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Investigations on Respiratory Dust Disease
in Operatives in the Cotton Industry

by

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PREFACE

This report is issued by the Medical Research Council on the recommendation of their Committee on Industrial Pulmonary Disease. It deals with an investigation which was promoted by the Council, at the request of the Home Office, into the particular question of respiratory dust disease in operatives in the cotton industry. For this purpose the Council were fortunate in securing the services of a distinguished investigator in industrial medicine, Professor Carl Prausnitz, who had had to relinquish his former appointment in the University of Breslau. The work was done in Professor H. B. Maitland's department in the University of Manchester, with the co-operation of the employers' organisations and trade unions concerned, and of many other persons to whom the author makes acknowledgement in the following pages. The expenses of the investigation were borne by the Medical Research Council, but the remuneration of Professor Prausnitz was mainly provided in the form of a personal grant from the Rockefeller Foundation of New York.

The handling of cotton in its early stages, especially in the process known as carding, is inevitably a dusty occupation. When the compressed bales of raw cotton arrive in this country from the plantations, much dust still remains mixed with it and has to be removed in a series of processes, preparatory to spinning the material into yarn. Important among these are the processes carried out in the blowing or scutching room, in which partially loose masses of cotton are thoroughly separated; and in the carding room, where the cotton is subjected to an intensive teasing action, by which its hairs are combed into a parallel arrangement and removed in the form of a filmy rope.

The Departmental Committee on Dust in Card Rooms in the Cotton Industry, appointed by the Home Office, concluded in their report (H.M. Stationery Office, 1932) that the dust in card rooms is still a cause of some discomfort and ill-health due to respiratory disease among operatives. They found that the main effects can be considered in three stages, which gradually merge as the malady progresses. The first evidence of the condition, when it occurs, consists of symptoms of irritation, particularly cough and a feeling of constriction in the chest, but these pass off on removal from the dusty atmosphere. After ten or more years' work the effects may become more persistent, with periods of incapacity, at first short and infrequent but tending to become more prolonged and to occur at shorter intervals. Cessation from work in the dusty atmosphere at this stage is generally followed by recovery, or at least by sufficient improvement to permit of work in another atmosphere. Finally, a stage may be reached in which there is total incapacity for work, with signs of chronic bronchitis and emphysema, and a strain on the heart which is apt to lead to cardiac failure. The very nature of the condition made it difficult to investigate: the absence of special clinical features which would serve to distinguish the disease of card-room workers from other non-specific forms of chronic

pulmonary disorder, indicated the importance of studying the underlying causes rather than the character of the condition.

While the inquiry of the Departmental Committee was in progress, the Council assisted the work by arranging for various relevant investigations. In the first place, Dr. A. Bradford Hill made a statistical inquiry on their behalf into sickness among operatives in card rooms in Lancashire cotton mills, and the results of this were published by the Council as a report of their Industrial Health Research Board. Secondly, Dr. J. C. Bramwell and Dr. R. Ellis, at Manchester, clinically examined for the Council many cotton operatives suffering from cardio-respiratory symptoms believed to be due to the inhalation of cotton dust: the results suggested that some form of sensitisation played an important part. Subsequent work by Professor H. B. Maitland, assisted by Dr. A. Brown, showed the discovery of the hitherto unsuspected presence of histamine in the cotton dust. The obvious desirability of following up this clue led to the investigation of which an account is now given.

In the present report Professor Prausnitz shows how he studied the problem of "strippers' asthma" from many angles, so that he was led ultimately to the view that there is a specific agent in cotton dust capable of producing the observed symptoms and ultimately the pathological changes in the lungs which cause complete disablement in a number of workers exposed to cotton dust for a long time. As a result of an able and laborious research, he has shown the strong probability that this substance, or group of substances, is contained in the protein fraction of the dust and is responsible for the changes which may occur in the lung after prolonged inhalation. He does not think that histamine, although present in cotton dust, is the toxic agent at fault. Professor Prausnitz has also established the existence of super-sensitiveness (allergic sensitiveness) in all patients suffering from this respiratory dust disease, and concludes that in this respect it is related to ordinary asthma.

It seems clear from the results obtained that there is only one method of overcoming this disability of the cotton industry, and that is by preventing access of the finest dust to the respiratory tract. It would appear that the ventilating and exhaust appliances which are now generally in use, although they remove the coarser particles of cotton dust from the atmosphere, do not in fact prevent access to the worker of the finer particles which are particularly liable to produce intense irritation of the respiratory system in those susceptible to the dust. Now that this essential fact is established by Professor Prausnitz, the practical problem seems to rest on the need of discovering a method of removing these finer particles. The ingenuity of the engineer which is shewn in the modern machinery of the cotton industry ought to have relatively little difficulty in solving this mechanical problem and so eliminating an important cause of ill-health among industrial workers.

MEDICAL RESEARCH COUNCIL,
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INVESTIGATIONS ON RESPIRATORY DUST DISEASE IN OPERATIVES IN THE COTTON INDUSTRY

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INTRODUCTION

A.—THE CONDITIONS INVESTIGATED

Considerable attention has been given for many years to the occurrence of non-tuberculous respiratory disease in that group of cotton operatives which is engaged in the removal of dust from cotton. The chief stages in the work carried out in the cotton mill are the following: Raw cotton arrives in this country in hydraulically compressed bales. After removal of the covering, the contents are passed through "openers", "scutchers", and "blowing machines" in which the material is exposed to successive processes of intensive decompression, spreading out, beating and the action of strong currents of air. At an early stage of the work the cotton is "mixed": in order to obtain a fibre of uniform nature, cotton of various qualities is fed into the openers where the different portions are thoroughly mixed together in the machinery which disintegrates the originally densely matted masses of material. Apart from the feeding, which is usually done by hand, all these machines are enclosed in dust-proof covers, so as to prevent any escape of air which would interfere with the cleansing action of the air blown into them. Although, therefore, not much dust is evolved in the neighbourhood of these machines, the periodical cleaning out of the dust from the machines, the air ducts, and the "fanny-hole" at the bottom of the outlet tower for the dust-laden air, is a very dusty job, as it is done by hand.

The web emerging from the blowing-room passes to the carding machines. These consist of large horizontal cylinders the surface of which is covered with a great number of sharp bent wires. The cylinders rotate rapidly around a horizontal axis. In the modern carding machines "revolving flats" rotate around them in the same sense, but at a lower velocity. Their surface is also covered with a great number of similar sharp wires the ends of which are close to the ends of the wires on the cylinders. The cotton passes between the two. It is drawn forward by the spikes on the cylinder, whilst the spikes on the flats tend to retard its movement. Thus the fibres are combed out so as to lie straight and parallel. At the same time the combing process has the effect of removing practically all the short fibres and fragments of fibres, as well as the dust from the cotton, leaving the "cardroom sliver" to pass as a thoroughly cleaned mass to the spinning machines.

A great amount of dust accumulates on and between the wires on the cylinders and flats. It has to be removed at frequent intervals during the day. From time to time it is also necessary to sharpen the ends of the wires, which rapidly become blunt and lose their power of drawing apart the fine fibres. This "stripping" and "grinding" is the work of a highly skilled group of men, the

“strippers and grinders”, who are engaged in it almost without interruption during the whole working-day. Formerly stripping was done by hand with a brush, and whilst it was going on the whole neighbourhood of the machine was enveloped in clouds of dust. During the last 15 or 20 years great improvement has been brought about by the introduction of brushes fitted with an exhaust or by the “vacuum” method without brushing. In modern, well-ventilated cardrooms, even while stripping is being carried out, there is little more as a rule than a faint haze.

The chief *complaints of respiratory trouble* come from strippers and grinders, but some blowing-room operatives, cotton mixers, and other categories of cardroom workers are also affected. It is difficult to give an exact estimate of the number of sufferers, nor would that estimate give a fair conception, since a large proportion of the persons affected acquired the disease under the old conditions of hand-stripping. Yet it would be a mistake to assume that some cases do not arise even now, under the greatly improved conditions of the modern mill. It does not appear that any special grade or quality of cotton is responsible for the trouble, as large numbers of cases have occurred in mills working with high-grade Egyptian, as well as in those employing the lower grades, such as Indian cotton. Several patients have, however, insisted that their condition has become considerably worse since more dusty cotton was used, and others believe that modern conditions tend to pass a greater quantity of cotton through the carding machine every day, thus increasing the amount of dust dealt with.

The *histories* of their illness, given with a surprising uniformity by most of the patients, are as follows: After working for years without any appreciable trouble except a little cough, they notice either a sudden aggravation of their cough, which becomes dry and exceedingly irritating, or peculiar attacks of breathlessness. These attacks usually occur on Mondays, whilst the rest of the week finds them in fairly good condition. For a long time the trouble may be almost or entirely limited to this “Monday fever”, but gradually the symptoms begin to spread over the ensuing days of the week; in time the difference disappears, and they suffer continuously. When, ultimately, they are forced to give up work, some improvement may occur. But if they resume work, they are forced sooner or later to give it up again. In some, this occurrence is most characteristic: A rest of some weeks or months gives them an opportunity of recovering so far that they feel perfectly fit; yet on the day that they return to the mill, they are struck down with the disease and are hardly able to return home unaided. Some patients definitely state that breathlessness is their chief, or even their only complaint. In others the disease began with an intensely irritating cough, which was followed, usually a good deal later, by the development of sputum. Expectoration is not a prominent feature of the disease. Only in the minority is it ever profuse; usually the patients succeed only after prolonged exhausting attacks of coughing in bringing up

small quantities of very sticky, glairy sputum. Clinical examination of patients with established symptoms reveals the signs of chronic bronchitis and emphysema.

B. PREVIOUS INVESTIGATIONS

The first mention of the disease appears to have been made in the report by Dr. Greenhow, which forms part of the Report of the Medical Officer of the Privy Council for 1861. It is repeatedly referred to in the subsequent reports. In 1863, Leach described the symptoms of the malady. Mixers, he stated, suffered from sneezing and cough with much slaty expectoration, which was shown by the microscope to contain very fine short cotton fibres; their arms and hands were often affected with urticaria-like rashes. Similar symptoms were described in scutchers. Strippers and grinders were stated mostly to suffer from spasmodic cough, bloody expectoration and asthma.

TABLE I

Respiratory Disease Mortality according to Occupation

Standard Mortality of Males aged 20-65 years from pulmonary diseases in certain dusty occupations, with no siliceous dust risk, compared with the Standard taken as 1,000, for the years 1921-23.

<i>Occupation.</i>	<i>Respiratory Tuberculosis.</i>	<i>Bronchitis.</i>	<i>Pneumonia.</i>
All occupied and retired males ..	1,000	1,000	1,000
Cement workers and lime burners ..	706	542	1,271
Sawyers, wood turners	978	792	694
Grain millers	714	847	978
Coal hewers and getters	686	1,425	978
Cotton spinners	1,072	1,431	1,180
Metal moulders	1,070	1,724	1,709
Coal-boat laders	1,018	1,982	1,959
Brick and plain tile makers	1,023	1,994	763
Cotton strippers	798	5,579	1,593

A detailed study of the condition is given in Dr. Collis' report (Annual Report of the Chief Inspector of Factories, 1908) and in his later publications. He described the early form of irritation, often called "mill fever", which was experienced also by chance visitors to the mill: transient fever setting in within twelve hours after the first exposure to the dust. Many cardroom workers suffered from mill fever at the beginning of their work, but they soon became inured. It was only five to twenty years later that their chest became affected. At first they found difficulty in breathing on Monday mornings or after any interval in which they had been away from their work. After the first day was over, they might remain unaffected for the remainder of the week. As time passed, the trouble became worse and extended later and later throughout

the week, developing into the typical form of asthma as long as the operatives were in a dusty atmosphere. They lost flesh, became thin in face and body. The action of the diaphragm grew less effective, the intercostal muscles and extraordinary muscles of respiration were called into play more and more in ordinary breathing. The sternum became prominent, the chest assumed the barrel-shape, and emphysema developed. There was little or no sputum, which was expectorated with difficulty. Exposure to dust called forth spasmodic asthma. There was little tuberculosis, but the death rates from pneumonia and bronchitis were high. Similar changes were observed in flax-hecklers. The figures given in a later publication (Collis, 1931) illustrate the peculiar distribution of lung disease (Table I).

Dearden, in 1927, published an extensive study of the disease which agrees on the whole with the results of Collis. The chief discrepancy is in his statement that strippers and grinders and blowing-room operatives suffered from tuberculosis as well as from pneumonia, bronchitis, and circulatory disease much more than the average worker. This is not, however, borne out by subsequent investigations. The Registrar-General supplied the following figures to the Departmental Committee on Dust in Cardrooms in the Cotton Industry (Table II) :

TABLE II

Mortality in 1921-23 compared with that in 1910-12 taken as 100.

	<i>All occupied and retired males.</i>	<i>Cotton strippers and grinders.</i>
Respiratory tuberculosis	77	58
Bronchitis	84	120
Pneumonia	85	82
Other respiratory diseases	73	66

Middleton (1926a) carried out a very thorough examination of cardroom dust by means of the Owens' jet dust counter and Owens' settlement dust counter. He found great variations in the number of particles and the nature and size of the predominant ones. There was nothing characteristic for any particular set of conditions. The greater bulk of the dust was composed of vegetable debris—fragments of cotton-hairs, husks, fungus mycelia, conidia spores, etc. One variety of sharp-pointed hair was found in every record but was usually scanty; the author considered it unlikely to be the cause of the malady. Mineral matter was found in every record, but most of the particles were rounded and above the size of 2 microns; it was consequently improbable that they were concerned in the disease. (This is borne out by the absence of fibrosis, as shown by the evidence given to the Departmental Committee, *vide infra*.)

The question as to the aetiological role of moulds in industrial pulmonary affections was raised by the same author (1926b) who

considered the evidence in favour of "weaver's cough" being due to moulds. This affection bears a far greater resemblance to acute attacks of asthma than the disease of cardroom workers. It is, too, strictly limited to definite localities, in which it only occurs at rare intervals. From the description of the former condition there is little reason to believe the two to have anything in common.

Very full information about the whole problem was obtained by the Departmental Committee on Dust in Cardrooms in the Cotton Industry, appointed by the Home Office in 1927. Its report was published in 1932. The Committee was "to inquire and report (1) whether, and if so to what extent, dust in cardrooms in the cotton industry is a cause of ill-health or disease among cardroom operatives; (2) if so, what is the nature of such ill-health or disease; (3) how the sickness rates among cardroom operatives compare in these respects with those of the general population in the same locality; (4) what are the constituents (if any) in the dust which are particularly responsible; and (5) what remedies can be proposed." The Committee heard a large amount of important evidence and caused a number of valuable investigations to be undertaken, the chief of which are hereunder briefly summarized.

A. B. Hill (1930) carried out a statistical inquiry into sickness among operatives in Lancashire cotton spinning mills. The chief results were the following: The occupational death rates for 1921-23 had proved that strippers and grinders, other workers in the cardroom, and blowing-room hands have higher death rates from respiratory diseases than other operatives in the cotton industry, and all occupied and retired males in England and Wales. The sickness records studied by Hill corroborated these results for the men. From all causes of sickness the strippers and grinders up to age 30 suffered approximately the same as the comparative group working in ring-room and warehouse. After that age they had some excess of sickness. When, however, this sickness experience was divided into non-respiratory and respiratory causes, it was found that strippers and grinders and other cardroom workers had somewhat *less* sickness than male workers in the ring-room and warehouse from *all causes of sickness excluding a group of respiratory disease*. On the other hand, from *these particular diseases* they had, after age 30, a pronounced excess of illness, their rates being two to three times as high as the rates found for the workers in the ring-room and warehouse. Between the cardroom workers and the blowing-room and cotton-room operatives very little difference was found. Some of the most convincing figures have been extracted from Hill's tables and arranged in form of a graph (Fig. 1.) The curve of sickness rates naturally rises with the age of the groups studied, but it is very evident that this rise is steepest for the strippers and grinders and the ex-cardroom men (chiefly persons who have been forced by ill-health to retire); then come the blowing-room operatives; the ring-room and warehouse workers follow a curve of an entirely different character.

RESPIRATORY DUST DISEASE

Further evidence obtained from the Committee subsequent to this report showed that "(1) exhaust ventilation for stripping was introduced in some mills in 1909, and by 1913 such progress had been made that this date would appear to indicate a more or less definite stage in stripping dust removal, when the stripping dust to which the cardroom operatives were subject began to be materially reduced,

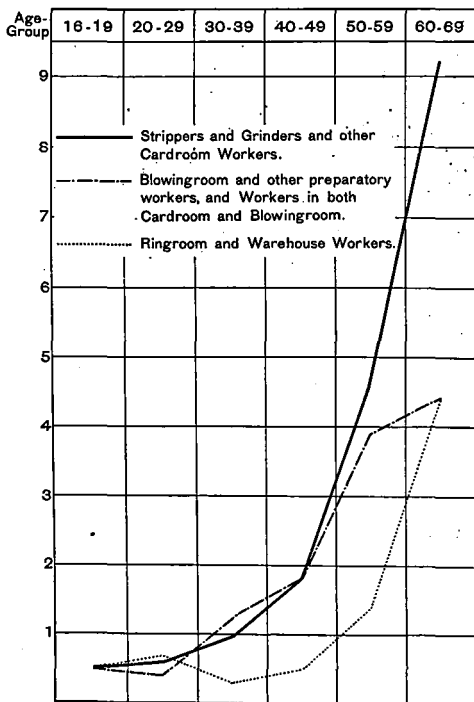


FIG. 1.—Graph, compiled from Dr. Bradford Hill's report, Table XI. Number of days of sickness per person-year. Male cotton-operatives.

....., since that date, the improvements made have reduced still further the amount of dust to which they are exposed ; (2) cardroom operatives who have always worked under the improved conditions of ventilation may, in fact, suffer from a respiratory condition clinically indistinguishable from that so frequently found in older operatives ; (3) cardroom operatives are still, as in the past, subject

To face page 13

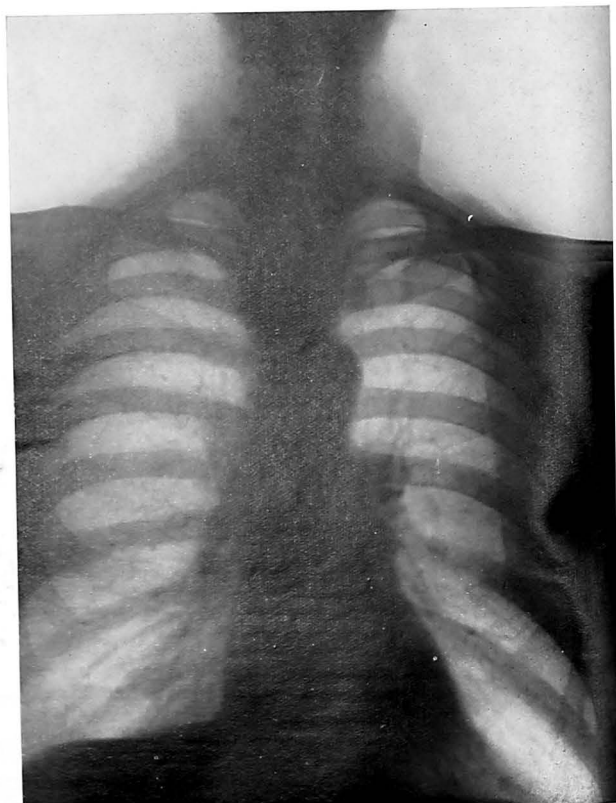


FIG. 2.—X-ray photograph of the chest of a diseased stripper and grinder.

to the dust which is liberated in the ordinary process of carding ; (4) the respiratory disease occurring in cardroom operatives does not usually cause illness sufficiently severe to necessitate absence from work, until they have been exposed to the dust for ten or more years ; and (5) the investigation of the nature of the dust in the region of the drawing and speed frames, where the majority of the female cardroom operatives work, suggests that the finer particles, which are of greater numerical importance, are conveyed in the air from the region of the carding engines."

Clinical examinations were carried out for the Committee by Dr. Morris at the Salford Royal Hospital, by Dr. Fletcher at the Tuberculosis Dispensary of the Lancashire County Council, and by Dr. Crighton Bramwell and Dr. Reginald Ellis at the Manchester Royal Infirmary. Dr. Morris examined 49 strippers and grinders and 1 blowing-room operative, all but two of whom were affected with the disease. His radiological examination did not demonstrate any organic change in the lung which he could describe as specific, such for instance as is found in silicosis.

Dr. Fletcher examined 100 cases radiographically ; he considered that certain changes were shown in the lungs which were consistent with chronic bronchitis and some degree of emphysema, but they did not reveal any condition which could be described as specific for cardroom operatives. He was, however, under the impression that his examination of the cardroom operative's lung by X-rays showed some excess of the root and bronchial shadows to a degree that did not obtain in ordinary bronchitis.* Only 8 of his patients suffered from asthmatic attacks, and he considered that their dyspnoea was generally due to emphysema rather than to asthma. He also drew attention to the diminishing capacity of the chest to expand as age advanced, the average amount of expansion for patients of 35 years of age and under being $2\frac{1}{4}$ inches, which diminished progressively in successive groups, until it was $1\frac{1}{2}$ inches at 61-65 years of age. This was borne out by spirometric investigation which gave an approximately normal vital capacity of 3.5 litres for the age group to 35, but one of only 1.5 litres for the 61-65 group.

Dr. Davey, of the Department of Preventive Medicine of the University of Manchester, examined the sputum of these patients, but his investigations failed to show any specific microbe which could be regarded as causal.

Dr. Bramwell and Dr. Ellis examined 18 men of whom 13 were regarded by them as typical examples of the affection. The only constant lesion found was emphysema, complicated in some cases by bronchitis. Two types of dyspnoea were noted in their patients : one seemed to be related to spasmodic asthma, attributable to bronchial irritation, and occurred when the subject came into contact with the dust in the cardroom ; the other, less common type

* The radiological changes are clearly visible in Figure 2, from one of my patients. The original photograph was kindly supplied by Dr. R. W. Higson of Bolton.

appeared to be due to cardio-respiratory insufficiency, and was brought on by exertion; the men who complained of it were found to have a poor tolerance for exercise. Rickety deformities of the chest were so common that they were regarded by Dr. Bramwell as a probable predisposing cause. Dr. Bramwell and Dr. Ellis were led to assume the disease to be of an allergic nature. Sixty-nine persons were, therefore, tested with an extract prepared from cardroom dust. Marked, in some cases severe, reactions were caused in the majority by intradermal injection of this extract, but the difficulty was encountered that several normal controls also showed reactions which in a few cases were fairly severe.

These tests were subsequently carried on under Professor Maitland at the Department of Preventive Medicine of the University of Manchester by Dr. Brown; again fairly severe reactions were observed in controls as well as in patients. This led to an examination of the dust for histamine, which was performed by Maitland, Heap and Macdonald (1932) with a positive result.

Post-mortem examination of 10 cases was performed by Professor Shaw Dunn and Dr. H. L. Sheehan. In all but one case definite changes of the respiratory system were found which were of the type of bronchitis and chronic emphysema. In addition, they noted the frequency of cardiac changes, especially dilatation of the right heart. The latter finding corroborated the evidence of Dr. Stevenson, according to whom the most characteristic feature of the mortality of cardroom and blowing-room operatives was not the respiratory excess, but the circulatory. It should, however, to my mind, be considered that mortality figures and post-mortem findings deal only with the last stage of the disease, and that chronic respiratory disease, especially such as this form, must ultimately induce severe cardiac changes which need not be to the fore in the earlier stages.

Among the most important recommendations of the Committee should be mentioned the improvement of methods for dealing with the dust, compulsory wearing of respirators during specially dusty work, and medical examination and re-examination.

C. OCCURRENCE OF RESPIRATORY DISEASE IN COTTON OPERATIVES IN VARIOUS OTHER COUNTRIES

Little is known as to the occurrence of similar affections outside of England. In Germany an investigation into the health of cotton operatives was undertaken in 1924 by Ludwig Schmidt of the Hygienic Institute and Karl Schilling of the Medical Department of the University of Freiburg. They do not mention any illness like that described. Bronchitis and emphysema occurring in older operatives is mentioned, but the writers state that they did not find evidence of pneumoconiosis.

Koelsch and Lederer described, in 1933, an affection in hemp workers which closely resembles the disease discussed here. When commencing to work in the factory many operatives suffer from

"heckling fever"; they complain of tightness in the chest, oppression, lassitude, shivering, headache, symptoms of irritation in the upper and deeper air-passages, occasionally of nose-bleeding, vomiting, and diarrhoea; in some cases there is fever up to 104° F. Some of the operatives had suffered in this manner continuously for decades, in others the symptoms gradually faded away after the first few years, whilst some had no such trouble whatever. The persons affected always suffered worst on Mondays or after an interval in their work. The clinical findings were emphysema with or without bronchitis, less frequently tuberculosis, which was almost always a more or less benign apical affection. In the face of this report it is particularly noteworthy that in an investigation of the health of German cotton workers, carried out by Koelsch in 1932, there is no mention of anything resembling the disease of Lancashire cotton operatives; among 34 operatives examined Koelsch only records 4 cases of chronic bronchitis, one of which was of a more asthmatic type, 10 cases of tuberculosis, and 13 of cardiac enlargement, mostly among younger individuals.

Only one reference has been found in German literature which bears upon the subject, but it is so important as to deserve being quoted in full. Zipperlen carried out, in 1935, an investigation of patients suffering from asthma in Württemberg and reports as follows: "A few words should be said concerning industry. There the textile industry plays a large role. In spite of all protective appliances cotton dust cannot be excluded, and we have actually observed a large number of severe asthma patients in whom strong allergic reactions could be obtained with suitably prepared dust from the factories."

Among a series of references kindly supplied by the Librarian of the Royal Society of Medicine there were three Russian publications, viz. :—Mikhlin, diseases of the respiratory tract and ear caused by dust particles in the textile industry (1931); Bokser and Ryabova, pneumoconiosis in cotton mill workers (1932); Klionskiy and Yapolskiy, pneumoconiosis in textile workers (1934). Unfortunately, it has only been possible to consult the last-mentioned paper, whilst the Russian journals in which the others have appeared are not available and reviews have not been found. Klionskiy and Yapolskiy have possibly seen similar conditions to those observed in Lancashire, but the account is not sufficiently detailed to decide the question. They examined 116 workers in the dustiest processes of one of the greatest textile mills. A considerable proportion suffered from respiratory trouble, 82 per cent. had cough, three-quarters of them with expectoration, chiefly during their work.

From the United States Britten, Bloomfield and Goddard reported (1933) on the examination of 1,628 cotton operatives, of whom 438 were engaged in carding processes, although only 53 were actually carders. The sickness rates undoubtedly were higher among the carding operatives than among those engaged in spinning or weaving, as is shown in the following table.

RESPIRATORY DUST DISEASE

TABLE III

Sickness rate by room-groups and shift (2-day and longer cases)

Room groups.	Rate per 100.		Number of cases.	
	Day shift.	Night shift.	Day shift.	Night shift.
ALL CAUSES				
Weaving	62.6	134.6	109	222
Carding	99.0	150.4	110	175
Spinning	44.5	81.7	54	92
RESPIRATORY				
Weaving	32.7	78.2	57	129
Carding	50.4	75.6	56	88
Spinning	28.8	40.0	35	45
NON-RESPIRATORY				
Weaving	29.7	56.4	52	93
Carding	48.6	74.7	54	87
Spinning	15.7	41.7	19	47

It is interesting to note that the incidence of respiratory diseases is greatest among the weavers, that the cardroom operatives follow close behind them, whilst the spinners show a consistently lower rate in all groups. Whether a disease similar to that observed in this country does occur, cannot be inferred, especially as no distinction is made between tuberculous and non-tuberculous respiratory affections. It does not, however, appear very probable since the vital capacity and chest expansion were approximately the same in all three groups (Table IV).

TABLE IV

Percentage of persons with respiratory impairment (day workers)

Room groups.	Total number examined.	Number of persons with impairment.	Percentage.
Weaving	159	106	67
Carding	46	31	67
Spinning	40	21	53

Pronounced symptoms as are exhibited by our cotton operatives could not well have escaped the apparently careful and thorough inspection carried out by the American authors.

It has not been possible to obtain any other data bearing on the subject. Even the International Labour Office was unable to give any information on the subject.

D. COTTON SEED ALLERGY

Since it has repeatedly been suggested that the respiratory symptoms in cotton operatives may be of an allergic nature, it will not be out of place to give a brief review of the question of such allergy in persons not directly connected with the dusty work in cotton mills.

G. T. Brown of Washington, D.C., published, in 1929, the result of tests performed on 530 persons suspected of suffering from some form of allergy. He found 13 definitely sensitive to cotton seed protein; 2 of them suffered from hay fever, the other 11 from asthma with or without eczema or angioneurotic oedema. All of them were also sensitive to other proteins. Other cases of cotton seed idiosyncrasy have been reported from the United States by Duke, Coca, and Fineman.

In England, H. H. Moll (1933), Physician-in-charge of the Leeds Asthma Clinic, obtained a positive skin reaction to cotton seed in 12 out of 119 cases of asthma who showed a positive reaction to other proteins also.

An interesting case with an unusually high specificity was published by Herms (1932). A cotton broker in Hamburg suffered from itching of the eyes and an intense irritating cough whenever he had examined a sample of Peruvian cotton. No other cotton brought on an attack. He stated that two of his colleagues suffered in similar manner. Skin tests and the Prausnitz-Küstner reaction were positive with the patient for extracts of Peruvian cotton, but negative for extracts of African, Indian, Chinese, North American, Brazilian, and Argentine cotton.

E. ACKNOWLEDGMENTS

The Medical Research Council decided, in 1933, at the suggestion of Professor H. B. Maitland, to institute a further research on the aetiology of the respiratory diseases of cotton operatives, with special reference to the histamine and allergy problems. I desire to express my deep and sincere gratitude to the Medical Research Council for entrusting this task to me, and to thank the Industrial Health Research Board and its Secretary, Air Vice-Marshal Sir David Munro, as well as the Committee on Industrial Pulmonary Diseases and its Chairman, Sir Arthur J. Hall, for their recommendation. To Professor Edward Mellanby I am particularly grateful for his constant interest in the work and much valuable help which he has given me.

I would also warmly thank the Rockefeller Foundation for contributing a considerable sum towards the grant awarded by the Medical Research Council.

It was my privilege to carry out the investigation in the Department of Preventive Medicine of the Victoria University of Manchester. It is, therefore, a specially great pleasure for me to thank the Director, Professor H. B. Maitland, for the kind and generous

hospitality shown me and for the interest which he has throughout bestowed upon the work. A large share of any credit which may be given to the work is due not only to his initiative in starting the enquiry, but above all to his wide knowledge of the subject and his critical appreciation of the results, as well as many suggestions for further lines of investigation.

In an undertaking of this kind much necessarily depends on the assistance of the authorities. I have been very fortunate in receiving liberal help from the officials of the Home Office, Dr. J. C. Bridge, H.M. Senior Medical Inspector of Factories, Dr. S. A. Henry, H.M. Medical Inspector of Factories, and Dr. E. L. Middleton, H.M. Medical Inspector of Factories and Secretary to the Committee on Industrial Pulmonary Disease. Much valuable assistance has also been willingly rendered by the local officials in Manchester, in particular Mr. E. F. May, late H.M. Superintending Inspector of Factories, Dr. W. D. Hood, late H.M. Medical Inspector of Factories, and Dr. J. M. Davidson, H.M. Medical Inspector of Factories.

The Federation of Master Cotton Spinners Associations, Limited, have kindly given permission for me to visit some of their mills and collect samples of cotton dust at various stages of the processes; Mr. J. Pogson, General Secretary to the Association, has kindly rendered assistance in this work. Thanks are also due to Dr. R. H. Pickard, Director of the Shirley Institute of the British Cotton Industry Research Association for the help and advice he has given in this connexion.

The Amalgamated Association of Card, Blowing and Ring Room Operatives have given liberal facilities for the examination and testing of a large number of operatives. To the Association, especially to the Managing Secretary of the Insurance Branch, Mr. S. Sanderson, I am greatly indebted for this assistance, which has been essential for the work.

Since the field of the investigation touched, and in many cases encroached upon, the domains of physiology, pathology, pharmacology, chemistry, mycology, and clinical medicine, frequent consultations with the various departments were necessary and much valuable advice has been readily given. I wish specially to thank Professor H. S. Raper and Dr. F. W. Lamb of the Department of Physiology, Victoria University of Manchester; Professor B. A. McSwiney and Dr. Esther Margaret Killick of the Department of Physiology, University of Leeds; Professor S. L. Baker, Dr. H. L. Sheehan and Dr. W. Susman of the Department of Pathology Professor A. D. Macdonald, of the Department of Pharmacology Professor I. M. Heilbron of the Department of Chemistry, Mr. H. Heap, Lecturer in Sanitary and Bacteriological Chemistry, Professor W. H. Lang of the Department of Botany, Dr. G. J. Langley Reader in General Therapeutics, Dr. J. C. Bramwell, Lecturer in Clinical Medicine, Dr. L. Savatard, Honorary Clinical Lecturer in Dermatology, Victoria University of Manchester Dr. R. Ellis, Medical Officer to Outpatients, Manchester Royal

Infirmary; Dr. G. Fletcher, Consulting Tuberculosis Officer, Lancashire County Council; Dr. H. H. Moll, Physician-in-charge of the Asthma Clinic, Leeds General Infirmary; Dr. Glen Parker, Certifying Factory Surgeon for Bolton; and Dr. H. L. Green, Physics Department, Chemical Defence Experimental Station, Porton.

A number of colleagues have given their kind and willing assistance by allowing skin and other reactions to be carried out on them. Particular thanks are due to Miss G. Bergheimer who, undeterred by the very pronounced after-effects caused by one such test, persisted in the investigations. Mr. Ernest Haworth rendered valuable help in the chemical part of the research.

To the staff of the Departments of Preventive Medicine and Pathology of the University I am indebted for a great deal of advice and practical assistance, especially to the stewards of the departments, Mr. V. C. Moore and Mr. H. C. Taylor, as well as to my laboratory technician, Mr. Percy Horridge.

The microphotographs were kindly taken by Mr. H. C. Taylor, the coloured plates were prepared by Miss D. Davison.

PART I.—THE NATURE OF COTTON DUST

A. THE SAMPLES EXAMINED

On examining samples of dust taken from various parts of the process their outward appearance was found to vary considerably. Originally, 21 samples were obtained from five mills, one of which was in Shaw (Indian and American cotton), two in Oldham (American cotton), and two in Atherton (one of which worked with Egyptian cotton only, the other with Egyptian and West Indian cotton). Some of the samples consisted of a thickly interwoven mass of fibres from which comparatively little dust could be extracted by shaking or sieving, whilst others readily yielded a large amount of actual dust. This was especially the case with the samples taken from the scutcher, from underneath the carding machine, and from the "fanny hole" (the base of the tower up which the dust-laden exhaust air is passed out of the mill, *see* page 7).

Whilst certain special questions were examined in connexion with these samples, it was decided to concentrate on one kind of dust which might be regarded as fairly uniform and representative of the various ingredients of the different kinds of dust. In their investigations Maitland, Heap and Macdonald (1932) had employed "Shirley cage" dust, and the present work was continued with further specimens of this material. The Shirley cage is a modern device introduced at the far end of the scutcher. As has previously been mentioned, a considerable portion of the larger fragments and broken fibres is removed from the raw cotton in the earlier stages of scutching, whilst the bulk of the finer dust is taken away by the carding machines. The advantage of the Shirley cage is that it removes a great part of the finer dust before the cotton reaches the carding machines, thus relieving these of a part of their work and consequently reducing the amount of dust which the strippers have to clean away from them. The Shirley cage dust, therefore, represents a cross-section of the scutching and blowing room dust and the cardroom dust. The material, one part of which was derived from North and South American, the other from North American and Egyptian cotton, was kindly supplied by Messrs. Thomas Nuttall and Sons, Ltd., Farnworth.

B. PHYSICAL EXAMINATION OF COTTON DUST

The Shirley cage dust at a first glance appears to consist of loose, fleecy material, resembling masses of dirty greyish-brown cotton wool. When it is gently shaken or beaten, clouds of a fine grey dust arise from it and remain floating in the air for a considerable time.

Portions of the whole dust were placed in a set of sieves and shaken for 10 minutes on a mechanical shaker with a to-and-fro

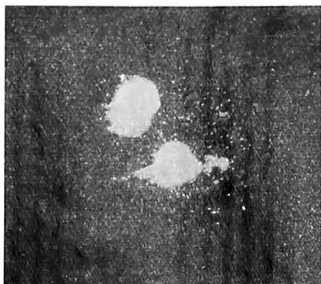


FIG. 3.—Dark-ground microphotograph of cotton dust.

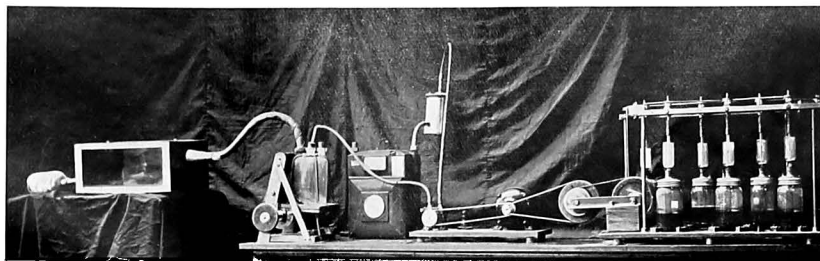


FIG. 4.—Stirring apparatus used for extraction of cotton dust, and apparatus for dusting guinea-pigs.

movement of 5½ inches, the number of shakes being 125 per minute. Four fractions were obtained, viz. :—

- (1) Coarse fraction, retained by a sieve of 30 meshes per inch. It consisted of cotton wool pledgets, 5–10 mm. in diameter, which still retained a little fine dust and some fragments of seed husks.
- (2) Intermediate fraction (*a*), passing through the former, but retained by a sieve of 60 meshes per inch. It consisted of similar, but smaller pledgets, a greater proportion of husk fragments, and only traces of fine dust.
- (3) Intermediate fraction (*b*), passing through the last-named, but retained by a sieve of 90 meshes per inch. It consisted of smaller pledgets, about 2–3 mm. in diameter, and a considerable amount of finer fragments of husk.
- (4) Fine fraction, passing through the 90-mesh sieve. It consisted of fine grey dust which had a marked tendency to flake, but when shaken gave off clouds of fine floating dust.

The proportion of these fractions was No. 1 21·7, No. 2 4·9, No. 3 20·8, No. 4 52·6 per cent. Over one-half of the whole "dust" therefore consisted of this fine material.

Microscopical examination of each fraction showed all of them to consist of similar material, namely, fragments of cotton fibres, greenish and brownish scales derived probably from pieces of leaves and husks, but practically no sand. This explains the fact that the dust is very light (100 g. of the finely sieved dust loosely filled into a measure occupy a space of about 200 c.c.). It also accounts for the tendency of the dust to flake. This is best seen when portions of finely sieved dust are placed in the shaker for half-an-hour, when they accumulate in pledgets of a smaller size but exactly the same appearance as those found on the other sieves.

In his examination of cotton dust Middleton had pointed out the extreme scarcity of siliceous particles below the size of 2 microns. This has been confirmed in the present investigation. The dust disengaged by shaking the whole sample of Shirley cage material was examined qualitatively in Owens' dust counting apparatus; it proved to contain almost no mineral matter but almost exclusively the vegetable débris already described.

As this examination gave only a rough idea of the sizes of the particles, a supplementary examination of the dust floating in the air after beating the sample was carried out with the aid of the ultramicroscope. The cover-glass of Owens' apparatus was thinly and evenly coated with cedar-wood oil, exposed to the dust and then placed face downwards on a slide so as to embed the dust particles in the oil. Under the dark-ground microscope a surprising result was obtained. Besides the particles previously seen, which ranged from about 100 microns to the range of visibility, a far greater number of ultra-fine particles now became visible, and when the preparation was photographed with a powerful arc-light, the number of particles increased progressively with the time of exposure (Fig. 3).

This proves that there is practically no lower limit to the size of the dust particles, and that the greater amount of the "fine dust fraction" actually consists of ultramicroscopic particles, i.e., of a size under 0.2 microns. It is clear that they will readily be inhaled into the finest and deepest portions of the respiratory system. They are even so fine as to be able, probably, to pass through the alveolar wall into the inter-alveolar tissue. Their relatively large surface will allow any of their constituents soluble in the alveolar mucus and the intercellular lymph to enter into solution, as the case may be, in or beyond the alveolar surface.

C. CHEMICAL EXAMINATION OF COTTON DUST

Isolation of the various fractions of cotton dust by chemical means is rendered difficult by the tendency of the dust to clump and cake together. In earlier attempts with the Soxhlet method this caused great inconvenience, and it proved necessary to keep the material thoroughly agitated throughout the processes of extraction. The following stirring machine was constructed (Fig. 4). Six glass preserve jars of cylindrical shape and a quart capacity were fitted with screw-on metal covers bearing one hole in the centre and one near the periphery. A perforated rubber stopper placed in the central hole held a mercury-seal stirrer. The six jars and stirrers were held in a metal frame fitted with pulleys to which the stirring rods were connected by rubber tubing. The stirrers were driven by a $\frac{1}{4}$ h.p. electromotor at a rate of 200 r.p.m. The lateral hole in the cover served for syphoning off the supernatant extracting liquid.*

As a rule each jar was filled with 60 g. of finely sieved dust and 200 c.c. of extracting liquid. After about 6 hours' stirring the motor was stopped, the dust allowed to settle, and the supernatant fluid drawn off and filtered through filter paper. The filter residue was subsequently returned to the jars. In every case it proved necessary to carry out a number of successive extractions with each extracting liquid in order to attain approximately quantitative results. Routine extraction was performed with (1) petroleum ether (B.P. 40-60° C.), (2) methylated spirits, (3) 5 per cent. NaCl solution, in later experiments Coca's solution (Solution A: NaCl 50.0, KH_2PO_4 3.63, Na_2HPO_4 14.31, H_2O ad 1000.0; Solution B: 5 per cent. watery solution of phenol. For use mix Solution A 200 c.c., Solution B 160 c.c., H_2O 640 c.c.).

1. The *petroleum ether fraction* was distilled off at about 60° C. The residue was a brown waxy mass, solid at room temperature. In the incubator (37° C.) part of it only melted, in the paraffin oven (56° C.) the whole mass melted. At this temperature it gave off a pleasant smell like bee's wax, very different from the unpleasant sickly odour pervading the cotton mills and given off in the other

* The apparatus was constructed by Messrs. Baskerville and Lindsay, Chorlton-cum-Hardy, Manchester. The mercury-seal stirrers were made by the Scientific Glass-Blowing Co., Wright Street, Manchester 12.

stages of treating the dust. It should be noted that this fraction is entirely different from the petroleum ether extract of cotton seed ; cotton-seed oil is lighter yellow, remains liquid at room temperature, and has not the smell of bee's wax when heated. The difference is probably due to the cotton dust wax being derived mainly from debris of the seed husks, whereas cotton-seed oil is contained in the endosperm (kernels).

2. After several extractions with petroleum ether the residue was dried in the incubator and repeatedly *extracted with alcohol*. The alcoholic extract is dark olive green, on slight acidification with HCl it turns amber. It gives the characteristic spectrum of chlorophyll, thus confirming the presence in the dust of fragments of leaves. The alcoholic solution was distilled off at 40-50° C. under about 10 mm. pressure. To prevent "kicking" a steady stream of air was sucked through the liquid by means of a fine capillary. The residue was a sticky greenish-brown mass, almost completely soluble in 50 per cent. alcohol, poorly soluble in absolute alcohol as well as water.

For the determination of histamine (*see* page 26) the dust was extracted with alcohol slightly acidified with hydrochloric acid, so as just to give a faint pink colour to litmus paper ; this is necessary as histamine is unstable in neutral or alkaline solution. Distillation was carried on until about 100 c.c. were left, the residue was evaporated almost to dryness on the water-bath and taken up with 10 c.c. of water under thorough stirring, filtered, and stored in the refrigerator. The clear, amber-coloured, acid liquid was tested by Professor Macdonald on the cat (page 26). Strongly positive reactions were regularly obtained. It proved almost impossible to extract the histamine quantitatively ; even after 15 consecutive treatments the extract was still positive.

3. The residue after alcohol extraction (in this case neutral alcohol was used) was again dried in the incubator and *extracted with saline solutions*. This was precipitated with ten volumes of absolute alcohol or saturated with ammonium sulphate. The separation of the alcohol precipitate by filtration proved impracticable, as the filter rapidly became clogged. It was fairly easy to bring down the precipitate by centrifugalization at 4,500 r.p.m. With the ammonium sulphate precipitates centrifugalization was more difficult, as the density of the saturated and even the half-saturated solution closely approximates to that of the precipitate ; often part of the precipitate only went to the bottom, some of it remained floating at various levels, and part of it formed a scum on the surface.

It was found more satisfactory to filter the fluid through a glass-wool pledget fitted into a funnel which retained almost all of the particulate matter, and subsequently to remove this from the glass-wool by thorough shaking in a stoppered wide-mouth bottle with a little ammonium sulphate solution or water. This suspension was then dialysed in the presence of a thymol crystal.

The dialysers were prepared as follows : Pure celloidin (Schering) is washed in distilled water, dried, and dissolved in equal parts of

absolute alcohol and absolute ethylic ether. A one-half saturated celloidin solution is prepared. Into a cylindrical, round-bottomed glass tube, measuring 150×40 mm., about 20 c.c. of the solution are poured carefully so as to avoid formation of bubbles; it is essential that the temperature of the tube and the solution is the same. By tilting and turning the tube the liquid is brought in contact with the whole inner surface of the tube, and the bulk of the liquid is drained off by inverting the tube. After 1 or 2 minutes the celloidin begins to set, and immediately afterwards water is carefully run into the tube up to the brim. After a few minutes the celloidin begins to show fine longitudinal wrinkles. It is now ready to be detached from the glass. The edge is cut away with a sharp knife, a blunt edged glass spatula is carefully inserted at a point where the film is working loose from the tube, and gently moved round and round in a downward direction. When the film has been detached, the water is poured slowly out of the tube into a dish, and the film comes away with it. The opening of the dialyser is tied with tape around a rubber stopper which bears a piece of glass tubing passed through a central hole, the whole being kept under water or 1 per cent. phenol solution. The dialysers retain their permeability well for at least a week. Provided the celloidin layer is sufficiently stout, there is no difficulty in sterilizing them in the steamer.

The substance obtained by dialysis, which is subsequently referred to as "protein from cotton dust", is not, however, a pure protein; it is more or less coloured and does not give as strong protein reactions as a pure protein would do. It appears to contain a considerable proportion of proteoses, probably hemicelluloses. The alcohol precipitate is yellowish-grey, the ammonium sulphate precipitate is dark brown.

The proportion in which the various fractions were found varied somewhat with different samples. The results of a fairly representative experiment which was carried out by a large number of extractions practically to the end, was as follows: Wax 0.8 per cent., alcohol-soluble substances 14.4 per cent., protein fraction (alcohol precipitate) 4.5 per cent.; the remainder was made up of water-soluble substances and totally insoluble dust. Precipitation with ammonium sulphate regularly yielded a considerably smaller amount of protein than treatment with alcohol, the mean amount obtained with the former precipitant being only 0.3 per cent. The obvious assumption that in spite of its deeper colour this substance was more highly purified, was confirmed by biological tests on Man and animals (*see* pages 35, 43). Precipitation with ammonium sulphate was originally carried out in two stages, first by half-saturation to obtain the globulins, then by complete saturation for the albumins. The proportion of albumin to globulin was inconstant, denoting that this method was too rough for the purpose; usually the ratio was as 1 : 2.

Since Wells and Osborne (1911) had reported on the presence of alcohol-soluble proteins in various cereal seeds (but never in other seeds), the alcoholic solution of cotton dust was repeatedly examined for such soluble proteins. The result in every case was negative.

The detailed chemical separation and purification of the various fractions described is a very difficult problem, requiring highly expert knowledge of organic chemistry which the writer does not possess. Mr. Ernest Haworth has been awarded the Dr. Angus Smith Scholarship of this university for the purpose of carrying on this study.

D. THE PREPARATION OF SPECIMENS FOR BIOLOGICAL TESTS

For biological tests a stock of several grammes of the dried protein has been prepared. In order to obtain sterile material from the very badly contaminated cotton dust the attempt was at first made to filter the protein solutions through Berkefeld or Seitz filters. Unfortunately, the dried protein, when emulsified with normal saline solution in an agate mortar, dissolves incompletely, and the resulting suspension forms a thick, viscid layer on the surface of the filter, thus causing a great quantitative and probably qualitative loss. The method ultimately adopted was the following: The dust was freed from its waxy constituents with petroleum ether; alcoholic extraction was dispensed with so as not unduly to denature the protein. Thorough extraction was then performed with Coca's solution, the liquid was centrifuged, and filtered, successively, through paper, a Seitz "clearing" disk, and a Seitz bacterial filter disk. It was thus possible to remove the ultra-fine dust particles present in the suspension so far as not to interfere with the fine filtration through the last membrane. The whole process of graded filtration was accomplished within a day, the last filtration lasted only a few hours; hence there was little danger of the loss of active material by adsorption. The subsequent precipitation with ammonium sulphate and dialysis were carried out under sterile precautions, the salt being sterilized in the hot-air oven.

In view of the presence of considerable amounts of histamine in the raw cotton dust it was necessary to ensure its absence in the protein. It was found by biological tests that 1 per cent. solutions of the various protein fractions were free from histamine. Actually, the solutions employed in allergy tests (page 47) were far weaker—1:10,000 to 1:100,000, and the reactions produced by them have an entirely different appearance from that of histamine reactions (page 47).

PART II.—BIOLOGICAL INVESTIGATIONS

A. ANIMAL EXPERIMENTS

1. THE HISTAMINE PROBLEM

By

A. D. Macdonald and C. Frausnitz.

The presence of histamine-like substances in cotton dust was first demonstrated by the investigations of Maitland, Heap and Macdonald (1932). The amount of active substance was seen to vary with different bulk samples and with different fractions of one sample which had been graded according to the size of the dust particles.

A further investigation was carried out by Macdonald and Maitland (1934) with two samples of Shirley cage dust from a Texas and Argentine mixing. The mean amount of histamine estimated in each of them was 0.02 to 0.04 mg. per 100 g. of dust, and in each sample the finer dust fractions were proportionately richer in it than the coarser ones. They also examined a sample of coir (Algerian coconut fibre) dust and esparto-grass dust; the coir dust gave only a weak reaction, the esparto-grass an even weaker one.

The method employed in their investigations was Soxhlet extraction, first with ether, then with absolute alcohol, and lastly water. Previously only the alcoholic extract had given the histamine reactions, but in the second series they obtained a slight reaction with the ether extract. In the present investigation the Soxhlet method was not used as it was desired to examine larger samples and to obtain, as it were, a cross-section of the whole bulk of the dust. Wherever possible, the sample was passed through the shaker sieve, chief attention being given to the fine dust which was extracted in the stirring machine. Where it was not possible to liberate sufficient dust by shaking the sample, owing to its thickly matted, felted character, 50 g. of the whole material were placed in one-litre gas jars, soaked with the extracting liquid and repeatedly stirred. After two preliminary extractions with petroleum ether (B.P. 40–60° C.) the material was dried and twice extracted with acidulated alcohol; the total time of alcohol extraction was 2–3 days. The filtered alcoholic extract was distilled down to a small volume at 40–50° C. under a reduced pressure; the residue in the distillation flask was then evaporated almost to dryness on the water bath, stirred with 10 c.c. of distilled water, and filtered. The liquid was kept in the refrigerator until the time of testing—normally 2 or 3 days, but even after several weeks' storage no loss of activity was demonstrable. Immediately before injection into the animal the material was neutralized.

The routine biological tests consisted in the intravenous injection to cats completely anaesthetized with chloralose. If a typical depressor

To face page 27

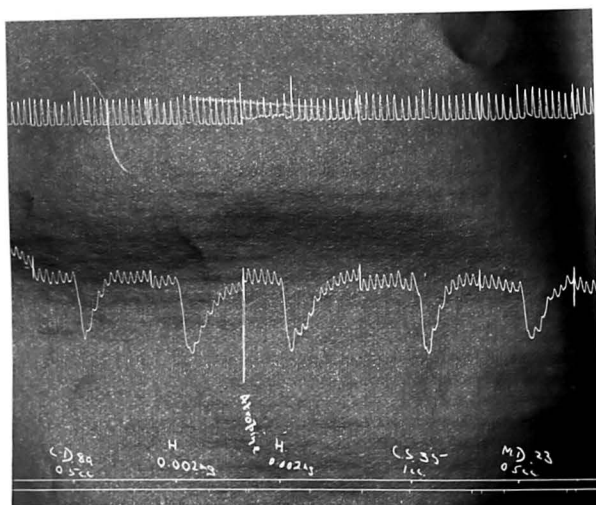


FIG. 5.—Blood pressure curve in chloralosed male cat, weight 3kg. 17.5.34.
The reactions, read from left to right, were the result of intravenous injections of the following substances: Alcoholic extract of cotton dust; 0.002 mg. histamine; 0.002 mg. histamine; alcoholic extract of delinted Russian cotton seed; alcoholic extract of barley dust.

effect was found, the tests were repeated after injection of 1 mg. atropine. As the intensity of the reaction tends to vary with individual cats, control injections were performed in each instance with graded amounts of pure histamine (ergamine acid phosphate of Messrs. Burroughs, Wellcome and Co.). A specimen curve obtained in this manner is shown in Fig. 5. The animals were killed immediately after each experiment.

In one series the results of the intravenous injection were controlled on a strip of cat's intestine suspended in Ringer's solution to which the various test substances were added. The results obtained with the two methods were in close agreement.

The results of the tests performed with cotton dust samples are given in the following table.

TABLE V

Histamine Content of Cotton Dust

N. American, .	Opener	0.006 mg. per 100 g.
" ..	Cardroom, taker-in ..	0.012 "
" ..	Under carding machine ..	0.006 "
" ..	Cardstripping waste ..	0.012 "
Egyptian, ..	Opener	0.008 "
" ..	Scutcher	0.012 "
" ..	Cardroom, taker-in ..	0.012 "
W. Indian, ..	Opener + Scutcher ..	0.0015 "
N. American +	Argentine, Shirley Cage ..	0.006 "

Although certain quantitative differences were therefore observed, there appears to be no doubt that a substance of histamine-like character is regularly present in cotton dust.

The next question was concerned with its origin. As microscopical examination shows the dust to be derived mainly from the seed husks and fibres, these were obtained from a number of different specimens of cotton seed and examined separately. The specimens were kindly supplied by Mr. J. W. Pearson, Managing Director, The British Oil and Cake Mills, Ltd., London. In one case the husks and kernels were examined individually. The seeds were split longitudinally and the kernels extracted with the point of a needle. In some cases the "linters", i.e., the raw fibres as they had been removed from the seed in the ginning process, were also examined. The kernels were ground in a seed mill and stirred in the machine, the husks and linters were soaked with the extracting liquid in glass jars. The results are summarized in Table VI.

The results of these tests appear to prove conclusively that the histamine-like substance present in cotton dust is already present in the original cotton seed, both the husks and kernels. The small amount found in the linters may possibly be accounted for by assuming them to have been contaminated in the ginning process with fragments of husks. Actually, of course, the linters examined are nothing but samples taken from the raw cotton bales and therefore still containing the cotton dust. By contrast, no histamine

From the stock sample of cotton dust several species of moulds present in fairly large numbers were isolated. They were, in the order of their frequency, a *Mucor*, a black *Aspergillus*, a bluish-grey *Aspergillus*, two species of *Penicillium* and a further species, No. 7, which was not identified. All the cultures grew luxuriantly on malt-agar. As there was reason to believe that fairly anaerobic conditions exist in the interior portions of the bales, the possibility of their development under such conditions was tested. Malt-agar plates, inoculated with the various strains, were placed in the anaerobic jar, which was evacuated and filled with mixtures of hydrogen and air at various percentages; the bottom of the jar was filled with a little water to give sufficient moisture for the development of the moulds. In a mixture of 1 part of air and 9 parts of hydrogen *Mucor* and mould Nr. 7 grew poorly, the others not at all. In a mixture of 1 part of air and 7 parts of hydrogen *Mucor*, mould No. 7 and one *Penicillium* strain showed a moderate, the other strains rather poor growth.

In a further set of experiments half-ounce ointment tins were filled to the brim with fine cotton dust, sterilized in the hot-air oven for 2 hours at 140° C., and dried in the desiccator. Sterile normal saline solution was added to the dust in each tin in varying amounts, so as to make up a moisture content of 5, 10, 15, and 20 per cent. respectively. The moist surfaces of the dust were inoculated respectively with pure culture material of the different strains of moulds; the tins were hermetically sealed with their covers and strips of adhesive plaster. After 9 days' incubation at 37° C. the 20 per cent. tins showed a luxuriant growth of *Mucor* and both species of *Aspergillus*, whilst the other moulds had only grown poorly. The 15 per cent. tins showed a scanty growth of the black *Aspergillus*, none with the other strains. The tins containing smaller amounts of water gave no growth. Subsequent incubation at room temperature gave the same results.

Although, therefore, the possibility of the development of moulds in the interior of the bales was hardly probable, the question as to their power of producing histamine was investigated. One-litre flasks containing 400 c.c. of Czapek-Dox's medium (Glucose 50, NaNO_3 2, KH_2PO_4 1, KCl 0.5, $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ 0.5, $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ 0.01, H_2O 1,000) and 5g. finely sieved cotton dust were autoclaved and inoculated, respectively, with the different mould cultures. All but mould No. 7 grew very well, the latter moderately. After 10 days' incubation the fluid contents of each flask were drawn off, slightly acidified to prevent decomposition of any histamine present, most of the water was distilled off in a vacuum, and further treatment carried out as described previously for the residue of the alcoholic extracts. A control flask of uninoculated Czapek-Dox's medium was treated in like manner. In every case the histamine reaction was negative. It appeared, therefore, that even the slight amounts of histamine present in the added dust had either been broken down by the moulds or, more probably, destroyed by the autoclaving.

The result of this series of experiments appears finally to disprove the possibility that moulds commonly present in cotton dust have any connexion with its histamine content.

In continuation of the earlier investigations by Macdonald and Maitland fresh samples of coir dust and esparto-grass dust were obtained and treated in the same way as cotton dust. Coir dust contained about 0.0015 mg. per 100 g. dust, whilst esparto-grass dust contained as much as 0.005 mg.

Since respiratory affections somewhat resembling those seen in cotton operatives had been observed rather frequently in maltsters, Dr. J. C. Bridge, H.M. Senior Medical Inspector of Factories, suggested examination of malt dust for histamine. Dr. A. N. Currie, H.M. Medical Inspector of Factories, Glasgow, kindly supplied various samples of such dust. The samples were examined in the manner previously described; the results are given in the following table.

TABLE VII

Histamine Content of Barley and Malt Dust

Whole Barley, Czechoslovakian	0.004 mg. per 100 g.
do. Californian	nil.
do. Scottish	trace.
Barley dust from screens	0.002-0.008 mg. per 100 g.
Malt dust from screens (2 factories) . .	nil.

These results prove that a histamine-like substance is present in barley dust at similar orders of magnitude as in cotton dust. Its absence in malt dust is explained by the conditions of heat and moisture under which malt is produced from barley; these conditions acting in a slightly alkaline medium would suffice to destroy histamine effectually.

As a control to the examination of various vegetable dusts, Dr. S. A. Henry, H.M. Medical Inspector of Factories, suggested extending the investigation to wool dust. Through the courtesy of the Manager of Messrs. Paton and Baldwins, Ltd., Wyvern Mills, Melton Mowbray, two samples of wool dust were obtained and examined in the routine manner. Microscopically, the fibres present in each sample were pure animal hair, no trace of cotton fibre was found. The following results were obtained.

TABLE VIII

Histamine Content of Wool Dust

Wool dust, fettleing waste = or <	0.001 mg. per 100 g.
Wool dust, opening machine = or <	0.002 ,,

Conclusions.—It has thus been possible to demonstrate a substance or substances showing the characteristic biological reaction of histamine in various vegetable and certain animal dusts. Whether

the active substance actually is histamine has not as yet been determined. Very large quantities of dust have to be extracted in order to obtain sufficient material for chemical analysis, and this has not, so far, been possible. With regard to cotton dust experiments in this direction are being carried out with the assistance of Mr. Ernest Haworth (*see* page 25).

The question as to the causal relations between histamine and the respiratory disease of cotton operatives will be discussed in a later section (*see* page 54).

2. INHALATION EXPERIMENTS WITH WHOLE COTTON DUST

The object of this series of experiments was to reproduce in the animal the effects caused in man by prolonged inhalation of cotton dust. It will be recalled that in the operatives respiratory changes are not usually noticeable before they have passed through ten to twenty or more years' work in the cardroom. In view of the short life-time of experimental animals and the necessity of obtaining concrete results within a limited time, the conditions of the experiment had to be considerably intensified. A further difficulty consists in the fact that, as compared with man, all experimental animals possess noses far more highly developed and far better suited to filter off the dust from the air before it reaches the deeper air-passages.

It was decided to use guinea-pigs for the investigation ; owing to their small size it is possible to subject a fair number of them to the same conditions, and, in addition, this animal is best used in any anaphylaxis experiments. In an attempt to induce mouth-breathing the guinea-pigs' noses were covered with strips of adhesive plaster or cotton wool soaked with mastisol during their stay in the dust-laden air. They soon learned, however, to scratch the material away, and therefore it was necessary to renew the covering at short intervals. It is doubtful for how much of the whole time of exposure to the dust the nose was completely occluded, but there is no doubt that some oral respiration was actually induced by this means.

The dust-cage consisted of a box, 18 in. long, 12 in. wide, 8 in. high. The two long sides were made of glass. Each short side was fitted with a $\frac{3}{4}$ in. brass tube, one for admitting the dusty air, the other for carrying it away ; the latter was plugged with cotton wool to remove the dust from the air passing into the laboratory. The bottom of the cage was fitted with a removable tin plate on which the excrementa were collected. The upper edges of the four side walls ended in a tin gutter, $\frac{1}{4}$ in. wide and $\frac{3}{4}$ in. deep, which was filled with liquid paraffin. The cover of the cage was loose ; it consisted of a plate of sheet metal, on the lower surface of which was fixed a $\frac{1}{2}$ in. ridge, which dipped into the paraffin when the cover was placed on the box. This afforded an air-tight seal. As the animals tended to huddle together in one corner of the cage, the inside was divided into three compartments by transverse plates of perforated zinc. Six animals at a time were exposed to the dust.

By means of a small electrically driven "AKO" blower air was driven in a steady current through a two-litre Wulff bottle containing the finely sieved cotton dust, and thence into the cage. The amount of air blown through the cage was about 25 cubic feet per hour, the amount of dust carried with it, apart from unavoidable losses in the connecting tubes, was about 5 g. per hour. The Wulff bottle was kept constantly agitated to prevent clumping of the dust. The bottle was held by four steel springs, fitted to a brass collar on its neck, in a recess in the horizontal plate of an L-shaped bracket. The upper end of the bracket could rotate to-and-fro in a nutatory manner by means of a pin-and-hole hinge. The lower end of the vertical plate was fitted with a steel plate kept in touch with a revolving cam by means of a strong spiral spring which pulled the horizontal plate of the bracket towards the bench. The cam revolved at the rate of 50 r.p.m. ; when its point touched the steel plate, the Wulff bottle was tilted, and when it passed the plate, the spring drew the bottle down again with a smart jerk* (Fig. 4, page 21).

In this manner 40 guinea-pigs were treated for 3-4 hours every weekday. The majority of the animals appeared to remain in good health, although at the end of each day's dusting they were thickly coated with dust. Their weight increased steadily and rapidly. Some of them, when placed in the cage, sneezed and coughed a little, but all soon got used to the treatment and appeared not to mind it. When taken out of the cage they usually breathed rapidly, but their first response on returning to their proper cages was to feed ravenously. In a few the fur grew patchy and some bald spots developed, but in the majority no changes of the skin occurred. Some of them developed a little local eczema in consequence of the plastering-up of their noses, but this cleared up rapidly after the plaster had been left off for a few days.

A few animals died intercurrently, one of Gaertner infection, which was prevalent in the laboratory at the time, and three of pneumonia (1 after 14, 1 after 16, 1 after 30 weeks). Three more animals died intercurrently without any noticeable post-mortem changes (1 after 2½, 1 after 3, and 1 after 8 weeks). The remaining animals were killed after varying intervals ranging from 3 to 36 weeks.

All the animals killed after at least two months' dusting showed pronounced macroscopical changes of the lungs. The pleural surface had remained smooth and glistening, but it was more or less deeply pitted and had a peculiar mottled greyish-black colour. This was particularly marked in animals which had been killed by cutting the throat: in controls the lungs were uniformly pale white, whilst in the dusted animals the greyish-black spots were in strong contrast to the white colour of the remainder of the lung. These changes are shown in Figs. 6 and 7. Usually, the discolouration was greatest along the lower and anterior borders of the middle and inferior lobes.

* The blower was supplied by the Scientific Glass-Blowing Co. ; the shaker was constructed by Messrs. Baskerville and Lindsay.



FIG. 6.—Lung of dusted guinea-pig, showing black spots on the surface.



FIG. 7.—Lung of another dusted guinea-pig, showing cicatricial retraction of lung surface.

For histological examination the lungs were very gently inflated with fixing solution according to the technique employed by Shaw Dunn and Sheehan in their post-mortem examinations of deceased cardroom workers (*see* Fig. 8). Heart and lungs were removed together, and a cannula was tied into the trachea. The cannula was attached by a short piece of rubber tubing to the lower end of a funnel which projected through one opening of a two-hole rubber bung fitted into a wide-mouthed bottle. Through the other hole of the bung a glass tube passed down to the bottom of the bottle, its other end being connected by a yard of rubber tubing with the opening of an aspirator bottle containing 10 per cent. formol saline solution. The funnel was filled with the same solution to a height of 4 cm. Before the stopper was fitted tightly into the bottle, the

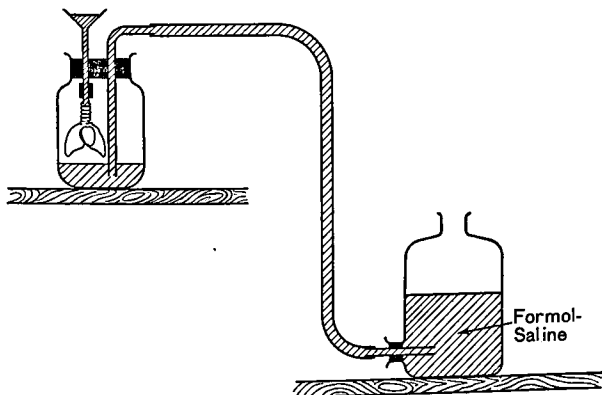


FIG. 8.—Apparatus used for filling the lungs with the fixing solution.

aspirator was raised and some of the solution allowed to run into the bottle. Then the stopper was pressed home, and the head of liquid in the aspirator was allowed to compress the lungs for about a minute. After that the aspirator was lowered 2 ft. below the bottle, thus producing a gentle suction upon the lungs and drawing a little of the solution out of the funnel into the bronchi. Suction was carried out for a few seconds only, so as not to produce artificial emphysema. Then the organs were removed, placed in formol-saline solution, and subsequently embedded in paraffin.

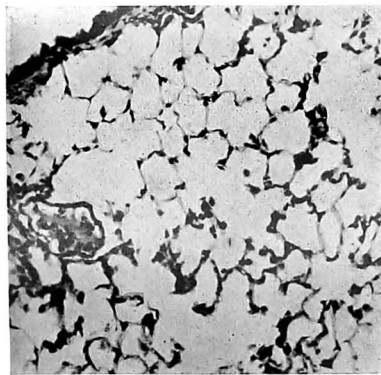
The changes produced by inhalation of the dust were very pronounced. In a normal animal sections of the lung fixed in this manner show a typical reticulated appearance; the inter-alveolar walls are delicate and thin. Such a section looks rather like a string-bag. In the dusted animals the early changes, appearing after about

a month, consisted in scattered peribronchial nodules. Soon after, the nodules spread and coalesced, forming a peculiar thick network of the lung tissue. Instead of the string-bag appearance there now was that of a section through a thick rubber sponge. The alveoli, on the whole, remained patent in most of the animals, but there was a great thickening of the alveolar walls. This appeared to be due in part to oedema, in part to infiltration with leucocytes and dust-cells. In the animals which had been dusted for 6 months or more practically the entire lungs had undergone this change. In addition, localized patches of chronic pneumonia were found in some of the animals, although during their life-time pronounced signs of illness had not been observed. Under a higher magnification the thickened alveolar walls were found to contain a large number of polymorphonuclear leucocytes, very many dust particles, and a small or moderate number of dust-cells. Only slight and doubtful traces of fibrosis were seen in Mallory-stained sections; probably, time had been too short for it to develop. The changes are illustrated by the Figures No. 9-14.

In order to determine whether the changes were specific for the dust employed, and whether histamine played any part in them, three control experiments were undertaken with an inert dust. Unfortunately, no vegetable dust which was free from histamine could be found. It was therefore decided to employ french chalk, which is also very fine and easily dispersed by currents of air. The dusting apparatus was arranged so that the blower, which had several nozzles, was attached to three dusting bottles and three cages of the pattern previously described; one of the bottles contained french chalk, the other french chalk + 1 : 100,000 histamine the third finely sieved cotton dust. Six guinea-pigs, 200-300 g. in weight, were used in each of the three series; one of the french chalk and one of the french chalk + histamine animals died intercurrently. The rest were killed after 3 to 4 months. In all the six dust animals the changes previously described were found; in four of them they were very extensive. In the french chalk animals, one out of five showed a little thickening of the inter-alveolar walls around the edge of the lower lobes; the other four animals of the series were normal. In the animals, treated with french chalk + histamine, two out of five showed slight changes of a similar nature, the other three were normal. It is thus evident that even the inhalation of an inert dust may in time lead to some changes of the type described; there is not sufficient evidence from the small number of animals to show whether histamine may intensify these changes slightly. But there is no doubt that by far the most marked changes are produced by the cotton dust. Although it would therefore not be justified to look upon the changes observed in the guinea-pigs treated with cotton dust as purely specific, the experiments here outlined demonstrate that *cotton dust has a great power of penetrating into the deepest parts of the lungs and of producing in them very extensive irritative changes.*

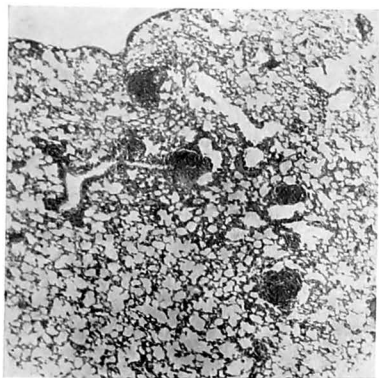


(a)

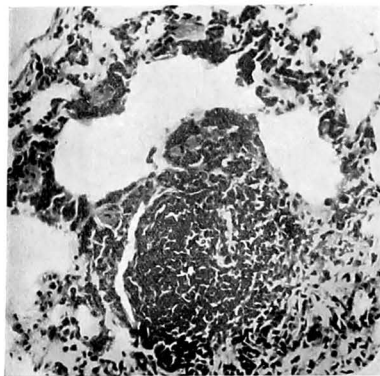


(b)

FIG. 9.—Section of normal guinea-pig's lung.—(a) $\times 30$; (b) $\times 250$.

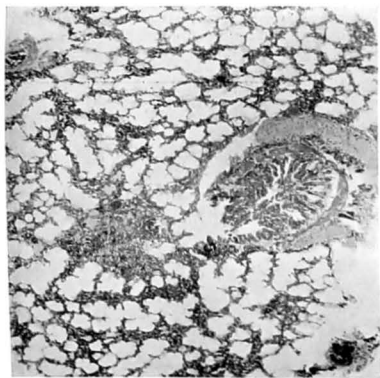


(a)

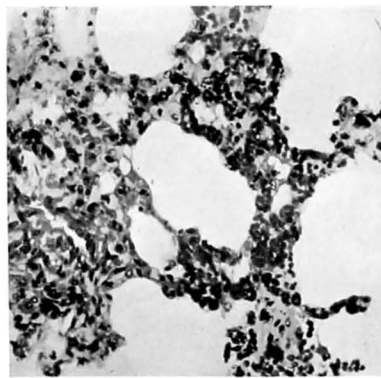


(b)

FIG. 10.—Section of dusted guinea-pig's lung. Early stage: several peribronchial nodules.—(a) $\times 30$;
(b) $\times 250$.



(a)

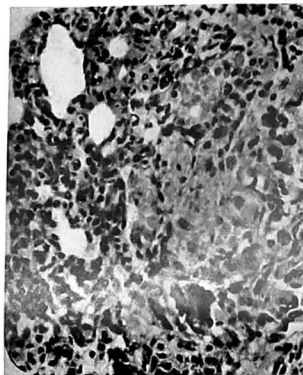


(b)

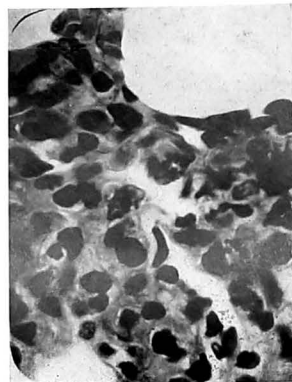
FIG. 11.—Section of dusted guinea-pig's lung. Later stage: pronounced thickening of inter-alveolar walls around peribronchovascular nodule.—(a) $\times 30$; (b) $\times 250$.



(a)

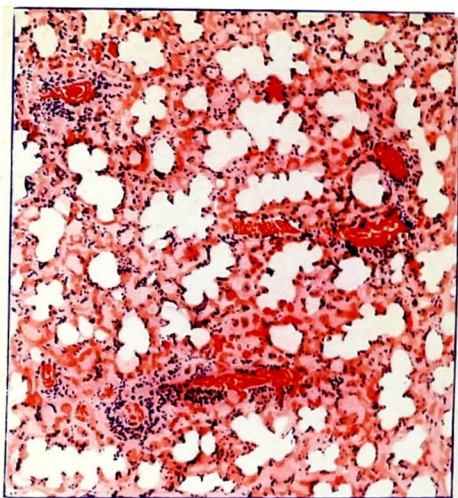


(b)



(c)

FIG. 12.—Section of dusted guinea-pig's lung. Final stage: thickening of inter-alveolar walls throughout the lung; some patches of chronic lobular pneumonia. Animal clinically in good health and increasing steadily in weight.—(a) $\times 30$; (b) $\times 250$; (c) $\times 2,000$, showing dust cells and some dust particles.



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Fig. 13. Same section as in fig. 12.

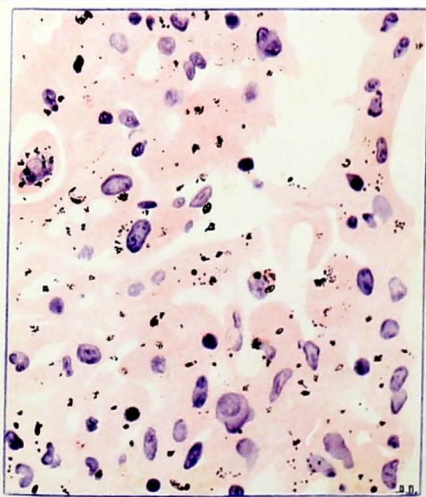


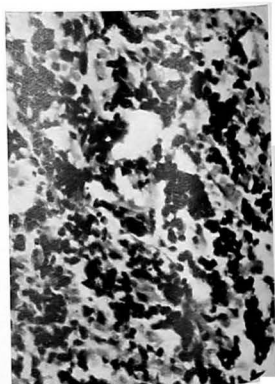
Fig. 14. Same section as in fig. 12.
Infiltration of alveolar walls with numerous cells,
countless dust particles, and some dust cells.



FIG. 15.—Section of the skin of a normal rabbit at the site of intradermal injection of phenol-saline solution, removed on the day after injection, $\times 50$.



(a)



(b)

FIG. 16.—Section of the skin of the same rabbit at the site of intradermal injection of cotton dust protein solution 1 : 100, removed on the day after injection, showing extensive leucocytic infiltration.—(a) $\times 50$; (b) $\times 250$.

3. EXPERIMENTS WITH COTTON DUST PROTEIN

(a) *Intradermal Injection*

The changes observed in the lungs of guinea-pigs after prolonged inhalation of cotton dust gave rise to the question whether they could have been due to the protein constituents. Intradermal injection of small quantities of the protein were found to produce characteristic changes in the rabbit, the guinea-pig, and in Man (for the latter, *see* page 45). Two albino guinea-pigs were epilated on the abdomen; on the following day they received the following intradermal injections, *viz.* :—

- (1) 0·1 c.c. cotton dust protein, ammonium sulphate precipitate, 1 : 100 ;
- (2) 0·1 c.c. cotton dust protein, ammonium sulphate precipitate, 1 : 1,000 ;
- (3) 0·1 c.c. cotton dust protein, alcoholic precipitate, 1 : 100 ;
- (4) 0·1 c.c. cotton dust protein, alcoholic precipitate, 1 : 1,000 ;
- (5) 0·1 c.c. normal saline.

On the following day No. 5 showed nothing apart from the site of the prick, Nos. 3 and 4 an indistinct localized blurring of the skin contours. The site of No. 1 was marked by a distinct, firm, pink papule, 5 × 6 mm. in diameter; No. 2 was similar, but only 3 mm. in diameter.

A black and white rabbit was injected in like manner into the white portions of its skin with solutions 1, 2 and 5; the results were the same as in the guinea-pigs.

The histological changes were very characteristic: The site of injection of protein 1 : 100 showed a dense infiltration of polymorphonuclear leucocytes, that of protein 1 : 1,000 a less intense, but still very pronounced reaction of the same type; the normal saline control presented no changes apart from a few scattered leucocytes. The changes were, if anything, a little more intense in the rabbit than in the guinea-pigs (*see* Figs. 15, 16). As will subsequently be described, the changes observed in Man are of the same nature.

(b) *Intravascular Injection*

As a control to the anaphylaxis experiments described subsequently (*see* page 36), several normal guinea-pigs were given parenteral injections of cotton dust protein. Subcutaneous and intraperitoneal injections caused no noticeable changes, but in a few of the animals injected intracardially definite signs of irritation were observed.

Guinea-pig No. 23.—0·005 g. protein intracardially. 1 min.: runs about excitedly. 2 min.: shivering, hunched up, chewing, respiration accelerated. 4 min.: recovered. Found dead next morning. Post-mortem: Extensive subcutaneous congestion, 5 c.c. bloody fluid in peritoneal cavity, adrenal glands dark red, lungs poorly retracted, very pale. Cultures from lungs, spleen and liver sterile.

Guinea-pig No. 24.—Same treatment. 2 min.: shivering, huddled up, restless, fur ruffled, eyes half-closed. 3 min.: respiration about 110 per

minute, irregular, sometimes gasping. 5 min.: recovering; a few chewing movements. 12 min.: slight dyspnoea, which soon afterwards passes off.

Guinea-pig No. 39.—0.04 g. cotton dust protein, albumin fraction. No immediate signs. Found dead on second day: Bronchopneumonia. This was probably not caused by the injection, as a few cases occurred in other animals at that time.

Guinea-pig No. 41.—0.04 g. cotton dust protein, albumin fraction. 1 min.: Three definite convulsions, otherwise normal.

Five other guinea-pigs injected with 0.01, 0.04, and 0.05 g. of cotton dust albumin respectively remained entirely normal.

Injection of the separated globulin was rather difficult, as the substance is very hard to emulsify. A few animals which showed certain traces of convulsions and dyspnoea can not be cited as proof of the toxic nature of the substance, since these changes may have been due to embolism.

It is thus seen that even a single intravascular injection produced a slight shock in two and a fatal shock in one animal, whilst five animals showed no signs whatever. The guinea-pig which died of bronchopneumonia should probably be left out of consideration.

This result is in contrast to the experiments related in the next section, where re-injection without exception led to definite shock.

(c) *Anaphylaxis Experiments*

The first series of tests was performed on animals which had been sensitized by one intraperitoneal or intracardial injection with cotton dust protein. The results are given as follows:—

Guinea-pig No. 4.—0.005 g. cotton dust protein intraperitoneally. 77 days later 0.01 g. of the same protein intracardially. Result: 1 min.: Chewing movements, scratches nose, slight dyspnoea lasting until the tenth minute. After that normal.

Guinea-pig No. 24.—0.005 g. cotton dust protein intracardially. 27 days later 0.025 g. same protein intracardially. Result: 1 min.: Shivering, slight dyspnoea. 2 min.: Jerky respiration. 3 min.: One convulsion, chewing movements, pronounced dyspnoea (flank breathing). 6 min.: Apparently normal. 31 min.: Huddled up, respiration 120 per minute, jerky. 4 hours: Respiration laboured. Died in the night. Post-mortem: Moderate congestion of subcutaneous tissue and some intestinal loops. Lungs very oedematous, a little haemorrhagic liquid in both pleural cavities.

Guinea-pig No. 48.—0.02 g. cotton dust albumin intraperitoneally. 57 days later 0.05 g. of the same substance intracardially. Result: Immediately afterwards continuous twitching of the whole body lasting for a minute. During the next 2 minutes occasional twitching, coat ruffled, some dyspnoea. Rhythmic spasms in muscles of thorax and limbs last for about an hour longer. Recovered.

Guinea-pig No. 49.—0.02 g. cotton dust intraperitoneally. 57 days later 0.01 g. of the same substance intracardially. Result: 2 min.: Chewing movements, slight dyspnoea. 8 min.: Recovered.

In the following animals, which also responded to re-injection of the protein by more or less marked shock, a third injection was subsequently given in order to test for anti-anaphylaxis.

Guinea-pig No. 26.—*First injection:* 0.005 g. protein subcutaneously. Result: nil. *Second injection:* Intracardially after an interval of 71 days: 0.01 g. albumin. Result: 1 min.: Lies on its side. 2 min.: Repeated short spasms, considerable dyspnoea. 3 min.: Very weak. 4 min.: Head twitches. 5 min.: Very weak and dyspnoeic, coat ruffled, hind quarters depressed. 19 min.: Dyspnoea, repeated scratching of the sides of cage. 23 min.: Recovering. Next day: Normal. *Third injection* (interval of

2 days): 0.05 g. albumin intracardially. Result: 1 min.: Twitching and moderate dyspnoea, lasting for 2 minutes. 4 min.: Respiration wheezy. 10 min.: Recovered.

Guinea-pig No. 27.—*First injection*: 0.01 g. protein subcutaneously. Result: nil. *Second injection* (after an interval of 71 days): 0.06 g. albumin intracardially. Result: Immediately afterwards convulsions of the whole body, lasting for 15 seconds, repeated sneezing. 3 min.: Lies on its side, limbs stretched out, breathing laboured, occasional clonic convulsions, some pawing movements of hind legs. 5 min.: Turns over on other side, still occasional twitching. 7 min.: Tries to right itself, still dyspnoic, scratches nose. 8 min.: Better, but still dyspnoic. 15 min.: Recovered. *Third injection* (after an interval of 12 days): 0.05 g. albumin intracardially. Result: 2 min.: Convulsions. 4 min.: Jerky respiration, marked dyspnoea. 5 min.: Lies flat on its side, convulsions, very weak. 6 min.: Tries to right itself. 8 min.: Still weak, rolls on to its side, tries to sit up again, considerable dyspnoea. 11 min.: Almost normal. 12 min.: Recovered.

Guinea-pig No. 28.—*First injection*: 0.005 g. protein intraperitoneally. No immediate consequences. Next day: Hunched up, shivering. Second day: Normal. *Second injection*: (after interval of 71 days): 0.02 g. albumin intracardially. Result: 1 min.: Severe convulsions, lasting for 5 minutes, a few minutes afterwards recovered. *Third injection* (after 1 day's interval): 0.05 g. albumin intracardially. Result: 1 min.: Moderate spasms at intervals of a second or two. 2 min.: Spasms still frequent, intense dyspnoea. 8 min.: Still occasional slight twitching, weak and dyspnoic. 1 hour: Recovered.

Guinea-pig No. 29.—*First injection*: 0.01 g. protein intraperitoneally. Result: Next day: Hunched up, shivering, coat shaggy. Second day: Normal. *Second injection* (after interval of 71 days): 0.05 g. albumin intracardially. Result: 2 min.: Marked dyspnoea, shivering. 4 min.: Scratches nose once. Recovered. *Third injection* (after interval of 4 hours): 0.05 g. albumin intracardially. Immediately afterwards, a few severe convulsions. 7 min.: A few slight twitchings, dyspnoea. 8 min.: Continuous twitching of the ears, occasional jerky movements, breathing wheezy. 9 min.: Unchanged. Within the next few minutes rapid return to normal.

The results of the foregoing three sets of experiments are not quite conclusive. Nevertheless, it should be noted that a single intravascular injection in previously untreated guinea-pigs (series (b)) caused mild shock in two and fatal shock in one animal, whilst five others showed no symptoms. But in series (c) all the animals which were re-injected intravascularly suffered from more or less pronounced shock. The last four animals provide some indication of the occurrence of anti-anaphylaxis; the third injection produced as severe reactions as the second if the two were separated by several days, but the shorter the interval between second and third injection, the less severe were the consequences of the latter.

The cause of death or shock after a single injection has not been determined. But it appears noteworthy that *in vitro* cotton dust protein solutions cause no haemolysis and even in strong concentration only a trace of agglutination of guinea-pig's red blood corpuscles. In conjunction with the previously described results of intradermal injection such occurrences, even though only occasional, deserve serious consideration.

Although, therefore, the results of these experiments are not absolutely typical of anaphylaxis, it should be borne in mind that typical anaphylaxis in guinea-pigs is not always seen with vegetable

proteins. This has been specially shown by the experiments of Wells and Osborne (1911) on the differentiation of vegetable proteins by the anaphylactic method. For this reason, the results of anaphylaxis experiments in guinea-pigs which had been sensitized only by prolonged inhalation of cotton dust are particularly important. These tests were performed on 10 animals, of which 3 had been dusted for 4 weeks, 2 for 26 weeks and 5 for 36 weeks. The injections were given intracardially 4 days after the last inhalation. The consequences in 2 were mild and doubtful, but 8 showed pronounced anaphylactic shock, and 2 of them died. As specimens of each type of reaction the following cases are described.

Guinea-pig No. 60.—Sensitized by 36 weeks' dusting. Injection, intracardially, 0.01 g. cotton dust protein. Result: 1 min.: Chewing movements, dyspnoea, "Roman nose". 2 min.: Defaecation, slight twitching. 3 min.: Slight fit of trembling, continuous defaecation. 4 min.: Severe shivering. 15 min.: Lies on its side. 20 min.: Recovered.

Guinea-pig No. 54.—Same treatment as No. 60. Result: 30 secs.: Rubs nose. 1 min.: Convulsions. 2 min.: Lies on its side, respiration spasmodic. 3 min.: Tries to right itself, falls back again. 4 min.: Raises itself on forelegs, hindlegs extended flat. 6 min.: Recovered. 2 hours later: Continuous shivering and twitching; lies down, gets up again, recovers for a time. Twitching continues at intervals throughout the afternoon. Next day: Perfectly well.

Guinea-pig No. 7.—Sensitized by 4 weeks' dusting. Injection, intracardially, 0.01 g. protein. Result: 2 min.: Hyperextension of forelegs; body stretched out tonically, shivering. 3 min.: Energetic rubbing of nose with forepaws, respiration deep and rapid, repeated chewing movements, fur ruffled, great weakness (on trying to right itself, its legs seem to slip away under the body). These signs observed repeatedly during the following minutes. 8 min.: A few forced long-drawn expirations. 12 min.: Apparently recovered. 1 hour: Lying on its side, apparently rather lazy than ill; temperature 96.6° per rectum. Died in the night. Post-mortem: Intense congestion of subcutaneous tissue and small intestine; spleen enlarged and cyanotic, liver nil, kidneys engorged, adrenal glands nil. Lungs engorged, surface crinkled, as if they had been oedematous until shortly before death and then shrunk; cut surface of lungs not very moist.

4. SUMMARY OF ANIMAL EXPERIMENTS

Prolonged inhalation of cotton dust causes marked thickening of the inter-alveolar walls due, apparently, to oedema as well as leucocytic and dust-cell infiltration.

Intradermal injection of cotton dust protein causes intense leucocytic infiltration.

Intracardial injection of the protein occasionally causes pronounced vascular inflammatory changes.

Evidence of anaphylaxis was obtained by intracardial injection of solutions of cotton dust protein to animals sensitized, either by one parenteral injection of the protein, or by prolonged inhalation of cotton dust.

Before concluding this section the discovery of peculiar changes in the adrenal glands by Dr. Susman must be noted. This was a chance observation made when he kindly performed an autopsy on one of the guinea-pigs in my absence. As the changes observed by

him may prove to be of importance for the dust problem in general, his report is inserted here.

B. THE HISTOLOGICAL CHANGES IN THE ADRENAL GLANDS OF ANIMALS EXPOSED TO COTTON DUST INHALATION

By William Susman, B.A., M.D.

(From the Department of Pathology, Victoria University of Manchester)

At an early stage in the general investigation a post-mortem examination of one of the guinea-pigs exposed to the inhalation of cotton dust revealed alterations in the adrenal glands, although elsewhere no naked-eye changes were obvious. The adrenal glands showed a striking diminution in the bright yellow fatty zone characteristic of the adrenal cortex in practically all types of animals. This finding suggested that in this particular experiment the endocrine organs in general and the adrenal glands in particular should receive some further study.

Forty-nine adult guinea-pigs weighing between 255 and 735 g. were divided into five groups. Group 1 contained 10 animals that had been exposed to the inhalation of cotton dust for some considerable time; Group 2, 5 animals exposed to cotton dust for a short time; Group 3, 6 animals exposed to the inhalation of french chalk; Group 4, 8 animals exposed to the inhalation of a combination of french chalk with histamine; and Group 5, 20 untreated animals. All but the 20 in Group 5 were animals used in the inhalation experiments described above. The animals in Group 5 were healthy untreated guinea-pigs.

In Group 1 the post-mortem examinations were complete. All the organs were examined histologically, but the only organs to disclose any abnormality were the adrenal glands where with few exceptions the cortical zone of vacuolation was greatly reduced and in some cases practically absent. The remainder of this report will be concerned, therefore, with the appearances in the adrenal glands only.

At the initial stage in this investigation the primary purpose was to find out whether any lesion was present in the adrenal glands. Hence, in all cases these glands were sectioned longitudinally in order to include as much tissue as possible in the sections. The first naked-eye examination of the internal organs of guinea-pigs subjected to long exposure to cotton dust had suggested haemorrhage in the adrenal glands; therefore the glands were fixed in Helly's fluid and the sections prepared by the paraffin method, and stained with haemalum and eosin. In Group 1 all the tissue was utilized for this method of preparation and no material was available for staining for fat and fatty substances. For this reason, only material

prepared by the paraffin method and stained with haemalum and eosin was used throughout. Hence, in this report it is only possible to refer to the extent of the vacuolated area and not to the presence or absence of fat or the fatty substances, although the one probably is significant of the other.

A camera lucida drawing was made from these sections giving the outline of each adrenal gland and the zone occupied by the vacuoles. By means of a planimeter the proportion of this area to that of the whole section surface of the adrenal gland was calculated and recorded as a percentage. The data so obtained are shown in Table IX.

TABLE IX

Ratio of vacuolated zone to whole adrenal gland surface

Group	Inhalation		G.P. No.	Sex	Weight at death	Percentage ratio of vacuol. zone to whole gland			
	Substance employed	Period (weeks)				Indi-vidual animal	Averages for		
							Sex	Group	
1	Cotton dust, long exposure.	38	54	m.	665	22	males	32.80	
		38	60	m.	660	20			
		28	75	m.	385	24			
		38	52	f.	340	13	females		
		38	53	f.	605	57			
		38	56	f.	400	33			
		38	58	f.	735	38			
		38	61	f.	685	38			
		38	63	f.	590	57			
		36	64	f.	640	26			
2	Cotton dust, short exposure.	19	78	m.	580	37	males	46.00	
		19	80	m.	535	47			
		19	82	m.	390	25			
		19	77	f.	560	67	females		
		19	81	f.	510	54			
3	French chalk ..	19	86	m.	645	32	males	53.67	
		11	97	m.	360	65			
		11	98	m.	550	57			
		11	100	m.	535	46			
		19	89	f.	540	56	females		
		11	99	f.	410	66			
4	French chalk + histamine.	19	90	m.	635	69	males	50.00	
		19	93	m.	500	32			
		9	95	m.	370	24			
		11	97	m.	360	65			
		11	98	m.	550	57			
		11	101	m.	450	59			
		19	91	f.	500	51			females
		19	94	f.	370	43			

TABLE IX—*contd.*

Group	Inhalation		G.P. No.	Sex	Weight at death	Percentage ratio of vacuol. zone to whole gland			
	Substance employed	Period (weeks)				Indi- vidual animal	Averages for		
							Sex	Group	
5	Normal controls ..	—	201	m.	345	53	males 51.45	56.40	
		—	202	m.	335	44			
		—	205	m.	385	50			
		—	206	m.	285	51			
		—	208	m.	325	51			
		—	210	m.	325	62			
		—	213	m.	450	47			
		—	215	m.	305	64			
		—	216	m.	375	62			
		—	218	m.	455	44			
		—	220	m.	520	38			
		—	203	f.	315	59			females 62.44
		—	204	f.	255	70			
		—	207	f.	255	54			
		—	209	f.	335	60			
		—	211	f.	355	57			
		—	212	f.	345	53			
		—	214	f.	425	71			
		—	217	f.	335	71			
—	219	f.	430	67					

The figures obtained from Table IX were kindly subjected to statistical analysis by Mr. W. J. Martin, of the staff of the Statistical Committee of the Medical Research Council. His results are given in Table X.

TABLE X
Statistical Analysis of the Results of Table 9

	Ratio of vacuolation zone to whole gland				
	N	Mean	Difference controls minus treated	t	P
MALES					
Cotton dust, long exposure ..	3	22.00	29.45	5.89	P < .01
Cotton dust, short exposure ..	3	36.33	15.12	2.62	P > .02
French chalk	4	50.00	1.45	0.25	P > .8
French chalk + histamine ..	6	51.00	0.45	0.07	P > .9
Normal controls	11	51.45			
FEMALES					
Cotton dust, long exposure ..	7	37.43	25.01	4.21	P < .01
Cotton dust, short exposure ..	2	60.50	1.94	0.33	P > .7
French chalk	2	61.00	1.44	0.25	P > .8
French chalk + histamine ..	2	47.00	15.44	2.74	P > .02
Normal controls	9	62.44			

In view of the fact that statistical significance is normally admitted only in cases with P less than .01, the above results show a significant reduction in the ratio of the vacuolated area to the whole adrenal gland to have been obtained in the guinea-pigs subjected to long exposure to cotton dust—so far as any conclusions can be drawn from this relatively small series of experiments.

The changes observed are illustrated by the accompanying microphotographs, taken from two typical animals, Nos. 54 and 216 of the table (Figs. 17 and 18).

Discussion

Before the above table is examined in detail, it is necessary to consider the fallacies, if any, that may exist. In the first place, the number in each group is small. Further, it is well known that many types of disturbance, especially those of an acute character, may cause some degree of depletion of the vacuolated zone of the adrenal gland. However, this factor can be excluded in that practically all the animals in all groups were killed and showed no signs of disease other than the lung changes induced by the experiment. The only exceptions were guinea-pig No. 82, which died of pneumonia, and No. 95, which died during inhalation and in which no post-mortem changes were visible to the naked eye.

On the technical side it must be borne in mind that the drawing of the vacuolated zone is at best only a rough approximation, and to a lesser degree the same applies to the final percentage values obtained from the planimeter readings. In other words, the calculations can only be considered as approximate. However, those errors that do exist are common to all groups.

Examination of the above table shows that the average in percentage for the whole groups is lowest in Group 1, and somewhat below the normal in Group 2. The sex averages, and also the total averages in Group 1, are about 50 per cent. below the normal averages. In Group 2, however, only the male figure shows any reduction. The results obtained in Groups 3 and 4 are fairly near to the average figures obtained in the normal controls, Group 5.

Throughout the groups the results obtained for the males differ appreciably from those found for the females. This bears out the observations of many investigators that a sex difference does exist in the adrenal glands.

That the animals exposed to the inhalation of cotton dust were the only ones to show any appreciable reduction in the zone of vacuolation would appear to suggest that the cotton dust does contain some substance that may be responsible for this change in the adrenal glands. As no lesion was found in any of the adrenal glands examined, one is forced to consider the change as a functional one.

C. EXPERIMENTS ON MAN

1. LIPOIDS

The wax from cotton dust was administered by the scratch test to 15 diseased cardroom workers (subsequently called "patients"),

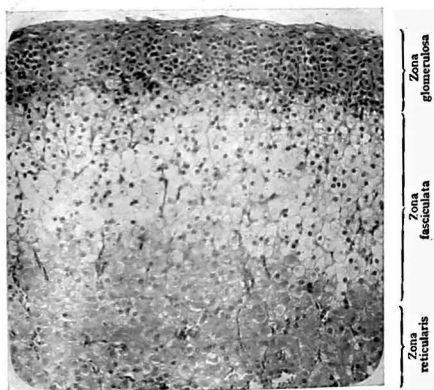


FIG. 17.—Section of the adrenal gland of guinea-pig No. 54 (cotton dust inhalation, long exposure). $\times 125$.

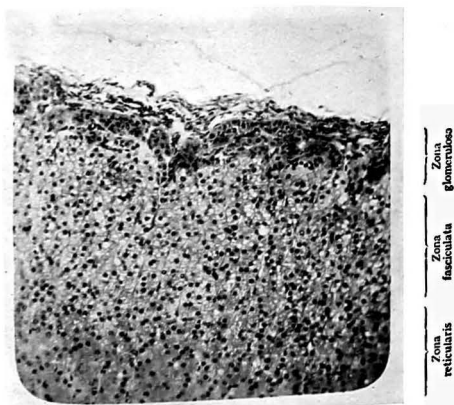


FIG. 18.—Section of the adrenal gland of normal guinea-pig No. 216. $\times 125$.

with completely negative results. The papules forming at the site of the scratch were usually not more than 2 or 3 mm. in size, often smaller than those produced by normal saline, and always disappeared after a short time.

It was pointed out by Professor Heilbron that signs of intoxication observed in animals fed with cotton seed have been referred to *gossypol*, one of the lipoids of the seed (e.g., Alsberg and Schwartze, 1919; Macy and Outhouse, 1924). Professor Heilbron suggested the desirability of carrying out comparative tests on man with this substance, of which he kindly placed a sufficient supply at our disposal. It consisted of fine yellow crystals, soluble in weak alkali. A stock solution was prepared containing 1 per cent. gossypol in a solution of *N/10* NaOH 10.0, phenol 0.5, normal saline 100.0. Falling dilutions were made with the same diluent. A normal person was injected intradermally with 0.1 c.c. of gossypol 1 : 100, 1 : 1,000, and 1 : 10,000. At each site there was immediate burning, a papule with pseudopodial area developed within a few minutes and faded away within half an hour. As the reaction was the same with all three dilutions, it appeared to be due to the alkali. The two weaker solutions caused nothing further. At the site of injection of the 1 per cent. solution there slowly developed within the next 3 days a scarlet papule, 5 mm. in diameter, which lay in the centre of a bright red area, 30 × 14 mm., with irregular borders; papule and area were not sharply demarcated from one another. The site of the reaction itched very much. Within the next 5 days the papule grew to 10 mm. at the expense of the area, which gradually faded away. A hard knob which still itched from time to time remained for about 5 weeks. The test was repeated a week later with exactly the same result.

The testing of patients was carried out with a tenfold dilution of the stock solution in phenol saline, i.e., a solution 1 : 1,000. 0.1 c.c. was injected intradermally to 6 patients. The result was completely negative in each case.

Considering this fact and the comparatively small amount of the substance which can be contained in cotton dust, there appears to be hardly any reason to assume that gossypol is connected with the cotton workers' respiratory disease.

2. HISTAMINE

In the absence of alcohol-soluble proteins (*see* page 24) the only substance present in the alcoholic extract likely to produce any morbid changes in the patients was histamine. The following set of experiments was, therefore, not carried out with the whole alcoholic extract (which was unsuited for the purpose owing to its high content in sticky colouring matter), but with a purified preparation of histamine (ergamine acid phosphate, Burroughs, Wellcome and Co.). The solutions were in every case prepared a few minutes before the test.

The scratch test was carried out with solutions 1 : 1,000, 1 : 10,000 and 1 : 100,000 on 10 patients. The size of the reactions was somewhat

variable. In the later tests on 11 patients the intradermal method was employed, the dose being 0.1 c.c. of a solution 1 : 100,000. Within a minute or two the reaction invariably flared up ; it consisted of a tense white weal, about 10 mm. in diameter, with a circular or slightly dentate border, and a scarlet area with an irregular, pseudopodial border. The area was sharply demarcated from the weal and the surrounding normal skin. Its size varied from 40 to 75 mm. Within about half an hour it had usually disappeared. The reaction in normal controls was of the same appearance and order of magnitude. There is nothing to indicate either increased or decreased sensitivity to histamine in the patients.

3. PROTEIN

All the experiments described here were performed with a single batch of protein obtained from a mixture of American and Egyptian cotton dust in the manner previously described by precipitation with ammonium sulphate. In addition, certain parallel tests were carried out with the alcohol precipitate of a corresponding sample of cotton dust solution, but as they gave a consistently weaker reaction, they will not be discussed here. The sterile ammonium sulphate precipitate was made up into a 1 per cent. stock solution which was kept in the refrigerator. The solvent was 0.5 per cent. phenol in normal saline solution. At fortnightly intervals the lower dilutions required were made up from the stock solution.

All the diseased cotton operatives, all the healthy cotton operatives, and many of the other controls were males.

The first tests carried out on 9 patients by the scratch method gave very weak, often no definite reactions ; only one patient responded to the scratch application of 1 per cent. protein with a marked weal and an area 24×15 mm. in size. In view of these results it appeared justifiable to proceed to the intradermal method, the results of which will be described subsequently. The most important point brought out by them is that the protein produces a *primary toxic effect in normal and diseased individuals* ; to this may be superimposed a *secondary allergic reaction* which latter was regularly present in diseased cotton operatives. The dual nature of the reaction has also been observed in normal and sensitized animals (see pages 35, 36).

Prolonged inhalation of cotton dust leads to pulmonary symptoms, some of which may indeed be attributable to super-sensitiveness ; but the major changes are based on chronic irritation and inflammation. The fact that allergy is not at the root of the trouble is already very probable from the extreme rarity of skin or eye changes in the operatives and is emphasized by the peculiar phenomenon of the *delayed reaction to intradermal injection of the protein*. As in the animal experiment, this reaction was shown to be principally inflammatory, and only sometimes complicated with vascular congestion. Now, the dominant change in the allergic reaction occurs in the smooth musculature of the capillaries, bronchioles, intestine,

etc. It is not accompanied by cellular infiltration, therefore it is a *transitory* phenomenon; it disappears soon after the causal agent has ceased to act upon, or in, the tissues. Most toxic substances, on the other hand, produce a more or less *persistent* local lesion, the dominant nature of which is inflammation; histological evidence of this is shown by cellular infiltration. It would be a mistake to suppose a reaction to be of an allergic nature solely because the response to a given dose of the substance in question differs in various individuals (this was the case in the present instance). Individual differences may be very pronounced also in the reaction of various individuals to poisons such as lead, diphtheria toxin, etc.

(a) *Experiments illustrating the Toxic Effects of the Protein*

The foregoing remarks are illustrated below by observations of delayed reactions to intradermal protein injection in normal persons and diseased cotton operatives, and by the histological examination of the skin lesions thus produced in a normal man.

The first observation was on patient No. 1, who had a surprisingly severe reaction after intradermal injection of 0.1 c.c. of a 1 per cent. protein solution. After 15 minutes there was a weal of 7 mm. and an area of 35×24 mm. with an irregular border; within two hours there was hardly any change, but soon afterwards the forearm injected began to swell, the patient was hardly able to undress, and spent a restless night. 24 hours later there was a tense, tender, oedematous, bluish-red swelling which extended along the whole palmar surface of the forearm; there were a few inflamed lymphatic vessels above the elbow and a swollen axillary gland. Temperature 99.3° . Alcohol compresses were administered and next morning the patient felt much better, the temperature had dropped to 98.3° , the inflammation of the lymphatic vessels and gland had disappeared; the swelling had decreased on the palmar surface and begun to creep round to the dorsal surface. The reaction had disappeared by the fifth day.

Two other severe reactions were observed. They occurred in normal controls who had shown hardly any early reaction. Here, too, the swelling began to develop after two or three hours and increased in the course of the next two days, until the arm had almost assumed the appearance of elephantiasis. The first of these cases, a student who received 0.1 c.c. of a solution 1:1,000, will be referred to subsequently because this treatment produced typical allergic sensitization (*see* page 47). The other case was that of a doctor who received 0.1 c.c. of a solution 1:10,000; he had taken part in the earlier experiments of Dr. Bramwell and Dr. Ellis, described on page 13, and was one of their controls giving a very severe reaction to the injection of cotton dust extract.

Moderate delayed reactions have been observed in two of the diseased cotton operatives who had given a typical early allergic reaction after injection of 0.1 c.c. of a solution 1:10,000. In both of them the delayed reaction did not develop until the following day and was so pronounced as to incapacitate them from work.

Mild delayed reactions have been repeatedly noted, both in diseased operatives who had given a positive early allergic reaction, and in controls who had failed to do so; in each of these cases the dose

had been 0.1 c.c. of a solution 1 : 100,000. The reaction consisted in a very hard nodule about the size of a pea.

Further data were obtained by the *histological* examination of the excised reactions. In experiments on myself, the first intradermal injection performed with 0.1 c.c. of a 1 per cent. solution caused a weal 10×7 mm. and an area 40×18 mm. to develop in 10 minutes. The reaction was very hot and tender. After 3 hours the area had increased to 59×23 mm. and was intensely swollen and oedematous. After 18 hours it had become very hard and cyanotic. In order to differentiate the different stages of the reaction and to compare it with the histamine reaction at its maximum, the following solutions were injected intradermally in my abdomen, viz. :—

- (1) 0.1 c.c. 0.5 per cent. phenol-saline solution (the diluent employed in all the tests) 16 hours before the excision ;
- (2) 0.1 c.c. histamine 1 : 10,000, 20 minutes before the excision ;
- (3) 0.1 c.c. cotton dust protein 1 : 100, 1 hour before the excision ;
- (4) 0.1 c.c. cotton dust protein 1 : 100, 16 hours before the excision.

The excisions were performed by Dr. L. Savatard and the portions excised were immediately placed in formol-saline solution. In order not to complicate the results anaesthesia was dispensed with. The report on the histological examination, which was kindly undertaken by Dr. Savatard, is introduced here. It shows the complete agreement with the results of intradermal injection of cotton dust protein to normal animals. The histological findings clearly demonstrate the progressive nature of the lesions ; they are far more intense and extensive after 16 hours than after 1 hour. This confirms the evidence of inspection and palpation previously recorded. The changes are illustrated by the microphotographs and drawing, Figs. 19-23.

REPORT ON THE HISTOLOGICAL EXAMINATION OF THE PIECES OF SKIN EXCISED AFTER INJECTION OF COTTON DUST PROTEIN, HISTAMINE AND PHENOL-SALINE SOLUTION, RESPECTIVELY

By

Louis Savatard,

Honorary Clinical Lecturer in Dermatology, Victoria University of Manchester.

My histological findings in the four lesions of the skin are as follows :—

(1) *Phenol Saline, 16 hours after injection* ; (2) *Histamine 1 : 10,000 (20 minutes after injection)*.—No variation from the normal could be detected either in the epidermis or the dermis. The fact that no undue vascularity could be detected in the latter specimen may be due to the escape of blood from the small portion as it was excised.

(3) *Cotton dust protein 1 : 100, 1 hour after injection*.—The epidermis is apparently normal, but in the papillary region of the dermis there is slight dilatation of the capillaries and a polymorphonuclear leucocytic infiltration which is practically confined to the regions of the sweat glands, sweat ducts, and hair follicles.

(4) *Cotton dust protein 1 : 100, 16 hours after injection*.—Though the epidermis is again practically normal, the capillaries in the papillary area are more markedly dilated than in the former specimen. There is a very marked leucocytic infiltration *throughout* the dermis. It is not confined to the regions of the sweat glands, sweat ducts and follicles, but permeates between the collagen fibres. Very careful examination revealed no plasma

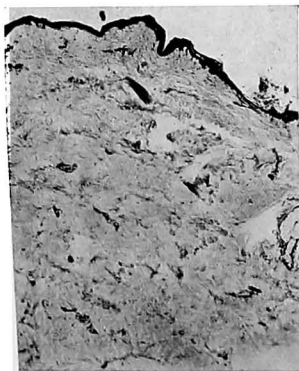


FIG. 19.—Section of the skin of a healthy man at the site of intradermal injection of phenol-saline solution, removed 16 hours later. $\times 50$.

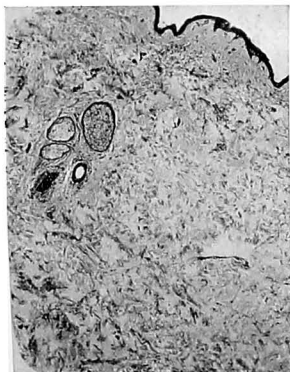


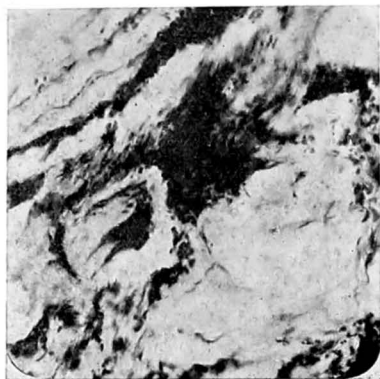
FIG. 20.—Section of the skin of the same man at the site of intradermal injection of histamine solution 1 : 10,000, removed 20 minutes later. $\times 50$.



FIG. 21.—Section of the skin of the same man at the site of intradermal injection of cotton dust protein solution 1 : 100, removed 1 hour later. $\times 50$.

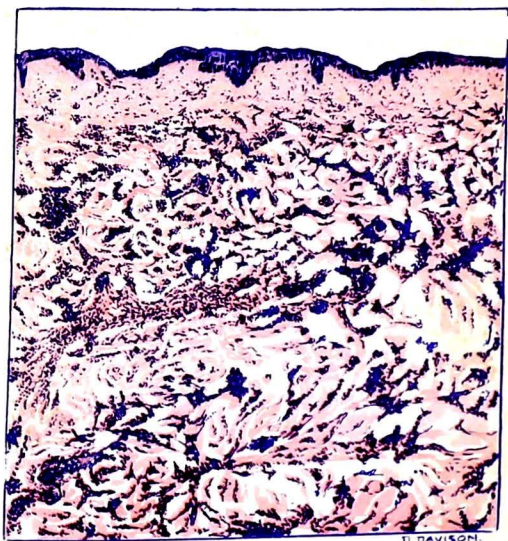


(a)



(b)

FIG. 22.—Section of the skin of the same man at the site of intradermal injection of cotton dust protein solution 1 : 100, removed 16 hours later. —(a) $\times 50$; (b) $\times 250$.



D. DAVISON.

Fig. 23. Same section as in fig. 22.
x 60.

cells and only an occasional mast cell. There is some oedema of the collagen bundles. The picture presented is that of a marked inflammatory reaction.

(b) *Examination for Specific Allergy*

In one instance, mentioned on page 45, the development of specific allergy to the protein was observed. At the first (sensitizing) injection the person, a healthy medical student, was injected at various parts of the forearm with solutions of the protein 1 : 1,000, 1 : 10,000, and 1 : 100,000. The reaction to 1 : 1,000 has previously been described; the other two solutions caused quite insignificant and transitory reactions, about 10 mm. in size. Two months later re-injection was performed with 1 : 10,000 and 1 : 100,000. Within 30 minutes the latter had caused a weal 13×8 mm. and an irregularly bordered area 21×14 mm. large. At the same time the reaction to 1 : 10,000 had developed into a soft white weal of 11 mm. and a characteristic pseudopodial area of 61×46 mm., which was mottled and dusky pink in colour; after 32 hours the weal had disappeared, but the area had grown to 95×71 mm. Next day the reaction had diminished, soon after it disappeared.

The examination for allergy has been made on a number of cotton patients and various controls. In several of them comparative tests were made with the protein and histamine. The appearance of the two reactions is entirely different. The histamine reaction (1 : 100,000) develops within a few minutes, its weal is hard, white, and sharply demarcated from the bright scarlet area; it disappears within about 30 minutes. The cotton dust protein reaction (1 : 10,000 to 1 : 100,000) does not usually appear before 10 or 15 minutes, it reaches its acme after 30 minutes and disappears slowly in the course of an hour or more. The weal is much harder, it is not so characteristically white and therefore often difficult to distinguish from the area. The area always has irregular, often distinctly pseudopodial borders, but its colour is comparatively pale and has a peculiar cyanotic to livid tinge.

The origin of the irritating and the allergic constituents of the cotton dust protein, which very likely are identical, has not been determined. It was considered probable that it was derived from the cotton husks which have been stated to preponderate in the dust. Consequently a number of patients and controls were tested with various such substances, a protein prepared from an extract of the whole cotton seeds (black Egyptian seed), a protein prepared from the separated husks of the same specimen of seed, and a commercial product made by the Arlington Chemical Company of Yonkers, N.Y. The result was not what had been expected. Sometimes one, sometimes the other gave a reaction, but in a number of persons reacting to the cotton dust protein in a typical manner, no reaction was obtained with the seed proteins. When a reaction did occur it was almost invariably smaller with a seed protein solution 1 : 10,000 than with the dust protein 1 : 100,000. It is possible that the seed proteins do take some part in the antigenic constitution of the dust

protein, but this can be but a minor part. The active principle can hardly be derived from the cotton fibres, as these contain practically no protein at all. The solution of this problem must be left to expert chemical investigation.

The results of the allergy tests are summarized in Tables XI a, b, c and d. They were carried out on four groups of people, viz. :—

- (a) Cotton operatives affected with the respiratory disease ;
- (b) Cotton operatives who had worked under similar conditions but had remained in good health ;
- (c) Persons suffering from other forms of asthma. (These tests were kindly performed in the Asthma Clinic of the Leeds General Infirmary by Dr. H. H. Moll) ;
- (d) Normal persons.

TABLE XIa
Allergic Reactions in Cotton Patients

Patient No.	Age.	Work in mill.		Duration of pronounced resp. sympt. years.	Mean size of allergic reaction.§		
		Nature.	Duration : years.		Dust protein.		Seed protein. I : 10,000.
					I : 10,000	I : 100,000.	
2	46	s.g.	25	3	—	21	—
3	33	s.g.	22	20	—	26	—
4	58	s.g.	33	18	—	51	—
5	46	s.g.	25	15	—	53	—
6*	53	s.g.	26	7	48	trace	—
7	44	s.g.	20	few	21	10	—
8	52	bl.	32	17	—	50	—
9	45	s.g.	18	11	—	26	—
10	48	s.g.	30	13	16	14	—
11	44	s.g.	27	11	—	22	—
12	50	s.g.	20	11	—	39	—
13*	54	s.g.	34	11	32	12	—
14	58	s.g.	40	20	—	32	36
15	46	s.g.	9	3	—	41	40
16	47	s.g.	31	9	—	63	11
17	56	s.g.	20	2	—	24	16
18	53	s.g.	30	15	—	57	28
19	43	s.g.	15	8	—	19	10
20	52	s.g.	30	8	28	16	nil
21	62	s.g.	39	10	—	43	14
22	64	s.g.	35	8	18	18†	6
23	59	s.g.	30	14	—	15	9
24	51	s.g.	22	13	33	9	nil
25	44	bl.	22	6	—	23	14
26	27	s.g.	5	5	—	24	nil
27	40	bl.	24	24	56	29	14
28	54	s.g.	30	4	—	15	18
29	50	s.g.	28	16	—	30	11
30	52	bl.	30	20	—	11	7
31	43	mix.	10	10	—	32	44

* Severe after-effect—swelling of arm, lasting for 2 or 3 days.

† Reaction to dust protein 1 : 100,000 only weak, reaction to dust protein 1 : 10,000 typical weal and area.

‡ s.g. = stripper and grinder.

bl. = blowing-room operative.

mix. = cotton mixer (variable quantity of dust according to whether hand-or-machine mixing).

§ The measurements of the allergic reactions are the mean diameters of the area in millimetres.

TABLE XII
Allergic Reactions in Healthy Cotton Operatives

Patient No.	Age.	Work in mill.		Mean size of allergic reaction		Remarks.
		Nature.	Duration : years.	Dust protein, 1 : 100,000.	Seed protein, 1 : 10,000.	
1	32	c.r. ..	16	19	—	Doubtful reaction.
2	31	bl. ..	11	28	12	
3	47	bl. ..	27	28	25	
4	63	s.g. ..	50	nil	nil	
5	61	s.g. ..	10	nil	nil	
6	37	bl. ..	6	nil	nil	
7	63	cop-pack.	53	nil	nil	
8	50	cop-pack.	38	nil	10	
9	52	cop-pack.	42	nil	9	
10	64	cop-pack.	40	nil	nil	
11	63	cop-pack.	50	nil	nil	
12	55	cop-pack.	44	nil	44	
13	27	mixer ..	6	83	44	
14	34	mixer ..	6	nil	nil	

c.r. = cardroom hand (fly gatherer).

bl. = blowing-room operative.

cop-pack. = cop-packer in warehouse (very little contact with cotton dust).

mixer = cotton mixer (variable quantity of dust according to whether hand- or machine mixing).

s.g. = stripper and grinder.

TABLE XIc
Allergic Reactions in Cases of Idiopathic Asthma

Patient No.	Age.	Occupation.	Allergic reaction to		Also sensitive to the following proteins.
			Dust protein, 1 : 100,000.	Seed protein, 1 : 10,000.	
1	32	Doctor ..	50	—	Not tested.
2	37	None ..	nil	nil	Dog, feathers, house-dust, wool.
3	30	None ..	46	—	Grass pollen.
4	11	None ..	nil	—	Grass pollen, feathers, dog, milk.
5	40	Hairdresser..	nil	—	Orris-root, feathers, house-dust.
6	9	None ..	nil	—	Grass pollen, beans, dog, feathers, egg-dust.
7	50	Wool-weaver	nil	—	Wool, house-dust.
8	26	Baker ..	37	—	Wheat.
9	33	Cotton weaver	nil	nil	Not tested.
10	33	Wool-weaver	29	21	Wool, dog, house-dust.
11	42	Wool-weaver	nil	—	Wool, house-dust.

Nos. 2, 3, 5, 7, 9, 10, 11 were women.

TABLE XI
Allergic Reactions in Normal Controls

Control No.	Age.	Occupation.	Allergic reaction to			Remarks.
			Dust protein.		Seed protein.	
			1 : 10,000.	1 : 100,000.		
1	40	Professor..	—	nil	—	
2	58	Doctor ..	—	nil	25	See note below.
3	18	Student ..	—	22	—	
4	39	Doctor ..	—	nil	—	
5	22	Lab. technic.	—	nil	—	See note below.
6	32	Doctor ..	16	nil	—	Reaction doubtful.
7	26	Student ..	24	21	—	

Note.—Controls 2 and 5 were engaged in this dust research. Nos. 6 and 7 are the cases of severe delayed reaction. In No. 6 this occurred at the site of injection of protein 1 : 10,000. In No. 7 there was no delayed reaction at the site of injection of 1 : 10,000 and 1 : 100,000, but only around the place where at the same time 1 : 1,000 had been injected (see page 45). This subject, a lady, subsequently developed super-sensitiveness to dust protein in weak solutions (page 47). She also proved to be super-sensitive to the proteins of duck feathers (+++), horse dander (++), sheep wool (++), oats (+), wheat (+), but not to those of dust, egg and milk. The proteins employed in this test were those of the Arlington Chemical Co. in a dilution of 1 : 10,000.

In order to confirm the specific nature of the allergic reactions described, the Prausnitz-Küstner test was performed with the serum of four patients (Table XIa, Nos. 14, 15, 16, 18) and the control who had been artificially sensitized to the protein (Table XIc, No. 7). The object of the test is to demonstrate in the serum the presence of specific anti-bodies, i.e., specific substances capable of transferring the allergic state from the super-sensitive person to a non-sensitive normal one. It is performed in the following manner: 0.1 c.c. of the serum to be tested is injected intradermally to a normal individual. On the following day 0.1 c.c. of a solution of the substance to which the patient is believed to be super-sensitive is injected intradermally into the site previously treated with the serum, and into a site not treated. The test is positive if an allergic reaction occurs in the former place only. The reactions obtained are described in the following table.

TABLE XII

0.1 c.c. serum.	0.1 c.c. protein, 1 : 100,000.	Reaction after 20-30 minutes.	
		Weal.	Area.
Patient 14 ..	Next day	10 x 5 mm., pale ..	Nil.
.. 15 ..	Do.	12 x 18 mm., pale ..	40 x 15 mm., livid, pseudo-podial.
.. 16 ..	Do.	12 x 8 mm., pale ..	25 x 11 mm., livid, pseudo-podial.
.. 18 ..	Do.	7 x 6 mm., poorly demarcated.	33 x 15 mm., livid, pseudo-podial, intense burning sensation.
Control 7 ..	Do.	13 x 9 mm., pale ..	20 x 13 mm., livid, pseudo-podial.
No serum ..	Do.	7 x 5 mm., pale ..	Nil.

With four out of the five sera tested the experiment therefore had a positive result. This fully confirms the *true specific nature of the allergy observed*.

The allergy tests described in Tables XIa, b, c and d show that a distinct super-sensitiveness to cotton dust protein is regularly present in the cotton operatives suffering from the respiratory disease; it is variable in degree, but invariably present. In healthy cotton operatives, similarly exposed, the reaction was inconstant. The same holds good for persons affected with other forms of asthma. In normal controls, of whom unfortunately a small number only could be tested, the reaction also appears to be inconstant, but the chief significance obviously attaches to the comparison of the first three groups. The fact that different individuals, all of whom are sensitive to the same allergen (e.g., pollen) show quantitative differences in their response to the allergy tests is well known, and so is the fact that occasionally positive results are obtained in persons not affected.

It is, perhaps, not unreasonable to believe that under suitable conditions such persons having an allergic diathesis are in danger of acquiring the definite allergic disease if they are exposed to a greater amount of the allergen. This view appears particularly justified with the reactors of Group (b). Here we find a number of persons, all of whom have been exposed for a variable length of time to the same substance; some of them, notably individuals who had only worked in the dust for a relatively short period, have become super-sensitive, whilst others who may have worked for a lifetime in the dusty atmosphere have failed to acquire this disposition. In this connexion it is interesting to note that a very experienced mill-manager told me that he believed himself to be able to pick out at a glance those strippers and grinders who would remain healthy and those who would in the future become ill. It appears probable that the allergy test will give a scientific basis for such a distinction. From this point of view it would be wise to counsel all positive reactors, although they may still be apparently well, to give up their occupation or at least to employ all possible means of protecting themselves against inhalation of the dust.

D. DISCUSSION OF THE RESULTS OF THE BIOLOGICAL TESTS

Experience in man has shown that prolonged exposure to cotton dust is liable to bring on a peculiar respiratory affection. This has been confirmed by the animal experiments. It has been shown that the protein fraction of cotton dust exercises a distinctly irritating action upon the tissues of Man and animals. The plausible patho-genetic explanation of the lung changes produced in the persons affected is that when the finest particles of the dust penetrate into the alveoli, they are deposited on the alveolar surface, and that either they as a whole, or their protein constituents, in course of time,

pass through the alveolar walls into the interstitial tissues of the lung and exert a similar chronic irritation upon them.

Doubtless, a contributory feature is the action of the coarser portions of the dust upon the mucous membrane of the upper respiratory tract. But it has been found on questioning a large number of sufferers that in at least one-half of the cases the predominant symptom, and often the earliest symptom noted by them, was dyspnoea. At the end of the day's work, especially on Mondays, they were so breathless, they had such a degree of "tightness on the chest," that they could hardly drag themselves home. Many of them said that it took them as much as half an hour to walk a few hundred yards uphill, as they had to stop again and again and lean up against a wall to regain their breath.

It must be admitted that bronchitis and emphysema are commonly found in patients who have been suffering from the disease for a long time. It is, indeed, probable that the coarse dust settling in trachea and bronchi will produce symptoms of respiratory irritation similar to those which are assumed to be caused by the finer dust in the alveolar portion of the lung. But the crucial point appears to be that the coarser part of the dust can be, and owing to better ventilation actually has been, excluded to a great extent. It has been claimed that a great improvement in the sanitary conditions of the mills has thus been brought about. Yet there can be no doubt that fresh cases of the disease are still occurring.

The Report of the Departmental Committee on Dust in Card Rooms in the Cotton Industry (page 8) says: "From official records, and from the evidence of Professor Collis and of those members of the Factory Department who are in a position to form an opinion on the matter, it is considered that by the time war broke out in 1914—probably even a year before then—these exhaust appliances had been installed throughout the trade, and that the installation of any material number after that date was necessitated either by the introduction of new machinery or the replacement of defective appliances." In the light of this statement it appears important that I have examined several young men who have commenced work in the mill as strippers and grinders since the War and yet have acquired the disease. It is true, the Federation of Master Cotton Spinners' Associations, Ltd., in the Report of Employers' Representatives on the Departmental Committee (page 6) take exception to the statement quoted above. Nevertheless, there can hardly be any doubt that even nowadays, in the best appointed mills, irritating dust does find its way into the atmosphere in sufficient amount to produce intense irritation of the respiratory system in persons who have become susceptible to the dust. It is, therefore, only reasonable to infer that this amount of dust will be sufficient to produce the actual disease in a certain proportion of the persons exposed to its influence.

It would have been most desirable to supplement the experiments and tests described by autopsies of patients. It will be recalled

that the post-mortem findings of Shaw Dunn and Sheehan were inconclusive. The reason for this is probably that in the majority of their ten cases the patients had been suffering for many years from their disease and had ultimately died of it. These autopsies were therefore carried out in the terminal stage of the illness, when secondary changes—chronic bronchitis, emphysema, dilatation of the right ventricle—were bound to have become established. What is required in order to test the hypothesis propounded here is to perform autopsies on such patients during the earlier stages of the disease; that would be possible in persons who have died acutely of an accident or some intercurrent disease. But in view of the comparatively small proportion of strippers and grinders in the general population, the opportunities for such examinations are small. Actually, in spite of the interest shown in the question by a number of physicians and pathologists, it has been impossible for me to obtain post-mortem examination of a single case. This question must therefore be left in suspense.

The respiratory disease of cotton operatives is frequently called "stripper's asthma". There can be no doubt that in some of the patients the symptoms resemble those of asthma. Thus, there is definite irritation whilst they are in close contact with the dust, and some improvement when they are away from it. The symptoms are almost invariably worst when they return to work on Mondays, or after any interruption of work. Several patients have told me that they had to give up their work; after some weeks or months their troubles had subsided so far that they desired to resume their tasks. But every time they tried to do so, they were forced on the first day after their return to the mill to stop work, as their sufferings and weakness were intolerable. Such observations obviously point to allergic super-sensitiveness.

Yet there are two possible objections to regarding the disease as simple asthma. The first is that with a single exception all the patients questioned by me insisted that their breathlessness was strictly inspiratory. They stated that the tightness in their chest was like an iron ring preventing them from drawing air into their lungs; they endeavoured, by pressing the palms of their hands against the upper part of the thighs, to aid their inspiratory efforts. They said that there was no difficulty at all in pressing the air out of their lungs. There is some evidence for this in the results of spirometer tests (*see* page 57), which show that the patient's efforts at forced expiration are more successful on the whole than his efforts at inspiration. Still, it is a known fact that genuine asthmatics sometimes are not clear about the difference between expiratory and inspiratory dyspnoea, and therefore this objection cannot be regarded as final.

The second objection is concerned with what at first sight appears to be the strongest evidence in favour of allergic sensitization, namely, the "Monday fever". The same exacerbation of symptoms has been described in similarly affected hemp-workers by Koelsch

and Lederer (1933). But it is particularly noteworthy that a shale-worker suffering not from asthma but fibrosis, who was attending the Asthma Clinic at Leeds, definitely stated that he had the same exacerbation of his symptoms when he returned to his work on Mondays. It therefore seems to be more probable that the undoubted prevalence of attacks on Mondays is due to a physical and perhaps a psychological shock occurring when the patients resume their dusty work after one and a-half day's life in a clean atmosphere. During the following days of the week they would gradually become accustomed to the dusty air and resume their typical habit of shallow breathing. At the week-ends they would be out of doors a good deal and breathe deeply. This they would continue to do on their return to work on Mondays with the result that a relatively great amount of irritating material would rapidly be drawn into the lungs. This would appear at least a possible explanation.

Nevertheless, the existence of true allergic sensitiveness in every patient does prove the illness to be in some manner related to the asthmatic condition. There is indeed reason to believe that this super-sensitiveness plays a part in causing the symptoms of the disease. We are thus led to the following conception of the pathogenesis of the illness: (1) Irritating soluble proteins of the cotton dust penetrate into the alveolar tissue and gradually produce thickening of the alveolar walls. (2) Simultaneously, or perhaps even before that, super-sensitiveness is acquired. (3) Superficial irritation of the bronchial mucous membrane by the dust leads to chronic bronchitis, cough, in some cases accompanied by intensive expectoration, and ultimately to emphysema. In this manner the gradually increasing dyspnoea would be explained as well as the frequent attacks of intensive coughing, and the chronic bronchitis and emphysema of the later stages of the malady.

It is difficult to assess the role played by histamine in the causation of the disease. Experimental evidence is hardly in favour of the view that the chronic respiratory changes are due to it, since the reactions set up by histamine are fleeting. Besides, histamine is normally present in appreciable quantities in the various organs of the body, notably the lung. Furthermore, the skin reaction to histamine in patients resembles, in quality and size, that seen in normal persons; no sign has been observed of either raised or lowered sensitiveness to it in patients. It is possible, however, that the acute attacks of "mill fever" experienced by many persons immediately after their visit to, or their first work in, a cardroom may be due to histamine. Such symptoms have frequently been described. After my first visit to a few mills for the purpose of collecting cardroom dust I experienced a rather severe attack of sneezing and irritating cough, followed in the night by an attack resembling asthma. As I have not developed super-sensitiveness to cotton dust protein in the course of my work, there would appear to be some evidence in favour of that assumption.

PART III.—CLINICAL AND PHYSIOLOGICAL EXAMINATION OF PATIENTS AND CONTROLS

A. BLOOD EXAMINATION

In view of the possible connexion of the respiratory disease of cotton operatives with spasmodic asthma the eosinophile count was determined in 25 patients. The counts ranged from 0 to 4.0 per cent., the average was 1.2; figures over 2.6 per cent. were found in two of the cases only. Even in the patient No. 1 (*see* page 45), who had a severe reaction after intradermal injection of 0.1 c.c. of a 1 per cent. protein solution, the eosinophile count was found to be 0.8 per cent. immediately before the test, 0.8 on the following day at the height of the reaction, and 0.35 on the fifth day after the injection, when all symptoms had disappeared. In one of the controls who had a severe reaction after injection of 0.1 c.c. protein 1:1,000, the eosinophiles were found to be 0 per cent.

The basophile count ranged from 0 to 2.9 per cent., the average being 0.8.

It was not possible to perform the total leucocyte count.

B. SPUTUM EXAMINATION

It has been mentioned previously that sputum is not as a rule a predominant symptom in the patients; sometimes it is practically absent even in relatively long-standing cases. The examinations of Dr. Davey, alluded to on page 13, were carried out by the direct microscopical method only. In the present investigation this was supplemented by cultural methods.

Forty-four specimens from 42 patients were examined; most of them were taken when the patients were being tested, a few were sent by post. Practically all of them were fresh at the time of their examination. The majority of the specimens were colourless and very viscid; in one case the sputum stuck to the Petri dish so firmly that it did not shift when the dish was stood up on its edge or inverted. Some specimens, however, were rather watery, some distinctly muco-purulent. There did not appear to be any relation between the nature of the sputum and the duration of the illness.

Routine examination consisted in the examination of Gram and Ziehl-Neelsen preparations, and cultivation on blood-agar (aerobically and anaerobically), and malt-agar plates. Where the sputum contained greyish-yellow spots or flakes, these were employed in particular. Microscopic examination in most cases revealed only scanty squamous epithelial cells and a small or moderate number of polymorphonuclear leucocytes, usually some Gram-positive diplococci, sometimes Gram-negative cocci, Gram-positive and negative rods, but never tubercle bacilli.

Culturally, the predominant organism almost always was the pneumococcus, usually Group IV; there was 1 case with Type I,

1 with Type III, and 2 with Type II. Green streptococci were encountered in 10, non-haemolytic streptococci in 7, haemolytic streptococci in 4, haemolytic staphylococci in 3, *Micrococcus tetragenus* in 4, *Micrococcus catarrhalis* in 3, Pfeiffer's bacillus in 1, Friedländer's bacillus in 3 cases. Moulds were present in 17 specimens, but there were only a few colonies on the malt-agar plates, so that the possibility of air-borne contamination cannot be ruled out. *Aspergillus niger* was found 9 times, once together with *Aspergillus fumigatus*, once with *Penicillium*; *Mucor* alone 4 times, once together with *Penicillium*, *Penicillium* alone 4 times. In no case was there any evidence of a mould infection of the lung. Mycelia or spores were seen only once in a specimen; this had been two days on the way to the laboratory.

Conclusions.—There does not appear to be any evidence of an abnormal bacterial or mycological flora in the sputum of the patients, and hence there appears to be no reason to attribute the disease to any specific micro-organism.

C. EXAMINATION OF THE RESPIRATORY FUNCTION

The working efficiency of the lungs is a function of many variables, such as the free expansion and contraction of chest and diaphragm, the elasticity of the lungs, the free passage of air to and from the alveoli, the velocity of its penetration through the alveolar walls, the circulation rate of the blood, and psychical factors. Where dyspnoea occurs in consequence of an exertion which would normally be regarded as not excessive for the individual in question, impairment of respiratory efficiency is proved to exist; still more so where it occurs even during complete rest. But a mild degree of dyspnoea is not readily noticed by an unobservant patient and is often even difficult to diagnose by the physician; the border-line between normal and slightly impaired efficiency is exceedingly difficult to trace. Hence, a number of investigators have in the past sought after methods for estimating it more accurately by means of reliable physiological data. A summary of this work is given in the introduction of Moncrieff's report to the Medical Research Council (1934). The method ultimately adopted by Moncrieff consisted in the determination of the vital capacity, ventilating efficiency, dead space, and expiratory pressure. A special recording apparatus was used. The results obtained by him in 86 patients show this procedure to give valuable objective records.

In the present investigation the vital capacity, expiratory pressure, and dead space were also determined, but for reasons of economy a simpler technique was adopted. In addition, a method recently elaborated in the Department of Physiology of the University of Leeds by Professor McSwiney and Dr. Killick has been tried. It consists in measuring the respiratory response to increasing carbonic acid concentrations of the inspired air. It has been known for some time that this response tends to be delayed and irregular

in patients suffering from emphysema. These investigators have found a normal response in healthy controls, but pronounced delay in other instances, e.g. in cases of pulmonary asbestosis, fibrosis, etc. Lastly, an endeavour has been made in the present series of investigations to estimate the rate of passage of oxygen through the alveolar walls. For this purpose a foreign gas was employed. The patients inhaled a mixture of air and acetylene as employed in Grollman's method for determining the cardiac output. The methods involved in this work were learned and practised in the Departments of Physiology of the Universities of Leeds and Manchester, thanks to the kind permission of Professor McSwiney, Dr. Killick, Professor Raper and Dr. Lamb.

The subjects of the experiment were mostly available only in the evenings, after their work in the mill was over. This involved the drawback that they were tired and sometimes found difficulty in concentrating on the tests; but it had the advantage that their respiratory efficiency was examined whilst they were still more or less under the influence of their strenuous day's work.

Considerable difficulty was experienced by a number of subjects in learning to perform the tests correctly. This was noted not so much in obtaining samples of alveolar air as in other tests in which a breathing mouthpiece had to be held and a nose-clip was applied. Almost all the patients had false teeth, often badly fitting sets, a few had none whatever, and consequently they could not at first hold the mouthpiece firmly and close their lips over it satisfactorily. The nose-clip also caused difficulty to many as they were accustomed to nose breathing. In most cases, however, the difficulties were overcome, thanks to their patience and intelligent interest in the object of the investigations.

1. VITAL CAPACITY

A Hutchinson's bell spirometer was employed, and three series of experiments were performed, in each of which several ordinary breaths were followed by one maximum inspiration and expiration. The mean of the ordinary breathings gave the tidal air; this figure was corrected from the results obtained in the determination of the oxygen consumption and the preliminary stage of the rebreathing test (*vide infra*). In many cases the tidal air was found to be unusually low, corresponding to the very shallow and frequent respiration of these patients. The difference between the two maximum readings gave the vital capacity, the greatest value of the three series being utilized. The results are given in Table XIV, pages 64, 65. Unaffected cotton operatives (controls) had a vital capacity ranging from 2.4 to 4.0 litres—average 3.36; with the patients the corresponding figures were, respectively, 1.5, 3.6, 2.26.

2. MAXIMUM EXPIRATORY PRESSURE

This was determined by allowing the subjects to press air into a U-shaped tube filled with mercury without preliminary deep

inspiration. Two values were recorded: the highest level of the mercury column attained at all, and the pressure which could be maintained for about 15 seconds. Lower values were found with a number of patients (*see* Table XIV, pages 64, 65); but the differences did not seem sufficiently pronounced to allow any conclusions to be drawn from them.

3. DEAD SPACE

This was assessed on the quotient $\frac{\text{alveolar CO}_2 - \text{expired CO}_2}{\text{alveolar CO}_2}$ calculated as a percentage. The alveolar CO₂ was determined by the Deep Expiration Method of Haldane and Priestley, the expired CO₂ with the Douglas bag in the routine method for estimating the respiratory exchange. The interesting fact was noted that the respiration rate in many patients remained abnormally high even after prolonged rest, whilst in almost all the controls it was considerably lower. The dead space of the patients ranged from 35.0 to 68.4—average 52.63; that of the controls from 27.9 to 58.4—average 45.52. The details are given in Table XIV, pages 64, 65.

4. REACTION OF THE RESPIRATION TO INCREASING CO₂ CONCENTRATIONS OF THE INSPIRED AIR

In order to obtain a steadily increasing concentration of CO₂ whilst keeping the oxygen at the requisite level, the test is performed by rebreathing in a closed circuit under continuous addition of oxygen. A Douglas bag (Fig. 24) with two taps, is filled by a cycle pump with 25 litres of air, which are measured by passage through a dry meter. One of the taps is connected by a length of corrugated rubber tubing (*a*) with the inlet valve of the mouthpiece; this tube is provided with side tubes from one of which samples of inspired air are from time to time withdrawn for analysis. From the outlet valve of the mouthpiece another length of tubing (*b*) leads to the meter, and a third length (*c*) returns the air to the second tap of the Douglas bag. A steady stream of oxygen is introduced by a side tube into tube (*a*). A ten-litre bottle is fitted with a two-hole rubber stopper. Through one of the holes a piece of bent glass tubing (*d*) passes to the bottom of the bottle, through the other hole a short piece of glass tubing (*e*) is inserted. After the bottle has been filled with water through tube (*d*), it is filled with oxygen by connecting the outer end of tube (*e*) with the reducing valve of an oxygen cylinder; as the oxygen fills the bottle, the water is displaced. During the experiment, tube (*d*) is connected with the water tap, tube (*e*) to a side tube of tube (*a*). By regulating the inflow of water the oxygen supply may be kept at the adequate amount of about 300 c.c. per minute. The bottle is graduated by a slip of paper marked at intervals representing 300 c.c., which is pasted on the outside and varnished.

During the preliminary stage the patient breathes through open three-way taps from and into the air of the room until respiration rate and respiratory minute volume have become fairly constant. Then the taps are closed and the actual test commences. From minute to minute the respiratory minute volumes and respiration rates are read on the meter, whilst from time to time samples are taken into exhausted gas-sampling tubes. The CO_2 content of the inspired air is estimated for each minute: the times of taking the samples are plotted on the abscissa of millimetre paper, the corresponding CO_2 percentages on the ordinate, the resulting points are

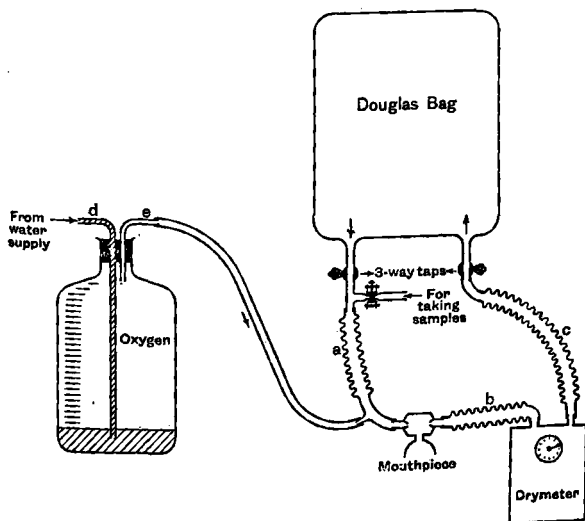


FIG. 24.—Apparatus for CO_2 rebreathing tests.

connected, and the values required found by interpolation. The curve of the respiratory minute volume is obtained by plotting the CO_2 percentages for each minute on the abscissa, the corresponding minute volumes (averages of three consecutive minute readings) on the ordinate of millimetre paper.

Normally, the curve at first rises gently and steadily, but in the neighbourhood of 4 to 5 per cent. CO_2 there is a rather sudden steep rise, when some difficulty or distress in breathing is usually felt.

In patients suffering from fibrotic changes of the lungs the curve has been found by Dr. Killick to rise later and far more slowly.

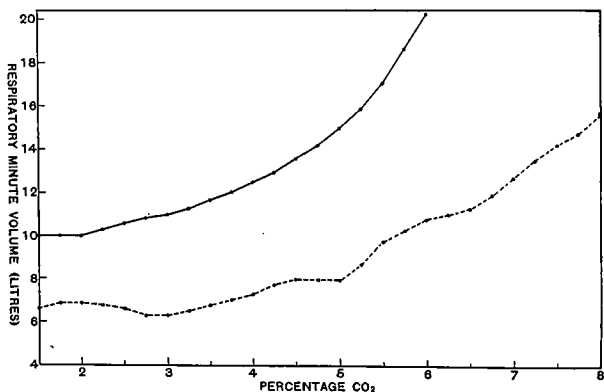


FIG. 25.—Respiratory response to increasing CO₂ concentration of inspired air: specimen curves from a healthy cotton operative No. 13 (—) and a severely affected cotton operative, No. 9 (-----).

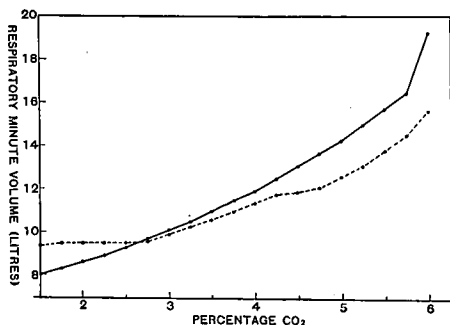


FIG. 26.—Respiratory response to increasing CO₂ concentration of inspired air: average curves for all normal individuals (—) and all diseased cotton operatives (-----).

The present series of tests on the whole confirms these results. Fig. 25 shows a "typical" curve from a normal individual

(uninterrupted line) and a "typical" abnormal curve from a patient (broken line). "Average" curves have been constructed by plotting the average respiratory minute volumes corresponding to each CO_2 percentage for each of the two groups separately (Fig. 26). Here, too, the differences are characteristic, although less pronounced, of course, than in the selected curves shown in Fig. 25. Table XIV gives the CO_2 percentage at which the curve begins to rise rather more steeply for each case examined. The average for the normal group is 5.52, for the patients 6.34 per cent. It is true that if the individual cases in each series are taken considerable differences are observed. In some normal persons the rise is not so very steep and begins well above 6 per cent. CO_2 ; in a few of the patients it is fairly steep and begins below that value. But the general trend is distinctly different in the two groups.

The abnormal reactivity of the patients is borne out by the somewhat irregular form of many of their curves. An initial rise is often followed by one or more depressions. It would seem as if their respiratory centre, after being at first stimulated, subsequently grew less responsive to the constantly increasing CO_2 concentration, and only reawakened to its duties when a relatively high level of CO_2 had been reached.

This conception is corroborated by the peculiar fact that pronounced irregularity of breathing is far more common in patients than in the controls. Especially during the earlier stages of the test, at 2 to 4 per cent. CO_2 , more or less marked Cheyne-Stokes breathing was regularly observed in the former, although the oxygen content of the inspired air was kept at 19 to 20 per cent.

5. ACETYLENE TEST

The source of acetylene was the commercial product (steel cylinders containing a solution of C_2H_2 in acetone under pressure). The gas was purified by passing it through four towers containing, respectively, $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ 16, 1 per cent. H_2SO_4 100; $\text{K}_2\text{Cr}_2\text{O}_7$ 10 per cent. in water acidulated with H_2SO_4 ; pumice stone saturated with CuCl_2 solution in HCl ; sticks of NaOH . The purified gas, which had a less unpleasant odour than the raw gas, was collected in a rubber bag. 500 c.c. of acetylene and 2,000 c.c. of air were mixed by means of a graduated aspirator bottle filled with a saturated watery solution of NaCl , and transferred to a 2.5 litre rebreathing bag fitted with two side tubes for taking gas samples, and a two-way tap holding the mouth piece. After mouth piece and nose-clip had been attached to the resting patient, he was instructed to breathe quietly and evenly through the tap set to the outer air, until he had become accustomed. Then at a given moment the tap was turned towards the bag, and the subject took a number of very deep breaths out of the bag and back into it. Equilibrium between the contents of the bag and the alveolar air are assumed by Grollman (1932) to be attained in 15 seconds, if six breaths of 2.5 or eight breaths of 2.0

litres have been taken. The first sample was taken after 15 seconds, the second 8 to 10 seconds later, i.e., before blood containing acetylene had begun to return to the pulmonary circulation.

The samples were analysed in a Haldane apparatus fitted with a third tube containing the following solution: $\text{Hg}(\text{CN})_2$ 20, NaOH 8, H_2O 100. Carbonic acid, acetylene, and oxygen were determined in this sequence in two or three tests for each sample. From the average results of each sample the nitrogen content was obtained by subtraction. The acetylene content of sample 1 was corrected for change of volume by multiplying it with the quotient

$$\frac{\text{nitrogen percentage of sample 2}}{\text{nitrogen percentage of sample 1}}$$

The quotient $\frac{\text{C}_2\text{H}_2 \text{ (corrected), sample 1} - \text{C}_2\text{H}_2 \text{, sample 2}}{\text{C}_2\text{H}_2 \text{ (corrected), sample 1}}$ was deter-

mined and calculated so as to correspond to a uniform period of 10 seconds. This value in percentage expresses the rate of acetylene absorption through the alveolar walls into the blood.

The figure thus obtained depends on two factors: (1) The permeability of the alveolar membrane, and (2) the circulation rate of the blood through the pulmonary vessels. Grollman has elaborated a formula by which the latter variable is determined from the acetylene loss by the aid of the resting oxygen consumption. But as it was desired in the present investigation to eliminate the cardiac output, it hardly seemed suitable to use the acetylene method for determining both of the two variables. As a simple, although rough, solution the quotient suggested by Liljestrand was determined: $\frac{\text{pulse-pressure} \times \text{pulse-rate}}{\text{mean blood-pressure}}$, and the percentage acetylene loss divided by this figure.

The acetylene test is comparatively easy to perform if the patient is able to concentrate his attention sufficiently, nor does it cause him any marked inconvenience. The unpleasant after-taste of the gas is removed by rinsing the mouth out thoroughly so soon as the test is over (during the test itself the taste is not noticed!). Even in patients with considerably impaired respiratory function no irritation was set up except such as was due to the forced breathing. Only in a few cases was it impossible to carry the determination out because a previously present irritative cough persisted during the test. One man complained for about a quarter of an hour afterwards of an unpleasant sensation which he could not define, but which was unaccompanied by any objective finding. The test was not performed where cardiac impairment was indicated by abnormally high pulse-rate or abnormally low blood pressure.

The results of the acetylene tests are given in Table XIV, pages 64, 65. Considerable individual variations have been observed, both in the acetylene loss and the value obtained after correction for cardiac output. Table XIII gives the range of figures found in patients and controls.

TABLE XIII

Summary of Values Found for Acetylene Loss

	<i>Patients.</i>		<i>Controls.</i>	
	C_2H_2 loss.	C_2H_2 loss corrected for cardiac output.	C_2H_2 loss.	C_2H_2 loss corrected for cardiac output.
Maximum ..	58.8	1.46	28.4	0.91
Minimum ..	1.2	0.03	6.0	0.15
Average ..	16.53	0.47	13.33	0.32

These results should be read in conjunction with the detailed figures in Table XIV. The striking fact emerges that the range between the figures in each group is very wide. Apart from that, the average results would appear to afford evidence that the ordinary result of the acetylene test was higher in patients than in healthy individuals. But the more important fact emerges that the minimum values are far lower in patients than in controls. This implies that in some of the patients the respiratory efficiency has been impaired so far as to interfere with the free passage through their alveolar wall of an easily diffusible foreign gas, and therefore probably still more so with that of a less diffusible gas like oxygen.

TABLE
Tests for Respiratory

Subject No.	Age.	Occupation.	Years in dust.	Years ill.	Vital Capac. litr.	Maximum Expir. pressure.	
						Reached.	Maintained.
(a) PATIENTS							
1	43	s.g.* ..	25	9	2.85	60	50
2	46	s.g. ..	28	3	3.15	90	70
3	33	s.g. ..	22	20	2.05	100	70
4	58	s.g. ..	33	18	2.05	60	44
5	46	s.g. ..	25	15	2.5	80	60
6	53	s.g. ..	26	7	2.2	80	60
7	44	s.g. ..	20	few	2.0	74	60
8	52	bl. ..	32	17	2.1	100	100
9	45	s.g. ..	18	11	2.2	64	44
10	48	s.g. ..	30	13	2.5	56	30
11	44	s.g. ..	27	11	2.55	70	44
12	50	s.g. ..	20	11	1.5	—	—
13	54	s.g. ..	34	11	1.7	—	—
14	58	s.g. ..	40	20	2.1	62	70
15	46	s.g. ..	9	3	2.15	90	70
16	47	s.g. ..	31	9	2.55	90	74
17	56	s.g. ..	20	2	2.35	40	40
18	53	s.g. ..	30	15	1.7	13	13
19	43	s.g. ..	15	8	1.9	60	50
20	52	s.g. ..	30	8	2.4	50	40
21	62	s.g. ..	39	10	1.6	70	60
22	64	s.g. ..	35	8	1.5	64	58
23	59	s.g. ..	30	14	2.35	50	50
24	51	s.g. ..	22	13	3.45	70	70
25	44	bl. ..	22	6	2.6	—	—
26	27	s.g. ..	5	5	3.6	65	60
27	40	bl. ..	24	23	2.3	40	30
28	54	s.g. ..	30	4	2.05	70	50
29	50	s.g. ..	28	16	1.35	40	40
30	52	bl. ..	30	20	1.7	80	70
31	43	mixer ..	10	10	3.1	72	60
(b) CONTROLS							
1	32	cardr. hand	16	0	3.35	60	60
2	31	bl. ..	11	0	3.45	120	100
3	47	bl. ..	27	0	3.8	130	120
4	63	s.g. ..	50	0	2.5	60	50
5	61	s.g. ..	8	0	3.05	80	80
6	37	blow. r. op.	6	0	3.25	64	64
7	63	cop-packer	53	0	3.75	90	70
8	50	cop-packer	38	0	3.3	60	60
9	52	cop-packer	42	0	3.65	80	70
10	64	cop-packer	40	0	3.5	50	44
11	63	cop-packer	53	0	2.4	70	55
12	55	cop-packer	44	0	3.4	60	50
13	27	mixer ..	6	0	4.0	90	80
14	34	mixer ..	6	0	3.7	70	70
15	26	student ..	0	0	3.2	—	—
16	58	doctor ..	0	0	—	—	—
17	18	student ..	0	0	3.75	—	—
18	39	doctor ..	0	0	—	—	—
19	40	professor	0	0	—	—	—
20	60	lecturer ..	0	0	—	—	—
21	22	lab. boy ..	0	0	—	—	—

* See foot-note †, page 48.

XIV

Efficiency

<i>Dead space per cent. of tid. air.</i>	<i>Rebreathing test: per cent. CO₂ at which curve bends up steeply.</i>	<i>Acetylene loss.</i>		<i>Remarks.</i>
		<i>Net per cent.</i>	<i>Corrected for card. output.</i>	
53.5	4.65	3.9	—	
53.2	5.75	8.8	—	
35.0	5.85	3.6	0.10	
68.4	over 6.75	30.3	0.77	
44.4	6.1	6.0	0.21	
61.0	8.5	14.5	0.62	
56.2	over 9.0	23.7	0.71	
54.0	—	58.8	1.29	
58.7	over 6.5	1.2	0.03	
50.3	over 7.0	2.2	0.07	
48.3	5.9	—	—	Kyphosis of thorax.
—	—	—	—	
56.1	—	15.0	0.56	
40.6	over 7.75	—	—	
51.4	—	—	—	
56.5	6.75	15.2	0.47	
49.4	—	—	—	
44.4	6.5	10.5	0.26	
39.9	—	3.9	0.14	
56.4	—	20.7	0.64	
—	—	5.5	0.07	
47.6	—	11.9	0.29	
61.2	over 5.6	—	—	
61.6	—	23.1	0.51	
—	6.6	16.8	0.30	
49.5	4.6	9.2	0.27	
55.3	—	29.3	1.46	
56.1	—	29.5	0.85	
61.8	—	34.5	0.44	
53.3	over 4.4	18.7	0.32	
49.4	6.0	—	—	
—	—	—	—	
50.0	—	7.6	0.28	
46.0	—	9.8	0.18	
54.4	5.7	9.1	0.15	
46.4	—	12.3	0.27	
44.6	5.4	9.1	0.26	
27.9	4.15	28.3	0.91	
48.6	4.85	—	—	
48.9	—	17.6	0.36	
42.0	over 5.55	6.0	0.15	
54.1	5.8	20.0	0.40	
58.4	6.7	14.3	0.28	
50.1	5.9	9.9	0.26	
35.7	5.15	—	—	
30.2	5.95	16.0	0.34	
40.5	4.6	14.1	—	
46.6	6.0	11.1	0.36	
26.5	5.85	—	—	
—	5.55	—	—	
—	—	15.4	0.55	
—	—	17.9	0.53	
—	—	—	—	
—	5.3	—	—	

The figures embodied in Table XIV have been kindly subjected to statistical analysis by Mr. W. J. Martin. The results of this analysis are given in Table XV.

TABLE XV
Statistical Analysis of the Results of Table XIV

	Patients.		Controls (cotton workers).		Difference Controls minus Patients.	t.	P.
	N.	Mean.	N.	Mean.			
Vital capacity ..	31	2.26	14	3.36	+ 1.10	6.4	< .01
Dead space ..	28	52.63	14	45.52	- 7.11	2.73	< .01
CO ₂ ..	18	6.34	10	5.52	- 0.82	1.93	.1 > P > .05
Acetylene loss, per cent.	24	16.53	12	13.33	- 3.20	0.78	.5 > P > .4
Do., corrected ..	22	0.47	12	0.32	- 0.15	1.27	.3 > P > .2

This table shows, therefore, that on the average the vital capacity is greater, the dead space, CO₂ response, and acetylene loss smaller in the controls than in the patients. But as only such groups of figures are statistically significant which give a P less than .01, the main conclusion to be drawn is that *the vital capacity and the dead space do actually show a statistically significant difference between the patients and controls.*

D. DISCUSSION OF THE RESULTS OF THE PHYSIOLOGICAL TESTS

Among the tests for respiratory efficiency employed in this section of the work Vital Capacity and Dead Space (viz.: its ratio to the Tidal Air) have given statistically significant differences between the patients and the controls, the former being regularly higher, the latter lower for the controls. This result was to be expected from the physical impairment which was more or less pronounced in the majority of the patients both by direct clinical observation and from their history. The measurement of vital capacity is probably best suited for examinations of this nature, as it is quickly performed, causes no discomfort, and affords few possibilities of error. The dead space, although giving fairly consistent results in the present investigation, has considerable drawbacks in the examination of persons not specially trained, since the determinations of the alveolar air and oxygen consumption are fraught with somewhat greater possibilities of error if the subject's breathing technique is slightly faulty.

The determination of the response to increased percentages of CO₂ in the inhaled air has not, it is true, given results which can be regarded as statistically significant. Nevertheless, inspection of the curves (Figures 25, 26) does show a pronounced difference in the reaction of patients and normal subjects; there can be no doubt that on the whole the curve rises more steeply at a lower CO₂ level

with the latter group. The results of this test are, however, less suited for statistical evaluation than those of the former two tests, and this may explain the discrepancy between the appearance of the two kinds of curves and the statistical analysis. The intrinsic drawback of the method lies in the fact that it is difficult to employ in individuals suffering from respiratory disturbance. The necessity for the subject's holding the mouth-piece firmly for about 30 minutes, the possibility of leaks occurring between mouth and mouth-piece, and the considerable discomfort at the final and crucial stage of the experiment raise serious objections to the routine use of this method.

The acetylene method, finally, has been a great disappointment. There had been some reason to expect that it might be possible to demonstrate by it some impairment in the passage of oxygen through the alveolar wall in our patients. The speed with which the determination can be carried out and the very slight discomfort it causes to the subject appeared to be special points in its favour. It has, however, been found that no conclusive results can be obtained with it; indeed, the averages work out slightly better for the patients than for the controls, but the difference is so slight as to be statistically insignificant. But it may appear worthy of mention that in a few of our patients remarkably low figures for the acetylene absorption were obtained, which might suggest that in exceptional cases some impairment of the passage of oxygen through the alveolar wall might play a part in the causation of the disease.

For the individual case all these tests do not lead much further. They only corroborate the clinical evidence of poor respiratory function, which, in its turn, is mostly the consequence of emphysema. But their value for the purpose of this investigation consists in the fact that the general trend of each test tends to support what clinical examination had merely rendered probable, namely, that the morbid process developing in the lungs has actually wrought serious damage to the organ.

PART IV.—PRACTICAL CONCLUSIONS

A. DIAGNOSIS

For the diagnosis of the disease we still depend primarily upon the history of the case. This is so typical that in the cotton district every physician is familiar with the malady and easily recognizes it. In difficult or doubtful cases it would probably be advisable for the physician to be given the opportunity of seeing the patient at his work, especially on Mondays. Under these conditions the typical symptoms and signs will undoubtedly be found, or their absence determined, as the case may be.

The intradermal test with a weak solution of cotton dust protein (1 : 100,000 to 1 : 10,000) gives a characteristic reaction which proves the existence of allergy to the substance. Every person super-sensitive to cotton dust, even if he is apparently healthy, should take rigorous precautions against inhaling the dust ; it would be advisable for him if possible to change his occupation.

In advanced cases the physiological tests, especially the determination of the vital capacity, afford valuable confirmation of the existence and extent of the damage rendered probable by clinical examination.

B. TREATMENT

Specific treatment of allergic conditions by desensitization has been so successful in many forms of idiosyncrasy, e.g., hay fever, spasmodic asthma, urticaria, etc., that the question as to its use in the treatment of the respiratory disease of cotton operatives naturally arises. Unfortunately, however, this affection is not the consequence of an allergic condition due to an otherwise harmless allergen. The causal agent has been shown to be *primarily toxic*, it produces severe inflammatory changes in normal persons, i.e., in subjects who are not super-sensitive to it. Assuming that it should be possible to free the patient from his super-sensitiveness, it is difficult to see what advantage would accrue. The inflammatory changes produced in the tissues of the lungs by the dust inhaled would continue and necessarily become ever more severe, no matter whether the specific super-sensitiveness had been abolished or not. The same remarks obviously apply to non-specific methods of desensitization, e.g., by X-rays, peptone, tuberculin, sulphur, etc.

The physical impairment of pulmonary function could in all probability be considerably benefited by adequate breathing exercises. Part of the patient's trouble is undoubtedly due to his having lost the power of properly using his lungs ; but part of it may be the result of his having permanently acquired the habit of very shallow and frequent breathing. In the dusty atmosphere this habit is quickly formed and it is possibly of some benefit there, since it may tend to diminish the amount of dust actually inhaled into the bronchi

and alveoli. But it would be most desirable to insist upon the patient's resuming the natural manner of deeper breathing at home and especially in the fresh air.

Apart from this, the physician is practically limited to symptomatic treatment, especially with ephedrine, which gives pronounced relief in suitable cases. As with every idiosyncratic or other affection due to extrinsic substances the greatest benefit can be obtained by removing the injurious substance from the patient, in the present instance, by persuading the patient to give up his work sufficiently early, i.e., before severe changes of pulmonary function have developed. It is surprising to see how much subjective relief can be obtained in this manner. The patients gradually regain much of their lost weight, they look better, the blood vessels of the skin are better filled, its turgor increases, and, above all, the irritation of their respiratory system rapidly diminishes. If this change of environment is brought about before secondary changes of the lung such as chronic bronchitis and emphysema have had time to develop, the chances of achieving something very like an actual cure may be regarded as favourable.

For the treatment of the severe nocturnal attacks of air-hunger it might be well to make judicious use of the administration of oxygen, combined perhaps with 5 per cent. carbonic acid.

C. PREVENTION

The foregoing remarks have made it evident that the utmost importance attaches to the prevention of the disease. Much has been done by the mill-owners in the last few decades to reduce the dust in cardrooms by better systems of ventilation, and above all by the introduction of exhaust or vacuum stripping, in some mills by the Shirley cage. It can hardly be doubted that owing to these improvements the incidence of the disease has been reduced. But it has not as yet been stamped out.

The most dangerous fraction of cotton dust are the smaller particles—under 2 microns in diameter; they form a high proportion of the dust. It is hardly imaginable that even far more powerful fans and exhaust systems will succeed in removing this fraction. The greatest attention must therefore be given to preventing its inhalation.

The respirators at present in use do not fulfil their object. The gauze or fabric layer which is to retain the dust rapidly becomes clogged with it, the moisture of the breath playing a part in the process; consequently, air-hunger forces the operative to remove the mask at frequent intervals or induces him to give up its use completely. It has been shown in the present investigation that an efficient screening effect can be obtained by a layer, 1 inch thick, of closely packed wood shavings soaked in liquid paraffin. As the air is sucked through this layer, the dust particles impinge on the oily surface and adhere firmly to it. The resistance of the filter is

negligible at the start and does not change during prolonged use, as it acts not by filtering the air but by deflecting the dust particles from their path within a system of wide air-channels.

No moisture is absorbed by the oily surface. The only difficulty consists in fitting this material to a suitable mask. The patterns used at present are light and easily adapted, but they fail to give an air-tight fit where they touch the face and nose, as their edges are of fabric. Sir Robert Davis, Managing Director of Messrs. Siebe, Gorman and Co., Ltd., kindly provided a new type of light rubber mask which can be fitted with the oiled shavings. In laboratory tests it caused no discomfort even when worn for a considerable time. The operatives who have tried it object to any rubber masks because they are troubled by the perspiration retained in them. It is to be hoped that the researches carried out elsewhere will soon lead to a satisfactory solution of these difficulties.

SUMMARY

1. Cardroom dust is rich in particles under 2 microns in size and comparatively still richer in ultramicroscopic particles. Such particles can easily penetrate into the deeper air-passages.
2. The lipid fraction of the dust appears to be harmless to the lungs.
3. The alcoholic fraction contains appreciable amounts of a substance resembling histamine and possibly identical with it. Similar substances have been found in cotton seed, as well as in the dust of barley, esparto-grass, coir, and wool. Whether this principle plays a pronounced role in causing the respiratory disease of cotton operatives is doubtful.
4. The protein fraction has been shown by experiments on man and animals to be primarily toxic; it has a characteristic irritating effect upon the deeper tissues and produces definite inflammatory lesions. In all probability the substance or group of substances contained in the protein fraction is responsible for the changes occurring in the lung after prolonged inhalation of the dust.
5. Allergic super-sensitiveness to the protein has been demonstrated to a greater or lesser degree in all the diseased cotton operatives examined; it is rare in healthy cotton operatives, in patients suffering from spasmodic asthma, and in healthy persons unconnected with the cotton trade.
6. Physiological tests have shown definite impairment of respiratory function in a large proportion of cotton operatives suffering from the respiratory disease.
7. Treatment of the disease by desensitization does not appear to provide satisfactory chances of improvement. Physical exercises directed towards improving the patient's respiration should give some benefit. The greatest importance attaches to removal of the patient from the injurious conditions of his work, before severe secondary changes have developed in the lungs. To this end the recommendation of the Departmental Committee on Dust in Cardrooms dealing with medical examination should be carried into practice.
8. The leading principle in the consideration of this disease, as of all industrial maladies, must be *prevention*. The ideal requirement would be to keep the air of the mixing, blowing, and cardrooms free from dust. Much has been accomplished in this direction, and yet the disease has not been eradicated. This appears to be due to the fact that even a powerful and well-directed ventilation will fail to act upon the lightest and smallest particles of dust, and it is these which have the greatest power of penetrating into the deeper portions of the lung. So long as this technical problem remains unsolved, it will be necessary to provide adequate respirators and insist upon their constant use during the dusty part of the work.

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The following publications relating to the work of the Medical Research Council can be purchased directly from H.M. Stationery Office, at the following addresses : Adastral House, Kingsway, London, W.C.2 ; 120 George Street, Edinburgh 2 ; York Street, Manchester 1 ; 1 St. Andrew's Crescent, Cardiff ; 80 Chichester Street, Belfast ; or through any bookseller.*

In addition, numerous memoirs upon work aided by the Medical Research Council have appeared in Scientific Journals : particulars of these may be seen in the Annual Reports.

Out-of-print reports are not included in the following list.

ANNUAL REPORTS

Medical Research Committee, Nos. 1-5, 1914-15 to 1918-19.

Medical Research Council, 1919-20 and subsequently.

(Price of each report from 1920-1 to 1925-6, † 3s. 6d. (3s. 8d.) ; from 1926-7 to 1929-9, 3s. (3s. 2d.) ; 1929-30 and 1930-31, 2s. 6d. (2s. 8d.) ; 1931-32, 2s. (2s. 2d.) ; 1932-33, 2s. 6d. (2s. 9d.) ; 1933-34, 1934-35, 3s. each. (3s. 3d.)

SPECIAL REPORTS, &c.

Alcohol :

No. 56. The effects of Alcohol and some other Drugs during Normal and Fatigued Conditions. By W. McDougall and May Smith. [1920.] 1s. (1s. 1d.).

No. 168. Alcohol and Inheritance : An Experimental Study. By F. M. Durham and H. M. Woods. [1932.] 1s. 3d. (1s. 5d.).

(Book). Alcohol : its Action on the Human Organism. Second Edition [1924.] 1s. (1s. 2d.) paper covers, 1s. 6d. (1s. 8d.) cloth bound.

Anaerobic Bacteria : see WOUND INFECTIONS.

Animals, Diseases of :

No. 121. Borna Disease and Enzootic Encephalo-Myelitis of Sheep and Cattle. By S. Nicolau and I. A. Galloway. [1928.] 5s. (5s. 3d.).

See also TUBERCULOSIS (Nos. 94, 122, 184, and 189).

Bacteriology (MISCELLANEOUS) :

No. 35. The Reaction of Culture Media, by S. R. Douglas, J. W. H. Eyre, P. P. Laidlaw, and C. G. L. Wolf. Second Edition, revised by P. P. Laidlaw. [1927.] 6d. (7d.).

No. 51. The Laboratory Diagnosis of Acute Intestinal Infections, including the Principles and Practice of the Agglutination Tests. By the Committee upon Pathological Methods. [1920.] 4s. 6d. (4s. 8d.).

* For overseas agencies see p. xii. † 1923-4 out of print.

- No. 64. Catalogue of the National Collection of Type Cultures. Third Edition. [1931.] 2s. (2s. 1d.).
- No. 169. The Haemolytic Streptococci : Their Grouping by Agglutination. By F. W. Andrewes and Ethel M. Christie. [1932.] 1s. 3d. (1s. 5d.).
- No. 203. The Pathogenic Aerobic Organisms of the Actinomyces Group. By Dagny Erikson. [1935.] 1s. (1s. 2d.).
- No. 210. Bacterial Nutrition : Material for a Comparative Physiology of Bacteria. By B. C. J. G. Knight. [1936.] 3s. (3s. 4d.).
See also MILK (No. 206), SURGERY (No. 138) and IMMUNITY.
- A SYSTEM OF BACTERIOLOGY IN RELATION TO MEDICINE. (See last page.)
- Blood Physiology :**
- No. 72. The Acid-base Equilibrium of the Blood. By the Haemoglobin Committee. [1923.] 2s. (2s. 1d.).
- Blood Vessels, Diseases of :**
- No. 193. Dissecting Aneurysms. By T. Shennan. [1934.] 2s. 6d. (2s. 9d.).
See also SHOCK, SURGICAL.
- Borna Disease :** see ANIMALS, DISEASES OF.
- Brain Surgery :** see SURGERY.
- Bright's Disease :** see NEPHRITIS.
- Burns :**
- No. 141. The Tannic Acid Treatment of Burns. By W. C. Wilson. [1929.] 1s. (1s. 1d.).
- Cancer :**
- No. 99. An Investigation into the Statistics of Cancer in Different Trades and Professions. By Matthew Young and W. T. Russell. [1926.] 1s. 6d. (1s. 7d.).
See also RADIUM.
- Calgut :** see SURGERY (No. 138).
- Cerebro-spinal Fever :**
- No. 17. (I.) A Report upon the Seasonal Outbreak of Cerebro-spinal Fever in the Navy at Portsmouth, 1916-17. By Paul Fildes and S. L. Baker. (II.) The Treatment of Cerebro-spinal Meningitis by Antimeningococcus Serum at the Royal Naval Hospital, Haslar, 1915-16-17. By G. P. Adshear. [1918.] 2s. 6d. (2s. 9d.).
- No. 50. Cerebro-spinal Fever. Studies in the Bacteriology, Preventive Control, and Specific Treatment of Cerebro-spinal Fever among the Military Forces, 1915-19. By M. H. Gordon and others. [1920.] 4s. (4s. 3d.).
- No. 124. The Meningococcus. By E. G. D. Murray. [1929.] 3s. 6d. (3s. 9d.).
- Chemotherapy :** see STREPTOCOCCAL INFECTIONS.
- Child Life (ANTENATAL AND POSTNATAL INVESTIGATIONS) :**
- No. 74. The Relation between Home Conditions and the Intelligence of School Children. By L. Isserlis. [1923.] 1s. (1s. 1d.).
- No. 81. The Effect of Maternal Social Conditions and Nutrition upon Birth-weight and Birth-length. By M. Bruce Murray. [1924.] 1s. (1s. 1d.).
- No. 82. Maternal Syphilis as a cause of Death of the Foetus and of the New-born Child. By J. N. Cruickshank. [1924.] 1s. 6d. (1s. 8d.).
- No. 86. The Estimation of Foetal Age, the Weight and Length of Normal Foetuses, and the Weights of Foetal Organs. By J. N. Cruickshank, M. J. Miller, and F. J. Browne. [1924.] 2s. 6d. (2s. 8d.).
- No. 101. Poverty, Nutrition, and Growth : Studies of Child Life in Cities and Rural Districts of Scotland. By D. Noel Paton, Leonard Findlay, and others. [1928.] 10s. (10s. 5d.).

- No. 109. A Clinical and Pathological Study of 1,673 Cases of Dead-Births and Neo-natal Deaths. Compiled by E. L. Holland and J. E. Lane-Claypon. [1926.] 3s. 6d. (3s. 8d.).
- No. 114. Social Conditions and Acute Rheumatism. [1927.] 2s. 6d. (2s. 8d.).
- No. 117. The Toxaemias of Pregnancy : A Clinical and Biochemical Study. By J. N. Cruickshank, J. Hewitt, and K. L. Couper. [1927.] 4s. (4s. 2d.).
- No. 118. The Cause of Foetal Death in 144 Cases. By A. C. Palmer. [1928.] 3s. (3s. 2d.).
- No. 157. Nutritional Anaemia in Infancy : The Influence of Iron Deficiency on Infant Health. By H. M. M. Mackay, L. Goodfellow, and A. Bradford Hill. [1931.] 2s. (2s. 2d.).
- No. 162. Intelligence and Disease. By Shepherd Dawson assisted by J. C. M. Conn. [1931.] 1s. (1s. 2d.).
- No. 190. A Study of Growth and Development : Observations in Successive Years on the Same Children. By K. M. Fleming. With a Statistical Analysis by W. J. Martin. [1933.] 1s. 6d. (1s. 8d.).
- See also NUTRITION ; RICKETS.

Dental Disease :

- No. 70. The Structure of Teeth in relation to Dental Disease. By J. Howard Mummery. [1922.] 2s. (2s. 1d.).
- No. 97. The Incidence of Dental Disease in Children. By the Committee for the Investigation of Dental Disease. [1925.] 1s. 6d. (1s. 8d.).
- No. 140. Diet and the Teeth : An Experimental Study. Part I. Dental Structure in Dogs. By May Mellanby. [1929.] 17s. 6d. (18s.).
- No. 153. Diet and the Teeth : An Experimental Study. Part II. A.—Diet and Dental Disease. B.—Diet and Dental Structure in Mammals other than the Dog. By May Mellanby. [1930.] 2s. 6d. (2s. 9d.).
- No. 159. The Influence of Diet on Caries in Children's Teeth (Interim Report). By the Dental Committee. [1931.] 6d. (7d.).
- No. 171. Facial Growth in Children, with Special Reference to Dentition. Part I, by Corisande Smyth. Part II, by Matthew Young. [1932.] 1s. 6d. (1s. 8d.).
- No. 191. Diet and the Teeth : an Experimental Study. Part III. The Effect of Diet on Dental Structure and Disease in Man. By May Mellanby. [1934.] 5s. (5s. 4d.).
- No. 211. The Influence of Diet on Caries in Children's Teeth (Final Report). By the Committee for the Investigation of Dental Disease. [1936.] 2s.

Diphtheria :

- No. 115. The Prevention of Diphtheria. By J. Graham Forbes. [1927.] 2s. (2s. 2d.).
- (Book). Diphtheria : its Bacteriology, Pathology, and Immunology. By the Bacteriological Committee. [1923.] 12s. 6d. (13s.).
- See also EPIDEMIOLOGY (Nos. 75, 137 and 195).

Dust : see RESPIRATION, etc., (No. 212), VENTILATION, ETC.

Dysentery :

- Reports upon Investigations in the United Kingdom of Dysentery Cases received from the Eastern Mediterranean :—
- No. 6. III.—Report upon recovered Cases of Intestinal Disease in the Royal Naval Hospital, Haslar, 1915-16. By Paul Fildes and others.
- IV.—Report upon combined Clinical and Bacteriological Studies of Dysentery Cases from the Mediterranean. By S. R. Douglas and L. Colebrook. [1917.] 4s. 6d. (4s. 8d.).

No. 7. V.—Report upon 2,360 Enteritis “Convalescents” received at Liverpool from various Expeditionary Forces. By E. Glynn and others. [1918.] 6s. (6s. 2d.).

No. 15. A Study of 1,300 Convalescent Cases of Dysentery from Home Hospitals: with special reference to the Incidence and Treatment of Amoebic Dysentery Carriers. By Clifford Dobell, H. S. Gettings, Margaret W. Jepps, and J. B. Stephens. [1918.] 1s. 3d. (1s. 4d.).

No. 29. A Contribution to the Study of Chronicity in Dysentery Carriers. By W. Fletcher and Doris L. Mackinnon. [1919.] 9d. (10d.).

No. 30. An Investigation of the Flexner-Y Group of Dysentery Bacilli. By H. S. Gettings. [1919.] 1s. (1s. 1d.).

No. 40. Studies of Bacillary Dysentery occurring in the British Forces in Macedonia. By L. S. Dudgeon and others. [1919.] 3s. (3s. 2d.).

No. 42. A Study of the Serological Races of the Flexner Group of Dysentery Bacilli. By F. W. Andrewes and A. C. Inman. [1919.] 2s. (2s. 2d.).

See also FOOD POISONING.

Encephalitis:

No. 108. The Sheffield Outbreak of Epidemic Encephalitis in 1924. [1926.] 1s. 9d. (1s. 11d.).

Enteric Infections:

No. 9. A Report upon the Use of Atropine as a Diagnostic Agent in Typhoid Infections. By H. F. Marris. [1917.] 1s. (1s. 1d.).

No. 48. A Report on the probable Proportion of Enteric Infections among Undiagnosed Febrile Cases invalided from the Western Front since October, 1916. By W. W. C. Topley, S. G. Platts, and C. C. Imrie. [1920.] 3s. (3s. 2d.).

No. 179. Chronic Enteric Carriers and their Treatment. By C. H. Browning with others. [1933.] 1s. 6d. (1s. 8d.).

See also BACTERIOLOGY; FOOD POISONING.

Epidemiology:

No. 75. The Schick Test, Diphtheria and Scarlet Fever. By S. F. Dudley. [1923.] 1s. (1s. 2d.).

No. 111. The Spread of Droplet Infection in Semi-isolated Communities. By S. F. Dudley. [1926.] 1s. 6d. (1s. 8d.).

No. 120. An Inquiry into the Relationship between Housing Conditions and the Incidence and Fatality of Measles. By J. L. Halliday. [1928.] 1s. (1s. 1d.).

No. 137. Scarlet Fever, Diphtheria, and Enteric Fever, 1895-1914: A Clinical-Statistical Study. By E. W. Goodall, M. Greenwood, and W. T. Russell. [1929.] 2s. (2s. 2d.).

No. 180. Epidemiological Study of Scarlet Fever in England and Wales since 1900. By Hilda M. Woods. [1933.] 1s. 3d. (1s. 5d.).

No. 192. Housing Conditions and Respiratory Disease. Morbidity in a Poor-class Quarter and in a Rehousing Area in Glasgow. By C. M. Smith. [1934.] 9d. (10d.).

No. 195. Active Immunization against Diphtheria: its effect on the Distribution of Antitoxic Immunity and Case and Carrier Infection. By S. F. Dudley, P. M. May, and J. A. O'Flynn. [1934.] 3s. (3s. 3d.).

No. 209. Experimental Epidemiology. By M. Greenwood, W. W. C. Topley, and J. Wilson. [1936.] 3s. 6d. (3s. 10d.).

See also SMALL-POX; TUBERCULOSIS; ETC.

Flying, Medical Problems of:

Reports of the Air Medical Investigation Committee:—

No. 28. The Sense of Balance and Stability in the Air. By Henry Head. [1919.] 9d. (10d.). (Included in No. 53.)

No. 37. The Effects of Diminished Tension of Oxygen, with especial reference to the Activity of the Adrenal Glands. By C. H. Kellaway. The Ear in relation to certain Disabilities in Flying. By S. Scott. [1919.] 1s. (1s. 1d.).

No. 53. The Medical Problems of Flying (including reports on oxygen want, selection of candidates for flying, sense of balance, and flying strain). [1920.] 6s. (6s. 4d.).

No. 84. The Application of the Air Force Physical Efficiency Tests to Men and Women. By L. D. Cripps. [1924.] 1s. 6d. (1s. 8d.).

Food Poisoning :

No. 24. A Report on the Investigation of an Epidemic caused by *Bacillus aertrycke*. By H. Marrian Perry and H. L. Tidy. [1919.] 9d. (10d.).

No. 91. An Investigation of the Salmonella Group, with Special Reference to Food Poisoning. By W. G. Savage and P. Bruce White. [1925.] 3s. 6d. (3s. 8d.).

No. 92. Food Poisoning : a Study of 100 Recent Outbreaks. By W. G. Savage and P. Bruce White. [1925.] 2s. 6d. (2s. 8d.).

No. 103. Further Studies of the Salmonella Group. By P. Bruce White. [1926.] 5s. (5s. 3d.).

Goitre :

No. 154. Iodine Supply and the Incidence of Endemic Goitre. By J. B. Orr. [1931.] 4d. (5d.). See also NUTRITION (No. 201).

Haemoglobin : see BLOOD.

Hearing :

Reports of the Committee upon the Physiology of Hearing.

No. 166. I.—The Localization of Sounds in the Median Plane. By J. H. Shaxby and F. H. Gage. II.—Some Factors in Auditory Localization. By H. E. O. James and Marion E. Massey. [1932.] 1s. (1s. 2d.).

No. 207. III.—The Localization of Sound. By H. E. O. James. [1935.] 9d. (10d.).

Heart :

No. 8. Report upon Soldiers returned as Cases of "Disordered Action of the Heart" (D.A.H.), or Valvular Disease of the Heart. By Sir Thomas Lewis. [1917.] 1s. (1s. 1d.).

No. 147. The Electrocardiogram. By W. H. Craib. [1930.] 1s. 3d. (1s. 5d.).

No. 208. The Course of the Oesophagus in Health, and in Disease of the Heart and Great Vessels. By William Evans. [1936.] 2s. 6d. (2s. 9d.).

Heredity : see IMMUNITY (No. 106).

Immunity :

No. 194. The Chemistry of Antigens and Antibodies. By J. R. Marrack. [1934.] 2s. 6d. (2s. 8d.).

No. 196. The Inheritance of Resistance to Infection in Animal Species. A Review of the Published Experimental Data. By A. Bradford Hill. [1934.] 1s. 3d. (1s. 5d.).

See also EPIDEMIOLOGY.

Industrial Health :

The Annual Reports of the Industrial Health (formerly Fatigue) Research Board, and special reports on particular subjects, are published for the Council in separate series. The subjects dealt with include accident causation, rest pauses, spells of work, movement study, vocational selection, and problems of particular industries. A list can be supplied on application to the Secretary of the Board, 38, Old Queen Street, Westminster, S.W.1.

Influenza :

- No. 36. Studies of Influenza in Hospitals of the British Armies in France, 1918. [1919.] 3s. 6d. (3s. 8d.).
 No. 63. Studies in the Aetiology of Epidemic Influenza. By J. McIntosh. [1922.] 2s. 6d. (2s. 7d.).

Jaundice :

- No. 113. Spirochaetal Jaundice. By G. Buchanan. [1927.] 4s. (4s. 2d.).

Malaria : *see* QUININE.**Maternal Mortality :** *see* CHILD LIFE and STREPTOCOCCAL INFECTIONS.**Measles :** *see* EPIDEMIOLOGY (No. 120).**Milk :** *see* TUBERCULOSIS, (No. 189).**Miners' Dietsaries :** *see* NUTRITION.**Miners' Diseases, etc. :**

- No. 89. Report on Miners' "Beat Knee," "Beat Hand," and "Beat Elbow." By E. L. Collis and T. L. Llewellyn. [1924.] 1s. 6d. (1s. 7d.).
See also JAUNDICE (No. 113).

Miners' Nystagmus : *see* VISION.**Nephritis :**

- No. 43. Albuminuria and War Nephritis among British Troops in France. By H. MacLean. [1919.] 2s. 6d. (2s. 8d.).
 No. 142. A Classification of Bright's Disease. By Dorothy S. Russell. [1929.] 8s. 6d. (8s. 10d.).
 No. 178. A Study of Nephritis and Allied Lesions. By J. Gray. [1933.] 2s. 6d. (2s. 9d.).

Nerve Injuries :

- Reports of the Committee upon Injuries of the Nervous System :—
 No. 54. The Diagnosis and Treatment of Peripheral Nerve Injuries. [1920.] 2s. (2s. 2d.).
 No. 88. Injuries of the Spinal Cord and Cauda Equina. [1924.] 1s. 6d. (1s. 8d.).

Nutrition :

- No. 87. Report on the Nutrition of Miners and their Families. By the Committee upon Quantitative Problems in Human Nutrition. [1924.] 1s. 3d. (1s. 4d.).
 No. 105. Diets for Boys during the School Age. By H. C. Corry Mann. [1926.] 2s. 6d. (2s. 8d.).
 No. 146. The Antiscorvy Vitamin in Apples. By Mary F. Bracewell, E. Hoyle, and S. S. Zilva. [1930.] 9d. (10d.).
 No. 155. Studies of Nutrition : The Physique and Health of Two African Tribes. By J. B. Orr and J. L. Gilks. [1931.] 2s. (2s. 2d.).
 No. 168. The Quantitative Estimation of Vitamin D by Radiography. By R. B. Bourdillon, H. M. Bruce, C. Fischmann, and T. A. Webster. [1931.] 1s. (1s. 2d.).
 No. 165. Studies in Nutrition. An Inquiry into the Diet of Families in Cardiff and Reading. By E. P. Cathcart and A. M. T. Murray, assisted by M. Shanks. [1932.] 6d. (7d.).
 No. 167. Vitamins : A Survey of Present Knowledge. By a Committee appointed jointly by the Lister Institute and Medical Research Council. [1932.] 6s. 6d. (7s.).

- No. 175. Vitamin Content of Australian, New Zealand, and English Butters. By M. E. F. Crawford, E. O. V. Perry, and S. S. Zilva. [1932.] 1s. (1s. 1d.).
- No. 187. The Chemistry of Flesh Foods and their Losses on Cooking. By R. A. McCance and H. L. Shipp. [1933.] 2s. 6d. (2s. 9d.).
- No. 201. The Determination of Iodine in Biological Substances. By C. O. Harvey. [1935.] 1s. (1s. 2d.).
- No. 213. The Nutritive Value of Fruits, Vegetables and Nuts. By R. A. McCance, E. M. Widdowson and L. R. B. Shackleton. [1936.]
See also CHILD LIFE; RICKETS; DENTAL DISEASE; STANDARDS (No. 202); BACTERIOLOGY (No. 210).
- Pituitary Extract:** see STANDARDS.
- Pneumonia:**
- No. 79. Bacteriological and Clinical Observations on Pneumonia and Empyemata, with special reference to the Pneumococcus and to Serum Treatment. By E. E. Glynn and Lettice Digby. [1923.] 5s. (5s. 3d.).
- Pneumothorax, Artificial:** see TUBERCULOSIS.
- Print, Legibility of:** see VISION.
- Protozoan Infections:**
- No. 59. A Report on the Occurrence of Intestinal Protozoa in the inhabitants of Britain. By Clifford Dobell. [1921.] 2s. (2s. 2d.).
- Psychology:**
- No. 170. Studies in the Psychology of Delinquency. By G. W. Pailthorpe. [1932.] 2s. (2s. 2d.).
- Quinine:**
- No. 96. Clinical Comparisons of Quinine and Quinidine. By the Committee upon Cinchona Derivatives and Malaria. [1925.] 1s. (1s. 1d.).
- Radium:**
- No. 62. Medical Uses of Radium: Studies of the Effects of Gamma Rays from a large Quantity of Radium. By various authors. [1922.] 5s. (5s. 3d.).
- No. 90. Medical Uses of Radium: Summary of Reports from Research Centres for 1923. [1924.] 1s. (1s. 1d.).
- No. 102. Ditto for 1924. [1926.] 1s. 6d. (1s. 7d.).
- No. 112. Ditto for 1925. [1926.] 1s. 3d. (1s. 4d.).
- No. 116. Ditto for 1926. [1927.] 1s. (1s. 2d.).
- No. 126. Ditto for 1927. [1928.] 1s. (1s. 2d.).
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- No. 160. Ditto for 1930. [1931.] 1s. (1s. 1d.).
- No. 174. Ditto for 1931. [1932.] 1s. 3d. (1s. 5d.).
- No. 186. Ditto for 1932. [1933.] 1s. (1s. 1d.).
- No. 197. Ditto for 1933. [1934.] 9d. (10d.).
- No. 204. Ditto for 1934. [1935.] 1s. (1s. 2d.).
- Respiration and Respiratory Diseases:**
- No. 198. Test for Respiratory Efficiency. By A. Moncrieff. [1934.] 1s. (1s. 2d.).
- No. 212. Investigations on Respiratory Dust Disease in Operatives in the Cotton Industry. By C. Prausnitz. [1936.]
- Rheumatism:** see CHILD LIFE (No. 114).
- Rickets:**
- No. 61. Experimental Rickets. By E. Mellanby. [1921.] 4s. (4s. 2d.).
- No. 68. Rickets: the Relative Importance of Environment and Diet as Factors in Causation. By H. Corry Mann. [1922.] 2s. 6d. (2s. 8d.).
- No. 71. The Aetiology and Pathology of Rickets from an experimental point of view. By V. Korenchevsky. [1922.] 4s. (4s. 3d.).
- No. 77. Studies of Rickets in Vienna, 1919-22. [1923.] 7s. 6d. (7s. 11d.).
- No. 93. Experimental Rickets: The Effect of Cereals and their Interaction with other factors of Diet and Environment in producing Rickets. By E. Mellanby. [1925.] 3s. 6d. (3s. 8d.).

Salvarsan : *see* VENEREAL DISEASES; STREPTOCOCCAL INFECTIONS; STANDARDS, BIOLOGICAL (No. 128).

Scarlet Fever : *see* EPIDEMIOLOGY (Nos. 137, 180).

Scurvy : *see* NUTRITION (No. 146).

Shock, Surgical :

Reports of the Committee on Surgical Shock and Allied Conditions:—

No. 25. Wound-Shock and Haemorrhage. [1919.] 4s. (4s. 5d.).

No. 26. Traumatic Toxaemia as a Factor in Shock. [1919.] 1s. (1s. 1d.).

No. 27. Blood Volume Changes in Wound-Shock and Primary Haemorrhage. By N. M. Keith. [1919.] 9d. (10d.).

Small-pox :

No. 98. Studies of the Viruses of Vaccinia and Variola. By M. H. Gordon. [1925.] 3s. 6d. (3s. 9d.).

No. 106. Small-pox and Climate in India. Forecasting of Epidemics. By Sir Leonard Rogers. [1926.] 2s. (2s. 2d.).

No. 143. Diagnostic Value of the "Vaccinia Variola" Flocculation Test. By W. L. Burgess, James Craigie, and W. J. Tulloch. [1929.] 1s. 3d. (1s. 4d.).

No. 156. Further Investigations on the Variola-Vaccinia Flocculation Reaction. By James Craigie and W. J. Tulloch. [1931.] 3s. (3s. 3d.).

Spectroscopy :

No. 177. Apparatus for the Rapid Study of Ultra-Violet Absorption Spectra. By J. St. L. Philpot and E. H. J. Schuster. [1933.] 1s. 3d. (1s. 5d.).

Spinal Deformities : *see* SURGERY (No. 161).

Standards, Biological :

No. 69. I.—Pituitary Extracts. By J. H. Burn and H. H. Dale. [1922.] 1s. 6d. (1s. 7d.).

No. 128. II.—Toxicity Tests for Novarsenobenzene (Neosalvarsan). By F. M. Durham, J. H. Gaddum, and J. E. Marchal. [1929.] 1s. 9d. (1s. 10d.).

No. 183. III.—Methods of Biological Assay depending on a Quantal Response. By J. H. Gaddum. [1933.] 1s. (1s. 1d.).

No. 202. IV.—The Standardisation and Estimation of Vitamin A. Edited by E. M. Hume and H. Chick. [1935.] 1s. (1s. 2d.).

See also VENEREAL DISEASES (No. 44) and NUTRITION (No. 158).

Statistics (MISCELLANEOUS).

No. 16. A Report on the Causes of Wastage of Labour in Munition Factories. By Major Greenwood. [1918.] 1s. 6d. (1s. 7d.).

No. 60. The Use of Death-rates as a Measure of Hygienic Conditions. By John Brownlee. [1922.] 3s. (3s. 2d.).

No. 95. Internal Migration and its Effects upon the Death-rates: with Special Reference to the County of Essex. By A. B. Hill. [1925.] 3s. 6d. (3s. 8d.).

Streptococcal Infections :

No. 119. A Study of some Organic Arsenical Compounds with a view to their use in certain Streptococcal Infections. By L. Colebrook. [1928.] 1s. 3d. (1s. 4d.).

No. 205. The Source of Infection in Puerperal Fever due to Haemolytic Streptococci. By Dora C. Colebrook. [1935.] 1s. 6d. (1s. 9d.).

Surgery :

- No. 138. The Preparation of Catgut for Surgical Use. By W. Bulloch, L. H. Lampitt, and J. H. Bushill. [1929.] 4s. (4s. 3d.).
- No. 161. The Intervertebral Discs. Observations on their Normal and Morbid Anatomy in relation to certain Spinal Deformities. By O. A. Beadle. [1931.] 2s. (2s. 2d.).
- See also* BURNS ; SHOCK, SURGICAL.

T.N.T. Poisoning :

- No. 11. The Causation and Prevention of Tri-nitro-toluene (T.N.T.) Poisoning. By Benjamin Moore. [1917.] 1s. (1s. 2d.).
- No. 58. T.N.T. Poisoning and the Fate of T.N.T. in the Animal Body. By W. J. O'Donovan and others. [1921.] 3s. (3s. 2d.).

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