THE SUBACUTE FORM OF MULTIPLE SCLEROSIS*

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In order to obtain a more correct understanding of the histology of multiple sclerosis it is necessary to examine the lesions when the course of the disease has been rapid. Cases of multiple sclerosis with necropsy are exceedingly rare in America, and therefore one in which death occurred within the second year after the onset, as it did in the case presented in this paper, should be of interest. This study permits me to conclude that, at least in some cases, multiple sclerosis may be regarded as multiple glioma. There is also a possibility that at times syphilis may play a rôle, and opportunity is taken to consider the findings justifying this point of view.

The patient who afforded the opportunity for the present study was a male, aged 25. The symptoms began in February, 1915, with headache. In June, 1915, vision began to fail. In July, 1915, optic neuritis was observed. Weakness of the limbs developed gradually, with nystagmus, incoordination, vertigo, scanning speech, intention tremor and progressive impairment of gait until walking finally became impossible and mentality very feeble. Death occurred Dec. 21, 1916.

The notes of this case are as follows:

History.—E. B., white man, aged 25, was admitted to the University Hospital of the University of Pennsylvania, July 21, 1916, and died Dec. 21, 1916. He had been well until February, 1915, when he began to have severe frontal headache. At this time he had no motor symptoms. In June, 1915, his vision began to fail. In the middle of July, 1915, he was admitted to the University Hospital on Dr. de Schweinitz's service. The diagnosis of optic neuritis was made. As vision failed the headache subsided. The sensation of twitching of the arms and legs grew worse and he became weak. He was greatly improved by one month's stay at the seashore. Since January, 1916, his condition has become steadily worse. In February, 1916, he developed ataxia of the lower limbs and vertigo, and the weakness of the lower limbs increased. His speech has become somewhat slurring, nasal, and monotonous since March, 1916. Since May he has had an intention tremor of the forearms. Since June 20, 1916, he has not been able to walk.

He has had chickenpox, whooping cough, influenza in infancy and early childhood. He denies venereal disease. His family history is negative. He does not use alcohol. He is a student in the Wharton School of the University of Pennsylvania.

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Examination.—The pupils are equal; irides react promptly and equally to light and in convergence. Horizontal nystagmus of large amplitude occurs when he looks to either side, and vertical nystagmus when he looks upward. Extraocular rotations are unimpaired. Facial musculature is unimpaired. Hearing of the watch tick is fair in each ear. The tongue is protruded slightly to the right of the midline without tremor and is freely movable to either side.

Extremities: Grip fair with the right hand, poor with the left. Marked ataxia and, at times, coarse intention tremor developed in both arms by finger to nose and finger to finger tests. Diadochokinesis is impaired in both forearms. Sense of position and stereognostic sense are normal in the hands. Biceps reflex is normal and equal on both sides. Triceps reflex is questionably present on both sides. Cremasteric reflex is prompt on the left side, sluggish on the right. Patellar reflex is slightly exaggerated on the right side, normal on the left. Achilles reflex is moderate on both sides and equal. Plantar stimulation induces plantar flexion on the left side, dorsal flexion on the right side. Ankle clonus was obtained on the right side at the first examination, but could not be elicited on either side at the second examination. Heel to knee test shows marked ataxia on both sides. Both legs show slight spasticity. Legs and trunk are weak and probably ataxic. The man cannot stand or even sit up unsupported. Sensations of touch and pain are normal throughout. Slight coolness is mistaken for warmth in the right calf. Otherwise objective sensation is unimpaired.

The voice is slow, monotonous, thick and somewhat slurring. The laugh is deep, expressionless, almost spastic, not unlike the laugh of Wilson's disease. The lower limbs are very weak. There is more power in extension than in flexion. There are frequent brief rapid changes in the amount of power in all the movements of the extremities. He passpoints outward with both hands spontaneously.

July 25, 1916: (Ocular report by Dr. Langdon.) O. D., vision 6/15; O. S., 6/45. Both disks show decided loss of capillarity, well defined central cups and sharply defined margins. There are no other fundus changes.

July 22, 1916: Blood: Red blood cells, 5,160,000; white blood cells, 8,400; hemoglobin, 80; polymorphonuclears, 78; lymphocytes, 19; large mononuclears, 1; transitionals, 1; eosinophils, 1; basophils, 1. Urine analysis: Cloudy, amber-colored; flocculent sediment; specific gravity, 1.025; acid reaction; albumen, none; sugar, none; casts, no cylindroids; mucus, plus; no red blood cells; white blood cells, occasionally present; epithelium was present, also calcium oxalate crystals.

July 28, 1916: Lungs are negative except for slightly increased vocal fremitus over the right upper lobe. Heart is negative except for slightly accentuated pulmonic second sound.

Sept. 18, 1916 (ocular report dictated by Dr. Shumway): There is a marked pallor of the temporal half of the optic nerve on each side and paralysis of the right internal rectus.

Oct. 10, 1916: Patient is somewhat delirious. Wassermann test of the blood has been taken several times in the hospital and was always negative. The patient's father states that the blood taken outside the hospital for the Wassermann test he thinks was positive. Owing to certain circumstances a lumbar puncture was not done.

Oct. 13, 1916: The patient is not able to take care of himself and lies in bed except when moved in a wheeling chair. He has marked ataxia, scanning

speech, nystagmus and intention tremor. His mentality has gradually failed and is now greatly impaired.

Dec. 21, 1916: This morning the patient's temperature, pulse and respiration suddenly went up above normal and he could not be aroused. He had been without change in his condition on retiring the night before. His heart was fast and irregular. At 8 a. m. on this date he was still unconscious and his breathing was difficult and irregular, and, while still fast, there was no increased area of cardiac dullness.

Postmortem Examination (Dec. 21, 1916).—The postmortem examination revealed practically nothing abnormal with the viscera. The areas of sclerosis are very numerous and are found in every section taken from the spinal cord, but they are more pronounced in the cervical and lumbar regions than in the thoracic. These areas are in some places fairly sharply defined from the normal tissue, but in many places the shading off into normal tissue is observed. Lacelike structure is found in some of the patches. The areas are infiltrated with numerous mononuclear cells, and these are especially numerous about the blood vessels within the cord and in some of the septa running into the cord. These cells are very numerous in both the pia of the cord and brain, and in some places form dense masses. The large spider cells (Deiters' cells) so numerous in the foci within the cerebrum, are not found in the cord.

The alteration in the medulla oblongata is as intense as in the cord. The Marchi sections of the cord and brain show intense recent degeneration except in areas of long standing in the cord. The nerve cells of the anterior horns of the cervical and lumbar regions are well preserved even in sclerotic foci, as shown in the thionin stain, and do not show pigmentary degeneration, although occasionally a cell showing chromatolysis and swelling may be found.

The optic chiasm, tracts and nerves are greatly degenerated and show much infiltration with cells of mononuclear type. Some foci of degeneration are found in the cerebellum, as in the right dentate nucleus.

Sections from many parts of the cerebrum show disappearance of medullary substance in the altered areas. The sharpness of definition of the degenerated from the normal tissue is possibly even more pronounced here than in the spinal cord. The nerve cells in the altered cortex are well preserved. The cerebral foci contain many large glia cells (Deiters' cells), mononuclear cells and fatty granular cells, and these foci differ greatly from the foci of the spinal cord in that the former are almost entirely cellular. These areas look like so many distinct gliomas, and while they appear under low power to be sharply defined, under high power scattered glia cells may be seen penetrating into the adjacent tissue like scouts of an invading army.

There have been few cases of multiple sclerosis with necropsy reported in this country — a statement also made by Taylor — and the study of this disease must be made chiefly from the foreign literature. There we find cases in which the brain has been seriously affected by the lesions, but in most cases the description has been based on the study of the spinal cord. In this case of subacute multiple sclerosis recently under my care every section taken from any part of the cerebrum shows foci with lesions peculiar to this disease. The alteration in the cerebrum is very different from that in the spinal cord, and my findings confirm the statement of Marburg, namely, that cellular

proliferation of glia is greater in the brain than in the spinal cord, and that the large glia cells are found more in the brain than in the spinal cord.

The glia proliferation of the spinal cord is in large measure of the character of the overgrowth of glia seen in the replacement of nerve fibers from secondary degeneration caused by some lesion at a higher level; it is therefore chiefly fibrillar. In the cerebrum the glia proliferation is of a different character, it is chiefly cellular and is more recent than that of the cord. Mental failure usually does not precede the other symptoms of multiple sclerosis, it occurs later in the disease

Fig. 1.—Vessel in the left paracentral lobule surrounded by many cells of mononuclear type.*

and the lesions producing it must be of late development. In this case the mental failure became pronounced and it is to be explained by the extensive alteration of the cerebrum. If one, therefore, desires to find the earlier changes of multiple sclerosis he should look for them in the cerebrum. The lesions are usually less numerous in the cerebellum.

The changes in the cerebrum in the case recorded in this paper were in overgrowth of the glia causing a microscopic picture resembling that of a glioma. Indeed, my studies of these sections lead me

*I am indebted to Dr. A. J. Smith for the photomicrographs.

to conclude that multiple sclerosis may be a process consisting of innumerable minute gliomas, although other types possibly may occur. It is no wonder, therefore, that the mentality of my patient became exceedingly feeble. The cellular infiltration of mononuclear type within the tissue about the vessels has been noted in many cases of multiple sclerosis, but it may be found also in glioma. The large glia cells, spider cells or Deiters' cells, I have found only in the brain, and they are indicative of chronic irritation. I have seen them in the spinal cord when the cord was severely distorted by the pressure

Fig. 2.—Part of the vessel shown in Figure 1 under higher magnification. Beyond the mononuclear cells are seen numerous other cells, some of which are glia cells.

of an extramedullary tumor, but I have not observed them to the same degree in syphilitic encephalitis.

The relation of the foci to blood vessels has been asserted by some investigators, disputed by others—I have not been able to establish it. About one vessel within the brain many mononuclear cells were found and beyond these were other cells, some of which evidently were glia cells. It seems as though some irritative substance either within the vessel or the perivascular sheath may have caused this proliferation (Fig. 2).

Wohlwill made a very thorough digest of the literature of multiple sclerosis for the ten years ending April, 1913. He says the definition of multiple sclerosis is made to include different lesions by different writers. From a pathologic viewpoint he defines the condition as the occurrence of circumscribed foci in the central nervous system in which the medullary sheaths have disappeared or are disappearing, the axis cylinders and ganglion cells are relatively intact, and a more or less intense glia proliferation exists without displacement of the adjoining nervous tissue. Siemerling and Raecke have stated that in those cases in which the cerebral cortex is implicated the cortex is the

Fig. 3.—A mass of proliferated glia cells included entirely within a low magnification, showing the small size of some of the altered cerebral areas.

chief seat of the lesions, but my examination in this case does not support this statement. Cases with great preponderance of cortical involvement he states have been reported by Dinkler, Fuller, Klopp and Jordan.

The most recent comprehensive work on multiple sclerosis has been done by James W. Dawson. He states that the etiology of the disease remains absolutely obscure. The supposition of a selective poison acting through the blood vessels, which has received the support of most recent investigators, is justified as an hypothesis, but remains undemonstrated as a fact. Dawson devotes special attention to the

early changes of the disease, and he states that our knowledge of the histology, especially of the early stages, has not kept pace with our recognition of the early clinical aspects of the disease. Experimental investigation, Dawson says, has proved only that disseminated areas of myelitis may result in a reparative growth of neuroglia, but it has not proved that area of typical disseminated sclerosis proceed from an acute myelitis.

I am unable to accept the view that multiple sclerosis is caused alone by some irritant circulated by the blood, but it seems to me

Fig. 4.—One of the cerebral sclerotic areas consisting largely of glia cells, under higher magnification than that represented in Fig. 3. The sharp definition of normal from altered tissue runs almost through the middle of the photograph. Mallory's neuroglia stain.

probable that such an irritant acting on tissue in which the disease is latent may hasten its development.

Dawson asserts that a study of the cerebrospinal fluid in multiple sclerosis has as yet thrown little light on the disease, but investigations along this line have not been extensive.

In the report of a case of multiple sclerosis he states that the "early" areas in the cerebrum consisted largely of closely arranged fatty granular cells between which were large protoplasmic, proliferated glia elements; of dilated vessels, with fatty granular cells and

other nucleated elements in their adventitial spaces; of markedly altered persisting axis cylinders; and of a gradual transition zone in which these changes were less marked and in which degenerating myelin fibers were found. These findings describe very accurately those in my case.

Dawson found the cerebral and spinal meninges almost normal in his uncomplicated cases; meningeal changes when present were diffuse and in no way confined to the meninges overlying areas of sclerosis.

As for syphilis, he says it has no significance in the etiology. Syphilis may produce disseminated areas in the central nervous system, but the histologic character of these have, as a rule, nothing in common with those of disseminated sclerosis, in which disease also the reactions of the serum and cerebrospinal fluid and the cytologic examination of the spinal fluid are all negative.

The cellular infiltration of mononuclear type in the cerebral pia in my case is a finding of considerable interest. It is exceedingly pronounced and suggests the findings of syphilis. Unfortunately, a lumbar puncture in this case was prevented by certain circumstances, but a Wassermann test of the blood done outside the hospital was supposed to be positive.

When working in Obersteiner's laboratory in 1893 and 1894, I found in a case of multiple sclerosis cell infiltration of mononuclear variety of considerable intensity about the blood vessels of the cord and within the spinal pia. This finding is referred to by Bikeles in his paper published in 1895.

Wohlwill, in his critical digest on multiple sclerosis, speaks of the frequency of the perivascular cellular infiltration, but says polymorphonuclear cells do not occur in the infiltration. The infiltration consists of lymphocytes, plasma cells, some mast cells and fatty granular cells. Plasma cells are not always present. The cellular infiltration usually does not extend beyond the perivascular limiting layer of glia, although lymphocytes occasionally are found within the degenerated focus.

The meninges he states frequently are thickened and may show cellular infiltration, consisting of lymphocytes, plasma and mast cells, endothelial and connective tissue cells, and the vessels may show similar changes to those of the vessels within the foci. The cellular infiltration about the vessels of the pia he states is described by Flatau and Kölichen.

Marburg in his paper on acute multiple sclerosis stated that the meninges in acute multiple sclerosis had not received so much attention as they deserve. In one case only he found meningeal changes. Cellular infiltration was chiefly with connective tissue cells, but also with endothelial cells from the vessels, mast cells, plasma cells and

lymphocytes, but the picture he gives does not show anything like the intensity of cellular infiltration seen in my case.

Rönne and Wimmer found in a case of acute multiple sclerosis pronounced cellular infiltration of the tissue, either diffuse or in little clumps, especially about a vessel or within its walls. The cells were mononuclear and polynuclear leukocytes, fatty granular cells, plasma cells and *Stäbchenzellen*. They found no evidence of spinal meningitis. They give much evidence justifying the opinion of multiple sclerosis as a myelitis—an inflammatory process.

Fig. 5.—Large collection of mononuclear cells in the pia of the left paracentral lobule, suggesting the finding of syphilis.

In a case of multiple sclerosis described by Finkelnburg the vessels in the foci were much distended and surrounded by broad masses of mononuclear cells, and in some places these cells hid the vessel walls, and in some places the tissue surrounding the vessels was infiltrated with the round cells, but there was no sign of meningitis. He found an infiltrated vessel in the midst of a focus, as a rule, and he states that in his case, as in Ribbert's and Goldscheider's, an infiltrated vessel was found in the center of most of the small foci. Finkelnburg found many vessels infiltrated with round cells that were not in sclerotic foci.

The case reported by Barbier and Gassier was in a child 5 years of

age, in whom the Wassermann reaction was positive, and the symptoms these authors thought could be attributed only to multiple sclerosis. Much improvement occurred in the child's condition. The case was without necropsy and is not altogether convincing, and does not prove that the condition was caused by syphilis.

Dr. Joseph McIver at my request has examined the fluid obtained by lumbar puncture from a typical case of multiple sclerosis of a few years' duration. He found 200 cells to the cubic millimeter, mostly mononuclear. An accident prevented a Wassermann examination of this fluid.

In 1909, I reported with Dr. Andrew H. Woods a case in which the symptom complex was one of spastic paraplegia of the lower limbs with contracture of the limbs, and pain produced by passive movement of these limbs, probably because of the contractures; exaggeration of tendon reflexes in both upper and lower limbs, although the reflexes could not be well demonstrated in the latter because of the position of these limbs; and loss of control of bladder and rectum, with preservation of objective sensation. These symptoms could be caused by multiple sclerosis.

Numerous areas of sclerosis were found throughout the cervical and upper thoracic regions of the cord, some of which resembled closely the degenerated areas found in multiple sclerosis. Slight cellular infiltration of mononuclear type in the pia, the gradually shading off of the sclerotic areas into the normal tissue instead of the sharp line of differentiation; the vascular and perivascular sclerosis in regions of the cord where there was no distinct focus of sclerosis, seemed to us to indicate that the process was syphilitic. I feel less sure of the correctness of this viewpoint at the present time, and am almost willing to accept Catola's opinion that the distinction between the different forms of multiple sclerosis are unreliable and that syphilis cannot be eliminated as a cause. It is well to recall the view of Orlowsky, and Thomas and Long, that syphilis and multiple sclerosis have occurred in the same person.

Wohlwill states that the pathologic distinction between multiple sclerosis and the multiple lesions of syphilis in many cases is not simple. The syphilitic lesions may be very similar. Barbier and Gassier try to establish a relation between certain cases of multiple sclerosis of childhood and congenital syphilis. Marburg has stated that he has found multiple sclerosis strikingly frequent in the descendants of syphilitic parents, even when the patients presented no evidence of syphilis. Statistics have not shown that syphilis is frequent in the history of multiple sclerosis cases. Berger found it only in 1.5 per cent. of the cases, Klausner in about 3 per cent. Hauptmann in

a comparatively short time found four cases of multiple sclerosis with syphilitic history.

Catola states that in certain cases syphilis is the only malady which seems to play a rôle in the etiology of multiple sclerosis, and refers to Babinski, Greiff, Orlowsky, Thomas and Long, and Wernicke, but concludes that the relation of syphilis to multiple sclerosis is far from being determined.

In the first case of Catola's paper the patient is said to have been syphilitic and had disseminated lesions which Catola regarded as like those of multiple sclerosis. The spinal pia was infiltrated by lympho-

Fig. 6.—Naked axis cylinders (Bielschowsky stain) in a sclerotic area of the spinal cord, showing the presence of these axis cylinders in apparently completely degenerated tissue.

cytes and polynuclear cells, and the infiltration was especially intense in the posterior longitudinal septum. The photographs represent an intense cellular infiltration of the pia. The polynuclear cells were found almost exclusively in the lower part of the cord and were attributed to infection from a bed sore. Catola concludes that syphilis may be very important in multiple sclerosis, and there is a syphilitic multiple sclerosis like a multiple sclerosis of any other infectious origin.

It seems probable that syphilis has some influence over multiple sclerosis. The typical lesions probably are not syphilitic in character, but the syphilis may be an *agent provocateur*. It would be well to treat early cases of multiple sclerosis as possibly syphilitic—the therapeutic test is well worthy of trial.

REFERENCES

- Taylor: J. Nerv. & Ment. Dis., p. 361, 1906.
 Marburg: Lewandowsky's Handbuch der Neurologie.
 Dawson, J. W.: Edinburgh M. J. **17**: 1916; later publication also in Rev. Neurol and Psych.
 Bikeles: Obersteiner's Arbeiten, **3**: 1895.
 Wohlwill: Ztschr. f. d. gesamt. Neurol. u. Psych., Referate und Ergebnisse. **7**:849, 1913; Neurol. Centralbl. p. 732, 1912.
 Marburg: Jahrb. f. Psych. **27**:211, 1906.
 Rönne and Wimmer: Deutsch. Ztschr. f. Nervenhe. **46**:56, 1912.
 Finkelnburg: Deutsch. Ztschr. f. Nervenhe. **20**:418, 1901.
 Barbier and Gassier: Bull. Soc. de pédiat. de Paris p. 14, 1912.
 Spiller and Woods: Interstate M. J. **16**: 1909.
 Orłowsky: Neurol. Centralbl. 1897.
 Thomas and Long: Compt. rend. Soc. de biol. 1899.
 Catola: Nouv. iconog. de la Salpêtrière **19**:337, 1906.
 Barbier and Gassier: Bull. Soc. de pediat. de Paris p. 9, 1912.
 Hauptmann, A.: München. med. Wchnschr. **57**:1581, 1910.
 Kuhn and Steiner (Med. Klin., No. 37, 1917), by inoculating rabbits and guinea-pigs with blood and cerebrospinal fluid from cases of multiple sclerosis produced paralysis and found spirochetes within the vessels of the liver of the inoculated animals.
 Siemerling (Berl. klin. Wchnschr., No. 12, 1918) discovered living spirochetes in the sclerotic foci of multiple sclerosis.
 Strümpell (Neurol. Centralbl., No. 12, 1918) urges caution in the interpretation of these findings.