ROUTINE EXAMINATION OF THE CEREBRO-SPINAL FLUID IN SYPHILIS:

ITS VALUE IN REGARD TO MORE ACCURATE KNOWLEDGE, PROGNOSIS, AND TREATMENT.*

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TO-DAY we know that dissemination of the organism takes place very rapidly after inoculation in syphilis. The first appreciation of this fact would appear to date from the realization that total excision of the early chancre does not abort the infection, as, for instance, in the case of the "malignant pustule" in anthrax. More recent experimenters have proved the presence of spirochaemes in the neighbouring lymph glands in rabbits in but half an hour following the cutaneous infection, and further, others claim to have obtained the organism from the cerebro-spinal fluid in the primary stages of syphilis in man.

The pathologists have provided us with a combination of most sensitive and accurate tests which can be applied to the cerebro-spinal fluid, by means of which we are enabled to detect the earliest evidence that the invasion has reached the central nervous system. Prior to this clinicians were dependent wholly upon the exhibition of signs and symptoms in a patient resulting from neural dysfunction—often irreparable—before such diagnosis could be arrived at.

Upon this early recognition of central nervous system involvement in syphilis depends so much with regard to subsequent management of the case and the prognosis from a neurological point of view. The examination of the cerebro-spinal fluid in syphilis, therefore, is imperative, and should be carried out as a routine in every up-to-date clinic.

In the earlier part of 1916, whilst in charge of the syphilis cases at Rochester Row Military Hospital, it occurred to me that with so much material at hand there was a good opportunity to carry out an investigation upon the cerebro-spinal fluid in syphilis in general. It was thereupon decided in future to examine the cerebro-spinal fluid prior to treatment in every patient. This was done, with the following results.

Primary Syphilis.

The number of cases of primary syphilis examined was 283. They comprised:

(a) Cases with negative blood Wassermann reaction	147
Number of these with pathological cerebro-spinal fluid	7 = 4.76%
(b) Cases with positive blood Wassermann reaction	136
Number of these with pathological cerebro-spinal fluid	18 = 13.23%
Total number of pathological cerebro-spinal fluids...	25 = 8.83%

Secondary Cases.

The number of secondary cases examined was 768. They consisted of:

(a) Previously untreated cases	559
Number of these with pathological cerebro-spinal fluid	178 = 31.8%
(b) Cases previously treated, showing relapse of blood Wassermann reaction within two years, with no clinical signs	62
Number of these with pathological cerebro-spinal fluid	27 = 43.5%
(c) Previously treated cases exhibiting clinical relapses of a "secondary" nature	147
Number of these with pathological cerebro-spinal fluid	69 = 46.9%
Total number of pathological cerebro-spinal fluids	274 = 35.4%

If we add the primary and secondary cases together we have a total of 1,051, in which were found 299 abnormal cerebro-spinal fluids (28.35 per cent.).

Extragenital Infections.

In view of the supposition that there is a high incidence of central nervous involvement following upon extragenital chancres, more especially with regard to those situated in close proximity to the brain, an analysis of the findings in these cases is given. With regard to the theory that direct invasion of the central nervous system might possibly take place by way of the perineural lymph

channels, in these cases the distance to be traversed by the organism would be comparatively short.

The number of cases with extragenital infections examined was 35; the *Spirochaeta pallidum* was detected in every chancre.

Of 29 secondary cases (advanced) the cerebro-spinal fluid was affected in	3 = 10.3%
Of the total 35 cases the cerebro-spinal fluid was affected in	4 = 11.4%

Taking into consideration the advanced stage to which the infection has progressed prior to examination, as is the rule unfortunately with these cases, one certainly would say, judging from this series, that the percentage of changes in the cerebro-spinal fluid is below the average found with genital infections of the same duration.

Tertiary Cases.

The total number of tertiary cases examined was 463. They comprised:

(a) Cases exhibiting active gummatous lesions	330
Number of these with pathological cerebro-spinal fluid	106 = 32.1%
(b) Cases with positive blood Wassermann reaction in which no active gummatous processes could be discovered	133
Number of these with pathological cerebro-spinal fluid	41 = 30.8%
Total number of pathological cerebro-spinal fluids...	147 = 31.7%

Congenital Syphilis.

The total number of cases (adults) examined was 87, of which 23 (26.3 per cent.) were found to have abnormal cerebro-spinal fluids. It must be pointed out that all these cases are from amongst men who had been passed for military service, and therefore the figures only apply to such cases as had escaped or survived some of the grosser stigmata associated with the congenital type of infection. Their ages ranged from 18 to 45 years. As might be expected, the large majority were cases of interstitial keratitis, of which there were 72, amongst which 14 (19.4 per cent.) were found with cerebro-spinal fluid changes.

Neurosyphilis.

The neurological cases investigated numbered 166, and the effect of various types of treatment was estimated by frequent clinical and pathological examinations.

With the evidence provided by the foregoing investigation, so amply supported by the findings of others, there can be no longer any question as to the absolute necessity of routine examinations of the cerebro-spinal fluid at all stages of the infection in syphilis. That the first attendance of a patient at a clinic should be accompanied by a minimum of discomfort, in order that an accurate diagnosis will be followed by a willing and regular attendance, is essential.

With this aim in view it might be urged that in the instance of the early case the performance of a lumbar puncture following upon scraping of the chancre, possible gland puncture, taking of the blood specimen for the Wassermann test, intravenous injection of arsenobenzol, deep subcutaneous or intramuscular injection of bismuth or mercury *plus* massage, might be calculated to increase the incidence of treatment defaulters. Here the personal equation, both in the surgeon and the patient, is a very important factor; an intelligent sympathy combined with gentle and careful technique in the former but seldom fails in engendering confidence and appreciation in the latter. It is wise to keep the patient in bed for the lumbar puncture, and for the ensuing twelve hours under aspirin and bromides. Unfortunately there is known, as yet, no infallible measure of eliminating that "bugbear" the reactionary headache; we can only lessen its incidence. Happily it is of the rarest occurrence in patients with grossly pathological fluids, and these are the cases in which frequent repetitions of spinal puncture are necessary.

If a patient is to be excused a lumbar puncture it is perhaps at the first attendance of the *primary* case that this might be permitted, but in such instances never should this examination be omitted at the termination of the initial course of treatment—that is to say, in the rest interval following upon the first ten to twelve arsenobenzol injections and their supplementary mercury or bismuth treatment. The subsequent progress of the untreated *primary* case with a pathological fluid should receive special scrutiny in this respect, and is one calling for somewhat more intensive early treatment than a similar case with a normal fluid at the onset. At all later stages of the infection an examination of the fluid should be insisted upon prior to drawing up the scheme of treatment.

* A paper introducing a discussion in the Section of Venereal Diseases at the Annual Meeting of the British Medical Association, Edinburgh, 1927.

	Blood Wassermann Reaction.	Cerebro-spinal Fluid.	Inferences.
Type (a)	Negative	Normal	The infection is well under subjection, and residual foci, if any, are inactive. Prognosis good.
Type (b)	Positive	Normal	Residual foci in general tissues as opposed to the parenchyma of the central nervous system, but early vascular lesions are not excluded. Prognosis good.
Type (c)	Positive ++	Wassermann reaction ++, ++, ++, ++, or +-, -- Cells 50 to 250 or more Globulin ++ Lange "luetic curve"	Points to active meningeal involvement. Prolonged and intensive treatment to be resumed at once, but commencing cautiously to avoid Herxheimer's reaction, "zipping" of cranial nerves, haemorrhagic encephalitis, etc. This is the type which in the absence of, or delay in "follow-on" treatment will develop "neuro-recidives." Subsequent cerebro-spinal fluid examination, after the meningo-vascular element is eradicated, will reveal the presence of possible coexisting parenchymatous involvement, though rare. With thorough treatment the prognosis is good.
Type (d)	Positive, but may be occasionally negative	Wassermann reaction ++, ++, +-, --, or ++, ++ Cells 10 to 50 Globulin ± to + Lange "paretic curve"	Should be regarded as strongly suspicious of parenchymatous involvement of the central nervous system, and repeated cerebro-spinal fluid examination at three-monthly intervals whilst under continuous treatment is imperative, combined with careful clinical neurological investigations. More especially is the prognosis bad if an initial examination of the cerebro-spinal fluid prior to treatment revealed early changes. Prognosis: general paralysis of the insane and tabes are frequent in this group.
Type (e)	Positive	Wassermann reaction ++, +-, -- Cells 5 to 20 Globulin ± or absent Lange "luetic" or <i>nil</i>	Suggests residual foci in general tissues, <i>plus</i> meningo-vascular involvement of central nervous system—the meningeal factor slight or under subjection. Will probably show normal fluid after further treatment. In the absence of such is a likely candidate for cerebral endarteritis (hemiplegia, gummata, etc.).

In my opinion the most critical epoch in the career of a syphilitic is this period at the termination of the initial course of treatment, for, in the light of our present knowledge, not until now are we enabled to "gauge" with some degree of accuracy the "depth of penetration" of the invasion by its response to treatment. In fact, this first course of treatment should be regarded in the nature of a "therapeutic test," and should therefore be "standardized" to consist of the administration of not less than 4 grams of salvarsan (or the equivalent of neo-salvarsan) *plus* bismuth and mercury over a period not exceeding fourteen weeks.

It is now that an examination of the cerebro-spinal fluid, read in conjunction with the blood Wassermann reaction, affords such valuable information, and should be made six weeks after the cessation of the initial course of treatment, and prior to resumption. (During the first four weeks of this "rest period" the patient is usually given iodides.) The accompanying table may be found useful as a rough guide as to the significance of certain types of fluids met with at this stage as regards diagnosis, prognosis, and future treatment.

What importance should be placed upon these findings in the cerebro-spinal fluid in deciding upon the subsequent management of the case?

Type (a).

Provided that sound treatment is continued for a minimum further two years, in the absence of any pathological findings it should yield 100 per cent. cures. The cerebro-spinal fluid should be examined at the end of the first, second, third, and fifth years.

Type (b).

As above, excepting that the "two years" should date from the time that the blood Wassermann reaction was rendered negative. Several workers have noted that a normal fluid at this period is a very good omen that the central nervous system will not develop evidence of involvement subsequently.

Schmidt investigated, in after-years, 155 cases in which at the initial examination the cerebro-spinal fluid was normal prior to treatment, or had been found to be negative five years after the termination of treatment. In those cases tested the cerebro-spinal fluid was found to be still negative. Wild and Marshall stated that in several thousand cases in which lumbar puncture was performed a positive fluid was found in only three cases which had previously been found negative. Moore and Kemp consider that the evidence gained by the repeated routine spinal punctures in a series of 54 patients justifies a general statement that in early syphilis, if the cerebro-spinal fluid is normal after six months' treatment, the patient will not develop clinical neurosyphilis, nor a positive fluid, unless a second dissemination of the organism is permitted to

take place, as evidenced clinically by recurrent secondary syphilides or a blood Wassermann relapse. Fordyce has stated that if the cerebro-spinal fluid is once found to be normal after treatment the probability is that the central nervous system will not be affected subsequently.

Type (c).

Changes as gross as those to be found only six weeks after cessation of arsenobenzol therapy would indicate severe meningeal invasion such as is more likely to be experienced after a longer rest from treatment. Moore and Kemp found the average time interval between the day of the last treatment and the onset of neuro-recurrences in 27 such cases to be 2.1 months. Kemp and Chesney reported a case in which syphilitic meningitis of the neuro-recidive type developed four months after cessation of treatment, which had been commenced in the primary sero-negative stage. Three cubic centimetres of the cerebro-spinal fluid (which was positive to all tests) was inoculated into a rabbit's testicle. Approximately sixty-eight days later the animal developed an orchitis, in which numerous *Sp. pallida* were demonstrated fourteen days afterwards.

Such relapses were seen far more frequently in the early days of arsenobenzol therapy when the dosage was what we know now to be very inadequate—in fact dangerous—in that it was usually sufficient to inhibit the natural output of antibody by effecting a temporary suppression of spirochaemes. Thus when residual "nests" of the organism awoke to renewed activity—whether situated in the meninges or elsewhere—they did so, as it were, upon virgin soil, just as in the secondary stage of the untreated case; in fact it seems possible that a second dissemination could take place. It is by means of the early recognition of meningeal involvement by routine examination of the cerebro-spinal fluid during this pre-symptomatic period that we are enabled entirely to prevent, by immediate resumption of treatment, the development of such evidences of gross inefficiency as cranial palsies, etc. In the type under discussion it is certain that the "protective mechanism" of the central nervous system has been called into action, and it is only by subsequent examination of the cerebro-spinal fluid, after the meningo-vascular element has been cleared up by treatment, that its efficacy in protecting the parenchyma is revealed.

The prognosis, assuming that the condition is recognized in the asymptomatic stage whereby prompt and intensive treatment can be cautiously resumed, is good. If irreparable damage has been caused prior to the resumption of treatment the processes can be arrested with perseverance, but permanent dysfunction will persist in proportion to the extent of neural destruction. Routine examination of the cerebro-spinal fluid should render impossible the development of any such disabilities. It is recognized by all that the case which relapses once is very prone to exhibit subsequent recurrences.

Type (d).

The importance of the early recognition of this type cannot be overestimated as regards diagnosis, treatment, and prognosis. It is in this group, perhaps more than in any of the others, that the findings at the initial pre-treatment examination of the cerebro-spinal fluid convey most. Should the first examination have revealed early changes, which under the "test" course of treatment have progressed as indicated, the presumptive evidence of parenchymatous involvement of the central nervous system is very strong.

With this evidence before us some workers go so far as to state that we are no longer justified in continuing treatment along the lines of the ordinarily accepted schemes of intravenous or deep-subcutaneous arsenobenzol therapy, whereby valuable time is allowed to elapse, during which the progress of the parenchymatous invasion is not materially checked. They urge that, at once, more drastic procedures should be employed. Bunker advocated the following four lines of therapy should the positive Wassermann reaction and paretic gold curve be present in the cerebro-spinal fluid after the initial course of treatment:

1. Intraspinal injections by Swift-Ellis technique at short intervals.
2. As above, supplemented by intra-cisternal injections.
3. Thorough trial of trypanamide.
4. Treatment with malaria.

He feels that two weeks given over to malaria in these "pernicious" cases may be worth several months under the other schemes of treatment, with which the malaria can be immediately supplemented. Kyrle of the Vienna school advocates an earlier exhibition of the malarial treatment in those cases of syphilis with resistant serological or cerebro-spinal fluid findings, rather than reserving it, as hitherto, for the proclaimed tabetic or paretic. Any treatment which has been proved capable of rendering normal the cerebro-spinal fluid in a general paretic should be given *at this period* to the type of case under discussion. Massive doses of silver-salvarsan intravenously, accompanied by sulfarsenol deep-subcutaneously, *plus* spinal drainage, has been spoken well of by Harrison in this respect in an advanced paretic.

Type (e).

Early recognition of the cases coming within this category is second in importance only to that of the preceding group, because, in the event of the immediate resumption of treatment which is hereby indicated, the prognosis in the great majority is good. On the other hand, in the absence of such resumption or where a protracted rest interval is followed by inadequate supplementary courses of treatment, the clinical disasters resulting from endarteritis of the central nervous system are of an alarming nature. The "plegias" always leave in their wake a varying degree of permanent damage, no matter how efficiently the case is treated after the onset of such. In the syphilitic who is willing to remain under prolonged observation, during which the blood Wassermann reaction and cerebro-spinal fluid are tested at regular intervals, endarteritis of the cerebral, spinal, or, in fact, any vessels, should never be allowed to progress unsuspected in the absence of treatment.

Possessed as we are to-day of modern improvements in specific therapy and the delicate tests for controlling the response of an infection to such, the development of, say, hemiplegia in a known syphilitic is to be regarded as the fault of the doctor or the patient—perhaps both—but not the disease. The findings in the cerebro-spinal fluid as indicated in this group might equally well occur with an early mild meningeal involvement, or one which has been partially cleared up by the initial course of treatment.

It matters nothing, however, whether it is the meninges or the vessels which are principally involved at this stage; what is of paramount importance is the immediate necessity for the resumption of treatment. Re-examination and comparison of the findings in the cerebro-spinal fluid after each "follow-on" course of treatment will provide most

valuable data in assessing the accessibility of the spirochaemes in a particular infection. Upon these findings everything will depend in deciding the subsequent management of the case.

The Importance to be placed upon the Various Tests and their Significance.

Lange Colloidal Gold Reaction.—Although the results obtained from its employment are not recorded by me in the series of cases mentioned, this test was used in all of the frankly neurological cases and, subsequently, to assess progress in the majority of those other cases in which a grossly pathological fluid was discovered at the first examination. The utmost care in the preparation of the colloidal gold solution and the cleansing of the glass utensils has a very important bearing upon the "readings" obtained with the test. From my clinical observations over the past ten years of the progress of a considerable number of neurosyphilitics, I am firmly convinced that a strong paretic curve, accompanied by a persistent positive Wassermann reaction in the cerebro-spinal fluid, is to be regarded as of the gravest prognostic significance. Miller and his collaborators found, upon examining the cerebro-spinal fluid from 252 cases composed of paretics, tabetics, and of cerebro-spinal syphilis, that the Lange reaction was invariably positive when the Wassermann test was positive, and in 4 cases was positive when the Wassermann test was negative. Wrendt considers its sensitiveness one of the main advantages of the colloidal gold test, in that it may indicate the necessity for further treatment when all other tests are negative. He also regards an early strongly paretic type of reaction in syphilis as an omen for a bad prognosis. Hunt believes that the "gold-sol," next to the cell count, is the most important of the four main tests supplied by the cerebro-spinal fluid, and in his experience has proved that most sensitive and delicate. It is both of diagnostic and prognostic value; it forecasts the future development of the disease more than any other laboratory measure. The gold curve, he considers, can be used as a guide, and with its first tendency to simulate the curve of paresis the malarial treatment could be instituted.

The Wassermann Reaction in the Cerebro-spinal Fluid.—It is infrequent to find a positive reaction in the cerebro-spinal fluid in the *primary* stages, and then only with two volumes of fluid, more rarely with one volume. In none of the primary cases in my series did it occur with the smallest amount of fluid. In the *secondary* cases one more frequently meets with stronger reactions, especially in the "relapse" cases. Amongst these the "meningo-" or "neuro-recidive" cases, in conjunction with a high cell count and excess of globulin, the Wassermann test may show ++ throughout the four dilutions. It is in this type that the Wassermann reaction in the cerebro-spinal fluid is most easily influenced by treatment, but may remain refractory with two volumes of fluid for a long time after the cells and globulin have disappeared. In later cerebral syphilis of the meningo-vascular type much the same conditions in the fluid commonly exist. Of all syphilitic conditions the Wassermann reaction is most constantly strongly positive in the cerebro-spinal fluid in general paresis, and also the most difficult to influence by treatment. In tabes it is somewhat more responsive, and especially is one liable to be too optimistic in the earlier part of treatment when the coexisting meningo-vascular element is being brought under subjection, as evidenced by the decrease in cells and globulin, and possibly the Wassermann reaction to a less degree. Eventually, however, a stage is reached when the Wassermann reaction remains rigidly positive with two volumes and with one volume of fluid, with the cells swinging between 5 and 15 per c.mm., which one feels to be representative of the true residual parenchymatous involvement. A persistent positive Wassermann reaction in the cerebro-spinal fluid after the initial course of treatment in the early, or, in fact, any stage of syphilis, should always be regarded as an absolute indication for prolonged and intensive continuation treatment, controlled by re-examinations of the cerebro-spinal fluid at regular intervals, at which the

Lange test is never omitted. I regard a positive Wassermann in the cerebro-spinal fluid as an indication of the existence of spirochetes within the central nervous system, and cannot accept Dujardin's theory that the Wassermann substance is not formed within the central nervous system, its presence in the cerebro-spinal fluid being dependent upon the permeability of the capillary walls to permit of its passage from the blood into the perivascular lymph spaces or not. We frequently meet with a positive Wassermann reaction in the cerebro-spinal fluid accompanied by a negative in the blood, a condition which can exist for many months and remain constant in spite of exhaustive spinal drainage up to 80 or 100 c.cm. twice weekly. Moreover, the organism has been proved to exist in the cerebro-spinal fluid, and interstitial and parenchymatous central nervous tissues.

Cells and Globulin.

"There is never smoke without fire," and in syphilis the cells and globulin in the cerebro-spinal fluid might be regarded as fairly reliable indicators of the intensity of the inflammatory meningeal blaze; thus in syphilis a severe involvement of the meninges is responsible for a gross excess in each, as with other infections. An increase in cells of from 5 to 10 was the most frequent first change to appear in the cerebro-spinal fluid of the primary cases previously described, the excess in globulin coming next, with a positive Wassermann reaction rare in comparison, and then usually accompanied by a pleocytosis. The detection, therefore, of an excess in cells or globulin in the cerebro-spinal fluid is invaluable in furnishing the first evidence of central nervous involvement in syphilis in order that treatment can be planned accordingly and its efficacy judged by subsequent examinations of the cerebro-spinal fluid. Some observers have found an invariable increase in pressure in fluids showing this early pleocytosis.

Should a cell count of, say, 8 to 15 be returned, after the initial course of treatment, as the only abnormality, I consider it to be an indication to push treatment, but would regard a solitary slight excess of globulin as of less importance, since it can persist over very long periods in cases which, by prolonged observation, have been proved subsequently to do well.

Since the methods are so simple it is better in the routine examination for globulin always to employ both the Pandey and Nonne-Apelt methods, for, as Greenfield and Carmichael point out, whereas a trace of globulin might be detected by the one, a negative with the other test would prove it to be within the normal limit.

Some General Views Expressed by Various Investigators.

O'Leary, Paul, and Nelson call attention to the fact that neurosyphilis may progress clinically in the presence of completely negative cerebro-spinal fluid findings. They found that continued treatment after the cerebro-spinal fluid has become negative is productive of 70 per cent. of clinical benefit, and 45 per cent. in those whose fluids returned to normal without treatment. They conclude that yearly investigations of the cerebro-spinal fluid *plus* clinical examinations should be made in all neurosyphilitics whose fluids have become normal, with or without treatment.

Bunker asserts that the purely clinical differentiation between the meningo-vascular and parenchymatous forms of neurosyphilis not only often presents considerable difficulty, but is, in fact, sometimes quite impossible during life. It matters but little what label one may elect to apply—meningo-vascular or parenchymatous, mesodermal or ectodermal; what, however, is of paramount importance is whether the treatment is proving efficient in a given case of neurosyphilis regardless of such label. This can only be judged by the definite and progressive influence exerted upon the positive findings in the cerebro-spinal fluid. This evidence cannot be obtained without repeated examination of the cerebro-spinal fluid as treatment progresses. A single examination of the cerebro-spinal fluid he regards as of about as much value as a single temperature reading in any acute infection. He points out how misleading and of what little value symptomatic amelioration may be in the absence of concomitant improvement in the cerebro-spinal fluid.

Fordyce pointed out that the signs and symptoms of involvement of the nervous system in the early months are sometimes absent or are so indefinite as to be easily overlooked. If lumbar puncture is limited to the cases with obtrusive signs irreparable damage may result—a low-grade parenchymatous encephalitis, with slight or no meningeal involvement, may exist for years with indefinite symptoms impossible to classify or interpret without the aid of spinal fluid tests. The absence of the paretic gold-sol curve in the majority of cases definitely excludes paresis. Cerebral meningo-vascular syphilis and general paralysis may give identical findings in the cerebro-spinal fluid and present very similar clinical pictures. The persistence of a strongly positive Wassermann reaction in the high dilutions with a paretic gold curve after intensive and prolonged treatment is the only practical way of differentiating these closely related clinical conditions. He and his co-worker (Rosen) had yet to detect a recurrence in an early case of neurosyphilis which had been discharged with a negative cerebro-spinal fluid after adequate treatment, or to observe a late infection of the fluid in one shown to be normal in the first two years of the disease. He considered that if the nervous system is not involved in the early period of the infection it is extremely improbable that it will be at a later date; vascular lesions and gummata being excepted. Certain types of neurosyphilis, including the purely vascular, the gumma unaccompanied by a meningitis, some unusual psychoses, and epilepsy of luetic origin, are often found with little or no change in the cerebro-spinal fluid. These exceptional conditions in no way alter the general rule that the cerebro-spinal fluid reflects the pathological process in the brain and cord.

Mott considered it probable that the cases in which the cerebro-spinal fluid remains positive after prolonged treatment are those which subsequently (average ten years after primary infection) develop tabes and general paresis. There is hardly any organic disease of the nervous system which may not be simulated by syphilitic disease, but, he added, it must be remembered that functional diseases may occur in syphilitic subjects. Neurasthenia *plus* syphilophobia, on account of the venereal disease propaganda, is frequently met with at the present time. (Another strong indication of the value of cerebro-spinal fluid examination.)

In a paper upon the diagnosis and treatment of neurosyphilis Hunt makes the following very sound observations. "The most successful diagnostician of all is he who has the clinical reports in his right hand, those from the laboratory in his left hand, and the patient in front of him." The reason for erroneous diagnosis and for unrecognized neurosyphilis is largely the fault of the physician; "it arises from his unwillingness to do a lumbar puncture." And again: "No neurological diagnosis should ever be made until syphilis has been eliminated by an examination of the cerebro-spinal fluid, and no diagnosis of neurosyphilis ought to be accepted until the cerebro-spinal fluid has been examined." In the vast majority of cases he considers that this one test will settle the question.

Conclusions.

1. Routine examination of the cerebro-spinal fluid is absolutely essential in the management of syphilis.
2. The cerebro-spinal fluid furnishes the earliest and most accurate indications governing diagnosis, treatment, and prognosis.
3. In the primary stage it is an advantage, in the later stages imperative, to know the condition of the cerebro-spinal fluid prior to the commencement of treatment.
4. The cerebro-spinal fluid should be re-examined after a period not exceeding six weeks from the cessation of the initial course of treatment, such "standardized" course of treatment to be regarded in the nature of a "therapeutic test."
5. In the earlier cases this is the most critical period in the management of the infection, since it is now that the cerebro-spinal fluid might provide possibly the first and only evidence to indicate invasion of the central nervous system, and within broad limits the depth of such invasion when present.
6. The warning obtained from routine cerebro-spinal

fluid examination at this period should prevent entirely the subsequent development of meningeal relapses, and their sequelae.

7. A positive Wassermann reaction in the cerebro-spinal fluid (especially if such existed prior to this initial course of treatment) accompanied by a paretic Lange curve is strong presumptive evidence of parenchymatous involvement of the central nervous system at this stage. Revised intensive schemes of treatment should be instituted forthwith for its eradication, by which much valuable time may be saved.

8. In every early case treated *ab initio* subsequent examination of the cerebro-spinal fluid should be made, accompanied by the blood Wassermann test at the termination of the first, second, third, and fifth year. Concurrent treatment and subsequent management to be controlled thereby.

9. All cases presenting a persistent positive blood Wassermann reaction, no matter at what stage of the infection the patient first comes under observation, should have the cerebro-spinal fluid investigated, accompanied by a careful neurological examination. The disasters attendant upon cerebral and spinal endarteritis would be anticipated thereby and entirely prevented by adequate treatment.

10. A routine blood Wassermann test should be made upon every patient at all medical institutions, irrespective of the nature of the complaint, and when found to be positive an investigation of the cerebro-spinal fluid should follow.

11. Once the cerebro-spinal fluid has been found to be pathological in a syphilitic case, subsequent examination of the fluid is imperative for many years after it has been rendered normal.

12. Especially are regular re-examinations indicated in those cases which have once relapsed, and in proclaimed cases of neurosyphilis after the fluid has become normal. The old aphorism, "Once a neurosyphilitic always a neurosyphilitic," must never be regarded lightly.

13. Neurosyphilis—more especially of the vascular type—can progress clinically in the presence of negative findings in the cerebro-spinal fluid, yet it can be much benefited by specific treatment. Much valuable assistance, therefore, is to be obtained from the skilled neurologist in assessing progress in such cases, and should always be sought.

14. The earlier treatment is commenced in the infection the greater the chance of preventing syphilitic involvement of the central nervous system; the earlier the recognition of such, should it have occurred, the greater the possibility of preventing the invasion of the parenchyma.

15. No patient with a history of syphilis should be given permission to marry without an examination of the cerebro-spinal fluid.

DISCUSSION.

Dr. G. RIDDOCH (London) said that a balance had to be struck between positive pathological changes in the cerebro-spinal fluid and negative clinical findings. If, after the initial six weeks' course of treatment, there were such pathological changes the patient should be treated for the rest of his or her life, or, at any rate, should be kept under periodic inspection. It might be asked whether a patient in whom the cerebro-spinal fluid had become negative after having once been positive was safe after five years had elapsed; the answer must be in the negative, for he might get tabes with an apparently normal cerebro-spinal fluid. It must be remembered that it was the business of the physician to treat human patients and not positive Wassermann reactions. Moreover, the remedies employed were poisonous, and it was possible to overdo antisyphilitic therapy. Severe headaches were liable to follow lumbar punctures, and one such might make a patient rebel against any further examination; hence it was important to take every precaution, one of the essentials being the use of a fine needle.

Dr. D. K. HENDERSON (Glasgow) thought that routine examination of the cerebro-spinal fluid was open to serious objection because in not a few cases the after-effects were serious. In his opinion it was essential that the patient should be kept in bed for at least twenty-four hours after

the puncture. The early diagnosis of parenchymatous syphilis was impossible, because patients with only the slightest clinical signs might present advanced pathological changes in the cerebro-spinal fluid. It often happened that the earliest cases, and consequently the most promising, turned out the most disappointing in treatment, while others who came under observation comparatively late did relatively well. There also occurred cases of tabes and general paralysis which showed no apparent pathological change in the cerebro-spinal fluid. He considered that no patient who had had general paralysis, even if supposed to be cured, should ever be allowed to hold a position of responsibility.

Dr. J. G. GREENFIELD (London) described several tests for the cerebro-spinal fluid in neurosyphilis, and said that the Kahn test was very fairly comparable with the Wassermann test, but it was sometimes weakly positive when the latter was negative. The test of Boltz was almost specific for general paralysis. Other tests recommended were those of Kafka, which corresponded with Lange's test, and Wu's colorimetric estimation of protein for estimating the actual quantity of protein present in the cerebro-spinal fluid. General paralysis was the only condition in which the globulin approached the albumin in quantity in the cerebro-spinal fluid. The Wassermann body was probably formed in the meninges, but this could not be considered proved. The persistence of a positive Wassermann reaction in the cerebro-spinal fluid was the strongest proof that the patient was suffering from general paralysis, not cerebro-spinal syphilis.

Colonel L. W. HARRISON (London) called attention to the fact that the term "spironeme" had now been disowned by its sponsor, Mr. Clifford Dobell. A compromise might possibly be found by testing the cerebro-spinal fluid for the first time in cases selected according to their behaviour to the first course of treatment. He had found at St. Thomas's Hospital that cases which were still sero-positive at the end of their first course of treatment remained so for numerous subsequent courses; in many of these the cerebro-spinal fluid was persistently positive. On the other hand, he had not found a single positive cerebro-spinal fluid in a case with a negative blood reaction at the end of the first course of treatment. He thought, therefore, that only those patients with a positive blood reaction at the end of the first or second course of treatment need have the cerebro-spinal fluid investigated, though it should be examined in all cases before discharge from treatment. Some means ought to be found for making the tissues of these non-responsive cases react better. Very little work had been done on the subject, but Major Pettit had reported some time ago that at Rochester Row an unresponsive early case had been made responsive by the administration of thyroid extract. By this means or by protein shock therapy something might be done to change the outlook. He was convinced that the employment of arsenobenzol simultaneously with another metal was followed by a much smaller incidence of nerve palsies than when arsenobenzol was given alone or was followed subsequently by a course of mercury or bismuth. In his own clinic, where the combined method was used, there had not been a single case of a cranial palsy, while at Johns Hopkins, where the "tandem" principle was followed, they had had 58 cases of neuro-recurrence out of 2,500 cases of early syphilis. In the early days of arsenobenzol therapy, when salvarsan was used alone, there had been a large number of neuro-recurrences, and in his own experience it had been mostly in the purely arsenobenzol treated cases that clinically manifest recurrences had occurred. If a system such as the simultaneous arsenobenzol and mercury (or bismuth) treatment was attended by a smaller incidence of neurosyphilis than was the case when arsenobenzol was employed first and mercury (or bismuth) afterwards, the former seemed preferable.

Mr. VOGÉ (Edinburgh) read a preliminary note of a test devised by Dr. W. O. Kermack and himself. Wright and Kermack had shown that when colloidal gum benzoïn was precipitated by varying concentrations of cerebro-spinal

fluids of different degrees of acidity, the abnormal fluids from a case of general paralysis of the insane were characterized by the development of a zone at a pH 5.8, under conditions which precluded the appearance of this zone when a normal fluid was employed. Syphilitic serums were in general distinguished from normal serums by the development of a similar zone at a concentration of serum varying from 1/4 to 1/16 of the undiluted serum. It had previously been suggested that this abnormal zone of precipitation might be occasioned by the presence of a protein of high iso-electric point. It had been found that clupeine, a protamine derived from herring milts, when added in the requisite small amounts to normal cerebro-spinal fluid or serum, caused these fluids to simulate syphilitic fluid and serum in their behaviour towards gum benzoïn. An attempt had been made to obtain evidence as to whether a basic protein was actually present in excess in syphilitic body fluids. The reaction of Sakaguchi (development of a red colour by protamines and other compounds containing a free guanidine group when treated with naphthol and sodium hypochlorite) had been slightly modified and applied to syphilitic serums and cerebro-spinal fluids. The preliminary results indicated that in fluids and serums of syphilitic origin the red colour developed more readily than in normal ones, and a high degree of correlation appeared to exist between the results of this colour test and the Wassermann test.

Dr. FREMONT SMITH (Boston, U.S.A.) agreed that it was of great importance to make the taking of cerebro-spinal fluid from patients by lumbar puncture as painless and free from unpleasant after-effects as possible. He said that by using a local anaesthetic and a small needle, and keeping the patient in bed, he was able to make this operation quite free from drawback.

The PRESIDENT of the Section gave a clinical demonstration of about twelve cases of neurosyphilis, especially with a view to showing the results of treatment, chiefly by trypanamide, which he had used in large doses without ill effect but with great benefit to the patient. The cases included several of juvenile general paralysis, also of acquired general paralysis of the insane, and of tabes. In many of these cases the results of treatment were striking and impressive. The President did not claim that it was possible to restore the afflicted individual to a strictly normal condition, but he did suggest that they were often able to arrest the degeneration of the nervous system and retain the patient as a useful member of society, able to work and self-supporting.

DISCUSSION

ON

EPIDEMIC ENCEPHALITIS.*

I.—EPIDEMIOLOGICAL CONSIDERATIONS.

BY

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HAPPILY it is not expected that in opening a discussion the speaker should make a systematic survey of the subject under review. He may assume that those who may take part are already familiar with the main facts and features of the subject, and it is his business to make appropriate and, if possible, provoking remarks, thus focusing attention on some of the problems suggested by his own experience.

In seven successive years, from 1918 till 1924, the attention of the profession in Glasgow was directed to a "new disease," accounts of which had come during the same period from various parts of the world, and a description of which had already been given a year earlier by von Economo in Austria. That it was new admits now of no question, for there is nothing in the literature of

medicine to compare with the phantasmagoria of disorder manifested in the course of this strange malady. There is scarcely a sign or symptom of nervous derangement which did not at one time or another make its appearance during the epidemics. Into the maze of contradictory phenomena it seemed almost impossible to read anything like a rationalized order of events which might be termed a disease entity. Profound and prolonged torpor, protracted and resistive sleeplessness, paralysis, violent jactitation, chorea, athetosis, and convulsions, pains referable to the head, limbs, and internal organs, every conceivable anomaly of movement of the external and intrinsic muscles of the eye, giddiness and rotatory displacement of the body, abnormal reactions of alimentation, circulation, and respiration, delirium, maniacal excitement and fever, comprise some of the outstanding features of this picture of chaos.

The original attempts to interpret the phenomena in the light of nosological principles took various directions. An anatomical basis was soon established in the non-purulent form of encephalitis which was discovered in every case which came to *post-mortem* examination. One result of this discovery, however, was to transfer the confusion to another field of discussion. Non-purulent encephalitis had been described in a variety of diseases. It was present in the cephalic form of poliomyelitis, in the cerebral paralysis of children, in Wernicke's syndrome, and as a sequela of a number of acute infections, chief among these being influenza.

The prevalence of influenza at the time of the outbreak lent colour to the view that the new disease was associated with that infection. There were others who, inspired either by aversion to "new diseases" or by doubt as to the existence of anything which might be termed a "disease entity," sought refuge in the proposal to regard the phenomena as a form of polio-encephalitis. Objection, moreover, was taken to the term "lethargic encephalitis," because, on the one hand, lethargy was not invariably present, and, on the other hand, the morbid reaction was not always confined to the encephalon.

Classification of symptoms, pathological anatomy, and logical disputation failed individually and collectively to unravel the tangle which the initial stages of the epidemic presented. The efforts of the laboratory were no more successful, for examination of the cerebro-spinal fluid and bacteriological investigation afforded no data of importance, and experimental research gave no results. It is a striking commentary on the nature of morbid processes, and on the part which the clinician plays in their interpretation, that the disease had to reveal its own identity in the course of time before it could be even partially understood. It soon became apparent that, however obscure the microbio origin, however bizarre and baffling the preliminary disturbances, the tendency of the human organism to preserve its identity found expression in the long run in sequelae which constituted a fairly reliable standard of reference. It is just this issue of encephalitis in peculiar and characteristic sequelae which justifies its recognition, not only as a disease entity, but as a new disease.

For what is it that constitutes a "disease entity" or a "new disease"? The physician is concerned not, like the naturalist, with a wide range of different organisms theoretically adapted in an average way to an average environment, but with a single organism, the human subject, striving to preserve its identity in adverse circumstances. In this struggle all those tendencies and activities which are stabilized in the processes of normal life assert themselves. The conflict is not confined to the part first afflicted. The unity of the organism provides for the participation of a variety of immediate and distant reactions in the attempt to maintain or restore order. If the initial assault be severe, as in an acute infection or a cerebral haemorrhage, confusion and disorder are likely to prevail. If this stage be survived, the course of events will be determined by the extent of the damage and by the efforts of the organism, successful or otherwise, to restore a state of equilibrium.

It is the organic substratum to the chaos of disease that has a deciding influence on the course of the morbid process: it determines the tendency of disease to manifest

* This discussion took place in the combined Sections of Mental Diseases and Neurology at the Annual Meeting of the British Medical Association, Edinburgh, 1927, under the chairmanship of Professor Edwin Bramwell.