A STUDY OF THE SPINAL FLUID IN ONE THOUSAND EIGHT HUNDRED AND SIXTY-NINE CASES OF SYPHILIS IN ALL STAGES

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In 1913, with the installation of the syphilis clinic at the University of Michigan, a study of the spinal fluid in all cases of syphilis was begun. Previous to this time important contributions suggesting the frequency of involvement of the nervous system in early syphilis had already appeared in the literature in France by Ravaut,¹ in Germany by Altman and Dreyfus,² and in this country by Engman³ and his co-workers. In 1914 and 1915 studies from this clinic appeared on the involvement of the nervous system, particularly in reference to the secondary period of the disease, by Wile and Stokes.⁴ The results of these studies showed that the invasion of the nervous system occurred extremely early, that it was frequently seriously involved without symptoms, and that serious involvement might escape detection unless the routine lumbar puncture was practiced on all cases. The high percentage of involvement in early syphilis led us at that time to state our belief that "the fate of every syphilitic with regard to the incidence of cerebrospinal lues, whether this occurs early or late in the course of the disease, is determined in the first months of the infection." Our results in the main have been confirmed by the contemporary writers and subsequent publications.

1. Ravaut: *Ann. de dermat. et syph.*, Ser. 4, No. 2:1 and 537; 1903; Ser. 4, No. 5:1057, 1904; Ser. 4, No. 8:1057, 1907; *Rev. mens. d. méd. inst.*, No. 3:1, 1909.

2. Altman and Dreyfus: *München. med. Wchnschr.* 5:465, 1913. Dreyfus: *München. med. Wchnschr.* 59:2567, 1912.

3. Engman, M. F.; Buhman, R.; Gorham, F. D., and Davis, R. H.: *A Study of the Spinal Fluid in One Hundred Cases of Syphilis*, J. A. M. A. 61:735 (Sept. 6) 1913.

4. Wile and Stokes: *A Study of the Spinal Fluid with Reference to Involvement of the Nervous System in Secondary Syphilis*, *Dermat. Wchnschr.* 59:1079, 1107 and 1128, 1914.

At present we have at our disposal, for the purpose of study, 1,869 cases of syphilis in all stages, on which routine lumbar punctures have been carried out, together with careful study of the associated findings. This number represents about one third of the total number of cases of syphilis seen during this period.

The cases included in this group have been selected particularly with reference to correct diagnosis, and the number is limited to those that have been accurately observed over a definite period of time. Cases of doubtful diagnosis and cases seen casually have been cast aside.

TYPES OF SYPHILIS STUDIED

According to the clinical findings, the cases have been divided into the following types: congenital syphilis, primary syphilis (chancre only present), secondary syphilis, late syphilis of the skin and mucous membranes (tertiary), latent syphilis, tabes, general paresis, taboparesis and diffuse cerebrospinal syphilis. In Table 1 will be found the number of cases in each group.

TABLE 1.—CLASSIFIED TYPES OF CASES

Type of Syphilitic Involvement	Number of Cases
Congenital.....	53
Primary.....	236
Secondary.....	508
Tertiary.....	155
Latent.....	568
Diffuse cerebrospinal.....	178
Tabes dorsalis.....	109
General paresis.....	49
Taboparesis.....	13

TABLE 2.—NUMBER OF CASES WITH PLEOCYTOSIS AS FOUND IN VARIOUS TYPES OF SYPHILIS STUDIED, WITH THE PERCENTAGE INVOLVEMENT

Type of Syphilitic Involvement	Number of Cases	Number With Increased Cells	Percentage With Increased Cells
Congenital.....	53	14	26.4
Primary.....	236	38	16.1
Secondary.....	508	173	34.0
Tertiary.....	155	39	25.1
Latent.....	568	163	28.6
Diffuse cerebrospinal.....	178	157	88.2
Tabes dorsalis.....	109	102	93.5
General paresis.....	49	47	95.9
Taboparesis.....	13	13	100.0

The ordinary criteria, as now accepted, indicating the involvement of the nervous system are the standards used in this study. Thus, a cell count of over 6, the presence of increased albumin and globulin and the Wassermann test on the spinal fluid are considered, as well as the Lange gold curve in a certain number of selected cases.

In order to determine the parallelism, if any exists, between the various criteria, separate tables are given. Table 2 shows the percentage of involvement as indicated by increased cell count. Table 3 indicates the percentage of involvement as shown by increased globulin and albumin content in the fluid. Table 4 shows the percentage of involvement as indicated by the positive Wassermann test on the fluid.

TABLE 3.—NUMBER OF CASES WITH INCREASED ORGANIC SOLIDS AND THE PERCENTAGE OF INCREASE IN THE VARIOUS TYPES STUDIED

Type of Syphilitic Involvement	Number of Cases	Number With Increased Albumin and Globulin	Percentage With Increased Albumin and Globulin
Congenital.....	53	7	13.2
Primary.....	236	45	19.0
Secondary.....	508	178	35.1
Tertiary.....	155	41	26.4
Latent.....	568	154	27.1
Diffuse cerebrospinal.....	178	173	97.2
Tabes dorsalis.....	109	107	98.1
General paresis.....	49	47	95.9
Taboparesis.....	13	13	100.0

TABLE 4.—NUMBER OF CASES WITH A POSITIVE WASSERMANN REACTION OF THE SPINAL FLUID AND THE PERCENTAGE WITH POSITIVE REACTIONS IN THE VARIOUS TYPES STUDIED

Type of Syphilitic Involvement	Number of Cases	Number With Positive Wassermann Reaction	Percentage With Positive Wassermann Reaction
Congenital.....	53	9	16.9
Primary.....	236	14	5.9
Secondary.....	508	135	26.5
Tertiary.....	155	48	30.9
Latent.....	568	159	27.9
Diffuse cerebrospinal.....	178	156	87.6
Tabes dorsalis.....	109	102	93.5
General paresis.....	49	47	95.9
Taboparesis.....	13	13	100.0

From a study of these tables it will be seen that in each group of cases a fair degree of parallelism exists in the ratio of involvement, as shown by each of the criteria. In the main, the increase in globulin is found slightly more frequently than any other single finding, and this increase was almost constantly parallel with an increase in the number of cells present. A slightly lower percentage of involvement is seen in the column of Wassermann tests.

From the standpoint of delicacy of all tests, general paresis and taboparesis yield the highest percentage, 100 per cent being found positive in all columns in the combined type and 95 per cent. in all columns in the straight, frank paresis. Tabes is slightly lower and the diffuse form of cerebrospinal syphilis ranks last in the uniformity of positive criteria, although still showing a high percentage of parallelism with the clinical findings.

The material included in this study presents many interesting points of discussion, each one of which might well be the subject of a separate paper. It is expected that these will so be treated in the near future. In this particular study we wish to emphasize three distinct interesting points that have been brought out in our analysis of the cases. First: The strikingly high percentage of neurosyphilis associated with syphilitic alopecia, iritis and leukoderma colli. Second: The association of neurosyphilis with late syphilids of the skin, bones and viscera. Third: The high percentage of asymptomatic neurosyphilis occurring during the indefinite period of latency.

NEUROSYPHILIS ASSOCIATED WITH SYPHILITIC ALOPECIA, IRITIS AND LEUKODERMA

Early in our study we were struck by the great frequency with which neurosyphilis, particularly as indicated by practically all criteria in the spinal fluid, was associated with syphilitic alopecia. From our cases of this complication we find that of forty-six cases showing this symptom, 73 per cent. had coincident involvement of the nervous system. Practically all cases in which involvement occurred were characterized by a considerable degree of pleocytosis. A few patients had symptoms of headache; none had distinct organic signs, except such indefinite ones as increased reflexes. Many with a high degree of involvement were absolutely without symptoms.

Alopecia as a complication occurred in about 6 per cent. of all of our secondary cases. The mechanism of specific alopecia is not clearly understood, and we suggest that this mechanism may actually relate, at least in some cases, back to a disorder of enervation, being associated with the coincident cerebrospinal involvement, rather than due to a direct involvement of the hair follicle by spirochetes.

A similarly interesting and uniformly high association was found in the complication of secondary iritis. In our series this occurred in twenty-one of 508 secondary cases of syphilis studied. Associated cerebrospinal involvement occurred in fifteen of these twenty-one cases, or 71.4 per cent.

Of the more tardy secondary syphilids, a high percentage of involvement of the nervous system was found in association with leukoderma colli. Our figures of this manifestation are rather small, only eleven cases having been seen. Of this number, however, 55 per cent. were found distinctly positive in the spinal fluid.

NEUROSYPHILIS AND SYPHILIS OF THE SKIN, BONES AND VISCERA

We may turn now to the association of the central nervous involvement with other forms of late syphilis, particularly those of the skin, bones and viscera. It is a common teaching and a general belief that

an inverse ratio exists between cerebrospinal involvement and other forms of late syphilis. For example, it is believed that tabetics and parietic patients and patients with other cases of late neurosyphilis with outstanding symptoms are seldom seen with late manifestations in the splanchnic system or in the skin and bones. This belief is at least held by some to be clinical evidence suggesting the existence of spirochete neurotropism. Whatever the merits of the question of spirochete strains are, and certainly considerable evidence exists tending to substantiate their existence, we are convinced from our study that this question cannot find a reliable argument in the lack of coincidence of late neurosyphilis and other forms of gummatous involvement. Thus, we find that in 155 cases of late syphilis involving the skin and mucous membranes, the bones and the viscera in the form of gummas and diffuse syphilomas, forty-eight cases, or 30 per cent., showed involvement of the nervous system at the same time. We found a frequent association, for example, of tabes and hepatic syphilis and aortitis, and in a few cases, of paresis and tabes with definite gummatous lesions in the skin.

The predominance of the neurologic symptoms and signs in cases of late syphilis of the nervous system and the fact that many of these cases are studied merely from the angle either of their psychiatric or neurologic aspects has undoubtedly led to the failure to recognize coexistent visceropathies.

Our studies have for the most part been made when patients showed definite involvement of the viscera, the skin or bones and when on examination we have been able to demonstrate the coincident cerebrospinal disease. From an experience extending over eight years, during which time we have had occasion to examine cases of late cerebrospinal syphilis in all forms referred to us from other services, we have been similarly struck with fully as high a percentage of associated splanchnic, cutaneous and osseous syphilis when the cases are viewed from this angle.

NEUROSYPHILIS OCCURRING DURING PERIOD OF LATENCY

Studying our figures from the standpoint of the occurrence of cerebrospinal involvement with asymptomatic syphilis, we find that in the latent period of the disease about 28 per cent. of all patients showed distinct involvement, as shown by increased cell count, increased organic solids and the Wassermann reaction in the fluid. This group of cases is made up largely of patients who have consulted the hospital for reexamination as to a preexisting syphilis. A large part of this group, however, is composed of those who had entered the hospital for some other complaint and who had been referred to this department:

on the basis of the positive Wassermann blood test. In this group, entirely asymptomatic from the standpoint of the nervous system as well as from the general constitutional manifestations, we found, studying these patients from the standpoint of the colloidal gold curve, that a number gave typical paretic curves, others the curve of tabes.

To state with any degree of definiteness that these asymptomatic patients would inevitably develop active manifestations is perhaps too dogmatic in the light of our present knowledge. Such cases, however, in which the existence of cerebrospinal involvement is unknown to the patient and makes itself known only through the lumbar puncture, findings are extremely important when viewed from the standpoint of the patient, the community and, in general, the prognosis of the disease. We believe that if these patients had been examined early in the course of the disease the involvement would have been demonstrated at that time and if through intensive treatment it had been directed to the nervous system, the patient might have been saved the later complication. In that particular type of case in which an acute meningeal reaction occurs early, with or without symptoms, we have been impressed with the rapidity with which the fluid can be restored to normal through intensive constitutional and intraspinal medication.

That some patients of this group, asymptomatic at the time of puncture, actually did develop symptomatic neurosyphilis, we were able to demonstrate in a few of the cases under observation for several years. Thus, for example, we have seen definite paretic symptoms develop in a few cases in which at the preliminary puncture the paresis was manifested only by the Lange gold curve.

CONCLUSIONS

1. The nervous system, if uninvolved as shown by the accepted criteria during the first months of the infection, is seldom invaded later. A negative preliminary puncture followed by positive findings at a later date occurred in only three of several thousand cases punctured.

2. Of the several criteria indicating involvement, the increase of organic solids is found to be slightly higher than either the cell count or the Wassermann reaction, the relative value being indicated in the order just mentioned.

3. A considerable degree of cerebrospinal involvement may be present in the latent period of syphilis without manifesting any signs or symptoms.

4. Such asymptomatic cases may become symptomatic later, and a study of the colloidal gold curve in these cases is of some value in estimating the ultimate prognosis of the case.

5. Comparing the large number of cases of primary and secondary syphilis in which positive findings are found, with the relatively small percentage of late neurosyphilis as compared to total syphilitic incidence, we must conclude that a large number of early cases are in the nature of a meningeal roseola, which is transitory in its clinical aspects.

6. The interpretation of the lumbar puncture findings, particularly early in the incidence of the disease, constitutes a valuable guide in estimating the ultimate prognosis of the disease with regard to the integrity of the nervous system.⁵

5. In addition to the references already given, the following may be of interest:

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