THE DIAGNOSIS AND TREATMENT OF CEREBRO-SPINAL SYPHILIS, INCLUDING TABES AND GENERAL PARALYSIS.*

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SYPHILIS may attack any organ or tissue of the body, but of the various syphilitic lesions with which we meet, those of the nervous system are the most serious. At one time it was believed that cerebro-spinal troubles occurred only in the later phases of syphilis, but we now know that even within a few weeks of the infection well-marked lesions may occur in the nervous system. I need only recall the familiar headaches of early syphilis, which are probably of meningeal origin. On the other hand, it may be many years after the original infection before the signs of cerebro-spinal syphilis first show themselves, so that the old syphilitic infection has sometimes been forgotten by the patient himself. Lastly, we have to remember that cerebro-spinal syphilis may develop extremely insidiously, and may have produced well-marked anatomical lesions long before any clinical signs or symptoms lead the patient to seek medical advice. This is notably the case, for example, in tabes dorsalis.

Importance of Early Diagnosis.

The importance of early diagnosis of cerebro-spinal syphilis cannot be over-estimated, and the neurologist should be prepared to recognize the disease at its earliest stage. Thus we no longer wait for the knee-jerks to disappear, or for the occurrence of ataxia before making a diagnosis of tabes. Many a tabetic is walking about to-day, with brisk knee-jerks and without ataxia, but with absence, say, of ankle-jerks, or even of one ankle-jerk, or with loss of the light-reflex in one or both pupils, and in whom, nevertheless, we are able to diagnose the presence of tabes by detecting certain changes in the cerebro-spinal fluid.

Pre-clinical Stage of Cerebro-spinal Syphilis.

It is evident that organic changes, whether they be vascular or meningeal, or whether consisting in a primary degeneration of the nervous structures, must precede the earliest clinical symptom. There is, in fact, what Ravaut has termed a "pre-clinical" stage of cerebro-spinal syphilis, which may last for months or years before the first clinical sign makes its appearance. The ordinary clinical stage of cerebro-spinal syphilis is relatively late. It is during the pre-clinical stage, however, that treatment is likely to be most effective. Fortunately, nowadays we are able to recognize the disease at this pre-clinical stage, mainly by examination of the cerebro-spinal fluid and of the blood.

Blood Reaction Insufficient to Exclude Cerebro-spinal Syphilis.

With regard to the Wassermann reaction (consisting in an abnormal fixation of the blood-serum complement, whereby the normal haemolysis no longer occurs in the presence of red blood corpuscles), it is now recognized that a positive reaction in the blood is present in a large proportion of cases of tabes, general paralysis, and cerebro-spinal syphilitic lesions of various sorts. So long as this reaction remains positive treatment of one kind or another should be persevered with. A negative reaction in the blood, however, does not always justify us in concluding that the disease is cured. Syphilitic lesions in the nervous system may sometimes still remain active and even progressive when the Wassermann reaction in the blood has become negative under antisyphilitic treatment. This is notably the case in the so-called "neuro-recidive," which we occasionally meet with some six or eight weeks after full doses of salvarsan, whilst it is not uncommon to meet with tabetic and general paralytic patients in whom the Wassermann reaction in the blood is completely negative. Evidently, therefore, we cannot rely upon blood examination alone to decide whether a patient is suffering from cerebro-spinal syphilis.

Wassermann Reaction in Cerebro-spinal Fluid.

Fortunately, however, in the cerebro-spinal fluid we possess means of detecting syphilitic changes in the central nervous system. Owing to the peculiar independence between the circulation of the cerebro-spinal fluid and that of the general blood circulation, the substances which produce the Wassermann reaction may be abundantly present in the cerebro-spinal fluid without necessarily passing into the blood. Our aim in treatment, therefore, should be to render this reaction negative, not only in the blood, but in the cerebro-spinal fluid as well.

Globulin Reaction.

In the examination of the cerebro-spinal fluid there are other reactions besides that of Wassermann which are of great importance. One is the reaction for albumin. In health there is a mere trace of albumin. A marked excess of albumin is found in acute meningitis from any cause and to a lesser degree in tabes, in general paralysis, and in active cerebro-spinal syphilis, the protein present in these syphilitic maladies being a globulin. It has been shown by Ravaut and others that when the Wassermann reaction is positive in the cerebro-spinal fluid the albumin content is high, and that when the globulin reaction is feeble or absent the Wassermann reaction is usually negative.

Pleocytosis of Cerebro-spinal Fluid.

Another point of great practical importance is the cytological examination of the cerebro-spinal fluid and the question of pleocytosis. In health the cerebro-spinal fluid contains very few cells, only a few flat endothelial plates, and perhaps an occasional lymphocyte, the total number of cells per cubic millimetre varying from zero to two or three. Sometimes we find no cells of any sort. But in subacute and chronic affections of the meninges, including those of syphilitic origin, and in cerebro-spinal syphilis generally (so long as it is in an active stage), also in tabes and general paralysis, it is the rule to find a marked excess of lymphocytes, which may number 300, 400, or even more, per cubic millimetre. In acutely advancing processes—for example, in acute "neuro-recidive," or during the "congestive attacks" of general paralysis—we may for a time find a considerable proportion of polymorph leucocytes. In general paralysis we also find "plasma cells"—large mononuclear cells each possessing an excentrically-situated nucleus with a characteristic "clock-face" arrangement of its chromatin granules.

The above-mentioned reactions, of meningeal origin, in the cerebro-spinal fluid are of the highest practical importance in enabling us to estimate the presence of cerebro-spinal syphilis and the degree of its activity. An acutely advancing lesion will show a high cell count with a considerable proportion of polymorph cells, whilst the globulin reaction will be marked and the Wassermann reaction positive. As the pathological process in the meninges subsides and becomes subacute or chronic, the polymorph cells rapidly disappear and are replaced by monomorphs, the plasma cells disappear and the lymphocytes become smaller in size and less numerous, whilst the globulin and Wassermann reactions correspondingly diminish in intensity. In old-standing cases, where the pathological process has long since come to a standstill—for example, in old sclerotic cases following vascular or other lesions—the cerebro-spinal fluid shows only a small excess of lymphocytes, whilst the globulin and Wassermann reactions are also diminished in intensity, and may ultimately disappear. It is worthy of note that the cytological changes disappear more rapidly under treatment than do the globulin and Wassermann reactions.

It is of importance to remember that changes in the cerebro-spinal fluid precede the ordinary clinical signs and symptoms of nervous disease, and that they may be extremely marked when the clinical phenomena are very slight. Thus, for example, I recently saw a schoolmaster, aged 42, who gave a history of two attacks of transient hesitation of speech only a few days previously when reading aloud. On physical examination he showed no abnormal signs in the sensory, motor, or reflex functions. There was, however, a suspicion of tremor in the face and tongue, whilst the pupils were of the Argyll Robertson type. His mental powers were absolutely unimpaired. Nevertheless, the cerebro-spinal fluid contained 419 lymphocytes per cubic millimetre and gave, strongly,

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positive Wassermann and globulin reactions. The Wassermann reaction in the blood was also positive. The diagnosis of early general paralysis was therefore established beyond dispute. It cannot be doubted that the changes in the cerebro-spinal fluid must have been present for some considerable time before his symptoms appeared, and could have been detected had the fluid been examined. So significant is the occurrence of changes of this sort in the cerebro-spinal fluid that their presence alone, apart from any clinical symptom whatever, is an indication for assiduous and energetic treatment without waiting for the appearance of signs of gross focal lesions. The modern neurologist, when dealing with a syphilitic patient, is no longer satisfied with the absence of clinical signs and symptoms indicating gross focal disease in the nervous system, not even when the Wassermann reaction in the blood is negative. To assure himself that the central nervous system has escaped, he examines the cerebro-spinal fluid.

Let us now pass on to those cases of cerebro-spinal syphilis where, following earlier changes in the meninges, gross focal lesions have actually occurred in the nervous system. Most patients by the time they come under observation have already reached this stage. The demonstration by Noguchi of spirochaetes in the brains of general paralytics has broken down the distinction formerly drawn between syphilitic and so-called parasymphilitic diseases, and has thereby given us a clearer outlook upon the whole question of cerebro-spinal syphilis.

VARIETIES OF SYPHILITIC LESIONS IN CENTRAL NERVOUS SYSTEM.

We have to recognize three distinct kinds of lesions. Firstly, we have gummata, arising in non-nervous tissues and compressing or invading the brain or spinal cord, or we may have diffuse gummatous infiltrations in the meninges or around the blood vessels of the brain or cord. Secondly, there is syphilitic endarteritis, which frequently culminates in thrombosis of the affected artery, producing an area of softening in the brain or cord, followed by corresponding sclerosis. Lastly, there is a group of parenchymatous nervous diseases characterized by primary decay and degeneration of various special nerve tracts and nerve cells, diseases which are neither the direct effects of gummatous deposits nor of arterial disease (although lesions of this sort may co-exist), but which result from the direct action of the syphilitic toxin upon the nervous structures. Primary degenerative lesions of this sort may be followed by sclerotic overgrowth of the neuroglia in the affected tracts, independent of any meningeal or vascular lesion. As examples of this primarily degenerative group we may mention certain forms of primary optic atrophy, a considerable part of the lesions in tabes and general paralysis, also Erb's syphilitic paraplegia and certain forms of organic nervous disease occurring in the children of syphilitic parents.

These three varieties of syphilitic lesions differ widely in their respective prospects of cure. Gummata, whether compressing or invading the nervous structures, may often be removed by medicinal means, and if the nerve-structures have only been compressed and have not undergone actual destruction, recovery may be complete. If, however, a gumma leaves behind it a fibrous cicatrix, or if actual degeneration of nerve tracts has occurred within the central nervous system, a certain amount of permanent damage necessarily persists, even after the original syphilitic process has ceased. In the second group, of syphilitic vascular diseases, the lesions in the arterial wall may yield to treatment; but here, also, if thrombosis has already occurred, and an actual area of softening has resulted, the damage which has been done to the structures within the territory of the diseased vessel must necessarily remain. The prognosis, therefore, of syphilitic softenings is relatively bad. Lastly, with regard to the primarily degenerative diseases, such as tabes and general paralysis, these have hitherto tended to pursue an irregularly progressive course, generally uninfluenced, or at the most only slightly alleviated, by the most assiduous anti-syphilitic treatment. Sometimes, however, these diseases, after attaining a certain degree of intensity, appear to come to a spontaneous standstill, an arrest which may last for years, although there is always the danger that

the disease may subsequently light up again to renewed activity.

I have deemed it advisable to direct attention to the foregoing points in the neuropathology of cerebro-spinal syphilis, because it is essential in the treatment of these various types of disease to have a clear idea of what exactly we are attacking and of how much improvement is anatomically possible, supposing the syphilitic infection be successfully removed. Let us now turn to the problem of therapeutics.

TREATMENT OF CEREBRO-SPINAL SYPHILIS.

The modern treatment of cerebro-spinal syphilis does not imply that we should discard any of the older remedies which for so many years have been proved of value. The classical method of attacking syphilis is by means of mercury, with or without the addition of iodides. Excellent results have been obtained in the past, chiefly in the meningeal, vascular, and gummatous types of the disease, as every neurologist can testify. More recently the introduction of an arsenical group of drugs, of which the most notable examples are salvarsan and neo-salvarsan, atoxyl and enesol, has added powerful weapons to our therapeutic armoury. Most physicians agree that salvarsan produces its best results when combined with mercurial treatment.

Besides deciding in each particular case which drug or combination of drugs he will employ, the physician has to consider the channel of administration, whether by the mouth, by inunction or fumigation into the skin, or by injections—hypodermic, intramuscular, intravenous, or intrathecal. In making his decision the physician is influenced by various factors, such as the acuteness or chronicity of the symptoms, the amount of personal supervision that is attainable, the advisability from the patient's point of view of rendering the treatment as little conspicuous as possible (this is often a special difficulty with regard to mercurial inunction), and upon the perseverance or otherwise with which the patient is likely to carry out a long course of treatment.

The present-day treatment, by a combination of mercury with salvarsan or neo-salvarsan, which is employed in "ordinary" syphilis, is applicable to cerebro-spinal syphilis as well, bearing in mind certain precautions. Thus, for example, in cerebro-spinal syphilis, I consider it risky to give salvarsan in the full intravenous dose of 0.6 gram. It is safer to give repeated doses of not more than 0.3 gram. In this way we diminish the chances not only of acute arsenical symptoms, but the series of smaller doses is less likely to be followed by the alarming group of intracranial syphilitic symptoms known as nerve-relapses or "neuro-recidive." Further, patients with renal disease or with well-marked cardio-vascular disease are, as a rule, unsuitable for salvarsan medication. The very rapidity with which the drug acts in removing syphilitic deposits may be a source of danger, for example, in the neighbourhood of diseased vessel walls.

Let me quote a few clinical instances of the effect of treatment of the various classes of cerebro-spinal syphilitic disease.

RESULTS OF TREATMENT IN GUMMATOUS DEPOSITS.

As illustrating the first group of gummatous lesions I will only mention a couple of examples:

CASE I.—Gumma of Spinal Cord.

E. G. was a woman of 34 who had been married for twelve years without pregnancies. One and a half years before admission she developed a cutaneous rash, with sore throat and falling out of hair. Two months ago she complained of subjective sensations of numbness in both legs and in the two ulnar fingers of the right hand. Three weeks ago her legs became stiff, and on several occasions she tripped and fell. About the same time she noticed that she had impairment of sensation in both legs. She then developed anaesthetic incontinence of urine and faeces. Within the last week the legs had begun to drag severely and she had become unable to stand or walk.

On physical examination there was profound anaesthesia to touch, pin-pricks and temperature, with loss of joint-sense in the lower limbs and trunk, up to the level of the second ribs in front, also along the ulnar border of the right upper limb from axilla to fingers. There was severe flaccid paraplegia of both lower limbs, the only movements which survived being feeble flexion of the left hip and feeble flexion of the toes in both feet. The knee-jerks and ankle-jerks were absent, also the plantar reflexes. There was retention of urine requiring the catheter. The cerebro-spinal fluid showed a marked excess of lymphocytes, numbering 52.6 per cubic millimetre.

She was admitted to hospital and treated by mercurial inunction. After three weeks' treatment the anaesthesia had diminished considerably in intensity but not in extent. The lower limbs could now move feebly at all joints, bladder control had partially returned, and the lymphocytosis had receded to 16.3 per cubic millimetre. After seven weeks she had regained sensibility to cotton-wool touches, and joint-sense was now everywhere normal. There was still considerable impairment to pin-pricks and to temperature. She was now able to walk, the gait being a combined spastic and ataxic one. The sphincters were normal. The knee-jerks and ankle-jerks were still absent.

In this patient, with all the evidences of severe spinal-cord disease, not only did the clinical phenomena rapidly improve under mercurial treatment, but concurrently the lymphocytosis of the cerebro-spinal fluid subsided also. This case occurred in 1905, before the introduction of the Wassermann reaction.

CASE II.—*Gummatous Meningitis ("Neuro-recidiv").*

F. L., a man of 36, acquired syphilis ten months ago. Three months ago he had two intravenous injections of salvarsan—apparently in doses of 0.6 gram—followed by six weeks of hypodermic mercurial injections. Two months ago he developed moderate deafness in both ears. Six weeks ago right-sided headache appeared; and two weeks ago he began to reel in walking and had diminution of vision in the right eye. Two days before I saw him he consulted Mr. Andrew Wylie, who observed his reeling gait, together with a certain degree of bilateral deafness; there was no facial weakness at that time. On the same day he saw Mr. George Thompson, who found intense right-sided optic neuritis with considerable impairment of vision, the left optic disc being normal. By the time I saw him, in addition to the unilateral optic neuritis, there was dilatation of the right pupil with a sluggish reaction to light, also moderate paresis of the right face, upper and lower. Save for a slight bilateral nerve-deafness the cranial nerves were otherwise normal. There was no cutaneous anaesthesia or analgesia, and no motor weakness of any kind. The gait was slightly reeling. The knee-jerks and ankle-jerks were increased, but there was no ankle-clonus and the plantar reflexes were flexor in type. Kernig's sign was positive on both sides. The cerebro-spinal fluid showed an enormous pleocytosis, amounting to 459 cells per cubic millimetre, with strongly positive globulin and Wassermann reactions. The blood gave a slightly positive Wassermann reaction.

The patient was at once placed on full doses of mercury with iodide, and six intravenous injections of salvarsan (0.3 gram) were given within ten weeks. Within the first three days the right facial palsy became complete and remained so for a week. It then began rapidly to clear up, and ultimately disappeared. The right-sided optic neuritis was slower in its recovery, but at the end of two months' treatment it had cleared up and vision was also practically normal. After eight weeks' treatment the lymphocytosis of the cerebro-spinal fluid had receded to 38.5 per cubic millimetre, with faint globulin and negative Wassermann reaction, and after twelve weeks the fluid contained only 7.9 lymphocytes per cubic millimetre, with negative globulin and Wassermann reactions. Four months after the commencement of treatment the blood was re-examined for the Wassermann reaction, which proved completely negative; the optic discs and vision were normal, and, save for a very slight widening of the right pupil, which reacted briskly to light, the cranial nerves were otherwise normal.

This patient presented most of the classical symptoms of nerve relapse with intense meningeal reaction, coming on about six weeks after the original salvarsan injections. It is interesting to note how rapidly all his symptoms cleared up under mercury, iodide, and salvarsan.

RESULTS IN SYPHILITIC ARTERIAL DISEASE.

Let me now mention one or two clinical illustrations of the second group of organic nervous lesions—namely, those following syphilitic endarteritis:

CASE III.—*Spastic Paraplegia: Syphilitic Myelomalacia.*

W. H., aged 34, contracted syphilis four and a half years ago, and was energetically treated in a New York hospital by intramuscular injections of mercury, being discharged apparently well. Two months after the original infection, after a premonitory month, during which his legs seemed to be constantly tired, he woke up one morning completely paraplegic and anaesthetic from the waist downwards, with retention of urine requiring catheter. Under treatment, apparently mercurial in character, he steadily improved, and by the time he came to us at Westminster Hospital the anaesthesia had completely disappeared, but there was still severe spastic paraplegia of both lower limbs, especially on the right side, with increased deep reflexes and extensor plantar responses. Micturition was still precipitate. He could only stand when supported on both sides. The cerebro-spinal fluid contained only 5.7 lymphocytes per cubic millimetre, and gave negative Wassermann and globulin reactions.

In this patient the active syphilitic process in the central nervous system had run its course over three years ago,

but the results of the original vascular obstruction still persist, and are permanent.

CASE IV.—*Spastic Paraplegia from Syphilitic Myelomalacia: Foerster's Operation.*

W. H., aged 30, was admitted to the West End Hospital in March, 1913. Eleven months ago he acquired syphilis. Three months later he had sudden and complete motor and sensory paralysis from the waist downwards, with retention of urine. Four months after the onset of his symptoms he was treated by salvarsan intravenously in another hospital on three separate occasions, but without improvement. When admitted to the West End hospital he had blunting of sensation, chiefly to heat and cold, from the second lumbar root area downwards, together with severe paraplegia of both lower limbs and intense flexor contracture of the hips and knees, so that, although no individual movement of the limbs was paralysed, he was unable to stand. He also had a sacral bed sore. The deep reflexes were exaggerated, and the plantar reflexes were extensor in type.

This patient, like the previous case, had evidently come to a standstill, and in spite of energetic mercurial and salvarsan treatment, carried out some months after the lesion, no improvement had occurred. Accordingly, after inducing the bed sore to heal, I asked my colleague, Mr. Wilfred Trotter, to divide the posterior roots in the lumbar region, with the object of diminishing the flexor spasm and of enabling the patient to make better use of whatever motor power he still possessed. This was done in June, 1913, the posterior roots on both sides from the first to the fifth lumbar being divided. The result was to produce root-anaesthesia of the lower limbs without affecting their motor power, but with considerable diminution of spasticity, so that the patient became able voluntarily to extend the hips and knees; a feat which was previously impossible. There still persists, however, considerable adductor spasm; and I have asked Mr. Trotter to divide additional posterior roots in the hope of overcoming this and of enabling the patient to get about again.

CASE V.—*Transient Paraplegia following Syphilitic Vascular Disease.*

W. M., aged 23, acquired syphilis six months ago. The condition was only recognized four months ago, when, concurrently with the rash, he developed sudden weakness of the right lower limb, with subjective tingling and with blunting of sensation. Two days later the left lower limb became similarly involved and micturition became delayed. Energetic treatment with mercury and salvarsan was at once begun, and in about ten days all the paraplegic symptoms cleared up. By the time he came under my observation the Wassermann reaction in the blood was negative and the cerebro-spinal fluid contained only 1.7 lymphocytes per cubic millimetre, and gave negative globulin and Wassermann reactions. There was no motor, sensory, or reflex abnormality.

This patient was fortunate in being treated by mercury and salvarsan at the very outset of his spinal symptoms, before actual necrotic softening had time to occur.

Cases like the above might be multiplied indefinitely, from the experience of every neurologist, and it will be agreed that the amount of recovery in a nervous lesion which is associated with syphilitic arterial disease depends on whether the arterial disease can be at once attacked by energetic treatment (for example, by salvarsan and mercury) so as to clear up the endarteritis and to restore the lumen of the artery before it becomes thrombosed; or whether thrombosis has already occurred, so as to produce an area of softening. In the latter case, despite the most energetic antisyphilitic treatment, the necrotic area necessarily remains, and, inasmuch as regeneration of nerve tissue in the central nervous system does not occur, permanent degeneration and sclerosis are the result. Degeneration of this sort is the secondary result of the arterial obstruction. It is not primarily or essentially syphilitic in nature, unlike the group of primarily degenerative or parenchymatous syphilitic diseases, which we shall now proceed to consider.

TREATMENT OF PARENCHYMATOUS NERVOUS SYPHILIS.

The third division of syphilitic nervous diseases includes a class of maladies in which certain groups of nerve elements undergo a primary decay and degeneration, due not to gummatous infiltrations nor to vascular or meningeal disease (although lesions of this sort may co-exist), but to the nerve fibres and cells being attacked directly by the syphilitic toxin. An important point to bear in mind is that this toxin has a selective action on special systems of nerve tracts, so that in one patient we

have the exogenous fibres of the posterior columns picked out, producing tabes dorsalis; in another the lateral columns are selected, as in Erb's syphilitic paralysis; in a third we have primary optic atrophy, whilst in a fourth the nerve cells of the cortex with the interconnecting tangential fibres are picked out, as in dementia paralytica. Sir David Ferrier emphasized these facts very clearly some years ago by proposing the names of spinal tabes, cerebral tabes, and optic tabes. We have also to remember that mixed types of these diseases occur. Thus the symptoms of optic tabes may be superadded to those of tabes dorsalis, whilst tabes dorsalis may also be combined with general paralysis.

Hitherto this class of diseases has been singularly resistant to treatment, and for several reasons. First, the diseased nerve elements within the central nervous system, unlike those in the peripheral nerves, are incapable of regeneration. This is not the occasion to revive the controversy between the central and peripheral schools of nerve regeneration. Both schools agree that within the central nervous system regeneration is impossible, and that primary degeneration of nerve cells or nerve fibres, once it has occurred, is permanent. The most we can hope to achieve by treatment is to arrest the degeneration at the stage to which it has attained, and to make the most of those cells and fibres which survive. Another reason for the resistance to treatment shown by this group of parenchymatous syphilitic nervous diseases consists in the peculiarity of the position of the syphilitic organisms with reference to the blood stream. The spirochaetes are situated in the nerve elements themselves. Now, the circulation in the central nervous system differs from that in any other part of the body, inasmuch as the capillary walls are not in contact with the nerve elements, but are separated by perivascular lymph spaces. Moreover each nerve cell has its pericellular lymph space. These lymph spaces are irrigated by the cerebro-spinal fluid. Thus medicinal substances destined for the central nervous system have to be secreted into the cerebro-spinal fluid before they can reach the nerve cells or the spirochaetes within them. The cerebro-spinal fluid is secreted by glandular ependymal cells covering the choroid plexuses within the brain. These secreting cells have a selective action, permitting some substances to pass from the blood stream into the cerebro-spinal fluid. Thus, if alcohol be administered by the mouth in sufficient quantities, it can subsequently be detected in the cerebro-spinal fluid, whilst urotropin taken by the mouth can be shown to yield formic aldehyde in the fluid. To other substances, again, the choroidal ependyma is impervious, notably to mercurial and arsenical salts, which at the present time are our most important spirochaetocidal drugs. Thus, no matter how assiduously the general circulation be drenched with mercury or salvarsan, the cerebro-spinal fluid does not transmit these drugs nor allow them to reach the nerve elements. Thus, whilst gummatas may be removed from the meninges and interstitial tissues, and although syphilitic endarteritis may clear up, those nerve cells and nerve fibres which are being destroyed directly by the syphilitic organism and its toxin, entrenched behind the pericellular and perivascular lymph spaces, continue to decay.

INTRATHECAL MEDICATION.

In order to reach and to destroy these organisms, our remedies must enter the cerebro-spinal fluid. The credit for directing attention to this important principle and of initiating a new form of treatment belongs firstly to Marinesco¹ of Bukarest in 1911, and to George Robertson of Edinburgh,² who in his Morison lectures on general paralysis of the insane in 1913, described the treatment by salvarsanized blood serum administered intrathecally; also to Swift and Ellis³ of the Rockefeller Institute in New York, who, following Marinesco, applied the same treatment to cases of tabes dorsalis. More recently Ravaut⁴ of Paris has introduced the method of administering neo-salvarsan by direct injection into the cerebro-spinal fluid.

The technique is, briefly, as follows: An hour after an intravenous injection of salvarsan 0.3 gram (or of neo-salvarsan 0.45 gram) 60 c.cm. of blood are withdrawn by venepuncture. This blood is allowed to clot, and the separated serum, after being diluted with normal saline solution to form a 40 per cent. mixture, is kept at a temperature of 56° C. for an hour. Next day 30 or 35 c.cm. of

this diluted serum are introduced intrathecally by gravity through a long rubber tube and lumbar-puncture needle, previously withdrawing a quantity of cerebro-spinal fluid for control. This procedure is repeated at intervals of seven to fourteen days.

With Ravaut's method bleeding is not necessary. A 6 per cent. solution of neo-salvarsan in distilled water (75 c.cm. containing 0.45 gram of neo-salvarsan) is made up at the patient's bedside. Of this 0.1 to 0.15 c.cm. (that is, from 6 to 9 mg. of salvarsan) is injected into the spinal theca by means of a specially fine syringe and lumbar-puncture needle, after withdrawing a quantity of cerebro-spinal fluid for examination. The remainder of the solution (that is, 0.45 gram of neo-salvarsan minus the 6 to 9 mg. previously used) is injected intravenously. In the case of tabetics the patient is kept in the horizontal posture for several hours after the intrathecal injection. In general paralytics the foot of the bed is raised, so as to attain the Trendelenburg posture and thus to favour the diffusion of the injected substance upwards to the cranial cavity.

Within the last six months I have treated by intrathecal administration either of salvarsanized serum or of neo-salvarsan 25 cases of parenchymatous nervous syphilis, including 13 of tabes, and 9 of general paralysis, and I will quote one or two illustrative cases.

CASE VI.—*Tabes.*

L. A., aged 63, a patient of Dr. Bruce-Porter, complained of delay and dribbling of urine of about two years' duration, with deficient sensation in that region, so that he could not be sure whether the bladder or rectum was about to be emptied. He also had loss of sexual power for the last year, and within the last four months had developed slight unsteadiness of the legs in walking downstairs. For about two months he had felt shooting pains in the thighs. There was no history of syphilis, but there had been a soft sore twenty years before.

The patient was a man of good physique and remarkable mental energy. The pupils were unequal and the larger one had a sluggish reaction to light, the other reacting briskly. The cranial nerves were otherwise normal. There was no cutaneous anaesthesia or analgesia, no ulnar or Achilles analgesia and joint-sense was everywhere normal. Vibration-sense was normal in the upper limbs, but markedly impaired in the pelvis and lower limbs, being absent in the feet. There was no weakness or ataxia of the upper limbs. The lower limbs were powerful, but showed slight unsteadiness with the heel-knee test. The gait was slightly stamping. The supinator-jerks were brisk, the knee-jerks and ankle-jerks were absent. The bulbo-cavernosus reflex was brisk. The cerebro-spinal fluid showed the characteristic lymphocytosis and globulin reaction of tabes. The Wassermann reaction was negative in the blood and positive in the cerebro-spinal fluid.

The patient was placed on a course of treatment by salvarsanized serum. The results in the cerebro-spinal fluid are shown in the following table:

Date.	Blood. Wassermann.	Intravenous Treatment.	Cerebro-spinal Fluid.			Intrathecal Treatment.
			Cells per mm. ³	Globulin.	Wassermann.	
Nov. 25 ...		Salvarsan	137	++	+	40% serum.
Dec. 3-4	0	0.3 g.	155	++	+	35 c.cm.
Dec. 11-12	0	0.3 g.	99.7	++	+	35 c.cm.
Dec. 16-17	0	0.3 g.	89.7	+	+	35 c.cm.
Dec. 22-23	0	0.3 g.	37.6	+	+	35 c.cm.
Jan. 1-2	0	0.3 g.	41.9	+	+	35 c.cm.
Jan. 12-13	0	0.3 g.	14.8	+ faint	+	35 c.cm.
Jan. 29-31	0	0.3 g.	6.07	+	+	35 c.cm.

Together with the improvement in the cerebro-spinal fluid the patient's clinical symptoms became arrested. The lightning pains disappeared. Bladder control was completely regained and sexual power also returned. The unsteadiness of the legs disappeared. The knee-jerks and ankle-jerks, however, remain absent.

CASE VII.—*Tabes, "Forme Fruste."*

F. W., aged 41, who had acquired syphilis ten years ago, complained of lightning pains in the legs of four years' duration. The pupils were irregular in outline and of Argyll Robertson type; the cranial nerves were otherwise normal, save for progressive deafness of twenty years' duration. There were scars of an old glossitis at the sides of the tongue. There was no cutaneous anaesthesia or analgesia. The ulnar nerves and Achilles tendons were insensitive to pressure. There was no

weakness or ataxia of the upper or lower limbs and the gait was normal. The knee-jerks and ankle-jerks were brisk, and the plantar reflexes flexor in type. The blood gave a positive Wassermann reaction. The cerebro-spinal fluid showed a well-marked lymphocytosis of 69.4 cells per cubic millimetre, with a positive Wassermann reaction.

The following table shows the effect of treatment :

Date.	Blood. Wasser- mann.	Cerebro-spinal Fluid.			Treatment.	
		Cells per mm ³ .	Globu- lin.	Wasser- mann.	Intravenous.	Intra- thecal.
Nov. 13-14	+	69.4	+ faint	+	Neo-salvarsan 0.45 g.	40% serum. 30 c.cm.
Nov. 20-21		40	+	+	Neo-salvarsan 0.45 g.	30 c.cm.
Nov. 27-28	+	13.4	(?)	+	Neo-salvarsan 0.45 g.	30 c.cm.

After three weeks, owing to business reasons, he left hospital, being free from pains.

CASE VIII.—*Tabes, "Forme Fruste," with Addison's Disease.*

S. H., aged 65, who denied syphilitic infection but admitted old gonorrhoea, complained of shooting pains in the lower limbs of about two and a half years' duration. Two years ago, beyond irregularity of the pupils, which were of the Argyll Robertson type, no abnormal physical signs were made out, the knee-jerks and ankle jerks being still present. The cerebro-spinal fluid was not examined at that time. Two months ago the patient began to have nocturnal enuresis. Mr. Thomson Walker found the bladder to be trabeculated, with 12 oz. of residual urine, and suspected some spinal cord lesion. Accordingly I saw him again. On re-examination the pupils were of Argyll Robertson type as before; the cranial nerves were otherwise normal. There was no cutaneous or deep anaesthesia or analgesia, and no weakness or ataxia of the upper or lower limbs. The supinator-jerks and knee-jerks were normal. The right ankle-jerk was normal; the left ankle-jerk was absent. The bulbo-cavernosus reflex was brisk. The Wassermann reaction in the blood and cerebro-spinal fluid was found by Dr. Bulloch to be strongly positive, and the cerebro-spinal fluid showed an extensive lymphocytosis, amounting to 487 lymphocytes per cubic millimetre. The patient was treated by injections of salvarsanized serum, with the following results :

Date.	Blood. Wasser- mann.	Cerebro-spinal Fluid.			Treatment.	
		Cells per mm ³ .	Globu- lin.	Wasser- mann.	Intravenous.	Intra- thecal.
Oct. 30 ...	+++					Serum 40%
Nov. 5 ...		487	++	+++		
Nov. 10-11	+++	300	++	+++	Neo-salvarsan 0.45 g.	35 c.cm.
Nov. 17-18	++	150	+	++	Neo-salvarsan 0.45 g.	35 c.cm.
Nov. 26-27	++	47	+	+	Salvarsan 0.3 g.	35 c.cm.
Dec. 5-6	++	35.4	+	+	Salvarsan 0.3 g.	35 c.cm.

Three days after his last injection he developed mild pyrexia, with headache and pains in the limbs. No abnormal physical

signs could be detected in any of the organs; the urine was free from albumin. There was no cervical rigidity or other sign of meningitis. There was no diarrhoea or evidence of arsenical poisoning. After a week the temperature became subnormal, and the patient became exhausted and died.

At the autopsy the only abnormality found was severe cystic degeneration of the suprarenal bodies. The spinal cord and membranes were healthy-looking and free from any signs of meningitis. Microscopically, early tabetic changes were found in the posterior columns of the cord.

This case, which, so far as the spinal cord affection was concerned, had pursued a satisfactory course, died of an intercurrent affection apparently unconnected with the treatment. The suprarenal disease was not suspected during life, probably because the patient was of partial Ethiopian extraction.

CASE IX.—*Tabes with Gastric Crises.*

E. S., aged 32, a patient of Dr. Tilbury, had a venereal sore ten years ago, not considered at the time to be syphilitic. He married eight years ago, and his wife has had three healthy children.

Eighteen months ago he developed acute retention of urine for a week, requiring catheterization. A year ago he had his first gastric crisis with violent vomiting and collapse. At that time the pupils were said to be normal, and the knee-jerks were still present. Seven months ago he had another gastric attack, and three months ago he was seen in consultation by another physician who recognized the condition as tabetic. He then had a course of sixty mercurial inunctions. Two weeks ago he had another gastric crisis, together with retention of urine, and followed by cystitis.

On examination he was pale, thin, and haggard. The optic discs, pupils, and cranial nerves were normal. There was no cutaneous anaesthesia or analgesia. The ulnar nerves and Achilles tendons were insensitive on pressure, as also were the testicles. There was no weakness or ataxia of the upper limbs. There was a slight degree of ataxia in the gait. The supinator-jerks, knee-jerks, and ankle-jerks were absent; so also were the plantar reflexes. The bulbo-cavernosus reflex was brisk. The cerebro-spinal fluid contained 33 lymphocytes per cubic millimetre. The Wassermann reaction was faintly positive in the blood and strongly positive in the cerebro-spinal fluid.

The effects of treatment were as follows :

Date.	Blood. Wasser- mann.	Treat- ment: Intra- venous.	Cerebro-spinal Fluid.			Treatment: Intrathecal.
			Cells.	Globu- lin.	Wasser- mann.	
Jan. 29 ...		Salvarsan.	33	+		40% serum.
Feb. 9-10	+	0.3 g.	21.9	+	++	35 c.cm.
Feb. 16-17	faint 0	0.3 g.	8.7	+	++	35 c.cm.
Feb. 23-24	+	0.3 g.	9.87	faint	++	35 c.cm.
Mar. 9-10	faint	0.3 g.	5.6	+	++	35 c.cm.
Mar. 17-18	faint 0	0.3 g.	4.9	+	++	35 c.cm.
Mar. 24-25	0	0.3 g.	2.4	+	++	35 c.cm.

After the third injection the patient had another gastric crisis, much less severe than formerly, and unaccompanied by

Results Obtained in Eleven Cases of Tabes.

Name and Age.	Observations before Treatment.				Number of Intrathecal Injections.	Observations after Treatment.			
	Blood.	Cerebro-spinal Fluid.				Blood.	Cerebro-spinal Fluid.		
	Wasser- mann.	Wasser- mann.	Globulin.	Cells.		Wasser- mann.	Wasser- mann.	Globulin.	Cells.
1. L. A., 63	0	+	++	137	7 salvarsanized serum	0	+	+	6.07
2. F. W., 41	+	+	+	69.4	3 " "	+	+	?	13.4
3. S. H., 65	+	++	++	48.7	4 " "	+	+	+	35.4
4. E. S., 32	+	+	+	33	6 " "	0	+	+	2.4
5. G. C., 44	+	++	++	322.6	6 " "	0	+	++	24.1
6. M. W., 56	+ weak	+	+	246.7	5 " "	0	+	+	13.4
7. J. C., 36	+	+	+	97	3 " "	+	+	+	44
8. F. B., 41	+	++	++	66	7 " "	faint	faint	0	16.7
9. Mrs. A. J., 55 ...	+	+	+	243.4	7 " "	+	+	+	37.6
10. T. F., 52	0	++	+	10.1	5 " "	0	++	+	18.3
11. L. L., 44	0	+ faint	+	85.2	5 neo-salvarsan	0	faint	faint	12

bladder trouble. He rapidly got over this, and by the end of his treatment had gained several pounds in weight.

I will not weary you with details of other tabetic patients, but give a short tabular statement of the results observed in 11 cases (see p. 953). In every instance the clinical signs improved, lightning pains and gastric crises subsided, sphincter control was improved, ataxia was frequently diminished, and in one patient the knee-jerks, previously absent, reappeared, though the ankle-jerks still remained absent. In every case save one the lymphocytosis of the cerebro-spinal fluid was markedly reduced. The exception to this rule was in Case x, which started with only a small excess of cells, and finished with a small increase in this number. Nevertheless, his lightning pains disappeared, and his slight ataxia completely cleared up.

Let me now mention a case of primary optic atrophy of syphilitic origin. Some might prefer to classify it as an optic tabes, and to include it in the foregoing list.

CASE x.—Primary Optic Atrophy (Optic Tabes?).

R. B., aged 34, was sent to me by Mr. George Thompson, whom he had consulted owing to rapidly failing vision of about three months' duration. Mr. Thompson found optic atrophy in both eyes. The patient, whose previous health had been excellent, denied venereal disease, but his blood showed a positive Wassermann reaction. On physical examination, apart from pallor of the optic discs, no abnormality was detected. The visual acuity in the right eye was $\frac{3}{4}$, in the left $\frac{2}{4}$. The visual fields were concentrically contracted, more in the left eye. The pupils were moderately dilated, reacted sluggishly to light, and briskly on convergence. The cranial nerves were otherwise normal. The sensory and motor functions were normal. The supinator-jerks, knee-jerks, and ankle-jerks were normal. The plantar reflexes were flexor in type; the abdominal reflexes were brisk. The cerebro-spinal fluid showed a large lymphocytosis, amounting to 142 cells per cubic millimetre, and gave positive Wassermann and globulin reactions.

Under treatment the following changes occurred:

Date.	Blood. Wassermann.	Treat- ment: Intra- venous.	Cerebro-spinal Fluid.				Treatment: Intrathecal.
			Cells.	Globu- lin.	Albu- min*.	Wasser- mann.	
Dec. 15-16	+	Salvarsan.	142	+			40 % serum. 30 c.cm.
Jan. 5-6...	+	0.3 g.	72	+	0.05 %	+	30 c.cm.
Jan. 12-13	+	0.3 g.	34	+	0.09 %	+	30 c.cm.
Jan. 19-20	+	0.3 g.	33.4	+	0.05 %	+	30 c.cm.
Jan. 26-27	+	0.3 g.	26.7	weak +	0.05 %	+	30 c.cm.
Feb. 2-3...	0	0.3 g.	10.7	+	0.09 %	+	30 c.cm.
Feb. 9-10	0	0.3 g.	12	weak +	0.05 %	+	30 c.cm.

At the conclusion of the course the Wassermann reaction, although still positive in the cerebro-spinal fluid, had become negative in the blood, whilst the lymphocytosis in the fluid had receded to 12 per cubic millimetre. The visual acuity in the right eye remained the same, whilst in the left eye the field, which was originally the size of a pea, had entirely gone. The patient was instructed to continue with daily mercurial inunctions for the next two or three months.

Enesol in Tabetic Lightning Pains.

Before leaving the subject of tabes, I should like to mention the usefulness of enesol (salicyl-arsenate of mercury) in the treatment of tabetic lightning-pains. This drug has the advantage of being suitable for simple hypodermic administration, a fact worth bearing in mind when the intravenous administration of salvarsan (which often relieves lightning pains also) is perhaps unattainable. Enesol in 1-grain doses, dissolved in 30 minims of water, is given hypodermically at intervals of two or three days for twelve or fifteen successive doses. Let me mention an illustrative case.

CASE xi.—Tabes; "Forme Fruste," Lightning Pains.

A medical man, aged 50, had suffered for six months from agonizing pains in the arms, occurring paroxysmally, day and night, and intractable to all the ordinary analgesic drugs. On examination the pupils were unequal, irregular in outline, and of Argyll Robertson type; the cranial nerves were otherwise normal. There was no cutaneous anaesthesia or analgesia, but the ulnar nerves and Achilles tendons were insensitive to

pressure. There was neither weakness nor ataxia of the upper or lower limbs. The radial-jerks, knee-jerks, and ankle-jerks were absent.

The patient had a course of fifteen hypodermic injections of enesol, on alternate days for a month. After the third or fourth injection the pains disappeared, the physical signs remaining as before.

The next case is one of cerebro-spinal syphilis, which may, perhaps, be an instance of early general paralysis.

CASE xii.—Cerebro-spinal Syphilis (? Early General Paralysis of the Insane).

R. K., aged 28, who denied venereal disease, complained of pain in the left knee and arm of about four months' duration. Two months ago he slipped on some railway steps and was apparently concussed. The pains in the left limb persisted, and his legs have since become feeble and spastic.

On admission to the West End Hospital he was intelligent, but mentally somewhat slow. The optic discs were normal. The pupils were slightly unequal, but reacted normally. The cranial nerves were otherwise normal. There was considerable tremor of the face and tongue. There was no cutaneous anaesthesia or analgesia. The arms and legs were powerful, but markedly spastic, and showed distinct unsteadiness with the finger-nose and heel-knee tests. The supinator-jerks were present, markedly increased on the left side. The knee-jerks were both brisk. There was bilateral ankle-clonus. The plantar reflexes were both extensor in type. The Wassermann reaction was positive in the blood and cerebro-spinal fluid. The cerebro-spinal fluid showed a lymphocytosis of 343.7 cells per cubic millimetre.

Treatment by salvarsanized serum was carried out as follows:

Date.	Blood. Wassermann.	Treat- ment: Intra- venous.	Cerebro-spinal Fluid.			Treat- ment: Intra- thechal.
			Cells.	Globu- lin.	Wasser- mann.	
Oct. 20 ...	+					40% serum.
Oct. 30 ...		Salvarsan 0.3 g.	343.7	+	+	
Nov. 7 ...		Salvarsan 0.3 g.				
Nov. 13-14	+	Neo-salvar- san 0.45 g.	102	+	+	30 c.cm.
Nov. 20-21	+	Neo-salvar- san 0.45 g.	24.6	faint 0	+	30 c.cm.
Nov. 27-28	+	Neo-salvar- san 0.45 g.	9.4	0	+	30 c.cm.
Dec. 4-5	+	Salvarsan 0.3 g.	6.6	0	+	30 c.cm.
Dec. 11 ...	No blood obtained	Neo-salvar- san 0.45 g.				
Dec. 18 ...	+	Neo-salvar- san 0.45 g.	Not sufficient fluid obtained.			
Dec. 24-26	+	Neo-salvar- san 0.45 g.	9.4	0	+	30 c.cm.
Dec. 31 to Jan. 1	+	Neo-salvar- san 0.45 g.	6.6	0	+	30 c.cm.

At the end of the treatment the lymphocytosis had almost disappeared, but the Wassermann reaction was still positive, both in the blood and cerebro-spinal fluid. Mentally he was much more alert. The tongue was still tremulous. The motor and reflex abnormalities remained as before.

GENERAL PARALYSIS.

Lastly, let us come to the subject of general paralysis. This has hitherto been the despair of neuro-therapeutics. Most cases run a progressive course, the mental symptoms demanding asylum treatment, where their duration varies from a few weeks in acute cases to many years in some of the chronic forms or in those where spontaneous and prolonged remissions occur. The average duration, from the time the disease is usually recognized, according to Sir George Savage, is about three years. This, of course, does not include the pre-clinical stage, where changes in the cerebro-spinal fluid can be demonstrated, if looked for. A most important fact in this disease is the occasional occurrence of spontaneous remissions, during which the symptoms cease to advance and the patient may even, for a time, regain mental power. These probably are cases where the brain cells are not destroyed in the first instance by the syphilitic spirochaete, but are poisoned by its toxin, so as to be still capable of recovery.

In the treatment of general paralysis, as in that of any other organic nervous disease, it is hopeless to try to restore nerve cells that are already destroyed. The best we can hope for is to arrest the disease at the stage which it has already reached. If the changes are not yet destructive, but merely of toxic origin, the chances of success are relatively brighter.

Influence of Pyrexia on General Paralysis.

For some time past it has been observed that general paralytics are often benefited as regards their symptoms if they happen to catch some intercurrent acute febrile disease, such as erysipelas or enteric fever. To infect the patient with a serious specific fever of this sort, however, is neither practicable nor judicious. Accordingly, other means have been suggested to induce a harmless temporary febrile reaction.

Treatment by Tuberculin.

For this purpose von Wagner began some years ago to treat cases of general paralysis by repeated hypodermic injections of Koch's tuberculin, beginning with doses of 0.5 to 1 mg., waiting a couple of days, and increasing the dose to 5 or 7 mg., and gradually raising it to 10, 20, or even 30 mg. Sufficient tuberculin was given to induce a temperature of about 102° F. Friedländer⁵ has recorded a number of cases thus treated, and with encouraging results. He relates several cases in which not only did the mental symptoms improve but the pupillary reflexes returned, and the knee-jerks, previously absent, reappeared. Personally I have not tried this method of treatment, for the reason that tuberculin is a two-edged weapon which, whilst possibly benefiting some symptoms, has a risk of stirring up latent tuberculous lesions elsewhere in the body.

Treatment by Sodium Nucleinate.

Another and perhaps a safer method of inducing artificial pyrexia is by means of large intramuscular injections of sodium nucleinate, as specially studied by Donath⁶ of Budapest. A 2 per cent. solution in fresh normal saline solution is made. The initial dose for injection is 50 c.cm. of this solution (that is, 1 gram of the salt) injected deeply into the gluteal or lumbar muscles. This is repeated once a week so long as a sufficient febrile reaction (101.4° F. at least) occurs. If the reaction is insufficient, the dose is increased to 75 c.cm. (0.15 gram), or even 100, 125, or 150 c.cm. After each injection the temperature rises, sometimes to 104° F., and may be accompanied by rigor. As a rule it only reaches 101.4°, attains its maximum in from four to ten hours, and returns to normal in one or two days. Meanwhile, a temporary leucocytosis of the blood occurs—numbering from 10,500 to 25,000 per cubic millimetre—which subsides about the fifth day. In Donath's series of cases the number of weekly injections varied from seven to nine. Out of 15 general paralytics thus treated by him, 3 were able to resume their ordinary work, 6 were improved, 5 were unchanged, and 1 died of apoplexy during the treatment.

I made a number of observations on this method of treatment, and with a moderate amount of encouragement. Let me relate illustrative examples:

CASE XIII.—Tabo-Paralysis.

F. D., aged 58, a patient of Dr. Gordon Lane, had syphilis over thirty years ago, and developed shooting pains in the legs five years ago. He had recently become emotional and his memory had been failing. On examination he was bilious in manner and laughed at trifles. The speech and articulation were normal. There were no facial or lingual tremors. The pupils were contracted, more so on the left side, and were of Argyll Robertson type. The optic discs and cranial nerves were otherwise normal. There was no cutaneous anaesthesia or analgesia, but the Achilles tendons were insensitive to pressure. The upper limbs were normal. The gait was slightly ataxic. The knee-jerks and ankle-jerks were absent. The sphincters were frequently uncontrolled. The cerebro-spinal fluid showed a lymphocytosis of over 200 per cubic millimetre and gave a positive globulin reaction.

The patient was placed under treatment by intramuscular injections of sodium nucleinate for nine successive weeks, commencing with 50 c.cm. of a 2 per cent. solution, and ultimately rising to 100 c.cm. After each injection there was a temporary pyrexia of 101° to 102° F., together with a transient leucocytosis in the blood. The normal number of leucocytes in this case was 11,000 per cubic millimetre, but after each injection this rose to between 16,000 and 18,000 per cubic millimetre. After a month's treatment his mental condition became much clearer, he regained his memory, and became able to discuss complicated business affairs without difficulty. Dr. T. B. Hyslop pronounced him fit to make a will at this stage. After the eighth injection of sodium nucleinate the lymphocytosis of the cerebro-spinal fluid had receded to 47.1 per cubic millimetre, and the globulin reaction was now negative.

The mental improvement was maintained for about three months. He then developed acute mental symptoms and had to be certified and sent to an asylum. Two years later he was

still alive and physically strong, although mildly demented. The sphincters, however, are under perfect control ever since the third injection of the series.

CASE XIV.—General Paralysis.

H. W., an architect's surveyor, aged 47, a patient of Dr. Sedgwick, began to have severe epileptiform fits about eleven months ago, occurring in batches at intervals of three or four months, the last attacks being a week ago. During all of these attacks the limbs of the left side twitched more than on the right side. He had recently become irritable over trifles, and his speech had become slightly hesitating.

On examination he was mentally clear. There was slight tremor of the outstretched tongue. The optic discs, pupils, and cranial nerves were normal. There was no sensory or motor abnormality of the limbs, the knee-jerks and ankle-jerks were normal, and the plantar reflexes were flexor in type. The heart, lungs, abdomen, and urine were normal. The cerebro-spinal fluid contained 76 lymphocytes per cubic millimetre.

He returned home and had eight weekly injections of sodium nucleinate. At the end of that time I saw him again. His epileptiform fits had not recurred. The tremor of the tongue was now absent. The lymphocytosis of the cerebro-spinal fluid had receded to 53.3 per cubic millimetre.

The remission in the mental symptoms lasted three months longer. He then became acutely insane, and had to be certified. He was still alive in an asylum, two years after the injections, when I last heard of him.

CASE XV.—General Paralysis.

B. B., aged 27, a patient of Dr. J. G. Emanuel, who had syphilis eight years previously, became forgetful and irritable about twelve months ago. His speech also became slightly confused, so that he would occasionally mix up his words.

On examination, he was mentally quite bright. His articulation was slightly indistinct; there were no facial or lingual tremors. The pupils were slightly unequal, but reacted normally. The optic discs and cranial nerves were otherwise normal. There was no cutaneous anaesthesia or analgesia, and no ataxia of upper or lower limbs. The knee-jerks and ankle-jerks were absent. The cerebro-spinal fluid contained 34.4 lymphocytes per cubic millimetre, and gave a positive Wassermann reaction.

The patient returned home and had eight weekly injections of sodium nucleinate under Dr. Emanuel's direction, commencing with 50 c.cm. and gradually increasing to 100 c.cm. After each injection there was a temporary pyrexia of 102° to 103° F., with a transient leucocytosis of from 18,000 to 25,000, the number of leucocytes falling between times to 10,000.

I saw him again at the conclusion of this course. He felt subjectively better, and his articulation was more distinct. The right knee-jerk, which had previously been absent, was now present. The ankle-jerks were still absent. The lymphocytosis of the cerebro-spinal fluid, however, had gone up to 142 per cubic millimetre, and the Wassermann reaction in the fluid was still positive.

When last I heard of him, fifteen months after the termination of the treatment, he was *in statu quo*. He was married and going daily to business, although his memory was still much impaired.

CASE XVI.—General Paralysis.

R. B., aged 46, a patient of Dr. Lennon, who had acquired syphilis sixteen years ago, and who had a transient attack of left hemiplegia twelve years ago, seemed to have recovered completely until six months ago, when he would occasionally repeat himself in speaking and became unusually emphatic in his manner. Four months ago he had a transient attack of aphasia which cleared up in a few days. Six weeks ago he had an attack of unconsciousness with epileptiform convulsions and was comatose for several days. Ever since he had been acutely confused and his articulation was now affected.

On examination the patient was excited, restless and noisy, talking incoherently, but with clear articulation. There were no facial or lingual tremors. The pupils were unequal, but reacted normally. The cranial nerves were otherwise normal. There was no motor weakness or ataxia of the limbs. The supinator-jerks and knee-jerks were brisk. The plantar reflexes could not be tested owing to the patient's resistance. The cerebro-spinal fluid showed an enormous lymphocytosis. (A counting chamber was not available for enumeration.) The globulin reaction was strongly positive.

The patient was put on weekly injections of sodium nucleinate. At first he improved, became calmer and less confused, and was able to play golf. The amount of sodium nucleinate was gradually increased until after eleven weeks he was getting 230 c.cm. at each injection. The patient appeared to be doing well, when he had a fresh attack of coma and convulsions, which proved fatal in a couple of days.

The results of treatment by sodium nucleinate, so far as I have been able to judge, appear to indicate that in a considerable proportion of cases a more or less prolonged remission occurs in the clinical symptoms, sometimes accompanied by a diminution in the intensity of the lymphocytosis of the cerebro-spinal fluid. I do not know of any case, however, whether under my own observation or amongst those recorded by Donath and his collaborators, in which a cure has resulted, in the sense of a permanent

return to normal, not only of the mental and physical symptoms and signs, but also of the cerebro-spinal fluid.

Treatment by Urotropin.

Amongst the drugs which have proved useful as accessories in the treatment of general paralysis urotropin is deserving of mention. Urotropin, when taken by the mouth, is partly eliminated in the cerebro-spinal fluid in the form of formic aldehyde, which is not only antiseptic in its action but appears to have a beneficial action upon the meningeal reactions induced by the syphilitic organism. My attention was first directed to the use of urotropin by Dr. Stoddart, of Bethlem Royal Hospital, and I have prescribed it to general paralytics for years. In one case—that of a medical man aged 44—urotropin has been taken in 10-grain doses three times a day for three years and a quarter. This has been the only treatment employed in his case. The patient's clinical symptoms have not advanced, and his cerebro-spinal fluid, which contained 52.9 lymphocytes per cubic millimetre when I first saw him, rose to 81.8 six months later, and now, after three years, contains 56.3. The long remission in the symptoms in this and other cases may only be a coincidence, but it is worth bearing in mind.

INTRATHECAL TREATMENT BY SALVARSANIZED SERUM OR NEO-SALVARSAN.

Let me now relate some of the results obtained in general paralysis by combined intravenous and intrathecal treatment, either with salvarsanized serum or with neo-salvarsan. The following are illustrative cases:

CASE XVII.—*General Paralysis.*

C. C., a schoolmaster aged 42, a patient of Dr. Fairhall, had a chancre ten or twelve years ago; but had no cerebral symptoms until five days before I saw him. He then had transient momentary hesitation in speech. Five days later this recurred when he was reading the minutes at a committee meeting. He found himself stumbling over an occasional word. The symptoms again passed off in a few minutes.

On examination, the patient was mentally alert and intelligent. His voice was slightly tremulous, and there was some tremor of the lips and tongue. The optic discs were normal. The pupils, which were moderate in size, were of the Argyll Robertson type. The cranial nerves were otherwise normal. There was no cutaneous anaesthesia or analgesia. The Achilles tendons were insensitive to pressure. There was no weakness or ataxia of the upper or lower limbs. The gait was normal. The supinator-jerks, knee-jerks, and ankle-jerks were normal, and the plantar reflexes were flexor in type. The cerebro-spinal fluid showed an enormous lymphocytosis, numbering 419 cells per c.mm., and the Wassermann reaction was positive both in the cerebro-spinal fluid and in the blood.

Treatment by salvarsanized serum was carried out as follows:

Date.	Treatment: Intravenous, Salvarsan.	Blood, Wassermann.	Cerebro-spinal Fluid.				Treatment: Intrathecal.
			Wassermann.	Cells.	Globulin.	Albumin.	
Jan. 16 ...		+		419	+		40 % Serum.
Feb. 9-10	0.3 g.	+		162	+	0.1 %	30 c.cm.
Feb. 16-17	0.3 g.	+		50.7	0	0.03 %	30 c.cm.
Feb. 24-25	0.3 g.	+		99	+	0.1 %	30 c.cm.
Mar. 2-3	0.3 g.	+		29	+	0.1 %	30 c.cm.
Mar. 9-10	0.3 g.	weak		18	+	0.1 %	30 c.cm.
Mar. 16-17	0.3 g.	weak			Fluid mixed with blood.		30 c.cm.

At the end of the treatment the tremor of the lips and tongue had disappeared. He had had no further difficulty with his speech. The pupils had regained a faint reaction to light, although their outline was still slightly irregular.

CASE XVIII.—*General Paralysis.*

H. N., aged 41, was originally seen by me in a private asylum. His mental symptoms had come on with great acuteness a fortnight before, and when I saw him he was full of grandiose obsessions; he had invented enormous aeroplanes each connected with fifty balloons and to be ballasted with acres of the Goodwin Sands; his workmen would require several miles of land roofed in for workshops; he was fond of fishing, and had invented a copper fishing-line with hundreds of fish-hooks through which he was to electrify the fish at various depths. The face and tongue were tremulous; the pupils, however, were equal and brisk in reactions; the cranial nerves, sensory,

motor, and reflex functions were all normal. He was placed under treatment by salvarsanized serum, with the following results:

Date.	Blood, Wassermann.	Cerebro-spinal Fluid.			Treatment.	
		Cells per mm. ³	Globulin.	Wassermann.	Intravenous.	Intrathecal.
Sep. 13 ...	++	94.8	+	++		Serum 40 % 30 c.cm.
Sep. 29-30	++	117.3	+	++	Neo-salvarsan 0.45 g.	30 c.cm.
Oct. 9-10.	++	32.7	++	++	Neo-salvarsan 0.45 g.	30 c.cm.
Oct. 20-22	+	11.3	0	+	Salvarsan 0.3 g.	30 c.cm.
Oct. 29-30	+ weak	13.4	0	+	Neo-salvarsan 0.45 g.	30 c.cm.
Nov. 5-6.	0	16	0	+	Neo-salvarsan 0.45 g.	30 c.cm.
Nov. 12-13	0	27	0	+	Neo-salvarsan 0.45 g.	30 c.cm.
Nov. 19 ..		22	??	+		
Nov. 24-25	?	36	?	+	Neo-salvarsan 0.45 g.	30 c.cm.
Dec. 2-3 ..		25.4	0	+		
Dec. 9-10	0	15.4	0	+		
1914.						
Jan. 22 ...		17.1	+ faint			
Feb. 19 ...		62.2	+ faint			
Mar. 13 ..		108.9	+			

For the first fortnight of the above treatment—that is, until October 10th—his mental symptoms persisted as before. He then rapidly improved, and by October 28th he was mentally clear and collected, free from facial or lingual tremors, and has since remained normal in these respects. The Wassermann reaction on the blood soon became negative, and also became less intense in the cerebro-spinal fluid. The lymphocytosis of the cerebro-spinal fluid, however, continued, although more moderate in degree, until January. In February it began to go up again, and accordingly in March, in view of this recurrence of lymphocytosis, and in spite of the fact that the patient showed no mental symptoms, a second course of treatment was commenced as follows:

Date.	Blood, Wassermann.	Cerebro-spinal Fluid.			Treatment.	
		Cells.	Globulin.	Wassermann.	Intravenous.	Intrathecal.
Mar. 13		108.9	++			
Mar. 17	0	89.7	+	++	Neo-salvarsan 0.45 g.	Neo-salvarsan 9 mg.
Mar. 30		32.6	+	++	Neo-salvarsan 0.45 g.	Neo-salvarsan 9 mg.
April 8		15.9	+	++	Neo-salvarsan 0.45 g.	Neo-salvarsan 9 mg.
April 20		6.9	faint	++	Neo-salvarsan 0.45 g.	Neo-salvarsan 9 mg.

The patient has been back at business since January, and is perfectly normal as regards his mental state.

Since the fourth intrathecal injection of neo-salvarsan he has developed slight paresis of the lower limbs without sensory loss, the knee-jerks and ankle-jerks being brisk and the plantar reflexes having become extensor in type. Micturition has also become delayed.

This case shows the importance of repeated observations on the cerebro-spinal fluid over a long period of time. Had we been content with disappearance of the ordinary clinical symptoms this patient might have been considered normal after a few weeks' treatment.

CASE XIX.—*General Paralysis.*

W. R., aged 48, presented the classical signs and symptoms of general paralysis. Eighteen months ago his disposition altered and he became tactless and erratic. Three months ago he became acutely exalted, had delusions that he was to be married, and invited various ladies to be bridesmaids. His articulation at that time was indistinct and his face tremulous. He was certified and admitted to a private asylum, where I saw him with Dr. Tukey three months after admission. When I examined him he was full of delusions of grandeur, was betting in millions—always winning—was a champion golf and billiard player, and was engaged to a royal princess. There were slight lingual tremors. The pupils were unequal and of Argyll Robertson type. The optic discs and cranial nerves were otherwise normal. There was no cutaneous anaesthesia or analgesia, but the Achilles tendons were insensitive to pressure. There was no weakness or ataxia of the upper or lower limbs. The

Results Observed in Seven Cases of General Paralysis.

Name and Age.	Observations before Treatment.				Number of Intrathecal Injections.	Observations after Treatment.			
	Blood.	Cerebro-spinal Fluid.				Blood.	Cerebro-spinal Fluid.		
	Wasser- mann.	Wasser- mann.	Globulin.	Cells.		Wasser- mann.	Wasser- mann.	Globulin.	Ce'ls.
1. H. N., 41	++	++	+	117.3	7 salvarsanized serum	0	+	0	15.4
2. W. R., 48	+	++	+	120	6 " "	+	+	+	15.4
3. P. B., 40	+ faint	++	++	48.1	6 " "	0	++	+	14.3
4. C. C., 42	+	+	+	419	6 " "	+ weak	+ weak	+ weak	18
5. C. B., 42	+ faint	+ faint	+ faint	120	6 " "	0	0	+ faint	25.4
6. R. S., 39		+	+	39.2	5 neo-salvarsan		+	+	4
7. M. B., 43		++	++	235.8	5 " "		+	+	8

supinator-jerks and knee-jerks were brisk, the ankle-jerks were absent. The cerebro-spinal fluid contained 120 lymphocytes per cubic millimetre. The Wassermann reaction was positive both in the blood and cerebro-spinal fluid.

He was placed under treatment as follows:

Date.	Blood. Wassermann.	Treatment: Intra-venous.	Cerebro-spinal Fluid.				Treatment: Intra-the- cal.
			Cells.	Globu- lin.	Albu- min.	Wasser- mann.	
Dec. 18 ...		Salvarsan	120	+		++	40 % serum
Jan. 1-2	+	0.3 g.	98.7	+	0.125 %	+	30 c.cm.
Jan. 8-9	+	0.3 g.	36	+	0.1 %	+	30 c.cm.
Jan. 14-15	+	0.3 g.	34	+	0.11 %	+	30 c.cm.
Jan. 27-28	+	0.3 g.	23.4	+ weak	0.05 %	+	30 c.cm.
Feb. 4-5...	0	0.3 g.	28	+	0.1 %	+	30 c.cm.
Feb. 18-19	+	0.3 g.	15.4	+	0.09 %	+	30 c.cm.

At the end of the treatment, although the lymphocytosis of the cerebro-spinal fluid had receded to 15.4 cells per cubic millimetre, his mental condition was unchanged, and he was as exalted as ever.

At the head of this page is a table showing the results on the cerebro-spinal fluid in a series of cases of general paralysis.

INTRACRANIAL METHODS.

Other methods besides those of lumbar puncture may also be employed in order to introduce remedies into the cerebro-spinal fluid. Thus in Neisser and Pollack's method of cranial puncture by means of a small drill through an area of frozen scalp, the remedy is injected through the dura directly on to the surface of the brain. This has been used by Marinesco and Minea,⁷ by Sicard and Reilly,⁸ and others. Or we can reach the basal sub-arachnoid space through the orbit, as shown by Beriel⁹ of Lyons, by penetrating the sphenoidal fissure with a hollow needle. Or remedies may be injected directly into the ventricles of the brain by the well-known callosal puncture (Balkenstich) of Anton and Bramann of Halle. This has been carried out by Förster¹⁰ in Germany and by my colleagues Dr. Harry Campbell and Mr. Ballance at the West End Hospital in London.¹¹

It seems to me that, of the various intracranial routes, we should select those which are least likely to cause damage to the brain structures. For this reason cortical applications possess certain advantages over intraventricular injections. Further, when comparing intraspinal with intracranial administration, we have to bear in mind that a long series of treatments is necessary in order to give the patient a chance of improvement, and we must consider whether we are justified in submitting a patient to the risks of repeated cranial operations, unless these can be shown to yield results which are materially better than those obtained by intraspinal injections.

In every one of the cases of general paralysis in the foregoing tables it will be observed that the lymphocytosis of the cerebro-spinal fluid diminished. In three of them

the Wassermann reaction disappeared from the blood. In the cerebro-spinal fluid the Wassermann reaction usually became less marked; in only one case did it disappear.

CONCLUSIONS.

What deductions are we justified in drawing from the foregoing observations? Before coming to definite conclusions we require numerous and prolonged observations over a large series of cases. One or two observations are not enough to justify a conclusive opinion in any case. The patients should be repeatedly examined, not only during the progress of the treatment, but at intervals for months and years afterwards.

Improvement in the condition of the cerebro-spinal fluid is a useful index of arrest of the disease. But we must remember that, in general paralysis at least, the cell count in the fluid may go down (as in Case XIX) without any corresponding improvement in the mental symptoms. This is readily understood when we bear in mind that, even if the diseased process be arrested, those nerve-cells and nerve-fibres which have been already destroyed, remain destroyed and cannot be regenerated.

It is therefore of importance to select only those cases of general paralysis which are in the early or toxic stage of the disease, before the cortex has become profoundly degenerated. The earlier the disease is recognized, the better are the prospects of improvement. Advanced cases with profound cortical degeneration are totally unsuitable.

The most thorough method of attacking general paralysis would be to administer our remedies concurrently by all three routes—intravenously, intraspinally and intracranially. It may be, in the future, that this combination will be adopted.

It is too early to claim that we yet possess a cure for tabes or general paralysis, but we can already in suitable cases do a good deal towards arresting both diseases. Whether such periods of arrest are permanent, time alone will show.

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At the next representative meeting of the medical profession in Germany (*derztettag*), which will be held in Munich on June 25th to 27th, Professor Lennhoff of Berlin will move a resolution calling upon all German medical practitioners to claim payment for all medical assistance rendered at the request of so-called public welfare (*gemeinnützige*) undertakings. In doubtful cases the decision as to whether payment shall be claimed or not shall be left to the local medical organization. Professor Lennhoff appeals to medical men and medical societies—both those in favour and those disapproving of the motion—to supply him with details of the work connected with certain institutions, in order that he may be in a position to discuss all aspects of the subject in moving the resolution. He includes in his definition of "public welfare" institutions the Red Cross Society, cottage and home hospitals, convalescent homes, institutions for the care of consumptives, inebriates and infants, reformatories, etc.