NEURO-SYPHILIS*

By GEORGE RIDDOCH, M.D., F.R.C.P.

Prognosis.—The course of syphilis of the nervous system depends upon many factors, all of which must be given due consideration if an attempt to predict the future is to have any value. In the first place, it should be kept in mind that neuro-syphilis, in its various forms, is not the disease in itself, but a collection of syndromes which indicate certain functional derangements brought about by a general infection at different stages in its evolution. Whilst, as we have reason to believe, general contamination is less complete and intense than in the so-called secondary stage of the disease, there is abundant pathological and clinical evidence to show that the localisation of the virus to the nervous system is never more than relative. The functions of other organs may also be deranged or the bodily efficiency, as a whole, impaired by the activity of the spirochæte.

There is another and equally important aspect of the problem that must be kept in mind for prognosis and treatment: namely, the defensive reaction of the patient to the invading spirochæte. Variability in progress of any one form of the disease, e.g., tabes, in different individuals and in the same individual, cannot be attributed solely to changes in the virulence and distribution of the virus. It is due to the varying interaction between two opposing forces—the invading organism on the one hand, and the defensive mechanism of the host on the other.

These preliminary remarks are perhaps unnecessary, but I feel that there is a danger of forgetting the disease when considering one of its clinical varieties and of being hypnotised by the sole importance of the invading organism, forgetting that the body does not accept it passively without a fight.

* Based on a Paper delivered before the Medical Society for the Study of Venereal Diseases on May 27th, 1927.
In prognosis, an attempt must be made to answer two questions: (1) Can the disease be arrested? and (2) if so, how much disablement is likely to develop before this can be attained?

Can the disease be arrested? Neuro-syphilis has for long been looked upon as a form of disease that is specially resistant to treatment. At the present time this view cannot be denied because, apart from its meningeal coverings, the nervous system is relatively isolated from the drugs now in use and the more deep-seated the lesions, as in dementia paralytica, the less can they be influenced by ordinary syphilitic remedies. What we have learned, however, is that persistent treatment, judiciously applied, does yield results that are very much better than would, previously, have been supposed to be possible. This is particularly true of meningo-vascular syphilis, tabes and syphilitic amyotrophies and even in general paralysis of the insane, it can be at least claimed that remissions may be prolonged by malarial treatment. The ideal treatment of neuro-syphilis has not yet been discovered, but we are, at any rate, in a better position for tackling it than were our predecessors twenty-five years ago.

In order to estimate whether the disease can be arrested in each case, various considerations have to be taken into account. There is probably no natural immunity to syphilis. Nevertheless, the history of the disease, from the time that it was first recognised in Europe, seems to indicate that some resistance to it has been acquired. It is less acute and deadly in its earlier stages than it was, for example, in the sixteenth century. At the present time, individual resistance may, to some extent, be judged in untreated cases by the length of time between infection or the first reaction to it and the appearance of neurological manifestations. This interval may be short, as when the symptoms and signs of meningitis develop with a secondary cutaneous eruption or is indicated only by the presence of increased protein and cells in the spinal fluid. On the other hand it is often prolonged for many years.

The Amount and Nature of the Disability already produced by the Disease.—It is obvious that if the malady is advanced there is less hope of arresting it than if treatment is begun at a stage when disorders of function are
NEURO-SYPHILIS

slight and the lesions more superficial. The importance of early diagnosis is further stressed by the recollection that because of the relative inaccessibility of lesions to remedies circulating in the blood, treatment, to be successful, has to be prolonged, and even in favourable cases further disablement has often to be expected before arrest of the pathological process can be attained. Early diagnosis must, therefore, influence prognosis to a considerable extent.

In addition, the presence of disorders of function, such as paralysis of the bladder, from the danger of secondary sepsis, makes the prognosis more grave.

The pathological basis of the clinical variety of the disease has to be taken into account. This is due to the fact, already mentioned, that lesions mainly in the meninges are more accessible to drugs circulating in the blood than are those more deeply seated in the neural elements. Hence there is therapeutic as well as pathological justification for the differentiation between meningo-vascular and parenchymatous neuro-syphilis. In general, the outlook is better in the former than in the latter variety, but to this rule there are prominent exceptions. Thus, in cerebrospinal syphilis (meningo-vascular syphilis) when meningitis, either cerebral or spinal, is predominant, it can, as a rule, be expected that the disease can be arrested, and, if it is attacked early enough, with little permanent disablement. When, however, there is marked arterial generation leading to hemiplegia or paraplegia, the sorder of function, to a considerable extent, is likely to persist because of the anatomical destruction that allows such a lesion. Further, as judged by serological tests, the infection, in a proportion of such cases, proves resistant to treatment, probably due to obliterative disease of the vasa vasorum preventing anti-syphilitic remedies from reaching the arterial lesions.

Mental disorders (syphilitic neurasthenia and dementia) apart from dementia paralytica, usually improve with ordinary methods of treatment, and the disease can often be arrested, but recovery is rarely complete. Cranial nerve palsies and optic neuritis, when due to syphilitic meningitis, are hopeful if dealt with early enough, but when the auditory nerve is attacked deafness is apt to persist. When epileptiform seizures develop they are apt to continue, demanding prolonged treatment with
drugs such as Bromides, Luminal, even when the infection seems to have been successfully combated.

The prognosis in tabes is much better than is generally supposed, provided that the condition is diagnosed and treatment begun in the early stages. The early symptoms and signs are well known, but it should be remembered that the ankle-jerks are generally affected before the knee-jerks, and that cutaneous analgesia of the nose, commencing on the tip, is almost as common an early sign as diminished sensibility to prick on the inner aspect of the upper limbs and on the chest below the second rib. So also inequality and irregularity of the pupils with sluggish and small reaction, especially if asymmetrical, to light, may be as significant as the fully developed Argyll-Robertson phenomenon. Usually these changes are early associated with partial ptosis. The lightening pains, as Buzzard has insisted, are practically pathognomonic, and, from faulty inquiry into their characteristics are too often missed and called "rheumatic." Since they form one of the earliest indications of tabes valuable time may be lost if they are not recognised. Briefly, they are described as sharp, momentary stabs of burning pain as if hot needles were being quickly thrust into the skin at right-angles to the surface. They recur in rapid succession for seconds, minutes or longer, and the area of skin involved in each attack is usually small. In the longer attacks the skin may become so tender that the patient cannot bear the contact of his clothes. Various parts of the body may be the seat of these pains, but especially the lower limbs in the anterior aspects of the thighs, the knees, the shins or the ankles, and one patch of skin after another may be affected. Attacks of lightning pains may develop at any time, but are especially liable to occur when the patient gets warm in bed or before any change in the weather. Of course, many other but less distinctive varieties of pain occur in tabes. Judicious treatment of tabes, when commenced in the early stages can be expected to lead to arrest of the pathological process in well over half the cases. As in all other forms of neuro-syphilis, however, the natural tendency to remit and relapse has to be kept in mind and demands lengthy supervision of the patient and prolonged treatment.

*Dementia paralytica* was, and still is, the most gra
NEURO-SYPHILIS

variety of syphilis of the nervous system. Until recent years, we had no means of influencing its progress, for the common anti-syphilitic remedies proved to be futile. Treatment by infection with benign tertian malaria, introduced by Wagner-Jauregg, in Vienna, although still on probation, has proved to be of definite value in, at any rate, a proportion of cases, and has produced results that were previously unknown. Spontaneous remissions lasting for months, and, in rare cases, for as long as two years, were, of course, recognised as phenomena of the clinical course of the malady, but improvement such as may follow malaria therapy is something quite new. The treatment is not without its dangers, and will be discussed later. Further, it is doubtful whether the claims for its efficacy in destroying the syphilitic infection made by some continental enthusiasts will prove in the future to be justified. Still, with a deadly disorder of this kind it can be said to have achieved results sufficient to justify its use until some other less drastic method is found. Gerstmann and others assert that not only are the patients vastly improved, mentally and physically, but after an interval of two or three years the Wassermann reaction may become negative in the blood and spinal fluid. In addition, histological examination of the brain in cases in which death has occurred some time after treatment shows healed lesions in which spirochaetes are not found.

The results of the treatment in 270 cases reported from Nonne's clinic by Reese and Peter in the main conform to those reported by workers in Vienna. The patients were under observation for one to two years after treatment. The cases are divided into four groups:—

**Group 1** comprised 50 per cent. of the total. Although certain mental and physical residua were left the patient could work.

**Group 2** comprised 20 per cent. in which the disease was practically cured.

**Group 3**, 29 per cent. uninfluenced by treatment. (Three juvenile cases were included in this group.)

**Group 4**, 10·6 per cent. fatalities, not necessarily from malaria.

In no less than 90 per cent. of cases did remissions occur
BRITISH JOURNAL OF VENEREAL DISEASES

and lasted for one and a half to two years, the period of observation.

The results in this country have not been so good, but have certainly been satisfactory enough to indicate that the treatment should be continued with. But, personally, I consider that it ought to be restricted to early cases, for no useful purpose is served in bringing back to life patients so deteriorated that improvement would be insufficient to allow of their discharge from a mental hospital. Further, cases in which there is gross vascular or renal disease are unsuitable because of the risk of collapse during the febrile periods. In the presence of such complications it would be safer to use Tryparsamide.

An interesting alteration in the mental part of the clinical picture of dementia paralytica is common as a temporary phenomenon after treatment with malaria. The patient may become suspicious and develop ideas of reference along with auditory and visual hallucinations which, under ordinary circumstances, are rare symptoms in G.P.I. This reaction, which does not always occur, begins to fade in a fortnight or so, and disappears in about six weeks.

If improvement is to follow malarial therapy it can be detected within a few weeks of the arrest of the fever, and, in favourable cases, continues for a year or more. It is of interest that this progressive amelioration in the patient’s mental and physical state appears to be influenced little, if at all, by the administration of antisyphilitic remedies.

Another remedy which may in the future prove to alter the prognosis in dementia paralytica is Tryparsamide. Experience in its use is as yet too brief for a proper judgment as to its value. All that can be said for the present is that it is not without promise.

In what has been called occult neuro-syphilis the clinical picture does not fall into any of the well-recognised categories, and, in consequence, when it is met with the possibility of syphilis, as a cause, is often forgotten. The disorders of function are mental rather than physical, consisting commonly of insomnia, headaches—varying in situation, and often severe, especially at night—irritability, depression, defective memory and concentration and emotional instability. There may be no obvious reflex, sensory or motor changes, and a history of syphilitic
NEURO-SYPHILIS

Infection may be absent. The Wassermann reaction is positive in either the blood or the cerebrospinal fluid or both, and the latter may contain an excess of cells and protein. In the majority of such cases the response to ordinary anti-syphilitic remedies is good if treatment, judiciously interrupted, is prolonged. But in a proportion of them the condition with these measures tends to progress and to be followed by the clinical picture of dementia paralytica. The differentiation for prognosis and treatment of the smaller from the larger group is of the utmost importance, but is often impossible. The colloidal gold test is, however, of some value, for when a definite paretic curve is obtained the case is likely to be one of dementia paralytica.

The problem of "latent" neuro-syphilis—in which the only indications of persisting syphilitic infection are positive findings in the cerebrospinal fluid—raises the thorny question of the prognostic significance of laboratory tests in syphilis. Whilst their value is unquestioned, there undoubtedly is a danger of elevating them to a position of undue importance, so much so that the patient himself may be relegated to the background. There is no one in this society who will not condemn such an uncritical and harmful attitude, but we will all agree that the results of the Wassermann and other tests cannot be neglected. For the present I feel that the position to take, for the patient, is to look upon a positive Wassermann reaction as indicating the persistence of active syphilis in the body. In consequence, an attempt should be made to eliminate it, always keeping in mind the patient's general health. If treatment on this basis, extending over a year, with interruptions, fails to influence the reaction, it should be stopped, and the patient re-examined every six or twelve months. This view may be over-cautious, but it is due to insufficient knowledge of the outcome in cases of latent syphilis.

Paradoxically, negative laboratory tests when the results had previously been positive, in either the presence or the absence of clinical signs, may also be ambiguous. For, as we all know, not only may, for example, the Wassermann reaction again become positive in the blood or cerebrospinal fluid, but, occasionally, tabes may progress in spite of completely satisfactory reports from the clinical pathologist.
These tests, therefore, must always be evaluated in relation to the general state of the patient.

Finally, in prognosis the patient's response to treatment has to be taken into account. The more one deals with neuro-syphilis, as with other chronic affections, for which something can be done, the more does one qualify statements on prognosis until it is ascertained how the particular individual responds to treatment. It is the practical experience of all that, even under apparently similar conditions in regard to general health, the stage and form of the disease and the methods of treatment employed, all cases are by no means alike as judged by the results obtained.

Treatment.—A general principle to be kept in mind is that the disease is primarily attacked by the natural resistances of the body against the infection. Our aim is to aid these defensive forces by the judicious use of the best and safest anti-syphilitic remedies at our disposal. But these remedies ought not to be looked upon as cures. Further, valuable as they undoubtedly are, if used unwisely, they probably weaken the defensive mechanism and certainly act as tissue poisons capable of producing serious disabilities of their own.

How can the inherent and acquired resistances of the body be kept at their highest level?

In the first place, the patient's general health and more of life should be supervised. Attention to diet, bo-weight, physical hygiene, sleep and relief from pain necessary. Excess of tobacco, alcohol or sexual intercourse should be prohibited, and, in married women preventive measures against pregnancy should advised. A quiet, well-regulated, healthy life is the ideal, but employment with adequate rest when possib is to be encouraged for psychological and physical as well as economic reasons.

The importance of keeping up the patient's morale cannot be over-emphasised. He will from time to time require much encouragement to continue with prolonged treatment that interferes with his free time. In those who are anxious for rapid cures it will be necessary to combat demands for more intensive treatment than is safe and in their best interests.

Secondly, anti-syphilitic remedies have to be chosen. Three main drugs are employed—organic Arsenic, Mer-
NEURO-SYPHILIS

ury and Bismuth. Along with these Potassium Iodide is undoubtedly of value. How should they be given? sacrid believes in the efficacy of small daily doses of an arsenical preparation injected subcutaneously or intra-muscularly, without Mercury, Bismuth or Iodide. As many as sixty injections may be given in series. This method of treatment is claimed to be the most effective and best tolerated, a somewhat surprising assertion; for, in the majority of cases, the ankle-jerks are abolished after six to ten injections, and erythema and jaundice, variations in weight and temperature are common, which would appear to indicate arsenical poisoning.

As the result of experience in different countries, it seems clear that so far as present methods are concerned, the use of organic Arsenic along with Mercury or Bismuth and Potassium Iodide is best. Care should be taken to employ the least toxic, most efficient and uniform preparation of Arsenic, and each course of combined treatment should be within the patient’s tolerance to the drugs. The aim should be to give the maximum amount that the patient can stand with improvement of his general health and without signs of poisoning.

In each case of neuro-syphilis the most effective method of treatment is a matter for experiment, and usually it is necessary to vary it throughout the course. At the same time a general plan of campaign is useful. For example, an adult, the following has given good results during past eight years: A course of six weekly intravenous injections of Novarsenobillon are given, the first dose being 0.45 gram, and the others 0.6 gram. At the same time the patient takes Mercury and Potassium Iodide by mouth: Liq. Hydrarg. Perchlor. 1 dr., Pot. Iod. 6 gr. rice daily after food. Attention is paid to the teeth and gums. The course is repeated at intervals of one to two months so long as the patient shows improvement, clinically and serologically. Should he begin to become intolerant to one or other drug the offender is eliminated temporarily or permanently. Thus, instead of N.A.B., either Mercury or Bismuth, given intramuscularly, may be employed. Personally, I have found Bismuth in glucose, given intramuscularly, an effective drug, especially in tabes.

Many reliable arsenical preparations are now on the market. Novarsenobillon is perhaps the most generally
used in this country. It has the advantage of being controlled in regard to its toxicity by the Medical Research Council. Silver-Salvarsan has its adherents especially for neuro-syphilis. Tryparsamide is advocated in America and elsewhere, and may prove a most valuable remedy in dementia paralytica as in other varieties of neuro-syphilis. The special risk of optic atrophy has, however, to be remembered, although this is slight if the dose is carefully regulated.

On the assumption that an arsenical compound circulating in the blood permeates the choroid plexus and meninges more when they are damaged, as in neuro-syphilis, than when healthy drainage of cerebro-spinal fluid by lumbar puncture after intravenous injection of the drug has been recommended. But, as with the use of Salvarsanised serum, the results obtained seem to be no better than those obtained by intravenous injection alone.

Intramuscular injection of organic Arsenic has no apparent advantage over the intravenous method and is more painful.

_How long should treatment be carried out?_ The aim should be to continue with treatment until clinical and serological evidence points to arrest of the pathological process and apparent absence of the infective agent. To attain this end, it may be necessary to persevere with anti-syphilitic remedies, at intervals, for at least two years, each course of treatment lasting from one to two months and the intervals between the courses, as a rule, varying from one to three months. The method adopted, however, must be flexible, and it is necessary always to keep in mind that in attacking the disease the patient’s health is of the first importance. That being so, the results obtained in a great proportion of cases of neuro-syphilis, excluding dementia paralytica, will be excellent from the clinical standpoint. Viewed from the aspect of the laboratory they are less good in the sense that abnormalities in the blood and cerebro-spinal fluid are not so frequently eliminated. In spite of apparent arrest in the course of the complaint, the Wassermann reaction may remain positive in the blood, as in syphilitic hemiplegia, or in the spinal fluid, as in tabes, or in both. _What should be done in such cases?_ Whatever the precise meaning of the Wassermann test may be, it is
NEURO-SYPHILIS

Reasonable to assume that it generally indicates the presence of active spirochaetes in the body and in contact with the blood-stream. On that assumption there is, therefore, always the possibility of relapse, a conclusion that is supported by experience, even in cases that have been stationary for long periods. On the other hand, it is equally true that the disease may, at least for years, how no signs of progression in spite of a persistently positive Wassermann reaction. The difficulty of the position is enhanced by the fact that to obtain negative serological tests at one time is no guarantee that they will not in the future again become positive. In addition, their fallibility as an index of cure is further shown by those cases, uncommon though they are, in which disorders of function increase although the Wassermann reaction remains negative.

In the present uncertain state of knowledge the following conclusions seem to be justified:

(i) Laboratory tests are of value as indications of the efficacy of treatment only when taken in conjunction with the clinical state.

(ii) We have no certain means of telling when neurosyphilis is cured. Patients should, therefore, be under periodic observation and treatment at intervals for many years and perhaps for the rest of their lives.

Treatment of Dementia Paralytica.—Until treatment by action with benign tertian malaria was introduced by von-Jauregg about ten years ago, clinicians were powerless to influence the course of dementia paralytica. It has already been indicated, it has proved of definite value and gives surprising results in a proportion of cases. The patient is infected either by mosquitoes or by subcutaneous or intramuscular injection of about 5 c.c. of blood from a patient successfully inoculated. After an incubation period which varies from five days to three weeks and is usually ten or twelve days, fever and rigors commence and the patient is allowed to have eight to twelve paroxysms. In simple benign tertian malaria, these recur every second day, and, in consequence, are less of a strain on the patient than when repeated daily, as in double benign tertian fever. It is of the utmost importance to make certain, by microscopical examination,
BRITISH JOURNAL OF VENEREAL DISEASES

tion of the blood, that the infecting parasite is not of the malignant type. The general treatment during the illness is that of fevers in general, and it may be advisable to use Digitalis and Strychnine or Brandy daily if the patient is not robust. Heart failure or jaundice are indications for arresting the treatment by the use of Quinine Bihydrochloride intravenously or intramuscularly. But if all goes well after the full number of paroxysms have been endured, Quinine Sulphate, 7½ grs., is prescribed thrice daily for three days, and then twice daily for a fortnight. Recurrences are rare.

Some advise subsequent courses of anti-syphilitic treatment, while others do not. In Nonne's clinic, for example, a six or eight weeks' course of Mercury by inunction is given in preference to arsenical medication.

INDICATIONS OF INTOLERANCE TO ANTI-SYPHILITIC DRUGS

Arsenic, Mercury and Bismuth are potent drugs, and when using them, one must continually be on the watch for signs of intolerance. These might be briefly described with.

(i) Arsenical Preparations.—(a) Early Reaction. Within twelve hours of intravenous injection of one of the arsenical compounds a train of symptoms develop, consisting mainly of erythema, nausea, vomiting, fever and diarrhoea. The patient should be purged and sweated. Arsenical treatment need not be discontinued but before the next injection, 15 minims of Liq. Adrenalin (1 in 1,000) should be given subcutaneously.

Sometimes within a few minutes of the injection N.A.B. œdema of the face and buccal mucous membrane may appear, which can be, however, dispelled by hypodermic injection of 20 or 30 minims of Liq. Adrenalin.

(b) Delayed Reactions.—These are more serious, and always indicate that arsenic must be discontinued for either a long period or permanently.

Hæmorrhagic Encephalo-myelitis.—Headache, vomiting, epileptiform seizures, coma, often followed by death, are the chief manifestations of this rare complication. Post-mortem, softening, hæmorrhages and inflammation in the brain and spinal cord are found. The condition
NEURO-SYPHILIS

Usually develops early in the treatment when only a small mount of Arsenic may have been given.

Jaundice, exfoliative dermatitis and polyneuritis are results of chronic arsenical poisoning, and in tabes the latter is liable to escape detection on account of the diminished sensibility to pain. The increasing disabilities in the limbs, especially ataxia, are apt to be looked upon as due to aggravation of the tabetic process, and treatment may be still further pushed with disastrous results. When a tabetic who has previously been doing well under treatment begins to complain of weakness and more unsteadiness of his lower limbs and hands along with an accentuation of pain in these parts, one should at once consider the possibility of arsenical polyneuritis. Suspicion becomes a certainty if, in addition, cutaneous and postural sensibility in the peripheral parts of the lower limbs has rapidly increased, and especially if the muscles below the knees have begun to waste.

Neuro-recurrences during treatment with Arsenic, as is generally agreed, are not the result of poisoning by the drug, but insufficient dosage.

(2) Mercury and Bismuth.—Both give rise to the same signs of intolerance, namely, stomatitis, dyspepsia, diarrhoea and albuminuria. Cutaneous eruptions, such as erythema and urticaria, sometimes develop, and it should be remembered that both drugs may give rise to polyneuritis.

Symptomatic treatment of neuro-syphilis as for pain, ataxia and so on, will not be dealt with, but, in addition, the importance of keeping a watchful eye on the patient's mental and physical health whilst dealing with disease is again stressed.