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THE
JOURNAL OF MENTAL SCIENCE

[*Published by Authority of the Royal Medico-Psychological
Association.*]

No. 308 [NEW SERIES
No. 272.] JANUARY, 1929. VOL. LXXV.

Part I.—Original Articles.

GENERAL PARALYSIS.

A DISCUSSION WHICH TOOK PLACE ON NOVEMBER 23, 1928, UNDER
THE AUSPICES OF THE GENERAL PARALYSIS SUB-COMMITTEE,
AT A GENERAL MEETING OF THE ROYAL MEDICO-PSYCHOLOGICAL
ASSOCIATION.

THIS discussion was arranged by permission of the President
to afford members the opportunity of considering certain points
raised relating to the diagnosis, pathology and treatment of general
paralysis in papers read by Dr. J. Brander and Dr. J. F. Smyth at
the Annual Meeting on July 13, 1928.

The Sub-Committee had previously circularized these points,
which were the following :

THE DIAGNOSIS.

1. Is the diagnosis of general paralysis justified on laboratory findings only, *i.e.*, without the support of (*a*) mental, (*b*) physical, or (*c*) both mental and physical signs? If not, then what physical and mental symptoms are necessary to support laboratory findings in order to justify a diagnosis of general paralysis?
2. Are cases now being diagnosed and treated as general paralysis in virtue of certain common laboratory findings, which otherwise would not have been diagnosed as such? If so, do these cases represent an altered type of general paralysis, or are they merely the cases which were formerly classed as cerebral syphilis and treated as such with a reasonable prospect of improvement or cure?
3. Can cases of acute cerebral syphilis be distinguished from general paralysis clinically or serologically? If so, how?
4. To what extent is there unanimity of opinion as to the laboratory findings which justify or support the diagnosis of general

LXXV.

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paralysis? [This question arises because of the necessity for a complete standard correlation between the mental and physical signs and the serological changes in such cases.]

THE PATHOLOGY.

1. Is there a special neurotropic strain of spirochæte in general paralysis?
2. Should cases of acute cerebral syphilis (infection *via* blood-vessels and not lymphatics) be regarded as suffering from general paralysis?
3. Is general paralysis due to a pure or a mixed infection?
4. Are the pathological findings in general paralysis pathognomonic or are they merely those found in all cases of dementia?

TREATMENT.

1. The application of malaria and tryparsamide therapy to cases of early syphilis showing pathological changes in the cerebro-spinal fluid.
2. The cause of the variation of the results of malaria and tryparsamide therapy in general paralysis claimed by different observers.
3. Should malaria therapy be supplemented by anti-syphilitic measures?

The PRESIDENT (Prof. J. Shaw Bolton) presided, and opened the discussion by calling upon Dr. J. Brander to give a short summary of the views he had expressed in his paper at the Annual Meeting, which had not yet appeared in the Journal.

Dr. J. BRANDER (Bexley) said that in his paper he had tried to create some certainty on the subject of the diagnosis of general paralysis. In the amount of time he was allowed on the present occasion it would be impossible for him to do more than indicate a few points which, he thought, should receive the serious consideration of the General Paralysis Sub-Committee.

The first and the most important point was, Did we know what general paralysis was? Had he been asked that question a few years ago he would have said, "Yes, certainly, we can make that diagnosis." But since serological methods were introduced in the diagnosis of general paralysis, many conditions were being called general paralysis which would not have been so classified at one time. This error, he thought, had arisen in two or three main ways, which it would be his effort to indicate.

Originally the diagnosis was based on clinical grounds; there was

a definite mental state which enabled one to say, "This condition can only be general paralysis, for there is no other mental disorder in which this behaviour is found." In the second place, the physical signs, when they occurred, were unequivocal. The kind of speech found in patients with the disease was said by the neurologist of thirty years ago to be one which could not very well be mistaken for anything else. On the mental and the physical condition the diagnosis of general paralysis was made, and on such diagnosis there was established a hopeless prognosis, for there was said to be a strong resistance to treatment. The speaker came into psychiatry at about the time when laboratory studies were commencing. He and his colleagues made the diagnosis of general paralysis, and then, as a matter of curiosity, they sent the specimens of blood and cerebro-spinal fluid to the laboratory, just to see what the pathologist would report. In one case, he remembered, the report came back that it was negative. He and his colleagues said, "This is general paralysis; we will send the specimens up again." The second time the people in the laboratory acknowledged that technical errors influenced the reactions. He had been through the case-papers of all patients admitted during his first five years at hospital, and during that time 166 cases were diagnosed as general paralysis, and the diagnosis was arrived at on clinical grounds. Of 111 cases the report was positive except in one, and that one patient was still alive in 1910, and on parole, meaning that 110 out of 111 diagnoses were confirmed by a positive Wassermann. He argued that this justified his contention that the clinical diagnosis was pretty reliable. During the same period 7 cases had had some other diagnosis, arrived at clinically, altered to general paralysis of the insane, on the strength of the laboratory findings. Those seven cases were all interesting. Three of them died of general paralysis. A fourth case remitted; after two years he was discharged. The fifth continued unchanged indefinitely. In 1910 all his reactions were positive, and in 1923 they were little altered. At the request of his friends he was transferred to another mental hospital, where they had more convenience for visiting. His blood and cerebro-spinal fluid still gave the reactions, therefore he was treated with malaria. A month ago, when the speaker last made inquiries, he was in much the same state as eighteen years ago. From the speaker's experience he would say that eighteen years from now the man would be appreciably older, but not much altered otherwise.

The sixth case had had previous attacks of mental disorder—mania and melancholia. He was admitted in 1911, recovered from his attack, and was discharged to the care of his friends. During

the summer just past, having done much useful work in the meantime, he was re-admitted. He was discharged recovered last month.

The seventh patient showed all the reactions, and the diagnosis of dementia præcox was altered to that of general paralysis. Now, eighteen years afterwards, he was a very useful man, and all his reactions had cleared up spontaneously except that in the middle of the gold curve there was a 1, 3, 1. Thus, in four out of the seven cases in which the diagnosis turned on the Wassermann reaction, the patients were still alive. Of the 110 in which the clinical diagnosis was merely confirmed by the positive Wassermann, all were dead. The other cases, in which a Wassermann was not done, ran the ordinary course of general paralysis, and every one of them—150—showed typical general paralytic findings at the *post-mortem*. He hoped members present would agree with him that those figures showed that general paralysis was a definite clinical entity long before laboratory tests were heard of, and that laboratory tests might introduce a fallacy. He could mention many other types, but there was not now time.

He hoped his hearers would not think that this question of diagnosis was of purely academic interest. It was essential to recognize the difference between the general paralytic, the subject of syphilitic brain disease, and a case of ordinary mental disorder who happened to have syphilis. It was now known that one might get a positive reaction in the spinal fluid of secondary and tertiary syphilitic patients without symptoms, with increase of cells and protein and the paretic gold curve, but they were not absolute signs of general paralysis. Workers on the Continent—as probably most members knew—had been suggesting that the action of malaria in cases of general paralysis might be a completion of the cycle of reactions in the body, to convert the latent secondary syphilis into a tertiary syphilis, which then might either undergo spontaneous recovery, or might be amenable to treatment by ordinary anti-syphilitic remedies.

He would close by saying that not long ago he was reading some literature on the subject, when he came across an article relating a histological investigation which had been made into some cases. It gave an account of a man supposed to have general paralysis who, a year after admission, was given malaria. A fortnight later he died of lobar pneumonia, and the observer found that some of the appearances of the brain were consistent with the man having had general paralysis, therefore the malaria had contributed to the cerebral syphilis. He mentioned that simply to show that the only way to prevent such reports was to obtain as clear an idea as

possible of what was meant by general paralysis, and that was the object of this meeting.

Dr. W. A. CALDWELL (The Maudsley Hospital) said he wanted to say a few words upon the theory of there being neurotropic and dermatropic strains of the spirochæte. For many years it had been realized that though many people acquired syphilis with the usual characteristics, only 4% of those suffering from syphilis developed general paralysis later, and only 3% of them became tabetics. A hypothesis advanced to account for this was that there was a special causal strain of spirochæte, which had as its natural habitat the central nervous system, as compared with the ordinary strain of spirochæte, which grew in the dermal structures and the viscera of the body. Much evidence had been adduced to support that theory, both in the way of statistics and of experimental investigation. One important piece of evidence was the fact that in tropical and subtropical countries—China was the one most quoted—where syphilis was rife, general paralysis was almost unknown, workers in such countries having seldom, if ever, come across a case of general paralysis. But that evidence might be refuted by the fact that no one had really, with specific purpose, gone out to look for cases of general paralysis in those countries; they had been aliens in a strange land, not knowing the native tongue, and knowing but little of the psychology of the people, in addition to which they had large clinics and a large amount of work to do. Hence it was very likely that no real search had been made for cases of general paralysis. Another point which was brought up was the incidence of conjugal and consanguineous neuro-syphilis. Many observers had described cases of conjugal and consanguineous neuro-syphilis, but when one studied the relatively few cases described in comparison with the tremendous number of general paralytics, it would be seen that the mere fact that a few of them had been described—and they had been described because of their fewness—did not lend much evidence to the theory of the dual type of spirochæte.

Another point brought forward in favour of the view was that several people infected from the same source had developed general paralysis. The fact that those cases were cited in all the text-books and were classical, and that everyone had read or heard about them at some time, rather condemned the theory. If such cases had been common, if they had been the usual sort of happening there would have been no occasion to quote them.

Fournier brought stronger evidence to support the theory of a dual type of spirochæte. He had examined the histories of several

hundreds of general paralytics, from the primary stage, through the secondary, right up to the onset of general paralysis, and he stated that in the primary stage the sore was a very transitory one, the secondary stage was present in relatively few of the cases and was of a very fleeting character. In only 4 of 187 cases was he able to find recognizable tertiaries. The fallacy lay in the fact that since the infection produced such a transitory primary lesion, and since there were few or no secondary lesions, might not those people have developed general paralysis because treatment had been inefficient.

Another point brought up to support the hypothesis was that tertiary syphilitic lesions were seldom found in general paralytics. Perhaps the reason was largely because *post-mortem* examinations on general paralytics had been carried out in a rather lax manner. Several authorities in Lancashire last year published a report on *post-mortems* they had held over 100 cases of general paralysis, the examinations having been carried out in a systematic and thorough manner, and in almost all the cases there were found evidences of syphilitic lesions elsewhere than in the brain. In a large majority of the cases there was evidence of involvement of the aorta, and in many of the cases the examiners were able to demonstrate the presence of the spirochæte in the walls of the aorta. This showed that in general paralysis the syphilitic lesions were distributed generally throughout the body, as in ordinary cases of syphilis. Levaditi and Marie, who perhaps had investigated this subject more thoroughly than anybody else on the experimental side, chose for their experiments rabbits, but it was a bad choice, as that animal was liable to infection in the ordinary way by a spirochæte which was morphologically and biologically similar to the *Treponema pallidum*. Those workers infected a certain group of rabbits with the blood from a general paralytic, and they infected another group of rabbits from a human chancre. The primary lesion of the rabbits infected from general paralytics differed from the others in that it was a much shallower lesion; it was of a papulo-squamous nature, in comparison with the typical indurated, hard-based chancre. In the chancre which arose from the general paralytic infection the spirochæte was confined to the superficial layers of the skin; there was only a periarteritis, no evidence of endarteritis. The incubation period was a very long one, in comparison with the usual short incubation period in the rabbits infected from the ordinary chancre, also the virulence of the infection was very much less. The serum of a rabbit which had been inoculated from the general paralytic was inoculated into a human subject, and he showed no lesions, whereas a volunteer who was

inoculated with the serum of a rabbit infected by the more virulent strain of spirochæte, which came from the human chancre, produced typical signs of primary syphilis and gave a positive Wassermann. These findings showed a definite difference between the two types of spirochæte. But the authors condemned their own work by publishing, three or four years later, similar differences which they found in cases that had been inoculated from various strains of spirochæte found in human chancres—just as marked differences as were found in the investigations previously mentioned.

The conclusion was that the spirochæte, as was the case with all other organisms, differed from day to day, from source to source, differed in virulence and in its degree of adaptability. Carandette and Yawnill supported the hypothesis that, rather than there being a difference caused by one being a specific neurotropic organism and the other a dermatropic, the spirochætes were one and the same family, only differing in virulence, and that the reason one infected person developed visceral syphilis and another general paralysis was due to a difference in the soil—the person infected—rather than an essential difference in the spirochæte itself.

Dr. W. D. NICOL (Horton) remarked that there was one thing he wanted to make a plea for, especially as he had had the opportunity, in the last year, of visiting hospitals throughout Great Britain on behalf of the Ministry of Health in connection with the malarial treatment of general paralysis. Besides the mental hospitals, he had also had access to general hospitals in his inquiry into these cases. During the course of that inquiry he had been struck with the absence, in a large proportion of cases, of physical signs, and with the vagueness of the mental symptoms. His plea, therefore, was that these cases should be seen and placed under treatment as early as possible. Dr. Brander had said that general paralysis of the insane was a definite clinical entity, which stood alone, and that it was known before serological investigations were made. The speaker admitted that much depended on the skill of the individual clinician, but the importance of early diagnosis should encourage all to examine cases of mild psychosis more frequently from the point of view of the serological findings they presented. There occurred an early stage, in which the patient was free from physical signs and symptoms, but the all-important syphilitic changes were present in the cerebrospinal fluid. Dunker, in a paper read in America last year, analysed 74 early cases of general paralysis of the insane, and that authority found that—in the order of frequency—the most common symptoms were emotional irritability, the patient being restless and fidgety,

though some were abnormally quiet and preoccupied, listless, and apathetic; loss of body-weight was marked. Some had forgetfulness, in some there was an increased tendency to sleep; others showed defective judgment. Admittedly, all those were vague symptoms, but they were present. Therefore anyone between 30 and 50 years of age who had an indefinite neurotic complaint should be examined from the standpoint of the possibility of general paralysis of the insane, as also should those who got epileptiform attacks at or after middle life. The practitioner, as a rule, was too easily satisfied with the diagnosis of "neurosis" or "neurasthenia" in the first case, and of "epilepsy" in the second place. The fully developed psychosis was preceded, for some months or longer, by these general, indefinite neurasthenic complaints. In Vienna they were now treating even cases of primary syphilis with malaria. They were also treating with malaria a certain type of case—of which the speaker saw a number during the war—that had had a sound course of anti-syphilitic treatment, but whose serological findings were obstinately positive. And according to reports the results had been fairly good, in that after the malaria treatment the serological findings had been definitely improved.

He agreed that the malarial treatment was not easy to look after and control, and that it called for much care and management; but, given proper skill and nursing, it was not such a serious matter as was sometimes maintained by doctors in general hospitals.

Dr. NATHAN RAW (Lord Chancellor's Visitor) said this was a subject in which he had taken an intense interest for a long time. He thought all were agreed with the dictum—"No syphilis, no general paralysis." Even fifty years ago it was thought that general paralysis was associated with syphilis. Bearing on the last remark of Dr. Caldwell, that there was something to be said for the environment, the speaker had had a very interesting experience, and it might to some extent provide a reason for the fact that only 4% of the people attacked with syphilis developed general paralysis. In 1888 he was assistant medical officer at the Durham County Asylum, where there was a very astute medical superintendent, Dr. Robert Smith. Dr. Smith was always impressed with the fact that he had so many cases of general paralysis at his asylum, while superintendents at other mental hospitals did not, and he could find no reason for the difference. Sir David Drummond, a distinguished physician in the North—still alive, he was glad to say—was the first to suggest that tabes was a direct result of syphilis; Sir David also suggested that general paralysis was probably associated with syphilis, and the surmise, Dr. Raw thought,

had now been universally accepted as true. He, the speaker, proceeded from the Durham County Asylum—where the residents in the asylum led a rather strenuous life—to the calm of the Kent County Asylum, Barming Heath, where there was not the same strenuous life. In the latter institution he was impressed with the fact that there was practically no general paralysis in the whole of that asylum. For his M.D. thesis he prepared careful notes of 100 cases of general paralysis, and at that date the people who examined him, both the external examiner and the professor, admitted they had not seen a case of general paralysis, or one which had been recognized as such, in a general hospital. He, Dr. Raw, agreed that the spirochæte which caused syphilis was a universal spirochæte, and that there were no differences in virulence or in character between the different forms of spirochæte, but he did think that the environment—or, as Dr. Caldwell put it, the soil—had a great deal to do with whether a man attacked with syphilis would or would not develop general paralysis. And the kind of life he led, whether quiet or exciting, whether he took much alcohol or not, had, he thought, an important bearing on whether the spirochæte with which he was infected would or would not attack his nervous system.

Another curious thing was the rarity with which women were attacked with general paralysis. Out of the 100 cases of general paralysis which he saw at Durham County Asylum only 3 were in women. It was very difficult to explain the disparity, unless it was that, on the whole, the woman's life was less strenuous than that of the man.

He did not think any further progress had been made in the ætiology of general paralysis, because the older physicians were just as acute in diagnosing general paralysis as were present-day physicians; and he thought the Wassermann test could only be regarded, in a very large percentage of cases, as confirmatory rather than diagnostic in itself.

Dr. T. SAXTY GOOD (Oxford) said he did not feel very competent to speak on this subject, as his own experience of general paralysis was confined to a comparatively small number of cases, but he would like to say a few words supporting Dr. Brander's remarks as to the importance of correlating the clinical and pathological data in the diagnosis of general paralysis. He, the speaker, was attached to a general hospital, and that hospital used the Sigma test for syphilis. This test indicated the degree of infection in units. General paralysis always gave a positive cerebro-spinal fluid, but a positive cerebro-spinal fluid might not be general paralysis.

During the war he first noticed that cases came to his department who had been treated by salvarsan, with clinical symptoms of acute general paralysis, which symptoms appeared to have been greatly accelerated by the anti-syphilitic injections. These cases ran a very rapid course and at death *post-mortems* showed undoubted general paralysis. Clinical cases, however, of general paralysis which, both at the general and mental hospitals, had been treated at first with malaria and after treatment had undergone a course of injections by salvarsan and bismuth, seemed on the other hand to have further improved by the anti-syphilitic remedy. The Sigma test after malarial treatment often showed no diminution in the number of units. Some cases showed an increase. The clinical condition generally improved. In all cases first treated by malaria and subsequently given a three months' course of salvarsan and bismuth there was a diminution in the units in both cerebro-spinal fluid and blood. Therefore, his experience seemed to indicate :

(1) That malaria produced improvement of the patient clinically but had no effect in diminishing the number of units in the Sigma test of the cerebro-spinal fluid.

(2) That after malarial treatment, salvarsan and bismuth injections were not only well borne, but appeared to lower the number of units of infection.

(3) That whereas some cases of general paralysis treated primarily by salvarsan preparations appeared to rapidly become worse, cases treated first by malaria did not show this tendency. On the contrary the malarial treatment appeared to, as it were, enhance the value of the anti-syphilitic injections.

He was putting these points forward tentatively. What he wished to emphasize was, that cases having a positive cerebro-spinal fluid should be verified by a goldsol test and clinical findings before being treated by salvarsan preparations. Cases having a positive cerebro-spinal fluid showing any symptoms even suggesting general paralysis were probably safer to treat by malaria and possibly these cases, if treated afterwards by anti-syphilitic injections, might be cured.

Dr. I. FROST (Horton) said he believed that some very important work by Monrad-Krohn, of Oslo, threw considerable light on this question of the ætiology of general paralysis. He wished to address a question specially to those members of the Association whose experience went back some thirty years. About that time there was one physician in Oslo who refused to use any mercurial preparation or iodide of potash in the treatment of syphilitic cases. Twenty years later it was found that none of the general paralytics

who entered the hospitals at Oslo had been treated for their syphilis by this physician who obstinately refused to use mercury. The theory was that those cases of syphilis which were treated by these remedies had a greater liability towards the later acquisition of general paralysis than those not so treated. He was asking whether the experience of any members of the Association bore that out in any way.

Dr. R. M. STEWART (Leavesden) said he had gained the impression from remarks which had been made, and particularly from the phrasing of paragraph 1 of the "Points for Discussion," that laboratory findings were in danger of being given too prominent a position in the diagnosis of general paralysis, and he asked what would the great psychiatrists of the past have said of the question, "What physical and mental symptoms are necessary to support laboratory findings in order to justify a diagnosis of general paralysis?" Surely laboratory technique must always have a subordinate place in diagnosis, and could never supplant the results obtained from careful clinical observation.

With regard to the second question, "Are cases now being diagnosed and treated as general paralysis in virtue of certain common laboratory findings?" he would only express the hope that the refinements of laboratory technique had not yet brought them to such a stage.

Admittedly, general paralysis had altered in type during the last decade, just as the clinical manifestations of syphilis had altered. It was exceptional now to see the classical grandiose type with all the physical signs described in text-books.

He considered that the distinction between acute cerebral syphilis and general paralysis was possible, both clinically and serologically—clinically by a careful analysis of the neurological signs, and serologically by noting the effect of treatment. Alterations in the cerebro-spinal fluid were rapidly effected if the case was one of cerebral syphilis, whereas treatment by arsenical preparations had little or no effect on the fluid in general paralysis, the reactions remaining unaltered.

Lastly, in answer to the question, "To what extent is there unanimity of opinion as to the laboratory findings which justify or support the diagnosis of general paralysis?" the speaker thought the consensus of opinion was in favour of the view that no single test or combination of tests was sufficient to establish the diagnosis of general paralysis; while of great value in indicating syphilitic infection of the nervous system, they could not be relied upon to

differentiate with certainty general paralysis from other forms of neuro-syphilis.

Drs. Greenfield and Carmichael, who had a very wide experience of neurosyphilis at the National Hospital, stated, "No single reaction suffices to establish the diagnosis, and a thorough examination of all the elements of the fluid can, at most, prove that there is severe syphilitic disease of the nervous system." From experience gained in the examination of nearly 5,000 fluids the speaker had arrived at a similar conclusion.

The experimental work of Levaditi and Marie, which seemed to prove the existence of a special neurotropic strain of spirochæte, was largely discounted by clinical data. The recorded instances of families, whose several members, after acquiring syphilis from widely different sources, had all developed neuro-syphilis did not favour such a view. Another serious objection to this theory was to be found in the well-authenticated reports of syphilitic twins, one of whom developed juvenile general paralysis or tabes, while the other showed cutaneous and visceral signs of syphilis, but no involvement of the nervous system.

The absence of general paralysis in certain races, notably those of China and Persia, was also used as an argument to support the theory of different strains of organism, but it was of some importance to note that in such countries malaria was literally a universal disease, and it might well be that these races owed their freedom from neuro-syphilis to the protective value of malarial infection.

The question whether cases of acute cerebral syphilis could be regarded as suffering from general paralysis could be answered in the negative without any reservation. No one had shown the clinical and pathological distinctions between the two conditions more clearly than the late Sir Frederick Mott.

General paralysis must be regarded as a pure infection, but in its late stages the cerebro-spinal fluid was often invaded by numerous other organisms. Obviously the presence of a secondary infection did not improve the prospect of cure, hence the importance of early treatment.

He thought that the pathological findings in general paralysis were pathognomonic and, as Alzheimer had pointed out, the entire nervous system was involved. In no other disease did one see such a pronounced destruction of cortical neurons and association-fibre systems. Perivascular infiltration was of less importance, being imitated in cerebral syphilis, trypanosomiasis, lethargic encephalitis, rabies and other diseases. The sprouting and formation of new capillaries was very characteristic of general paralysis, and the

demonstration of the spirochæte in the brain clinched the pathological diagnosis.

With regard to the treatment of general paralysis by induced malaria, he had found little benefit from its use in juvenile cases. It certainly prolonged life, but did little else. At one time he thought its failure could be attributed to the mass invasion of the juvenile parietic's brain by the spirochæte, but he had been compelled to abandon this view, since in several cases coming to *post-mortem* a careful search had failed to reveal any spirochætes. The resistance of the juvenile general paralytic to this form of treatment was a problem which demanded further study.

Prof. G. M. ROBERTSON (Edinburgh) said he was not present in time to hear some of the arguments and statements which had been advanced in the earlier part of the meeting.

The subject under discussion was undoubtedly a most interesting one. It was said by Baillarger that the most important event in the history of mental medicine was the discovery of general paralysis, and he thought those present would agree that the full and proper understanding of general paralysis was the most important knowledge one could have of mental disorders.

One of the points which had been raised in this question, concerning which printed notes were issued, was with regard to the certainty of diagnosis of general paralysis. His own opinion—with which he thought his hearers would agree—was that there was no important disease from which the human being suffered that could be diagnosed with such certainty as general paralysis. There were some cases, but they were only a small proportion, in that one could not be quite sure, but in the vast majority the diagnosis, he thought, was as certain as it was in respect of any other important disease. Not only were there mental symptoms, which were not very diagnostic from the differential point of view, not only were there the physical signs, but there were also the laboratory findings, which were very various and largely independent of each other. And if there were in a given case a consensus of all these points, the diagnosis was certain. As the last speaker said, however, those engaged in laboratory tests made the statement that there was no laboratory test or finding which could be regarded as absolutely diagnostic of the disease, and with that he agreed, because every one of the laboratory findings could also be found in conditions other than general paralysis. The important point in diagnosis was the presence of a combination of the various symptoms. No one had the right to diagnose general paralysis from the mental symptoms alone, nor from the physical

signs alone, nor from the laboratory findings alone. The difficult point was, to what extent must there be this combination? It might be a very slight combination; there might be but slight harmony between these various conditions, but there must be some species of harmony for the diagnosis to be made.

As another speaker said, the factor which differentiated general paralysis from any other syphilitic condition was the test of treatment. Some time ago a writer stated that once a method of curing general paralysis was discovered, then general paralysis as a specific entity would disappear. And it would appear that that stage had now nearly been reached. In the year 1922 there was held in Paris an International Congress to celebrate the discovery of general paralysis, and the organizers were good enough to appoint him, the speaker, a vice-president. At that Congress the workers on the Continent stated that there was no cure for general paralysis, and the statement was repeated again and again at the meetings. In the summer he, Prof. Robertson, was President of the Section of Neurology and Psychiatry at the British Medical Association meeting at Glasgow, and there were representatives from this country, America and elsewhere. General paralysis was discussed, and there again it was stated that there was no remedy or cure for general paralysis. It was now known that there were two remedies which, apparently, cured many cases of general paralysis. Perhaps sufficient time might not have elapsed to enable one to use the word "cure," but there might be such remissions, and they might take place so frequently, that the possibility of cure could well be entertained. The treatments he referred to were malaria and tryparsamide. He, the speaker, was the first to introduce the intrathecal treatment of general paralysis by salvarsanized serum, but, though improvement ensued, one never got such remissions as could be seen now, with a negative Wassermann in blood and cerebrospinal fluid. At present it was not known how the treatments acted. It was not known how malaria acted, but it was thought it so stimulated the defences of the body that it enabled the body to overcome the activities of the spirochæte. He supposed tryparsamide acted in the same way as salvarsan did in ordinary syphilis. As some of these cases recovered, the dividing line became narrower and narrower. And this made necessary some definition as to what one meant by general paralysis and what one meant by disease. He would not, however, pursue that line now. There might be mono-symptomatic tabes, and tabes related to general paralysis, and there might be many symptoms of general paralysis. He, the speaker, delivered his course of the Morison Lectures at the Royal College of Physicians of Edinburgh, which were the first

lectures to appear after the discovery of the spirochæte in the brain. Noguchi sent over a specimen, and it was shown at a Quarterly Meeting of the Association in London in the year 1913 or 1914. The spirochæte having been found in the brain of these cases, he said it was a syphilitic disease. He pointed out that there were all sorts and degrees of general paralysis, and probably in the future cases would be recognized which had not been diagnosed in the past. The diagnosis was now more accurate, more certain, and he thought more cases of it were being diagnosed to-day than before, because in the old days the physicians said that no one had a right to diagnose general paralysis until he was absolutely certain of it—that making such a diagnosis was consigning the patient to his death.

Dr. B. H. SHAW (Stafford) : I regard general paralysis as syphilis, and any claim of cure must, therefore, as generally accepted, depend on the return of negative blood Wassermann taken quarterly for a continuous period of at least two and preferably five years. I tend to look on the distinction between general paralysis and purely vascular cerebral syphilis as dependent on serological improvement as a result of present-day treatment. In general paralysis, a "Wassermann-fast" state of the blood exists which in my experience is as yet unamenable to treatment.

As regards a neurotropic form of spirochæte, we really know very little about the organism ; it may exist in granular form, in which case, if there are varieties, the conveyance of malarial parasites from one syphilitic person to another either directly or *viâ* mosquitoes might give rise to a mixed infection, but I am of opinion that the explanation of why general paralysis occurs in such a small proportion of syphilitics is dependent on the character of the medium in which it grows. The factor influencing this may possibly be alcoholism. One does not now meet, in my experience—and I have heard it alluded to by others—expansive ideas and delusions so commonly as in pre-war cases, and this might be correlated with the fact that between 1914 and 1919 the mortality from alcoholism and its results fell by about 60%, and between 1917 and 1919 the deaths from general paralysis fell from 65 per million persons to 40, at about which figure it has practically remained. Intensive treatment of syphilis by arsenical preparations began in 1916. Malarial therapy was introduced in 1923, and has not apparently caused any marked alteration in the Registrar-General's returns as yet—there is a slight rise between 1926 and 1927.

At present I confine treatment to tryparsamide, with fairly good clinical results so far, and am of opinion that it is from improvement

in arsenical treatment that we may expect the best results. The discharge of any patient clinically and serologically diagnosed as general paralysis should be very carefully safeguarded, as I have recently heard of some financial disasters resulting in cases stated to have recovered. If any temporary benefit occurs after malarial infection, such alteration is probably due to stimulation of cellular metabolism ; but that any real improvement occurs in the syphilitic process and pathological changes present is hardly credible.

I have known a considerable number of syphilitics who contracted malaria, and malarial people who got syphilis. One is especially recalled to my mind—a man who had the three plasmodia actively present, *viz.*, B.T., M.T. and quartan. He one day contracted syphilis, which ran a normal course. I have a healthy respect for the aggressiveness of the spirochæte, and in a rough and tumble with an army corps of malarial plasmodia my money would go on little J.T.S. every time.

I can imagine, in an after-history of the war of 1914–1918, written in the year 2500 A.D., one coming across the following : “ A curious and interesting commentary on the psychological state of the people was an organized attempt to deplete their insane population by infecting them with a disease known as malaria. Some historians of the period state that this was really due to an obsession on the part of the medical authorities of that time to the effect that a terminal disorganized condition of the central nervous system due to infection by the spirochæte of a disease known as syphilis was curable by infection with malaria. Although all obsessions are necessarily difficult to comprehend, the rationale of this seems peculiarly so, inasmuch as the medical profession must have been aware at that time that no such antagonism really existed between these organisms. The suggestion, therefore, that the real reason was that first mentioned is most probable, since the introduction of a benign type of malaria, easily combated even at that period in healthy persons, would undoubtedly result in increased mortality amongst the debilitated insane.”

By the way, I do hope the term “ general paralysis ” will continue to be used on death certificates and not be replaced by “ syphilis,” because in the latter event the Registrar-General’s returns will show a complete disappearance of the former and the triumphant vindication of the efficacy of malarial so-called therapy.

Dr. F. H. STEWART (Cheddleton) : With reference to the diagnosis of early cases of general paralysis, one does not, in the nature of things, see cases devoid of symptoms in county mental hospitals, and I will therefore confine my remarks to those points which are

necessary to prove that the cases which we are treating as paretics do actually suffer from that disease.

In our series of cases at the Cheddleton Mental Hospital all had some mental symptoms, sufficient to be certifiable, and all had some physical signs, such as inequality of the pupils, Argyll Robertson reaction, exaggerated or lost knee-jerks. They also all showed the following laboratory findings: positive Wassermann in the blood and cerebro-spinal fluid, marked increase in cells, and the paretic curve in the colloidal gold or benzoin test. It is the latter test which marks them off sharply from the cerebral syphilitics, but having said this I am obviously laying myself open to the criticism which I am trying to combat, and in order to prove my contention that our statistics are not falsified by showing cured syphilitics as cured paretics, I will quote briefly the symptoms of the last eight cases of our series, which are considered as cured or greatly improved.

Case 1: No knee-jerks; Argyll Robertson pupil. Foolishly garrulous and exalted; wandered from his home and committed petty theft.

Case 2: Unequal pupils; Argyll Robertson reaction. Said he won the war, and was making a new race of giants. Sleepless.

Case 3: Slurring speech; unequal pupils; insomnia for one year. Said he was born in 1925. Hallucinated.

Case 4: Argyll Robertson pupils; no knee-jerks. Bought two motor cars with worthless cheques, his position being that of an undertaker's assistant.

Case 5: Contracted pupils, not responding to darkness; depressed. Described amorous adventures in South Africa, where he had never been. Hallucinated.

Case 6: Sluggish pupils; restless, childish, sleepless; had a seizure.

Case 7: No pupil reflexes. Grandiose delusions: said he was the Postmaster-General.

Case 8: Immobile pupils. Said he could do anything and that he had bought two expensive motor cars, although his pay was £2 per week.

Cases such as these cannot be called anything but paretics.

Having, then, made it clear that the cases which are included in my statistics were really suffering from general paralysis, I wish to pass to the subject of treatment, and especially to paragraph 2 of the syllabus. And I wish to suggest that the cause of the variation in results of malarial therapy claimed by different observers is as follows:

Malarial therapy includes three separate factors: (1) the anti-genic action of the malarial parasite, (2) the stimulating and

alterative action of short sharp pyrexia, and (3) the prostrating effect of long-drawn-out fever and prolonged severe illness when the malaria is allowed to continue for more than three or four days. We all know the condition to which a patient is reduced at the end of three weeks of malaria.

Now, in the conventional course of malarial treatment, which prescribes twelve rigors, all three factors are allowed free play, and the result to the patient will depend upon whether factors (1) and (2), which are beneficial, outweigh factor (3), which is disastrous, or *vice versa*.

During the last two years I have treated my cases by the first two factors only, on the following plan. The patient is inoculated in the usual way and allowed to develop malaria, but the fever is stopped by quinine after the first, second or third rigor. He nearly always shows prompt improvement, to such an extent that he can be put through a course of mental and physical re-education, combined with tryparsamide. After an interval of one to three months he is again inoculated and the same course is gone through again. If he is still not fit to return to his business, the course is repeated again and again until he is, or until it is clear that no further improvement can be expected. Patients have already been put through four such courses. Little difficulty is experienced in re-inoculating; if one strain of parasite does not succeed, another should be tried or the dose raised.

Twenty-five cases have been treated so far on this plan, but as the last six are too recent to judge, I will base my figures on the first nineteen only. For comparison I will give the analysis of twenty-six cases treated prior to 1927 on the conventional twelve-rigor plan.

Twelve-rigor method :

Cured or greatly improved	23·6%
Improved	11 %
Not improved	65·3%

Short or apyrexial method :

Cured or greatly improved	42·1%
Improved	26·3%
Not improved	31·5%

In neither series were the cases selected, all patients diagnosed as paretics being treated except the moribund.

The standard set for cure or great improvement is that the patient should either return to his proper work outside or carry out intelligent and valuable work in hospital. "Improved" implies manual labour in hospital—the condition of a good working dement. "Not improved" includes non-workers and the dead.

These figures are, of course, not based on a very large number of cases, but they seem to support my contention that the most important factor in malarial treatment is not the fever, but the specific although heterologous antigenic power of the malarial parasite. We find a parallel in the interaction of vaccinia and rabies in rabbits. If these two viruses are inoculated simultaneously rabies does not develop; it is overcome by the antibodies called out by the heterologous antigen of vaccinia.

This view will then explain the lack of success reported by some observers, since by continuing a debilitating illness they are doing away with the resistance aroused in their patients. We must learn to use malaria in the same way in which we use a bacterial vaccine—by repeated doses, well spaced, and so adjusted in dose as to cause gradual progressive cure.

Dr. G. DE M. RUDOLF (Claybury) : The variations in the results of treatment of general paralysis claimed by different observers depend, to my mind, upon—

- (1) Diagnosis by different observers.
- (2) Whether only certain types of cases are selected or not.
- (3) The relative proportion of cases with certain characteristics in an unselected series.
- (4) The size of the series.
- (5) The method of treatment.
- (6) The standard of improvement adopted by different observers.
- (7) Other factors, largely unknown, collectively termed "chance."

The effect of diagnosis by different observers is clear, and it is also clear that series containing favourable types only will show a high rate of improvement. Perhaps it is less obvious that an unselected series of cases may also contain a greater proportion of a certain type of case than does another unselected series. For instance, we know that a higher proportion of cases with a short history in a series give a high rate of improvement, but this is not the only factor involved, for not all cases with short histories improve, nor do all those with long histories of general paralysis fail to improve. In a comparatively small series of 89 unselected cases treated with malaria under standard conditions, I found that the highest discharge-rates occur in the cases with short histories, in the younger patients, in those with the most strongly positive Wassermann reaction in the cerebro-spinal fluid, in those in good health, amongst those reported as abstainers from alcohol and in

the expansive and depressed types. However, a classification of cases based on the mental types is to some extent unreliable, not only because the mental characteristics of some general paralytics change, but also because a patient may be placed in more than one group. For instance, a patient who is expansive and maniacal, or a patient who is depressed and demented, could be placed in one of two groups.

Thus, a patient who shows good prospects of improvement from the short duration of his general paralysis may not do so from other aspects. So a selection of apparently favourable cases is of no value for comparative purposes, as all the factors likely to affect the result of the treatment cannot be taken into consideration.

The relative magnitudes of the series to be compared is of great importance. If tests, such as Poisson's formula, be applied to small series the fallacy of judging by such series is at once apparent. Poisson's formula gives the probabilities of an event occurring in a similar but much smaller series than that to which the formula is applied. The formula can only be applied to series in which there are only two possibilities, *i.e.*, only if the event can happen or cannot happen. For instance, if the series of 89 patients already referred to be studied it is found that 33, or 37.1%, of cases were discharged from the hospital and 62.9% were not discharged. On applying Poisson's formula, it is found that in a similar but smaller series of cases there is a probability of the discharges varying from 46.1 to 28.1%. Owing to the relative smallness of a series of 89 patients a variation of 18% may be expected in other similar, but smaller, series of cases.

The method of treatment adopted may affect the results. With regard to therapeutic malaria there is, at present, no definite information as to whether mosquito or blood inoculation is the better. If blood inoculation gives the better results, should the blood be injected intravenously, intramuscularly, intracutaneously or subcutaneously? The number of febrile paroxysms, the duration and degree of pyrexia, the frequency with which the temperature is recorded, the amount of quinine given may all be important factors in the treatment.

There is no common standard as to what condition constitutes an improvement. An acute observer will notice an improvement where a less acute observer will fail to do so when minor degrees of improvement are being studied. A decision that a patient is fit for discharge made by one observer may not be agreed with by a second observer. The social circumstances of the patient may also affect his discharge. Certain cases who have improved but are not normal could be discharged to the care of an intelligent relative

with ample time to attend to the patient, whereas the same patients could not be discharged if they had no one to take care of them.

Finally I must include all those factors, largely unknown, that influence the results of treatment and which we call "chance." However, as we know that the great bulk of the fluctuations of sampling lies within a range of plus or minus three times the standard deviation, it is possible to determine whether the differences in two series indicate differences in the conditions in the universes from which the two series were drawn, or whether the difference is due to fluctuations of sampling and is not significant.

Summing up, it would appear impossible to explain, in any simple fashion, the differences in results of treatment obtained by indifferent observers.

Point for discussion No. 3 :

The question whether malarial therapy should be supplemented by other anti-syphilitic measures may, I think, be answered in the affirmative. In 1925 a committee from the London County Mental Hospitals was formed under the chairmanship of Dr. Golla. This committee reported in 1926 (*Brit. Med. Journ.*, 1926, ii, p. 603) that of 87 patients treated with malaria but with no arsenic 35.6% were discharged and 32.2% had died. Of 36 patients treated with malaria and arsenic 41.7% were discharged and only 5.5% had died. All cases had been watched for at least six months after treatment.

Dr. DOUGLAS McRAE (who was heard very indistinctly by the reporter) spoke of his association with Dr. W. Ford-Robertson in his investigations into the cause of general paralysis. He also drew attention to the work of Prof. Bevan Lewis in regard to the clinical and pathological aspects of general paralysis (*vide* President's summary of the discussion later).

Dr. J. GREIG SOUTAR said he had nothing to contribute to this discussion in the way of statistics, but for his own information he had a few questions to ask. He thought that general paralysis at an early stage had become very difficult to diagnose. As Prof. Robertson said, it was easy for one who has had experience to diagnose it when certain physical and mental signs and symptoms were present. It was, however, very important that one should be able to diagnose it at an early stage, and it was that stage which really needed clearing up. Patients were seen who showed certain indications, some irritability perhaps, some failure of memory, etc., all departures from normality, and on examination it would be found there was a little failure in the reaction of the eye, a little tremor of the face or tongue perhaps. One had the cerebro-spinal fluid examined, and the report was that the Wassermann was

positive. Was that case necessarily a general paralytic? If it were a general paralytic in the early stage, treatment ought to be applied at once. He had had early cases in which the malarial treatment was applied, and there had been excellent recoveries, but one was not sure whether it was general paralysis. Others of doubtful character were treated in the same way, but they went on and died. It was right to try the malarial treatment; it did the patient no particular harm, and it might be that one was treating an early case in the stage when the disease was specially amenable. But simply because a person had got a positive Wassermann he did not exclude every form of mental disorder other than general paralysis. There was no reason why syphilitics who had a positive Wassermann should necessarily have general paralysis; they might be suffering from any other form of psychosis. It might be an ordinary melancholia or a variety of delusional insanity. And that was a point he would like to have more firmly established in the investigations being made in this most important study. What he had said, though no real contribution to the discussion, was in the nature of suggestions for the General Paralysis Sub-Committee.

Dr. J. R. LORD (Horton) said that they could always rely upon something helpful from Dr. Soutar, whose opinion commanded universal respect in the Association. Continuing, he remarked that from his own personal experience general paralysis was being cured, and even cases showing advanced symptoms of the malady so far improved as to be considered of sound mind. Whether such results were of a permanent nature time alone would show, but so far there was good evidence that in many cases they were. His experience in this matter was one of the most remarkable and amazing he had ever had. He had seen cases admitted—not one, but many—of undoubted general paralysis as definite as any cases could be, and they had been a few weeks or months later presented to him as fit to return to their homes—all after malaria treatment. There was no imagination about this—it was solid fact, and one to which he could not shut his eyes.

He warned them against belittling this work by arguing that either the form of general paralysis had changed, or that such cases as got better were not general paralysis but some other undefined condition. One could always argue like that of any advance in medicine. Let them take care not to repeat London's reception of the Lister antiseptic treatment of surgical cases, and at some future time have to look back upon the delaying of good work for humanity with regret and not a little shame.

They would shortly have before them a report on this subject

by Admiral Meagher, an eminent naval neurologist, who had toured widely at the instance of the Board of Control, making a personal investigation in regard to malarial and other modern forms of treatment of general paralysis, which should convince to the contrary those who did not believe in the results already obtained.

The General Paralysis Sub-Committee proposed to establish a national register of general paralytics, their symptoms and form, and the results of treatment, and the immediate point was to determine what symptomatology qualified for admission to this record. The cases would in any event need classification. On what lines were they to be classified? Such a register would record all form of treatment.

That was the basic reason for the interest this sub-committee were taking in this and any future discussion on this subject, and the points put down on the programme were not statements of facts, but queries to be threshed out. In the Journal he intended to publish in full both that and any discussion which subsequently might be held at any and every meeting of the Association or of its Divisions. Additional remarks might be sent in, because speeches that afternoon were necessarily curtailed by time.

In these days medical students were taught that preventive medicine was the all-important matter in practice; the necessity for "cures" should be avoided. All this applied with great force to general paralysis, which hitherto had destroyed annually a small army of the most virile and useful section of the community, the go-ahead and active fighters in every walk of life, men who enjoyed life to the uttermost.

To reduce that waste of life was the particular object of the General Paralysis Sub-Committee which the Research and Clinical Committee of the Association had appointed.

Dr. DONALD ROSS warned members against trusting too implicitly to serological tests. Such tests when positive should be regarded as confirmatory of the clinical findings.

Dr. J. F. SMYTH (Wakefield) said that a general survey of results of his investigations led to the conclusion that there were two distinct pathological processes at work in general paralysis:

(1) A local irritative and destructive change, confined mainly to the cortical regions supplied by the anterior and middle cerebral arteries. This change was associated with the presence of spirochætes in those regions, and was characterized by a distinct specific neuroglial reaction in the deeper layers of the cortex.

(2) A general vascular proliferative change accompanied by destruction and degeneration of neurons. This he believed to be mainly the reaction of the brain to the prolonged effects of syphilis,

and analogous to the marked vascular changes occurring in the other body tissues in systemic syphilis and in general paralysis. It did not appear to depend on the actual presence of the spirochæte in the cortex.

The relative intensity and persistence of each process accounted for the variation in the clinical signs and the morbid changes in the different types of case. A preponderance of vascular change with few spirochætes was to be inferred in the confused or demented type of case, while the presence of the spirochæte in large numbers in the cortex was characteristic of the more active grandiose or emotional type.

It was interesting to record, from the therapeutic point of view, that in the treatment of general paralysis by malarial inoculation and tryparsamide, the best results had been obtained in grandiose cases and in those with agitated melancholia. In cases of the confused or demented type little or no improvement had followed. That might seem paradoxical, but there was no doubt that the majority of the confusional cases did not reach a mental hospital until the disease had advanced sufficiently to cause permanent damage to the cortex. Such cases could not be cured, and arrest of the morbid process was the most that could be hoped for. The emotional type of case, by reason of a more active mental alienation, came under observation at an earlier stage of the disease.

Whether the removal of the spirochæte from the cortex would result in inhibition of the vascular proliferation and the neuronc degeneration was a matter for speculation. There was little alteration in the cerebro-spinal fluid reactions after treatment by the present therapeutic methods, which suggested that all the pathological factors had not yet been countered.

Examination of the other organs of the body in general paralysis also revealed this tendency to excessive vascular proliferation, and the marked fibrosis of the aorta and other arteries showed the process in the vascular tissue itself. These changes were a manifestation of a pathological process which reached its climax in the central nervous system, and it would seem that the vascular process was capable of proceeding for a considerable time until neuronc breakdown at last developed and the least stable parts of the cortex precipitated the onset of mental symptoms.

The work of Fildes and McIntosh on parasymphilis of the nervous system had led them to conclude that hypersensitization of the nervous system was produced, in all probability, by the passage of the spirochæte or its toxins up the nerves from the skin and mucous membranes during the secondary period. If such were the case, the routine examination of the cerebro-spinal fluid in early syphilis

offered the best hope of diagnosing involvement of the nervous system. Only 2% showed any change in the cerebro-spinal fluid, yet it was significant that only 2% of all cases of syphilis developed general paralysis. Thus it was not unlikely that cases of early syphilis which showed changes in the cerebro-spinal fluid were potential paretics, and it was to such cases that present therapeutic methods might, with advantage, be applied.

SUMMARY OF DISCUSSION BY THE PRESIDENT.

After some further remarks by Dr. Brander, the President summed up the discussion in the following words:

Dr. Brander's paper is of peculiar interest owing to the fact that it has been written by a comparatively young man and, nevertheless, contains subject-matter which one would have expected to hear from a member of thirty or more years' experience. In a word, Dr. Brander's thesis is that general paralysis, when diagnosed on clinical grounds, has a fatal issue in approximately 100% of cases, and he disputes the diagnosis of general paralysis for the very large number of cases which improve, react to treatment, or remain stationary for very long periods. There can be little or no doubt that Dr. Brander's thesis is correct for the disease as known some thirty or forty years ago, namely, for the acute fulminating confusional cases of text-book type. The term "general paralysis" has, however, gradually come to include numerous cases with atypical symptomatology and course. As examples I may mention the two types of juvenile general paralysis and the tabetic and chronic adult types of cases. Using the term "general paralysis" in the wider sense, I have myself little doubt that certain aberrant types, namely, the imbecile juvenile, the senile and many cases in women, give a cerebro-spinal Wassermann reaction less frequently than do the more typical cases. There is also little doubt that cases of the text-book type exhibit a vicious circle of degeneration of neurons, protective proliferation of vessels, and over-reaction of repair on the part of the neuroglia, every one of these three factors tending to accentuate the other.

The chief questions which have become prominent during the discussion are whether we should revert to a more restricted definition of what is meant by general paralysis, whether the disease itself is entirely due to spirochætal invasion of the cortex, and, if not, what influence is exerted by this factor, and lastly the question of the success of treatment by malaria and other modern methods.

Dr. Caldwell, in his remarks, discusses the question whether one type of spirochæte exists in primary, secondary and tertiary

syphilitic lesions, or whether syphilis of the central nervous system is due to a special variety of spirochæte. He holds the former view.

Dr. Nicol refers to an inquiry concerning malarial treatment which has been taking place in certain general and mental hospitals, and states that remarkable results are obtained in early cases, which exhibit few clinical and physical symptoms. He urges the early examination of all cases in which the slightest premonitory symptoms are to be found.

Dr. Nathan Raw holds firmly to the thesis of "no syphilis, no general paralysis." He discussed the influence of the general physiological make-up of the individual with reference to the onset of general paralysis, and also laid stress on the influence of extraneous factors, such as a strenuous life in contrast to a quiet one. He regards the value of the Wassermann reaction as much greater from the confirmatory than from the diagnostic point of view.

Dr. Good, on the other hand, states that he often makes his diagnosis on the examination of the cerebro-spinal fluid alone. He refers to the fatal effects of salvarsan in early cases, and states that in early cases malarial treatment followed by salvarsan results in considerable improvement, whereas malarial treatment employed without the later use of salvarsan results in no change.

Dr. Frost raised the question of what effect early antisyphilitic treatment has on the subsequent development of general paralysis, and whether such treatment predisposes to the occurrence of general paralysis.

Dr. R. M. Stewart expresses the opinion that too much stress has been laid on laboratory procedures, and would support diagnosis based on clinical symptoms and physical signs only. He remarks that out of a personal experience of some 5000 cerebro-spinal fluids no one laboratory test is diagnostic of general paralysis. On the question whether general paralysis and cerebral syphilis can be with certainty diagnosed from one another, he remarks that this can be done only by treatment.

Prof. Robertson spoke from a similar point of view. He remarked that no important disease could be diagnosed with such certainty as can general paralysis, and he suggests that in order to arrive at this certainty there should be a consensus of the various clinical and pathological tests. He remarks that no laboratory test taken alone, no physical sign taken alone, and no clinical symptom taken alone, can be regarded as conclusive; there must be an agreement between all three. He lastly remarked that the test of treatment finally settled the question, and he referred to the two methods, malaria and tryparsamide.

Dr. Shaw remarked that in order to obtain a cure he should treat general paralysis as a variety of syphilis, and as evidence of cure should rely upon the same test as he would in syphilis, namely, a negative Wassermann for five years continuously. He remarked that, in his opinion, diagnosis should depend upon the question of whether there was serological improvement as the result of treatment. He opposed the idea of a second variety of spirochæte, and thought that many aberrant types might be explained as the result of a combination of alcohol and syphilis. He thought that some association existed between the present markedly decreased incidence of alcoholic insanity and the incidence of general paralysis.

Dr. F. H. Stewart gave a lengthy description of the malarial treatment they had carried out at Cheddleton. With regard to the question whether the cases were general paralytics or not, he remarked that all cases treated exhibited some clinical signs and some physical signs, and all gave positive Wassermans in blood and cerebro-spinal fluid, together with a paretic curve. He remarked that the effects of malarial therapy were produced by the antigenic action of malaria, by the stimulating effects of pyrexia and by the prostrating effect of illness, and he appeared to lay chief stress on the first of these. He referred in detail to the eight last cases which had been treated and as the result had been either cured or greatly improved. I must say that the description of the clinical types in these eight cases when compared with the results of treatment given by him agreed remarkably with the spot prognoses made by me as he described the cases. I marked down Cases 1, 2, 3, 4, 7 and 8 as "improved," Case 5 as "recovered," and Case 6 as "not improved." Dr. Stewart stated that Cases 1, 2 and 3 were sent out on trial after working very well in hospital, that Case 4 was discharged cured, that Case 5 was known to be well eighteen months after discharge, that Case 6 was still in the hospital and was working, that Case 7 had improved and would probably be discharged, and that Case 8 had been discharged. This comparison certainly made me feel a reasonable doubt as to whether the malarial treatment had very much effect on the course of any of the cases.

Dr. Rudolf, of Claybury, discussed the question of diagnosis and treatment at some length, and concluded that it was impossible to explain the differences in the results obtained by different observers, and that a careful study of the subject made him satisfied that the fallacies were so numerous that nothing definite followed at all.

Dr. McRae referred to the work on diphtheroid bacilli by Ford-Robertson, with whom he worked, and, therefore, had felt

intensely interested in the discussion. He remarked on the disparity between the clinical and pathological aspects. He said that one hears a lot about cures, but that he himself would prefer to hear as much at least on the subject of diagnosis. He suggested that great caution should be exercised in diagnosis, and in particular in drawing conclusions on the subject of remissions. He drew attention to the fact that most remissions took place soon after admission to hospital in consequence of the improved treatment received by the case, and suggested that statistics with regard to remissions after admission would produce interesting results. He remarked that in his experience he had met many cases which exhibited prolonged remission, long before the modern treatment was heard of. He earnestly expressed a warning against hasty conclusions, and ended his contribution by a kindly reference to Prof. Bevan-Lewis, referring to the five types of general paralysis described by him in 1896.

Dr. Soutar referred to the necessity for the earliest possible diagnosis in order that treatment might be commenced as early as possible. When cases recovered after malarial treatment the question might readily arise whether the case had really been one of general paralysis or not. From the practical point of view, he especially stressed the necessity for early diagnosis in the hope of stopping the symptoms, whether they were due to general paralysis or not.

Dr. Lord remarked that the subject should be approached with care and with the full appreciation of the fact that prevention was better than cure. What were the earliest indications of general paralysis was a very important question for determination. Hence the suggestion of a national register put forward by the General Paralysis Sub-Committee for this purpose.

Dr. Ross stated that the early diagnosis of general paralysis followed the war. He referred to 400 cases in hospital three years ago with no clinical information whatever, and he stated that 77 of these cases gave a positive Wassermann for the blood and 7 a positive Wassermann for the cerebro-spinal fluid, and he referred in this connection to the 5% or so of general paralytics who occurred amongst known subjects of syphilis. He warned the meeting, however, not to trust entirely to laboratory findings, and reported a case of his which had previously been under treatment eighteen years ago, and was at the present time just the same as on that occasion. This case was certainly not one of general paralysis in spite of positive Wassermans in the blood and cerebro-spinal fluid. He preferred to make his diagnosis primarily on clinical grounds, and to regard pathological findings as a useful help.

Before noting the concluding remarks of Drs. Smyth and Brander,

I should like to refer on behalf of Dr. Paddle, of Wakefield, to seven cases of general paralysis treated by tryparsamide. Of the seven, two, who were both in the last stage of general paralysis when treated, died. A third, also in the last stage, showed no improvement; three cases were improved, and the seventh was much improved and has since been discharged. Of the five cases in which the serological test was taken before and after a course of tryparsamide, in only one did the cerebro-spinal fluid Wassermann change from positive to negative. In two the blood Wassermann changed from positive to negative, and in one from positive to doubtful. The least number of weekly injections given was three of 3 grm. each, and the maximum was twelve. Only in one case was there any constitutional reaction of any importance. Of the seven only one was a recent case, and only that one improved continuously both mentally and physically. He also was of the grandiose and exalted type with little confusion, whereas the other six were of the dull and apathetic type, with much confusion and few and vague delusions of grandeur. Writing with a knowledge of Dr. Smyth's histological investigations, Dr. Paddle remarks that, in his opinion, an improvement or a cure is to be expected in recent cases of the grandiose and exalted types with little confusion, in which there are many spirochætes in the cortex and little vascular change.

Dr. Smyth, as his contribution to the discussion, summarized his histological investigations, which had been carried out on fifty-two cases of verifying *post-mortems*, with the object of correlating the symptomatology and course with the histological findings. He states that spirochætes are found most frequently amongst males in rapid subacute grandiose cases and amongst females in euphoric and emotional cases, also in cases of depression. They are scanty or absent in chronic and acute confused cases. They exist in the lower part of the pyramidal layer and thereabouts in the gyrus rectus, prefrontal, motor and first temporal regions. They are, therefore, presumably due to lymphatic infection in the distribution of the anterior and middle cerebral arteries. The vascular changes present have no relation to the number of spirochætes, and the same remark applies to cerebral wasting. The neuroglial reaction which exists in the deeper layers of the cortex is, however, definitely proportionate to the number of spirochætes present. Hence, of the three changes found in the cortex, the neuroglial reaction is the only one which is definitely related in degree to the presence and number of spirochætes. The vascular proliferation is a generalized process throughout the cortex and occurs in all regions independently of their presence. The cerebral wasting which occurs, though

generally profound where large numbers of spirochætes exist, does not vary in area in proportion to the numbers present, but, on the contrary, progresses in definite order, beginning in the most recently evolved and least stable parts, and being to some extent indefinitely variable. Regarding the question of a neurotropic type of spirochæte, Dr. Smyth remarked that the view appeared to him unnecessary, and that the reason for the differences in the spirochæte was really the fact that it was living in an adverse environment. He remarked upon the generally accepted statement that of all cases of syphilis 2 to 4% eventually develop general paralysis, and that of all cases of syphilis 2 to 4% eventually give a positive Wassermann in the cerebro-spinal fluid. It was therefore likely that the latter were potential paralytics.

Dr. Brander drew attention to the fact that certain symptoms of general paralysis, such as loss of expression, tremors, spasticity, etc., were not necessarily or even probably symptoms of disease of the cortex. They might be due to change in the basal ganglia or substantia nigra. He referred to changes around the ventricles and to the granulations in the ventricles, and also to changes in the posterior lobe of the pituitary body, which disappeared after treatment by malaria. He asked, therefore, whether general paralysis was syphilis of the cortex, or of the mid-brain, or of the pituitary body, and whether it was a peculiar form of syphilis. He remarked that, in his opinion, general paralysis was a particular reaction of the body to the spirochæte which might last for years without showing any frank lesion.

The discussion was then adjourned to the next Quarterly Meeting.
