THE TREATMENT OF SYPHILIS OF THE NERVOUS SYSTEM BY INTRATHECAL INJECTIONS.

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SYPHILIS is much the most common cause of organic disease of the nervous system. When it attacks the central nervous system it gives rise to two sharply differentiated forms of disease—so-called cerebro-spinal syphilis and parasyphilis. Inasmuch, however, as both forms are now known to be produced by the *Spirochaeta pallida*, the term "parasyphilis" must be abandoned. Rather should we speak of "interstitial" and "parenchymatous" syphilis of the nervous system.

In the interstitial variety the non-parenchymatous tissues of the nervous system—the meninges, the blood vessels, the neuroglia—are primarily affected (with the production of gummata, meningitis, meningo-encephalitis, meningo-myelitis, endo-vasculitis, etc.), the neurons being secondarily involved, for example, by compression and ischaemic softening. In the parenchymatous variety, of which the most frequent manifestations are general paralysis, tabes, and tabo-paresis, the spirochaete toxin appears to act upon the affected neurons directly.

These two varieties of syphilitic nervous disease exhibit certain striking contrasts: The *interstitial* variety occurs, on an average, two and a half years after infection, though it often shows itself much earlier. It is more apt to develop after a "virulent" than a "mild" infection, evidence of gross syphilitic disease of the skin, bones, and mucous membranes being frequently forthcoming. The symptoms tend to begin suddenly, and the morbid process not infrequently remains stationary, or even retrogrades. Finally, vigorous treatment by means of mercury, potassium iodide, or salvarsan has both a powerful prophylactic and a powerful curative influence on the disease. On the other hand, the *parenchymatous* variety develops on an average twelve years (Head gives fourteen) after infection. It occurs for the most part after "mild" infection, and evidence of gross lesions of the skin, etc., is rarely to be obtained. The symptoms begin insidiously, and the morbid process steadily progresses to a fatal termination. Finally—and most important of all—treatment by mercury, iodide, or salvarsan has little, if any, prophylactic, and the former two at least have practically no curative, influence on the disease.*

MacIntosh and others have sought to explain the parenchymatous variety as being the result of sensitizing, during the early period of infection, of the central nervous system, so that when subsequently attacked by a local invasion of spirochaetes the sensitized (anaphylactic) tissue undergoes parenchymatous degeneration. This explanation is possibly quite right, as far as it goes, but it does not cover the whole ground. How, for example, are we to account for the mildness of the infection in parenchymatous syphilis? We seem compelled to postulate one of two alternatives—either the virus of parenchymatous syphilis is different from that of interstitial syphilis, or the patients respond differently in the two cases to the same virus. How, again, are we to explain the intractability of parenchymatous syphilis to antisiphilitic treatment? Mott has suggested that in this variety the spirochaete exists in a latent granular intraneuronic form, and that the granules from time to time develop into active spirochaetes. It is conceivable that the parasites, ensconced within the nerve cells of the central nervous system, might be difficult to reach with remedies. The true explanation, however, is probably to be sought for in the difficulty of getting spirillicidal substances to percolate the capillaries of the central nervous system. It is probable that the spirillicidal action of mercury and arsenic is not direct, that it is effected by means of antibodies† to which these drugs give rise, and that these antibodies never gain entrance to the perineuronic lymph stream. It is noteworthy in this connexion that the blood of a syphilitic patient may give a strong positive

Wassermann reaction while his cerebro-spinal fluid gives not the faintest response. There is, indeed, abundant evidence that the capillaries of the central nervous system are very jealous as to what substances shall be permitted to enter the perineuronic lymph stream, for of all cells of the body the neurons are the most susceptible to chemic influences. Not only are these capillaries impermeable to the substance which is responsible for the Wassermann reaction, but also to the compounds of mercury and arsenic, neither of which metals can be extracted from the central nervous system *post mortem*, no matter how lavishly they have been administered. It is, moreover, well known that both the central nervous system and the cerebro-spinal fluid remain unstained in jaundice, and a similar absence of staining is noticeable after the intravenous injection of large quantities of trypan blue.

The problem, therefore, which confronts us in the treatment of parenchymatous syphilis is how to get the spirillicidal antibodies to enter the perineuronic lymph stream. This end can be gained by intrathecal injections of salvarsanized serum. Whether or not we accept the view of Mott—that the cerebro-spinal fluid constitutes the lymph of the central nervous system—certain it is that substances introduced into the subarachnoid space do actually penetrate the central nervous system. If trypan blue be injected through a trephine hole into the cranial subarachnoid space above the tentorium cerebelli, not only the cortex cerebri, but the entire cerebro-spinal axis is found *post mortem* to be stained. If, on the other hand, the pigment be injected into the spinal subarachnoid space, by means of a lumbar puncture, the cortex cerebri remains unstained, the staining in these cases being confined to the spinal cord and brain stem. It would appear that the cerebro-spinal fluid flows from the cranium spinalwards—probably in a meagre current—and also that some slight ebb and flow takes place between the fluid in the subarachnoid space at the base of the cranium and the spinal subarachnoid space, in accordance with variations in the quantity of intracranial blood.

That medicaments injected into the spinal subarachnoid space do, in some measure at least, reach the cranial cavity is shown by the fact that cocaine thus introduced causes anaesthesia of the entire body, so that by this means it is possible, for example, to enucleate an eyeball painlessly.

It will thus be seen that intrathecal spinal injections afford a ready means of bringing remedial agents into immediate relation with the neurons of the spinal cord and brain stem. (Quite recently my colleague, Dr. Golla, has shown that pigment injected intrathecally actually enters the perineuronic lymph spaces.) While it is probable that the neurons of the cortex cerebri may in some degree be reached in this way, a far more effectual means of reaching them would undoubtedly be by injecting the cranial subarachnoid space through a trephine hole, but up to the present I have not seen my way to adopt this method.

In our choice of remedies for intrathecal injections we are met with the difficulty that in attempting to kill the spirochaetes we may do serious injury to the nervous system. By adopting the method introduced by Swift of the Rockefeller Institute, and carried out by Fisher of the Rockwood Hospital, Kingston, Canada, and in this country by George Robertson and Mott, of injecting salvarsanized serum intrathecally in cases of parenchymatous syphilis, no injurious results ensue, while, in many cases at least, a marked improvement of the symptoms results. The treatment adopted in the cases here recorded differs somewhat from that of Swift, notably in the employment of neo-salvarsan, in the much longer interval allowed between the salvarsan and intrathecal injections, and in the mode of separating the serum from the blood clot.

The patient, prepared as for general anaesthesia, is given 0.9 gram of neo-salvarsan intrathecally, while at the same time a course of mercury is begun. He is kept in bed on a light diet for a couple of days. After an interval of a week the dose of salvarsan is repeated, and two hours later 4 oz. of blood are drawn off from a vein by means of a syringe and transferred to a 4-oz. bottle duly sterilized. The bottle is then placed in a jar containing a 1 in 20 carbolic solution, and set aside in a cool place. After twelve hours the serum has separated sufficiently for injection. It will be found to be somewhat stained with haemoglobin and to contain a few erythrocytes, but no harm comes from the injection of these. The advantage

* It is too early yet to speak of the prophylactic influence of salvarsan on parenchymatous syphilis of the nervous system.

† Mott concludes that mercury and arsenic are spirillicidal either by causing the development of antibodies or by furthering their spirillicidal action.

of allowing the clot to separate out in this way over the more rapid process of centrifuging the blood is that it offers less opportunity for septic contamination.

The serum thus prepared is injected by means of a lumbar puncture made in the usual way, into the spinal subarachnoid space, a quantity of cerebro-spinal fluid, equal to the amount of serum to be injected, being first allowed to escape. Some of this is collected in sterilized test tubes for testing purposes, but not until the fluid runs quite clear—unmixed, that is, with any blood.

Water, distilled under personal supervision, must be employed for the salvarsan injection, and it need hardly be said that the intravenous and intrathecal injections must be carried out under the strictest aseptic precautions. Olive oil, which has a much higher boiling point than water, is employed for sterilizing the syringes and needles, and it has the further great advantage of not blunting the needles.

The reaction of the blood serum and the cerebro-spinal fluid to the Wassermann test, and the condition of this fluid in respect to lymphocytosis, give important indications not only with regard to the diagnosis of syphilis of the central nervous system, but also as to the effects of treatment upon it. A few words may therefore be said on these tests here.

Interstitial Syphilis.—A positive Wassermann reaction of the serum may or may not be present. Even when the serum gives the reaction in an intense degree, the cerebro-spinal fluid may not show the slightest reaction. The majority of cases, even with active meningitis and enormous leucocytosis of the fluid, give a negative reaction of the latter. Antisyphilitic treatment generally causes a speedy disappearance of the positive reaction, both as regards the serum and the fluid, the effect being more rapid in the latter than in the former case. In only about one quarter of the cases of interstitial syphilis of the nervous system is there well marked lymphocytosis of the fluid. This yields to antisyphilitic treatment.

Parenchymatous Syphilis.—In dementia paralytica, tabo-paresis, and actively progressing tabes, both the serum and the fluid practically always give a strong positive reaction. In quiescent tabes both may give a negative reaction. In tabes a negative reaction is slightly more common for the serum than for the fluid, and the strength of the reaction is somewhat less than for dementia paralytica. A negative reaction both for the serum and the fluid practically excludes the latter disease. The spirochaetes, lodged as they are within the central nervous system, cannot be reached by the blood; hence treatment by mercury or iodide has no effect upon the Wassermann reaction either of the serum or the fluid. Salvarsan alone has little or no effect, but the intrathecal injections of salvarsanized serum causes a diminution, or even disappearance, of the reaction. This result is more easy to obtain in tabes than in dementia paralytica. The lymphocytosis is equally amenable to this form of treatment; salvarsan alone actually increases it.

The results of the intrathecal method in the cases of syphilis of the central nervous system are set forth below. Five of the patients are under my own care. I am able to include the other five through the courtesy of my colleagues, Dr. Frederick Palmer and Dr. Eric Macnamara, who have kindly placed them at my disposal. The list includes 8 cases of parenchymatous syphilis (5 cases of tabes, 2 of tabo-paresis, and 1 case of dementia paralytica), and 2 cases of interstitial syphilis.

Four Cases of Tabes which have had Two Series of Injections.

1. G. F., bricklayer (under Dr. Macnamara). The reaction of the cerebro-spinal fluid to the Wassermann and globulin tests was positive, both before and after injection. The lymphocytosis per c.mm. was 66 before and 25 after injection. *Symptoms and signs:* Return of knee-jerks; some very slight reaction to light in left pupil; Rombergism less; inco-ordination less; ataxia less; hypotonia of muscles less; no return of lightning pains; area of loss of sensation diminished. Before treatment the patient had marked incontinence of urine; he is now able to hold water 2½ hours. His general health is better; he has gained 12 lb. in weight, and has returned to work.

2. J. G., grocer (under Dr. Campbell). The cerebro-spinal fluid reacted positively both to the Wassermann and the globulin test, before injection, but negatively after. The lymphocytosis per c.mm. fell from 37 before treatment to 4 after. *Symptoms and signs:* Rombergism less; lightning pains better (one slight attack since treatment); subjective sensations better. Before treatment there was retention of urine; the catheter is not required now. The patient shows marked improvement in general health, and has gained 7 lb. in weight.

3. W. T., postman (under Dr. Palmer). Before treatment both Wassermann and globulin reactions were positive; after treatment both were negative. The leucocytosis per c.mm. fell from 80 before to 4 after treatment. *Symptoms and signs:* Rombergism less; no return of lightning pains; one attack of gastric crisis, much less severe; ataxia much less; vasti on left side felt to contract. There are no urinary symptoms. The patient's general health is better, and his weight shows an increase of 8 lb.

4. W. H., waiter (under Dr. Macnamara). Before treatment the cerebro-spinal fluid reacted positively to both the Wassermann and globulin tests; after treatment both tests showed a negative reaction (in the Wassermann test the cerebro-spinal fluid was blood-stained and there were many red cells). The lymphocytosis per c.mm., which was 8 before treatment, rose to 10 after. *Symptoms and signs:* Ataxia is less; no return of lightning pains; there is still marked inco-ordination. No urinary symptoms. The patient's general condition shows some improvement, and he has gained 6 lb. in weight.

One Case of Tabes, with Primary Optic Atrophy, which has had One Series of Injections.

M. W., clerk (under Dr. Campbell). The reaction of the cerebro-spinal fluid to the Wassermann and globulin tests was positive before treatment. The lymphocytosis was 144 per c.mm. Neither the tests nor the lymphocytosis have been retaken. *Symptoms and signs:* No alteration in vision; entire disappearance of lightning pains. There was slight retention of urine, which has improved under the treatment. The patient feels better in general health; he has not been weighed.

One Case of General Paralysis of the Insane (Advanced) which had had Three Series of Injections.

M. W. (under Dr. Campbell). Before treatment the reaction of the cerebro-spinal fluid was positive to both the Wassermann and globulin tests. After treatment the Wassermann test was weakly positive, and the globulin test negative. The lymphocytosis, which was 47 per c.mm. before treatment, fell to 26 per c.mm. The patient was at first taciturn and morose; he is now somewhat elated and has some memory for recent events. Weight not taken.

Two Cases of Tabo-Paresis which have had only One Series of Injections.

1. G. S., electrician (under Dr. Campbell). Both Wassermann and globulin tests positive before treatment. Lymphocytosis, 60 per c.mm. The cerebro-spinal fluid not tested since treatment. *Mental state:* Memory much improved; he now answers questions quickly. *Physical signs and symptoms:* Speech improved; inco-ordination better; ? left pupil reacts sluggishly; subjective sensations improved. His weight has increased by 10 lb. Has worked ever since he left hospital.

2. F. B., painter (under Dr. Macnamara). Wassermann and globulin tests positive before treatment. Lymphocytosis, 25 per c.mm. Cerebro-spinal fluid not yet retested. *Mental state:* His memory is better; he is more controllable. *Physical signs and symptoms:* Inco-ordination better; speech and writing improved. He has lost 3 lb. in weight, probably due to want of nourishment outside hospital.

Two Cases of Interstitial Syphilis; One Series of Injections.

1. N. G., costerhonger (under Dr. Campbell). Before treatment the Wassermann reaction was positive and the globulin reaction negative. Lymphocytosis, 35 per c.mm. Cerebro-spinal fluid not yet retested. *Physical signs and symptoms:* Ataxia and Rombergism much improved. *Urinary symptoms:* Retention greatly improved. The patient was not weighed.

2. J. S., carman (under Dr. Palmer). Wassermann and globulin tests both positive. Lymphocytosis, 29 per c.mm. Cerebro-spinal fluid not yet retested. The patient's mental condition has improved under treatment; the pains are much less.

It will be seen from the list of cases that improvement has occurred in many directions:

Cerebro-spinal Fluid.—Leucocytosis: There was a fall in all four cases in which a second examination was made; namely, from 66 to 25, from 36 to 4, from 80 to 4, from 46 to 26. Wassermann reaction: In three of the five cases in which a second examination was made a positive reaction was converted into a negative one; in one of the other two a strong positive one was converted into a weak positive. Globulin test: In four of the five cases in which globulin was tested for a positive reaction was converted into a negative one.

Weight.—In the first four cases (all tabetics) the weight rapidly went up by 12, 7, 8, and 6 lb. respectively. In one of the two tabo-paretic cases it increased by 10 lb.; in the other there was a loss of 3 lb.

Ataxia and Rombergism.—In all the cases in which these symptoms were present they showed a marked improvement.

Lightning Pains.—These when present were exaggerated for the first twelve hours or so after the intrathecal injection. Thereafter they disappeared. In one case they reappeared, but disappeared after the second injection.

Knee-jerks.—In one of Dr. Macnamara's cases the lost knee-jerks not only returned but in an exaggerated degree. In another case, though the jerks did not return, the quadriceps could be felt to contract.

Urinary Symptoms.—In all cases in which these were present they showed improvement.

General Health.—Nearly all the patients expressed themselves as feeling much better as the result of the treatment. This improvement in the general health has, indeed, been one of the most striking results of the treatment.

While it would be impossible wholly to eliminate the influence of suggestion in bringing about some of the improvement referred to (for example, the diminution of the ataxia, lightning pains, and urinary disturbances), other effects of the treatment (for example, the rapid increase of weight,* the return of the lost knee-jerks, and the marked changes for the better in the cerebro-spinal fluid) obviously cannot be placed to its credit.

CONCLUSIONS.

In parenchymatous syphilis the intrathecal treatment is the only one yet devised which is capable of arresting the morbid process. It acts by destroying the spirochaetes within the central nervous system and the cerebro-spinal fluid. The treatment should be begun as early as possible. Neurons, once destroyed, are incapable of regeneration. Unfortunately, cases of general paralysis and tabes rarely come before us until wide tracts of nervous tissue have been irretrievably damaged.

The intrathecal treatment is also indicated in cases of interstitial syphilis, especially of the spinal cord, which do not readily respond to salvarsan, mercury, or iodide of potassium. The latter drug should be given in not less than drachm doses three or even four times daily.

All the details in connexion with the injections were supervised and carried out by Mr. H. E. Batten, and to his unremitting care the entire absence of any kind of complication is to be attributed. To him I am also indebted for careful notes of the cases. The examination of the blood and cerebro-spinal fluid were undertaken by Dr. Braxton Hicks with his accustomed care and skill.

NOTE.—Since this paper was written Mr. Ballance has treated two of my patients suffering from general paralysis by introducing salvarsanized serum intracranially. The operation was well borne, and both patients made a speedy recovery. It is yet too early to speak positively of the therapeutic result, though the indications, in one of the cases at least, are distinctly hopeful.

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SOME PROBLEMS IN THE TREATMENT OF VENEREAL DISEASES.†

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THE problem of the treatment of venereal diseases is at present creating a considerable amount of interest in the medical profession, more especially from the standpoint of the relationship of these diseases to the general health of the community. In the light of modern research it has been shown that they are far-reaching in their consequences, and are more prevalent than was hitherto supposed. By means of laboratory tests it has been found that many diseases of obscure origin are now traced to the incidence of venereal disease either in the individual himself or in his parents before him. It is a subject which is closely related to such questions as infant mortality, care of the blind and insane, the maintenance of mentally defectives, and the treatment of patients under the Poor Law administration. If so much evil arises from the transmission of venereal diseases as we are led to believe, and if they influence the creation of the unfit, then it is the duty of the State to attack the source and take measures leading to eradication if possible. Such measures in time will be found to lessen the present financial expenditure

upon institutions for the reception of mental and moral degenerates. Eradication of venereal diseases, or even a certain degree of control over their dissemination, would cause a considerable diminution in the numbers of those blinded by ophthalmia neonatorum, and those mental defectives who go to swell our pauper and criminal classes. One could almost have wished that the Royal Commission had not been appointed until some time later, when, as the result of further investigation, the evidence of the prevalence of venereal diseases, more especially among the poorer classes, would have been so overwhelming that the public itself would have awakened up to a sense of the dangers and the necessity for some measures of reform.

NOTIFICATION.

In the discussion of methods for prevention and treatment the most prominent question is that of notification. It is argued that if this measure has done so much for the control of other contagious diseases, why should it not be employed successfully with regard to venereal diseases? Two arguments against notification to the public health authority may be mentioned. The first is that the length of time taken for the treatment and cure of syphilis would be out of all proportion to that required for the treatment of other diseases—such as diphtheria or scarlet fever—and would necessitate a very great expenditure on the part of the State, and a loss of the wage-earning capacity of the individual under treatment. This argument has much in its favour, but when compared with tuberculosis it is unfounded, although the latter disease having a more direct influence upon the shortening of life appeals for more active measures for its treatment. The second reason against notification is that it conveys with it a moral stigma, and brands the individual as an outcast from the society of his family and friends. It is admitted by all that private interest must give way to public safety, but if the history of many patients suffering from venereal disease were known, the punishment seems out of all proportion to the transgression, which has been committed in so many cases through ignorance, or under the influence of strong temptation; not to mention those cases of the innocent victims of disease, hereditary or acquired. Even if notification on the usual lines were enforced, evasions would be so numerous that the ends of the measure would be entirely defeated. In private practice, more especially, many conditions suggesting the presence of venereal disease would be purposely ignored, and cases requiring skilled advice and treatment would seek relief at the hands of unqualified persons who at least were free from the duties of a moral policeman. Notification in a modified form, however, is necessary if we are going to cope with these diseases in any efficient manner. We must have an estimate as to their prevalence and suitable measures for prevention will follow. Our information as to the amount of venereal diseases in the community is at present confined to the publication of clinical records of groups of cases, and to investigations as to the origin of certain clinical manifestations by means of bacteriological and serological methods. These, however, as a rule apply to the hospital class of patient, and not to private practice. Statements in the lay press as to the percentage of the general community having acquired venereal disease are entirely without any scientific or accurate basis, as any numbers estimated hitherto by the medical profession are in the form of ratios to those suffering from other pathological conditions, and not to average healthy individuals. The majority of statistics so given are supplied from patients of the hospital or lower classes, among whom, for obvious reasons, the percentage is greater. We want much more work on the lines of that published by Dr. Carl Browning.¹

Statistics as to the returns on death certificates are utterly worthless and their discussion a waste of time. As long as the certificate is public property and not a confidential document, the medical attendant will endeavour to allocate the cause of death to some other source when possible. It will ever be *De mortuis nil nisi bonum*. The medical profession is the only one for the supervision and treatment of venereal diseases; it is in close confidential relationship with the community, and to it should be entrusted all measures of notification and

* The difficulty of getting tabetics to put on weight is well known.

† Read at the Scottish Nursing Conference.