

THE
JOURNAL OF MENTAL SCIENCE

[*Published by Authority of the Medico-Psychological Association
of Great Britain and Ireland.*]

No. 248 [NEW SERIES
No. 212.] JANUARY, 1914. VOL. LX.

Part I.—Original Articles.

The Morison Lectures, 1913.—The Serum and Cerebrospinal Fluid Reactions and Signs of General Paralysis. By GEORGE M. ROBERTSON, M.D., F.R.C.P.Ed., Physician-Superintendent, Royal Asylum, Morningside, and Lecturer on Mental Diseases, University of Edinburgh.

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 seventeen 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 in 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 twenty 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 inquiries into the causation of locomotor ataxia, he found that general paralysis ran a parallel course with it ætiologically. Fournier’s special views were summarised by him in his work on parasymphilis in 1894, and these were that general paralysis was syphilitic in origin, but not in nature, as it was unaffected by anti-syphilitic remedies, and its lesions were not circumscribed, but diffuse.

The discovery of the specific organism of syphilis, the *Spirochæta pallida*, was made by Schaudinn in 1905, and in the following year Wassermann, Neisser and Bruch 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 or its chemistry, but its clinical aspects.

The Wassermann 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:

Venepuncture.

The most accessible veins to puncture are generally the median basilic and the median cephalic immediately in front of the elbow-joint. These often show 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, push it 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, she obtained 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 1 *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 both been 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 twelve 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 Quincke 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 :

Lumbar Puncture.

A special hollow needle, about 4 in. long, made of platinum-iridium is required, as a steel needle might break across if caught between the vertebræ 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 vertebræ prominent, and to separate the laminæ as much as possible. The skin of his back over the lumbar vertebræ is prepared by scrubbing it with a solution of corrosive sublimate in alcohol, one 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 fourth and fifth spines to mark the level of the site of the 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 $1\frac{1}{2}$ to $2\frac{1}{2}$ in., 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 the needle should be twisted round, and if this be unsuccessful it is safer to withdraw the needle and insert another in the space between the third and fourth or second and third lumbar vertebræ. 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, 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 of general paralysis, 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. | Number of cases. | Positive reaction. | <i>Per cent.</i> |
|--|------------------|--------------------|------------------|
| 1. Nonne and Holzmann | 23 | 22 | 95 |
| 2. Eichelberg | 61 | 57 | 93 |
| 3. Smith and Candler | 64 | 59 | 92 |
| 4. Marinesco | 35 | 32 | 91 |
| 5. Plaut | 150 | 144 | 96 |
| 6. Marie, Levaditi and Yamano- nouchi | 30 | 28 | 93 |
| 7. Stertz, Morgenroth and Stertz | 53 | 48 | 90 |
| 8. Raviart, Breton and Petit | 72 | 67 | 93 |
| 9. Morton | 30 | 30 | 100 |
| 10. Muirhead, Royal Edinburgh Asylum | 100 | 95 | 95 |
| | <u>618</u> | <u>582</u> | <u>94</u> |

Note.—1 to 5 quoted from Mackintosh and Fildes, 6 to 8 from Plaut, and 9 from Browning and 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 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 histo-

logical 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 fifty-four 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 five cases in which a negative reaction was obtained by us, the diagnosis was confirmed by *post-mortem* appearances in one 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 lecithin-cholesterin 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 shown that the reacting substance in the spinal fluid was of a fatty or lipid 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."

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 show on an average more than two or three 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 show on an average ten, twenty, 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, 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 are recommended. The diluent is drawn up to mark 1, fresh uncentrifuged spinal fluid up to mark 2, 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 five 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, chiefly 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 pathognomonic of general paralysis, as it occurs occasionally in epilepsy and dementia præcox, 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 develop-

ment 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 half to one 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 micro-millimetres 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 shown in the following table, with similar observations, for purposes of comparison, in dementia præcox; these may be provisionally accepted as

representing the normal. The average cell-count per c.mm. in twenty-six cases of general paralysis was 47, and in eleven cases of dementia præcox it was only 1·3 per c.mm.

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

| | General paralysis. | | | Dementia præcox. | | |
|-------------------------|--------------------|------|----------|------------------|------|----------|
| | Min. | Max. | Average. | Min. | Max. | Average. |
| 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 nineteen cases of general paralysis were as follows: Lymphocytes, 73 *per cent.*; endothelial, 13 *per cent.*; polymorphonuclear, 9 *per cent.*; plasma, 2 *per cent.*; phagocytes, 1 *per cent.*; and unclassified cells, 2 *per cent.*

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 cerebro-spinal 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 præcox. 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 molecule, and is precipitated with it.

The Presence of Albumen and its Amount.

The constant presence of albumen in the cerebro-spinal 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 albuminimeter. 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 albuminous 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 amount 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.

Summary.

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 lymphocytosis or 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 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.

Vaccine Treatment in Asylums. By W. FORD ROBERTSON,
M.D., Pathologist to the Scottish Asylums.

THE treatment of bacterial diseases by means of specific vaccines is a branch of therapeutics that has been steadily growing in importance in recent years. It is now being applied to every bacterial infective malady, from acne to acute septicæmia. Nevertheless, it is admittedly only at an early stage in its development. Every worker at the subject is still endeavouring by observation and experiment to improve its methods, to understand better its mode of operation, and to determine the extent of its useful application. It has already had brilliant triumphs, although, in common with other forms of medical treatment, it has to admit many failures. While it is now being extensively employed both in general and in hospital practice, it has not yet been utilised in our asylums as it deserves to be. The chief purpose of this paper is to endeavour to show some of the useful applications vaccine therapy may have in such institutions, and to encourage its employment.

It must be admitted that as a direct means of combating the known causes of insanity vaccine therapy has as yet a very limited utility. Its present importance in relation to the inmates of asylums lies mainly in the fact that these patients, in common with others, not infrequently suffer from chronic bacterial infections of a kind now being successfully treated by means of vaccines. At the same time, I think experience has already proved that in asylum cases the successful treatment of these maladies of bacterial origin by vaccine methods often