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THE MORISON LECTURES FOR 1906

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Lecture I.

Delivered on 24th January 1906.

I have been led to select the pathology of general paralysis of the insane as the subject of these lectures, chiefly owing to the fact that its elucidation has formed the principal object of research in the Laboratory of the Scottish Asylums during the last three or four years. There are, however, other reasons for which it is fitting that I should on this occasion direct attention to some of the problems connected with this special form of insanity. General paralysis of the insane, dementia paralytica, or progressive paralysis, is a very common and important disease. It appears to be increasing; it is certainly one of the most terrible maladies that can afflict a human being; it is fatal, with rare exceptions, within a few years; and its etiology and pathogenesis, notwithstanding many positive and dogmatic assertions regarding them, have hitherto been a profound mystery.

In 1904, 1795 persons succumbed to this disease in the asylums of England and Scotland. In the same year, 49 out of

a total of 262 admissions to the Royal Edinburgh Asylum, or 10·7 per cent., were cases of this disease. In some English asylums the proportion is even higher. Thus at the Durham County Asylum it reaches to about 16 per cent. On the continent of Europe the disease is even more prevalent than in our own country. For example, at the asylum of Naples, about 30 per cent. of the patients admitted are general paralytics.

The disease has lately been increasing both in this country and abroad. For example, the annual mortality from general paralysis in the Royal Edinburgh Asylum has risen from 25·5 per cent. of the total deaths in the five years 1890-1894, to 31 per cent. in the five years 1901-1905. The total number of deaths from general paralysis in the English and Scottish asylums has risen from 1321 in 1894 to 1795 in 1904.

To show the gravity of the disease, it is sufficient to mention its leading features. These have been summed up by Dr Clouston[1] in a concise clinical definition, as follows:—"An organic disease of the cortical part of the brain, characterised by progression, by the combined presence of mental and motor symptoms, the former always including mental enfeeblement and mental facility and often delusions of grandeur and ideas of morbid expansion or self-satisfaction; the motor deficiencies always including a peculiar defective articulation of words, and always passing through the stages of fibrillar convulsion, incoordination, paresis, and paralysis; the diseased process spreading to the whole of the nerve tissues in the body; being as yet incurable, and fatal in a few years."

It may be added that general paralysis is a disease of the rich and the great as well as of the poor. It is by no means confined to the lower social strata. A few years ago a great statesman fell a victim to it, and to-day is the anniversary of his death. Unlike tuberculosis, cancer and many other maladies, it is a disease about which the public understands almost nothing. By them it is merged with other forms of insanity, which, even in this intellectual age, they still look upon as a mysterious and fatal visitation of a nature entirely different from that of disease as they comprehend it. Nevertheless, it may be said that if general paralysis, and the closely allied disease tabes dorsalis, had been unknown, and were then suddenly to make their appear-

[1] *Clinical Lectures on Mental Diseases*, 1904.

ance and to assume the proportions they now attain in this and many other countries, the occurrence would certainly be universally regarded as one of the most appalling calamities that had ever visited the human race.

Now, the subject of the pathology of general paralysis is far too large to be dealt with exhaustively in three lectures, and I shall not attempt so impossible a task. The time I have at my disposal I shall devote mainly to giving an account of the researches recently carried out by my colleagues and myself. I shall refer to controversial questions merely in so far as it is necessary to do so in order to make clear the new position reached as the result of our investigations.

Before proceeding to give an account of these researches, I must briefly indicate the present position of authoritative opinion regarding the pathology of general paralysis. The question chiefly discussed in recent years has been that of the relation of the disease to syphilis. Professor Bianchi [1] has well remarked that three periods may be recognised in the progress of this discussion. In the first period it was maintained that general paralysis is simply a manifestation of syphilis. It was, however, soon found that antisyphilitic remedies have no beneficial effect, and consequently the second period was reached in which it was maintained that the disease is determined, not by the direct action of the syphilitic toxines, but by a secondary auto-intoxication which may follow this action. This was the parasyphilitic or metasyphilitic period. The third period is the present, in which there has arisen a feeling of scepticism as to the parasyphilitic toxines, the existence of which has never been demonstrated, and which are indeed entirely hypothetical. There are still many who hold that the disease is essentially syphilitic in its origin, but probably most writers on the subject now dissent from this view, and maintain that there are other no less potent factors, such as alcoholism, the excessive use of nitrogenous foods, heredity, etc. "Parasyphilis in the genesis of progressive paralysis," says Professor Bianchi, "is a neologism that harmonises with no proven and demonstrable fact. It is, indeed, the product of a premature induction."

There is similar difference of opinion as to the exact nature of the pathological processes initiated by these supposed etiological

[1] *Annali di Nevrologia*, 1902.

factors. Some writers maintain that there is what they term "a premature involution" of the cortical neurons, and that all the other changes are secondary. Others hold that the cerebral vascular lesions are the first to occur, and that the destructive alterations in the nervous tissues follow as a consequence. It is now becoming more and more generally recognised that the cerebral lesions are dependent upon some form of toxæmia.

The pathological anatomy of the disease, as far as it concerns the nervous system, has been minutely studied by hundreds of investigators. The outstanding facts already ascertained are briefly as follows. The cortical nerve cells show acute and chronic degenerative changes, which, like the other cerebral lesions, affect the anterior portion of the brain more severely than the posterior. The medullated nerve fibres of the brain also show more or less extensive degeneration. The tangential fibres are, as a rule, specially involved, though certainly not in all cases. The neuroglia undergoes hypertrophy and proliferation, leading to a condition of cerebral sclerosis. This morbid process, occurring in localised areas in the walls of the ventricles, gives rise to the well-known granulations of the ependyma. The vessels of the brain constantly show chronic or acute irritative changes in their walls, marked by increase of fibrous tissue and proliferation of cellular elements. Special attention has in recent years been directed to the presence of plasma cells in this situation. These are angular cells having a granular protoplasm which stains deeply with methylene blue, but which generally presents a distinct, comparatively clear area. Their presence is said to be almost pathognomonic of general paralysis. The pia-arachnoid is always more or less thickened by inflammatory changes. The spinal cord commonly shows some degenerated fibres, especially in the crossed pyramidal tracts and in the posterior columns. Not infrequently there are well marked tabetic lesions. The cranial and peripheral nerves are often involved in the morbid process. Much attention has lately been directed to the presence of lymphocytes in the cerebro-spinal fluid withdrawn by means of lumbar puncture. Normally this fluid contains very few cell-elements. When the existence of other inflammatory conditions can be excluded, a distinct increase in the number of lymphocytes, or lymphocytosis, is regarded as an important sign of either general paralysis or tabes dorsalis.

I come now to the researches carried out in the Laboratory of the Scottish Asylums and at the Royal Edinburgh Asylum. I shall take them in chronological order, and endeavour to lead you step by step along the road that has been traversed. Before the end is reached, I hope to have laid before you such evidence as will satisfy you that the commonly accepted hypotheses regarding the pathology of general paralysis are erroneous, that, notwithstanding the enormous amount of labour that has already been expended in investigating the disease, the great essential fact in its pathology has hitherto been missed, and that general paralysis is an infective disease, as specific in its causation as tuberculosis, typhoid fever, or diphtheria.

For several years I studied the brains of general paralytics in the orthodox way, and succeeded only in repeating the observations of others. In course of time it became apparent to me that in studying the cerebral changes I was only examining the effects of a toxic action, and that the toxines must have their origin somewhere outside the brain. Further, I was convinced, then as now, that the syphilitic hypothesis does not account for the known facts regarding the disease. I therefore endeavoured to find evidence of the occurrence of a general toxæmia, and to localise the seat of origin of the toxines. About the same time Dr Lewis C. Bruce made independent clinical investigations, having a similar aim. He studied especially the temperature changes, the condition of the blood, the gastro-intestinal disorders, and certain reactions of the blood serum. In a paper [1] published in 1901, he recorded the results of continuous observations made upon the temperature and leucocytes in individual cases. He endorsed Dr Macpherson's opinion that the most characteristic temperature in general paralysis is a recurrent febrile attack every one or two weeks. He also ascertained that leucocytosis and hyper-leucocytosis accompany the rises of temperature, and that in the third stage leucocytosis commonly occurs from time to time without any elevation of temperature. He inferred from these observations that each febrile attack represents the resistive reaction of the body to some toxic substance, and each inter-febrile period an intermission when the resistive powers of the patient have subdued the action of the toxine. He concluded that general paralysis is a disease directly due to poisoning by

[1] *Brit. Med. Journ.*, June 29, 1901.

the toxines of bacteria, whose point of attack is through the gastric and intestinal mucous membrane. There was evidence that the *bacillus coli* is one at least of the organisms concerned in the production of this toxæmia. In a paper[1] published at the same time as that of Dr Bruce, I maintained similar views on the ground of the results of an examination of the pathological changes occurring in the alimentary tract in a series of cases. I found that there was constantly a severe degree of chronic atrophic catarrh affecting the stomach or small intestine, or both, and that the morbid changes appeared to be associated with excessive development of bacteria in the alimentary tract.

Further evidence of the existence of a chronic toxæmia was found in the occurrence of chronic endarteritis in the extra-cerebral vessels. Dr A. Ainslie examined numerous arteries from various parts of the body and found that the condition was constant, though irregular in distribution, and that it was often extremely well marked. About this time another worker in the Laboratory of the Scottish Asylums, Dr Chalmers Watson,[2] advanced very similar views regarding the pathogenesis of tabes, arguing that all we can logically conclude from the fact that a syphilitic history can be traced in a large number of tabetic subjects is that syphilis alters the physiological conditions in such a way as to favour the attack and operation of the actual cause of tabes and allied conditions.

In 1902, Dr Douglas M'Rae, Dr John Jeffrey and I commenced a bacteriological investigation of cases of general paralysis with a view to ascertaining if any facts could be elicited that would throw light upon the nature of the supposed bacterial toxæmia. It may be noted here that five Italian observers had previously made bacteriological investigations in cases of this disease. The blood, the urine, and the cerebro-spinal fluid were examined by one or more of these observers, various micro-organisms being found, but I think it may be said with fairness that no very noteworthy addition to our knowledge of the pathogenesis of general paralysis has resulted from their researches. Dr M'Rae, Dr Jeffrey and I made post-mortem cultures from the inflamed gastro-intestinal tract, the bronchi, lungs, brain, etc. Among the numerous organisms obtained there was one which, from the constancy of its presence in the alimentary or respiratory tract,

[1] *Brit. Med. Journ.*, June 29, 1901. [2] *Brit. Med. Journ.*, June 1, 1901.

by its occasional occurrence in the brain and in view of the ascertained pathogenic characters of the group to which it appeared to belong, there seemed reason to believe might have special importance. This was an organism resembling the Klebs-Löffler bacillus. Cultures of a bacillus of this nature were obtained from seventeen cases out of twenty examined. In the remaining three a similar organism was afterwards found in sections of the alimentary tract. Cultures were obtained from the brain in four out of seventeen cases. On the grounds of our observations, we advanced the hypothesis that general paralysis is the result of a chronic toxic infection from the respiratory and alimentary tracts, permitted by general and local impairment of the defences against bacteria, and dependent upon the excessive development of various bacterial forms, but especially upon the abundant growth of a Klebs-Löffler bacillus of modified virulence, which gives the disease its special paralytic character.[1] In our later investigations, Dr M'Rae and I have simply been putting this hypothesis to the test, and every step forward has been attended with the elucidation of some fresh fact that has rendered it more probable.

I followed up these bacteriological researches by a histological investigation of the supposed infective foci. In a series of twenty cases of general paralysis I was able to recognise in the catarrhal exudations in the respiratory and alimentary tracts a bacillus identical in form and staining reactions with the organism isolated by cultural methods. In several of the cases it was present in very large numbers. In the course of these histological investigations, a filamentous organism having special characters was observed in five cases, either in the walls of the bronchi or alimentary tract, or of both. I stated that there were some grounds for supposing that this organism is a thread form of the diphtheroid bacillus and that its presence in great numbers in the lymphatics of the respiratory or alimentary tract represents a terminal invasion by this bacillus.[2]

Dr Shennan and I have made two series of experimental observations with a view to ascertaining if these diphtheroid bacilli are capable of producing in lower animals changes in any way resembling those that occur in general paralysis. We used

[1] *Review of Neurology and Psychiatry*, May 1903.
[2] *Review of Neurology and Psychiatry*, July 1903.

chiefly a bacillus isolated from the bronchus of a case in which in this situation there was found to be a very abundant invasion by the filamentous form of the organism. We have made two series of experiments, but an account[1] has as yet been published only of the first series, and I shall confine myself to it.

It was ascertained that the organism was non-pathogenic to guinea-pigs. Intra-pleural injection in a white rat resulted in death of the animal in five days. Microscopical examination of the tissues showed that the organism had multiplied at the seat of injection and had spread to the adjacent pulmonary tissues and also to the pericardium. The invading organism was beginning to assume a thread form. Three rats were fed for several weeks upon bread mixed with unsterilised broth cultures of the bacillus. After three or four weeks they began to show morbid symptoms, which gradually increased in severity until the animals became acutely ill. At first they showed especially slowness and uncertainty of gait and drowsiness. Later they manifested distinct motor weakness, marked inco-ordination of movement, dyspnœa and great drowsiness. One rat was killed with chloroform when it appeared to be moribund. In the other two the disease was allowed to go on to a fatal termination, which occurred about two months from the time of the commencement of the feeding with cultures. Control animals remained healthy. Microscopical examination of the tissues revealed in each animal a similar series of morbid changes. There was well marked catarrh of the alimentary tract in all three, and a similar condition of the bronchi in two, accompanied by some catarrhal pneumonia. The diphtheroid bacillus was found in the catarrhal exudations, but its detection presented the same difficulties as in cases of general paralysis. A large proportion of the nerve cells of the cerebral cortex and spinal cord were markedly degenerated. The neuroglia, especially in the first layer of the cortex, showed slight but distinct proliferative changes. There was distinct increase of the cell-elements in the walls of the cortical vessels, and also proliferation of the mesoglia cells and of the cells of the pia-arachnoid.

In the two rats in the case of which the illness was allowed to go on to a fatal termination, there was extensive invasion by the filamentous organism already referred to. In one animal the

[1] *Review of Neurology and Psychiatry*, April 1903.

threads were found in the lymphatics of the stomach, duodenum, and ileum, as well as in the liver and in the walls of the bronchi. In the last named situation this invasion exactly reproduced the histological picture to be observed in the case of general paralysis from which the bacillus was isolated. In the other rat this filamentous organism was found in the walls of the stomach, duodenum, and ileum, and also in the capsule of the spleen and in a lymphatic gland. Beyond question these animals present evidence of the occurrence of many of the morbid processes that can be recognised in the nervous system of the general paralytic, but they survived too short a time to make it possible for the complete histological picture to be developed.

At this stage of the investigation, I summarised the case for the diphtheroid hypothesis of the etiology of general paralysis in opening a discussion on the pathology of the disease at the annual meeting of the British Medical Association, held at Swansea in 1903.[1]

An interesting experimental observation has also been made by Dr Lewis C. Bruce. He used cultures derived from the bacillus that was employed by Dr Shennan and myself in our experiments upon the rats. From time to time in the course of several months Dr Bruce injected a goat subcutaneously with these cultures for the purpose of obtaining an immune serum for therapeutic use. After a time the animal developed signs of alimentary disturbances. It had been known to lick the spots at which the injections were made, and probably in this way its alimentary tract became infected with the bacillus. The animal became tottering in its gait, and about six months from the time when the last subcutaneous injection had been made, it had a seizure closely resembling the congestive attack of a general paralytic. It rallied to some extent, but died a few days later. A culture was made from the œsophagus after death, and a growth of a diphtheroid bacillus was readily obtained. Dr Bruce kindly sent me the brain and some of the other organs for examination. The brain shows proliferative changes in the vessel walls, proliferation of the neuroglia and degeneration of the nerve cells, but each of these morbid alterations is slight in degree. Nevertheless, among the proliferating cell-elements in the vessel walls, several distinct plasma cells have been detected.

[1] *Brit. Med. Journ.*, October 24, 1903.

I think it is certain that in this case the part of the nervous system chiefly affected was the spinal cord, which unfortunately was not obtained. The condition of the brain indeed corresponds exactly to that of a case of tabes dorsalis in which mental symptoms have been absent or only very slight.

In May of last year, Dr M'Rae and I reported the results of an investigation in which it was sought to ascertain if diphtheroid bacilli are commonly present in the genito-urinary tract in cases of general paralysis. We have since extended these observations. We have ascertained that female general paralytics constantly suffer from chronic leucorrhœa, and that the discharge always contains abundant diphtheroid bacilli. In three instances the first cultures made from the discharge have yielded a diphtheroid bacillus alone. Diphtheroid bacilli are also constantly present in the urethra of the male general paralytic. Similar organisms have also been found, but generally only in comparatively small numbers, in the same situations in a considerable proportion of cases in which there was no ground for suspecting that the patient was suffering from general paralysis. In seven consecutive cases of general paralysis combined with tabes, we have found the urine to be loaded with diphtheroid bacilli. We have now obtained a culture of a diphtheroid bacillus from the brain in nine cases of general paralysis out of twenty-three from which cultures have been made from this organ. We have also examined the cerebro-spinal fluid removed by lumbar puncture from five cases of general paralysis. In the centrifuge deposit, in addition to lymphocytes, there was always a considerable amount of granular débris, and among this débris, or within the lymphocytes, we have observed in three cases bacilli, which have very little affinity for staining reagents, but which, nevertheless, can not infrequently be recognised to have the morphological characters of diphtheroid bacilli. We have also examined blood films, staining them by methods suitable for the detection of diphtheroid bacilli. We have obtained the blood by a method, already described, which reduces to a minimum the risk of contamination from the skin of the patient. In a preparation from one paralytic, presenting the signs of a slight congestive attack, we have observed a small group of typical diphtheroid bacilli, with distinct metachromatic granules.

Lastly, we have searched for evidence of the presence of

diphtheroid bacilli in the walls of the inflamed cerebral vessels, using chiefly various modifications of Neisser's method. No definite results were obtained until last summer, when examining sections of a portion of the brain subjacent to a purulent area in the pia-arachnoid, from which we had obtained a pure culture of a diphtheroid bacillus. Here we found, in a preparation stained by Neisser's method, a small group of faintly coloured, but still quite definitely recognisable diphtheroid bacilli lying in the walls of an inflamed vessel.

The occasional presence of diphtheroid bacilli, generally incapable of taking the stain in the ordinary way, in films of the centrifuge deposit from the cerebro-spinal fluid, in blood films and in sections of the brain, raised the question whether these bacilli were not from time to time gaining access to the blood circulation, and being rapidly destroyed by phagocytic and lysogenic actions. Dr M'Rae and I therefore resolved to study experimentally the action of the phagocytes and blood serum upon diphtheroid bacilli isolated from cases of general paralysis. The flood of light that has been thrown upon the problem of the pathogenesis of general paralysis and of tabes dorsalis by putting this hypothesis to the test, I hope to show in the next lecture.

Lecture II.

Delivered on 26th January 1906.

To-day I wish to deal chiefly with the results of an experimental enquiry into the action of the living blood and of the blood-serum upon pure cultures of diphtheroid bacilli isolated from cases of general paralysis. As explained at the end of the previous lecture, Dr M'Rae and I were led to take up this study because we had reason to suspect that certain indistinct granular or rod-like bodies observed in the cerebro-spinal fluid, in the walls of the cerebral vessels, in the blood and in the urine, were really diphtheroid bacilli that had suffered from the effects of a lysogenic or solvent action. We have also, however, had in view the possibility of being able to discover some specific reaction on the part of the blood or blood-serum of the general paralytic towards the diphtheroid bacillus, for, if such a specific reaction were found, it would not only serve to establish our hypothesis regarding the etiology of general paralysis, but it

would at the same time probably furnish a method of serum diagnosis.

Before entering upon this subject I must clear the way by describing the morphological and biological characters of the bacillus with which we have worked. When, in our published communications, my colleagues and I have spoken of a diphtheroid bacillus, we have simply meant a bacillus that has the general cultural and morphological features and the staining reaction to Neisser's method which characterise the Klebs-Löffler bacillus. The organism that is so abundant in cases of general paralysis is certainly neither Hoffmann's bacillus, nor the xerosis bacillus. It forms acid when grown in glucose broth, and it also differs from these two species in its morphological characters. Now it is laid down by such authorities as Muir and Ritchie that an organism differing from the diphtheria bacillus solely in its want of virulence must be regarded merely as a diphtheria bacillus in an attenuated condition, and should be spoken of as such. Neisser and several other authorities have expressed a similar opinion. We have therefore, I think, been perfectly justified in provisionally regarding the organism we have studied as an attenuated form of the Klebs-Löffler bacillus. In doing so we have left it an open question if the organism differs in certain essential respects yet to be discovered from the attenuated form of the Klebs-Löffler bacillus, and is therefore a special bacillus. Our more recent observations strongly incline us to the view that it is a special organism; but, whether this supposition should turn out to be correct or not, if an organism of this nature is really the essential pathogenic agent in general paralysis and tabes dorsalis, as we believe we have evidence to prove, then surely it is deserving of a special name. We therefore propose to refer to it as the *bacillus paralyticans.*

We have studied very numerous cultures of this bacillus, and, in a large number of instances at least, we had good grounds for believing that we were dealing with an organism that had been exerting a pathogenic action upon the patient from whom it was isolated. As has been indicated, it has the general morphological characters of the Klebs-Löffler bacillus. It is capable of assuming the granular, barred, and solid-colour forms of Wesbrook. Perhaps its most striking characteristic is

its polymorphism, and in this respect it would appear even to excel at least the virulent form of the Klebs-Löffler bacillus. When grown upon bynohæmoglobin agar at 37° C., it constantly shows more or less distinct metachromatic granules in preparations stained by Neisser's method. When grown upon blood-films it has the same appearance. Cultures upon the ordinary agar medium very rarely show any metachromatic granules. Individual strains of the organism differ greatly in regard to the size of the metachromatic granules they are capable of displaying. Some have very large granules which, after two days' growth of the organism upon bynohæmoglobin agar at the ordinary temperature, present in Neisser preparations a peculiar metallic lustre which we have not been able to observe in bacilli isolated from cases of acute diphtheria. The organism grows feebly under anærobic conditions, but, nevertheless, it is capable of multiplying rapidly with a very limited supply of oxygen. The appearance of the *bacillus paralyticans* varies not only with the medium upon which it is grown, but also with the temperature employed. Strains of the organism which, when grown at a temperature of 37° C. upon bynohæmoglobin agar, show prominent metachromatic granules, when cultivated at a temperature of 30° exhibit extremely minute granules. This difference is accentuated if the cultures are made upon blood-films. At the lower temperature the bacilli may then be entirely devoid of metachromatic granules.

In old cultures, clubbed and elongated forms are very abundant. Short threads may often be observed. It is hardly open to question that the filamentous organism, already described as having been observed in the tissues, is a special form of this bacillus. It has been found invading the tissues in four rats fed, or injected, with cultures of the bacillus, and in one of these animals the segments of the threads show metachromatic granules exactly like those of the bacillary form. As a rule, however, metachromatic granules are not visible. We have endeavoured to determine the precise conditions under which the thread form is assumed. There are grounds for believing that this special morphological character is, in part at least, one that is gradually impressed upon the organism by environmental influences, for, in several instances, the bacillus has shown a strong tendency to form short threads during the first two or three days

after having been isolated from the patient, irrespective of the culture medium employed and at the normal temperature. We have ascertained that threading is not due to the presence of the toxic products of the bacillus, to growth at a low temperature, or to limitation of the supply of oxygen. It appears to be in large part due to an abnormally high temperature, but also to be favoured by semi-anærobic conditions. When the bacilli are grown upon a blood-film at a temperature of 42° C. in a tube sealed with hard paraffin, they become attenuated and elongated, and tend to cohere by their extremities so as to form at first chains and then distinct filaments. The threading is well marked in two or three days, but it becomes still more distinct if cultivation is continued upon a fresh blood-film under the same conditions. The segments forming the threads generally show two or three minute metachromatic granules.

In view of the extreme variability of the morphological characters of this bacillus, it is not to be expected that it should always appear in the general paralytic in the form with metachromatic granules. It has indeed been definitely ascertained that in the living body it is the exception for the bacillus to present these granules. Even when growing in catarrhal secretions it shows them only occasionally. When it invades the tissues it is almost constantly devoid of visible metachromatic granules. It then generally assumes a simple granular and often a diplo-bacillary form. This corresponds to the appearance that the organism tends to take when grown upon the ordinary agar medium at the normal temperature, or upon a blood-film at a subnormal temperature. In other instances the invading bacillus, as already indicated, assumes a thread form, and this special morphological change is to be attributed in part at least to the occurrence of pyrexia.

By way of further preface it is necessary that I should say a word regarding the mechanism of natural and acquired immunity. Here, as in other departments of progressive science, there is much conflict of opinion. The facts that bear upon the observations I am about to record are, however, few in number and among those that are pretty generally admitted. When foreign invaders, such as bacteria, pass through the first line of defence formed by the skin and mucous membranes, they are normally engulfed by leucocytes and destroyed by the solvent action of

certain intra-cellular ferments. Some authorities also attach importance to the extra-cellular action of similar ferments (that is to say, to the alexines or complements), and of certain substances termed inter-bodies which combine with the invading organisms. Such in brief is the mechanism of natural immunity. In acquired immunity, that is to say the establishment of an increased power of resistance to a particular micro-organism or to some special toxine, the mechanism is more complicated. In response to the inimical stimulus the cells of the body, after a certain interval, produce specific anti-bodies capable of neutralising the toxines or of combining with the micro-organisms, which are thereby so affected that they are quickly dissolved by the alexines. Metchnikoff, in opposition to many other authorities, holds that this process is, in natural conditions, entirely an intra-cellular one, although when the blood is shed and undergoes coagulation the protective substances soon pass into the blood-serum. I specially mention this view because certain of the results we have obtained with the *bacillus paralyticans* harmonise with it. Recently, E. A. Wright has shown that the power of the leucocytes to take up bacteria is dependent upon the existence of certain substances in the blood plasma or blood serum, which he has termed "opsonins."

One of the points which we have specially studied is the phagocytic action of the leucocytes upon the *bacillus paralyticans*. The method we have employed is as follows :—

Apparatus, etc., required.—Specimen tubes of 2·5 c.c. capacity (with corks), carefully cleaned and sterilised by dry heat. Portable incubator for maintaining tubes at temperature of 37° C. Large platinum loop (ring), 4 mm. in diameter (No. 24 wire). Small platinum loop, 1 mm. in diameter. Bacillary emulsion prepared by mixing one small loopful of 24-hour culture (upon bynohæmoglobin agar) of *bacillus paralyticans* (*i.e.* a diphtheroid bacillus isolated from the blood or cerebro-spinal fluid of a patient suffering from general paralysis) with 5 c.c. of ·75 per cent. salt solution in distilled water. Sterilised vaseline.

Wash and dry dorsum of thumb. Apply absolute alcohol and, after a minute or so, allow it to evaporate. To the dry surface apply a drop of hot sterilised vaseline. Allow the vaseline to solidify and then prick the thumb through the vaseline with sterilised needle. Place four large loopfuls of blood in specimen tube, and immediately reinsert cork. Maintain the tube at temperature of 37° C. After half an hour, remove the clot with the aid of platinum loop. To the mixture of blood-serum and corpuscles remaining in the tube, add one large loopful of bacillary emulsion (heated to 37° C.) and mix. Incubate for time desired (see below), and then, after having stirred the contents of the tube, make coverglass films of the fluid with the aid of the small platinum loop. Allow the films, which must be very thin, to dry

in air, and then fix them for two minutes with absolute alcohol. Stain with carbol thionin, Löffler's methylene blue, or other suitable staining reagent.

Two separate actions require to be studied, namely, the power of the polymorpho-nuclear leucocytes to take up the bacilli, and the power of these leucocytes to dissolve the bacilli when engulfed.

The first action was studied in films prepared after incubation at 37° C. for thirty minutes (Fig. 1), the second after incubation for three hours. We have found that the power to take up the bacilli is extremely variable, both in control blood and in the general paralytic's blood. No constant alteration in this power could be recognised in the latter.

On the other hand, the power to dissolve the bacilli taken up has, in most instances, been distinctly greater on the part of the leucocytes of the general paralytic than on that of the leucocytes of the controls. Bacilli which have not been taken up by leucocytes remain, with few exceptions, perfectly normal in appearance after three hours' incubation. The intra-cellular changes are, however, within this time always very considerable (Fig. 2). It would appear that, as maintained by Metchnikoff to be the general rule, the bacteriolytic action is in this case essentially an intra-corpuscular one. The dissolving organisms show a progressive diminution in their affinity for the ordinary staining reagents (Fig. 3). In the last distinguishable phase of this bacteriolytic process the organisms appear as faintly tinted rods, and are generally somewhat attenuated. It is only recently that we have succeeded in sufficiently perfecting the method of demonstrating this bacteriolytic action to warrant the making of comparative observations with it in a series of cases, and therefore the number of these observations that we can as yet record is somewhat small. In films fixed with absolute alcohol and stained for ten minutes with Löffler's methylene blue, we have estimated the percentage of altered bacilli among those engulfed by the leucocytes. This percentage we term the *intra-corpuscular bacteriolytic index.* The following table shows the results obtained in twelve cases of general paralysis and in six control cases :—

INTRA-CORPUSCULAR BACTERIOLYTIC INDICES.

I. General Paralysis.		*II. Controls.*	
1. A. (w.)	77	1. V. (w.) Adolescent Insanity	16
2. R. (w.)	64	2. I. (w.) Imbecility	31·5
3. R. (w.)	67	3. Nurse J.	5·8
4. K. (w.)	63	4. Nurse H.	15
5. C. (w.)	78	5. S. (w.) Adolescent Insanity	10·5
6. W. (w.)	70·6	6. M. (w.) Adolescent Insanity	13
7. S. (m.)	86		
8. W. (m.)	64·4	*III. Clinical Diagnosis Doubtful.*	
9. A. (m.)	43·5	1. W. (w.)	15
10. D. (m.)	80		
11. G. (m.)	65		
12. N. (m.)	51		

We have also studied the bacteriolytic or lysogenic action of the blood serum upon the *bacillus paralyticans.* After the blood has been allowed to stand for twenty-four hours, the bacteriolytic substances are contained in the serum owing to the disintegration of the white corpuscles. The elaboration of a suitable technic by means of which to compare the bacteriolytic power in different cases has proved somewhat difficult. It has, however, already been possible to determine in several cases of general paralysis that the solvent action of the blood serum, like that of the active leucocytes, was greater than the solvent action of the serum of a normal person.

After having thus studied experimentally the phagocytic and bacteriolytic actions of the blood upon the *bacillus paralyticans,* Dr M'Rae and I endeavoured to ascertain if there was any evidence of the occurrence of similar processes in the tissues and body fluids of general paralytics. Every case studied with this object has given the same answer, an emphatic " Yes."

Diphtheroid bacilli, more or less altered by lysogenic action, are present in great numbers in the catarrhal pneumonic foci that occur in most general paralytics who die in congestive attacks (Fig. 4). They are contained chiefly, but not exclusively, in the leucocytes that fill the alveoli. They have also been found in the blood stream in the neighbourhood of such pneumonic foci. They are also generally demonstrable, sometimes in great numbers, in the adventitial spaces of the inflamed cerebral

vessels and in meshes of the pia-arachnoid. Further, they can be observed in films made from the blood of the living paralytic, more especially when the patient is in a congestive attack (Figs. 7). They can also be detected in the centrifuge deposit from the cerebro-spinal fluid. They may be present in great numbers in the urine of paralytics, especially during congestive attacks. If 5 c.c. of the fresh urine are centrifugalised, and if films of the deposit are then stained by Neisser's method or with carbol thionin, abundant organisms are generally to be observed. These may be of various kinds, but in several cases we have found that to all appearance only dissolving diphtheroid bacilli were present. That this was really so was demonstrated in a striking way in one of our cases in which these altered bacilli were abundant in the centrifuge deposit (Fig. 6). We made cultures from the deposit, and after 48 hours' incubation there was on first inspection seemingly no growth of any kind. On closer examination, however, a single minute colony was observed. It proved to be a pure growth of a diphtheroid bacillus. In cases of simple general paralysis it is unusual to find among the diphtheroid bacilli in the centrifuge deposit from the urine any that show metachromatic granules. In cases of general paralysis combined with tabes dorsalis it is, however, different. In all of seven such cases that we have been able to examine at the Royal Edinburgh Asylum, Dr M'Rae and I have found abundant living bacilli with distinct metachromatic granules also to be present. I shall discuss the significance of these facts in the concluding lecture.

The experimental study of the action of the living blood upon the *bacillus paralyticans* has, however, led to another result of a different kind. It has taught us how to grow the organism from the blood and cerebro-spinal fluid of the living general paralytic. More than four years ago Dr M'Rae, Dr Jeffrey, and I began to make attempts to grow the bacillus from the blood, for we felt that it should be possible to do so if the hypothesis we were testing was correct. Every method that we could think of has been tried from time to time during these years, but, until quite recently, all in vain. It is now clear, in the light of our experimental observations, that we failed to get cultures chiefly for the reason that we incubated the tubes with

as little delay as possible. By so doing we were really adopting the most certain method of completing the destruction of the few living bacilli that might be present. From several cases of general paralysis we have recently placed fresh blood upon bynohæmoglobin agar and allowed the tubes to remain in the cold for twenty-four hours before incubating them at 37° C. By thus delaying the incubation, two important ends are attained. First, the leucocytes are killed and their phagocytic action therefore abolished; and second, time is allowed for the alexines, which, with the disintegration of the leucocytes, have passed into the blood serum, to be destroyed by contact with the dead organic matter contained in the culture medium. When the tubes are placed in the incubator the blood has more or less completely lost its bactericidal properties, and any living organisms it may contain are able to multiply.

By using this method, or slight modifications of it, we have succeeded in obtaining pure cultures of a diphtheroid bacillus from the blood in four cases of general paralysis. The first case was that of a woman in a congestive attack from which she recovered. The growth of the bacillus was at first very feeble, but in sub-cultures it has gradually increased in vigour (Fig. 5). The second case was that of a woman, also in a congestive attack, which proved fatal a few days later. In this case only extremely feeble colonies were obtained. The bacillus was readily recognised in film preparations, but it was found impossible to obtain a growth in sub-cultures. The third case was that of a man suffering from general paralysis combined with tabes dorsalis. The disease was progressing rapidly, but the patient was not in a congestive attack. In this case also the growth obtained was extremely feeble, but we still have the bacillus growing in sub-cultures. The fourth case was one in which the patient had been a tabetic for some years before he developed the signs of general paralysis. He was suffering from a congestive attack which proved fatal three days later. In this case also the growths were very feeble, but sub-cultures have been successful. We have on several occasions observed this initial feebleness of growth in cultures of diphtheroid bacilli isolated post-mortem from internal organs. There is reason to believe that it is an effect of the previous bacteriolytic action of the patient's blood. In such instances the bacillus, as a rule,

increases in vigour in successive sub-cultures, but sometimes it refuses to continue to grow. We have ascertained that a feeble diphtheroid bacillus can be invigorated by being sub-cultured upon blood-films.

Dr M'Rae and I have made cultures from the centrifuge deposit from the cerebro-spinal fluid withdrawn by lumbar puncture in four cases of general paralysis with negative results, but in each of these instances the tubes were incubated at once, and the patients were not suffering from congestive attacks. Quite recently, two patients suffering from congestive attacks have been examined in the same way, excepting that the tubes, after having been inoculated with the deposit, were allowed to remain cold for several hours. From both we have obtained pure growths of a diphtheroid bacillus. In the first case the colonies were numerous and the growth fairly vigorous. In the other the growth was extremely feeble.

I come next to the observations that my colleague and I have made with the object of obtaining, if possible, evidence of some specific action of the blood of the general paralytic upon the *bacillus paralyticans*. I am not quite sure that we can yet say that we have succeeded, but we have certainly come very near doing so.

We have tried agglutination tests, using chiefly the technic devised by Dr M. H. Gordon, and employed by him with some success in an experimental research with the *bacillus diphtheriæ*. We have, however, failed to obtain results of a distinctive nature. In our experience the bacilli form clumps so readily, even in normal blood-serum, that it is difficult to be certain of the occurrence of any specific agglutinative action in the serum of the general paralytic.

We have also endeavoured to compare the bacteriolytic power of the blood-serum of the general paralytic with that of control cases. As already indicated, we have found it extremely difficult to devise a serviceable technic, and all I can say at present is that we have in several instances found the power of the twenty-four hour serum of the general paralytic to dissolve the *bacillus paralyticans* to be distinctly greater than that of the serum of a normal individual.

We have had more definite success in estimating the intra-corpuscular bacteriolytic power. The method employed has

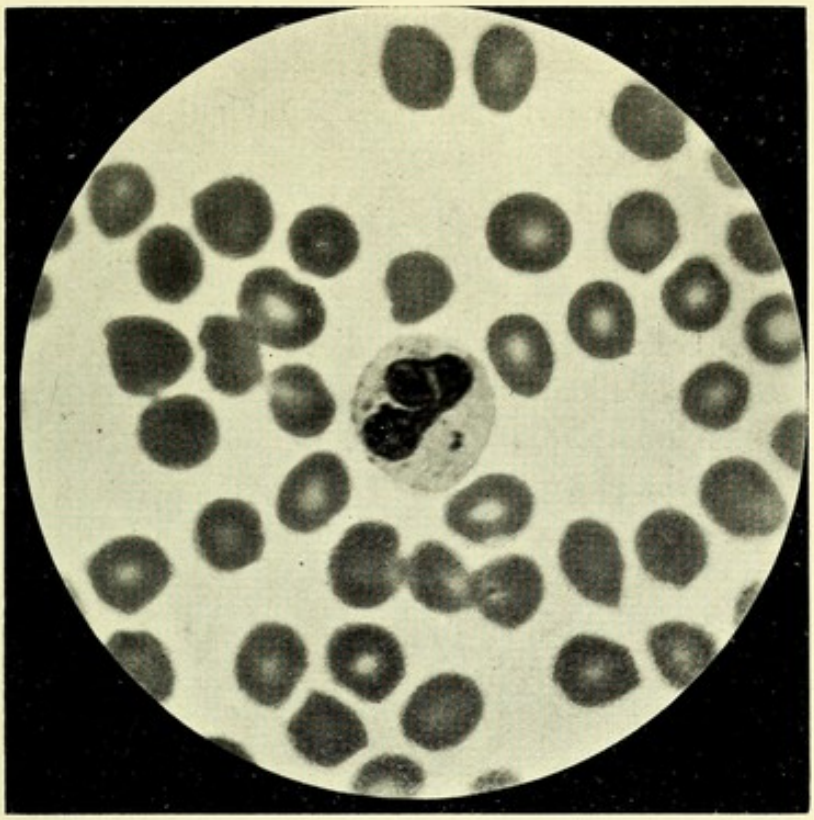

FIG. 1.

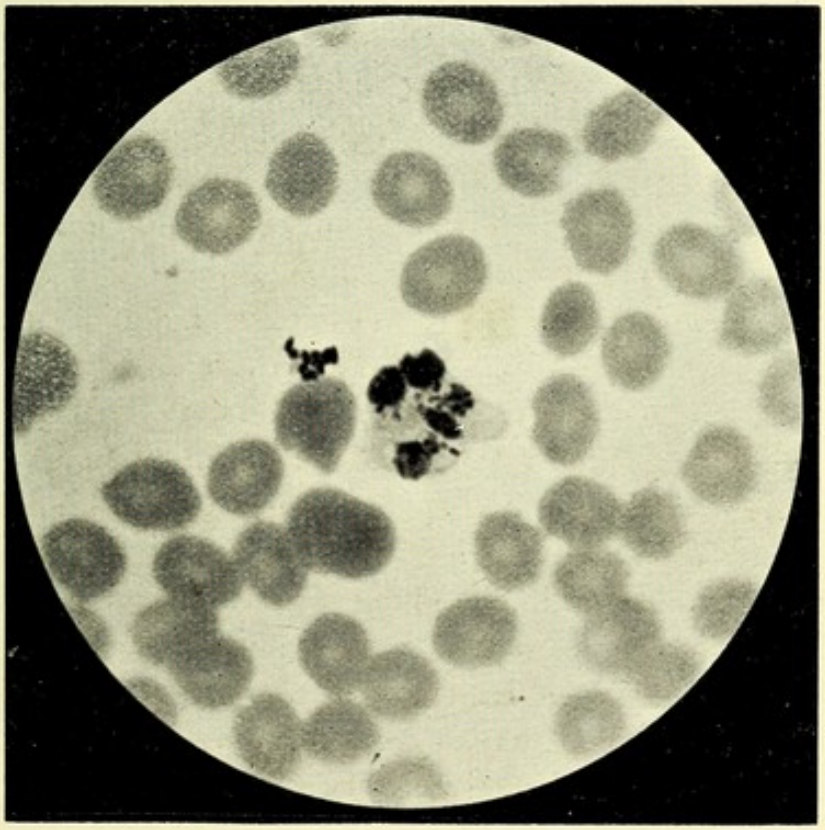

FIG. 2.

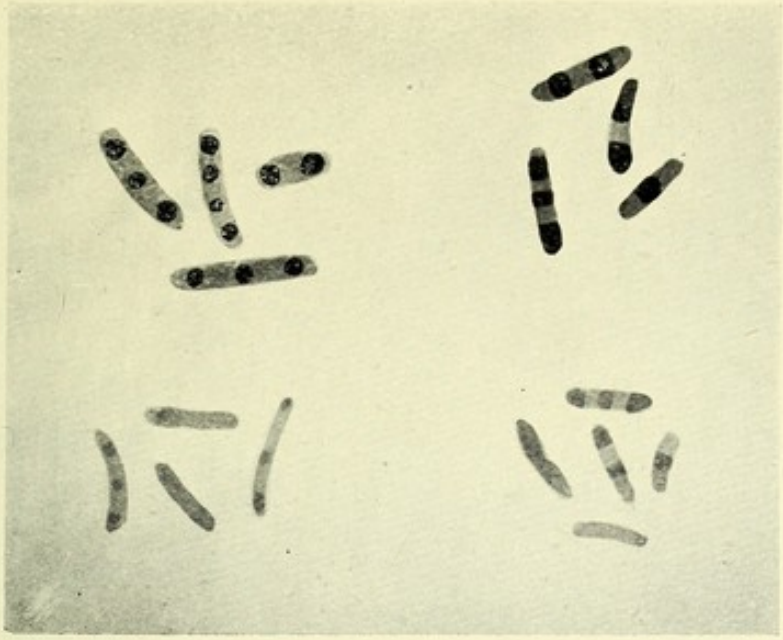

FIG. 3.

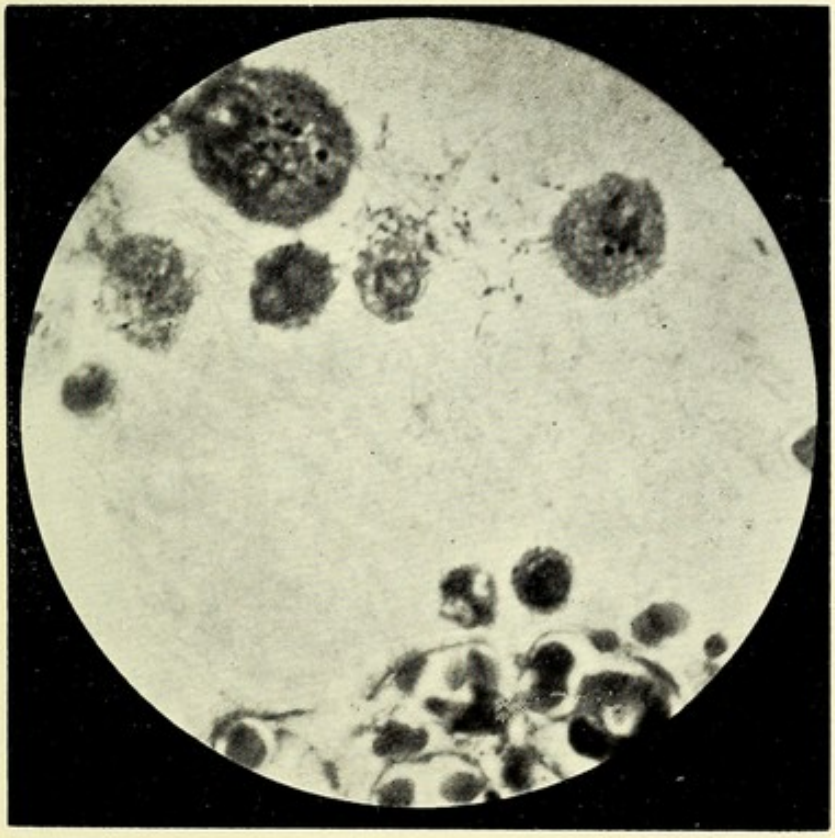

FIG. 4.

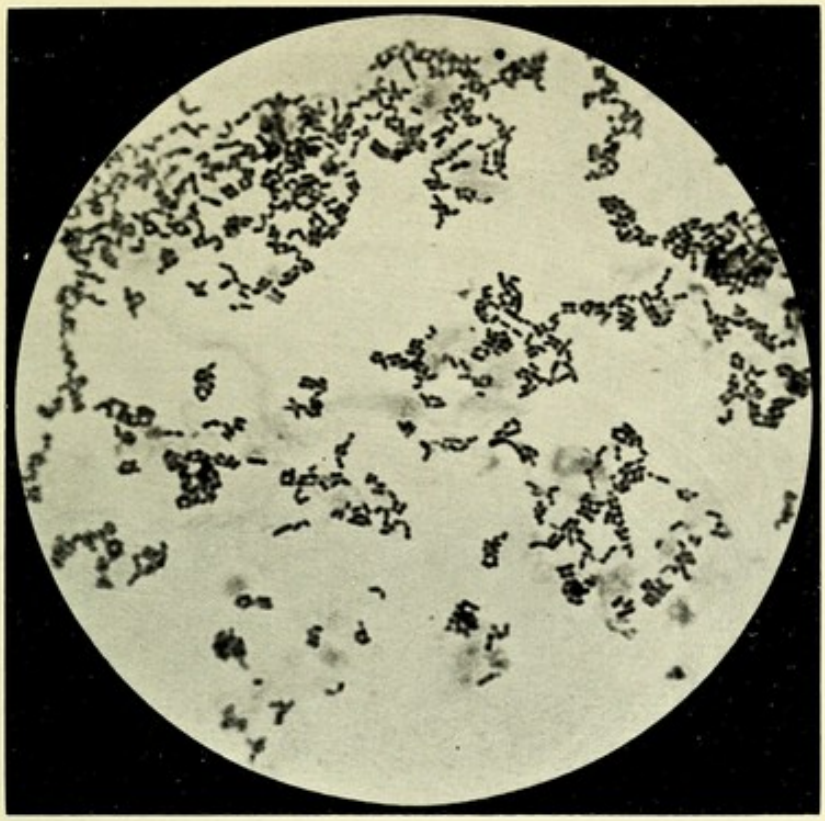

FIG. 5.

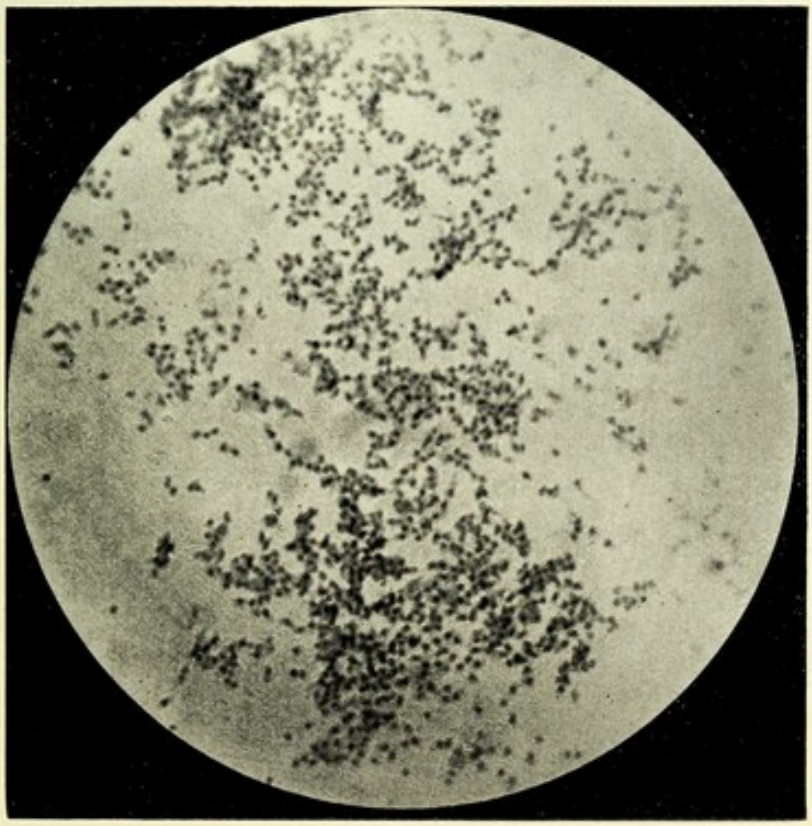

FIG. 6.

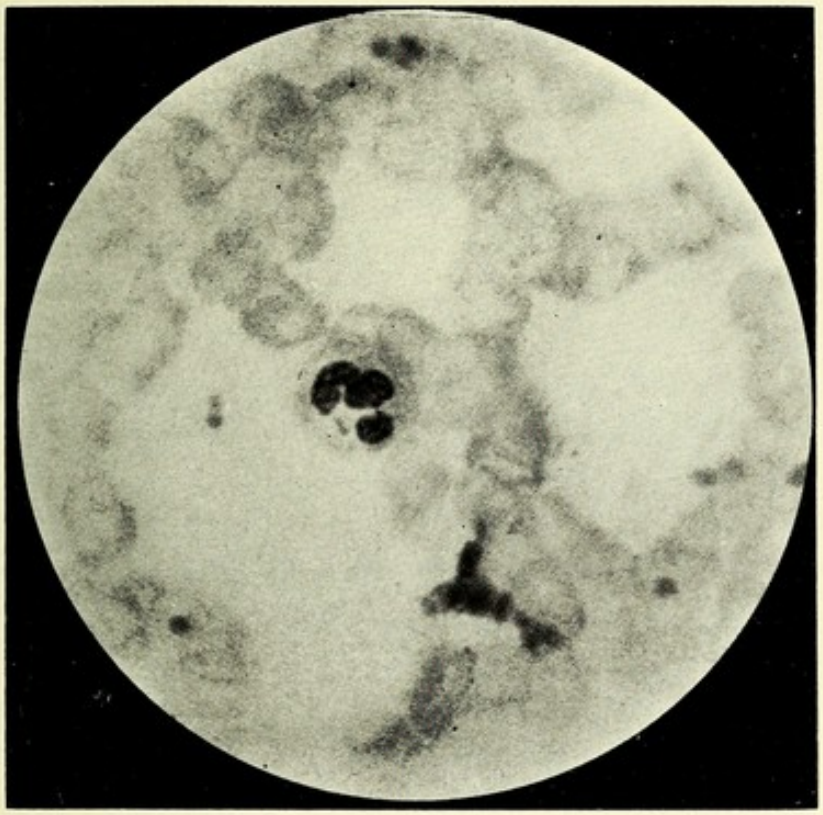

FIG. 7.

already been described, and the results obtained have been given in tabular form. If these initial results should be confirmed in a sufficiently extensive series of cases, the reaction would form the basis of a method of serum diagnosis of general paralysis.

The results of the researches of Wright, Bulloch, and others upon the "opsonic" action of the blood-serum, suggested to us that it might be worth while to apply some similar test in this investigation. We have not, however, used Wright's technic for the reason that we had already in use our method of studying the phagocytic action of the leucocytes, and it readily adapted itself to the purpose we had in view, namely, to ascertain if the addition of a definite proportion of the blood-serum of a general paralytic to normal blood-serum containing active leucocytes would increase the power of these corpuscles to take up the *bacillus paralyticans*. The blood, the serum of which was to be tested, was obtained in a sterilised glass tube with capillary ends. The ends were then sealed by means of heat. After twenty-four hours the contents of the tube were centrifuged, and the clear cell-free serum was pipetted off and placed in a sterilised specimen tube (2·5 c.c. capacity). This tube was then corked and placed in the incubator. Two tubes of normal blood were obtained in the way already described, and kept at a temperature of 37° C. After half an hour the clots were removed. To one tube, forming the control, there was added one large loopful of bacillary emulsion (heated to 37° C.); to the other there were added a similar loopful of bacillary emulsion and one loopful of the serum to be tested. Both tubes were incubated for 40 minutes. Films were then made from each and stained with carbol thionin or with Löffler's methylene blue. The control and experimental films were compared with regard to (1) the percentage of polymorpho-nuclear leucocytes containing bacilli, and (2) the average number of bacilli in each leucocyte.

In a test of this kind there is inevitably a considerable margin of error, for at least two reasons. First, the result may be affected by slight differences in the quantity of the bacillary emulsion added respectively to the control tube and to the tube containing the serum to be tested; and, second, the result may be affected by slight differences in temperature, as it has been proved that the power to take up the bacilli is very greatly lessened by lowering of the temperature even 3 or 4 degrees below

the normal. Every effort has, of course, been made to render the conditions uniform.

Test IV.

Difference between Experiment and Control.

	Percentage of Polymorphs containing Bacilli.	Aver. Number of Bacilli in each Leucocyte.
I. General Paralysis—		
1. S. (m.)	+ 38	+ 2·2
2. L. (m.)	+ 56	+ 3·6
3. A. (m.)	+ 12	+ ·9
4 D. (m.)	+ 9·9	+ 2·8
5. G. (m.)	− 5	+ ·5
6. W. (w.)	+ 5	+ ·5
7. C. (w.)	+ 40	+ 4·9
8. K. (w.)	− 2	+ ·4
9. A. (w.)	+ 13·5	+ 1·5
10. R. (w.)	+ 9	+ 3·5
II. Controls—		
1. V. (w.) Adolescent Insanity	− 14·8	− 2·9
2. K. (w.) „ „	+ 33·2	+ 2·6
3. F. (w.) Epilepsy	+ 6	+ 1·6
4. H. (w.) Adolescent Insanity	− 10	+ ·3
5. Nurse A.	+ 7	+ 1
6. Nurse S.	+ 1	− ·2
7. Nurse M.	− 7	− ·7

The results obtained are perhaps those that might have been predicted on the ground of what is already known. Dr Wright, from his studies upon the subject of opsonic action, has come to the following conclusion :—" In one class of infections the opsonic power with respect to the infecting micro-organisms hardly varies from day to day, remaining always inferior to that of the normal blood. In another class of infections, the opsonic power is continually fluctuating, the range of variation being very far below the normal and very far above the normal. These categories of infections correspond respectively to strictly localised and systemic infections." [1] As in general paralysis, there is not merely a local

[1] The *Lancet*, December 2, 1905.

infection, but a succession of systemic invasions, the disease would come under the second class, and we should expect to find considerable variation in the opsonic power of the blood in relation to the infecting organism. It may be that very high readings are indicative of stimulation of certain specific resisting mechanisms, but this conclusion is hardly warranted by the results as yet obtained.

Whilst a trustworthy method of serum diagnosis would unquestionably be very useful in dealing with suspected cases of general paralysis, it seems not improbable that more direct methods of bacteriological diagnosis may become generally available. They may already be said to be available in some cases. There can be little room for doubt that the patient is suffering from the paralytic toxæmia if diphtheroid bacilli can be grown from his blood or from his cerebro-spinal fluid, or if they can be detected in microscopical preparations of the blood or of the centrifuge deposit from the cerebro-spinal fluid. The presence in the urine of great numbers of diphtheroid bacilli that have suffered lysogenic action must, I think, also be regarded as a positive sign. Lastly, if, in addition to altered bacilli, the centrifuge deposit from the urine shows very abundant diphtheroid bacilli with metachromatic granules, then the case is one of tabes dorsalis, or at least will soon manifest the recognised signs of this disease.

There are still some additional facts that I wish to record, but they will be more conveniently dealt with when I endeavour, on the ground of the results of our investigations, to formulate new and definite conclusions regarding the etiology and pathogenesis of general paralysis and tabes dorsalis in the next lecture.

Description of Figures.

Fig. 1.—Polymorpho-nuclear leucocyte containing two unaltered diphtheroid bacilli. Experimental observation; normal blood corpuscles and emulsion of diphtheroid bacilli; incubation for half an hour. Carbol thionin. ×1000.

Fig. 2.—Polymorpho-nuclear leucocyte containing numerous diphtheroid bacilli, most of which are altered by lysogenic action. Group of unaltered bacilli lying free. Experimental observation; normal blood corpuscles and emulsion of diphtheroid bacilli; three hours' incubation. Löffler's methylene blue. ×1000.

Fig. 3.—Drawing of diphtheroid bacilli in films made from mixture of

normal blood corpuscles and emulsion of diphtheroid bacilli after three hours' incubation. To show the changes produced in the appearance of the bacilli by lysogenic action. Above there are shown examples of unaltered bacilli, below examples of altered bacilli to be observed within the protoplasm of many of the leucocytes. The organisms to the left are from a preparation stained by Neisser's method, those to the right from one stained with carbol thionin.

FIG. 4.—Group of altered diphtheroid bacilli in alveolus of lung of general paralytic who died in a congestive attack. Carbol thionin. ×1000.

FIG. 5.—Diphtheroid bacillus isolated in pure culture from the blood of a general paralytic suffering from a congestive attack which did not prove fatal. Two days' growth upon blood-film. Carbol thionin. ×1000.

FIG. 6.—Centrifuge deposit from urine of general paralytic in third stage. Neisser's method. Shows diphtheroid bacilli considerably altered by lysogenic action. ×1000.

FIG. 7.—Leucocyte in blood of general paralytic in a congestive attack. Löffler's methylene blue. ×1000. Shows in the protoplasm a body which under the microscope can be recognised to be a diphtheroid bacillus that stains faintly. A pure growth of a diphtheroid bacillus was obtained from the blood of this patient.

LECTURE III.

Delivered on 29th January 1906.

GENERAL paralysis of the insane, and the obviously allied disease tabes dorsalis, have in recent years probably given rise to more discussion than any other morbid conditions that specially manifest themselves in nervous disorders. There are at least three special reasons for which it may be said that it is natural that this should have been so. In the first place, general paralysis and tabes dorsalis, both on account of their frequency and of their gravity, are among the most important of all the nervous diseases that the practitioner is called upon to treat; in the second place, it may safely be said, even without risk of contradiction from the most extreme advocate of the syphilitic theory of the origin of these maladies, that there is very much regarding them that has hitherto remained obscure; and, in the third place, general paralysis and tabes dorsalis still rank among the opprobria of medicine, for all efforts to combat them with success have hitherto proved unavailing.

In discussing the problem of the etiology and pathogenesis of these two diseases in the light of the investigations detailed in the two preceding lectures, I wish, as far as possible, to aviod

a controversial attitude. My purpose is simply to endeavour to show that a new and solid edifice can be constructed out of the facts elicited by my colleagues and myself. A passing critical reference to the syphilitic hypothesis is, however, unavoidable. It is the only view of the etiology of general paralysis and tabes that really conflicts with the one I am going to maintain. There are many who think it is already thoroughly established, and if this is really so there is no room for any rival explanation.

As remarked in the first lecture, there can be observed in the recent literature of general paralysis and tabes dorsalis an increasing dissatisfaction with the syphilitic hypothesis, and a steadily growing conviction that the essential etiological factor has yet to be discovered. The most able discussions of the question that I am acquainted with are those that are to be found in the recently published works upon insanity by Professor Bianchi of Naples [1] and Professor Tanzi [2] of Florence. Professor Bianchi recognises that syphilis is one of the causes of general paralysis, but he does not admit that it is the specific etiological factor. He attaches almost equal importance to alcoholism, and enumerates also many other predisposing factors. He has observed several cases in which general paralysis developed during the secondary stage of syphilis, and this fact, he maintains, is inconsistent with the view that general paralysis is a tertiary or quaternary syphilitic infection. In common with several other observers, he has seen cases in which general paralysis has preceded infection by syphilis. Among numerous other facts likewise tending to weaken the syphilitic hypothesis, he mentions that he has observed some cases complicated by genuine tertiary syphilitic lesions, which quickly disappeared under antisyphilitic treatment, whilst the paralysis progressed in the usual way. He emphasises the fact of the essential uniformity both of the clinical picture and of the pathological anatomy of general paralysis, and, recognising the difficulty in making such uniformity harmonise with the view that the disease has numerous different etiological factors, expresses the opinion that it is possible that it may yet be demonstrated that these various causes simply prepare the soil for a single intoxication, perhaps of a bacterial nature; and in the facts recorded by

[1] *Trattato di Psichiatria*, chap. xxx. [2] *Trattato delle malattie mentali*, chap. xiv.

my colleagues and myself regarding the evidence of constant infection by a diphtheroid bacillus, he sees a possible solution of the problem.

Professor Tanzi, whilst provisionally accepting the syphilitic hypothesis as the one most strongly supported at the time of writing, is obviously dissatisfied with it. Few, if indeed any writers upon mental diseases have displayed so fine a gift of critical analysis in handling scientific evidence. His examination of the question inevitably leaves in the mind of the reader the conviction that, whether the syphilitic hypothesis is in accord with fact or not, the evidence upon which it rests is extremely incomplete and of very doubtful value. He clearly shows the necessity of invoking other etiological factors. He points to features of the disease that prove it to be dependent upon the action of some poison that gradually accumulates and then becomes destroyed or eliminated. He shows that this poison cannot be attributed directly to syphilitic toxines, and that therefore it must be assumed that it results from a consecutive auto-intoxication. He recognises the unsatisfactory vagueness of this theory, and refers to the more positive evidence of the occurrence of a bacterial toxæmia of gastro-intestinal origin, brought forward in 1901 by Dr Lewis Bruce and myself, as well as to some observations of Idelsohn upon the defective bactericidal power of the blood-serum of the general paralytic.

On several occasions, either independently or in conjoint papers, I have contended that the rôle of syphilis in the etiology of general paralysis and tabes dorsalis is only that of weakening the general and local defences, and that these diseases must be dependent upon an active bacterial toxæmia. The facts that seem to me to support this view are briefly the following.

Only a small percentage of syphilitics ever become general paralytics or tabetics. General paralytics have been known to become infected by syphilis, and it is extremely improbable that this could occur if general paralysis were essentially a late manifestation of syphilis. General paralysis may develop during the secondary stage of syphilis, and this is inconsistent with the view that the disease is either a tertiary or a quaternary manifestation of syphilis. Numerous cases of general paralysis in which previous syphilitic infection could be reasonably excluded have been known to many competent clinical observers. Anti-

syphilitic remedies, so promptly efficacious in tertiary syphilis, are useless or even harmful in general paralysis and tabes. Statistics showing the high percentage incidence of previous syphilis are quite inconclusive. They leave entirely open the question of the occurrence of a secondary bacterial infection of a different nature, predisposed to by the syphilitic infection, just as tuberculosis is predisposed to by a previous attack of measles. Some of the arguments used to support the syphilitic hypothesis, as, for example, that drawn from the fact of the occasional occurrence of conjugal paralysis or of conjugal tabes, would better support the view that general paralysis and tabes result from a special venereal infection distinct from syphilis. The syphilitic hypothesis is devoid of the support of a single fragment of experimental evidence.

The theory that the toxæmia of general paralysis is a secondary auto-intoxication, directly dependent upon the previous action of syphilis, does not accord with the clinical and pathological facts. These point most conclusively to a struggle between the defensive forces of the individual, on the one hand, and an aggressive bacterial foe on the other, and indeed furnish evidence that places it beyond question that the general paralytic suffers from an active bacterial toxæmia. I have already, in the first lecture, referred to the evidence in support of this view brought forward in 1901 by Dr Lewis Bruce and myself. I have also described how Dr M'Rae, Dr Jeffrey and I were led, in 1903, to advance the hypothesis that in the production of this bacterial toxæmia, which is beyond doubt a mixed bacterial toxæmia, a diphtheroid organism probably plays a predominant part, and how Dr M'Rae and I, continuing to test this hypothesis, have gradually ascertained fresh facts which seem to us to warrant the conclusion that general paralysis and tabes dorsalis are essentially dependent upon infection by a special diphtheroid bacillus. The chief facts have already been stated, and it remains for me now merely to summarise the evidence in support of the conclusion that the *bacillus paralyticans* is the specific etiological factor in the production of general paralysis and tabes dorsalis, and to describe the morbid processes to which it gives rise.

I would have it clearly understood that the question is, in the meantime, left an open one whether this bacillus is merely

an attenuated Klebs-Löffler bacillus or an altogether distinct micro-organism. The decision of this question is not in the least vital to the argument that it is to follow. At the same time, I would say that, in my opinion, the evidence bearing upon the point is such as to render it probable that it will eventually be determined that the organism is a special one.

The evidence that this bacillus is the specific etiological factor in these diseases is, in brief, as follows :—

A bacillus of this nature is, according to the results of our investigations, present in large numbers in either the alimentary or respiratory tract, or in both, and in the genito-urinary tract in all cases of advancing general paralysis. This bacillus has a thread form which has been found invading the walls of the respiratory or alimentary tract in five cases of general paralysis. It can be shown that this organism in its bacillary form invades the pulmonary tissues in cases of general paralysis, and that it is commonly the only micro-organism present in large numbers in the catarrhal pneumonic foci that occur in most of such cases dying in congestive attacks. A growth of a diphtheroid bacillus has now been obtained in cultures made from the brain post-mortem in ten cases of general paralysis out of twenty-four in which cultures were made from this organ. Diphtheroid bacilli exhibiting metachromatic granules in Neisser preparations have been detected in the fresh blood in one case and in sections of the brain in two cases. It has been ascertained by experimental methods that these diphtheroid bacilli in contact with the living blood are rapidly taken up by the polymorpho-nuclear leucocytes, and that they may be completely digested in the course of two or three hours. Bodies exactly corresponding in appearance to these dissolving bacilli can be detected in the blood and cerebro-spinal fluid of the living general paralytic, especially during a congestive attack. Whilst the fact that most of the bacilli present are in process of disintegration satisfactorily explains the long succession of negative results of endeavours to obtain cultures from the blood and cerebro-spinal fluid, we have, by the use of special methods, succeeded in obtaining pure growths of a diphtheroid bacillus from the fresh blood in four cases of general paralysis, and from the cerebro-spinal fluid withdrawn by lumbar puncture in two cases. In sections of the brain prepared by special methods, disintegrating diphtheroid bacilli can be recog-

nised in the walls of the vessels and in the pia-arachnoid in many cases of general paralysis. The centrifuge deposit from the urine of the general paralytic, especially during a congestive seizure, commonly contains abundant diphtheroid bacilli that have been more or less affected by lysogenic action (Fig. 6). In seven consecutive cases of general paralysis combined with tabes, we have found the centrifuge deposit from the urine to contain not only these altered diphtheroid bacilli, but also living ones showing distinct metachromatic granules in preparations stained by Neisser's method. In such cases a culture of the bacillus can be obtained from the urine. Experimental infection of three rats and a goat with diphtheroid bacilli isolated from a case of general paralysis has resulted in the production of symptoms and tissue-changes resembling those of general paralysis. Lastly, there is evidence that the active polymorpho-nuclear leucocytes of the general paralytic have, as a rule, a greater power of dissolving these diphtheroid bacilli than that possessed by the normal leucocyte. It would, therefore, appear that the general paralytic has acquired against these diphtheroid bacilli a certain degree of specific immunity, by means of which he is enabled to maintain the struggle against these bacilli, notwithstanding an otherwise defective local and general power of resistance.

I have next to answer the question, Does the view that this bacillus is the specific etiological factor in general paralysis and tabes dorsalis accord with the known clinical phenomena and the ascertained facts regarding the pathological anatomy of these diseases? In my judgment it does. I shall first sketch the pathogenesis of general paralysis as it appears to me in the light of the facts that have been ascertained, and afterwards I shall in a similar way consider the pathogenesis of tabes dorsalis.

The specific bacillus would appear to be conveyed from individual to individual by contagion, although there are grounds for believing that less direct methods of infection are not uncommon. It is capable of living as a saprophyte at the surface of the various mucous membranes. There is ample warrant for the conclusion that, to a person whose general and local defences against bacteria are intact, the *bacillus paralyticans* is quite innocuous. It can neither multiply to any important extent upon a healthy mucosa nor penetrate into the subjacent tissues. The case is, however, different if the bacillus becomes implanted

upon the surface of a mucous membrane that has been damaged in consequence of a long-standing catarrhal process, and more especially if the general defences of the individual have also become impaired. In normal conditions, epithelial surfaces, such as those of the respiratory and alimentary tracts, are protected from bacterial attack by a delicate layer of mucus, which has been shown to have not only a mechanical action, but also to be powerfully bactericidal (Arloing). As the result of certain forms of prolonged chronic catarrh, the function of the mucous glands tends to become exhausted ; various saprophytic bacteria, normal or occasional inhabitants of the mucous tracts, are then liable to assume a pathogenic rôle. They do so, either in consequence of their excessive development at the surface of the mucosa and the absorption of their toxic products, or by actual invasion of the tissues. In cases of general paralysis a condition of severe chronic catarrh is constantly present, either in the alimentary or respiratory tracts, or in both. The mucous glands show marked signs of exhaustion, and there is excessive development of the common saprophytic bacteria. There are also good grounds for believing that the general paralytic, before he manifests signs of his disease, has suffered some impairment of his general defensive forces. There is, at least, almost constantly a history of his having been subjected to conditions that are known to cause such impairment. There are very numerous inimical forces that may produce such a condition of impaired local and general defence, but there are three that seem to have special importance in relation to general paralysis and tabes dorsalis. They are the pathogenic agent of syphilis, alcohol, and a too highly nitrogenous diet.

Syphilis is known to produce a severe drain upon the leucoblastic function of the bone marrow, whereby the general power of resistance must be injuriously affected. It is also known that it frequently determines the occurrence of chronic inflammatory lesions of various mucous membranes, more especially those of the mouth, throat, and respiratory tract. In this relation, it is perhaps not without significance that it has been ascertained that the *spirochæte pallida* lodges within various epithelial cells, including those of the bronchi.

The prolonged excessive use of alcohol, it is now well established, not only impairs the general power of resistance to

bacteria, but leads to severe morbid changes in the gastro-intestinal mucosa.

The prolonged excessive use of nitrogenous foods has also a disastrous action upon the general power of resistance and upon the local defences of the mucous membranes, as has lately been demonstrated by the experimental researches of Dr Chalmers Watson.

One or more of these three causes of impairment of the general and local defences against bacteria are almost constant in the individual history of the general paralytic.

It is upon such damaged mucous membranes that the *bacillus paralyticans* is capable of effecting a permanent lodgment. The organisms multiply in the catarrhal secretion, and also find their way into the ducts of partially exhausted mucous glands. Such saprophytic infection may continue for a long time without leading to any important toxic effects. It is probably only when the state of the local and general defensive forces is such as to permit of the bacillus invading the tissues that the paralytic toxæmia becomes of any great intensity. Our more recent observations have led Dr M'Rae and myself to attach special importance to the bronchi as a seat of chronic infection, although there are many cases in which bacillary invasion can be shown to have taken place from the gastro-intestinal tract. As in the case of other local infections, a veritable battle is waged between the attacking organisms, on the one hand, and the defensive forces of the individual on the other. It is virtually a life and death struggle between the bacilli and the polymorpho-nuclear leucocytes. It is a conflict in which the leucocytes, after a long succession of victories, are ultimately defeated, for their power of renewal is limited, whilst that of the bacilli is virtually unlimited. Moreover, there is warrant for the belief that in the course of a struggle of this nature, extending over many years, the virulence of the bacillus, especially in respect of its power to invade, becomes gradually increased. Under certain conditions the defensive forces are temporarily placed at a disadvantage and the bacilli become more aggressive. At least one of these conditions has been ascertained experimentally. It has been found that lowering of the temperature four or five degrees below the normal almost completely suspends the power of the leucocytes to take up the *bacillus paralyticans*. It is, therefore, reasonable to believe that lowering

of the body temperature of the general paralytic is an important cause of aggravation of the bacillary attack. Local invasion manifests itself clinically in a congestive attack, characterised generally by rise of temperature, always by leucocytosis and aggravation of the mental and bodily symptoms. After a few days, or a shorter time, the defensive forces, stimulated by the attack, may gain the upper hand and repel the invasion. The invaders are locally seized by the leucocytes and other phagocytic cells and rapidly destroyed. Others are dissolved, not by intracellular digestion, but by the action of the bacteriolytic ferments derived from leucocytes that have disintegrated. Large numbers of the invading bacilli reach the circulation either by way of the lymphatics, or more directly through the capillary walls. They may be seen in the blood-stream in the neighbourhood of the infective foci and also in films made from the patient's blood. In the blood, they are likewise quickly seized by leucocytes and digested; but here, as in the infective focus, it is not always the leucocyte that wins. There is evidence that very many of these cells, after partially digesting a number of bacilli, succumb to the action of the bacillary toxines and disintegrate, or at least disgorge their captives. The bacilli thus liberated, and others that have escaped the leucocytes altogether, pass out from the blood-stream by one or other of at least two ways. One is through the capillaries of the kidney into the urinary tract, and the other is through the damaged endothelial lining of the cerebral vessels into the adventitial spaces and other channels that constitute the lymph-system of the brain. That micro-organisms which have reached the blood-stream are commonly excreted by way of the kidneys is now a well recognised fact. That it occurs in this infection has been demonstrated. Why these bacilli should also be capable in certain cases of penetrating the endothelial lining of the cerebral capillaries is certainly not very easy to understand, but that they do so we can show. It probably depends upon certain special structural features of the cerebral vessels, as well as upon chemiotactic influences which direct the bacilli towards the nerve-tissues, with which their toxines most evidently combine. The disintegrating bacilli lodge for the most part in the adventitial lymph-channels, but many also reach the pia-arachnoid and subdural space. Within the lymph-channels of the brain, various endothelial and connective

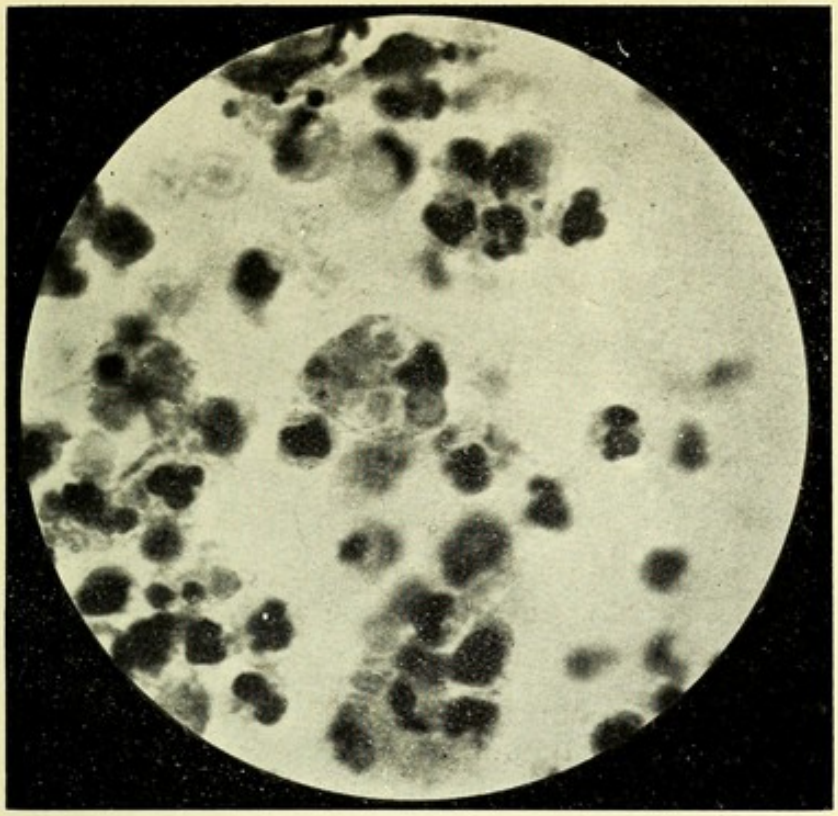

FIG. 8.

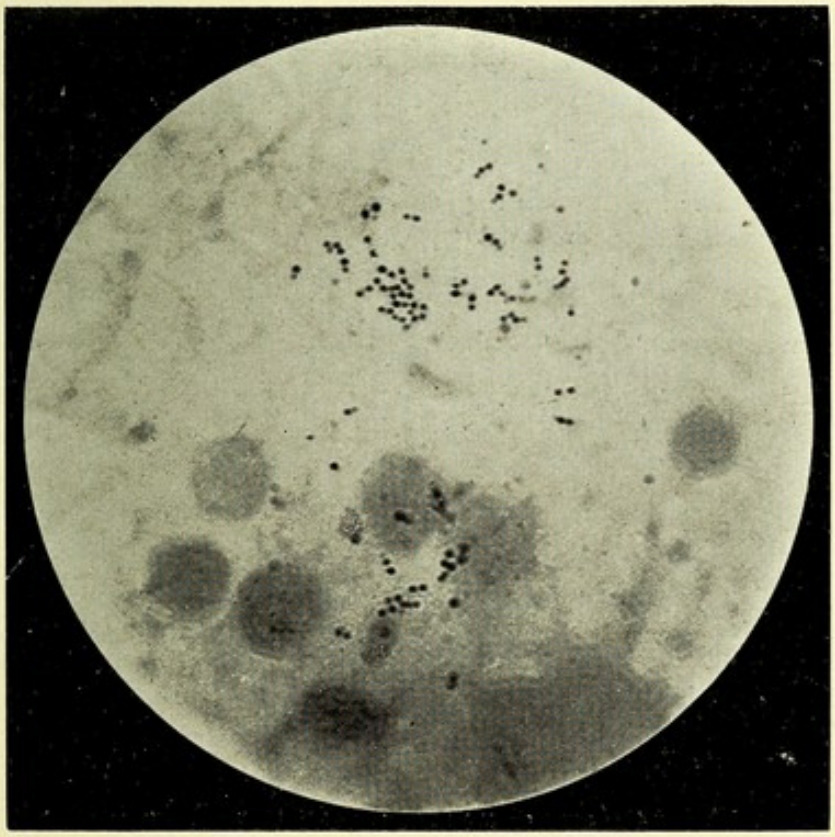

FIG. 9.

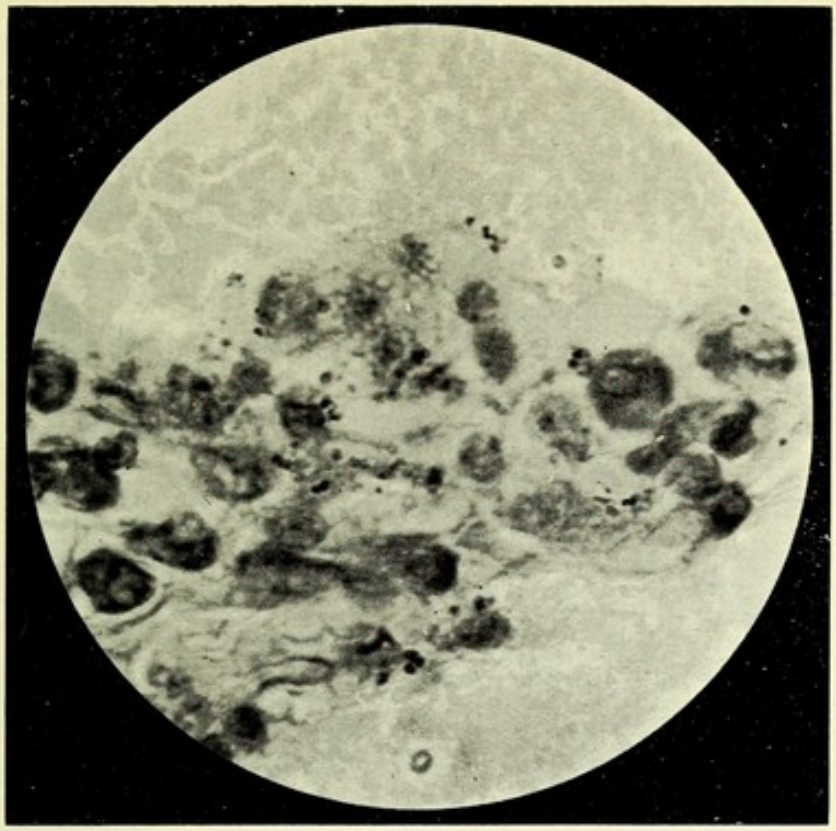

FIG. 10.

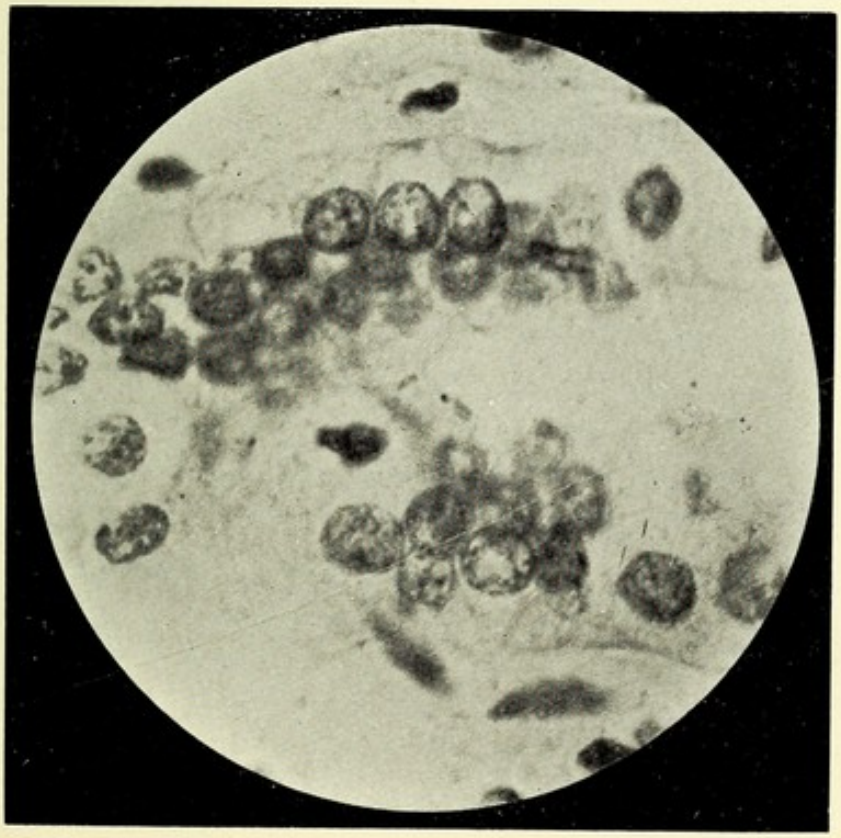

FIG. 11.

tissue elements exercise a phagocytic action and complete the destruction of the bacilli. These micro-organisms have been seen within lymphocytes in the centrifuge deposit from the cerebro-spinal fluid. The disintegration of the bacilli is attended by the formation of intense toxines. There is thus a general toxæmia resulting from the disintegration of the bacilli at the seat of invasion and in the blood, and an added local toxic action in the nervous centres, in consequence of the passage of the partially disintegrated bacilli through the endothelium of the cerebral vessels. The pathological changes that occur in the nervous system, already briefly described in the first lecture, are the result of this general toxæmia and local formation of toxines.

In some instances a successful repulsion of an invasion is followed by a prolonged period in which the bacillus is kept at bay. Clinically this corresponds to a remission. More commonly, however, there is a continuous comparatively slight absorption of toxines from the infective focus and a succession of more or less severe invasions, which time after time are repelled; in the end, however, the defensive forces are generally overcome. There is then a fatal congestive attack. General paralytics may, of course, die in other ways. In patients who die in congestive attacks there is commonly a more or less extensive catarrhal pneumonia. The catarrhal exudation is loaded with diphtheroid bacilli in various stages of disintegration. In other instances there is similar invasion from the stomach or small intestine. If pyrexia precedes death for some days, the bacillus tends to assume its thread form.

I come now to the subject of tabes dorsalis. That general paralysis and tabes dorsalis are in some way intimately related to each other is now so generally accepted that I need not argue the question here. On the anatomical side, apart from the systemic lesions of the posterior columns, there is in tabes evidence of a toxic action in the cord similar to that which occurs in the brain in general paralysis. There are two types of cases that especially require to be considered. There are cases of general paralysis which towards the end develop signs of tabes dorsalis, or at least show in the spinal cord the early changes characteristic of this disease, as indeed most cases of general paralysis do; and there are cases of pure tabes dorsalis

which, clinically at least, are not complicated by dementia paralytica.

I think we are greatly helped to a right understanding of this matter by the observations recently made by Drs Orr and Rows[1] upon the production of tabetic lesions of the cord. They have found that a systemic lesion affecting the posterior columns can be produced as a result of absorption of toxines from a peripheral septic focus, such as a bed-sore, and that there is distinct evidence that the toxines pass along the perineural sheaths of the nerves to the spinal cord. The peripheral nerve fibres remain unaffected, being protected by their neurilemma sheath, but the toxines injure the nerve fibres of the posterior root at the point at which they lose their neurilemma sheath, that is to say, as they pass into the cord. This is the vulnerable point of Obersteiner. They have also shown that the posterior column lesions in general paralysis, which are simply early tabetic lesions, start at the same point. These observations of Drs Orr and Rows, which are founded upon experimental evidence, as well as upon evidence drawn from cases, have confirmed the view long advocated by Obersteiner, Redlich, Dr Alexander Bruce and others, that in tabes dorsalis the systemic lesion begins where the posterior root enters the cord. In order to account for these lesions of the posterior root in general paralysis and tabes dorsalis, it is necessary to ascertain the source of the toxines that produce them. The morbid changes can in part, but not fully, be accounted for simply by toxicity of the spinal lymph. A peripheral toxic focus in close relation to the pelvic retro-peritoneal tissues is also required. In cases of general paralysis in which tabes supervenes, the toxic lesion of the posterior roots is, I think, in most cases sufficiently explained by the passage of disintegrating diphtheroid bacilli from an infective focus in the respiratory or alimentary tract through the blood and kidneys. In the urinary tract, further disintegration of these bacilli occurs, and the toxines thus produced are in part absorbed, and, entering the sheaths of the nerves, pass up the lymph-channels and so reach the vulnerable point of Obersteiner. In cases of pure tabes, in which there is an extreme degree of the same systemic lesion of the cord as that which occurs in almost every case of general paralysis, the

[1] *Brain*, Winter 1904 ; *Review of Neurology and Psychiatry*, January 1906.

source and nature of the toxines causing this lesion should be similar to those in general paralysis. In seven consecutive cases of tabes dorsalis we have found the centrifuge deposit from the urine to contain abundant unaltered diphtheroid bacilli, showing distinct metachromatic granules. Dr David Orr has at my request kindly sent me films of the centrifuge deposit from one case of simple tabes and from two cases of tabo-paralysis. In all of these three cases the films also show abundant diphtheroid bacilli with metachromatic granules. In these ten cases at least there was therefore what may be termed a diphtheroid cystitis. Whether this condition is constant in tabes dorsalis or not I cannot say, but if further observations should confirm the testimony of these ten cases, then I think we shall be bound to conclude that in tabes dorsalis there is in the urinary tract an infective focus comparable to that which occurs in the respiratory or alimentary tract in general paralysis. The bacilli are invading, and therefore produce toxic effects far in excess of those that result from simple passage of disintegrating bacilli through the urinary tract. We have had an opportunity of examining only one case of this kind post-mortem, and this so recently that there has not been time to make a complete histological examination ; but, so far as we have been able to study the case, it bears out completely the view that in such cases a diphtheroid bacillus has obtained a hold upon the mucosa of the urinary tract. I may mention that in this case we readily obtained a growth of a diphtheroid bacillus from the urine ; some weeks later the patient had a congestive seizure and we obtained a pure culture of the same bacillus from his blood ; the congestive attack proved fatal, and we again obtained the bacillus in cultures from the brain. Sections of the bladder show the thread form invading in characteristic fashion.

There are two supplementary points that I wish to deal with very briefly. There are probably many who will find a difficulty in the way of accepting these views in the fact of the frequent presence of diphtheroid organisms in the alimentary, respiratory, and other mucous tracts of persons who are not suffering from general paralysis. I would recall such facts as that the Klebs-Löffler bacillus in its virulent form may not infrequently be found in the throats of healthy persons, and that the pneumococcus, which is the most common cause of pneumonia, can often

be isolated from the saliva of people who are perfectly well. I have already sufficiently insisted upon the importance of alterations in the local and general defences as a preliminary to the pathogenic action of the *bacillus paralyticans*, and what I have said should, I think, be a sufficient answer to this objection. It should also, however, be borne in mind that many of the diphtheroid bacilli that occur in other conditions may have much lower virulence than the micro-organism which we assert to be the essential etiological agent in general paralysis.

It has lately been shown that many persons who do not, strictly speaking, suffer from tabes dorsalis, nevertheless show many of the physical signs of this disease. Dr M'Rae has made observations which seem clearly to prove that a similar statement may be made in regard to general paralysis. It is only the more severe cases of this disease that are commonly recognised. Very numerous other persons are apparently infected by the specific bacillus, but resist it successfully, and show only very slight signs of having suffered from the paralytic toxæmia.

If the etiology and pathogenesis of general paralysis and tabes dorsalis are such as we assert them to be, how are these diseases to be combated? It is obvious that certain measures, such as are taken in other chronic infective diseases, should be adopted to prevent, as far as possible, the transmission of the bacillus to susceptible persons. I do not, however, wish to say more upon this point at present. Of more immediate interest is the question whether or not there is any reasonable prospect of these hitherto incurable diseases becoming amenable to treatment. On the ground of facts observed, I feel justified in saying, with considerable confidence, that there is. The general paralytic defends himself, and often with prolonged success, by manufacturing specific bacteriolytic anti-bodies, with the aid of which the invading bacilli are repelled. Such specific anti-bodies can be produced in suitable lower animals and used as therapeutic agents, and it seems probable that with their aid it may be possible to induce a prolonged remission of the paralytic toxæmia. If this could be effected at an early stage of the disease, the damage to the nervous system would be slight, and the result might legitimately be regarded as a cure. Dr M'Rae and I have for a considerable time been anxious to attempt to produce an anti-serum of this kind, but hitherto the difficulties

in the way have been insuperable. Thanks, however, to the energy of Dr Clouston, who has ever been ready to do all in his power to facilitate these researches, and whose unceasing interest in them has been one of the chief encouragements in our work during the last four years, these difficulties have at length been overcome. We are, at least, going to give such serum treatment a trial.

Allow me to make three acknowledgments before I close. I wish to express my indebtedness to Dr Harry Rainy for the great trouble he has taken in connection with these lectures, more especially in regard to the arrangements for the microscopical demonstrations. I have also to thank Dr M'Rae for so kindly relieving me of all trouble in connection with the laying out of the microscopical preparations; and, lastly, I desire to acknowledge my great indebtedness to the General Board of the Laboratory of the Scottish Asylums, that is to say, to the superintendents of the Edinburgh, Glasgow, Dumfries, Aberdeen, Perth and other Scottish Asylums, as well as to the lay members of the Board, for the facilities they have afforded my colleagues and myself for the carrying out of these investigations.

Description of Figures.

Fig. 8.—Cell in alveolus of pneumonic lung showing two diphtheroid bacilli in vacuole. From a case of general paralysis. Death in a congestive attack. Carbol thionin. ×1000.

Fig. 9.—Group of diphtheroid bacilli in blood-film taken from a general paralytic suffering from a slight congestive seizure. Neisser's method. ×1000.

Fig. 10.—Section of brain from a case of general paralysis, showing, in the adventitial lymph spaces of a cortical vessel, partially dissolved micro-organisms, which, in the microscopical preparation, can, in many instances, be recognised to have the characters of diphtheroid bacilli. Acidulated methylene blue. ×1000.

Fig. 11.—Section of kidney from a case of general paralysis. Shows, in a convoluted tubule, micro-organisms morphologically identical with diphtheroid bacilli, slightly altered by lysogenic action. Carbol thionin. ×1000.

Fig. 12.—Section of bronchus from a case of general paralysis. Shows the thread form of the diphtheroid bacillus invading. Carbol thionin. ×600.

Fig. 13.—Section of bronchus of rat fed for several weeks with bread mixed with unsterilised cultures of a diphtheroid bacillus isolated from the bronchus shown in Fig. 12. Shows similar invasion by the thread form of the diphtheroid bacillus. Carbol thionin. ×600.

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