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Part I.—Original Articles.

The Morison Lectures, 1913.—*General Paralysis of the Insane.*

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THE EARLY DIAGNOSIS OF GENERAL PARALYSIS.

GENERAL paralysis is common in our large cities, and assumes so many disguises that it is necessary to be ever on the alert for it. About a third of the male admissions to asylums between the ages of thirty-five and fifty suffer from it, and the possibility of its presence should always be remembered in the case of a man of this age presenting mental symptoms. Such men are usually the heads of families, and occupy positions of responsibility, for as a rule those who suffer from general paralysis are no weaklings. The social troubles and inconvenience produced by the occurrence of adolescent or senile insanity, bad as they may seem, are therefore trivial compared with those produced by a disease such as this, which attacks the bread-winner of a family and the head of a business in the prime of his life.

A feature of general paralysis which adds to the anxiety of relatives is the alteration of character without any obvious sign

of insanity, which is often one of its early symptoms. A man whose sanity is not yet questioned scandalises his neighbours and ruins his good name by his conduct in public places, or he dissipates his means and brings his family to want by senseless extravagance or by muddling his affairs.

Nothing more need be said to indicate the value of an early diagnosis of this disease, yet it often goes undiagnosed. Till within the last five years the diagnosis, even when well-marked symptoms were present, was not infrequently in error, and in the early stage of the disease suspicion may have been justified, but a definite diagnosis never was. The anxiety produced by this uncertainty was often very trying, and when important matters are at stake it has been found so intolerable that the skull has been trephined and a small portion of the cortex removed and examined microscopically to settle the question one way or another.

Uncertainty of Diagnosis.

This uncertainty of diagnosis was well illustrated by the fifty-four cases upon which Wassermann and Plaut first started their syphilitic investigations, when the one thing they desired was clinically certain material from the institutions of Berlin and Munich. They were informed that "no doubt of the diagnosis of paresis could exist," for the cerebro-spinal fluid came from cases almost all of which were in the "undoubted advanced" stage of the disease, or were "ordinary straightforward cases" of "clinically undoubted" general paralysis. In spite of every precaution three cases of mistaken diagnosis were found after death in the fifty-four cases, an error of nearly 6 *per cent.*

A most instructive investigation into this subject was made a few years ago in America by Southard. He followed to the *post-mortem* room and the laboratory forty-one well-marked cases in which the entire medical staff of an asylum had unanimously agreed on clinical grounds that the diagnosis of general paralysis was certain. He found on examination after death that there were six errors of diagnosis in the forty-one cases, or 15 *per cent.* From my own experience I am certain that this is not an over-estimation, and if an attempt were made to diagnose not merely well-marked but also early cases, and those

showing slight clinical phenomena, the error would be much greater.

Caution was recommended by the most experienced physicians of the past, who pointed out that as the diagnosis of general paralysis was tantamount to passing sentence of death on the patient, every other possibility should be excluded before coming to this conclusion. Much likewise required to be excluded, for there were at least ten other conditions from which a differential diagnosis might have to be made. These included alcoholic and syphilitic insanity, senile insanity, and organic brain disease with paralysis, traumatic insanity, certain toxic conditions and neurasthenic states, epilepsy, mania, and imbecility. It was often impossible to arrive at a definite diagnosis, and this was especially the case with certain forms of alcoholic insanity resembling the confusional psychoses of Korsakoff. A provisional diagnosis only could be made, and the course of the disease watched, for any other policy sooner or later led to most regrettable mistakes. In cases of organic brain disease with paresis similar mistakes were also liable to occur. Neurasthenic states in middle-aged men who had been exposed to infection from syphilis often gave great anxiety, and in doubtful senile cases above sixty-four, owing to difficulties and uncertainties, a diagnosis of general paralysis was seldom made.

New Methods of Diagnosis.

The methods of investigating general paralysis have now been revolutionised, and its diagnosis has been placed on a sure basis by the six new serum and spinal fluid reactions and tests. The method of diagnosing it now consists of two processes which are complementary. There is first the *clinical process* in which the patient is examined by the usual methods employed in psychology and neurology. If, as a result of this examination, the presence of general paralysis be suspected, it is then necessary to apply the second or *laboratory process* to verify this first impression. The employment of the latter resembles chemical analysis in the method of its application and in the certitude of its results. By obtaining certain definite reactions in sequence and noting the presence of certain positive signs in association with the clinical symptoms, an accurate diagnosis

can almost always be made. There are only two conditions in which there is any uncertainty with regard to the presence of general paralysis, namely, when mental symptoms exist in association with its twin sister, tabes, or its first cousin, cerebro-spinal syphilis.

It is not my intention to give a description of the classical symptoms of general paralysis, as these can be found in any text-book. My object is rather to arouse suspicion of the presence of the disease at an early stage by drawing attention to those symptoms, often not serious in themselves, which appear early. In the past such suspicions would have been futile had they arisen, for nothing further could have been done to complete the diagnosis but to await developments. Now we can apply the laboratory tests referred to, and in almost every case say definitely and at once whether general paralysis be present or not.

Mental Symptoms.

The fundamental symptom of general paralysis is enfeeblement of function. There is a steady process of deterioration going on, producing first impairment and finally destruction or paralysis of the mind, known as dementia. Weakness of judgment, loss of memory, and a blunting of the sensibilities are present in one shape or another in every case, and these are the characteristic symptoms. In the early stages the patient is not insane: he is merely a changed man. There is an alteration in his intelligence, character, habits, and feelings, and this change is for the worse. He may continue to do his work, though in a more mechanical and less efficient way than before, and it costs him a greater effort. Forgetfulness is usually a noticeable symptom, and failure of memory may lead to unexpected mistakes in spelling and calculation, but there are also more serious lapses when important matters are forgotten. Lifelong habits of courtesy, of decent behaviour, and of personal honour may be departed from, and in their place there may arise a tendency to alcoholism, immorality, or even criminal acts, such as absurd theft. Moodiness and irritability may develop, or else apathy and indifference. It is said that 12 *per cent.* of the cases are conscious of these defects, but it is probable that at this early stage the percentage is really very much higher.

Deterioration of Conduct.

It is only possible to illustrate this mental change by a few concrete examples. The weakened judgment, which, with failure of memory, is the most characteristic early symptom of general paralysis, is best shown by the conduct. The experienced man of business makes foolish investments for which no tyro could be excused; the careful man makes numerous purchases of useless articles, or presents gifts which he cannot afford to strangers; the clerk's book-keeping is muddled, and his ledgers are full of errors and miscalculations; the considerate parent will grab the food on the table and eat to excess, regardless of his family; the working man's wife will meet her husband with a smiling face, but with no explanation to give why his dinner has not been cooked for him; the particular man neglects his personal cleanliness and dresses carelessly or absurdly; the owner of a motor-car drives so fast that no one will enter his car. He knocks down a child, and not only does not stop to see if she has been injured or not, but does not worry about it. A golfer, playing in a mixed foursome, stands aside from the teeing-ground and urinates openly. Loss of control over the temper in a man not naturally hot-tempered is a frequent symptom. At tennis, billiards, or cards, unless he wins, he is unbearable, and makes unpleasant scenes. He will not scruple to take a mean advantage at these games, or even to cheat. All these symptoms can be traced to a loss of the better judgment, of the finer feelings, and of memory, and, though they do not amount to actual insanity, they nevertheless indicate a serious deterioration of intelligence and character from the normal, which, if associated with any of the physical signs of general paralysis, should not be overlooked.

These occasional mental failings may exhibit themselves for a period of a year or more before serious and continuous signs of mental disorder become superadded. Sooner or later a state of confusion, depression, excitement, or only hypochondriacal neurasthenia develops, and the patient is recognised to be mentally affected. Not infrequently the presence of general paralysis is unsuspected at first, especially if the patient be melancholic, which he is more frequently than is thought. These superadded phenomena mask the fundamental symptoms of deterioration to which I have alluded, but the expert, especially if he has had

his suspicions awakened by pupillary anomaly or by a knowledge that the patient has had syphilis, can usually detect them. There is often, but not always, something atypical in the mental disorder. The paralytic melancholic may thus take his food ravenously, or may sleep soundly, or may make silly remarks, or show great loss of memory, none of which are features of typical melancholia.

Physical Signs.

There are mental symptoms so typical and characteristic of general paralysis, like the absurd and grandiose delusions of the second stage, that they at once suggest that disease. Those I have just described may be due to other causes, and they only suggest general paralysis if they are associated with the physical signs of that disease. It is this combination of mental symptoms with physical signs which is so ominous and important. As general paralysis may attack any part of the nervous system, any physical sign or symptom known to neurology may be present, but the disease shows a selective power, and certain symptoms are more common than others. Generally speaking, it may be said that these early physical signs are those which are also found in tabes, but any neurological sign such as a convulsive seizure, a temporary aphasia, or an attack of unconsciousness may give warning of the onset of the disease.

The Pupil.

The pupils in general paralysis are usually unequal, but unless very marked this sign is of no diagnostic value, owing to its prevalence. The outline is frequently uneven or irregular, and if markedly so this has more diagnostic value. It may, however, be congenital or be due to syphilitic adhesions, and I have seen extreme temporary irregularity of both pupils due to toxic conditions.

The Argyll-Robertson Phenomenon.

The most important diagnostic sign is the fully developed Argyll-Robertson phenomenon, or complete loss of the light reaction in one or both eyes. This symptom is regarded by Babinski and Gowers as a definite sign of antecedent syphilis

and as a warning of the danger of tabes or general paralysis. It may occur in rare organic lesions, but these are not likely to be confused with either of those diseases. It is a most valuable phenomenon, due to the selective action of a particular toxin on certain nerve-cells and fibres, the exact position of which is still a matter of doubt. It is not always due to actual degeneration, as the phenomenon may come and go from time to time.

It has an early or incomplete stage, as Argyll Robertson pointed out in his original paper in 1869, in which the light reaction is not abolished but is only delayed or sluggish. Thus in a patient when first diagnosed to be suffering from general paralysis a sluggish reaction of the pupils was obtained, while later on, as the attack culminated, the reaction became totally abolished, the change taking place during the course of one night. As the acute symptoms passed off six weeks afterwards the reaction returned, but was still sluggish. The reaction may be present in one eye only, or be in the early or incomplete stage in one eye and in the advanced or complete stage in the other. It is not difficult to distinguish this sluggish reaction from the normal, as the necessary skill is soon acquired after seeing a few cases, especially if a case be studied in which there is one normal eye for the purpose of comparison. The normal contraction is stated to last about one-fifth of a second, and the sluggish reaction probably lasts twice as long. While the complete Argyll-Robertson phenomenon is almost always a post-syphilitic sign, sluggish reaction of the pupils of a temporary nature is frequently observed in alcoholic and other conditions.

The Indirect Light Reflex.

The light reflex should be tested with different degrees of illumination, and the best results are not got in a bright light. If the pupils be contracted, as sometimes happens in general paralysis, but not so frequently as in tabes, it may be difficult to get satisfactory results under any conditions. The most delicate method of testing for the presence of the Argyll-Robertson phenomenon is the test for the indirect or consensual light reflex. This is performed by fixing open the lid of one eye with the thumb and watching the pupil of that eye attentively, while with the other hand the other eye is alternately opened and closed. This method of examination possesses two

advantages—it enables the pupil to be very closely and continuously observed without any interruption from the process of alternate illumination and shade, so that the quickest and slightest movement cannot possibly escape detection; it also applies a feebler light stimulus for the purpose of eliciting the reflex than the direct method, especially if with the latter both eyes have been illuminated, and failure is therefore more likely to occur if the pathway be obstructed. The afferent fibres in the optic nerves conveying the light stimulus decussate in the chiasma in the same way as the visual fibres. They possibly do not decussate equally (Oppenheim), the smaller bundle crossing over, for if a bright light be made to shine in one eye it will often cause a greater direct contraction of that eye than a consensual contraction of the other. Unequal intensity of the stimulus is undoubtedly an important factor in the production of the Argyll-Robertson phenomenon, for the greater intensity of the stimulus which actuates the accommodation reflex is the explanation which is usually offered for the retention of the accommodation reflex, while the light reflex is lost. A sluggish contraction may thus be obtained by the indirect method of testing in the earliest stage of the Argyll-Robertson phenomenon, while the reaction still appears to be normal by the method of direct illumination whatever the explanation may be.

According to these views there are three stages of the Argyll-Robertson phenomenon or loss of the light reflex:

(1) A normal direct reflex and a sluggish indirect reflex.

(2) A sluggish direct reflex with a more sluggish or absent indirect reflex.

(3) Abolished direct and indirect light reflexes.

Sluggish light reflexes are far more commonly met in the early stage of general paralysis than the complete Argyll-Robertson phenomenon, but the latter may precede the development of general paralysis by many years, although this experience is not so common as in the case of tabes. A sluggish or abolished light reflex is present in 70 *per cent.* of the cases of general paralysis (Franz). They are therefore signs of primary importance on account of their frequency alone, and in their absence a diagnosis must be made with caution.

Bevan Lewis records the opinion that the loss of the sensory reflex, a dilatation produced by pain as from the prick of a pin

near the eye, is the earliest pupillary symptom in general paralysis. This reaction varies in normal persons, and the application of the test is more open to error than that of the indirect light reflex.

The Knee-Jerks.

In 75 *per cent.* of the cases of general paralysis the knee-jerks are either exaggerated or else sluggish or absent (Franz). These two abnormal reactions do not have the same diagnostic value, for exaggeration, unless very marked, occurs in so many nervous conditions that it does not point specially to general paralysis. It is different, however, with the sluggish or abolished reaction, which occurs in over a fourth (28 *per cent.*) of the cases of general paralysis. It is very significant of that disease or tabes, and like the incomplete Argyll-Robertson phenomenon it is often an early symptom.

The examination must be carefully made, and the attention of the patient should be distracted by directing him to look upwards at some object and by asking him a question, such as his age. The leg should be in a favourable position, with the foot on the ground, the knee flexed at a slightly obtuse angle, and a proper percussion hammer employed to strike the blow.

Comparison of Jerks.

Valuable information can be gained by comparing the reactions, and in an early stage the one knee-jerk can be compared with the other, for only one may be found to be sluggish. At other times the knee-jerks may be compared with those obtained in the arms. Thus in one case my suspicions were aroused by eliciting an active radial jerk by percussing the end of the radius, while the knee-jerks were very poor. In all cases of sluggish knee-jerks the Achilles tendon should also be tested, and this can be very easily and conveniently done by asking the patient to kneel on a chair with one leg at a time, facing the back. It is sometimes found in these cases that the Achilles jerk is already absent, for it tends to disappear sooner than the knee-jerk. The longer the nerve-fibre the more vulnerable apparently is the neurone to degeneration, hence these abnormalities appear earlier at the ankle than they do at the knee, and at the knee earlier than at the elbow. The examination of the Achilles jerk should therefore be a routine procedure.

The Speech and the Writing.

Both the speech and the writing are affected in general paralysis, but the latter is not of much diagnostic value as an early sign for many reasons. The standard of caligraphy varies greatly—even well-educated people may write badly—and much depends on the pen or on the environment at the moment. As a practical test it fails on the one hand because of nervousness, and on the other because by taking more time and care a patient suffering from early general paralysis may turn out better writing than his normal or average. These variations in writing can be studied by comparing the carefully written address on the envelope with the less careful writing in the letter itself, and the beginning of a letter with the signature at its end.

The disorders of speech are more important, and they can be more accurately tested by asking the patient to repeat words or phrases more and more quickly. Every person attains to a practical efficiency of articulation, but it is possible by combining syllables together which are awkward to pronounce, and by urging him to speak faster and faster, to reach a stage when blunders will necessarily occur with all. In testing the articulation in general paralysis this must be remembered, and the tests should not be made too severe, or they fail in their object. The pronunciation of the labials and the linguals should be separately tested, as in the early stages the defect is usually limited to one or other. For the labials the words "Hippopotamus" "Hopping Hippopotamus" repeated three times quickly are sufficiently discriminating, and for the linguals "British Constitution" or "Third Territorial Artillery" will serve.

In making these tests the examiner should repeat the form of words at the same pace as he demands from the patient. He must remember that in states of exhaustion and neurasthenia defects of speech may be elicited, that dental plates or missing teeth and parched lips or tongue are a handicap to articulation, and that this function may be affected by nervousness.

In the early stages of general paralysis the errors that may occur are of two kinds, either a stumbling and stopping at a letter, or a missing and passing over of a letter. By the first blunder a syllable may be repeated once or twice, as, for example,

"Hip-pip-pip Potamus," and by the second the syllables are slurred or run together, as, for example, "Bri'sh Const'ution." In other cases the speech is only less facile and slower. At this stage the high-pitched and tremulous intoning speech has not yet developed.

Facial Expression.

When the patient speaks tremor of the lips may be noticed, but this may be only emotional in origin. Tremor of the tongue may also be present, but this symptom occurs in so many nervous and toxic conditions that it is not of much diagnostic value. Of more value is the expression of the face, which is often heavy, immobile, or mask-like at a comparatively early stage. The natural and ceaseless play of the muscles of expression, which accurately reflect every variation and phase of mental feeling, is lost or much diminished, a condition termed "amimia." This stiff and expressionless look, of the lower part of the face chiefly, is often associated with labial defects of the articulation.

Laboratory Methods.

If some, but not necessarily all, of these physical signs relating to the expression, articulation, knee-jerks, or pupils—and of these the last are the most important—be found associated with mental symptoms indicating deterioriation, such as failure of memory, impairment of judgment and moral laxity, and especially if these occur in a man of middle age who has had syphilis about ten years previously, then general paralysis should be suspected. The case should now be submitted to laboratory methods for the application of the six new serum and cerebro-spinal fluid tests, in order that the diagnosis may be confirmed and certainly attained. In the first place 5 c.c. of blood drawn off by venepuncture should be sent to a thoroughly reliable serologist to test for the Wassermann reaction.

A Negative Wassermann Reaction in the Serum.

If the Wassermann reaction in the blood-serum be found to be negative, general paralysis can be almost certainly excluded, for in experienced hands a positive reaction is obtained in 99

per cent. of the cases of general paralysis. In those cases in which the clinical symptoms are few and indefinite, and mere suspicion of general paralysis existed, this negative result is sufficient to allay suspicions, and further examination need not be made.

Negative Reactions in Serum and Spinal Fluid.

In those cases, however, in which the clinical symptoms are numerous or fairly typical of general paralysis, lumbar puncture should next be performed, and 5 c.c. of spinal fluid withdrawn. If the Wassermann reaction be negative in the spinal fluid as well as in the blood-serum, then general paralysis may now, with almost absolute certainty, be excluded in spite of the clinical symptoms. One of my cases of stationary but undoubted general paralysis, which had lasted twelve years, gave, however, a double negative Wassermann reaction.

A Positive Reaction in the Serum and a Negative in the Spinal Fluid.

In those cases in which a positive reaction has been found in the blood, proof of latent syphilis has been obtained, and lumbar puncture must always be performed. If the reaction in the spinal fluid be then found to be negative, the case is one of mental symptoms in a person who has had syphilis, but whether these symptoms be due to cerebral syphilis or not can only be decided by a clinical study of the case. In 6 *per cent.* of the cases, however, a negative reaction has also been obtained in the spinal fluid in general paralysis, so the other tests should be applied and further close study of the clinical symptoms made to exclude it.

Positive Reactions in Serum and Spinal Fluid.

If the reaction in the spinal fluid as well as in the blood be positive, then the case is either one of general paralysis, or of tabes with mental symptoms, or of syphilis of the nervous system with mental symptoms, or of any two or all of these three conditions in combination. By far the most probable diagnosis, however, is general paralysis, for while the positive reaction in the cerebro-spinal fluid is obtained in 94 *per cent.* of

all cases of general paralysis, it is obtained in 53 *per cent.* of tabes (Bayly) and in only 17 to 50 *per cent.* of syphilis of the nervous system (Bayly, Henderson).

A Negative Reaction in the Serum and a Positive in Spinal Fluid.

Whether the reaction in the serum be positive or negative does not matter if a positive reaction has been obtained in the spinal fluid. The latter is the paramount sign, and even alone definitely indicates an involvement of the nervous system by one or more of the three diseases mentioned. The greatest use of the blood test is not to give confirmatory evidence, but to avert the necessity of lumbar puncture in those cases in which the blood is found to have a negative reaction. It has, however, already been stated that a negative reaction is obtained in the blood-serum in 1 *per cent.* of cases of general paralysis, with (and in one very chronic case without) a positive reaction in the cerebro-spinal fluid.

Lymphocytosis.

The cytological examination of the spinal fluid must next be made, and if a lymphocytosis be present in association with a positive Wassermann reaction of the fluid, it confirms the previous diagnosis that the nervous system is involved by one of the three diseases mentioned. If a definite lymphocytosis be absent it does not negative the presence of general paralysis, as it is known to be absent in 10 *per cent.* of the cases; moreover, the absence of lymphocytosis is against the diagnosis of cerebro-spinal syphilis.

If the Wassermann reaction in the spinal fluid has been negative, but in the blood positive, and a lymphocytosis is found, this combination usually points to syphilis of the nervous system, but it may occur in 6 *per cent.* of cases of general paralysis, and the differential diagnosis of these two conditions in this percentage of cases must be made on clinical evidence.

Presence of Globulin, Albumin, and Plasma-Cells.

The three minor tests are the excess of globulin demonstrated by means of a saturated solution of ammonium sulphate (the

Ross-Jones test), the presence of over 0·1 *per cent.* of albumen tested by Aufrecht's albuminimeter, and the presence of plasma-cells in the cell-count. These tests confirm the results of the three major tests, or in the absence of these confirm a provisional diagnosis of general paralysis made on the strength of the clinical symptoms.

Summary.

By means of the positive Wassermann reaction of the cerebro-spinal fluid general paralysis can be differentiated from every other condition which simulates it but tabes and syphilis of the nervous system, and the other five tests assist very little in the differential diagnosis of these three conditions, which must be made on clinical grounds. The necessity for the exact study of the clinical symptoms of these diseases is now not less but more necessary than ever, and a short account is therefore added of the chief diagnostic features of tabes and cerebral syphilis with mental symptoms.

Tabes with Mental Symptoms.

According to Dr. Byrom Bramwell's statistics, 11·4 *per cent.* of tabetics pass into general paralysis, and it is computed that at least one-third of the cases of general paralysis present tabetic signs. Excluding these cases of tabo-paralysis it is found that persons suffering from pure tabes seldom present mental symptoms, and it is notorious that many intellectual and distinguished men have been afflicted with this disease.

If tabes occurs in a member of a neurotic family the patient will be subject to the same neuroses and psychoses as his relatives, and if he be alcoholic to alcoholic insanity. In such cases neurasthenia is common and gives rise to some anxiety, as it is difficult to differentiate it from the early neurasthenia of general paralysis. Certain forms of alcoholic insanity may also cause anxiety by simulating general paralysis, but they may also mask its development.

There are, however, three types of mental disorder which seem to be specially associated with tabes :

(1) An insanity of persecution, with more or less systematised delusions and irritability.

(2) A mild melancholia, with hypochondriacal fancies and some enfeeblement. The delusions in these two types are possibly founded on the lightning pains.

(3) Lastly, in some old-standing cases a mild degree of dementia may develop, associated with an emotional condition of either indifference or optimism. In some of these cases the lesions of general paralysis have been found in the brain, but in others, including two cases examined by Alzheimer, they were not found.

The appearance of mental troubles in a tabetic ought always to awaken the suspicion of general paralysis, especially if accompanied by signs of confusion, of mental weakness, and of loss of memory, and in which the deterioration is progressive. The development of speech difficulties and of a heavy, mask-like expression of the types characteristic of general paralysis are ominous physical signs. It is believed that the tendency to pass into general paralysis is greater in the early years of tabes than after the disease has existed many years.

With regard to the Wassermann reaction and the other reactions and signs, while these may be exactly the same as those obtained in general paralysis, they are not nearly so constant. The Wassermann reaction is obtained in the serum in about 60 *per cent.* of the cases, and in the cerebro-spinal fluid in about 50 *per cent.* (Bayly). These low percentages as compared with the 99 and 94 *per cent.* in general paralysis probably indicate that the disease is not so extensive nor so active. I also express the opinion with some diffidence that in a considerable proportion of mild cases the activity of the disease process diminishes, and may cease altogether. I would thus account for the existence during a life-time of solitary symptoms like optic atrophy, the Argyll-Robertson phenomenon, or the loss of the knee-jerks, and for those stationary cases which give a double negative Wassermann reaction. The continuation of the pains and other symptoms in these cases is possibly not due to any active disease, but to the organic changes which have already taken place. Treatment also, while not influencing the organic changes, has, according to Boas, a definite effect on the Wassermann reaction in rendering it negative in about one-half of the cases, and very often in the early stages the symptoms are ameliorated. In the nature of its response to treatment by salvarsan, tabes occupies an

interesting position midway between general paralysis and cerebro-spinal syphilis.

Cerebro-spinal Syphilis with Mental Symptoms.

Cerebral syphilis with mental symptoms may simulate general paralysis so closely as to make the differential diagnosis an impossibility during life. The nine errors of diagnosis in Plaut's and Southard's ninety-five cases were chiefly due to this cause, which includes gumma, meningitis, and endarteritis, both of the large arteries and the terminal vessels, the so-called Heubner's and Nissl's types. There is little doubt also that most of the supposed recoveries from general paralysis have been cases of cerebral syphilis. On the other hand, general paralysis may be complicated by the presence of focal lesions, which may simulate those of cerebral syphilis. The distinctive lesions of the two conditions have also been found combined after death, and a number of cases have been reported in which the patient first presented symptoms of cerebral syphilis, and subsequently developed general paralysis.

The mental symptoms do not help materially in distinguishing certain cases of cerebral syphilis from general paralysis, and more reliance must be placed on the physical signs. These are more definitely localised in cerebral syphilis, and less diffused or general. They usually appear more suddenly, and are more permanent than similar signs in general paralysis. The speech defects have not the distinctive character of the articulation in general paralysis, and are more often associated with ordinary aphasia. The Argyll-Robertson phenomenon is not usually present in cerebral syphilis, whereas ocular paralyses occur earlier and are more frequent. The extensor reflex of the great toe is rarely present in general paralysis unless it is complicated by a focal lesion.

The history of the attack of syphilis in cerebral syphilis often shows it to have been a severe one, which is unusual in general paralysis. It usually develops much sooner after the infection, and may co-exist with other tertiary or even secondary manifestations. Of 228 cases of syphilitic hemiplegia Fournier found that nearly 40 *per cent.* (39·4) occurred before the end of the third year, while of 112 cases of general paralysis only one occurred during that period and only 4 *per cent.* before the

sixth year, the majority occurring between the eighth and twelfth years. Many persons suffering from cerebral syphilis, owing to its early development, are under thirty years of age, whereas few general paralytics are, unless those who suffer from congenital syphilis. Lastly, the effect of anti-syphilitic treatment is usually beneficial to the symptoms of cerebral syphilis, but not so to those of general paralysis.

In cerebral syphilis it is usual to find a positive Wassermann reaction in the blood, a negative reaction in the cerebro-spinal fluid, a very high lymphocytosis and a moderate excess of globulin. In a number of cases, varying from 17 to 50 *per cent.* (Bayly, D. K. Henderson), a positive reaction is also obtained in the cerebro-spinal fluid. The reaction is most frequently obtained in recent cases, while in old-standing cases it may disappear not only from the cerebro-spinal fluid but from the serum as well, the active disease having apparently become extinct. These reactions and signs are influenced so greatly by treatment, in contrast to what obtains in general paralysis, that this forms perhaps the most reliable diagnostic test of cerebral syphilis. The excess of globulin quickly disappears, the high cell-count falls to a little above normal, and the positive Wassermann reaction usually disappears, first from the spinal fluid and then from the serum. In cerebral syphilis the power of the spinal fluid to reduce Fehling's solution, which is present normally and in general paralysis, may be lost, but it returns under treatment (Kaplan, *Am. Journ. of Insanity*, vol. lxix.)

General Paralysis without Clinical Symptoms.

So far I have only considered the new reactions and signs as evidence which confirmed that of the clinical symptoms, and therefore as a subsidiary element in the diagnosis of general paralysis. Are they not the most important element, and would we not be justified in diagnosing the disease from their presence alone? They are present at a very early stage, exactly how early no one yet knows, and it is quite possible these reactions and signs may exist before there are noticeable clinical symptoms. There is nothing impracticable in their discovery under these circumstances, for everyone who is now infected with syphilis ought to have his blood examined for the Wassermann reaction, and if this be persistently positive, his

cerebro-spinal fluid should be examined too. If such a patient's blood and cerebro-spinal fluid gave a double positive Wassermann reaction, associated with lymphocytosis, plasma-cells, albumen, and an increase of globulin, it would scarcely be possible, in my opinion, to avoid the diagnosis of general paralysis or tabes, even in the absence of any definite psychological or neurological symptom. The subsequent development in such a case of mental and nervous symptoms would be conclusive, and would confirm the diagnosis of general paralysis. It would be a very satisfactory result of the progress made in medicine if one could make such an early diagnosis before any symptoms of degeneration could be observed, and it might yet prove invaluable as regards treatment.

It is possible that in the future transient mental episodes and neurological phenomena, resulting from latent syphilis, may be noted, which may bear some relationship to, and occupy some intermediate position to, general paralysis, and be of a more benign character. *Formes frustes* may also be discovered, as has usually been the case with other diseases when our knowledge of them has become more accurate, but in the whole field of psychological medicine there is still not a more responsible problem, or one requiring the exercise of more prudence and caution, than the early and definite diagnosis of general paralysis.

The Ætiology, Prophylaxis and Treatment of General Paralysis.

Ætiology.

It is impossible to discuss the prophylaxis and treatment of general paralysis without disposing of the vexed question of its ætiology, but the more this is investigated the more is one impressed by the mass of circumstantial evidence in support of the syphilitic hypothesis. A short *résumé* of this will be given.

Relationship to Tabes.

General paralysis and tabes have the same ætiology, the facts relating to the one running an exactly parallel course to those of the other. Of a whole family infected with syphilis some members may develop one disease and some the other, and of

several men infected from one source the same may be true. Souques reports a family where the father had general paralysis, the mother tabes, and two daughters tabes, and Moenkemöller a converse instance in which the father had tabes, the mother general paralysis, and a daughter general paralysis. Of five glass-blowers mentioned by Brosius who simultaneously contracted chancre of the lip in their occupation, four ultimately suffered from tabes or general paralysis; and of four men infected by one woman, mentioned by Erb, all developed in time either tabes or general paralysis (Mott). The two diseases may develop together or in sequence in the same subject, forming tabo-paralysis. They are similar diseases, differing chiefly in the locality, in the extent, and in the intensity of the disease process, and evidence relating to the ætiology of the one is applicable to the other.

History of Syphilitic Infection.

Of 1,100 male cases of tabes among the better classes Erb found that 89·45 *per cent.* had been infected with definite syphilis, and he wrote that in his opinion general paralysis had the same relationship to syphilis (*Les Affections Parasyphilitiques*). It is difficult to get so high a percentage of syphilitic infection in general paralysis, as, owing to mental enfeeblement and loss of memory, the history supplied by the patient is more often imperfect. The length of time that elapses from the date of the infection, the mildness of the symptoms and the absence of tertiary complications which usually obtain in general paralysis, contribute also to obliterate the facts of infection from the memory. Fournier, nevertheless, gives a list of twenty authorities who have obtained a definite account of previous syphilis in from 66 to 92·8 *per cent.* of their cases. Such statistics vary, for those supplied by private patients of the rich classes give higher results than those of the poor, who are less observant; and men give higher results than women, as infection in the latter is often not noticeable.

Taking the average of the higher statistics as being nearer the truth, for in them a fuller history has probably been obtained, in about 80 *per cent.* of those suffering from general paralysis proof of syphilitic infection exists. Failure to obtain evidence in the remaining 20 *per cent.* is not remarkable under the circum-

stances already mentioned, and when we recall the fact that in the tertiary lesions of undoubted syphilis there is failure to obtain a history of syphilitic infection in a percentage as high. Lang, of Vienna, failed to get a history of infection in 36 *per cent.* of late forms of syphilis (Krafft-Ebing), Pernet failed in 20 *per cent.* of obvious syphilitic skin disease (Mott), and Fournier failed in 15 *per cent.* of cases of gumma of the palate (Ballet).

Syphilis without Manifestations.

The Wassermann reaction has thrown a new light on cases of unsuspected, undiagnosed, and unrecovered syphilis which helps us to understand why many cases of general paralysis do not give a history of syphilis. It has taught us that a person may acquire syphilis without showing any symptoms. Colles's law affirms that the mother of a syphilitic child is immune to infection, and the explanation of this fact is simply this—that she has already acquired syphilis. It is found that her blood gives a positive reaction in three cases out of four, although in two thirds of the cases the woman is unconscious of having been infected (Mackintosh and Fildes). It has also taught us that syphilis may persist for many years in the form of latent syphilis without any symptom. The vast majority of the cases of general paralysis suffer in this way, and in them no history can be obtained of any active syphilitic signs or manifestations. The Wassermann reaction has also been of use in clearing up difficulties due to the presence of congenital syphilis without any stigmata or symptoms of syphilis, or even malnutrition or defective development, which we now know is possible. These cases may ultimately suffer from adult general paralysis, and if congenital syphilis be unsuspected and acquired syphilis can be excluded, they present great ætiological difficulties. Percy Smith has described such cases in adult women in whom syphilitic parentage was ultimately traced. An instructive account of two virgin sisters, the victims of congenital syphilis, who died of general paralysis at the ages of forty-two and forty-three, is given by Christian Müller. In these women the stigmata of congenital syphilis were fortunately present and the existence of the disease was recognised, but had they been absent these two cases might very easily have served as conclusive examples of general paralysis without syphilitic infection.

Varying Incidence of General Paralysis.

What is quite as impressive as the high percentages of syphilitic infection is the faithful way the incidence of general paralysis varies in localities, professions, sexes and ages in accordance with the estimated variations in the amount of syphilis. It is more prevalent in urban than in rural asylums, and it reaches its maximum in large seaport towns like Leith, and its minimum in districts like the Highlands of Scotland. It is eighteen and a half times more frequent in the Royal Edinburgh than in the Inverness District Asylum among a similar class of patients. Soldiers and sailors are more frequently attacked than the clergy, and men with means leading a fast life in town than wealthy members of the Society of Friends. It accounts for a half to three-quarters of the insanity occurring among German officers. Men are attacked on an average about four times oftener than women; but in the richer classes the proportion may be 10 or even 20 to 1, while in the poor it may be less than 3 to 1, these figures, according to Blaschko, representing the proportion of syphilis in the two sexes (Mott). An exception to the general rule occurs in juvenile and adolescent general paralysis, where the two sexes are attacked in equal numbers, because the incidence of congenital syphilis is naturally equal in the two sexes at birth. It usually develops after an incubation period of eight to twelve years, and it is rare before thirty or after fifty-five, but is common between the ages of forty and forty-five. Contrary to what holds good in men it is commoner in married women than in single, and among single women of the richer classes the disease is practically unknown, although it exists among prostitutes above thirty years of age. Conjugal general paralysis develops almost always in the wife after the husband (Moenkemöller), and if the reverse order occurs it will probably be found that the wife had acquired syphilis before marriage and then infected her husband. The relative frequency with which conjugal general paralysis occurs, namely, 2·5 *per cent.* of the married couples affected, does not give any support to the hypothesis that there is a special or neurotoxic type of syphilis or spirochæte (Mott).

Countries and Races.

General paralysis, it is thought, is not so prevalent in primitive societies in the tropics where syphilis exists as in more highly

civilised countries, and this may be due to the simpler and less strenuous life led in the former, or it may be due to early marriage, different social customs, or to living mainly in rural communities. This opinion regarding its prevalence, on the other hand, may be based on erroneous or imperfect observation. The Japanese, for example, were formerly believed to be singularly free from general paralysis but not from syphilis, yet 15·8 *per cent.* were admitted to the Tokyo Asylum during the quinquennium from 1887 to 1901 (Peterson). The same opinions were expressed of the Abyssinians, and von Halban states that tabes is now more common in their country than in Vienna (Mott). The native Egyptians likewise were believed by Peterson in 1892 to have much syphilis but little or no general paralysis, but Dr. Warnock records in his annual report that 8 *per cent.* of the male admissions to the Cairo Asylum in 1909 were cases of general paralysis, the majority being Egyptians. According to Hutton, the disease has not yet appeared among the Eskimos of Labrador in spite of their terrible sexual excesses, but syphilis was introduced among them for the first time only in 1902. General paralysis is rare among Icelanders, and so is syphilis, and I am informed on good authority that the same facts are true of the West Indian negroes.

Percentage of Syphilitics Attacked.

General paralysis and tabes only develop in 3 to 5 *per cent.* of those infected with syphilis, and many have thought that this small percentage-rate was a fact telling against the syphilitic hypothesis, indicating possibly that syphilis alone could not cause the disease, and that another cause was probably associated with it. The tertiary lesions of syphilis affecting all the systems and not the nervous alone, according to Sir Douglas Powell, only occur in about 12 *per cent.* of all the cases originally infected with syphilis, and such lesions usually occur early, 40 *per cent.* of the lesions of the nervous system arising before the end of the third year (Byrom Bramwell). The soil for their development is nearly co-extensive with the number infected. On the other hand, only 4 *per cent.* of the cases of general paralysis occur before the sixth year, during which interval, judging by the results of the Wassermann reaction in

1490 cases of late latent syphilis examined, 63 *per cent.* of those originally infected have recovered (Mackintosh and Fildes), and a few may have died. General paralysis, being a late manifestation, therefore occurs in 9 to 15 *per cent.* of the remaining third who have not recovered from the attack of syphilis at the end of five years. This must be considered a fair proportion in contrast to the incidence of tertiary lesions of all the systems and in comparison with similar conditions, such as post-diphtheritic paralysis, only occurs in 15 *per cent.* of those affected, and it tells against the theory of a special type of syphilis in general paralysis.

Accessory Factors.

Among the causes believed to assist syphilis in the development of general paralysis the principal are alcohol, sexual excess, overwork, worry, trauma, infections, intoxication, and heredity. No doubt the combined action of two injurious agents like syphilis and alcohol will be much greater than the action of each singly, and the strictly specific action of each will be intensified owing to a diminished general resistance. Moreover, it is possible that neurotoxic infections may by their action determine the onset of general paralysis just as a trauma may start a gumma. The occurrence of juvenile and adolescent general paralysis does not, however, lend support to the view that these accessory factors play an important, far less an essential, part. In these early cases all the additional factors can usually be excluded with the exception of heredity, yet the disease develops after the same incubation period as adult general paralysis, and the symptoms present the same features, usually those of the feminine type.

A Diphtheroid Bacillus.

Special reference may be made here to Dr. Ford Robertson's hypothesis that a diphtheroid bacillus, to which he gave for convenience the name of *Bacillus paralyticans*, was the chief cause of general paralysis. I am in a position to affirm from numerous observations, mostly negative, conducted with great skill and care at my instigation in the laboratory of the Stirling District Asylum by Dr. Muirhead, that diphtheroid bacilli are to be found in the blood or cerebro-spinal fluid in about 33 *per cent.*

of the cases of general paralysis. These observations are confirmed by very few workers, and almost all of those who have carried out such investigations assert that they have found the blood and spinal fluid sterile. This was also Dr. Muirhead's experience with the vast majority of her cultures, but by repeating the experiments again and again, especially in relation to cerebral seizures, she was successful once or oftener in 33 *per cent.* of the cases. Not only have many pure cultures been thus made, but in a few cases the bacilli have been seen in blood-smears, and on one slide in particular they are to be found in thirteen different places and in two groups of four and five. The significance of their presence is a subject on which, however, with all deference, I do not agree with Dr. Ford Robertson, among other reasons, owing to the fact that they are also to be found in the blood in a similar proportion of cases of delirious insanity or acute hallucinatory confusion. These diphtheroid bacilli may possess a neurotoxic action, and may produce nervous and mental phenomena, but they can hardly be the essential cause of general paralysis under such circumstances. They have been found, for example, in the blood of a girl suffering from post-rheumatic or choreic insanity associated with a streptococcus, who in a short time made a perfect recovery.

Krafft-Ebing's Inoculation Experiments.

In the year 1897 Krafft-Ebing created a sensation by announcing that a friend of his had inoculated with active virus nine of his advanced general paralytic patients from whom no history of syphilitic infection could be obtained, and found that they were all immune. From this result he concluded that they had all previously been infected with syphilis, as well as the others in whom a definite history of infection had been obtained. This drastic experiment was, however, not scientifically conclusive, for there were no control cases inoculated with the same material, and no one knows if some of the healthy may not be immune to syphilitic inoculation. Had a reaction occurred this would not necessarily have disproved syphilitic infection, for it is believed that a virulent and extensive re-inoculation may produce local symptoms or superinfection in unrecovered syphilis. Unless, however, we assume that all

patients suffering from general paralysis have been previously infected with syphilis, it is remarkable that none are seen suffering from either the primary or the secondary symptoms of syphilis, considering the frequency with which they expose themselves to infection in the early stage. A few instances of recent syphilis have been recorded, but the significance of these exceptional observations remains in doubt (Tanzi, Ballet).

The Positive Wassermann Reaction.

The finding of a positive Wassermann reaction in the blood and cerebro-spinal fluid of persons suffering from general paralysis in 1906, like Krafft-Ebing's experiments, was believed at first to have conclusively demonstrated its syphilitic nature. Though the reaction is a very reliable clinical test of syphilitic activity, it is an empirical reaction and is not strictly specific, for it can be obtained by other means than by the union of syphilitic antigen with antibody. In spite of this objection the undeniable presence of the reaction in over 99 *per cent.* of the cases of general paralysis has added enormously to the strength of the syphilitic hypothesis, if it cannot be held to have proved it conclusively.

Links with Active Syphilis.

It enables us also to differentiate general paralysis and tabes from every other condition that simulates it, excepting cerebro-spinal syphilis, which is in itself a strong proof of a very close relationship between these diseases and syphilis. In some cases an active tertiary syphilitic process of the nervous system has co-existed with general paralysis, and the combined lesions have been found after death. Links such as these between general paralysis and active syphilis are very important, for it is believed by Plaut that the nervous system is always prepared for the development of general paralysis by syphilitic changes. It is possible, too, that some of the so-called premonitory symptoms of general paralysis, isolated phenomena such as temporary confusion, paralysis, or convulsion, which occur years before the development of the disease, are due to cerebral syphilis, and are not early symptoms of general paralysis. For example, one of my patients acquired syphilis in 1883. Fourteen years later, during his honeymoon, he had a transient

attack of aphasia; twenty-one years later he had a similar attack after an exhausting bicycle run, and twenty-nine years later had a third seizure which ushered in a typical general paralytic delirium; and he has had several since. Were these first two seizures early symptoms of general paralysis, or were they a syphilitic complication? According to Magnan most probably the latter, but it is possible they were isolated symptoms with prolonged remissions, a species of *forme fruste* or an intermediate benign condition.

The Parasyphilitic Hypothesis.

These observations, and the belief that the Wassermann reaction is a sign of active syphilis, have greatly weakened Fournier's hypothesis of parasyphilis, which is that general paralysis, tabes, and other diseases, while of syphilitic origin, were not of a syphilitic nature. This view was founded on the two observations that these diseases were not amenable to anti-syphilitic remedies, and the lesions found in them were diffuse and did not possess the characters of syphilitic lesions. The lapse of time between infection and the onset of the symptoms is no doubt also a factor to be reckoned with. There was much that was fascinating in this ingenious hypothesis, but it was never anything more than speculation. Our conception of the curability of syphilis has entirely changed since the Wassermann reaction has been employed to control its treatment. In the past many were unfortunately content to remove merely the external manifestations and call this a cure, although others wisely insisted on a prolonged course of treatment. We know now that while the manifestations of tertiary syphilis respond wonderfully to salvarsan and mercury, it is not possible in some cases to remove the positive reaction from the blood. Not only do such cases form a link in this respect with so-called parasyphilis, but there are occasionally cases of true syphilitic manifestations which are quite intractable. As a general rule, the later the lesion the less amenable is it to treatment, and general paralysis of course occurs very late. On the other hand, to affirm that a lesion, in spite of strong evidence, is not syphilitic because it is unlike any other known lesion, is an unscientific assumption, especially as our knowledge of late syphilitic phenomena, thanks to the Wassermann reaction, is only in its infancy as yet. The parasyphilitic hypothesis is an

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offence against the *lex parsimoniæ*, which affirms that the simple explanation should be preferred to the more complex, and according to this general paralysis and tabes should be considered signs of active syphilis and not of parasyphilis.

The Discovery of Spirochætes in the Brain.

The problem of the ætiology of general paralysis appears to have been finally and conclusively settled by the finding, at the end of the year 1912, by Noguchi, of the *Spirochæta pallida* in the brains of fourteen cases of general paralysis (*Journal of Experimental Medicine*, February, 1913). He employed a modification of the Levaditi method of staining, and he hopes by improving the technique to find it in a larger proportion of cases than 1 in 5. This is a most important and epoch-making discovery, for it not only decides for all practical purposes many theoretical questions, but it also points with confidence to one way, and one alone, of prophylaxis and treatment. The spirochætes are found in large numbers, as many as a dozen being sometimes seen in the field, in the grey matter of the convolutions. None are seen within the peripheral or neuroglia layer of the cortex or in the pia arachnoid, and few are found either in the white matter or round the vessels. In almost all instances the spirochætes seem to be burrowing among the nerve-cells. All these cases were of undoubted general paralysis, for the possibility of tertiary syphilis was carefully excluded by microscopical examination. A very interesting and important point is the localisation of the spirochætes among those cells, whose functional disturbance and degeneration is the probable explanation of the symptoms of the disease, and their proximity to the cells points to them as the immediate cause of their disordered function and degeneration. The theories of a para-syphilitic toxin, of secondary infections or of other accessory factors, sink into insignificance beside this convincing fact, and no other conclusion can be drawn from it than this, that general paralysis is one of the manifestations of active syphilis—a late manifestation, it is true, for which no doubt explanations will be forthcoming, but nevertheless one of genuine or true syphilis.

A Special Type of Spirochæte.

Noguchi's discovery does not dispose of the hypothesis that there is a special type of spirochæte in general paralysis, causing

mild symptoms, resistant to treatment, and with an affinity for the nervous system. The hypothesis originated when the ætiological difficulties appeared unsurmountable, but, with the facts we now possess, it appears to be an unnecessary elaboration. Dreyfus has found changes in the spinal fluid in 80 *per cent.* of cases of primary and secondary syphilis, so that nearly all types of syphilitic spirochæte at an early state seek the nervous centres. I have shown how probably 9 to 15 *per cent.* of cases of unrecovered syphilis at a late stage, after five years, may suffer from general paralysis or tabes—a larger proportion than was realised. Mild cases, in which adequate treatment has probably not been thought necessary, form a large percentage of these non-recoveries, and while the relationship of syphilis with mild manifestations and general paralysis has long been known, Fournier has also traced a connection between inadequate treatment and general paralysis. Finally, with regard to the results of treatment, the Wassermann reaction has shown us that tertiary and latent syphilis is not the simple and curable disease it was once thought.

The recorded instances of familial general paralysis and tabes and of several individuals infected from one source, while remarkable, are too few to found any theory upon, while on the other hand, the proportion of cases of conjugal general paralysis, namely 2·5 *per cent.* (Moenkemoller), is so low that it is evidence against the hypothesis (Mott).

Conclusion of Etiology.

In conclusion, it cannot be alleged that this great discovery by Noguchi is either unexpected or overturns our conceptions of general paralysis. The previous evidence, on the contrary, is in complete harmony with it; frequent references to the possibility of this discovery are to be found in recent literature; and many a futile search has been made in our laboratories for the spirochæte before the skill and perseverance of Noguchi were rewarded. Rather can it be said that it was owing to our failure to demonstrate the organism that the theories of parasyphilitic and other toxins continued to exist. The keystone has now been found and fitted to the arch, completing a solid structure on which we can safely base our theories of prophylaxis and treatment.

Prophylaxis.

The first and best measure for the prevention of general paralysis is the thorough treatment to complete recovery of the attack of syphilis. The earlier this is begun the more likelihood is there of attaining success, for primary syphilis is more curable than secondary, secondary than tertiary, and tertiary than latent syphilis. Cure, too, is tested, not by the disappearance of all visible manifestations of the disease, but by a permanently negative Wassermann reaction for anything else is futile. One dose of salvarsan or a course of mercury may cause a skin eruption to disappear completely without curing the disease or influencing the Wassermann reaction in the blood at all, and we know from experience that most of those who develop general paralysis suffer from latent syphilis presenting no visible signs.

The employment of the Wassermann reaction as a test of recovery from syphilis is its most useful service, for the chief cause of the tragedy of the past was the absence of such a test, one-third of the cases treated not having been cured of their disease. The evils resulting from this we are only now beginning to realise, and they include not only general paralysis and tabes, aneurysm and aortic disease, but many other organic and nervous diseases with an obscure ætiology. Sufficient time has not elapsed to enable anyone to say that a complete cure of syphilis by salvarsan, with a permanently negative Wassermann reaction, will prevent the development of general paralysis, but it is reasonable to think so.

In a third to a half of the cases of tertiary and latent syphilis the Wassermann reaction continues positive in spite of anti-syphilitic treatment (Boas), and in these prophylactic measures must be adopted. In all cases with a persistent positive reaction in the blood the cerebro-spinal fluid should be examined, because from a very early stage the nervous system may be involved. Dreyfus found in 80 *per cent.* of his cases of primary and secondary syphilis, irrespective of the presence or absence of any symptoms pointing to involvement of the nervous system, a lymphocytosis of the cerebro-spinal fluid. This lymphocytosis varied with the efficiency of the treatment and the course of the disease, being well marked when the disease was active, and diminishing under treatment. It would then seem that

the nervous system attracts all types of syphilitic organisms, and these observations do not support the view of a special or neurotoxic type. If lymphocytosis be found in the spinal fluid of persons suffering from latent syphilis with a positive reaction in the blood, it is necessary for these persons to lead very quiet lives, avoiding all sources of mental or nervous excitement, or exhaustion and the use of alcohol. Cases of latent syphilis with lymphocytosis have been found presenting no nervous symptoms, and there is no proof existing that cases with a lymphocytosis are more likely to develop general paralysis than those without it; indeed in 10 *per cent.* of the cases of general paralysis itself there is no definite lymphocytosis. Nevertheless, while all cases of latent syphilis should avoid nervous excitement or strain, this precaution seems specially needed in those cases with a lymphocytosis. It seems also desirable that persons suffering from latent syphilis with a persistent positive reaction in the blood, should periodically submit themselves to courses of salvarsan and mercurial treatment. Although in a third to a half of the cases of tertiary and latent syphilis the positive reaction will persist in spite of the treatment, in over 93 *per cent.* of the cases (Boas) the intensity of the reaction will be diminished, indicating a lowering effect on the activity of the disease, which it is also reasonable to suppose must be beneficial.

In 9 to 15 *per cent.* of those suffering from late latent syphilis with a positive Wassermann reaction in the blood, either general paralysis or tabes will develop. If in the course of the periodical examinations of the cerebro-spinal fluid a partially positive Wassermann reaction be found to occur, with an increase of globulin and the presence of albumen, a very grave view should be taken of the situation. The case should be regarded as one of commencing general paralysis, and the treatment recommended for that disease should be adopted.

Treatment with a View to Cure.

The course of a case of general paralysis offers many opportunities for treatment, but I shall only deal here with treatment with a view to cure. The question at once arises—Can general paralysis be cured, and have recoveries ever taken place? No satisfactory answer can yet be given to this question, for although

in the past many cases of supposed general paralysis have recovered, it is not possible to say with absolute and scientific accuracy that these were cases of general paralysis and not of mistaken diagnosis. On the other hand, no one can deny the possibility of general paralysis recovering in the face of the evidence that exists and so long as the diagnosis is uncertain. Till the new serum and cerebro-spinal fluid tests were introduced, the chances of error in diagnosis in experienced hands varied from 6 to 15 *per cent.*, and the probability of an error being made was much greater than that of a recovery. Some cases of cerebral syphilis and of alcoholic insanity not only simulate general paralysis exactly, and cannot be differentiated by clinical symptoms during life, but they are also the very class of case which tends to recover, and therefore they are the more likely to be mistaken for supposed cases of general paralysis that have recovered.

Remission, Arrest and Attenuation.

The subject of remissions is one which is not without some bearing on this problem, and they offer possibly more valuable information than doubtful recoveries. It is well known that they not infrequently occur in general paralysis, and while they usually last about six months or a year, in rare instances they may last for four or five years. Although all the acute symptoms of the disease are in abeyance during this time, the patient usually shows some mental and physical abnormality, the result of the damage already done. If a disease, by character progressive, ceases to show any signs of activity for four or five years, it is not inconceivable that it may do so for eight or ten, sixteen or twenty years, or even become arrested permanently.

The most remarkable instance of remission is one recorded by Sir Thomas Clouston of a patient, also observed by me, who lived for over thirty years. During the first five years the patient presented the typical symptoms of general paralysis, and was unhesitatingly diagnosed as such on admission by Dr. Skae. During the next fifteen years the acute symptoms were absent and the disease was stationary. During the twenty-first year of his illness the acute symptoms returned, only to disappear again for seven years. They finally appeared again during the last two years of his life, the twenty-ninth and thirtieth since his admission to the asylum. After death, the brain was examined

by Dr. James Middlemass, and found to present the characteristic appearances of general paralysis. The clinical symptoms of this case are vouched for by three physician-superintendents of the Royal Edinburgh Asylum, and the histological signs by a most careful and competent pathologist.

Arrest of the disease or remission of the symptoms of a permanent kind may also occur. Thus, Kraepelin quotes the case of Tuczek, which presented the typical clinical symptoms of general paralysis for two years and then lived for over twenty years afterwards. On his death the cortex was examined by Nissl, who found the characteristic anatomical changes of general paralysis. Dana, of New York, writing on this subject, states that as tabes is often arrested in its early stages, so that the patient lives for ten, twenty or thirty years after, without change or symptom, may not the same process occur in the related disease, general paralysis?

Two of my cases of general paralysis rather favour the view that the active process tends in the course of years to die out in some cases. One of these had suffered from general paralysis for twelve years, with stationary symptoms for the last seven or eight, and the Wassermann reactions in both the blood and the cerebro-spinal fluid, were negative. The diagnosis of this case was confirmed by the naked-eye appearances after death. The other, with very slight and stationary symptoms, had been affected for eleven years, and his cerebro-spinal fluid gave a negative reaction, and there was no lymphocytosis. though there was a positive reaction in the blood. This was found to be an undoubted case of general paralysis by Dr. Muirhead and Dr. Ford Robertson, but the histological signs were less extensive and less marked than usual. All of this evidence, if not of a very favourable or conclusive character, at least does not give any support to the contention that general paralysis is hopelessly incurable and fatal.

Anti-Syphilitic Treatment.

For a disease that is believed to be incurable and fatal it is surprising how many remedies have been found, almost all of which have been alleged at one time or another to cure it. It is useless to go over a list which contains such diverse agents as pilocarpin and trephining, radium emanations and injections of

tuberculin, or seriously consider such assertions as that of one observer, who stated that he cured 50 *per cent.* of his cases by injections of nucleic acid.

The form of treatment which I have devised consists in the employment of the following agents, and I am indebted to Dr. Dods Brown, Dr. Muirhead and my other assistants for their valuable aid in carrying out its details.

(1) *The intra-venous injection of salvarsan.*—The amount used varied with the strength of the patient, but was ·3 to ·6 of a grm. for the average man, and ·2 to ·3 grm. for the average woman. These were repeated three or four times at intervals of a month or so.

(2) *The intra-spinal injection of anti-syphilitic serum.*—This serum was obtained through the co-operation of Mr. Dowden from patients suffering from the secondary stage of syphilis, who had three days earlier been given an injection of salvarsan. This serum is highly charged with syphilitic antibodies, and it was administered because it had been suggested that a possible explanation of the disappointing results of anti-syphilitic treatment in general paralysis was the inability of the patient through exhaustion to produce antibodies. This serum was injected intra-spinously in order to bring the remedy near the seat of disease. It was usually administered in the intervals between the salvarsan injections, and it seldom produced any noticeable reaction.

Preparation of serum.—The method of preparation was as follows: 20 or 30 c.c. of blood were withdrawn with aseptic precautions by venepuncture from the arm of a syphilitic patient who had been treated three days previously with a full dose of salvarsan. This was allowed to clot, and care was taken to separate the clot from the side of the tube, which facilitates the formation of the serum. At the same time cultures were made from the serum, and the clotted blood was left on ice for about twenty-four hours. If the serum was sterile it was gently poured into a sterile flask with other sera, thus making a mixed serum, and in some instances it was found necessary to centrifuge the serum. Ten or 15 c.c. of this mixed serum, twenty-four or forty-eight hours old, was used for injection. A non-sterile or suspicious serum was always discarded. A record syringe was used for the injection of the serum, as the point fits the end of the lumbar puncture needle

accurately. Before making the injection an amount of spinal fluid was withdrawn, equal to that of the serum which it was intended to inject.

(3) *The intra-spinal injection of salvarsan serum.*—Owing to the cerebro-spinal fluid being chiefly a secretion, many drugs, *e.g.*, iodide of potassium, do not reach it ; salvarsan administered intra-venously is found in it, though only in minute quantities. The salvarsan serum injected intra-spinously was a means devised of bringing the drug in fair quantities into the fluid and into immediate contact with the membranes. It was obtained by drawing off by venepuncture some of the patient's own blood an hour after he had received an intra-venous injection of salvarsan. It was only administered on a few occasions, and it was followed by a slight rise of temperature. The direct administration of salvarsan itself intra-spinously would almost certainly be fatal, judging by its results on rabbits, when thus administered.

The salvarsan serum was collected and treated in exactly the same way as the anti-syphilitic serum, but the injection was given before the serum was twenty-four hours old and in smaller doses, 3 or 4 c.c.

(4) *Urotropine.*—While the patient was undergoing the anti-syphilitic treatment he received full doses of urotropine (10 gr., *t. i. d.*), as marked improvement has been reported in several cases of general paralysis while undergoing this form of treatment. It is secreted in larger quantities than most drugs into the cerebro-spinal fluid, and thus its bactericidal powers may act here as well as in the bladder.

(5) *Calomel.*—This was given twice weekly.

Results of Treatment.

The solid results obtained by this treatment were disappointing, but it seldom happened that a patient did not show some slight improvement in his symptoms after the first or second injection. As an instance of this I mention the case of one patient who wrote several characteristically insane letters just before receiving his injection. Next day he was much improved, and asked the matron for the letters he had written the day previous, and, on receiving them, tore them up and threw them into the fire. In five out of the twelve cases

treated at Craig House there was considerable excitement, and all of these benefited and became calmer. Three of the twelve cases recovered sufficiently to be discharged from the asylum, and of these one relapsed after six months; another several months afterwards met with a fatal accident at home; while the third has remained well for a year. This last case was exceptional in the long duration of the incubation period, having been definitely infected thirty-eight years previously, but there was also the history of a possible re-infection six years later. Unfortunately, so far as deductions favourable to salvarsan are concerned, it has been my experience to see a similar temporary improvement in the symptoms of general paralysis from every form of vigorous treatment that I have applied, especially if applied soon after admission.

In none of our patients did the Wassermann reaction become negative, but in a number there was a distinct diminution in its intensity, which increased again later on. On the Continent, Alt and Willige (Browning and Mackenzie, p. 193) report that they produced a negative reaction in the serum in one-fifth of their cases, but these also in a few months became positive again, although in some cases not for a year and a half. In some cases, however, it remained negative for a year and a half. In three of our twelve cases there was a marked and durable diminution in the number of lymphocytes, and in three others it was slight and of a temporary nature. We have found that the number of lymphocytes and the amount of complement deviated in the Wassermann reaction vary without treatment and without apparent relation to the acuteness of the symptoms, but the above changes were of a sufficiently striking nature to be noticed. There was no change in the amount of the globulin or albumen. Roughly speaking it may be said that in one-half of our cases there was evidence of improvement as regards the Wassermann reaction and the lymphocytosis—signs that the activity of the disease process had diminished.

Criticism of Treatment.

On carefully weighing these results of the use of salvarsan in the treatment of general paralysis, which are similar to those recorded by others, the opinion I have arrived at is that the treatment was not vigorous enough either as regards the amount

of salvarsan administered, the number of the injections, or the rapidity with which these succeeded one another. We were dealing with a new drug, the administration of which in a severe nervous disease was not without an element of danger. Our measures, too, were half-hearted, because our belief in the syphilitic nature of general paralysis was wavering and inconclusive so long as the parasyphilitic theory of Fournier could not be disproved or held to be improbable. The situation is now entirely changed by the experience we have gained during the last two years of the treatment of other forms of syphilis by large and repeated doses and by Noguchi's discovery of spirochætes in the brains of those suffering from general paralysis. Very few persons will now be found to deny the syphilitic nature of general paralysis, and I cannot conceive of any medical man denying that the spirochætes found among the nerve-cells of the cortex are one factor in the causation of the symptoms, in those cases at least in which they are found. With this sure foundation on which to base our treatment we can now act with vigour and determination, unhampered by doubt.

It has been found that, speaking generally, the longer syphilis has lasted the more intractable it is to treatment by salvarsan, and general paralysis is a very late manifestation. Judging from this fact alone it might be concluded that it would prove to be intractable, and from the intensity and constancy of the Wassermann reaction it might be inferred that it was not only a late but a very extensive and active infection. It, therefore, calls for the maximum intensity of anti-syphilitic treatment.

In syphilis of the nervous system, Dreyfus (*Munch. med. Woch.*) recommends the total administration of 6 to 9 grm. of salvarsan, injected in doses of 0·3 to 0·4 grm., twice a week for a period of eight to twelve weeks. This is four times the quantity, administered eight times more rapidly than was our practice. If the reaction after each injection be severe, the succeeding injection should be delayed till the temperature has fallen. In addition to this enormous dosage of salvarsan he recommends the employment of mercury, but even this vigorous and combined treatment had no permanent effect on general paralysis, though he claims to have benefited tabes. One wonders whether the injection of salvarsan serum intraspinously in addition would have made a difference, or whether

the administration of twice or even three times the quantity of salvarsan would not finally have had some arresting effect on general paralysis.

Although success has not been attained there are hopeful indications, for it appears that the disease process, if not suppressed, is at least touched in a half of the cases. The decrease in the lymphocytosis, the diminution in the intensity of the Wassermann reaction, and its disappearance for over a year in some cases are hopeful signs of the most convincing and satisfactory kind.

The Problem of Treatment.

The question now arises, Are we justified in pushing this antisyphilitic treatment to the extreme? Desperate diseases call for desperate remedies, and surgeons operate under conditions in which a definite percentage of their cases are certain to die from the immediate results of the operation, feeling their action justified if the lives of the majority are saved. General paralysis is as desperate a disease as any cancer, for 50 *per cent.* of those suffering from it die in one year, 75 *per cent.* in two years and 90 *per cent.* in three years, and the existence of the few who survive this period is a living death. Are the ethics of the surgeon and physician so different that a principle of the former cannot be followed by the latter under circumstances as hopeless and desperate? Are physicians, then, justified in general paralysis in pushing salvarsan and mercury to the most extreme limits compatible with survival, in the hope of curing at least a percentage of their cases? No doubt under these circumstances, owing to the amount of salvarsan probably required, like the surgeon, the physician would require to be prepared for a certain percentage of deaths from the drug itself.

The time seems ripe for a determined effort on these lines, but the weak point in the advocacy of such a course is the fact that, however hopeful the prospects may seem, no one can assert with confidence that a single case would recover. Syphilis, therefore, should be treated when it is possible to cure it, and seeing that the cause of it is known, an accurate test of its activity exists, and a powerful remedy found for it, it will be a slur in the future on the profession of medicine if the seeds of general paralysis and tabes are permitted to remain in the human soil till it is too late.