

STUDIES IN ASYMPTOMATIC NEUROSYPHILIS

I. A TENTATIVE CLASSIFICATION OF EARLY ASYMPTOMATIC NEUROSYPHILIS *

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Although we are as yet ignorant of the exact route followed by the *Spirochaeta pallida* in its invasion of the central nervous system, we know definitely that in many cases this invasion occurs with the generalization of the infection preceding secondary manifestations. In other words, the onset of neurosyphilis coincides in most instances with the onset of syphilis. Apparently the only exceptions are those instances in which central nervous system invasion takes place during subsequent periods of generalization of the infection, such as are believed to precede recurrent outbreaks of a secondary type; or by direct extension from an intimately associated focus of syphilitic bone or vascular disease. We may conclude that in untreated or inadequately treated cases more than one invasion of the central nervous system may occur. Ample proof of the early invasion may be found in studies of the cerebrospinal fluid in primary and early secondary syphilis.¹ In early untreated syphilis, from 30 to 50 per cent. of the fluids show more or less abnormalities, although most workers have found that only from 1 to 4 per cent. of such fluids have a positive Wassermann reaction. By means of routine lumbar puncture, therefore, it is possible in primary and early secondary syphilis to differentiate four groups of cases: one in which the fluid is normal; a second with minimal fluid abnormalities, such as slight increase in the globulin content and cell count; a third in which minimal abnormalities are associated with a positive Wassermann reaction when large amounts of fluid are used, and with a syphilitic zone gold curve or mastic "3"

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1. Fordyce, J. A.: The Diagnostic and Prognostic Significance of Spinal Fluid Findings in Syphilis, *Med. Rec.* **91**:927 (June 2) 1917. Ellis, A. W. M., and Swift, H. F.: *J. Exper. Med.* **18**:162, 1913. Wile, U. J., and Stokes, J. H.: Involvement of the Nervous System During the Primary Stage of Syphilis, *J. A. M. A.* **64**:979 (March 20) 1915. McIver, Joseph: The Spinal Fluid in Primary and Secondary Syphilis, *ibid.* **73**:1765 (Dec. 6) 1919. Wile, U. J., and Hasley, C. K.: Involvement of Nervous System During the Primary Stage of Syphilis, *ibid.* **76**:8 (Jan. 1) 1921.

reaction; and a fourth group with maximal positive findings in all tests. In the first group fall the cases which presumably escape central nervous system invasion. It must be emphasized, however, that an unknown though small percentage of these may show gross abnormalities on subsequent investigation, particularly if treatment is omitted. This point is emphasized by the investigation of Steiner,² who with Mulzer showed that with three of twenty spinal fluids from patients with early syphilis positive inoculations in animals were obtained, although these three fluids were otherwise entirely normal. In the second group, an undetermined number are probably normal, the globulin and cell increase being irritation phenomena, comparable to the slight transient albuminuria and the appearance of a few casts so frequently observed in the urine of patients with secondary syphilis, without demonstrable kidney damage. This group, nevertheless, must be considered to contain a high percentage of cases with recent neurologic invasion, in which tissue reactions are still in abeyance or only slightly developed. The third group contains principally cases of early meningovascular neurosyphilis with possibly a small proportion of cases with incipient parenchymatous or central involvement. All cases falling in the fourth group, with all tests positive, are obviously neurosyphilitic.

DIAGNOSIS AND TREATMENT OF NEUROSYPHILIS

Although the diagnosis of early asymptomatic neurosyphilis depends on information derived from spinal fluid studies only, it is interesting to note in these patients, as reported by one of us,³ the prevalence of persistently positive blood Wassermann reactions in treated cases and the incidence of minor pupillary abnormalities—headache, lassitude, rheumatic pains and nervousness. Of a series of 642 routine spinal fluid examinations, 173 fluids were from patients presenting these manifestations (Table 1), not of themselves diagnostic of neurosyphilis, with an abnormality incidence of 28.3 per cent., while in the remaining 469 only 7.3 per cent. presented abnormalities. In this series treatment had been instituted before the lumbar puncture was done, and, as will be shown, had a modifying influence on the results.

The factor of a persistently positive blood Wassermann reaction as an indication of asymptomatic neurosyphilis may be shown by a regrouping of the results obtained in primary and secondary syphilis (Table 2). In twenty-two cases in which the blood Wassermann reaction was still positive after six doses of arsphenamin, six or 27.2

2. Steiner: Impfexperimente mit Spinalflüssigkeit von syphilitikern, *Neurologische Centralbl.* **33**:132, 1914.

3. Moore, J. E.: The Cerebrospinal Fluid in Treated Syphilis, *J. A. M. A.* **76**:769 (March 19) 1921.

per cent. of the spinal fluids were abnormal. When the blood Wassermann reaction had become negative by the end of the first course of treatment, only 15.3 per cent. of the fluids were abnormal. If, after two or more courses of treatment the Wassermann reaction was still persistently positive, 38.4 per cent. of the fluids were positive; if negative, only 7.8 per cent. showed abnormal fluids. This shows, furthermore, that the prompt disappearance of a positive blood Wassermann reaction is not a guarantee against the existence of asymptomatic neurosyphilis.

Treatment as a preliminary to the study of spinal fluids in early syphilis was adopted by us a number of years ago, principally because we felt that more information could thus be gained. If the early minor abnormalities in the fluid were an expression of the general infection

TABLE 1.—SPINAL FLUID ABNORMALITIES IN PRIMARY AND SECONDARY SYPHILIS AS COMPARED WITH BLOOD WASSERMANN REACTION AND TREATMENT

Blood Wassermann Reaction	Cerebrospinal Fluids			
	Total Number of Fluids Examined	Positive	Negative	Percentage Abnormal
After one course of treatment:				
Positive.....	22	6	16	27.2
Negative.....	39	6	33	15.3
Total.....	61	12	49	19.6
After two or more courses of treatment:				
Positive.....	13	5	8	38.4
Negative.....	102	8	94	7.8
Total.....	115	13	102	11.3

as an irritation phenomenon, a small amount of treatment would cause them to disappear as the general infection diminished. Under these conditions remaining abnormalities would have greater significance as indicating actual spirochetal invasion of the nervous system. That in some instances the invasion might be obscured by this amount of treatment was no objection, because, if it could be so readily obliterated, long continued treatment, our routine plan, would fully safeguard the patient. The routine treatment would not be altered because of spinal fluid abnormalities, unless their persistence indicated some alteration or addition to the therapy.

We do not advocate long delay in making the puncture nor do we believe that a single puncture should be depended on to rule out asymptomatic neurosyphilis, although negative findings in early punctures minimize the possibilities if followed by adequate treatment. In more than 100 patients in whom an early negative spinal fluid examination

was obtained, reexamination of the fluid has yielded positive results in only two. In both of these an explanation for the late invasion of the nervous system was apparent. In one it probably occurred during a fresh generalization of the disease; in the second, by direct extension from syphilitic involvement of the inner cranial table. A recent communication from one of us⁴ considers this point in detail.

From the foregoing it will be appreciated that the treatment of early asymptomatic neurosyphilis is so intimately dependent on the interpretation of cerebrospinal fluid findings that the two cannot be considered separately. The choice of therapeutic measures cannot be compared in importance with early recognition. We believe, however, that adequate therapy has, at this period of the invasion, a most beneficial influence on what may follow. The incidence of neurosyphilis during the period of general invasion is the strongest argument in

TABLE 2.—SPINAL FLUID ABNORMALITIES IN SECONDARY SYPHILIS AS INFLUENCED BY TREATMENT

Amount of Treatment	Cerebrospinal Fluids			
	Total Number of Fluids Examined	Positive	Negative	Percentage Abnormal
None or very little.....	19	5	14	26.3
Six doses of arsphenamin + mercury.....	42	9	33	21.4
Twelve doses of arsphenamin + mercury.....	37	7	30	18.9
Eighteen doses of arsphenamin + mercury..	22	2	20	9.0
Twenty-four or more doses of arsphenamin + mercury.....	31	1	30	3.2

favor of the adequate treatment of all syphilis. In addition to the data already available in the literature, a series of cases studied by us from this point of view tends to confirm this opinion.

The influence of treatment in 151 cases of primary and secondary syphilis as indicated by changes in the cerebrospinal fluid was studied (Table 2). Nineteen patients had received little or no treatment and five, or 26.3 per cent., presented fluid abnormalities; of forty-two cases following six doses of arsphenamin with or without a course of mercury nine or 21.4 per cent. presented abnormalities in the fluid; of thirty-seven patients receiving twelve doses of arsphenamin with courses of mercury, fluid abnormalities were present in seven or 18.9 per cent.; 9 per cent. of patients in twenty-two cases following eighteen doses of arsphenamin with courses of mercury had abnormal fluids; and in thirty-one patients there were only 3.2 per cent. abnormal fluids

4. Moore, J. E.: The Genesis of Neurosyphilis, Arch. Dermat. & Syph., to be published.

after twenty-four or more doses of arsphenamin with courses of mercury. In this series, then, effective therapy reduced the prevalence of asymptomatic neurosyphilis from 26.3 to 3.2 per cent. If a comparison is made between the first three groups and the last two, it will be seen that after twelve or less doses of arsphenamin and courses of mercury, the spinal fluid showed abnormalities in 21.4 per cent. while after eighteen or more doses of arsphenamin plus mercury the percentage dropped to 5.7.

CLASSIFICATION OF EARLY ASYMPTOMATIC SYPHILIS

Further investigations are under way but we feel that a preliminary observation on the classification of early asymptomatic neurosyphilis based on the type of spinal fluid abnormalities and the corresponding results of treatment is permissible. Our four groups may be further described as follows:

Group 1.—Normal fluids. Neurosyphilis is not definitely ruled out, but we have no means of predicting which cases will later show abnormalities, except by animal inoculation experiments. The great majority of patients in this group certainly remain free from late clinical or serologic evidence of neurosyphilis.

Group 2.—Neurologic damage minimal or questionable. The spinal fluid shows pleocytosis and increased globulin content, but negative Wassermann and colloidal gold and mastic tests. These findings may be in some cases the expression of meningeal irritation only, without definite tissue invasion. Patients showing this type of spinal fluid uniformly do well on routine treatment without the addition of intraspinal therapy. The routine may be that for patients without spinal fluid changes.

Group 3.—Tissue invasion moderate. The usual early complaint is headache. The spinal fluid shows cells from 10 to 100, usually less than 50; globulin + or ++; the Wassermann reaction is negative with small quantities of fluid, and either positive or negative with larger amounts; colloidal gold curve syphilitic or meningitic zone; mastic curve to 3, or, in some instances, parietic. In general this type of patient does well, both clinically and serologically, on routine treatment without intraspinal therapy. However, we believe that to obtain the best results the dosage of arsphenamin and the number of doses to a course should be increased over the routine used for patients without neurologic invasion, that the interval between doses should be decreased, and that the total amount of arsphenamin administered should be relatively greater and the total amount of mercury relatively less than in uncomplicated cases. In only one instance have we found it necessary to resort to intraspinal therapy in order to accomplish a

serologic cure. It is probable that spinal fluid changes of this type represent future meningovascular cerebrospinal syphilis, though a minority of the patients may ultimately develop parenchymatous neurosyphilis.

Group 4.—Tissue invasion definite. Complaint may be absent, or may be that of nervousness, lassitude or neuralgic pains. If careful sensory examination is omitted, neurologic abnormalities are not detected. The spinal fluid shows from 10 to 100 cells, usually more than 50; the globulin is greater in content than in the preceding two groups, ranging from +++ to ++++; the Wassermann reaction is positive with 0.2 c.c. or less, and the colloidal gold and mastic curves are paretic. The majority of patients in this group are not serologically cured by routine treatment, regardless of alterations in the individual dose or the total amount of arsphenamin, or the interval between doses. An occasional patient may be serologically improved, but the improvement is difficult or impossible to maintain. If, after six months' treatment, no change in the intensity of the spinal fluid findings is manifest, intraspinal treatment is an indispensable adjunct to routine treatment. Even when this plan is adopted, improvement, which may be looked for in a large percentage of the cases, is slow and treatment prolonged. In all probability, this group represents future cases of parenchymatous neurosyphilis—paresis and tabes. Indeed, we have observed the development of paresis in two patients with such spinal fluid findings discovered early in the course of syphilis.

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