TREATMENT IN GENERAL PRACTICE

This article is one of a series on the management of some diseases of the nervous system met with in general practice.

TREATMENT OF SYPHILIS OF THE NERVOUS SYSTEM

BY

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Before undertaking the treatment of a patient who is presumably suffering with syphilis of the nervous system it is essential to be certain not merely of the diagnosis but also of the nature of the lesion. This requires a full and careful clinical examination as well as laboratory tests of the blood and cerebro-spinal fluid.

In the first place it is obvious that the presence of a positive Wassermann reaction does not alone, or even in conjunction with changes in the cerebro-spinal fluid, necessarily indicate that the lesions responsible for the patient's symptoms are of syphilitic origin, for unfortunately even syphilis does not safeguard us from other troubles. As an instance I may refer to two patients, recently at the same time and in the same ward under my care with signs of increased intracranial pressure and positive Wassermann reactions, in whom on operation simple gliomatous tumours were found. On the other hand, symptoms of disease which is beyond doubt of luetic origin may occur in the absence of the so-called "positive serological signs," and these symptoms may be active and even progressive. In this category may be included certain forms of paraplegia of spinal origin developing in patients who have had syphilis, or in whom after death pathological examination reveals lesions of a syphilitic nature. In tabes dorsalis this is occasionally so too; for example, a patient with this disease whom I have had under observation for years has, despite negative Wassermann reactions in both the blood and the cerebro-spinal fluid and no pathological changes in the latter, grown more ataxic, suffered in succeeding years as intensely, or perhaps more severely, with lancing pains, and has developed arthropathies and gastric crises. Such cases are not rare, and they emphasize the importance of studying carefully the clinical features of each patient, of refusing to lose sight of the patient behind the test tube, of "*Menschenbehandlung nicht Syphilisbehandlung*" (the treatment of the patient, not of the syphilis) as Nonne, whose experience in the treatment of neurosyphilis is probably unrivalled, has insisted—in fact, the importance of dealing with a case of nervous syphilis as we do with disease of other organs of the body.

Uses and Limitations of Laboratory Findings

Insistence on the necessity of directing and controlling treatment by clinical observation and of a recognition of the exact nature of the lesions in the nervous system does not mean, of course, neglect of laboratory methods, which can frequently supply us with valuable information on the activity and the course of the disease. Examination of the cerebro-spinal fluid is always essential before treatment is instituted, provided that time is not lost in dealing with acute lesions, and it should be repeated during the course of treatment. The findings in the fluid are particularly useful in the exudative types of meningeal syphilis, as they are an indication of the state and the degree of the involvement of the membranes: a diminution in the number of cells and a return of the protein to approximately normal proportions point to

success and also, often, to the advisability of a change or modification of treatment. The Wassermann reaction in the cerebro-spinal fluid is also a useful guide in these cases, as with successful treatment it gradually weakens or disappears, often while it is still positive in the blood. The Lange gold reaction is less important, as a positive response frequently persists in spite of treatment and after all signs of active disease have disappeared; it seems to be of little significance in prognosis.

In my experience the state of the cerebro-spinal fluid is of less importance in the treatment of vascular and parenchymatous nervous syphilis, and particularly in tabes dorsalis and general paralysis, though it is valuable as an accessory means of diagnosis. A positive Wassermann reaction may persist in these diseases despite the most vigorous treatment and though all signs of activity or of advance of the pathological processes have been absent for years. I could cite many cases of tabes in which the Wassermann reaction is still positive though the patients suffer only with the effects of the structural lesions acquired in the earlier stages of the disease, and in some of the cases I have seen of general paralysis which have been most successfully treated by malarial infection the reaction in the fluid is still positive. There can be no doubt that in such instances prolonged and indiscriminate treatment is not only unnecessary, but may be even harmful.

Types of Disease

It is well known that the nervous system may be involved in any stage of syphilis, but the earlier affections, as the acute meningeal reactions which occur during the secondary stage, do not come within the scope of this article. Here we have to deal with patients with established lesions. These, which may take various forms, can be, to simplify the principles of their treatment, divided into

1. *The meningeal type*, in which the predominant lesion is acute or chronic infiltration by gummatous cells of the membranes of the brain or spinal cord. As, however, the underlying nervous tissue is almost always involved too, these conditions would be more accurately described as meningo-encephalitis or meningo-myelitis.
2. *The vascular type*, in which endarteritis may reduce the blood flow to, or occlusion produce softening of, the nervous tissue within the distribution of the vessel. A periarteritis, either accompanying the intimal lesion or associated with meningeal infiltration, also may damage the nervous tissues around the arteries.
3. *Systemic or parenchymatous syphilis*, characterized by the predominant affection of neural tissues.

Treatment by Drugs

Each of these groups requires special consideration before treatment is instituted, but it is necessary to deal first with the therapeutic agents at our disposal and what can be expected from their use. These are mainly the heavy metals—arsenic, mercury, and bismuth—but the iodides should be included here too. Mercury and iodide, which were the chief standbys of thirty years ago, have been to some extent superseded by arsenic in the form of salvarsan or allied substances, and by the salts of bismuth which have been more recently introduced.

Arsenical Preparations.—The most valuable of these is undoubtedly arsenic, though there are certain risks and disadvantages associated with its use. The preparations most commonly used are salvarsan (606), neosalvarsan or novarsenobillon (914), and silver salvarsan, but drugs containing arsenic in a pentavalent form are also favoured in the treatment of special conditions, as tryparsamide, particularly in America, and stovarsol or its sodium salt, in France. The first course of neosalvarsan or of novarsenobillon may be given at five- to seven-day intervals, as follows:

1st dose	... 0.3 gram	4th dose	... 0.6 gram
2nd "	... 0.45 "	5th "	... 0.6 "
3rd "	... 0.45 "	6th "	... 0.9 "

In second and subsequent courses the initial dose may be 0.6 gram, provided no complications occurred during the first. The risks in the employment of these arsenical compounds are undoubtedly less than in the use of those originally introduced, but any of them may, particularly in the early stages of the treatment, excite local reactions around syphilitic lesions and thus aggravate the symptoms or produce new ones; in early or acute cases it is therefore advisable to start treatment with mercury or bismuth. Tryparsamide and stovarsol, on the other hand, may affect the optic nerves and lead to rapidly progressive loss of sight. During their use a careful watch is necessary on the state of vision. Further, patients occasionally show an idiosyncrasy to arsenic, and the necessity of long-continued intravenous injections is a handicap—in private practice at least.

Bismuth.—The toxicity of bismuth salts is much less, but I have seen a few cases of polyneuritis result from their indiscriminate use, and they are not so apt to produce such focal reactions in the central system as is arsenic. The administration of bismuth by intramuscular injections is also easier, and though probably not so immediately effective as arsenic its action persists longer. It is therefore both useful and convenient in the treatment of latent and chronic affections. Any preparation of bismuth hydroxide (3 grains in each injection) may be used, or the more soluble salts—for example, the salicylate or the iodobismuthate of quinine. Doses should be calculated according to their content of the bismuth metal, of which 2 to 3 grains should be given in each injection.

Mercury.—Though mercury has been to some extent eclipsed in favour of newer remedies it still remains one of the most valuable agents we have in the treatment of syphilis of the nervous system, and if properly employed I do not believe the results are surpassed by those of either arsenic or bismuth, except perhaps in the treatment of acute attacks in the earlier stages of infection. The most effective and the most easily controlled method of administration is by inunction, which is preferable to and safer than intramuscular injections of the metal or of any of its salts. Oral dosage can be recommended only in chronic cases between more intensive periods of treatment. But to obtain full benefit from mercury it is essential that it is administered in adequate amounts. Gowers's method, which has been generally followed in the National Hospital, is the thorough rubbing in of a drachm of blue ointment or other suitable preparation twice a day until the patient slightly salivates or experiences a metallic taste; the inunctions are then stopped and the patient is given, after a few days, large doses of iodide for ten days to a fortnight; the inunctions are then recommended. Three, four, or more courses of inunctions are given, as may be necessary, at appropriate intervals. During treatment the teeth and mouth should be carefully looked after; though salivation and swelling of the gums may be for a few days inconvenient to the

patient who is fully under the influence of the drug, these discomforts soon subside. For injection, mercury can be administered in the form of calomel ($\frac{3}{4}$ to 1 grain) or of salicylate of mercury ($1\frac{1}{2}$ to 2 grains), in a suitable base.

Iodides.—The fact that even large and prolonged doses of iodide have no influence on the Wassermann reaction has allowed it to wane from favour in the treatment of syphilis, though the older clinicians proved its value in gummata and other superficial lesions. It has certainly a similar action on the infiltrative lesions of the nervous system, but the heavy metals are preferable, owing to their more rapid and effective action. Its chief use in neurology is in the prolonged treatment of vascular disease and of chronic lesions which have passed their acute stages. In such conditions doses as large as the patient will tolerate should be given, starting with half a drachm and increasing to one drachm a day.

Attempts to produce active immunization to syphilis by injection of non-pathogenic spirochaetes have been frequently made, especially on the Continent. Benedek has recently employed the method introduced by Hilgermann in the treatment of nervous syphilis with promising results, but it is still in the experimental stage.

Necessity for Prolonged Treatment

It is, however, in the combination of these various drugs that the most effective treatment of syphilis of the nervous system, as of general infection by the spirochaete, is to be found; though arsenic, bismuth, mercury, and the iodides are all of particular value in the treatment of certain forms of neurosyphilis, there are few cases in which we can rely on one only to the exclusion of the others. Some authorities, for instance, advise where active and rapid treatment is necessary, as in early infection by syphilis, the simultaneous administration of arsenic and bismuth, or of arsenic and mercury; others prefer to alternate these drugs. The essential point is prolonged treatment while the disease is active, or when any risk of a recurrence of active lesions exists. The diagnosis of neurosyphilis makes it imperative to insist to the patient on the necessity of continuous or intermittent treatment for months, perhaps for years.

Acute Meningeal Syphilis

Either the membranes of the vertex or the base of the brain may be predominantly affected, the former producing palsies, local or general convulsions, or mental changes: the latter, paralysis of the cranial nerves, often associated with other signs of a basal meningitis. Or the membranes of the spinal cord may be chiefly or exclusively involved, usually with the symptoms of a myelitis. It is, however, the acuteness of the process rather than its distribution that should determine the mode of treatment. An attack of acute syphilitic cerebral meningitis, or of spinal meningitis accompanied by a transverse or diffuse myelitis, demands early and energetic treatment, as every day it lasts increases the risk of permanent damage of the nervous tissues. Fortunately prodromal symptoms often occur which, when recognized, indicate immediate action.

Though there is a slight risk of exciting reactionary changes, the so-called "neuro-recidives," by the use of arsenical preparations, the danger of permanent damage resulting from the primary lesion is so much greater that this risk must be taken and an intravenous injection of neosalvarsan (0.6 gram) or of novarsenobillon (0.6 gram) be given at the earliest possible moment. It should be repeated on the fourth or fifth day unless any contra-indication appears. Intramuscular injections of a suitable preparation of bismuth may be given at the same time, preferably in soluble form, as it is more rapidly absorbed,

or a vigorous course of mercurial inunctions may be started.

The full course of injections of the arsenical drug should be administered, usually six to eight doses, five to seven days elapsing between each injection. When these are completed the patient should have a series of intramuscular injections of bismuth or of mercurial inunctions, and then another course of arsenic: in fact, courses of arsenical and bismuth injections should alternate until all signs of active disease have passed and examination of the cerebro-spinal fluid reveals a fall in the number of cells and of protein to the normal, or approximately thereto. The Wassermann reaction in the blood is a more reliable guide to the necessity of prolonged treatment than that in the cerebro-spinal fluid. In the treatment of acute meningeal lesions arsenic and bismuth surpass mercury, as they act more quickly and more effectively; but in certain cases, after the acute stage is over, efficient inunction of mercury till salivation or other signs of saturation appear gives excellent results.

Chronic Syphilitic Meningitis

Chronic syphilitic meningitis, either cerebral or spinal, demands treatment on the same lines, but as the lesions vary in nature as well as in their distribution and severity more discrimination is necessary in deciding on the methods to be adopted, the duration of the cure, and especially in giving a prognosis.

There is usually a diffuse chronic infiltration of the membranes by cells and considerable thickening of the meninges by increase of connective tissue within them, which, as in the case of the so-called hypertrophic meningitis most commonly met with in the cervical region of the spinal cord, may reach massive proportions. In other cases the roots of the spinal and cranial nerves are chiefly involved, producing pain or palsies in their peripheral distributions. The underlying nervous tissue is always affected in some degree by the extension into it of infiltrating cells (first along the sheaths of the vessels), and by compression or interference with its blood supply. The symptoms which the patient presents are, of course, due to these disturbances in the nervous tissue, and on the intensity and nature of them the prognosis depends. As the necessity of treatment is not so urgent as in acute cases, and as there is a risk of exciting reactionary changes by the injections of arsenical preparations, it is advisable to begin with intramuscular injections of bismuth or inunctions of mercury. Later, energetic courses of neosalvarsan should be instituted and alternated with further administration of bismuth or mercury. Treatment should be kept up for several months at least, and the cerebro-spinal fluid should be repeatedly examined as its state is a helpful guide in prognosis as well as in therapy. In these cases iodide in large doses is particularly useful, as it undoubtedly favours the resolution of the gummatous infiltration and has probably some influence on the secondary fibrosis in the meninges and blood vessels.

The treatment of *gummata*, which can be regarded as local accentuations of the meningeal process, should be essentially the same as that of other chronic meningeal lesions. Potassium iodide in large doses is particularly useful when the infiltrative changes have been checked by more vigorous measures. The limitations of medical remedies must, however, be recognized; they cannot lead to complete absorption of the necrotic material and of the fibrous tissue which form a large part of each gumma, and no matter how successful drugs may be a scar is eventually left behind. When this produces symptoms of compression, and especially of irritation, as it may when situated in the cortex of the brain, it may be necessary to deal with it as with any other tumour or irritative lesion by surgical measures.

Syphilitic Lesions of Vascular Origin

Lesions of this nature are among the most serious complications and are certainly the least amenable to treatment, as when the patient comes under observation there is usually occlusion of one or more arteries and consequently complete or partial necrosis of the tissue supplied by the vessel. The most common form is hemiplegia resulting from thrombosis of an artery in which there is advanced endarteritis. It is rarely possible to hope for restoration of the circulation, and the most at which one can aim is to prevent a spread of the thrombosis. The immediate injection of neosalvarsan or other arsenical preparation is rarely advisable. The administration of iodide in large doses and the intramuscular injections of a soluble salt of bismuth are safer and probably equally effective measures. Mercurial inunctions can be started too. After ten to fourteen days arsenic may be safely given intravenously, and may be supplemented by injections of bismuth. Iodides should be continued for several weeks at least. The intravenous administration of a 2 per cent. solution of sodium iodide has been recommended, but it is doubtful if it is more effective than potassium iodide by the mouth.

Tabes Dorsalis

It is now universally recognized that tabes is always secondary to infection by syphilis, but this does not mean that it can be treated on the same lines as other syphilitic affections, or that corresponding benefit can be expected. Many of the older authorities in fact doubted the efficacy of anti-syphilitic treatment, but most neurologists are now agreed that it may at least influence favourably the course of the disease. The essential lesion is a degeneration of certain afferent fibres of the peripheral nervous system, particularly of the posterior roots, which according to some authors results from inflammatory processes in the roots or of the meninges through which they pass. Such inflammatory changes may be present though they are not constant, nor can they explain the selective nature of the degeneration. It is more probable that the essential factor is the action of a toxin, probably of syphilitic origin, on the nerve fibres. The nature and pathogenesis of the disease therefore impose serious limits on the benefit that can be expected from anti-syphilitic measures. In tabetic optic atrophy there are inflammatory as well as degenerative changes in the optic nerve, but this condition is notoriously resistant to treatment.

The difficulty in estimating the value of anti-syphilitic therapy is due to the fact that tabes is usually not a gradually progressive disease; in a considerable proportion of the cases, as Gowers taught, the symptoms remain stationary for long periods and may never advance; or if it is progressive it may be by temporary exacerbations, after each of which some improvement may occur independently of the treatment. There can be no doubt, however, that anti-syphilitic therapy when judiciously employed benefits many patients suffering with tabes, and considerable improvement may be effected in acute cases or during acute exacerbations. The lancinating pains are often relieved to some extent by intravenous injections of arsenic, but it occasionally happens that for a time at least they are more frequent or severe after treatment. The intramuscular administration of bismuth is in my experience the most useful anti-syphilitic remedy in chronic cases of the disease. Two or four courses of twelve injections may be given each year, or they may be alternated with inunctions of mercury, or mercury and iodide may be taken by the mouth between each course of bismuth. Although neosalvarsan cannot produce the striking benefits which it may in acute syphilitic lesions of the nervous system, some patients experience

from it subjective improvement at least, and its rational use tends to prevent the development of other lesions to which, however, the tabetic seems to be less prone than other syphilitics. Excessive or too prolonged dosage is inadvisable, as it occasionally has an unfavourable influence on the patient or on his disease. Course after course of treatment merely to abolish a positive Wassermann reaction, which has little relation to the severity or progress of the disease, is to be deprecated.

General Paralysis

Before malarial treatment was introduced it was the almost universal experience that no anti-syphilitic remedies had any curative influence in general paralysis, and in most cases did not influence the course of the disease. More recently arsenic in pentavalent form has been employed with some success. Tryparsamide by intravenous or intramuscular injections has been used extensively in America and sodium stovarsol subcutaneously

on the Continent. Unfortunately both are apt to produce optic atrophy, and their administration therefore must be immediately stopped if there is any complaint of impairment of vision. The first dose of tryparsamide should not exceed 1 gram, but if the drug is well tolerated it can be increased to 3 grams. Ten to fifteen injections may be given at weekly intervals. As stovarsol may excite neuro-recidival reactions an injection of bismuth should be given before or at the same time.

The introduction of malarial therapy has, however, revolutionized the treatment of general paralysis; no form of anti-syphilitic treatment can give at all comparable results. But as malarial infection should be undertaken only by those experienced in it, and in suitable conditions, it will not be described in this article. Energetic anti-syphilitic treatment, preferably by one of the arsenical preparations, is essential when the patient has completed his series of rigors, and should be repeated at intervals during the subsequent two years at least.

THE RELATIONSHIP OF THE RECENTLY DISCOVERED ERGOT ALKALOIDS

During the past year considerable interest has been roused by announcements in British, American, and Continental scientific journals concerning new active alkaloids isolated from ergot, which have as one of their characteristic features the ability to produce remarkably quick and vigorous uterine action when given by the mouth to a woman in the post-partum period. Although four such alkaloids have now been described and diversely named, no satisfactory evidence is as yet forthcoming to show that they are not one and the same substance. Before discussing the relationship of these alkaloids—ergometrine,¹ ergotocin,² ergostetrine,³ and ergobasine⁴—it may be well to review the present position of the new substance (or substances) in therapeutics.

Clinical Properties of the New Alkaloid(s)

Two papers have appeared lately dealing with the clinical use of ergometrine and ergotocin respectively. Moir⁵ in this country discusses the relationship of ergometrine to the previously known ergot alkaloids, and concludes that the new principle combines the obstetrically useful characteristics of the previously known alkaloids with other valuable properties which the latter substances lack—namely, rapid action when given by the mouth or injection; complete freedom from immediate toxic effects (headache, depression, and nausea); and complete, or almost complete, absence of gangrene-producing properties. He stresses the usefulness of ergometrine in post-partum haemorrhage associated with uterine atony, and advocates its administration by intravenous injection when a maximum effect is desired in a minimum time; by this means a powerful uterine spasm is produced within one minute. In comparison with pituitary extract the uterine action is more constant, and for patients presenting signs of shock and loss of blood ergometrine is stated to be a safer drug—pituitary extract in similar circumstances carrying with it the risk of reduction of cardiac output, because of constriction of the coronary arteries, and hence an aggravation of the symptoms of shock. Moir points out that the clinical action of ergot, reported by obstetricians more than a century ago, has its exact counterpart in the action now known to be characteristic of ergometrine. The spasm-producing properties of this drug make it dangerous to use during parturition (as distinct from the puerperium), for it is this very spasm which caused the

pulvis ad partum of the earlier writers to be cynically renamed the *pulvis ad mortem* by later disappointed users. Adair, Davis, Kharasch, and Legault of Chicago⁶ discuss the clinical action of ergotocin. Their conclusions are in many respects similar to those just quoted with regard to ergometrine. The value of intravenous injection of ergotocin in cases of post-partum haemorrhage is also stressed, and special reference is made to its use in Caesarean section as a preliminary to incision of the uterus. In such circumstances the administration of ergotocin is quickly followed by a blanching of the uterine musculature and a wrinkling of its surface. Separation of the placenta is greatly accelerated. Ergotocin is also recommended for use in incomplete abortion. The writers emphasize the safety of the new substance, and show that undesirable side effects—such as the temporary suppression of urinary secretion seen after injection of pituitary extract—are absent in the case of ergotocin. The new drug is recommended wherever oxytocic therapy is indicated.

Clinical reports on ergostetrine and ergobasine are not yet available, but there is no reason to doubt that their clinical action will be found to be identical with that of ergometrine and ergotocin.

The Relationship of the New Alkaloids

There is no doubt that these new alkaloids are already an important addition to therapeutics, and their use is likely to increase greatly as their properties become more widely known. It is therefore highly desirable that the identity, or non-identity, of the various new substances should be finally decided with as little delay as possible. Meanwhile, it can be said that their chemical and pharmacological properties, as recently reported,^{3 7 8 9 10 11} present such remarkable similarity that little doubt is left that the four alkaloids are in fact identical substances. Assuming that this is so, the question of nomenclature becomes important, and it is earnestly hoped that the already complicated relationships of the ergot alkaloids will not be confused by alternative names for the same substance. There are many unhappy examples of such confusion in medical literature.

The question of identity of the ergot alkaloids has already been the subject of discussion in the *Lancet* and in the American journal *Science*. In the latter journal a judicial summing up of the situation has been made by Sir H. H. Dale,¹² who, basing his views on the available evidence and assuming that the four alkaloids are identical, makes out a very strong case for the adoption