The Morison Lectures for 1906 (1): *The Pathology of General Paralysis of the Insane.*

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ABSTRACT.

STATISTICS seem to indicate that general paralysis of the insane has been increasing during recent years. The etiology and pathogenesis of the disease, notwithstanding many positive and dogmatic assertions that have been made regarding them, have hitherto remained a profound mystery. In the recent literature of the subject there can be recognised a growing dissatisfaction with the syphilitic hypothesis. The pathological alterations known to occur in the nervous system consist chiefly in acute and chronic degenerative changes in the cortical nerve cells, degeneration of the medullated fibres of the brain, especially in the first layer of the cortex, hypertrophy and proliferation of the neuroglia in the cortex and elsewhere, formation of granulations of the ependyma, proliferative changes in the walls of the cerebral vessels, generally accompanied by the development of plasma-cells, thickening of the pia-arachnoid in consequence of chronic proliferative changes in its tissues, the appearance of large numbers of lymphocytes in the cerebro-spinal fluid, and early tabetic lesions in the spinal cord. During the last six years a series of researches have been carried out in the laboratory of the Scottish asylums with the object of elucidating the essential pathology of the disease. Dr. L. C. Bruce has also made independent clinical investigations of a similar nature. In 1901 Dr. Bruce recorded the results of continuous observations made upon the temperature and leucocytosis in individual cases. He showed that febrile attacks generally occur every two or three weeks, and that these attacks are accompanied by leucocytosis, and that in the third stage leucocytosis may occur from time to time without rise of temperature. He concluded from his observations that general paralysis is a disease directly due to poisoning by the toxines of bacteria, whose point of attack is through the gastric and intestinal mucous membranes. In a paper published at the same time, the writer maintained similar views on the ground of the results of an examination of the pathological

changes in the alimentary tract in a series of cases. Further evidence of chronic toxæmia was found by Dr. A. C. Ainslie in the constant occurrence of widespread and often well-marked chronic endarteritis of the extra-cerebral vessels, even in cases in which senile changes could be excluded. In 1902 Dr. G. Douglas McRae, Dr. Jeffrey, and the writer commenced a bacteriological investigation. It was found that a diphtheroid bacillus was specially prominent in the gastro-intestinal and respiratory tracts in cases of general paralysis, and that a similar organism could frequently be isolated from the brain. The hypothesis was advanced 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. Dr. McRae and the writer have since been continuing these bacteriological investigations, and every step forward has resulted in the elucidation of some fact that has made this diphtheroid hypothesis more probable. Histological investigations have yielded much confirmatory evidence. Dr. Shennan and the writer have made a short series of experimental investigations with diphtheroid bacilli isolated from cases of general paralysis. The organisms have proved non-virulent to guinea-pigs. Rats fed upon bread mixed with unsterilised broth cultures developed nervous symptoms and died in about ten weeks. These animals presented 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. In three of the animals there was a widespread invasion of the tissues by the bacillus in a filamentous form, which has also been found invading the tissues in several cases of general paralysis. Dr. L. C. Bruce has made a similar observation upon a goat which he injected with cultures derived from the same source as those used in the experiments upon the rats. The goat became paretic, and died in a condition resembling a "congestive attack." Its brain shows changes resembling those in an early case of general paralysis. In May of last year Dr. McRae and the writer recorded that

they had found that diphtheroid bacilli are constantly present, often in very great numbers, in the genital tract in both male and female paralytics. Further, in seven consecutive cases of general paralysis combined with tabes the urine has been found to be loaded with diphtheroid bacilli. It was also ascertained that bacilli having little affinity for staining reagents, but having a distinct resemblance to diphtheroid bacilli, could be observed in the blood during congestive attacks, in the centrifuge deposit from the cerebro-spinal fluid removed by lumbar puncture, and in the urine. These and other similar observations raised the question whether diphtheroid bacilli are not from time to time gaining access to the blood and being rapidly destroyed by phagocytic and lysogenic actions. In order to gain light upon this question, Dr. McRae and the writer have investigated experimentally the action of the living blood upon pure cultures of diphtheroid bacilli isolated from cases of general paralysis. It has been ascertained that the bacilli are taken up by leucocytes with great rapidity and that they may be completely dissolved in the interior of the leucocytes within two or three hours. An endeavour has been made to estimate exactly the power of the leucocytes of different individuals to dissolve these bacilli, and it has been found that this power is distinctly greater on the part of the leucocytes of the general paralytic than on that of the leucocytes of controls. The appearances of the dissolving bacilli in the experimental films are identical with those presented by the imperfectly staining micro-organisms that can be seen in various situations in the general paralytic. The results of this experimental study suggested that failure of previous attempts to obtain cultures from the blood and cerebro-spinal fluid is dependent upon the fact that most of the bacilli are dead and that the few living ones that are occasionally present are quickly killed by the continued action of the phagocytic cells. An endeavour was, therefore, made to obtain growths by leaving the tubes in the cold for twenty-four hours and then incubating them. This plan has proved successful with the blood from four cases, and with the centrifuge deposit from the cerebro-spinal fluid in two. In all of these cases pure growths of a diphtheroid bacillus were obtained. The growths are at first generally extremely feeble. A feeble culture may be invigorated by subculturing upon blood-films.

There are many weighty arguments against the view that general paralysis and tabes dorsalis are essentially syphilitic in their origin. They have been ably stated by Bianchi and some others. The part played by syphilis is no doubt an important one, but it is only that of weakening the general and local defences against bacteria. There is the clearest evidence that the general paralytic suffers from an active bacterial toxæmia. The evidence that a diphtheroid bacillus—either an attenuated form of the Klebs-Löffler bacillus or more probably an altogether distinct micro-organism—is the specific etiological factor in general paralysis and tabes dorsalis is briefly as follows: A bacillus of this nature is, according to the results of our investigations, present in large numbers, either in 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 bacillus 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 recognised 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. 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 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 polymorphonuclear 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. The bacillus appears to be conveyed from individual to individual, as a rule by contagion. There is ample warrant for the conclusion that if a mucosa is healthy the organism can neither multiply at the surface to any important extent nor invade the tissues. A preliminary weakening of the local and general defences is evidently necessary. There are numerous inimical forces that can produce this condition of impaired local and general defence, but there are three that seem to have special importance. They are the pathogenic agent of syphilis, alcohol, and nitrogenous foods used in excess. There is evidence that a mere saprophytic infection may continue for a long time without leading to any important toxic effects. It is probably only when the bacillus invades the tissues that the paralytic toxæmia becomes of any great intensity. Invasion appears to take place most commonly from the bronchi, although it can also be shown to have taken place from the alimentary tract in many cases. At

the seat of such invasion what is virtually a life-and-death struggle between the bacilli and the leucocytes takes place. 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. Local invasion manifests itself clinically in a congestive attack. Large numbers of the bacilli reach the circulation either by way of the lymphatics or through the capillary walls. They can be seen in the blood-stream in the neighbourhood of infective foci. Most of the bacilli that reach the blood are quickly seized by leucocytes and digested, but many escape from the circulation in one or other of two ways, namely, through the capillaries of the kidney into the urine and through the walls of the cerebral vessels into the adventitial lymph channels. The further disintegration of the bacilli that takes place in these lymph-channels gives rise to a local toxic action. There is thus a general toxæmia due to the disintegration of the bacilli at the seat of invasion and in the blood, and an added local cerebral toxic action dependent upon the disintegration of the bacilli that have passed through the endothelium of the cerebral vessels. In some instances the 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 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 overcome. There is then a fatal congestive attack. With regard to the pathogenesis of tabes dorsalis, it is to be noted that Orr and Rows have recently shown that tabetic lesions of the cord can be produced by the absorption of toxines from peripheral septic foci. The toxines pass up the perineural sheaths without injuring the nerve-fibres, and affect the fibres of the posterior root as they enter the cord at the spot where they lose their neurilemma sheath. In order to account for the similar lesions that occur in tabes it is necessary to find some peripheral toxic focus. The evidence at present points to this focus being in the bladder. In ten consecutive cases of tabes (three being cases from which material was supplied by Dr. Orr of Prestwich Asylum) abundant living diphtheroid bacilli have been found in the urine, and therefore these patients were suffering from a

diphtheroid cystitis. In these cases the bacilli were present in too great numbers to have come merely from the urethra, which in other cases very frequently contains some diphtheroid bacilli. If further observations confirm the testimony of these ten cases, we shall be bound to conclude that in tabes 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 greater than those that result from the simple passage of the disintegrating bacilli through the urinary tract.

There is evidence that the general paralytic defends himself, and often with prolonged success, by manufacturing specific bacteriolytic anti-bodies. It seems therefore worth while to produce such anti-bodies in suitable lower animals and to use them as therapeutic agents. This method of treatment is at least going to be given a trial at the Royal Edinburgh Asylum.

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The Prognosis in Dementia Paralytica. (1)

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THE difficulty of informing the relatives of patients suffering from dementia paralytica on the probable duration of the disease led the writer to inquire into those symptoms and signs which appeared to be of value in prognosis.

Text-books on insanity give little information concerning the subject, beyond stating that the affection usually lasts less than three years. This statement, as will presently be shown, is of little value, since some patients die within a few weeks after the onset of the disease, whilst others survive for many years.

The subject will be dealt with in the following order :

(1) Variations in the course of the disease at different periods of life.

(2) The influence of sex.

(3) The effect of alcohol.

(4) Variations in the course of the disease according to the associated mental state.