OBSERVATIONS ON THE EARLY DIAGNOSIS, ETIOLOGY, PROPHYLAXIS, TREATMENT AND SIGNS OF GENERAL PARALYSIS OF THE INSANE.

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Recent Observations relating to General Paralysis of The Insane.

The Early Diagnosis.

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 35 and 50 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 inconveniences 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 breadwinner of a family and the head of a business, in the prime of 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 were 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 54 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 54 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 41 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 41 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 shewing slight clinical phenomena, the error would be much greater.

Caution was recommended by the most experienced physicians of the past and they 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 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 64 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 in the first of 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 the first impression. The employment of this 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 finer 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 and immorality, or even criminal acts, such as absurd theft. Moodiness and irritability may also 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.

Alteration 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 shewn by his 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. The 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 although 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 symptom of deterioration to which I have alluded, but the expert, especially if he has had his suspicions awakened by a 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 shew 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 shews 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 a 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 these 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 many 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 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 reflex does 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 cause a greater direct contraction of that eye than a consensual contraction of the other eye.

This 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.

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

1. A sluggish indirect reflex.
2. A sluggish direct reflex with a more sluggish or absent indirect reflex.
3. Abolished direct and consensual 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 sommon 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 Bulletin 2). 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 pricking 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 Bulletin 2). These two abnormal reactions do not have the same diagnostic value, for exaggeration occurs in so many nervous conditions, including neurasthenia, that it does not point specially to General Paralysis. It is different however with the sluggish or abolished reaction, which occurs in nearly a third (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.

Valuable information can be obtained 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 very easily and

conveniently be done by asking the patient to kneel on a chair with one leg at a time, with his face to 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 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 easily tested, by asking the patient to repeat words and 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 or 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, 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 deterioration, 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 Reaction in the Serum.

If the Wassermann Reaction in the blood serum be found to be negative, General Paralysis can almost always be 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 12 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 is found to be negative , the case is probably 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.

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 only 53 per cent. of Tabes (Bayly p.133) and in only 17 to 50 per cent. of syphilis of the nervous system.

A Negative Reaction in the Serum and a Positive in the 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, as 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 positive in the blood 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, Albumen 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 .1 per cent. of albumen tested by Aufrecht's

Albuminimiter 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.

By means of the 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 and detailed 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. 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 indeed 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. 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 antisyphilitic treatment, 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 9 errors of diagnosis in Plaut's and Southard's 96 cases were chiefly due to this cause, which includes gumma, meningitis and endarteritis, both of the large arteries and terminal vessels (Heubner's and Nissl's types). There is little doubt also that most of the so-called 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 diffuse 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 history of the

attack of syphilis in cerebral syphilis, often shews it to have been a severe one which is unusual in General Paralysis. It usually develops much sooner after the infection and may coexist 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 8th and 12th years. Many persons suffering from cerebral syphilis owing to its early development are under 30 years of age, whereas few general Paralytics are, unless those who suffer from congenital syphilis. Lastly the effect of anti-syphilitic treatment is usually very beneficial to the symptoms in cerebral syphilis but not so in 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. (Bayley - 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, that

this forms perhaps the most reliable diagnostic test of cerebral syphilis. The positive Wassermann Reaction usually disappears, first from the spinal fluid and then from the serum, the high cell count falls to a little above normal, and the excess of globulin disappears quickly under treatment. 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. J. of Insanity LXIX)

Diagnosis by Signs, 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 symptom of degeneration could be observed and it might prove invaluable as regards treatment.

It is possible that in the future transient mental episodes and neurological phenomena may be noted, resulting from latent syphilis which may bear 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. Cases can certainly be diagnosed now at a stage when even professional men can continue to discharge their duties, but in the whole field of psychological medicine there is still not a more responsible problem, requiring the exercise of more prudence and caution, than the early and definite diagnosis of General Paralysis.

Etiology.

It is impossible to discuss the prophylaxis and treatment of General Paralysis without disposing of the vexed question of its etiology 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 resumé of this will be given.

Relationship to Tabes.

General Paralysis and Tabes have the same etiology, 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 Moenkemoller 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 etiology of the one

is applicable to the other.

History of Syphilitic Infection.

Of 1100 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 (p.160 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 obtains in General Paralysis contribute also to obliterate the facts of infection from the memory. Fournier nevertheless gives a list of 20 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 circumstances 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 p.579) Pernet failed in 20 per cent. of obvious syphilitic skin disease (Mott p.218) and Fournier in 15 per cent. of cases of gumma of the palate (Ballet p.104).

Syphilis without manifestation.

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 shewing any symptoms. Colles' 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 3 cases out of 4, although in two thirds of the cases, the woman is unconscious of having been infected (Mackintosh & Fildes p.141). 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 etiological 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 42 and 43 is given by Christian Muller. 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 (Mott).

Varying Incidence of General Paralysis.

What is quite as impressive as the high percentage 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 18½ times more frequent in the Royal Edinburgh Asylum 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 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 (Mott p.220) representing the proportion of syphilis in the two sexes. 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 8 to 12 years and is rare before 30 or after 55, but is common between the ages of 40 and 45. 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 30 years of age. In conjugal General Paralysis it develops almost always in the wife after the husband (Moenkemoller p.225 Mott) and if the reverse order occur, 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, 2.5 per cent. does not give any support to the hypothesis that there is a special or neurotoxic type of syphilis or spirochaete.

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 in the former. or it may be due to early marriage,

different social customs or to living mainly in rural communities. This opinion on the other hand regarding its prevalence 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 p.4). 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 p.236). 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 the same facts are true of the West Indian Negroes, I am informed on good authority.

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 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. The soil for their development is nearly co-extensive with the number infected (Bramwell's Studies p.179). On the other hand only 4 per cent. of the cases of General Paralysis occur before the fifth year, the usual period for its appearance being from 8 to 12 years after infection, during which interval, judging by the results of the Wassermann Reaction, 63 per cent. of those originally infected have recovered (Boas, late latent syphilis) 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 comparison with similar conditions, e.g. post-diphtheritic paralysis which occurs in 15 per cent. of those affected.

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, intoxications 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 13, different places and in two groups of 4 and 5. 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.

Fifteen years ago Krafft-Ebing created a sensation by announcing that a friend of his had inoculated with active virus 9 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 syphiltitic inoculation. Had a reaction occurred, this would not necessarily have disproved syphilitic infection, for it is believed, that a virulent and extensive reinoculation 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 reliable clinical test of syphilitic activity, it is an empirical reaction and is not 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.

The Wassermann Reaction enables us 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 the General Paralysis and combined lesions have been found after death. Links such as these between General Paralysis and active syphilis are very interesting, 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, 14 years later he had a transient attack of aphasia. 21 years later, he had a similar attack after an exhausting bicycle run and 29 years later he 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 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 also 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 offence against the Lex Parsimoniae, 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 Spirochaetes in the Brain.

The problem of the etiology of General Paralysis appears to have been finally and conclusively settled by the finding at the end of last year by Noguchi of the Spirochaeta Pallida in the brains of 14 cases of General Paralysis (Jour. of Experimental Medicine, Feb. 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 spirochaetes 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 and few are found either in the white matter

or round the vessels. In almost all instances the spirochaetes seem to have wandered 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 spirochaetes among those cells, whose functional disturbance and degeneration, is the probable explanation of the symptoms of the disease. Their proximity to the cells points to them as the immediate cause of their disordered function and degeneration. The theories of a parasyphilitic 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.

Conclusion.

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 it before the skill and perseverance of Noguchi was 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 step to be taken 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 possibly 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, Aneurism, and Aortic Disease, but many other organic and nervous diseases with an obscure etiology.

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 seems to 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, diminishing under treatment and increasing again when there was a relapse. It would thus 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 persists in spite of the treatment, in over 93 per cent. of these 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 all the more likely to be mistaken for supposed cases of General Paralysis that have recovered.

Remission and Arrest.

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 shews some mental and physical abnormality, the result of the damage already done. If a disease, by character progressive, ceases to shew any signs of activity for 4 or 5 years, it is not inconceivable that it may do so for 8 or 10, 16 or 20 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 30 years. During the first 5 years, the patient presented the typical symptome of General Paralysis and was unhesitatingly diagnosed as such on admission by Dr. Skae. During the next 15 years the acute symptoms were absent and the disease was stationary. During the 21st year of his illness the acute symptoms returned, only to disappear again for 7 years. They finally appeared again during the last two years of his life, the 29th and 30th 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 the 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 symptoms of General Paralysis for two years and then lived for over 20 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 10, 20 or 30 years after, without change of 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 12 years, with stationary symptoms for the last 7 or 8, and the Wassermann Reaction in both the blood and the cerebro-spinal fluid were negative. The diagnosis of the case was confirmed by the naked eye appearances after death. The other, with very slight and stationary symptoms, had been affected for 11 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 intravenous injection of Salvarsan. The amount used varied with the strength of the patient but was .3 to .6 of a gramme for the average man and .2 to .3 of a gramme for the average woman. These were repeated three or four times at intervals of a month or so.

2. The intraspinal injection of antisyphilitic 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 antisyphilitic treatment in General Paralysis was the inability of the patient through exhaustion to produce antibodies. This serum was injected intraspinously in

order to bring the remedy near the seat of the disease. It was usually administered in the intervals between the Salvarsan injections and it seldom produced any noticeable reaction.

The method of preparation and the amount injected were as follows : Twenty or thirty c.c. of blood was 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 24 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 fifteen c.c. of this mixed serum, 24 or 48 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, the amount of spinal fluid was withdrawn, equal to that of the serum which it was intended to inject.

3. The intraspinal 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 intravenously is found in it, though only in minute quantities. The Salvarsan serum injected intraspinously 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 intravenous 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 intraspinously 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 antisyphilitic serum, but the injection was given before the serum was 24 hours old and in smaller doses - 3 or 4 c.c.

4. Urotropine. While the patient was undergoing the antisyphilitic treatment he received full doses of urotropine (10 grs. t.i.d.) as marked improvement had 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.

The solid results obtained by this treatment were disappointing but it seldom happened that a patient did not shew 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 5 out of the 12 cases treated at Craig House there was considerable excitement and all of these benefited and became calmer. Three of the 12 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 having been definitely infected 38 years previously, but there was also the history of a possible reinfection 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) 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 three of our twelve cases there was a marked 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. 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 been diminished.

On weighing carefully 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 as 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 spirochaetes 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 spirochaetes 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 grammes of Salvarsan, injected in doses of 0.3 to 0.4 of a gramme, twice a week for a period of 8 to 12 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 injections 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 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 question now arises are we justifed in pushing this anti-syphilitic 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 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.

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.

The Serum and Cerebro-Spinal Fluid

Reactions and Signs of General Paralysis.

It is sometimes cast up as a reproach to those engaged in Psychiatry that zeal in research and progress in knowledge in this subject have not kept pace with other departments of Medicine, but I now describe some valuable additions to our knowledge which have all been made during the last decade, on the diagnostic signs of General Paralysis of the Insane. Although the full title of this disease is a perpetual reminder of the fact that the credit of its discovery belongs to Physicians engaged in Asylum practice, it is desirable to drop the final qualification and refer to it simply as General Paralysis.

Discovery of General Paralysis.

It is not generally known that this disease has been recognised as a separate entity for less than a hundred years. It was not till 1822 that Bayle asserted that certain "paralytic symptoms complicating insanity" which Esquirol and his pupils had observed for 17 years were due to a definite disease, passing through three stages, to which he gave the name of Chronic Arachnitis, in many respects the most important observation that has ever been made in Psychological Medicine.

Burrows writing six years after Bayle stated that the number of "cases of paralysis complicating insanity" was comparatively trivial and remarked on the singular discrepancy in respect to its prevalence between France and England. To this Esquirol retorted that when he

was better able to distinguish the symptoms he would find as many cases of the disease in London as there were in Paris, the correctness of which surmise was supported by the clinical experience of Sir Alexander Morison. Writing in 1840 in his classical work on the Physiognomy of Mental Diseases, he stated that it was well known at Bethlem Hospital, and he gave illustrations of several of his patients there.

The Syphilitic Hypothesis.

Esmarch and Jessen in 1857, and Kjelberg in 1863, expressed the opinion that syphilis was invariably the cause of General Paralysis. This view received a chilly reception from Griesinger, then the greatest psychiatric authority on the Continent, who described it as "a very improbable assumption" and it passed into obscurity. The facts were brought to light again by Fournier nearly a generation afterwards. He had suggested in 1875 that Locomotor Ataxia, a disease described about 20 years previously was syphilitic in origin but like the similar suggestion regarding General Paralysis this was received with scepticism by authorities like Erb and Westphal. Fournier however maintained his opinion and in a few years brought forward more statistics of a nature, that convinced most of his former opponents. During these enquiries into the causation of Locomotor Ataxia, he found that General Paralysis ran a parallel course with it etiologically. Fournier's special views were summarised by him in his work on Parasyphilis in 1894 and these were that General Paralysis was syphilitic in origin but not

in nature, as it was unaffected by antisyphilitic remedies and its lesions were not circumscribed, but diffuse.

The discovery of the specific organism of Syphilis, the Spirochaeta Pallida was made by Schaudinn in 1905 and in the following year Wassermann. Neisser and Bruck obtained a reaction in the serum of an ape infected with syphilis, now known as the Wassermann Reaction. An interesting point in the application of this test to the human being is the fact that Wassermann and Plaut, firmly convinced of the syphilitic origin of General Paralysis, immediately applied the test to the cerebro-spinal fluid of patients suffering from this disease, and obtained a positive reaction. They were under the belief that the spinal fluid, being near the chief seat of the disease, would possibly be more fully charged with the antibodies of syphilis than the blood serum. It was also believed by them that clear proof of an active syphilitic process in General Paralysis had thus been obtained, but with further experience of the Reaction, doubt has arisen on this point.

The Wassermann Reaction in General Paralysis is the first of the additions to our knowledge to which I shall refer and it is not my intention to describe its technique nor its chemistry, but its clinical aspects.

Wassermann's Reaction in the Blood Serum.

In every case in which the clinical symptoms point however slightly to General Paralysis, blood should be drawn off by venepuncture for the application of the Wassermann Reaction as it is very necessary to exclude

the presence of this fatal disease. The operation of venepuncture is simple and is performed as follows : The most accessible veins to puncture are generally the median basilic and the median cephalic immediately in front of the elbow joint. These often shew up much better in one arm than in the other but by getting the patient to open and close the hand several times the veins can as a rule be rendered prominent and the most convenient should be chosen. In fat people with small veins there may be difficulty. Having selected the most suitable vein, lay the arm on a table, fasten a tourniquet or a tight bandage round the upper arm, and wash the skin with a lotion of corrosive sublimate in alcohol, 1 to 500. Steady the vein between the finger and thumb of the left hand, then directing the point of a sterile needle of fairly large bore along the line of the vessel pushed steadily into the vein. If properly performed the blood will at once flow freely and should be collected in a large test tube. Allow the blood to flow till the tube is full, then if sufficient has been obtained loosen the tourniquet, withdraw the needle, apply a firm pad over the punctured spot and fix with a bandage. In a few hours the pad and bandage may be safely removed and no more oozing should take place. The tube and stopper, for which a plug of cotton wool may be conveniently used, must, like the needles and everything else employed, be absolutely sterile and the strictest asepsis must be observed throughout the operation.

The blood should be examined by an expert in the technique of the Wassermann Reaction, for the sources of error from imperfect technique and faulty materials are many and it is exceedingly unsatisfactory to have an unreliable report on a point such as this upon which the diagnosis of a fatal disease may hang. In General Paralysis the serum gives a positive reaction in practically every case. That has been my experience of the test as applied by Dr. Winifred Muirhead in the Laboratory of the Royal Edinburgh Asylum, and her work only confirms the observations of Plaut and many others, including Dr. Ivy Mackenzie, who originally instructed her in the technique. When the test was first employed and before knowledge of some sources of error had been gained, there was a small percentage of negative results, most of which were afterwards rectified, but in her last 100 cases she has obtained 99 per cent. of positive reactions. In one per cent. of the cases examined by other reliable workers a negative reaction in the serum has also been obtained, but even in these few cases a positive reaction has sometimes been associated with it in the cerebro-spinal fluid, so that the reactions have not been both negative. In 9 per cent. of the sera examined by us the reaction was feeble or partially positive but these cases were also examined by the delicate and accurate Lecithin-Cholesterin method of Browning, Cruickshank and Mackenzie and were found to give by this process a definite positive reaction.

The statistics available for illustrating percentage results are unsatisfactory because the early ones erred on the side of giving too low a percentage of positive

reactions. Thus, Plaut working with Wassermann himself obtained only 78 per cent. of positive reactions in the first 41 cases he examined (Browning and Mackenzie). Three years later he reports that he got 100 per cent. or a positive reaction in every case out of 156 examined (Plaut p.49) and he accordingly committed himself to the belief "that the serum in paresis always reacts positively." It would however appear that one of the next 44 cases examined by him unexpectedly gave a negative reaction for it is recorded that of 200 cases examined in Kraepelin's Clinique, he found a positive reaction in 99.5 per cent. (Browning and Mackenzie). Adding together the numbers examined by selected observers who have each dealt with at least 50 cases, namely, Ross and Neve 131 cases, Lesser 62, Plaut 200, Glasgow District Asylum, Gartloch 94, and Dr. Muirhead, Royal Edinburgh Asylum 100, we find that out of these 587 cases of General Paralysis the blood serum gave a positive Wassermann Reaction in all but 3 or in 99.48 per cent. This power of the serum of giving the Wassermann Reaction is so constant a sign that its absence in a case is very strong evidence indeed that General Paralysis is not present. It however just falls short of being absolute proof of this, for we have already stated that in 1 per cent. of the cases examined by experienced workers the reaction has not been obtained. It should be added that our failure occurred in a case in which the symptoms were stationary and which had lasted 12 years.

On the other hand if the reaction be present the error must not be made of concluding that the patient

suffers from General Paralysis. Of itself it proves nothing more than that the patient has been and still is infected with syphilis. If found associated with the clinical symptoms of General Paralysis it is of course a most sinister combination, without however being conclusive of the presence of that disease.

It is interesting to note that the Wassermann Reaction is present in the blood serum of General Paralysis more constantly and in greater intensity than in any form of active syphilis with the exception of acute secondary syphilis and even here a positive reaction is not obtained more frequently. The significance of this fact of course depends on the exact interpretation that is placed on the Wassermann Reaction and that problem has not been settled. If it is not in the strict sense a specific sign of syphilis, it is at least so closely associated with it clinically that it is very strong empirical evidence of active syphilis in General Paralysis.

Wassermann Reaction in the Cerebro-Spinal Fluid.

In order to test the Wassermann and other reactions in the cerebro-spinal fluid it has to be drawn off by lumbar puncture. This operation was first proposed by Corning of New York in 1885 and it was in 1891 that Quinke demonstrated its usefulness as a means of diagnosis, but we are mainly indebted to Widal and his associates for its extensive employment in neurology. It is performed as follows :

A special hollow needle about 4 inches long made of platinum-iridium is required as a steel needle might break across if caught between the vertebrae owing to the patient moving. The point of the needle should be very sharp as the dura mater is tough and it should be absolutely sterile. Several test tubes also sterile are required to catch the fluid.

The patient, if weak, may lie on his side at the edge of the bed with his knees flexed on his abdomen and his shoulders raised. It is much more convenient to perform the operation with the patient seated on a stool, stooping and arching the back, to render the spines of the vertebrae prominent and to separate the laminae as much as possible. The skin of his back over the lumbar vertebrae is prepared by scrubbing it with a solution of corrosive sublimate in alcohol, 1 in 500.

An imaginary line is now drawn joining the highest points of the iliac crests and this crosses the middle line over the spine of the fourth lumbar vertebra.

The thumb of the left hand can now be placed in the interval between the 4th and 5th spines to mark the level of the site of puncture, which is half an inch to one side of the middle line. If ethyl chloride be sprayed over this point or cocaine injected it not only lessens the discomfort of the patient but in effecting this, materially assists the operation. The needle should be plunged boldly in, directed slightly upwards and inwards, for a distance of about 1½ to 2½ inches depending on the patient's condition. If the needle

strikes against bone it need be withdrawn only a little, manipulated and again pushed forward.

As soon as the needle has penetrated the meninges, which can be felt, the fluid should flow readily. The first few drops are usually blood-stained and should be rejected and allowed to flow into a separate tube and the collection for examination purposes made of clear fluid only.

When about 5 to 7½ c.c. have been collected, the needle should be quickly withdrawn and a little collodion applied over the puncture. The test tube should be plugged with sterilised wool.

It is advisable to keep the patient in bed for the rest of the day or for some hours at least after drawing off the fluid in order to prevent headache or sickness from occurring. If the fluid does not flow, owing to a plug of skin or membrane it is safer to withdraw the needle and insert another in the space between the 3rd and 4th or 2nd and 3rd lumbar vertebrae. Very rarely owing to an obliteration of the sub-arachnoid space fluid cannot be obtained.

The cerebro-spinal fluid in General Paralysis almost always gives a positive Wassermann Reaction and in this important respect it differs from active syphilis, in which the reaction is negative. The only exceptions to the latter statement are a certain proportion of cases of syphilis involving the nervous system and the twin sister of General Paralysis, namely Tabes. Unlike the positive reaction of the blood serum, this reaction is characteristic and distinctive of General Paralysis,

but not exclusively so. At some stage or other of every case of syphilis which ultimately develops into General Paralysis, during the interval between the infection and the appearance of the clinical symptoms, the reaction of the cerebro-spinal fluid changes from negative to positive. It would be a most instructive research to follow this change and the associated symptoms, but this has not yet been done. We do know however that in every case of General Paralysis, however early it may be examined or however slight the symptoms may be, a positive reaction is nearly always obtained.

Out of 100 cases of General Paralysis examined at the Royal Edinburgh Asylum and in my private practice, 95 per cent. gave a positive Wassermann Reaction in the cerebro-spinal fluid. The percentage is thus less than that obtained in the serum. In 13 per cent. of the cases examined, the fluid gave a feeble or partially positive reaction and these were also examined by the Lecithin-Cholesterin method of Browning, Cruickshank and Mackenzie and in every instance gave a definitely positive reaction. Plaut obtained a positive reaction in 144 out of 150 specimens of spinal fluid or a percentage of 96, as contrasted with the 99.5 per cent. of positive reactions obtained by him in the blood serum. Of 618 cases of General Paralysis examined by the ten following selected observers, a positive reaction was obtained in the cerebro-spinal fluid in 582 or 94 per cent. of the cases.

Percentage of Positive Wassermann Reactions of the Cerebro-Spinal Fluid in General Paralysis.

Observers	No. of Cases	Positive Reaction	Per Cent.
1. Nonne & Holzmann	23	22	95
2. Eichelberg	61	5.7	93
3. Smith & Candler	64	5.9	92
4. Marinesco	35	32	91
5. Plaut	150	144	96
6. Marie, Levaditi & Yamanouchi	30	28	93
7. Stertz; Morgenroth & Stertz	53	48	90
8. Raviart, Breton & Petit	72	67	93
9. Morton	30	30	100
10. Muirhead, Royal Edin. Asylum	100	95	95
	618	582	94

Note : 1 to 5 quoted from Mackintosh and Fildes
6 to 8 from Plaut & 9 from Browning & Mackenzie.

If these results be not quite so high as the percentage of positive reactions obtained from the blood serum, they are nevertheless remarkable for so distinctive a sign and at least two causes which may in time be eliminated have combined to lower these results. There have been for example errors of technique, for when some of these observations were made it was not realised that the reacting substances were in more dilute solution in the spinal fluid than in the serum and that it was necessary to use a larger quantity of spinal fluid than that of serum. In the next place it is probable that some of the cases which failed to give a reaction were not cases of General Paralysis at all. Some of these cases are still living and the diagnosis will have to be confirmed by histological examination when they die. Others have died and post mortem examinations have been refused, so that the diagnosis could not be verified. In all these cases a diagnosis was made on clinical grounds and we know that mistakes are frequent if these alone be relied upon. It was found for example after death that there were three cases of mistaken diagnosis in the first batch of 54 cases of supposed General Paralysis whose sera were examined by Plaut. As all the six cases out of 150 in which he failed to get a positive reaction in the spinal fluid are exceptional cases which do not conform to the ordinary clinical types of General Paralysis, it is possible that some have been wrongly diagnosed and may ultimately prove to be cases of syphilis of the nervous system.

Plaut has expressed the opinion that a positive reaction in the cerebro-spinal fluid may yet be found

in every case and prove to be THE diagnostic sign of General Paralysis. Our experience is contradictory of this opinion, for of the 5 cases in which a negative reaction was obtained by us, the diagnosis was confirmed by post-mortem appearances in 1, and by histological examination in other three. The spinal fluid of these three cases was examined many times and always with negative results, although large quantities of fluid were used. The delicate Lecethin-Cholestrin method of Browning, Cruickshank and Mackenzie was also tried in vain. In 4 to 6 per cent. therefore of cases of undoubted General Paralysis, the Wassermann Reaction in the cerebro-spinal fluid may be negative.

Ever since it has been shewn that the reacting substance in the spinal fluid was of a fatty or lipoid nature and that possibly it was not a specific antibody of syphilis, it has been suggested that its source was degenerating nerve cell and nerve fibre, which are particularly rich in fatty substances. Certainly the most marked anatomical change in General Paralysis is the extraordinary wasting of brain tissue that occurs, sometimes amounting to a loss of one third of its weight and the possibility of this suggestion cannot be denied.

Signs of "Chronic Arachnitis."

We now pass on to another kind of sign. Bayle, the original discoverer of General Paralysis, called the disease "Chronic Arachnitis" and by examining the cerebro-spinal fluid obtained by lumbar puncture microscopically and chemically, it is possible during life to demonstrate the sign of this chronic meningitis to which

he attached such importance. These signs are an increase in the number of cells, an increase of globulin and the presence of albumen.

Increased Number of Cells in the Cerebro-Spinal Fluid.

Widal's Rough Method of Enumeration.

As a result of the chronic meningitis which is invariably present in General Paralysis, the number of free cells in the cerebro-spinal fluid is almost always much increased. The simplest method of testing for this increase is known as Widal's rough method. Five c.c. of cerebro-spinal fluid are placed in centrifuge for five minutes. The supernatant fluid is now gently decanted and the bottom of the inverted tube is scraped with a fine pipette to collect the sediment. This is now blown on to a cover glass fixed and stained with Methylene Blue, Jenner's or Leishman's stains. With a magnification of 400 diameters the normal fluid should not shew on an average more than 2 or 3 cells to the field and there may be none present. In general paralysis on the other hand the lymphocytes are almost always markedly increased and the specimens shew on an average 10, 20 or more cells in the field. This rough method has the great advantage of being very easily applied and in the great majority of cases it is sufficiently accurate and supplies the information desired.

Fuchs- Rosenthal Counting Chamber Method.

Scientific accuracy of enumeration which is needed in doubtful cases, can only be obtained by a counting chamber method. This method requires the employment of a special cell constructed by Zeiss, with square

rulings and for ease of counting the cell is divided into sixteen sets of sixteen small squares. A Zeiss W.B.C. pipette is used for mixing the fluids, and as a diluent 1 part methyl violet, 2 parts glacial acetic, and 50 parts of distilled water is recommended. The diluent is drawn up to Mark 1, fresh uncentrifuged spinal fluid up to Mark 11 and the mixed fluids are thoroughly shaken for five minutes. After discarding the first two or three drops one drop is placed on the slide and all the cells are counted inside the chamber. This count is repeated with a second drop, and the average obtained. This number is now divided by three, and the result gives the number of cells per c.mm. in the cerebro-spinal fluid. In the normal fluid not more than 5 cells in the c.mm. are seen, whereas in General Paralysis any number from 10 up to 100 or more per c.mm. may be counted. In a few cases of stationary General Paralysis and in cases with slight symptoms, but also in my experience in acute cases, the number of cells may be increased so slightly that the cell count is only between 6 and 10 per c.mm. In one case only in the Royal Edinburgh Asylum out of 100, of a very chronic and quiet type, was it below normal or 5 cells per c.mm. These cases with low enumerations do not occur oftener than once in ten so that in about 90 per cent. of cases of General Paralysis there is a well marked lymphocytosis of the cerebro-spinal fluid. It sometimes happens that the fluid from the first and even the second puncture may give a negative cell count and therefore in doubtful cases with a negative count, the examination of the fluid should be repeated. These varying samples of spinal

fluid may be due to meningeal pockets but it is also found that during the course of General Paralysis the cell count varies from time to time, without any relationship to treatment or the acuteness of the symptoms.

This lymphocytosis of the spinal fluid is not pathognomic of General Paralysis as it occurs occasionally in epilepsy and Dementia Praecox and it is possibly a sign of syphilis. It is found in the secondary stage of syphilis and this early mild meningitis, of which headache may be the only symptom, is a more constant and perhaps a more important symptom than has yet been realised by syphilologists and neurologists. It is not infrequently found in persons suffering from tertiary symptoms not relating to the nervous system and also in latent syphilis presenting no symptoms whatsoever, save the presence of the Wassermann Reaction in the blood. In meningeal and gummatous lesions of the nervous system it is of course very marked and a much higher count is usually obtained than the usual number for General Paralysis, which seldom exceeds 100 per c.mm.

It is important to know whether there is any causal connection or association between the presence of a persistent lymphocytosis in the spinal fluid and the subsequent development of General Paralysis and Tabes, in view of the constant presence of chronic meningitis in these diseases. It is possible that these persons may have, since the time of their secondary symptoms, presented the sign of a persistent lymphocytosis of the

spinal fluid. If such a connection were established, vigorous prophylactic measures would be adopted at a very early stage. It is possible on the other hand that the original mild meningitis may die down and disappear, only to flare up suddenly after some years in those cases which develop General Paralysis. It has also to be remembered that in nearly 10 per cent. of the cases of General Paralysis there is no marked lymphocytosis.

Differential Examination and the Presence of Plasma Cells.

An additional aid to accuracy of diagnosis is supplied by the differential examination of the cells in the spinal fluid. The best method devised for this purpose is that of Alzheimer the technique of which is not difficult. It consists of centrifuging 3 or 4 c.c. of the cerebro-spinal fluid with double the quantity of 96 per cent. alcohol for from ½ to 1 hour, depending on the speed of the centrifuge and by this means the proteid is coagulated into a hardened plug. It is then still further dehydrated and hardened by means of pouring on absolute alcohol, then equal quantities of alcohol and ether, and finally ether for a variable number of hours, depending on the thickness of the plug. The plug is next loosened from the side of the tube by a fine flattened needle, embedded in celloidin and cut in sections of 15 micromillemeters in thickness. The cut sections may be stained by Pappenheim's pyronin-methyl green or with Unna's polychrome methylene blue.

From the researches of Dr. D.K. Henderson and Dr.

Winifred Muirhead in the Laboratory of the Royal Edinburgh Asylum it would appear that there are four varieties of cell normally present in the cerebro-spinal fluid and all of these are found in General Paralysis. These were lymphocytes, mononuclear leucocytes, polymorphonuclear leucocytes, and endothelial cells, the lymphocytes predominating as they do normally. The proportions are shewn in the following Table, with similar observations, for purposes of comparison, in Dementia Praecox, which may be provisionally accepted as representing the normal. The average cell count per c.mm. in 26 cases of General Paralysis was 47, and in 11 cases of Dementia Praecox, it was only 1.3 per c.mm.

Differential Cell-Count in Spinal Fluid in Percentage of Total Cells.

	Min.	Max.	Av.	Min.	Max.	Av.
Lymphocytes	52	84	72.2	59	78	70
Mononuclear	7	40.6	16	21	40	28.6
Polymorphonuclear	.3	16	3.5	0	4	.9
Endothelial	0	3	.8	0	2	.4
Plasma	1.5	16	6	0	0	0
Gitter or Lattice	0	1.6	.5	0	0	0

Cotton and Ayer's Results in 19 cases of General Paralysis were as follows : Lymphocytes, 73 p.c.; Endothelial, 13 p.c. Polymorphonuclear, 9 p.c. Plasma, 2 p.c. Phagocytes, 1 p.c. and unclassifed cells 2 p.c.

The differential cell count in General Paralysis is subject to more extreme fluctuations than in other Psychoses, the average percentage of mononuclear leucocytes is distinctly low and the percentage of polymorphonuclear leucocytes and endothelial cells is high and is sometimes very high.

Plasma and Lattice Cells.

The most characteristic cell in the spinal fluid in General Paralysis is the Plasma cell and it is one which is not normally present. It is always present in General Paralysis and it varies from 1.5 per cent. to 16 per cent., the average being 6 per cent. It is also found in smaller numbers in tabes and in cases of cerebral syphilis but it is not peculiar to these conditions for it and the other cells to be mentioned are also found in Tubercular Meningitis.

Another cell as characteristic of General Paralysis as the Plasma cell is the Gitter or Lattice cell, so called from the lattice-like effect produced by vacuolation of its protoplasm. It is frequently not seen but on other occasions it may form 1.6 per cent. of the cells present, the average being .5 per cent. These cells and the mononuclear cells (1.5 per cent. of the total) may be phagocytic, and may be found containing one or two strange nuclei, which they have enveloped.

Two other types of cells, Transitional cells and Fibroblasts are also occasionally found in the cerebrospinal fluid in General Paralysis.

It is interesting to note that although the total cell count in exceptional cases may be low and not much more than normal, the varied character of the cells in General Paralysis is in our experience always adhered to and Plasma cells are always to be found if a thorough search be made for them.

An Excess of Globulin.

A certain amount of globulin is normally present in the cerebro-spinal fluid but the amount is greatly increased in General Paralysis. Noguchi has devised a reliable test for demonstrating its presence but the best clinical test for it is what is known as the Ross-Jones Test. It is as easy of application as the Nitric Acid test for the presence of albumen in the urine. An inch of a saturated solution of Ammonium Sulphate is poured into a test tube and over the surface of this cerebro-spinal fluid is carefully allowed to trickle from a pipette. At the line of junction of the two fluids a very definite white line of precipitate forms if globulin be present in excess, very similar to the line produced in urine when there is albumen present. There is usually no doubt whatsoever about the presence of this line when the test is positive but if any doubt exists it can be at once dispelled by diluting the cerebro-spinal fluid with a half of its bulk of distilled water before applying the test. If any line be now visible at all after this dilution, the reaction must be regarded as strongly positive. This reaction

in our experience is always present in General Paralysis but Noguchi and other reliable workers have found it to fail in 2 or 3 per cent. of cases. A slight and transitory excess of globulin may be found in acute forms of insanity such as delirious insanity, epileptic insanity and dementia praecox. It is found in syphilis of the nervous system but contrary to what is the case with lymphocytosis it is less intense than in General Paralysis. Excess of globulin alone in a person who has not had syphilis will not give a positive Wassermann Reaction although the substance which produces the reaction in General Paralysis is united to the globulin moelcule and is precipitated with it.

The Presence of Albumen and its Amount.

The constant presence of albumen in the cerebrospinal fluid of General Paralysis can be demonstrated by the Nitric Acid reaction and the test is of use as it is not present in the normal fluid. Its value is greatly enhanced as a diagnostic sign if a quantitative estimation be made and this can be conveniently done by means of Aufrecht's Albuminimiter. Four c.c. of spinal fluid are mixed with 3 c.c. of the reagent, which consists of a mixture of equal parts of 5 per cent. picric acid and 3 per cent. citric acid. The mixture of the reagent and the spinal fluid is placed in a graduated Aufrecht tube and centrifuged for five minutes at 2000 revolutions. The albumenous contents are precipitated and read off in terms of percentage on the scale. The normal proteid content is always less than .05 per cent.

whereas in General Paralysis it is always increased three or four times in amount and varies from .1 per cent. upwards. There may also be an increase in other forms of acute insanity, but in them it never exceeds .1 per cent., whereas in General Paralysis it is never below that figure. In these other forms of insanity albumen or globulin may be present singly but they do not constantly appear together nor in the same amounts as in General Paralysis. In acute meningitis, the amount of albumen present is of course much in excess of that ever found in General Paralysis.

Diagnostic Value of Reactions and Signs.

These six reactions and signs of General Paralysis are independent of one another in origin and different in nature, so they supplement and confirm one another. The Wassermann Reaction of the blood serum is independent of the reaction in the spinal fluid and this is apparent from the fact that in ordinary syphilis the former is positive and the latter negative. The converse has been occasionally met in General Paralysis, but not infrequently the reaction has been found much stronger in the spinal fluid than in the blood. Similarly there is no connection between the excess of globulin and the Wassermann Reaction, although the lipoid reacting substance if present is precipitated with the globulin. Nor is there any essential relationship between the presence of globulin and of albumen, or of lymphocytosis and the presence of plasma cells.

A combination of independent signs of this kind increases their value enormously for diagnostic purposes and if, as usually happens in General Paralysis, all the signs are positive, their cumulative effect on the diagnosis is irresistible. Should one sign fail, owing to an unusual circumstance, the other signs will almost certainly indicate the fact if General Paralysis be present. If all fail, then the case cannot be considered one of General Paralysis.

The signs which may occasionally fail are the Wassermann Reaction in the cerebro-spinal fluid in 6 per cent., in the blood serum in 1 per cent., and a definite lymphocytosis in 10 per cent. of the cases. Any one of these may fail singly and a diagnosis of General Paralysis may be correctly made, provided all the other signs are positive and the clinical symptoms are typical.

The three minor signs, the increase of globulin, the presence of albumen and of plasma cells very rarely fail in General Paralysis, so they are valuable for the purpose of confirming the evidence of the three major signs, especially in those cases in which there is a failure of one of them. They also confirm a diagnosis made on clinical grounds, when it has not been possible to perform the Wassermann Reaction.

The Paramount sign is undoubtedly the presence of the Wassermann Reaction in the cerebro-spinal fluid for it is shared by only two other conditions, and these allied to General Paralysis, namely by its twin sister Tabes and its first cousin cerebro-spinal syphilis. If these

two conditions can be excluded by the clinical symptoms, the diagnosis of General Paralysis may be made even in the absence of the other two major signs, lymphocytosis and the Wassermann Reaction in the blood.

It is important to know from a diagnostic point of view that ordinary doses of Salvarsan have only a slight and temporary effect in altering these reactions and signs in General Paralysis and this only in about a half of the cases. The intensity of the Wassermann Reaction may be decreased or it may occasionally become negative for a time and the cell count may be lowered. In cerebro-spinal syphilis on the other hand the effect of Salvarsan is very different and is so marked as to form an important diagnostic feature. The excess of globulin quickly disappears, the cell count from being very high becomes markedly reduced to nearly normal and the Wassermann Reaction usually becomes negative in the cerebro-spinal fluid and may also become negative in the serum.

As a consequence of the discovery of these new reactions and signs we have attained to an accuracy in the diagnosis of General Paralysis unapproached in the past and not excelled in the case of any other disease as important. There are few departments of clinical medicine in which during the last ten years more valuable additions to our knowledge have been made.

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