | 84 | 0.26 | 151,613 | 275 | 273 | 0.18 |

$$P = 0.002$$

| <i>Non-Europeans.</i> | | | | | | | |
|-----------------------|----------------|------------|-------------|----------------|------------|------------|-------------|
| | Number treated | Deaths | Mortality % | Number treated | Deaths | Deaths | Mortality % |
| 1. Cords | 2,004 | 13 | 0.65 | 3,970 | 28 | 26 | 0.71 |
| 3. Killed phenol. | 23,245 | 117 | 0.50 | 68,060 | 441 | 443 | 0.65 |
| Total | 25,249 | 130 | 0.51 | 72,030 | 469 | 469 | 0.65 |

$$P = 0.65$$

STATISTICS ON RABIES

779

(b) 5 to 7 days

| <i>Europeans.</i> | Sixth review | | | Number treated | All six reviews | | Mortality % |
|------------------------------|----------------|-----------|-------------|----------------|-----------------|-------------|-------------|
| | Number treated | Deaths | Mortality % | | Deaths | | |
| | | | | | Observed | Calculated | |
| 1. Cords | 874 | 0 | 0 | 4,080 | 6 | 5.3 | 0.15 |
| 2. Dilutions ... | 4,226 | 11 | 0.26 | 9,534 | 21 | 12.3 | 0.22 |
| 3. Killed phenol | 979 | 1 | 0.10 | 5,598 | 4 | 7.2 | 0.07 |
| 4. Live phenol. | 65 | 0 | 0 | 469 | 1 | 0.6 | 0.21 |
| 5. Fermi's orig. | 93 | 0 | 0 | 757 | 1 | 1.0 | 0.13 |
| 6. Fermi's sero-vaccine | — | — | — | 54 | 0 | (0.07) | 0 |
| 7. Heated | 2,544 | 5 | 0.20 | 13,086 | 13 | 16.9 | 0.10 |
| 8. Killed ether. | 1,142 | 0 | 0 | 6,579 | 4 | 8.5 | 0.06 |
| 9. Mixed | 1,268 | 1 | 0.08 | 9,400 | 12 | 12.2 | 0.13 |
| 10. Yatren | — | — | — | 1,500 | 4 | 1.9 | 0.27 |
| Total | 11,191 | 18 | 0.16 | 51,057 | 66 | 65.9 | 0.13 |

P = 0.043

| <i>Non-Europeans.</i> | Number treated | Deaths | Mortality % | Number treated | Observed | Calculated | Mortality % |
|-----------------------|----------------|-----------|-------------|----------------|------------|------------|-------------|
| 1. Cords | 1,134 | 4 | 0.35 | 2,099 | 8 | 12 | 0.38 |
| 3. Killed phenol. | 6,296 | 28 | 0.44 | 20,898 | 121 | 117 | 0.58 |
| Total | 7,430 | 32 | 0.43 | 22,997 | 129 | 129 | 0.56 |

P = 0.24

(c) 8 to 14 days

| <i>Europeans.</i> | Sixth review | | | Number treated | All six reviews | | Mortality % |
|------------------------------|----------------|----------|-------------|----------------|-----------------|-------------|-------------|
| | Number treated | Deaths | Mortality % | | Deaths | | |
| | | | | | Observed | Calculated | |
| 1. Cords | 515 | 0 | 0 | 3,872 | 3 | 3.4 | 0.08 |
| 2. Dilutions ... | 2,779 | 5 | 0.18 | 6,084 | 6 | 5.3 | 0.10 |
| 3. Killed phenol | 646 | 1 | 0.15 | 3,876 | 4 | 3.4 | 0.10 |
| 4. Live phenol. | 44 | 0 | 0 | 364 | 0 | 0.3 | 0 |
| 5. Fermi's orig. | 42 | 0 | 0 | 440 | 0 | 0.4 | 0 |
| 6. Fermi's sero-vaccine | — | — | — | 46 | 0 | (0.04) | 0 |
| 7. Heated | 1,068 | 1 | 0.09 | 4,988 | 4 | 4.3 | 0.08 |
| 8. Killed ether. | 665 | 0 | 0 | 3,556 | 4 | 3.1 | 0.11 |
| 9. Mixed | 1,145 | 1 | 0.09 | 6,648 | 6 | 5.8 | 0.09 |
| 10. Yatren | — | — | — | 1,189 | 0 | 1.0 | 0 |
| Total | 6,904 | 8 | 0.12 | 31,063 | 27 | 27.0 | 0.09 |

P = 0.85

| <i>Non-Europeans.</i> | Number treated | Deaths | Mortality % | Number treated | Observed | Calculated | Mortality % |
|-----------------------|----------------|-----------|-------------|----------------|-----------|-------------|-------------|
| 1. Cords | 393 | 4 | 1.02 | 911 | 7 | 5.8 | 0.77 |
| 3. Killed phenol. | 3,991 | 17 | 0.43 | 13,586 | 85 | 86.2 | 0.62 |
| Total | 4,384 | 21 | 0.48 | 14,497 | 92 | 92.0 | 0.63 |

P = 0.61

(d) *More than 14 days*

| | Sixth review | | | Number treated | All six reviews | | Mortality % |
|-------------------------------------|----------------|-----------|-------------|----------------|-----------------|-------------|-------------|
| | Number treated | Deaths | Mortality % | | Deaths | | |
| <i>Europeans.</i> | | | | | Observed | Calculated | |
| 1. Cords | 154 | 0 | 0 | 1,118 | 1 | 1.5 | 0.09 |
| 2. Dilutions . . . | 1,189 | 5 | 0.42 | 2,770 | 8 | 3.8 | 0.29 |
| 3. Killed phenol | 354 | 1 | 0.28 | 1,591 | 2 | 2.2 | 0.12 |
| 4. Live phenol . | 40 | 0 | 0 | 224 | 0 | 0.3 | 0 |
| 5. Fermi's orig. | 18 | 0 | 0 | 155 | 0 | 0.2 | 0 |
| 6. Fermi's sero- vaccine | — | — | — | 5 | 0 | (0.007) | 0 |
| 7. Heated | 403 | 1 | 0.25 | 1,567 | 2 | 2.1 | 0.13 |
| 8. Killed ether. | 579 | 1 | 0.17 | 2,294 | 1 | 3.1 | 0.04 |
| 9. Mixed | 572 | 0 | 0 | 2,934 | 3 | 4.0 | 0.10 |
| 10. Yatren | — | — | — | 615 | 1 | 0.8 | 0.16 |
| Total | 3,309 | 8 | 0.24 | 13,273 | 18 | 18.0 | 0.14 |
| | | | | | P = 0.36 | | |
| <i>Non-Europeans.</i> | | | | | | | |
| 1. Cords | 169 | 4 | 2.35 | 430 | 10 | 5.3 | 2.33 |
| 3. Killed phenol. | 2,279 | 26 | 1.14 | 7,207 | 84 | 88.7 | 1.17 |
| Total | 2,448 | 30 | 1.23 | 7,637 | 94 | 94.0 | 1.23 |
| | | | | | P = 0.03 | | |

From the figures dealt with in the fifth review, all the values of P from the above groups were greater than 0.05, and hence there was no evidence of heterogeneity in any of the eight groups. In the combined figures collected this year relating to the figures for the whole set of reviews, significant differences appear in the group "European, 0 to 4 days" and in the group "Non-European, more than 14 days", whilst a value of P just on the borderline between homogeneity and heterogeneity appears in the group "European, 5 to 7 days".

In the case of the first of these "European, 0 to 4 days", the heterogeneity arises mainly from those treated by live phenol vaccines and by Fermi's vaccine, the observed mortalities being in excess of the expected. In the case of the group "Non-Europeans, more than 14 days", the percentage mortalities according to the two methods of treatment remain very similar to what they were for the first five reviews—i.e., 2.35 as compared with 2.30 for those treated by cords, and 1.14 as compared with 1.18 for those treated by killed phenol vaccines. The difference has assumed doubtful significance as the numbers have increased.

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

| | Number treated | Deaths | | Mortality % |
|-------------------------|----------------|------------|------------|-------------|
| | | Observed | Calculated | |
| <i>Europeans.</i> | | | | |
| 0 to 4 days | 151,613 | 275 | 237 | 0.18 |
| 5 to 7 days | 51,057 | 66 | 80 | 0.13 |
| 8 to 14 days | 31,063 | 27 | 49 | 0.09 |
| More than 14 days | 13,273 | 18 | 21 | 0.14 |
| Total | 247,006 | 386 | 387 | 0.16 |
| P = 0.0003 | | | | |
| <i>Non-Europeans.</i> | | | | |
| 0 to 4 days | 72,030 | 469 | 482 | 0.65 |
| 5 to 7 days | 22,997 | 129 | 154 | 0.56 |
| 8 to 14 days | 14,497 | 92 | 97 | 0.63 |
| More than 14 days | 7,637 | 94 | 51 | 1.23 |
| Total | 117,161 | 784 | 784 | 0.67 |
| P < 1 in a million | | | | |

Both these values of P are significant, and in general they would indicate that, in the case of Europeans, early-comers show a significantly higher mortality than late-comers, whilst, with regard to non-Europeans, early-comers show a significantly lower mortality than late-comers. The grouping of the periods of time is, however, somewhat arbitrary, and it seems more reasonable to compare the groups " Less than 14 days " and " More than 14 days ".

The figures are as follows :

| | Number treated | Deaths | | Mortality % |
|-------------------------|----------------|------------|------------|-------------|
| | | Observed | Calculated | |
| <i>Europeans.</i> | | | | |
| Less than 14 days | 233,733 | 368 | 365 | 0.16 |
| More than 14 days | 13,273 | 18 | 21 | 0.14 |
| Total | 247,006 | 386 | 386 | 0.16 |
| P = 0.50 | | | | |
| <i>Non-Europeans.</i> | | | | |
| Less than 14 days | 109,524 | 690 | 733 | 0.63 |
| More than 14 days | 7,637 | 94 | 51 | 1.23 |
| Total | 117,161 | 784 | 784 | 0.67 |
| P < 1 in a million | | | | |

Thus, the fact to which attention has been previously drawn is emphasised—namely, that, for some reason which does not appear, the handicap of late arrival, though pronounced in the non-European statistics, is not evident in the European statistics. Again, it may be noted that, in the successive periods 0 to 4, 5 to 7, 8 to 14, and more than 14 days, the ratios of non-European to European

mortalities are 3.6, 4.3, 7 and 8.8 respectively, so that the relative mortality increases progressively with lateness of arrival.

XII. PARALYTIC ACCIDENTS.

The figures relating to the occurrence of post-vaccinal paralysis are as under :

| | Number treated | Accidents | Proportion | Percentage | |
|-----------------------|----------------|-----------|-------------------|--------------|----------------|
| 1. Cords | 14,747 | 2 | 1 in 7,374 | 0.014 | 0 fatal |
| 2. Dilutions | 16,730 | 6 | 1 in 2,788 | 0.036 | 6 fatal |
| 3. Killed phenol ... | 59,804 | 6 | 1 in 9,968 | 0.010 | 1 fatal |
| 4. Live phenol | 301 | 0 | — | — | — |
| 5. Fermi's original.. | 351 | 0 | — | — | — |
| 7. Heated | 12,620 | 4 | 1 in 3,155 | 0.032 | 1 fatal |
| 8. Killed ether | 8,248 | 0 | — | — | — |
| 9. Mixed | 5,261 | 3 | 1 in 1,753 | 0.057 | 0 fatal |
| Total | 118,062 | 21 | 1 in 5,622 | 0.018 | 8 fatal |

The figures relating to accidents over the period covered by all six reviews are :

| | Number treated | Accidents | Proportion | Percentage | |
|-------------------------------|----------------|------------|-------------------|--------------|-----------------|
| 1. Cords | 78,400 | 26 | 1 in 3,015 | 0.033 | 3 fatal |
| 2. Dilutions | 43,770 | 18 | 1 in 2,432 | 0.041 | 13 fatal |
| 3. Killed phenol .. | 233,488 | 23 | 1 in 10,152 | 0.0099 | 5 fatal |
| 4. Live phenol | 2,268 | 0 | — | — | — |
| 5. Fermi's original. | 5,124 | 2 | 1 in 2,562 | 0.039 | 1 fatal |
| 6. Fermi's sero-vaccine | 255 | 0 | — | — | — |
| 7. Heated | 67,664 | 6 | 1 in 11,277 | 0.0089 | 1 fatal |
| 8. Killed ether ... | 46,547 | 4 | 1 in 11,637 | 0.0086 | 2 fatal |
| 9. Mixed | 41,358 | 19 | 1 in 2,177 | 0.046 | 2 fatal |
| 10. Yatren | 5,384 | 3 | 1 in 1,795 | 0.056 | 0 fatal |
| Total | 524,258 | 101 | 1 in 5,191 | 0.019 | 27 fatal |

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

| | Number treated | Accidents | | Proportion | Percentage |
|--------------------|----------------|------------|------------|-------------------|--------------|
| | | Observed | Calculated | | |
| (a) Killed | 280,035 | 27 | 54 | 1 in 10,372 | 0.0096 |
| (b) Live | 165,796 | 63 | 32 | 1 in 2,632 | 0.038 |
| (c) Heated | 67,664 | 6 | 13 | 1 in 11,637 | 0.0089 |
| (d) Other | 10,763 | 5 | 2 | 1 in 2,153 | 0.046 |
| Total | 524,258 | 101 | 101 | 1 in 5,191 | 0.019 |

$P < 1$ in a million

It appears that the liability to accident after treatment by live vaccines is about four times as great as after treatment by killed

vaccines or by heated vaccines. It is noteworthy that, whilst in the figures dealt with in the fifth review liability to accident after treatment by killed vaccines was about three times that after treatment by heated vaccines, the relative liabilities in the figures now available are practically equal (as 96 is to 89).

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

In summarising the experience up to this date as collected from the various schedules, and given above in tabular form in the combined figures for the whole six reviews, the main fact which presents itself is the remarkable degree of homogeneity indicated in Section V, in which the statistics are analysed separately for the two race-types—European and non-European. It appears that the mortality amongst 286,373 Europeans was 0.16 % and that the rates for the different methods of treatment did not significantly vary from this, and that, in the case of 219,681 non-Europeans, the mortality rate was 0.72 %, and, again, this figure did not appear to be influenced by method of treatment.

The reason for the difference in mortality of the two race-types has been discussed at length in previous reviews and need not be repeated here. But the question naturally arises as to whether the statistics are large enough for the detection of such differences of efficiency of treatment as one might expect to find. That is to say, one naturally asks whether the figures are sufficiently large for the detection of any significant difference, even though the various groups represented samples of, say, two populations between which a real difference of some particular amount existed. It is quite clear that, if the samples are not sufficiently large, it would be impossible to distinguish between differences due to varying efficiencies of treatment and those due merely to the variations introduced by random sampling. For example, assuming that there is in reality a difference of 10 % on a mortality rate of 1 %, it may be asked, what is the minimum number required in our sample, if that sample is to be expected to demonstrate the existence of any difference at all. Let us first consider the case where some particular treatment is compared with no treatment at all.

If the percentage mortality from the untreated disease is l , then if treatment results in the reduction of the mortality by yl , so that the final treated mortality is $(1-y)l$, we shall consider y to represent the efficiency of the treatment. If an experiment in which there are two equal groups each of size n —the one treated and the other untreated—it may be shown that, in order that any difference from advantage of treatment can be detected, then to a first approximation n must be greater than $385 \frac{(2-y)}{ly^2}$. Similarly, if we compare two different methods of treatment, we may say that there is an excess

of efficiency y in the one treatment relatively to the other, if the death-rate in the former case is $(1-y)$ times the death-rate in the latter ; and that, if the groups subjected to the two treatments are equal and each of size n , the minimum value of n which may be expected to lead to the detection of any difference in efficiency is again $385 \frac{(2-y)}{ly^2}$.

In the following table are given values of n calculated from the above formula for various values of l and of y :

| | $y = 1$ | $y = \frac{1}{2}$ | $y = \frac{1}{3}$ | $y = \frac{1}{4}$ |
|------------------|---------|-------------------|-------------------|-------------------|
| $l = 0.16$ | 2,400 | 14,400 | 67,200 | 456,000 |
| $l = 0.72$ | 530 | 3,180 | 14,840 | 100,700 |
| $l = 1$ | 385 | 2,310 | 10,780 | 73,150 |
| $l = 1.5$ | 256 | 1,280 | 6,912 | 48,384 |
| $l = 4.5$ | 85 | 510 | 2,380 | 16,150 |

In examining the tables in Section V, one finds that the numbers in the non-European group (for which $l = 0.72$) are, in general, insufficient to detect superiority of one treatment as compared with another, when the excess relative efficiency of the better treatment is about 10 or 15 % ; whilst in the case of Europeans (for which $l = 0.16$) the corresponding figure is about 25 %.

It is thus reasonable to conclude that it is unlikely that a difference of efficiency of more than 25 % between any two methods of treatment exists. It is clearly not possible to set out small differences of efficiency except with groups containing very much greater numbers.

Thus we arrive at the conclusion that the figures so far available are not yet sufficient to detect the existence of differences of efficiency of less than 25 %. The same argument and the same conclusion also relate to the various tables which appear in the later sections of the analysis.

It may at first sight seem surprising that figures amounting in all to about half a million are insufficient to demonstrate differences in efficiencies of various methods of treatment. 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 rabies, as shown above, the mortality rate may be as low as 0.16 %.

Another line of attack on the problem of the estimation of relative differences in methods of treatment has been suggested by

VAN STOCKUM.¹ She claims that treatment by dilutions of a monkey-brain fixed virus as employed at Bandoeng (Java) "guarantees almost absolute protection against cases of hydrophobia with an incubation period of more than thirty days". Thus, as to the fatal cases amongst persons who commenced treatment within a week of having been bitten, the proportions were, with incubation periods of less than thirty days, 95 % for those bitten on the head and 100 % for those bitten on arm or leg. In fact, twelve out of 2,500 persons bitten on the limbs and commencing treatment within a week developed rabies, and each of the twelve developed rabies within thirty days after having been bitten.

That this result is an unusual one appears from the following table, in which the data for all fatal cases (commencing treatment within one week after having been bitten, and bitten on the limbs) which were reported during the period covered by the first five reviews are collected :

| | Number less than 30 days | Total number | Percentage less than 30 days |
|--------------------------|-----------------------------|-----------------|---------------------------------|
| 1. Cords | 27 | 104 | 26 |
| 2. Dilutions | 9 | 20 | 45 |
| 3. Killed phenol | 146 | 594 | 25 |
| 5. Fermi's vaccine | 2 | 2 | 100 |
| 7. Heated | 19 | 37 | 50 |
| 8. Killed ether | 6 | 18 | 33 |
| 9. Mixed | 3 | 13 | 23 |
| 10. Yatren | 0 | 6 | 0 |
| 11. Van Stockum | 12 | 12 | 100 |

It would appear that, with the possible exception of those treated by Fermi's original method, in which the numbers are very small, van Stockum's result is unique.

¹ VAN STOCKUM, "New Principles of Antirabic Treatment and Rabies Statistics", Vol. 1. M. Nijhoff, The Hague, 1935.

ON THE DIAGNOSIS, TREATMENT AND EPIDEMIOLOGY OF VISCERAL LEISHMANIASIS IN THE MEDITERRANEAN BASIN

INTRODUCTION.

In pursuance of a recommendation passed by the first International Congress of Mediterranean Hygiene (Marseilles, September 20th to 25th, 1932), the Health Organisation convened a meeting of specialists¹ at Rome, in August 1934, to give their opinion as to the line of action it might usefully follow in regard to Mediterranean visceral leishmaniasis.

The conclusions reached at this meeting were as follows :

1. *The Committee wishes to emphasise that the most desirable method of diagnosis involves the finding of parasites through microscopic or cultural examination of material from the spleen, liver or bone marrow. They recognise, however, that there may be many occasions in which such a method of diagnosis is not possible and where serological tests may have to be employed. The relative reliability of various serological tests is therefore clearly a matter of importance and worthy of research. But it must be borne in mind that the value of the aldehyde and the antimony tests has been already established, both in Indian and Mediterranean visceral leishmaniasis. Further, investigation of the value of these and other serological tests under the auspices of the Health Organisation would, in the Committee's opinion, be difficult, except at some large research centre in a leishmaniasis area where adequate material is available.*

¹ The meeting was attended by Professor PITTALUGA (Chairman), Professor S. ADLER, Sir R. CHRISTOPHERS, Professor E. FRANCO, Professor M. MONACELLI, Professor Ed. SERGENT and Professor G. VERNONI.

Though, however, further research under the Health Organisation may not be indicated, the Committee considers that a useful short guide drawn up and issued by the Health Organisation giving the technique of these two important tests would greatly help in the study and treatment of leishmaniasis in Mediterranean countries.

2. *Similarly, in regard to treatment, the very great value of certain drugs has been so thoroughly established in Indian kala-azar and also in Mediterranean leishmaniasis that a further study of the value of these drugs would be difficult except in connection with well-established research stations. The Health Organisation might, however, perform a very useful purpose in issuing a brief authoritative description of the technique of treatment by these drugs. It is suggested that a useful procedure might be to obtain information from well-known authorities on Mediterranean visceral leishmaniasis and from the material so gathered to draw up the memorandum advised.*

3. *A brief account of the epidemiology of Mediterranean leishmaniasis, from the point of view of the medical practitioner, giving the latest known facts regarding the disease, might, it is thought, be very useful. Such an account would require to be very brief.*

Guided by these suggestions, the Health Organisation approached a number of prominent workers in this field, asking them to draw up a concise set of instructions for the use of practitioners on the three points raised—namely, serological tests, treatment and epidemiology.

At its meeting in October 1935, the Health Committee considered these notes and decided to publish them in the Bulletin.

I.

SEROLOGICAL TESTS

Note by Colonel Sir S. Richard CHRISTOPHERS.

INTRODUCTION.

Early blood tests in kala-azar.—BRAHMACHARI (1917) observed that, on diluting kala-azar serum with from two to twenty times its volume of distilled water, a cloudiness or copious precipitate formed not seen in other sera. On this he based a "globulin ring test" and a "globulin precipitation test". Later, with SEN (1923), he described a "globulin opacity test", in which the degree of opacity was measured by diluting in a graduated cylinder and observing the depth at which dark spots on a white ground placed below the tube were blotted out. RAY (1921) stated that the red cells in kala-azar do not undergo complete lysis in distilled water and described a "hæmolytic test" by adding two drops of blood to twenty of distilled water.

Though observations have been made in various parts of the world with BRAHMACHARI'S "globulin test" [*e.g.*, MILIO (1922), NASSO (1923) and CASTORINA (1923), in Italy; YOUNG (1923) and STRUTHERS and CH'I CHANG CH'UN (1924), in China], such early tests have now been entirely discarded in favour of the aldehyde and antimony tests. Nevertheless, they are of interest as the first indication of the remarkable serum changes which occur in kala-azar, a brief reference to which will not be out of place.

Serum proteins in kala-azar.—SIA and WU (1922), finding a similar phenomenon to that described by BRAHMACHARI, noted that, in kala-azar, the concentration of the serum globulin was greater than in any other disease. RAY (1924) found the proportion of serum albumen to globulin in kala-azar to be greatly reduced, whilst the globulin was relatively and absolutely increased. NAPIER,

CHOPRA and CHAUDHURY, LLOYD and PAUL, etc., have investigated more precisely the serum changes in this disease. The characteristic change is a decrease in serum albumen and a relative and absolute increase in serum globulin, especially of the euglobulin fraction. LLOYD and PAUL (1928) note that, whilst euglobulin forms about 5 % of the total globulin in normal serum, it may be from 40-50 % of this in kala-azar. The increase in euglobulin is not, however, the reason for the aldehyde reaction, a conclusion also arrived at by CHOPRA and CHAUDHURY (1931). Treatment was found by LLOYD and PAUL to change the proportion towards normal, and such changes and the dependent modifications in the aldehyde and antimony test have been largely employed in following clinically the progress of treatment (LLOYD, NAPIER and PAUL, 1929). So far, observations have not given any satisfactory explanation, based on the serum proteins, either of the aldehyde or of the antimony test, though both are presumably associated with the abnormal protein condition.

Aldehyde test.—NAPIER (1921) announced the test now generally referred to as the formol-gel or aldehyde test, and later (1922) gave more detailed particulars with an indication of its degree of specificity. The test is similar to that described by GATÉ and PAPACOSTAS (1920) as the "formol-gelification test" for syphilis,¹ but is an altogether different test, in that the characteristic reaction in kala-azar is not merely jellification, but, associated with this, a marked and characteristic white opacity. To avoid ambiguity, it is therefore more generally referred to as the aldehyde test.

In the test as originally described by NAPIER, 5 c.c. of blood drawn from a vein is allowed to clot and 1 c.c. of the serum placed in a small tube 1.5 cm. in diameter. To the serum is added 1 drop of formalin (30-40 % formaldehyde) and the mixture is shaken and put aside in a rack at laboratory temperature. In the characteristic reaction, within 3-20 minutes, the mixture becomes

¹ The test as performed by these authors is as follows : 1 c.c. of clear serum is pipetted into a small tube and 2 drops of commercial formalin added. After shaking, the tube is left at laboratory temperature for 24-30 hours, when the reading is taken. For a positive result the serum ought to be more or less solid, jelly-like, but clear. In a negative reaction, the serum remains fluid. An 85 % correspondence of positive results with the Wassermann test was observed. The test is also sometimes positive in laboratory animals and in some other human conditions.

completely solid and opaque, resembling coagulated white of egg. Modifications of the test have been tried, more especially in regard to the quantity of formalin added and the time-limits for observation, but no serious change in the technique has been suggested. Such difficulties as occur arise chiefly from doubtful reactions, + and \pm (see under "Technique"). About 81 % of known kala-azar cases give an unmistakable reaction (NAPIER, 1924). Negative results in kala-azar mostly relate to early cases (under six months' duration), and do not usually amount to more than 5 % of the total. Undoubted positive reaction in another disease is very rare. In cases under treatment, the test may vary from a full reaction to negative. The test appears to have no relation to the Wassermann test.

Observations on Mediterranean visceral leishmaniasis appear to show that results compare with those found in Indian kala-azar. DE CAPITE found the reaction positive in all of 18 cases of infantile leishmaniasis examined, but the reaction was not so rapid as described by NAPIER (7 cases within 30 minutes, 5 more within the hour, and 2 only shown after 6 hours). The reaction apparently does not occur in dermal leishmaniasis.

Various modifications to make the test as simple as possible have been described, including the use of whole blood. Probably the simplest form of the test, which is quite reliable, is that by FOX and MACKIE (1921) given in the section on technique.

Very weak reactions may be obtained in leprosy, also in advanced tuberculosis, especially intestinal, and in chronic malaria (NAPIER, 1924). It may also be positive in schistosomiasis (YOUNG, 1923).

Antimony test.—This test was first described by CHOPRA, GUPTA and DAVID (1927). The addition of kala-azar serum to a solution of urea stibamine or other organic antimony compound gives a thick flocculent precipitate. All organic compounds of antimony of the type of urea stibamine give the reaction, but some more markedly than others. The best results were given with urea compounds. Von Heyden 471 (stibosan) was found to give variable results. Von Heyden 693 (neostibosan) gave the most powerful effect, but some yield a precipitate with most sera, though much thicker and heavier with kala-azar. Antimonyl tartrates give no precipitate. Some organic compounds of arsenic, such as sulpharsphenamine, also give

well-marked precipitates with kala-azar and other sera, but such precipitates disappear if the tube be left standing for half an hour.

For the test, serum is placed in a Dreyer's tube and 4% solution of a suitable antimonial compound slowly added to form a layer. A thick flocculent precipitate forms at the junction of the fluids. The precipitate is immediate and permanent.

To increase the specificity in case of doubtful reactions, CHOPRA and DE (1929) dilute the serum with from 8-10 times its volume of distilled water. Five to ten minutes is given for reading the results. Formation of a flocculent precipitate only is taken as positive (see under "Technique").

NAPIER (1928), after a critical examination of the aldehyde and antimony tests, concludes that the antimony test is more delicate than the aldehyde. Later (1929), he considers that the two are of almost equal and of very considerable practical value in the diagnosis of kala-azar. These remarks apply to the test with diluted serum, the test as used with undiluted serum falling short of the other two. All cases of kala-azar, including early cases, give a positive reaction with the antimony test, but more non-kala-azar cases give the reaction than with the aldehyde test. During treatment, the test alters after ten or eleven injections. Using the diluted serum method, CHOPRA and DE (1929) found in 340 tests that a correct result was given in 88.2% of cases with the antimony dilution test and 81.2% with the aldehyde test. Doubtful and wrong results were about the same in the two tests. LABERNADIE and LAFITTE note that the presence of quinine in the blood may give a misleading result.

FABRIS (1928) found the test satisfactory in 25 cases of infantile leishmaniasis in Italy.

The test has been found negative in dermal leishmaniasis. The test has no relation to the Wassermann test (LLOYD, NAPIER and MITRA, 1930).

Reaction of the blood and other tests.—ARCHIBALD (1911) found the alkalinity of the blood considerably decreased in kala-azar. ROGERS and SHORTEN (1915), using the titration method of WRIGHT (1912), found the alkalinity lowered in cholera and kala-azar. BRAHMACHARI (1920) used a similar titration method, but with TOEPER's reagent as indicator, and obtained a similar result.

NAPIER (1924) found but little change in the pH, but the power of neutralising both acid and base was reduced, this indicating a reduced buffer effect.

Antigenic tests using the spleen of heavily infected hamsters or cultures of the flagellate form have been described by various observers (HINDLE, HOU and PATTON, 1926 ; AURICCHIO, 1927 ; BUSS, 1929; and others); but such tests are as yet of uncertain value.

PARADISO (1929) found that the leucopœnia accompanying visceral leishmaniasis prevented application of the test of AMATO (leucopœnia following injection of small doses of antagonistic substances, such as tuberculin in tuberculosis, antisyphilitic drugs in syphilis, etc.). The trials were made with small intravenous doses of tartar emetic.

Colloidal gold sols give a characteristic reaction with kala-azar serum (CHOPRA, GUPTA and DAVID, 1928). A few drops of kala-azar serum added to a few c.c. of colloidal gold solution in a test-tube gives a turbidity in a few minutes, which, in 24 hours, settles, leaving a clear supernatant fluid. With non-kala-azar serum, this does not occur; but some advanced malaria cases may show a similar turbidity.

NAPIER and HENDERSON (1931) found that the sedimentation rate of erythrocytes was greater in kala-azar than in other diseases, but that it was unlikely to prove a measure of practical diagnostic importance.

TECHNIQUE.

ALDEHYDE TEST.

A. *Field Test* (FOX and MACKIE, 1921).¹

Prick the finger and collect a Wright's capsule of blood. Allow serum to separate. Place a drop of serum on a slide and invert

¹ Rapid tests described by NAPIER are also :

(a) Place drop of serum on the inside of the wall of a test-tube in which a few grains of paraformaldehyde have been placed. Heat gently, liberating formalin vapour. The drop becomes solid and opaque.

(b) One part of 15 % formalin and ten parts of serum are drawn into a Wright's pipette and sealed. Observe against a dark ground and break capsule to ascertain consistency.

The drop test given above in the text is extremely simple and reliable and for a rapid test can scarcely be improved.

the slide over a small Petri dish containing a little formalin. Within a few minutes to half an hour in frank cases the drop becomes completely solid and *opaque*. When only jellification occurs, the test is negative.

B. *Clinical Test* (NAPIER, 1922).¹

5 c.c. of blood drawn from a vein is allowed to clot in a test-tube and the serum to separate. Place 1 c.c. of serum in a small tube (1.5 cm. diameter) and add with pipette 1 drop of formalin (30-40 % formaldehyde), shake well and place aside in rack at laboratory temperature. In the characteristic reaction (+++) the mixture in from 3-20 minutes becomes completely solid and *opaque*, resembling coagulated white of egg.

If reaction is given in 20 minutes, record as +++

If reaction is given after 2 hours, record as ++

If reaction is given in 24 hours, record as +

or the serum may be solid and markedly opalescent but not opaque (+). If solid but slightly opalescent, record as (±). If solid but clear after 24 hours, the reaction is negative (—). (+) and (±) are doubtful reactions.

The serum as collected for the test should be clear (DAS GUPTA, 1931).

ANTIMONY TEST.

A. *With Undiluted Serum* (CHOPRA, GUPTA and DAVID, 1927).

(a) Allow blood to clot and serum to separate. With a capillary pipette place some serum in a Dreyer's tube. Add slowly along the side of the tube some 4 % solution of an organic antimony compound.² With kala-azar serum a thick, flocculent precipitate forms immediately. With other sera, there is either no precipitate whatever

¹ A test with whole blood is also described by NAPIER (1922*b*). Four drops of blood from the patient's finger are allowed to fall into a small test-tube containing 0.5 c.c. citrate solution (NaCl 0.85, sod. citrate 0.5 %) in which there is 1 drop of formalin. If left overnight, the red cells will settle, and the supernatant fluid will be milky if positive.

² See Introduction. The preparation must be a suitable one—*e.g.*, urea stibamine or neostibosan. Stock solutions can be used and have been found effective (urea stibamine) for ten days or longer.

or only a slight precipitate at the junction of the two fluids. The precipitate is insoluble after standing 24 hours.

(b) As above ; but the separated serum is placed in a fine glass tube about 0.5 cm. calibre sealed at one end. Place in rack and add slowly with a capillary pipette some 4 % solution of a suitable antimony compound. Solution should not be added too slowly, as a certain amount of mixture of the fluids at the junction is desirable.

Readings should be taken after 10 minutes. Record as follows :

| | |
|---|---------|
| Precipitate immediate, thick and flocculent ; conglomerated into a mass at junction and difficult to break down on shaking tube ; insoluble on standing 24 hours | +++ |
| A definite flocculent precipitate but not so marked as above. May collect at junction or settle to bottom. Insoluble on standing ... | ++ or + |
| A definite precipitate or various degrees of haziness at junction ; not flocculent. May disappear in a few hours or not | ± |
| No precipitate or haziness | — |

Only strongly positive reactions should be considered as indicating kala-azar (NAPIER, 1928).

B. With Diluted Serum (CHOPRA, GUPTA and BASU, 1927) (NAPIER, 1928).

Dilute serum with 9 parts distilled water and proceed as with undiluted test (A (a)). Readings must be taken at 5-10 minutes. Later readings may be fallacious. A marked reaction shows a white *flocculent* precipitate. Record as follows :

| | |
|--|---------|
| Heavy flocculent precipitate | +++ |
| Fine flocculent precipitate | ++ or + |
| Homogeneous cloud without flocculation ... | ± |
| No change | — |

Only a plus reaction should be regarded as indicating kala-azar. If the spleen is more than 6 inches below the costal margin, only a +++ result should be taken as indicative.

C. *Finger-blood Test* (CHOPRA and MUKERJI, 1930).

CHOPRA and MUKERJI describe a test with whole blood superseding the test previously given by CHOPRA, GUPTA and BASU (1927).

A drop of blood from the finger is received into a small test-tube ($\frac{3}{8}$ inch internal diameter and 2 inches long) containing 0.25 c.c. of a 2 % potassium oxalate solution. Shake to mix thoroughly and allow corpuscles to settle (usually 10-15 minutes). Pipette off supernatant fluid and transfer to small test-tube (4-5 mm. diameter). Run in some 4 % solution of an organic antimony compound slowly down the side of the tube. The heavy antimony solution rapidly permeates through the diluted serum and, in the case of kala-azar, a coarse precipitate appears slowly in the whole column. The precipitate must be flocculent. Readings should be taken at 5-10 minutes and not more than 15 minutes.

D. *Some Other Techniques.*

NAPIER (1927).—To tubes containing 2 c.c. of 0.25 % urea stibamine in distilled water add 2 drops of serum, agitate, allow to remain 10 minutes, and then take a first reading. A second reading is taken after 2 hours. With a positive result, a heavy or light flocculent precipitate forms and settles, leaving clear supernatant fluid. Advantages are : (a) the small amount of serum required, (b) the test can be used with milky serum.

SANYAL (1927).—When the drug (urea stibamine or other antimonial in solution in distilled water) is being injected into a vein for treatment, a test may be made as follows : Before the actual injection is commenced a drop of blood is aspirated into the syringe, after which the contents of the syringe, with the exception of 0.1-0.3 c.c. are injected. The needle is withdrawn and about 2.3 c.c. of distilled water is drawn into the syringe. In kala-azar the mixture is distinctly opaque, the opacity diminishing as the treatment becomes effective.

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II.

TREATMENT.

A. NOTE ON THE TREATMENT USED IN ITALY

By Professor CARONIA.

I. *Tartar Emetic* (potassium antimonyl tartrate) (introduced by CARONIA and DI CRISTINA in 1914-15).

1 % solution in distilled water, autoclave-sterilised.

Dosage.—First inject 2 c.c. of the solution, then inject at two-day intervals, increasing the dose each time by 1-2 c.c. up to a maximum of 5-6 c.c. in the case of children under 2 years of age ; up to a maximum of 8-10 c.c. in the case of children over 2 and under 10 years of age ; and up to a maximum of 10-12-15 c.c. and even more in the case of older children and adults.

The same effects are produced by sodium antimonyl tartrate (Cannata).

Route of administration.—By intravenous injection only.

II. *Pentavalent Preparations of Antimony*, introduced by CARONIA in 1915 in the form of *Slibenyl*, prepared by Heyden, have attained their maximum effect and most convenient form in *neo-stibosan* (*p*-aminophenyl stibiate of diethylamine).

Dosage.—Initial dose : 5 cgr. leading up to 20 cgr., by increasing the dose by 5 cgr. every two days in the case of children under 6. In the case of older children, the maximum may be 30 cgr. In the case of adolescents and adults, the initial dose is 20 cgr. and the maximum dose from 40 to 45 cgr.

Route of administration.—Intravenous or intramuscular injection.

DURATION OF TREATMENT AND RESULTS.

Both with tartar emetic and with neo-stibosan the duration of the treatment may vary from one to two months and more according to cases. We generally interrupt the treatment when at least two weeks have elapsed since the date on which the temperature became normal again, and when the spleen has considerably decreased in volume. Whenever possible, we also examine microscopically the spleen pulp for parasites.

With these two preparations we have in the last few years obtained almost 100 % cures.

CONTRA-INDICATIONS AND DISADVANTAGES.

With all antimony preparations there may be contra-indications and disadvantages. In almost every instance these may, however, be obviated.

Contra-indications are as follows :

(1) Profound anæmia, in the final stage of the disease, in which the slightly hæmolytic action of the antimony may become dangerous. This contra-indication may be met by starting with smaller doses than the customary ones, either by intravenous or by intramuscular injection.

(2) The co-existence of renal lesions. This contra-indication may be met by giving small doses at longer intervals ; in most cases the renal lesions are due to the parasite itself, so that the treatment commenced with slight doses at longer intervals may bring about a rapid improvement that may allow of the regular intensive treatment being applied.

(3) The co-existence of more or less serious cardiac disorders. This is also only a relative contra-indication, since it may be met by the use of small doses administered intravenously, or by resorting to intramuscular injection.

The *disadvantages* are :

(1) The technical difficulty of effecting intravenous injections. Such cases are rare and difficulties may easily be overcome by resorting to intramuscular injection.

(2) Intolerance to antimony, owing to the drug's cumulative tendency. This is a very rare condition which may be met by the regular administration of doses neither excessively small nor administered at too long intervals. When, however, the symptom occurs, it may be countered by a brief interruption of the cure (for 15-20 days), which is then resumed with larger doses.

(3) The development of antimony-resisting properties by the parasite, which tends to render the drug inoperative. This disadvantage may also be easily overcome by proceeding in the same way as in the case of intolerance.

B. NOTE ON THE TREATMENT USED IN ALGERIA

By Professor SERGENT.

Neo-stibosan has yielded excellent results in the hands of all doctors who have tried it. Some physicians use stibyal where neo-stibosan is not available. In one case observed in an adult, stibyal and anthiomaline¹ produced no improvement, whereas neo-stibosan acted favourably and quickly.

These results are confirmed by trials in the treatment of canine leishmaniasis.

Anthiomaline improves the general condition but has little effect on visceral leishmaniasis and does not prevent early relapses.

C. NOTE ON THE TREATMENT USED IN SPAIN

By Professor PITTALUGA.

According to my own experience and that of Spanish pediatricians, covering a total of 3,000 cases treated during the last

¹ Anthiomaline is a preparation containing 16 % of Sb, and described as the lithium salt of stibiothiomalic acid. It is employed in a 6 % watery solution for intramuscular injections [*Editor*].

few years, there may be said to be two schools of thought—namely :

Those who advocate treatment by means of potassium antimonyl tartrate, and

Those who have a decided preference for compounds such as stibenyl, stibosan, neo-stibosan in which antimony is associated with amino ring compounds.

The former view prevails more especially in rural areas having no dispensaries or children's hospitals. The considerations which militate in favour of the use of potassium antimonyl tartrate are mainly economic, although treatment is more protracted.

The results obtained, especially with neo-stibosan, are highly favourable, since our statistics record 70 % of cures, with two courses of 15 days each and an aggregate dose per course of 2.5 gm.

The classical method, which an attempt was made to standardise for the treatment of Indian kala-azar (NAPIER), is wholly inadequate for the treatment of cases of Mediterranean visceral leishmaniasis. This has now been clearly established, and I myself, as well as the Spanish pediatricians, have taken occasion to emphasise it. The patients who do not derive any certain benefit from the treatment indicated include a certain number of genuine cases of antimony-resistance. Among them we found one or two who are certainly hereditary syphilitics. It is difficult to determine the causes and limits of this antimony-resistance. In any case, the whole problem of treating visceral leishmaniasis is a matter of early diagnosis.

III.

EPIDEMIOLOGY.

Note by Professor EDM. SERGENT and Professor S. ADLER.

Visceral leishmaniasis is endemic throughout the whole Mediterranean basin, but its distribution is uneven. There are foci of relatively high intensity, such as Catania in Sicily, where there are about 250 cases annually in a population of 250,000, while other foci have relatively few cases—*e.g.*, in Palestine only five cases have been recorded in the last seven years.

The records of cases are increasing steadily, but it is difficult to say, as far as we can be informed, whether this is due to a real increase of the spread of the disease or to the fact that medical practitioners are paying more attention to the disease and to increased facilities in diagnosis. In North Africa, for instance, leishmaniasis seems to be progressing from east to west. In recent years, several new important foci of the disease have come to light, particularly in Dalmatia and Montenegro, but it is highly probable that in these centres the disease has been endemic for a long period.

One of the main characters of the epidemiology of Mediterranean visceral leishmaniasis is its constancy. There are, till now, no violent outbreaks after periods of quiescence, as in Assam, and it is particularly noteworthy that, in Catania, where an out-patient department for visceral leishmaniasis exists, there has been no important variation in the number of treated cases per annum over a period of at least fifteen years.

The infection has been prevalent in certain Mediterranean countries probably for centuries, as evidenced by the existence of popular names for the disease among the peasantry of endemic foci—*e.g.*, "Ponos" in the Greek islands and "Mard el Bicha" in Malta. These names were prevalent long before the discovery of the causal agent and long before the disease was known as a clinical entity to the medical profession.

The most important character which distinguishes Mediterranean visceral leishmaniasis from Indian kala-azar is its association with canine visceral leishmaniasis. The age distribution, too, has been, for a long time, pointed out as another important differential character. The Mediterranean visceral leishmaniasis was regarded as an infantile disease, whereas the Indian kala-azar occurs amongst people of all ages. But, for some time, it has been found that numerous cases of visceral leishmaniasis exist amongst grown-up people in North Africa, Spain, France, Italy, Sardinia, Sicily.

ASSOCIATION WITH CANINE VISCERAL LEISHMANIASIS.

Canine visceral leishmaniasis is constantly present in endemic foci of Mediterranean visceral leishmaniasis, and, wherever sufficient investigations have been made, it has been found that the disease is commoner in dogs than in human beings—*e.g.*, Algeria, Tunis, Malta, Catania and Canea. It is probable that, as in man, the epidemiology of the disease in dogs has been constant over a long period. In Malta, the same percentage of infected dogs was observed in 1910, 1911, 1931 and 1932. In Algiers, it has been noticed that cases of canine leishmaniasis are more or less numerous according to the seasons.

It is practically certain that the causative agents of the human and canine disease are identical, for the inoculation of *Leishmania infantum* of human origin produces a condition in dogs indistinguishable from the natural infection. In addition, infected dogs have been found in the vicinity of houses in which human cases occurred.

SYMPTOMS OF CANINE VISCERAL LEISHMANIASIS.

The recognition of infected dogs in endemic centres is of paramount importance, for at present the only method of prophylaxis giving promise is an attempt at eradicating infected dogs.

Fully half of the naturally infected animals appear normal and the remainder show the following symptoms :

- (1) Seborrhea, with or without partial depilation. This is commonest of all symptoms. A dog showing seborrhea in

an endemic focus should, at once, be suspected of visceral leishmaniasis and destroyed.

- (2) Emaciation.
- (3) Ulceration in various parts of the skin.
- (4) Conjunctivitis.
- (5) Keratitis.

The above symptoms are not necessarily concurrent and one or more may be absent.

THE RELATIVE IMPORTANCE OF DOGS AND HUMAN BEINGS AS CARRIERS OF MEDITERRANEAN VISCERAL LEISHMANIASIS.

It has been pointed out that, in Catania, where there are the most complete statistics of any Mediterranean focus over a long period, the treatment and cure of most of the human cases has had no appreciable effect on the number of new cases per annum. Parasites can be demonstrated by blood culture in more than 90 % of cases, but they are very scarce and can only very rarely be demonstrated in blood smears. The above facts imply that human beings are not important as carriers of the disease.

The most significant phenomenon in canine infection is the presence of infected macrophages in various amounts throughout the entire dermis of the whole body, with or without visible changes in the skin.

TRANSMISSION.

Wherever the disease has been sufficiently investigated, it has been found to be associated with sandflies (*Phlebotomus*) of the major group—*e.g.*, in Algeria, Italy, Malta and Marseilles with *P. perniciosus*, in Greece with *P. major*; and it is practically certain that future investigation will reveal a similar association in other centres which have not yet been fully explored—*e.g.*, Spain and Portugal. In Sicily, the distribution of the disease is limited to that of *P. perniciosus*; in Crete, to that of *P. major*. These sandflies infect themselves readily by feeding on the unbroken skin of infected dogs by ingesting infected macrophages from the skin juices. The infection rate in *P. perniciosus* and *P. major* fed on naturally infected dogs may be as high as 90 %, while *P. perniciosus* fed on human

cases rarely show an infection rate of 5 %. It has also been shown in the case of *P. perniciosus* that, in a number of infected sandflies, flagellates invade the terminal part of the proboscis and are deposited in any medium on which the sandfly feeds. Moreover, flagellates of *L. infantum* introduced into the skin of susceptible animals produce visceral leishmaniasis. It is therefore practically certain that :

- (1) Sandflies of the *major* group transmit Mediterranean visceral leishmaniasis ;
- (2) Infected dogs are the principal reservoir from which sandflies infect themselves and transmit the disease to other dogs and to man.

PROPHYLAXIS.

It is difficult, in the present state of knowledge, to carry out prophylactic measures by a campaign against sandflies. A very good thing to do, when possible, is to destroy dead leaves or decaying vegetable matter, as it has been stated that it is a breeding-place for larvæ of *P. perniciosus*.

Treatment and cure of all human cases is hardly likely to affect the spread of the disease.

The only possible means of attempting to eradicate the disease is a campaign against infected dogs. The ideal procedure would be : (1) the ruthless destruction of all stray dogs ; (2) the detection and destruction of infected house-dogs, as recommended by A. LAVERAN long ago. The overwhelming majority of infection in house-dogs could be diagnosed rapidly by removing 1 c.c. of blood, defibrinating and performing the formol-gel reaction on defibrinated blood or serum.

This proposal would readily be practical even in villages and rural communities ; it is quite desirable to attempt, at least in big endemic foci, such as Canea and Catania, and it would be advisable to integrate the destruction of infected dogs in the legislation of the Mediterranean countries.

INVESTIGATIONS WITH A VIEW TO DEVISING A STANDARD METHOD FOR DETERMINING THE MORPHINE CONTENT OF OPIUM

Origin and Development of the Work of the Commission
of Experts (1931-1935).

At the thirteenth session of the Advisory Committee on Traffic in Opium and Other Dangerous Drugs (January-February 1930), the United Kingdom representative on the Committee pointed out that the methods of ascertaining the morphine content of opium as prescribed by the various national pharmacopœias yielded substantially different results,¹ and that this was both a hindrance to trade and a source of difficulty in the compilation and comparison of the statistical data relating to the control of narcotics.

The Advisory Committee accordingly referred this question to the Health Committee for study. It did so, not only in pursuance of the British suggestion, but mainly with a view to the Conference

¹ The same opium analysed in the laboratory of the firm of Harrison & Self, in London, according to the methods prescribed by ten different pharmacopœias, yielded the following results (see document O.C.1096) :

| | Percentage of morphine |
|--|---------------------------|
| British Pharmacopœia, 1914 | 12.50 |
| French Codex, 1908 | 12.90 |
| German Pharmacopœia, 5th edition | 11.44 |
| Swedish Pharmacopœia, X | 11.29 |
| | } 11.30 |
| Austrian Pharmacopœia, VIII | 12.20 |
| Belgian Pharmacopœia, 1906 | 11.96 |
| Danish Pharmacopœia, 1907 | 11.74 |
| Italian Pharmacopœia, 1920 | 11.55 |
| Hungarian Pharmacopœia, III | 11.90 |
| Spanish Pharmacopœia, VII | 11.64 |

for the Limitation of the Production of Narcotic Drugs which was to be held in 1931. The Opium Committee realised from the start that the production of morphine and its derivatives could not be limited unless subjected to the most stringent control, and that such control would be impossible in the absence of a standardised and comparatively accurate method of ascertaining the morphine content of opium.

Under the terms of Article 17 of the Convention for limiting the Manufacture and regulating the Distribution of Narcotic Drugs (Geneva, July 13th, 1931), the signatory States undertook to ensure that producers should notify their Governments once a quarter, not only of the quantity of opium purchased, but also of its morphine content, as determined by a method prescribed by the Governments.¹

Though the 1925 Convention required Governments to exercise a certain control over production, they do not as yet possess either a method of their own for determining the morphine content of opium or the administrative machinery for carrying out the control analyses. In practice, the Governments of all manufacturing countries, with the one exception of the United States of America, rely upon the analyses of private laboratories (for instance, Harrison & Self, in London, or Gilbert, at Hamburg), which are carried out for the manufacturers and serve as a basis in assessing the price of the opium offered for sale. The Government of the United States is the only one that has its own chemists, and the method employed by them is that of the American Pharmacopœia.

When, in September 1930, the Hungarian Government also proposed that a standardised method for determining the morphine content of opium should be devised, the Health Committee decided to entrust this study to a commission of experts. Professor L. VAN ITALLIE, of Leyden, was appointed Chairman of the Commission, and, on his proposal, a number of highly qualified experts were invited to serve on the Commission—namely :

Professor H. BAGGESGAARD-RASMUSSEN, Copenhagen ;
Professor R. EDER, Zurich ;

¹ " The manufacturer shall state the proportion of morphine . . . contained [in the opium] . . . as determined by a method prescribed by the Government and under conditions considered satisfactory by the Government " (Article 17, paragraph (a), of the Convention for limiting the Manufacture and regulating the Distribution of Narcotic Drugs of July 13th, 1931).

Professor A. GORIS, Paris ;

Professor E. KNAFFL-LENZ, Vienna ;

Professor Charles H. LA WALL, Philadelphia ;

Professor C. MANNICH, Berlin ;¹

M. J. R. NICHOLLS, B. Sc., F. I. C., Government Laboratory,
London ;

Professor J. ASAHINA, Tokio (replacing Professor Kotaro
NISHIZAKI, Tokio).

The Commission of Experts met for the first time at Geneva on April 9th, 1931, and drew up a programme of work which was approved by the Health Committee in May 1931. Since that time, the Commission has held the following sessions : July 1932, The Hague—Leyden ; August 1933, Zurich ; July 1934, Berne ; July 1935, Copenhagen.

In the intervals between the sessions, extensive experiments and comparative analyses were carried out in the laboratories of the members of the Commission. For this purpose, five samples of opium obtained from different sources were used (Turkish, Persian, Yugoslav opium, opium of unknown origin, and a mixture of different kinds of opium).

The Commission selected as the starting-point for its experiments the following four methods :

(1) The method prescribed by the British Pharmacopœia of 1914 ;

(2) The method prescribed by the Netherlands Pharmacopœia of 1926 ;

(3) A new method proposed for the new Swiss Pharmacopœia (5th edition) by R. EDER (known as the "benzene method") ;²

(4) A new method of exhaustion, the basic principles of which were formulated by H. BAGGESGAARD-RASMUSSEN.³

The various forms of the "Helfenberg method", adopted, for instance, in the German Pharmacopœia (6th edition), the Danish

¹ Professor MANNICH ceased to take part in the work when Germany withdrew from the League.

² Cf. R. EDER : " Ueber eine neue Bestimmungsmethode des Morphins in Opium (Benzolmethode)", *Tschirch-Festschrift*, 1926, page 392.

R. EDER & H. MAERKI : " Ueber die Morphinbestimmung in Opium", *Pharmaceutica Acta Helvetiæ* 1927, 2, 21.

³ Not published.

Pharmacopœia (7th edition), the Swiss Pharmacopœia (4th edition) and the Austrian Pharmacopœia (8th edition), were not employed for the purposes of this experimental study, because, it being obvious that those methods applied more especially to opium containing approximately 10 % of morphine (medicinal opium), they do not lend themselves to the analysis of raw opium which may contain a much higher proportion of morphine.

As regards the different known variants of the lime-water methods, the Commission at first decided to consider those described in the British Pharmacopœia and the Netherlands Pharmacopœia, since they lend themselves to the study and elucidation of certain fundamental points relating to these methods. There was no intention, however, of excluding other variants of this method—for instance, those prescribed by the American Pharmacopœia. The Commission also realised that the lime-water methods possessed certain defects—they may yield unduly low values, when, for instance, the whole of the morphine is not extracted from the opium and considerable quantities of the alkaloid remain in solution when the morphine is precipitated. In other cases, the resulting values may be too high, owing to the fact that the morphine obtained is not pure (morphine containing lime or accessory alkaloids).

In spite of these admitted defects, the Commission considered that, of all the methods then known, the lime-water methods were likely to yield the most satisfactory results from the point of view of the rapid formulation of a standardised and practical method of controlling narcotic drugs. The Commission hoped to be able to eliminate to some extent the defects of these methods.

* * *

The Commission also kept in mind from the outset the possibility of devising a method based on new principles which would furnish more accurate and more scientific results than the lime-water method.

If a method is to be of practical value and is also to yield satisfactory results from the scientific standpoint, it must satisfy the following requirements :

- (a) It should permit of the detection of 99 % at least of the morphine contained in the opium and obviate the need for any correction for loss ;

(b) The morphine obtained should, as far as possible, be free from substances the presence of which could affect the result of the analysis ;

(c) The method should, so far as possible, obviate the use of aliquot parts in the analysis ;

(d) It should be applicable to the largest possible number of different kinds of opium ;

(e) It should, so far as possible, give concordant results in the hands of different competent chemists. The difference should not exceed 0.5 % of the morphine in the opium ;

(f) It should be as simple to apply as possible ;

(g) It should also be as economical as possible from the point of view of time, materials and equipment.

With a view to devising a method superior to the lime-water method, the Commission first selected as the starting-point for its experiments the processes mentioned above under (3) and (4). As the work proceeded, a whole series of other processes and proposals were added—for instance :

The barium method of E. KNAFFL-LENZ ;¹

The exhaustion method of R. EDER and W. STUCKI.²

The following variants of the lime-water method were also studied :

The process of N. RUSTING ;³

The oxalate method of E. KNAFFL-LENZ.⁴

From 1931 to October 1933, experiments with the various methods were made in the laboratories of the members of the Commission and supplemented by a number of investigations of special aspects of the methods, only some of which were published.⁵

¹ Cf. E. KNAFFL-LENZ : " Ueber die Morphinbestimmungsmethoden in Rohopium ", *Pharmazeutische Monatshefte*, 1932.

² Cf. R. EDER & W. STUCKI : " Ueber eine neue Methode zur Bestimmung des Morphins in Opium ", *Pharmaceutica Acta Helvetica*, 1932, 10.

³ Cf. N. RUSTING : " Ueber die quantitative Bestimmung des Morphins in Opium ", *Archiv der Pharmazie*, 1931, 609, and 1932, 323.

⁴ Cf. E. KNAFFL-LENZ : " Ueber die Morphinbestimmungsmethoden in Rohopium ", *Pharmazeutische Monatshefte*, 1932.

⁵ Cf., for instance : A. GORIS & J. FOURMONT : " Sur le dosage de la morphine dans l'opium ", *Bulletin des sciences pharmacologiques*, 1932, 337. H. BAGGESGAARD-RASMUSSEN & F. REIMERS : " Die Löslichkeit des Morphins in verschiedenen Lösungsmitteln ", *Dansk Tidsskrift for Farmaci*, 1931, 145,

In October 1933, the Commission was able to propose to the Health Committee a standard method. This method, which will hereafter be described as the international method (I.M.), was then submitted through the Advisory Committee to all Governments, who were invited to send their observations and suggestions, if any, to the Health Committee.¹

This international method is an improved lime-water method which furnishes more accurate results and eliminates various errors inherent in the older methods. The chief improvements are as follows : taking of an aliquot part of the opium extract under more satisfactory conditions, since allowance is made for the degree of humidity and the extract content of the opium ; elimination of the impurities in the opium which may impair the results of the analysis.

The Commission was quite aware that the method still presented some of the defects inherent in all lime-water methods—in particular, the following :

(a) The method may not allow of the extraction of the whole of the morphine from the opium ;

(b) The coefficient of rectification for the quantity which, when the morphine is precipitated by this method, remains in solution in the mother liquor is relatively high as compared with the quantity analysed, and is to some extent arbitrary ;

(c) The morphine analysed is not 100 % pure.

(d) The differences in the results obtained with the same opium by different experimenters are not entirely negligible.

On the proposal of H. BAGGESGAARD-RASMUSSEN, ten chemists, who were given two samples of opium, made three analyses of each sample by the I.M. The results obtained were as follows :

| | Opium I | Opium II |
|---------------------------|------------------|------------------|
| Mean | 14.59 % | 14.06 % |
| Maximum differences | + 0.36 - 0.39 | + 0.45 - 0.43 |
| Average | 0.109 | 0.123 |

and *Archiv der Pharmazie*, 1935. H. BAGGESGAARD-RASMUSSEN, K. A. JACKEROTT & J. C. JESPERSEN : "Morphinbestimmung in Opium nach der Kalkmethode", *Dansk Tidsskrift for Farmaci*, 1934, 185 and 206.

¹ This international method was published by L. VAN ITALLIE in the *Bulletin de la Fédération internationale pharmaceutique*, 1933, 14, 98. Since then it has already been adopted by two new pharmacopœias, those of Switzerland and Denmark, with slight simplifications justified by pharmaceutical practice.

| Percentage difference as compared with the mean figure | 3.5-3.0 | 3.0-2.5 | 2.5-2.0 | 2.0-1.5 | 1.5-1.0 | 1.0-0.5 | 0.5-0 | Opium |
|--|---|------------|-------------|----------|----------|----------|------------|-------|
| | Number of analyses deviating from the mean, shown as a percentage of the total number of analyses made .. | + 0 - 0 | 0 3.5 | 3.5 7 | 10 7 | 4 7 | 17 10 | |
| | + 3.3 - 3.3 | 6.7 0 | 3.3 13.3 | 3.3 0 | 0 3.3 | 10 10 | 26.5 17 | II |

On the initiative of Herbert J. WOLLNER (Office of the Secretary, Treasury Department, Washington, D.C.), nineteen official laboratories of the United States arranged for some thirty-five chemists to make sixty-eight analyses of an opium sample by the I.M. The differences were as follows :

| Morphine content ascertained % | Difference % | Number of analyses | Percentage of the number of analyses made |
|--------------------------------|--------------|--------------------|---|
| 13.15-12.5 | 0.65 | 47 | 69 |
| 13.15-12.3 | 0.85 | 56 | 82 |
| 13.15-12.15 | 1.0 | 60 | 88 |
| 13.15-11.8 | 1.35 | 67 | 98.5 |

Notwithstanding the defects of the I.M., the Commission proposed it to the Health Committee as a standard method for the following reasons :

(a) An urgent duty devolves upon the League to propose to Governments as quickly as possible a method which will enable the latter to carry out their obligations under Article 17 of the Convention of July 13th, 1931.

(b) Although the proposed method does not answer all scientific requirements, it is sufficiently accurate in practice, and easy to apply.

(c) It is impossible to foresee how long it will take to devise a method which will be entirely satisfactory.

The Commission did not, however, give up hope of discovering a more perfect method—*i.e.*, a process which will satisfy more fully the conditions enumerated above ; it therefore decided to continue its researches.

* * *

During the period 1933-1935, analyses were also made by the method prescribed in the Pharmacopœia of the United States of America (1926) and according to the variant of this method recommended in the eleventh edition now in course of preparation. These are also lime-water methods and, in principle, possess the same defects as the I.M. The question of the advantages which the process of extraction prescribed by the American Pharmacopœia may offer is still being studied. The method of H. E. BUCHBINDER, which was also examined by the Commission, was shown to be not free from defects. It is also complicated, and, when certain analyses were made in the official laboratories of the United States and by members of the Commission of Experts, the differences in the results were much more considerable than in the case of the I.M.

* * *

As a result of the analyses made in 1934 and 1935 by various members of the Commission, the latter is at present studying three new methods :

A method published by C. MANNICH¹ based on an entirely new principle ;

A new method devised by R. EDER and E. WAECKERLIN ;

A new method proposed by E. KNAFFL-LENZ.

The Commission also gratefully noted the researches which have been carried out in various laboratories, particularly by A. H. HOMEYER in the Mallinckrodt Chemical Works at St. Louis (United States of America), and which have thrown useful light on the structure and value of the methods of morphine dosage.

The formulation of an entirely satisfactory standardised method has proved a much harder problem than was at first supposed. The difficulties are chiefly due to the following factors :

(a) The various kinds of opium differ considerably in nature and composition.

¹ C. MANNICH : " Eine neue Methode zur Bestimmung des Morphins insbesondere im Opium ", *Archiv der Pharmazie*, 1935, 97.

(b) At the time of extraction, no matter what process is employed, a more or less considerable quantity of accessory substances which are difficult to eliminate always finds its way into the extracts with the morphine. It is very difficult to separate quantitatively the extracted morphine from the accessory alkaloids and other foreign extracts.

It is to be hoped, however, that the efforts which have already been pursued for more than 100 years¹ with a view to the discovery of a satisfactory and really practical method for the assay of morphine will shortly lead to positive results.

¹ The first description of a method for ascertaining the morphine content of opium was furnished by the chemist GUILLERMOND in 1828 (*Journal de Pharmacie et de Chimie*, 1828, 14, 436).

THE BLOOD CULTURE OF THE TUBERCLE BACILLUS ACCORDING TO LOEWENSTEIN.

Under this heading there appeared, in the March 1935 issue of the Quarterly Bulletin, three papers on experimental research into the value of LOEWENSTEIN'S method of blood culture, together with the conclusions which, in the unanimous opinion of the experimenters, might be drawn therefrom.

We communicated these papers to Professor LOEWENSTEIN, who expressed the desire, to which we felt bound to accede, to reply to the criticisms levelled at him. A statement of his views is given in the following pages under the heading "Tuberculous Bacillæmia and its Significance in Medicine".

As in duty bound, we communicated Professor LOEWENSTEIN'S reply, at the time, to Dr. A. S. GRIFFITH, Dr. K. A. JENSEN and Dr. A. SAENZ, asking them whether they had any comments to make on the subject. Since all three wished to refute certain arguments advanced by Professor LOEWENSTEIN, we have thrown open our columns to them.

Readers, thus acquainted with the full facts of the case, will accordingly be able to form an unbiased opinion.

So far as we are concerned, we regard this discussion as now closed.

I.

**TUBERCULOUS BACILLEMIA AND ITS
SIGNIFICANCE IN MEDICINE**

by

Professor ERNST LOEWENSTEIN, Vienna.

Since 1902, I have been endeavouring to find a method of isolating tuberculosis bacilli direct from infectious material. In a conversation which took place in February 1910, Robert Koch encouraged me in this project, pointing out that progress in research and anti-tuberculosis action depended upon whether a suitable method could be devised which would enable pure cultures of tuberculosis bacilli to be grown direct from the infectious material without recourse to animal tests. After many experiments, I published the first paper on the subject in 1924. I had found that tuberculosis bacilli are very resistant to acids in high concentrations. The following table gives an excellent illustration of this behaviour. The technique used was to treat the same sputum with different concentrations of various acids, five seedings on to a medium being made with each sample.

TABLE I.

(From *Wiener Klinische Wochenschrift*, 1924, No. 10.)

By Professor E. LOEWENSTEIN.

| Acid or alkaline solution | 10 % | 15 % | 20 % | 25 % | 30 % | 35 % | 40 % | 45 % | 50 % |
|---------------------------|-------------------------------------|---|---|------------------------------|------------------------------|------------------------------|------------------------------|--------------|--------------|
| Sulphuric acid | 2 contaminated. 3 pure cultures. | 5 pure cult. | 5 pure cult. | 5 pure cult. | 3 pure cult. 2 rem. ster. | 3 pure cult. 2 rem. ster. | 4 rem. ster. 1 pure cult. | 5 rem. ster. | 5 rem. ster. |
| Hydrochloric acid | 5 pure cult. | 5 pure cult. | 5 pure cult. | 5 pure cult. | 3 pure cult. 2 rem. ster. | 1 pure cult. 4 rem. ster. | 5 rem. ster. | 5 rem. ster. | 5 rem. ster. |
| Caustic soda solution | 2 contam. 3 pure cult. | 3 pure cult. 1 contam. 1 rem. ster. | 2 pure cult. 1 contam. 2 rem. ster. | 3 pure cult. 2 rem. ster. | 3 pure cult. 2 rem. ster. | 1 pure cult. 4 rem. ster. | 5 rem. ster. | 5 rem. ster. | 5 rem. ster. |
| Acetic acid | 5 contam. | 3 rem. ster. 2 contam. | 5 rem. ster. | 5 rem. ster. | 5 rem. ster. | 1 pure cult. 4 rem. ster. | 5 rem. ster. | 5 rem. ster. | 5 rem. ster. |
| Lactic acid | 5 contam. | 5 contam. | 3 contam. 2 rem. ster. | 4 contam. 1 rem. ster. | 2 contam. 3 rem. ster. | 1 contam. 4 rem. ster. | 5 rem. ster. | 5 rem. ster. | 5 rem. ster. |

This table shows that tuberculosis bacilli are not killed by sulphuric and hydrochloric acid, even in concentrations of as much as 25 % (volume), when exposed to their action for not more than ten minutes. All other germs are killed ; only the tuberculosis bacillus is immune to these high concentrations of sulphuric and hydrochloric acid, presumably on account of its high wax content. It was upon this observation that my process of pure culture was based, and it may be taken that this simple method has now found universal acceptance. There have, it is true, been a number of authors who have claimed to have improved the method. In every case, these improvements consisted in lowering the sulphuric acid concentration, sometimes to 12, 10, 8 and 6 %. There is no evidence whatever to support these proposed improvements. As I can prove by many thousands of tests, the concentration of 15 % by volume is by far the best. Weaker concentrations are not advisable, since mixed infections with sporulating bacilli and moulds are extremely likely to occur. The concentration should therefore not fall below that level—in fact, highly infected material such as fæces, urine, and sometimes sputum, should be treated for preference with concentrations rising to 20 and 25 %. The above table proves that, even where a 25 % concentration of sulphuric acid was used, all seeded tubes gave pure cultures. In comparative series of tests performed without protective colloidal substances—that is to say, tests upon bacilli from cultures suspended in physiological saline solution—the cultures which had been in contact with 15, 20 and 25 % sulphuric acid grew even better than the control seedings. It is therefore advisable to adhere to my original method.

In the year 1930, I was able to report on a method of cultivating tuberculosis bacilli direct from the blood. As a matter of fact, I had succeeded in making cultures from the blood as early as 1905, but this work related mostly to animal experiments in which huge numbers of tuberculosis bacilli were used. In these circumstances, pure cultures could naturally be made from the blood without difficulty. Every drop of blood yielded a colony. In man, however, the attempts I made during many years to derive pure cultures from severe cases of tuberculosis were but rarely successful.¹

¹ *Zeitschrift für Tuberkulose*, 1925, 42, 177.

Only with the method which I described in 1930 was I able to obtain pure cultures from blood on an extensive scale. I then succeeded, in collaboration with Professor C. REITTER, Director of the Internal Diseases Department of Vienna City Hospital, in demonstrating the presence of the tuberculosis bacillus, not only in the familiar manifestation forms of the disease, but also in acute and chronic polyarthritis. These results were made possible by the close co-operation of an experienced internal disease specialist with the bacteriologist ; for it is essential that the moment for the taking of the blood sample should be correctly judged. Subsequently, however, I detected tuberculosis bacilli in the blood or cerebro-spinal fluid of a considerable percentage of cases of chorea, retro-bulbar neuritis, multiple sclerosis and dementia præcox. In view of the great importance of this question to medicine as a whole, I approached the League of Nations with a request that arrangements might be made for the fullest possible verification of my results. I imagined that, in making this verification, the members of the Committee, following my technique very exactly and using every available method, would proceed to test as many cases of the above diseases as possible for tuberculosis bacilli, examining say 1,000 cases of acute polyarthritis and applying all three methods of detecting the tuberculosis bacillus—viz. :

- (1) Direct staining of the hæmoglobin-free deposit ;
- (2) Animal tests with the hæmoglobin-free deposit ; and
- (3) My method of culture.

I myself proposed that blood samples from each case, bearing only numbers and without diagnosis, should be sent to me for examination. I forwarded my result and the corresponding original cultures month by month to the League of Nations, or alternatively to the Member of the Committee who had furnished the sample.

I received 755 blood samples, numbered, but without particulars of diagnosis. Of these 755 samples, 82 proved positive in my hands. I only learnt of the diagnosis of these cases from the printed report of the League of Nations. The 82 samples are distributed as follows over the diseases specified hereunder :

49 cases of tuberculosis, mainly pulmonary, including specimens from experimental animals ;

- 11 cases of lupus ;
- 6 cases of dementia præcox ;
- 3 cases of rheumatism ;
- 1 case of lymphogranulomatosis ;
- 1 case of sympathetic ophthalmia ;
- 11 cases with unknown diagnosis.

I should like to stress that, if I understand the reports of the League Committee aright, the blood samples thus sent to me included only 4—instead of the expected 1,000—cases of rheumatism. Yet acute rheumatism would have been the best subject of investigation, for it is precisely in acute polyarthritis that Ziehl-Neelsen staining sometimes discloses masses of tuberculosis bacilli, as a whole series of authors, COURMONT, BUSSON, CORONINI, JUBES, FANJUL, GERZNER and POPPER, have attested. JENSEN throws doubt upon the occurrence of capillary thrombi, consisting entirely of tuberculosis bacilli, despite my micro-photographs. Every bacteriologist knows, however, that such pictures can certainly not be artificially produced. I call such bacillary thrombi “straddling thrombi”, since they often occur on the vein junctions—mostly of the smallest veins. Apart from this, however, there are also simple thrombi.

In 11 cases, I have so far remained in ignorance of the diagnosis, and have not been able to determine it with certainty even from the League of Nations report, which reproduces only extracts from the laboratory protocols. *Every impartial mind must conclude from the findings as recorded, without any knowledge of the diagnosis, that tuberculosis bacilli can be cultivated from the blood by my method.* The report also clearly demonstrates, however, that tuberculosis bacilli can be cultivated, in the first place from the familiar manifestation forms of tuberculosis, but also from cases of dementia præcox, rheumatism, sympathetic ophthalmia and lymphogranulomatosis.

The practicability of my method has, moreover, been expressly acknowledged by SEIFFERT, of the Uhlenhut Institute, even though he does remark that the method is in need of further refinement. In his conclusion, SEIFFERT prints the following in thick types : “Considering the problems with which LOEWENSTEIN'S method confronts us, it is to be earnestly hoped that this refinement will be successfully effected”.

While the practicability of my method is sufficiently demonstrated by these statistics, its reliability is strikingly confirmed by a perusal of the reports made by the authors who were entrusted with the work of verification.

CALMETTE and SAENZ, of the Paris Pasteur Institute, must undoubtedly be credited with having done a great deal of work on this question. A scrutiny of their reports reveals, however, some highly interesting findings.

I received from the Pasteur Institute 8 blood samples without diagnosis, which were seeded by Dr. COSTIL on to my own nutrient medium as well as on to that prepared by my method in Paris. The test tubes were taken to the Paris Pasteur Institute by COSTIL, together with blood samples from a number of cases of disease which COSTIL had seeded himself at our Institute. To my great astonishment I gather from the League of Nations report¹ now before me that COSTIL's findings with my method were 100 % correct, for these 8 blood samples were taken from 4 tuberculous and 4 healthy rabbits. All 4 tuberculous rabbits gave a positive result, the 4 healthy ones a negative result. It would assuredly be difficult to adduce more striking proof of the reliability of my method than has been thus furnished by the Pasteur Institute. Of the 24 blood samples which COSTIL seeded here and immediately took under seal to Paris, 4 were positive, viz. :

1 case of acute polyarthritis, my Record Number 18204 ;

1 case of Bazin's disease (erythema induratum), my Record Number 18206 ;

2 cases of sympathetic ophthalmia, my Record Numbers 18228 and 18229.

These results secured in a wholly incontestable manner by Dr. COSTIL render the continuance of these experiments absolutely necessary. That is why I am utterly at a loss to understand Dr. Louis MARTIN when he says that "further research work would not bring any fresh evidence to light".

Emile Roux, who received me on April 23rd, 1933, at all events took a different view from Dr. MARTIN. He warned me at the time that it would take about ten years to secure recognition for these facts, about which he himself had no doubts.

¹ *Quarterly Bulletin of the Health Organisation*, "The Blood Culture of the Tubercle Bacillus according to Loewenstein", 1935, 4, No. 1, page 272.

CALMETTE and SAENZ acknowledge, at all events, that they obtained pure cultures in 12 cases. KOLLE and KÜSTER secured pure cultures in 5 cases of tuberculosis, 1 case of erythema nodosum and 1 case of dementia præcox. Much better results were achieved by SEIFFERT, who produced positive cultures in 17 cases of tuberculosis and 1 case of dementia præcox. Oddly enough, the results of JENSEN's tests were absolutely negative in 309 cases of tuberculosis of various forms, and thus contrast sharply with those of the other investigators. GRIFFITH (Cambridge) also failed to obtain pure cultures from 8 cases of severe pulmonary tuberculosis from which I had isolated pure cultures on 3 occasions. The samples in question were also received *bearing only numbers*. The results of CALMETTE and SAENZ, KOLLE and KÜSTER, SEIFFERT and even GRIFFITH's animal tests prove that the method yields positive results. These are naturally not so good as my own, for I have been working for thirty-three years on the question of pure cultures of tuberculosis bacilli and have, in the course of the last six years, investigated more than 23,000 cases. Such experience can obviously not be matched by twelve months' practice, especially if the tests are discontinued after a few hundred cases. Professor MARESCH himself pointed out that some thousand investigations are necessary for the mere acquiring of the technique. Now that the Maresch Institute has performed more than 14,000 tests, the results are exactly the same as mine. This is specially true of acute polyarthritis, which has been accurately studied by CORONINI and POPPER. Out of 162 cases of "rheumatic heart trouble", 44 yielded cultures of genuine tuberculosis bacilli, isolated partly from the blood and partly from the organs. Dozent CORONINI points out that the technique is difficult and calls for a high degree of manual dexterity, which can only be acquired by long practice. On December 31st, 1934, I had made 2,889 blood cultures during the preceding five years, and had obtained 617 positive results in cases of polyarthritis.

The reason for the complete failure of the pure cultures in JENSEN's hands may possibly be the following: I possess only centrifuges which do not exceed a speed of about 1,500 r.p.m. If the speed is too high—say 3,000 to 4,000 r.p.m.—the sediment is compacted by centrifugal force into a clump which is difficult to disaggregate. The tuberculosis bacilli can no longer be released from this clump and do not multiply, since they can only be grown on our artificial

medium when they be free upon the surface. If pieces of tissue are placed upon the medium or even introduced into the animal organism, it will be observed that growth frequently fails to occur *in vitro* and in the guinea-pig. Pure cultures can therefore only be successfully grown if the pieces of tissue are very carefully ground up in a sterile mortar to the consistency of a very fine emulsion. My experience in the making of cultures from the eye, tonsils and other tissues has invariably pointed to this conclusion. It may be, therefore, that institutes equipped with too powerful centrifuges obtain less favourable results for that very reason. The work should be done with the same centrifuge as I use, which is supplied by SCHULMEISTER, No. 5, Spitalgasse, Vienna IX.

SEIFFERT has drawn attention to another point, as a result of the following observation made by pure chance :

“ During my stay in Vienna, I had arranged for a number of blood samples to be sent on to me, half of the available quantity of blood being kept at Freiburg and tested by me after my return. These samples gave only negative results in my Vienna tests, whereas, a fortnight later, in Freiburg, four of them yielded cultures of tuberculosis bacilli, two of these being in fact luxuriant. Conversely, in Vienna, the collected samples of blood—*i.e.*, samples several days old—taken from definitely tuberculous animals, yielded bacilli much more frequently than the fresh material I used in my own investigations. This suggested the presence in the blood of a labile growth-inhibiting substance. We therefore took up the investigations by LOEWENSTEIN'S method once again, using one-half of every blood sample in the fresh state and one-half on the expiry of 10 to 15 days. The results so far recorded are as follows : Out of 13 cases of active phthisis, 2 proved positive at the first test and 2 only at the second (all microscopic) ; out of 9 cases of inactive phthisis, 1 was positive at the first test and 2 at the second test (all microscopic) ; out of 20 cases of glandular tuberculosis, 2 proved positive at the first test (1 macroscopic), and 2 at the second test (both macroscopic) ; out of 9 cases of lupus, 3 were positive at the first test (1 case macroscopic, 2 cases in KIRCHNER medium). Of the 14 positive cases, therefore, 6 were only detected at the second test ; the reverse

result of a first test yielding a positive, and a second test a negative, finding occurred, it is true, in two instances. Similar experiments were made with the blood of infected guinea-pigs. Thirteen animals were infected with virulent cultures ; their blood yielded 3 positive results at the first test, and 8 additional positive results at the second test (including 2 macroscopic). Of 10 guinea-pigs infected with avirulent cultures, none yielded cultures of bacilli at the first test, and 2 at the second test, both microscopically demonstrated. "1

Mention should also be made here of the excellent results obtained by my method in the making of cultures from cadaver blood. Thus, POPPER, BODART and SCHINDLER grew pure cultures from the heart blood of 85 % of patients dying from tuberculosis, and KÜSTER, member of the Committee, also secured 60 % of positive results with cadaver blood.

These two results surely afford an indication that fresh blood must contain substances which have an inhibitory effect upon the growth of tuberculosis bacilli. Hence it is absolutely essential to remove the hæmoglobin completely, in saying which I leave open the question whether the hæmoglobin is itself the disturbing substance or whether it merely serves as a kind of indicator witnessing to the complete removal of that substance. At all events, these experiments afford clear evidence of the reliability of my method, even in the hands of those performing the verification tests. " One single positive case proves a thousand times more than a thousand negative cases ", wrote that very experienced tuberculosis specialist, Professor W. NEUMANN.

Between November 5th and 10th, 1932, Dr. JENSEN tested 18 blood samples and took them immediately under seal to Copenhagen. He obtained 6 positive results in Copenhagen, distributed as follows over the undermentioned diseases :

- 1 case of endocarditis,
- 1 case of chronic polyarthritis,
- 1 case of tonsillitis in articular rheumatism,
- 1 case of tuberculosis of the bones,

¹ *Deutsche Med. Wochenschrift*, 1934, 35, page 1314.

1 case of pulmonary tuberculosis,
1 case of tuberculosis of the skin.¹

I presume that, whilst Dr. JENSEN performed the work himself in my laboratory, at Copenhagen he left it to others less experienced than himself. This is the only conceivable explanation which would account for the absolutely negative character of his findings, which conflict, be it said, with the Committee's Paris, Freiburg and Frankfurt results.

Of the specimens which Dr. JENSEN sent me without particulars of diagnosis, 16 yielded positive results, these being, as I learn from the report, from 6 cases of pulmonary tuberculosis, 7 cases of lupus, 2 cases of dementia præcox, and 1 case of sympathetic ophthalmia.

This fact of the conformity of my findings with the unknown diagnoses should not be overlooked. Now I always supplied all members of the Committee with several samples of every single isolated strain, for purposes of verification. Since these were in all cases original cultures, there may have been, in one or two, instances of contamination. That cannot be wholly avoided in original cultures. Now Dr. JENSEN compared these cultures of mine with those which he isolated from the sputum or tuberculous lesion, and in 4 cases found differences. JENSEN argues from the completely improved premise that the strains grown from the blood are in every way identical with those in the tuberculous lesion. Obviously, the many publications on the simultaneous presence of bovine and human strains in tuberculous patients, a fact which has been established both by the German Tuberculosis Commission² and by the English Tuberculosis Commission, have escaped JENSEN'S notice. These infections with both types are extraordinarily common; GRIFFITH also falls into the error of greatly over-estimating the botanical differences between the human and bovine—and indeed the avian—type. Has not the English Tuberculosis Commission clearly and unequivocally shown that no reliable differentiation can be arrived at between the human and bovine types, owing to the occurrence of so many transitional forms? How rightly the English Commission has judged the situation I am able

¹ *Quarterly Bulletin of the Health Organisation*. "The Blood Culture of the Tubercle Bacillus according to Loewenstein", 1935, 4, No. 1, page 313.

² Publications of the Robert Koch Foundation, Vol. I.

—by chance—to confirm by means of an excellent illustration. So eminent a specialist on types as Professor Bruno LANGE, Director of the Tuberculosis Department of the Robert Koch Institute, reported 5 strains, which I had cultivated from the blood of a polyarthritic patient, to be all of the *bovine type*. GRIFFITH judged these same strains to be of the *human type*.¹ Here is striking proof of the untenableness of these artificial discriminations. These conclusions are, moreover, fully confirmed by the research of recent years on the subjects of dissociation. The discovery of PETROFF that the BCG strain, which has been so carefully studied, can be divided into two variants, R and S—avirulent and virulent—has taken the whole question of types on to new ground. In any case, the old methods of differentiation have proved wholly useless. Dr. GRIFFITH's objection that I isolated the avirulent type of BCG on one occasion and the virulent type on another from the same animal is thus in a sense rebutted, or at any rate answered, by CALMETTE himself.

The division into dys- and eugonic strains (GRIFFITH, JENSEN) is not in keeping with the facts of the case, as well known to us, for we know that the growth of every strain depends to an extraordinary degree upon the medium, and, moreover, that any given poorly growing dysgonic strain may at any moment turn into a vigorously growing strain. We further know that there are strains which cannot, for a time, be successfully sub-cultured. This is characteristic more especially of tuberculosis and leprosy. Such cultures must be constantly reseeded, and every tube must be kept under observation for a year.

For the rest, I would refer to the work of BIRKHAUG²—suggested by CALMETTE himself and carried out in CALMETTE's laboratory at the Pasteur Institute. This extraordinarily thorough piece of work contains the following as the first two conclusions :

1. The avian, bovine and human strains, whether typical or no, of the tubercle bacillus do not present any *fixed*

¹ *Lancet*, 1933, September 9th.

² K.-E. BIRKHAUG, "Études sur la dissociation du 'Mycobacterium tuberculosis'", *Annales de l'Institut Pasteur*, 1935, 54, page 195.

*morphological*¹ features, but dissociate spontaneously into Ch, R and S colonies. This dissociation occurs more readily *in vivo* than *in vitro*. So far as the avian bacillus is concerned, the S variety is the predominant type, whilst the Ch and R varieties are comparatively rare ; among the bacilli of mammals, on the other hand, the R variety predominates, whilst Ch and S varieties are rarer.

2. None of these varieties has been observed to be absolutely stable.

In this paper of BIRKHAUG's, the extensive literature on the dissociation of BCG has also been quoted and discussed.

Neither GRIFFITH nor JENSEN has referred in his reports to the well-established fact of dissociation, but they have concentrated their attention upon the detection of botanical differences of little importance in themselves, among the numerous original cultures which I very straightforwardly placed at their disposal. Instead of bringing out the fact that my positive findings tallied completely with the clinical diagnosis, they have merely thrust the question of types into the foreground and—quite one-sidedly, from their own standpoint and ignoring work of other authors—have represented this question as solved.

Now my method of culture, with the single bacillus as the starting-point, is peculiarly well adapted to make the dissociation manifest ; in one and the same case we see the " Rough " type predominate in one tube and the " Smooth " type in the other. Distinct colonies of the two types can frequently be seen in the same tube.

The fact that my findings have been confirmed by important tuberculosis research workers, such as COURMONT, ARLOING, CALMETTE and SAENZ, BUSSON, HAGER, VONKEN, MOUTOUSSIS and a series of others mentioned in the bibliography, has also been left out of account by GRIFFITH and JENSEN. In particular, they have passed over in complete silence the work of MARESCH and his school on tuberculous bacillæmia in cases of acute articular rheumatism, although the MARESCH school has extensive data on 14,000 tests. I would refer, in particular, to the latest work of CORONINI.²

¹ Not in italics in the original text of BIRKHAUG [Editor].

² *Deutsche Med. Wochenschrift*, 1935, 23, page 913.

Surely it is not to be assumed that all those who verified my work, who, after first doubting, subsequently confirmed it at the cost of much labour, also fell victims to an error ! Some 110 papers, indeed !

In regard to dementia præcox, confirmation of my findings has come from the Pasteur Institute itself, through the celebrated Paris clinician CLAUDE, working jointly with such outstanding bacteriologists as VALTIS and VAN DEINSE. In 19 cases of dementia præcox, tests for tuberculosis bacilli were successful in 12 instances, the bacillus being detected sometimes in the blood, sometimes in the cerebro-spinal fluid and, in 3 cases, in both. These results prove that tuberculosis must certainly be envisaged in the ætiology of dementia præcox.

However, my work was carefully checked, not only by the League of Nations, but also by a number of professors of ophthalmology, internal medicine, dermatology, neurology, etc. My findings were arrived at in every case without any knowledge of the diagnosis and communicated to the professors concerned. I may refer here, for instance, to the work of Professor MELLER, Director of the Ophthalmological Clinic at Vienna, and Professor VON HIPPEL, Director of the Göttingen Ophthalmological Clinic. Professor BERGER, Director of the University Internal Clinic, Graz, with whom I investigated more than 900 cases without diagnosis, wrote¹ as follows on our results :

“ The LOEWENSTEIN culture has merely confirmed this experience, and, by its agreement with known facts, has come through a kind of ordeal by fire, even in the eyes of the sceptic.

“ The method of blood culture, combined with concordant tissue-culture tests, has made an even more valuable and novel contribution, in connection with uveitis and other eye diseases, including sympathetic ophthalmia.”

It is strongly recommended that this classical paper on the problem of rheumatism be carefully studied.

Testing without diagnosis certainly has the great disadvantage that, of the 23,000 tests, results which make up my material, more than 3,000 now lack particulars of the diagnosis. This is true for 1,558 cases of skin disease and 1,403 cases of disease of the central nervous system. In order, however, that all may be enabled to

¹ *Medizinische Klinik*, 1935, 24, page 773.

check my results, I nevertheless propose that the present method of providing blood or cerebro-spinal fluid samples *without particulars of diagnosis* be continued. Later, however, the diagnosis should be compulsorily communicated. Having regard to the difficulties of the technique, this is the only practicable way of clearing up this question, which is so important to medicine as a whole. I am absolutely certain that I am right, and leave the near future to decide what significance should be attached to tuberculous bacillæmia for purposes of diagnosis and treatment.

On October 24th, 1934, I proposed to Dr. SAENZ, of the Paris Pasteur Institute, that I should, jointly with him, examine at the Pasteur Institute about 500 blood samples from cases of poly-arthritis and nerve, eye and skin disease. I expressed my readiness to give 4 lectures, in order to establish co-operation with all the clinicians of Paris. This proposal was strongly supported by Professor MADSEN, Chairman of the Health Committee, in the realisation that progress could only come from extensive series of experiments performed in collaboration with clinicians. Unfortunately, this proposal was rejected by Professor L. MARTIN, Director of the Paris Pasteur Institute :¹

“ With great fair-mindedness, Professor LOEWENSTEIN expressed himself as willing to sign such a contract. The negotiations had reached that stage when, on November 26th, 1934, the Director of the Pasteur Institute, Dr. Louis MARTIN, advised Dr. MADSEN that he had consulted the heads of the Tuberculosis Service, Dr. BOQUET and Dr. NÈGRE, and that, in their opinion, ‘further research work would not bring any fresh evidence to light’.”

I, at all events, am ready now as ever to facilitate the verification of my results in every way. The fairest method appears to me precisely that of sending me the blood samples, without particulars of diagnosis, and bearing only numbers.

I should like to take this opportunity of tendering my most sincere thanks to the Chairman of the League Health Committee, Professor MADSEN, both for the support he has given me and for his unbiased statement of the facts of the case.

¹ *Quarterly Bulletin of the Health Organisation*, “The Blood Culture of the Tubercle Bacillus according to Loewenstein”, 1935, 4, No. 1, page 250.

II.

REPLY TO PROFESSOR LOEWENSTEIN

by

A. S. GRIFFITH, M.D., Ph.D., D.P.H., Cambridge.

Dr. JENSEN answers the various criticisms made by Professor LOEWENSTEIN so adequately that it is unnecessary for me to deal fully with all those particular points.

There are, however, two points upon which it is incumbent on me to say a few words.

1. LOEWENSTEIN charges me with having fallen into the error of greatly overestimating the botanical differences between the human and bovine—and, indeed, the avian—types. With regard to this statement, it is sufficient for me to remark that everyone who has done any work at all on the subject of differentiation recognises the reality and the definiteness of the cultural (and pathogenic) differences between human, bovine and avian tubercle bacilli. LOEWENSTEIN, however, in support of his contention that no reliable differentiation can be arrived at between the human and bovine types, claims that the English Tuberculosis Commission was also of that opinion, "owing to the occurrence of so many transitional forms" among the viruses it examined.

LOEWENSTEIN is under a misapprehension regarding the conclusions of the British Royal Commission on Tuberculosis. In their second interim report, the Commissioners divided the viruses which they had examined into three groups (I, II and III). With regard to Groups I and II, they found that the bacillus of Group I (bovine type) differed from the bacillus of Group II (human type), not only in being much more virulent, but also in the way in which

the two respectively grew on artificial media. In these two groups, the cases in each group differed so little from each other as to form an almost homogeneous group. In Group III, on the other hand, the cases differed widely from each other and were simply placed together for consideration on account of their exceptional features. The Commissioners put forward two possible explanations of the cases in Group III : (a) they were mixtures of viruses, of a virus from a human source and a virus from a bovine source, each possessing stable characters ; (b) the bacilli in question were in a special condition of instability and in process of being transformed from one type into another. On account of the far-reaching bearings of the conclusion, the Commissioners were unwilling, at that stage, to make any statement at all premature.

The further investigations of the Commission showed clearly and unequivocally that all the viruses which had been placed in this separate group (as well as some other later obtained viruses with similar anomalous characters) were either mixtures of human and bovine bacilli or attenuated forms of these two types, and that transitional forms did not occur.

After erroneously stating that the work of the Commission had shown the unreliability of cultural characters and pathogenic properties for differentiating human from bovine strains, LOEWENSTEIN proceeds to give what he describes as an excellent illustration "of the untenableness of these artificial discriminations". He states that Professor Bruno LANGE had reported 5 strains which he (LOEWENSTEIN) had cultured from the blood of a polyarthritic patient to be all of the bovine type and that I had judged these same strains to be of the human type. Until the moment of reading LOEWENSTEIN's note, I knew nothing of this alleged difference, and I wrote at once (July 1935) both to LANGE and to LOEWENSTEIN, asking them for the numbers of these strains. LANGE replied by return that, in December 1930, LOEWENSTEIN had sent him at his (LANGE's) request three strains, the numbers of which were given, grown from the blood of cases of acute rheumatism. On comparing the numbers of these strains with those of the strains which LOEWENSTEIN sent me in March 1932—and upon which I reported in 1933 (September 9th, *Lancet*)—I found that none of the strains which were sent to Bruno LANGE in 1930 corresponded to any of those examined by me in 1932. Although I have repeated my request for the

information, LOEWENSTEIN has not yet (November 1935) supplied me with the numbers of the strains which he asserts LANGE and I assigned to different types.

2. LOEWENSTEIN complains that, in my paper, I have nowhere referred to the well-established fact of dissociation. I did not refer to this phenomenon, because it never occurred to me that "dissociation" might be advanced as an explanation of the discrepant results obtained with the animal blood from Cambridge. On LOEWENSTEIN's hypothesis, we are asked to believe that typical dysgonic bovine bacilli inoculated subcutaneously into a goat can immediately on arrival in the blood change now into typical avian bacilli, now into typical human bacilli, and yet can never be found there in the form (bovine) in which they were inoculated. Also, that BCG may acquire virulence within a week of its injection into the blood-stream of a goat, or on another occasion change into the avian type in the course of a few hours in the blood of a calf. Also, that these forms were demonstrable only in those portions of the blood samples which were sent to Vienna, since in no single instance (13 in all) were similar results obtained at Cambridge with the duplicate specimens of blood. At Cambridge, blood specimens from those same animals yielded cultures which were always of the same type as those inoculated. Findings such as these cannot in my opinion be explained by "dissociation".

Addendum. — In my paper published in the *Quarterly Bulletin*, March 1935, the result "Micro + 2" obtained in Vienna with blood specimen 54, Experiment II, page 302, was inadvertently omitted from the table after the proof was returned to the printer.

III.

REPLY TO PROFESSOR LOEWENSTEIN

by

Dr. K. A. JENSEN, Copenhagen.

LOEWENSTEIN's remarks on my paper "Report on Investigations regarding the LOEWENSTEIN Technique of cultivating Tubercle Bacilli from Blood" reflect certain misapprehensions which I feel bound to correct.

In the first place, LOEWENSTEIN asserts that my results "contrast sharply with those of the other investigators". I do not understand how LOEWENSTEIN can draw such a conclusion from the reports under consideration: In my view, it would rather be correct to say that the findings of all the investigators, including those of LOEWENSTEIN himself, "contrast sharply" with LOEWENSTEIN's own earlier results. This will appear very clearly from the following table giving the percentage of positive findings (the figures of LOEWENSTEIN and SEIFFERT include also the microcultures) :

| | CAL- METTE & SAENZ 2nd and 3rd series | KOLLE & KUSTER | SEIFFERT | LOEWENSTEIN | | K. A. JENSEN |
|--|---|----------------------|----------|----------------------------|--------------------------------|-----------------|
| | | | | Danish blood samples | Seiffert's blood samples | |
| | % | % | % | % | % | % |
| Tuberculosis (all forms) | 1.2 | 0.8 | 6.1 | 13 | 6 | 0 |
| Dementia præcox | 0 | 0.8 | — | 5 | — | 0 |
| Rheumatismus and erythema nodosum. | 0 | 0.9 | — | — | — | 0 |
| Various | — | — | 4.5 | 10 | 7.6 | 0 |

When we come to consider the individual results arrived at by the different investigators, we note that the percentage of positive

findings is practically the same for the various diseases, whether tuberculous or non-tuberculous. The figures suggest, to my mind, a merely accidental distribution.

Such a conclusion is strongly supported by the following passage in SEIFFERT's report :

"As soon, however, as the Freiburg and Vienna results were subjected to detailed comparison, a very striking fact emerged—out of 17 of our positive cases, only 1 yielded a positive result at Vienna ; whilst, on the other hand, only 1 out of 16 positive Vienna cases yielded a positive result at Freiburg. The discrepancy became still wider if the Frankfurt and Berlin results were taken into account ; thus, of 45 samples tested at the Georg Speyer Haus, none yielded bacilli, although they included 4 which had proved positive at Freiburg or Vienna ; among 81 samples tested at the Reichsgesundheitsamt, 4 were found to yield acid-fast bacilli (2 only in the sediment), but these included only 1 which had proved positive—at all events at Vienna ; on the other hand, the Berlin negative results included 6 samples from which bacilli had been isolated either at Vienna or at Freiburg."

It would be interesting to know whether the three cases in which SEIFFERT obtained an abundant growth were examined elsewhere and, if so, with what result.

In the second place, LOEWENSTEIN says :

"Of the specimens which Dr. JENSEN sent me without particulars of diagnosis, 16 yielded positive results, these being, as I learn from the report, from 6 cases of pulmonary tuberculosis, 7 cases of lupus, 2 cases of dementia præcox, and 1 case of sympathetic ophthalmia. This fact of the conformity of my findings with the unknown diagnoses should not be overlooked."

To this I can only answer that I sent blood samples only from cases of such diseases which might be expected to yield a high percentage of positive findings according to LOEWENSTEIN's previous statements. The conformity is therefore not particularly striking.

LOEWENSTEIN further suggests that the discrepancies as between the results of blood cultures made by myself at Vienna and at

Copenhagen respectively may be due to the fact that, at Copenhagen, an inexperienced assistant conducted the investigation on my behalf. This suggestion is quite unfounded. I did all the work myself, except as regards the last 18 blood samples, which, however, all proved negative at Vienna, and I used exactly the same medium and technique as I had done at Vienna. To remove any misunderstanding, it should be said, however, that I did not personally take the blood samples from which I obtained positive results in Professor LOEWENSTEIN's laboratory.

In one respect only did the technique differ ; I used a centrifuge of a different make from the one in LOEWENSTEIN's laboratory, but I adjusted it when in use to the speed recommended by LOEWENSTEIN, as stated in the technical part of the report which he approved himself. Nevertheless, I can hardly believe that LOEWENSTEIN would really contend that tubercle bacilli cultures can be made from the blood only if the centrifuge used is of the same design and is made by the same firm as his own.

I am also somewhat sceptical as regards the growth-inhibiting agent, asserted by LOEWENSTEIN to be so difficult to remove from the blood sediment, especially bearing in mind the ease with which LOEWENSTEIN can cultivate tuberculosis bacilli from blood samples sent all the way from America.

Once more, I wish to point out that, in view of the enormous numbers of tuberculosis bacilli demonstrated in the blood samples in Professor LOEWENSTEIN's laboratory, it is entirely out of the question that small differences of technique should account for the practically negative results of the other investigators.

LOEWENSTEIN goes on to say that the explanation of the fact that he grew human type bacilli from the blood of 3 patients from whose lesions I had isolated bovine types may lie in the extreme frequency of mixed infections with human and bovine types. I cannot agree with LOEWENSTEIN that it is so. In the English statistics published by A. S. GRIFFITH,¹ only 8 cases of mixed infection were found among 2,823 type-determined strains. MÖLLERS' article² records only 18 mixed infections among 2,205 type-determined strains.

¹ *Zschr. f. Tub.*, 1932, 64, page 108.

² W. KOLLE, R. KRAUS & P. UHLENHUTH, *Handbuch der pathogenen Mikroorganismen*, 1928, 5, page 694.

Personally, I have found, in my own material of about 3,000 type-determined strains, only 5 cases involving both the human and the bovine type, although I have concentrated especially upon the detection of such cases and have, with that object in view, used a method of spreading which makes cultures containing a mixture of human and bovine colonies particularly easy to pick out.

Another explanation urged by LOEWENSTEIN is that there exists an abundance of transitional forms. In my material, only 8 strains were found which could not be readily classified.

What LOEWENSTEIN tells us as to the opinion concerning tubercle bacilli types which the British Royal Commission is supposed to have recorded shows only that he has not read the final report issued by that body in 1911.

In A. S. GRIFFITH'S report on the LOEWENSTEIN method, particulars are given of the type-determination of 15 strains isolated by LOEWENSTEIN from the blood of animals previously inoculated with tubercle bacilli of different types. Of these 15, 2 only proved to be of the same type as the original strain injected into the experimental animals. My report gives an account of the comparison, in 10 instances, of the strains cultivated from the blood by LOEWENSTEIN and the strains isolated by myself from the focal lesions of the same patients. In 4 out of these 10 cases, it was found that LOEWENSTEIN had isolated from the blood types completely different from those I had obtained from the focal lesions.

Clearly, discrepancies which appear with such frequency cannot be ascribed to the occurrence of mixed infections—which are extremely rare—or of atypical strains, which are no less infrequent.

The general impression which is produced by a perusal of LOEWENSTEIN'S remarks on type-determination and the dissociation of tubercle bacilli is that his experience on the subject is not very extensive. Thus it is surprising to note the decisive importance which LOEWENSTEIN attaches to differences in the appearance of colonies from the same tube or different tubes. Anyone who has worked on dissociation, were it but a short time, will have found that the same culture can yield colony formations of varying appearance. Close to the water of condensation, the colonies are usually smoother, whereas those located on the higher and drier portions of the medium usually have a wrinkled and rough appearance. This and similar phenomena are due to factors in the medium,

and need not be connected in any way with dissociation. If colonies from such cultures are transplanted, the secondary cultures will quickly be found to present no differences whatsoever. In order to establish true dissociation reliably, evidence must be brought to show that such colonies can be repeatedly sub-cultured and yet retain their characteristics in sub-culture. Only when this condition has been fulfilled is it permissible to speak of dissociation, and only when the two dissociated variants have been clearly separated in pure culture can they be tested for pathogenicity.

Again, it is somewhat difficult to understand what connection there can be between the dissociation into *R* and *S* forms of *old* laboratory strains which have, in most cases, lost their original characteristics as a result of artificial culture extending over many years and the type-determination of strains of tubercle bacilli quite recently isolated from human—or animal—organisms. All those who work on the type-determination of freshly isolated tubercle bacilli quickly come to realise the great and well-defined differences between the human and bovine types so far as growth and pathogenic properties are concerned. The stability of these type-defining properties can, moreover, be readily established.

Consequently, the dissociation of recently isolated strains can be observed but rarely. If, however, the investigator has the patience to study the dissociation of freshly isolated strains, he will, in my opinion, gain knowledge which will enable him to assign dissociation more accurately to its proper place within the type system.

My own experience, of which an account will be published in the near future, has been that dissociation is a phenomenon subordinate to type classification, since dissociation may occur only within the limits of each type, excluding any transition from one type to the other.

In order to go to the root of the whole problem of dissociation, it is essential, as I have already said, to work with quite fresh strains and, above all, to possess the qualification which is fundamental in this matter—viz., the ability to distinguish between different types. BIRKHAUG'S work illustrates very clearly the importance of this requirement. At a very advanced stage in his experiments on dissociation, he finds himself in doubt as to whether his strain is pure or a mixture of human and bovine types. I am quite at

a loss to understand how anyone can entertain the belief that a strain has been dissociated, without knowing or ascertaining whether the original strain was a pure culture or a mixed culture of human and bovine strains. If BIRKHAUG had worked with freshly isolated strains, he would never have had cause for uncertainty, for it is exceedingly easy to separate the bovine and human type components of a mixed culture and grow pure cultures of each.

I would therefore suggest that LOEWENSTEIN might obtain some cultures from a tuberculous cow and from the sputum of human cases of pulmonary tuberculosis, using for the purpose the LOEWENSTEIN medium described in my paper,¹ and, further, that he should examine the resulting cultures in regard to their growth properties on other media, and their virulence for rabbits intravenously inoculated in doses of 0.0001—1 mgrm.

I have no doubt that, by carrying out such an investigation, LOEWENSTEIN would quickly satisfy himself that the distinction between the two types is not founded upon "botanical differences, of little importance in themselves".

He would doubtless also appreciate the fact that, if an animal infected with a strain of the bovine type could, after a few days, yield blood cultures of 4 avian, 5 human and not a single bovine type strains,² the classification of tubercle bacilli into three types would never have been possible. Such discrepancies in regard to the culture having been observed quite independently both by A. S. GRIFFITH and by myself, I can think of no other explanation than that there must exist in LOEWENSTEIN'S laboratory some serious source of error which it is his duty to trace.

¹ *Zentralbl. f. Bakt.*, 1932, I. Abt., Orig., page 125.

² A. S. GRIFFITH, *Quarterly Bulletin of the Health Organisation*, 1935, 4, No. 1, page 302.

IV.

**REMARKS ON PROFESSOR LOEWENSTEIN'S REPORT
CONCERNING "TUBERCULOUS BACILLÆMIA
AND ITS SIGNIFICANCE IN MEDICINE"**

by

Dr. A. SAENZ

(Chef de laboratoire at the Pasteur Institute).

On reading Professor LOEWENSTEIN's reply to our report¹ on research into tuberculous bacillæmia, we find certain statements which we are obliged to challenge, for they are, in our opinion, unjustified.

Professor LOEWENSTEIN begins by stating that "COSTIL's findings with my method were 100 % correct". He bases this statement on the fact that four blood samples from fresh rabbits (see report, pages 271 and 272) taken to Vienna by Dr. COSTIL and previously infected by him with 4,000 or 40,000 mammal-type bacilli per c.c. yielded cultures.

In our view, the significance of this experiment is quite different; it merely shows—and, indeed, it was designed to show—that Dr. COSTIL was correctly applying LOEWENSTEIN's method of blood culture, and that the sensitiveness of the culture medium used by us at the Pasteur Institute was at least as great as that of the Vienna media.

It is now a well-established fact that the culture medium advocated by our Viennese colleague is highly sensitive and is capable (as we have shown in a large number of varied experiments) of yielding primary cultures of *B. Koch* of the human, bovine or avian

¹ A. CALMETTE & A. SAENZ, *Quarterly Bulletin of the Health Organisation*, 1935, 4, No. 1, page 257.

type, whenever seeded with material containing not less than 20 bacilli per c.c.

LOEWENSTEIN also makes the following statement :

“Of the 24 blood samples which COSTIL seeded here and immediately took under seal to Paris, 4 were positive—viz. :

“1 case of acute polyarthritis, my Record Number 18204 ;

“1 case of Bazin's disease (*erythema induratum*), my Record Number 18206 ;

“2 cases of sympathetic ophthalmia, my Record Numbers 18228 and 18229.

“These results secured in a wholly incontestable manner by Dr. COSTIL render the continuance of these experiments absolutely necessary.”

It is precisely this which is so very astonishing. With these blood samples which he did not take himself and which were supplied to him by Professor LOEWENSTEIN, COSTIL secured a percentage of positive results of 16. Professor LOEWENSTEIN does not explain how the same experimenter, using exactly the same method and the same culture medium in our laboratory at the Pasteur Institute (the facts set forth above prove that Dr. COSTIL was perfectly conversant with the method), failed to secure a single positive result in the course of many months' experimenting with some 100 cultures of blood samples taken from reliably diagnosed cases of tuberculosis.

We would emphasise this further, and in our opinion equally surprising, fact that, among the cases yielding positive results in the hands of our colleague at Vienna, there were two (No. 18204, acute polyarthritis, and No. 18206, Bazin's disease ; see page 272 of our report) in which, even before the seeding, the deposit from the centrifugalised blood was found, on simple direct examination, to contain enormous masses of acid-fast bacilli, of which photographs were reproduced in our last report (see pages 279 to 282).

As we have already said, we never found any acid-fast bacilli in hundreds of smears made from the deposits of the blood samples we tested.

As for PETROFF's work concerning the dissociation of BCG into non-virulent R type and virulent S type colonies which LOEWENSTEIN

quotes in order to explain the culture of virulent bacilli which he isolated from a goat which had been inoculated with BCG by GRIFFITH (see GRIFFITH's report, page 296), it is not substantiated experimentally. It is, in fact, common knowledge that PETROFF fell into an error of interpretation, as has been shown irrefutably and beyond the shadow of a doubt by all the authors who have taken the trouble to check his work. Apart from CALMETTE's assistants, NEUFELD, L. LANGE and Bruno LANGE, of the Robert Koch Institute, Berlin ; GERLACH, of Vienna ; PRAUSNITZ, of Breslau ; KOLLE and his assistants at Frankfort ; William PARK, of New York ; TENZEKOWITZER, of Kharkov ; Stanley GRIFFITH, ZEYLAND and P. ZEYLAND in Poland, and many others have demonstrated that BCG contained no virulent S colonies and that PETROFF's assertions were mistaken.

We cannot agree with Professor LOEWENSTEIN when, referring to the discrepancies in the results he secured by the seeding of blood samples (obtaining human-type cultures from persons or animals inoculated with bovine bacilli ; see reports by GRIFFITH and JENSEN, pages 283 and 304), he contends that these alleged errors are due to our present inability to separate clearly the human from the bovine types, since only "botanical differences of little importance in themselves" are involved.

These assertions are definitely at variance with our research work on the culture of *B. Koch* from various kinds of human or animal clinical material. Our experience, which is based upon the seeding of several hundred specimens of pathological material on to the very medium which is advocated by LOEWENSTEIN and described in our report (see pages 258 and 259), has enabled us to effect a reliable differentiation, by the characters of the primary cultures, between the human and bovine bacilli. It was in the course of these same experiments on the culture of the tubercle bacillus from pathological material that we were able to convince ourselves of the accuracy and practical value of GRIFFITH's classification into dysgonic and eugonic strains as a means of characterising, and discriminating between, the mode of the growth of bovine and human bacilli.

Whilst it may be true that colonies of varying appearance, which may render immediate type determination difficult, are frequently to be found in the same primary culture tube, our experience has shown that this difference in appearance is due to

factors inherent in the culture medium. Thus, on soft egg media, colonies tend to assume a more or less smooth form, whilst, on consistent or dry media, they retain the characteristics proper to the type. This phenomenon has, however, nothing to do with dissociation, since such colonies from human or bovine cultures need only be sub-cultured on fresh egg media or on glycerinated potato to revert to their characteristic appearance.

Thus, using human pathological clinical material, we were able to identify the bovine bacillus in one case of glandular tuberculosis of the neck in an infant from Léon BERNARD's clinic,¹ in seven cases of tuberculous meningitis in children.² (though most of these observations made with LESNÉ are still unpublished), and in a youth suffering from renal tuberculosis¹ (in collaboration with EISENDRATH). Among adults we found it in one case of skin tuberculosis (in collaboration with COSTE). As regards animal pathology, we found it in a case of spontaneous tuberculosis in a mink³ (in collaboration with TRUCHE), and, finally, in several cases of tuberculosis in cattle. In all cases—and we would repeat that we used LOEWENSTEIN'S medium—we were able to diagnose the bovine bacillus and to distinguish it clearly from the human bacillus, merely on the strength of the appearance of the culture, before inoculation into the rabbit. All these primary cultures behaved like characteristic dysgonic strains, in regard to the slowness of the appearance of colonies (29 to 75 days); the small number of these, their smooth, glossy, damp appearance, their size at the time of appearance (at the limit of visibility), their absence of pigmentation, their consistency under the spatula, and, finally, the ease with which they could be emulsified in physiological saline solution. These characters are unmistakably different from those presented by cultures of human bacilli of the eugonic kind, which form colonies within a short time (18 to 31 days), and are luxuriant, rough, pigmented and difficult to emulsify. Finally, our bovine strains, intravenously inoculated into rabbits in doses of 1/100 to 1/1000 mgrm., caused death within about two months from generalised miliary tuberculosis. The human strains inoculated in doses

¹ *Rev. de Phthisiologie*, 1933, 14, No. 1, page 20.

² *Soc. de Biol.*, 1935, 119, page 729.

³ *Soc. de Biol.*, 1934, 115, page 1478.

one hundred times as great never produced fatal disease in the rabbits. When killed after two or three months, they showed only insignificant lesions, which were always localised in the lungs.

Finally, LOEWENSTEIN refers to BIRKHAUG's work on dissociation as showing that cultures of *B. Koch* do not possess sufficient fixed morphological characteristics to enable a discrimination to be reliably made between the human and bovine types.

Now it is an undoubted fact that, with BIRKHAUG's technique, which consists in inoculating guinea-pigs with the strains to be dissociated and subsequently making cultures from their blood, smooth colonies are obtained presenting the characteristics described by BIRKHAUG. Repeating his experiments, and using the same strains, human, bovine or BCG, as he did, we arrived at the same results.

Subsequently, however, to the work of BIRKHAUG and ourselves, on the subject of dissociation, a new fact of the highest importance came to light, which showed that the conclusions which both BIRKHAUG and we ourselves had felt entitled to draw from our experiments were erroneous. Three years of research work enabled us to advance the new idea that fresh guinea-pigs in our experimental cages might be parasitised by two types of acid-fast bacilli, without outward signs of ill health.¹ These strains, of smooth appearance, which we detected by seeding material from the spleen of the animals, differ from acid-fast saprophytes by their antigenic and allergy-inducing properties.

In the course of this research work we isolated a total of 13 strains from fresh guinea-pigs; 4 of these presented the typical characteristics of the avian bacilli and the 9 others represented a new type of acid-fast bacilli whose morphological characteristics and growth and virulence properties were identical with those of certain S strains that BIRKHAUG and ourselves had secured in guinea-pig blood cultures.

SCHAEFER,² who has just been investigating all the varieties of the so-called BIRKHAUG S human and bovine types from the serological point of view, has, moreover, identified them with the two types which we isolated from fresh guinea-pigs.

¹ *Soc. de Biol.*, 1935, 118, pages 643 and 645; 119, page 1286.

² *Soc. de Biol.*, 1935, 120, page 590.

Similarly, other experimenters—NÈGRE, BRETEY and Mlle. GEHRART,¹ VALTIS and VAN DEINSE,² BATTAGLINI,³ A. GAIGINSKY,⁴ PETRESCO⁵ and others—have confirmed our work and adduced further cases of the parasitism of these types of bacilli in the body of fresh guinea-pigs.

On the other hand, the mechanism and characters of the dissociation of the avian bacillus, which we have been investigating for a number of years past and which are identical with those of the bovine bacillus studied by JENSEN and LAPORTE, have convinced us that the BIRKHAUG S colonies and those which we obtained from guinea-pigs have nothing in common with the dissociated varieties. We are happy that we have been able to clear up once and for all this error of interpretation.

In the last place, there remains for us to analyse the results which LOEWENSTEIN quotes in support of his views concerning the tuberculous ætiology of dementia præcox. He is surprised that negative results were obtained with the samples of cerebro-spinal fluid and blood from cases of dementia præcox which we tested.

He writes as follows :

“In regard to dementia præcox, confirmation of my findings has come from the Pasteur Institute itself, through the celebrated Paris clinician CLAUDE, working jointly with such outstanding bacteriologists as VALTIS and VAN DEINSE. In 19 cases of dementia præcox, tests for tuberculosis bacilli were successful in 12 instances, the bacillus being detected sometimes in the blood, sometimes in the cerebro-spinal fluid, and, in 3 cases, in both. These results prove that tuberculosis must certainly be envisaged in the ætiology of dementia præcox.”

M. CLAUDE and his assistant COSTE, thus referred to by LOEWENSTEIN, have replied as follows :

“We are surprised to find that, in his reply, LOEWENSTEIN makes no reference to the note we published in the records of

¹ *Soc. de Biol.*, 1935, 118, page 649.

² *Soc. de Biol.*, 1935, 119, page 933.

³ *Soc. de Biol.*, 1935, 118, page 305.

⁴ *Soc. de Biol.*, 1935, 118, page 218.

⁵ *Soc. de Biol.*, 1935, 119, page 165.

the Société de Biologie de Paris (meeting of July 21st, 1934, page 1356) under the heading 'Sur les relations de la tuberculose et de la démence précoce'. In this note, whilst referring to the clinical arguments which can be adduced in support of the contention that tuberculosis plays a part in dementia præcox, we explained that we were obliged to make reservations as to the value of the bacteriological results which we had secured, in connection with our patients, with VALTIS and VAN DEINSE. On the one hand, having given them blood and cerebro-spinal fluid samples from 24 fresh cases (including 15 of dementia præcox and 9 of general paralysis without tuberculosis), we were surprised to learn from them that they had secured 7 positive results by the inoculation of material from the cases of dementia præcox and 4 with material from general paralytics. The percentage was therefore the same in both diseases.

"On the other hand, having ourselves organised, in the laboratory of the St. Anne Mental Diseases Clinic, another series of experiments relating to 19 cases of dementia præcox (different from those which had previously been used for tests), we repeated the inoculations of blood and cerebro-spinal fluid, in this uncontaminated environment, and in an animal house in which there was not a single tuberculous animal, *and obtained negative results throughout* (despite the passages made in the cases that were in any way doubtful, and the seedings of the tissue and organs of the experimental guinea-pigs). We resorted concurrently to simple inoculation and inoculation followed by periodical injections of acetone extract continued for months.

"Other patients (dementia præcox cases and general paralytics) were also used for similar inoculation experiments at St. Anne, with negative results.

"These new findings, most of which are recorded in our note of 1934 to the Société de Biologie, when taken in conjunction with (1) Dr. SAENZ's discovery of atypical acid-fast strains in a certain number of uninoculated guinea-pigs at the Pasteur Institute, and (2) the regular absence of any chemical and cytological reaction in the cerebro-spinal fluid of dementia præcox cases, suggest, in our opinion, that the utmost caution should be

observed in regard to the supposedly positive results of the first inoculations we made with VALTIS and VAN DEINSE.

“If we consider the purely bacteriological findings, it seems to us a fact that the presence of tubercle bacilli in the blood and cerebro-spinal fluid of certain dementia præcox cases remains to be demonstrated.”

Thus, the experimenters to whom LOEWENSTIEN appeals to support his case destroy it completely.

Furthermore, BECK,¹ who tested 29 samples of blood, 27 samples of cerebro-spinal fluid and 2 samples of brain material from cases of dementia præcox, using the VALTIS and VAN DEINSE technique, obtained only negative results.

This author concludes as follows :

“It appears from these investigations that experiments on animals also failed to yield the slightest indication of the presence of the tuberculosis bacillus in cases of dementia præcox. Summing up our previous serological and bacteriological research, as well as the present experiments, we arrive at the conclusion that tuberculosis plays no part in the ætiology of dementia præcox.”

¹ *Soc. de Biol.*, 1935, 120. No. 31, page 311.