

A CASE OF DIFFUSE CEREBRO-SPINAL SCLEROSIS

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INTRODUCTION

Since Kelp (1871) and Schuele (1872) reported certain cases under the title *diffuse sclerosis* a great many have been described by different authors. Among these, Strümpell and Heubner were the first to describe the clinical symptoms and the anatomical findings more thoroughly than the preceding authors and to give a certain definition to this disease. According to these authors, diffuse sclerosis is characterized by a rapidly progressing mental deterioration and a peculiar spastic condition of the muscles of the body. Anatomically an abnormal increase in consistency of the medullary substance as a result of proliferation of the interstitial tissue was noticed.

As to the etiology of this disease, the opinions of the different authors vary greatly. Most writers seem to believe that diffuse sclerosis is, in reality, the terminal stage of a number of different diseases. Some of them are probably of a syphilitic nature, while others are possibly in the advanced stage of disseminated sclerosis. The discussion as to the genesis of the pathological changes is not exhausted. It is to be decided, if these changes be exogenous or endogenous in character, and what relation exists, if any, between the changes on the nervous parenchyma and those of the interstitial connective tissue element.

Thus the etiology and the genesis of this condition is not settled in spite of the large amount of research on the subject.

The following is a case of diffuse sclerosis showing very unusual clinical manifestations and very peculiar pathological findings:

ABSTRACT OF CLINICAL OBSERVATIONS

Preceding the mental disturbances, which occurred eighteen years before her death, the patient had a "shock," followed by eight weeks' aphasia. Upon recovering, there was no apparent speech defect. She limped somewhat. She was committed to the Worcester State

Hopsital when she was thirty-eight years of age, showing manic exhilaration. She stayed there seven years, during which time she manifested the alternating periods of excitement and depression. She was diagnosed as a typical case of manic depressive insanity. She showed, however, some impairment of the memory and poor insight as to her condition even in time of remission. The patient escaped from the Worcester State Hospital and was admitted to this hospital when she was forty-eight years of age. When admitted she presented a slight asymmetry of the face and evidence of mitral regurgitation and hyperactive reflexes. The Wassermann test of the blood serum was positive. Mentally, she still showed alternating excitement and depression and was considered to be a manic depressive case. But in a number of years she became gradually demented. From her forty-sixth year she had a number of fainting spells with short periods of unconsciousness. She gradually weakened and became rather indifferent and apathetic. From this time she was considered to be tuberculous and was cared for in that building, being in bed all the time. When about forty-nine years of age she was markedly demented, helpless and was suspected of general paralysis. The examination of the spinal fluid was negative. She failed progressively both mentally and physically. She became disoriented and apathetic. She died in this condition, eighteen years after the onset of the mental disorder. In this manner the clinical condition of the patient swayed from typical manic depressive to a suspicion of general paralysis, dementia præcox and possible epilepsy.

POSTMORTEM OBSERVATION

Autopsy twelve hours after the death. The anatomical diagnoses are as follows: Well developed and nourished (body length 156 cm., body weight 40 kg.); uterus sinistrotorted; high placing of the left tube and ovary; fibrous adhesive pleuritis of both sides; chronic vegetative endocarditis; congestion of the inferior lobe of the right lung; beginning sclerosis of the aorta; chronic diffuse nephritis; fibroid of the uterus; a small ovarian cyst; catarrhal cystitis; etc.

Description of the Brain: The calvarium is thick and heavy. The grooves of the meningeal vessels are shallow. The dura is not thickened but is slightly adherent to the pia mater. There is some subpial edema and milky of the pia mater. The vessels over the entire brain are injected. The basilar artery is slightly sclerotic. The brain is remarkably small, weighs only 870 grams.

Pituitary Body and Spinal Cord: Not remarkable.

The brain was carefully examined after two weeks' fixation in

10 per cent. formalin. Both hemispheres are about the same size; measuring 15 cm. in length, 5.5 cm. in breadth, 6.5 cm. in height. The convolutions of the cerebrum do not appear atrophic, though they are apparently simpler than normal. In the middle part of the

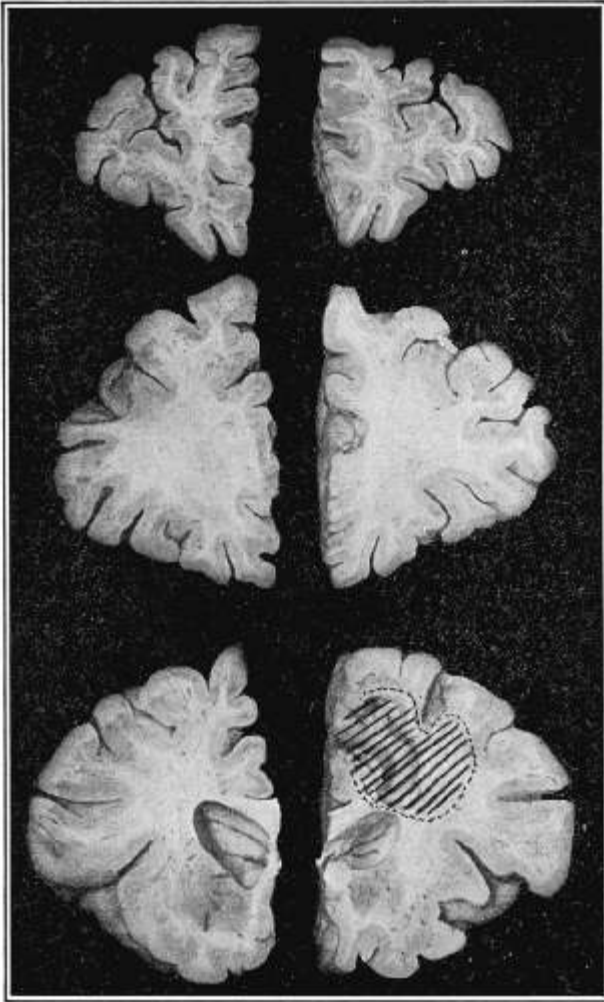


FIG. 1. Striated part shows cyst and softening.

right, first frontal convolution, chiefly on the medial aspect, there is a cyst as large as the tip of the small finger (Fig. 1). The wall of this cavity is smooth, white in color and not pigmented. The second frontal convolution at the junction to the anterior central convolu-

tion is very narrow and soft to the touch, indicating a softened area inside of this part. Otherwise, the brain is unusually firm in consistency and gives the feeling described as "lederartig."

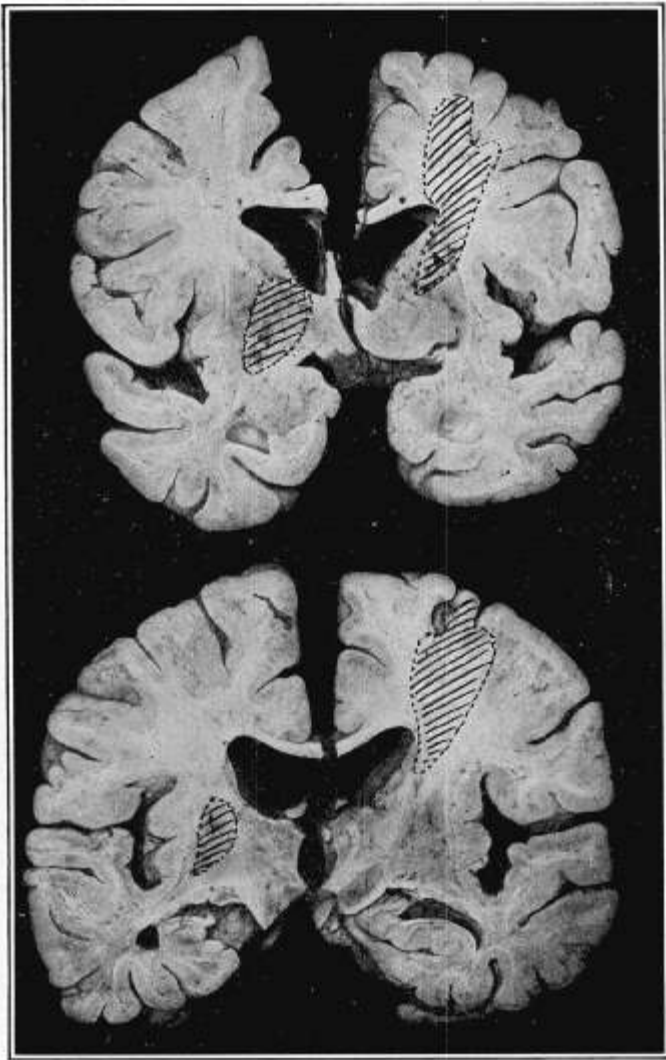


FIG. 2. Striated parts show cysts and softening.

Examination of the Cut Surface (Figs. 1 and 2): Beginning from the cyst of the right first frontal convolution and ending at the above-mentioned softened area of the right second frontal convolu-

tion, the larger part of the centrum semiovale of the right side is softened. This softening involves a part of the internal capsule, and on the cut surface through the precentral sulcus, there is a small cyst in the internal capsule (Fig. 2). The internal capsule and an adjacent part of the lenticular nucleus of the left side is also the seat of the softening, which appears somewhat brownish yellow in color.

Except in these softened areas, the white substance of the brain feels uniformly firm. The ventricles are not dilated. The ependyma is not granulated.

Sections of the brain stem reveal some softening and small cysts in the pons on each side, between the pyramidal tracts and medial lemniscus.

MICROSCOPICAL FINDINGS

The vessels of the pia mater show thickened walls and some regressive changes. Here and there a slight infiltration with lymphocytic cells is observed. No plasma cells are found even by careful examination with Unna-Pappenheim's method.

The changes pertaining to ganglion cells of the cortex and basilar nuclei are not remarkable. The cells around the cystic degeneration present very marked sclerotic changes (Nissl), combined with remarkable deposits of fatty, pigmented substance. Otherwise the parenchymatous involvement is not very conspicuous. The unusually small brain ought not to be considered as an atrophic condition due to the parenchymatous degeneration of the brain. The small brain with apparently simpler convolutions would indicate hypoplasia rather than atrophy of the brain.

The most striking alterations are those of the myelin-sheaths and the glia cells. In the areas of the softening, mentioned above, the myelin-sheaths show marked, but not complete degeneration (Fig. 3). The line of demarcation between normal and abnormal parts is not as sharp as in multiple or diffuse sclerosis as usually reported, but shows a gradual transition. Even in the center of the degenerated marrow, and in this respect differing from cases formerly reported, the myelin-sheaths have not entirely disappeared. The involved focus shows loosened myelin fibers and irregular degeneration. Some fibers are thin with light staining, while others are thick, showing irregular swelling and poor staining qualities. This kind of degeneration is found, not only in the softened areas of the right hemisphere, but in the whole extension of the right centrum semiovale, in the greater part of the left centrum semiovale, the internal capsule and the adjacent part of the left lenticular nucleus. In the

direct neighborhood of the cysts both myelin fibers and axis cylinders have entirely disappeared. The degeneration of the myelin-sheaths appears to have occurred hand in hand with that of the axis cylinders and in this respect it differs from the cases of Schilder and others.

By Weigert-Pal's staining the pyramidal tracts both in brain stem and spinal cord appear somewhat paler than other parts, suggesting possible secondary degeneration.

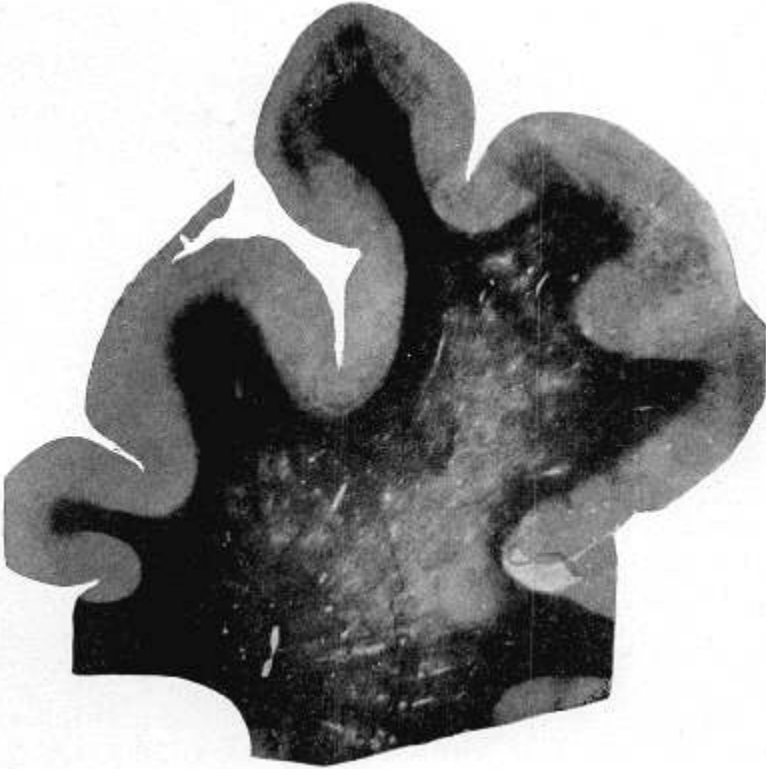


FIG. 3. Degeneration of myelin sheaths in the centrum semiovale of right side.

The most important pathological findings in this case, as the title of this paper indicates, consist in the changes found in the sustaining tissue. The glia cells are enormously increased both in the gray and in white matter of the whole central nervous system, *i.e.*, brain, brain stem, cerebellum and spinal cord. These cells are not only increased in number, but also show some striking peculiarities. The nuclei of these cells present unusual varieties of form and size. The superficial cortex layer is occupied by a great number of spider cells,

a smaller number of cells showing dark-stained, small, round nuclei and a few rod cells. In the 3-4 cell layer (Brodmann) of the cortex a remarkably large number of rod cells (Nissl and Alzheimer) of typical form are observed (Fig. 4). The nuclei of these cells are abnormally elongated (17-18 micra), having round ends and fine prolongations. In the deepest part of the cortex there is a larger number of the shorter and plumper form of rod cells, which correspond



FIG. 4. Rod cells and various forms of the nuclei of glia cells in third layer of the posterior central convolution.

to the second group in Ulrich's classification. In addition to these rod cells, there are small, round nuclei of various forms. There are still other forms, including transitory forms between rod cells and glia cells.

The rod cells in this case do not show direct topographic relationship to the vessels, contrary to the claim of Nissl and Alzheimer that this is one of the very common findings for these cells. Nevertheless, many rod cells are found as trabant (satellite) of ganglion cells as described by Cerletti. Some of them seem to embrace the body of

the ganglion cells and are found, not only along the apical prolongation, but at the base of the cell body. The rod cells have been observed by various authors in multiple sclerosis but not in diffuse sclerosis. According to Nissl the rod cells are not found in a sound brain, but are found principally in the paralytic brain and occasionally in other diseased conditions, but playing a less important part. Spielmeier found the rod cells in tubercular meningitis combined with general paralysis, while Dupré found them in arteriosclerotic

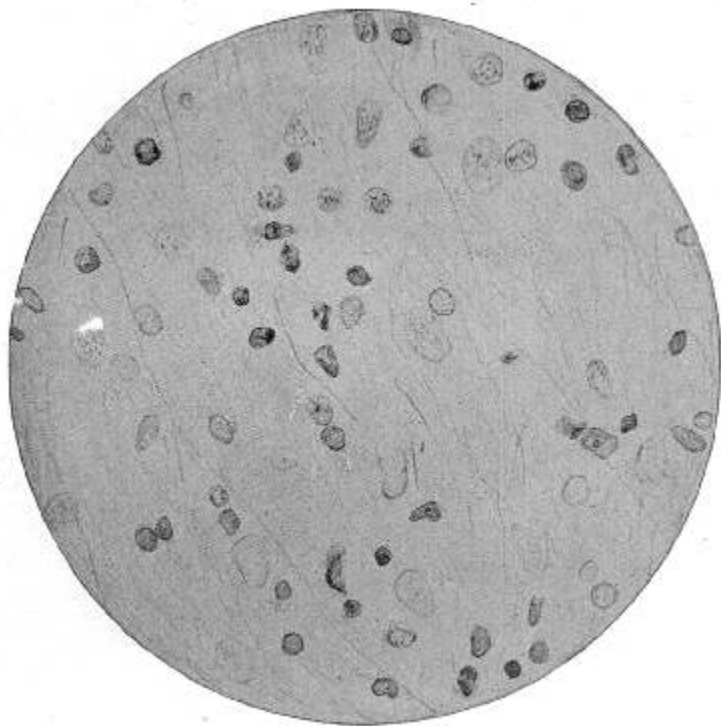


FIG. 5. The nuclei of glia cells in the white matter at the first frontal convolution not far from cystic degeneration.

processes associated with general paralysis. These authors are of the opinion that the rod cells indicate paralytic processes rather than other conditions. Sträussler found these cells in smaller numbers in a normal subject but abundant in congenital atrophy of the brain and gummatous meningitis. So far as the genesis of these peculiar cells is concerned the opinions of different authors vary. Some propose the ectodermal origin, others insist on the mesodermal. The second theory divides again into three different ones, namely: (1) derivation from the adventitia; (2) from the endothelium; and (3)

from the connective tissue of the pia mater. The first theory is affirmed by Cerletti and Sträussler and the second by Nissl and Alzheimer. Ris, Achúcarro and Ulrich believe both in mesodermal and ectodermal origins. In this present case the writer believes firmly in the gliogenous theory, because:

1. The rod cells are found together with abnormally increased glia cells.
2. There is every transitional form between rod cells and glia cells.

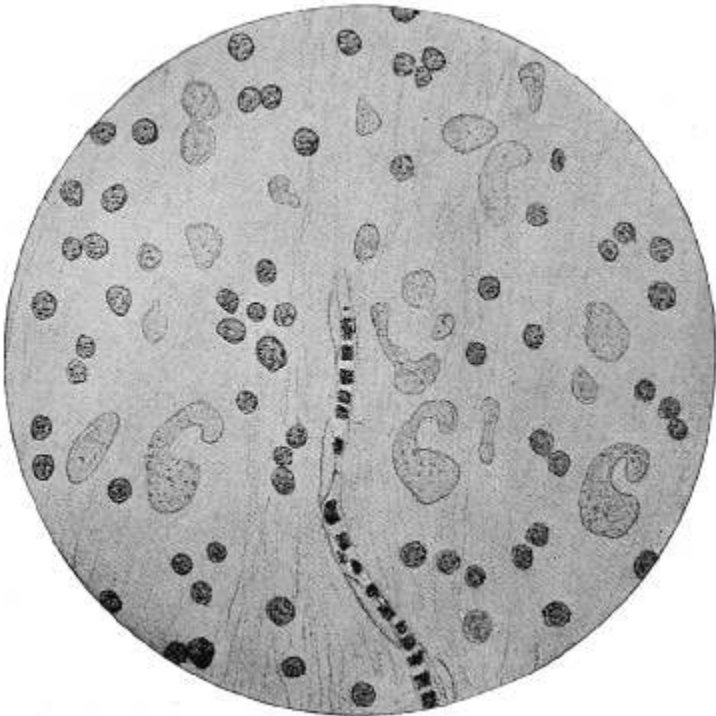


FIG. 6. Crook-neck squash formed nuclei of glia cells at pons.

3. There are many typical trabant rod cells as are illustrated in Fig. 4.
4. The direct relationship between vessels or pia mater and rod cells is not proved.
5. The rod cells are found in the cortex, where the alterations of the vessels are not remarkable.

In the white matter of the brain there are a greater number of pale, large nuclei of various forms, such as ovoid, elipsoid, pear-shaped, kidney-shaped, rod-shaped, etc. (Fig. 5). In the neighbor-

hood of the cystic areas the glia cells show more or less distinct regressive processes. The nuclei are dark stained, have no fine archi-

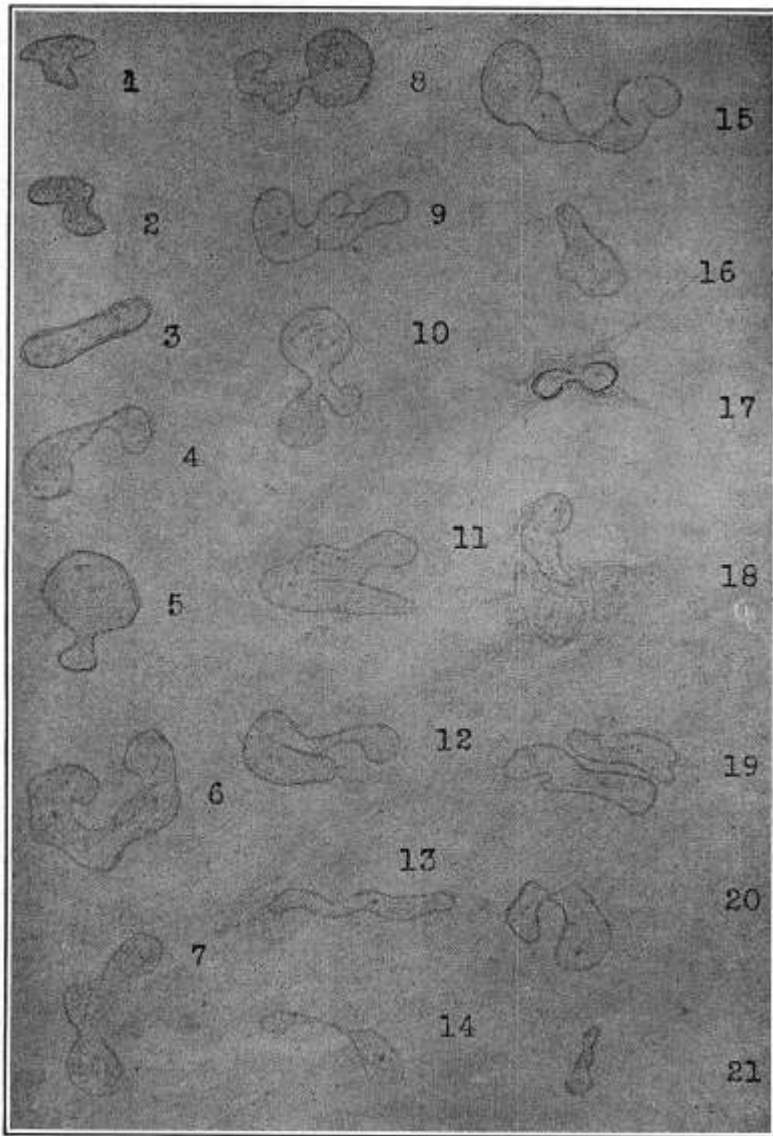


FIG. 7. Various forms of nuclei of glia cells found in peduncle and pons.

itecture and some of them appear to be contracted, while others show evidences of disintegration. There are only a few atypical rod cells in the white matter.

In the peduncle, pons and medulla the gliosis is most remarkable. There are almost all imaginable sizes and forms of the nuclei. In addition to the ones with round, oval, ovoid and spindle forms, there are many striking varieties of queer forms (Figs. 6 and 7). Club-shaped, biscuit-like forms, crook-neck squash forms and other

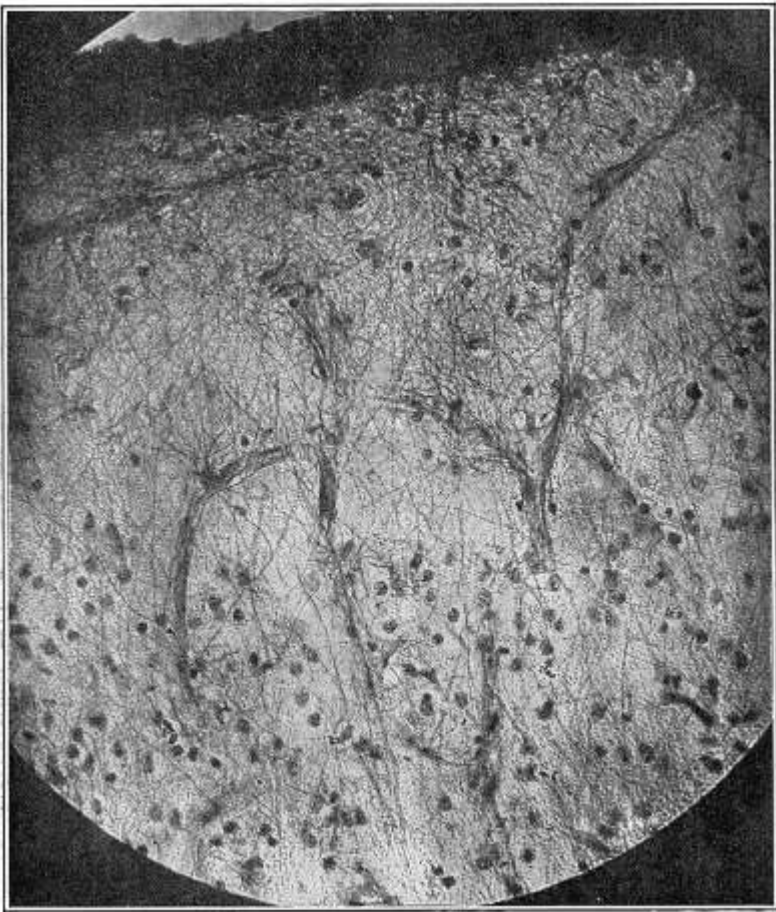


FIG. 8. Weigert's neuro-glia fiber staining, showing thickening of the border glia and fibers of the upper cortex layer.

peculiar shapes; bodies of nuclei with sprout, knob and prolongation, notching and lacing. Some of them are very well likened to the various forms of the motile ameba. The writer is of the opinion that these forms indicate the direct dividing of the nuclei, as was claimed by Lotmar in cases of glioma. Fig. 7 illustrates various

forms of the nuclei, in which 17 indicates a nucleus in the process of dividing, while 18 and 19 suggest the nuclei already divided.

In the cerebellum glia cells are found very much increased in the Purkinje cell layer and in the white matter. Forms and sizes of the nuclei are manifold as in other places, showing also fairly abundant specimens of the rod cells.

Throughout the spinal cord glia cells, though not so numerous as in the brain stem, are abnormally increased. Here, rod cells of atypical form are observed, together with nuclei of various forms and sizes.

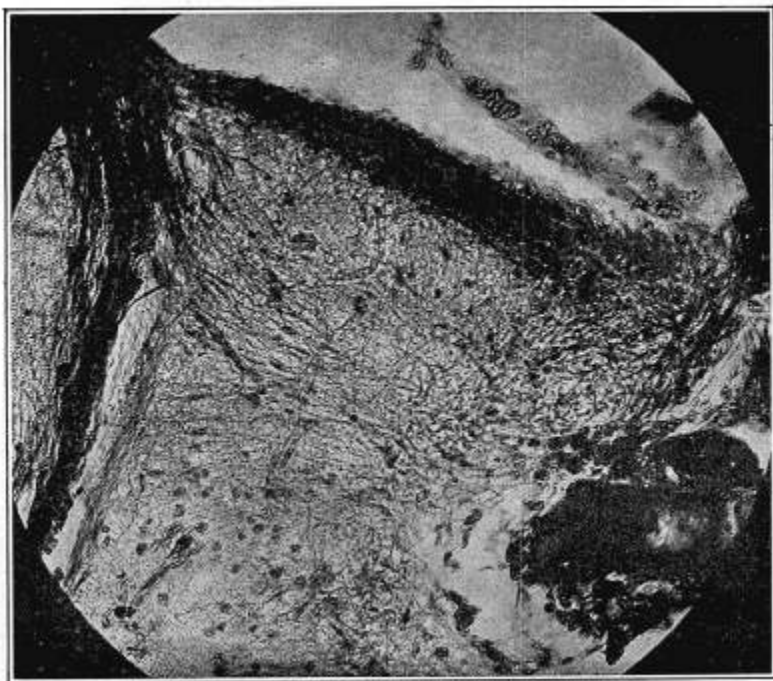


FIG. 9. Weigert's neuroglia fiber staining. Thickening of the glia-fiber of the cell free border. Envelope formation around the vessels.

The new formation of the glia fibers is remarkable at the cell free border of the cortex, especially at the central region of both hemispheres. This fiber network of the border is considerably widened, and at the same time, the increase of fibers going into the cortex layer is apparent; the fibers are well demonstrated deep into the 4-5 layer (Brodmann) (Fig. 8). The increase of glia fibers is not limited to the free surface of the cortex, but is also around the vessels,

making a thick envelope. This envelope formation is readily understood, if one is acquainted with the condition, which Nissl, in agreement with Weigert, has emphasized, that the vessels, being of mesodermal origin, behave toward the nervous tissue like a foreign body, and therefore are isolated by a layer of the glia. The envelope formation is extremely marked at the central region of the right hemisphere (Fig. 9). So marked a protecting wall is not seen in general paralysis or arterio-sclerosis, in which the perivascular growth of the neuroglia fibers is commonly observed. The extraordinary formation of the protecting wall should be considered as a result of the exaggerated function of the pathological neuroglia. In the region of the softening, the formation of the glia fibers is not remarkable, but at the internal capsule and the lenticular nucleus of the left side, the brain matter is entirely occupied by a dense network of rather fine fibers.

The vessels of the brain are more or less sclerotic. In the central region of the right hemisphere the walls of the vessels are considerably thickened, and in certain parts an abnormal growth of the adventitious tissue is seen forming tumor-like bodies. Some of the cells of the vessel wall seem to be isolated and are scattered in the brain matter. A similar process is observed by Bonome, Bielschowsky and Ranke in glioma. The perivascular lymph spaces, especially in the above-mentioned parts, are dilated and large numbers of cells carrying pigment, a smaller number of fat corpuscle cells and a few lymphocytic cells are observed. The alterations of the vessels are only marked in the circumscribed areas of the right hemisphere and not generally over the whole brain. Although there are softened areas and cells carrying pigment around the vessels, the whole process of the gliosis can not be considered as a secondary change due to the primary vascular alteration.

Besides the remarkable findings of the sustaining tissue, there are a number of interesting changes in the cerebellum. Here, the Purkinje cells are not remarkable in form and size. But a considerable number of Purkinje cells are found high up in the molecular layer and present a typical case of so-called Heterotopia (Fig. 10). In addition to this peculiar finding, there is swelling of the dendrites and the axis cylinders. The swelling of the latter has been observed by the writer in various kinds of brain diseases but the former is found only in selected cases and very rarely. Besides those of the amaurotic family idiocy, Sträussler described the same kind of swelling, with the enlargement of the axis cylinders in a case, which manifested certain cerebellar symptoms, agitation and intellectual weakness.

The author attributed this peculiar change of the dendrites to the acquired factor playing upon the congenital weakness. In our case the abnormal smallness of the brain and the heterotopy of the Purkinje cells all together point to the congenital disturbance of the development. The writer considers, therefore, that this peculiar swelling of the dendrites has resulted from the external factor

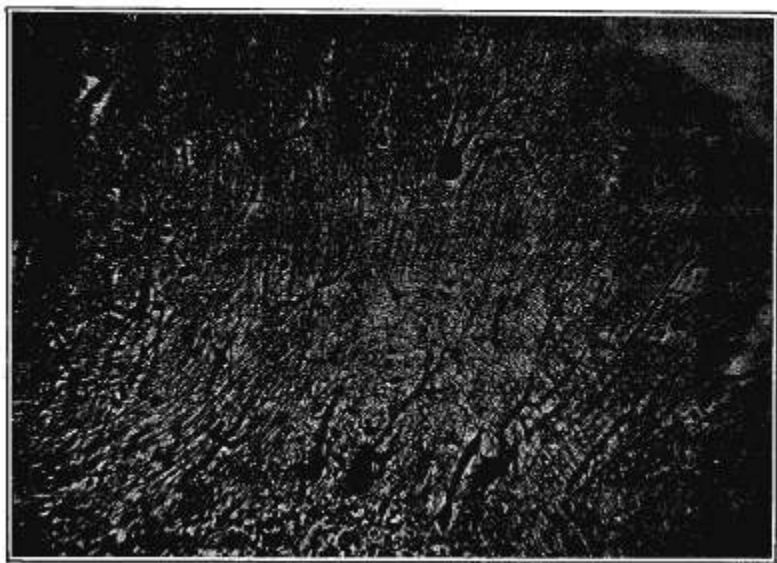


FIG. 10. Heterotopy of the Purkinje cell.

playing upon the inherited weakness. Upon this peculiar change, however, the writer intends to publish in a later communication his further observation and his opinion.

PATHOLOGICAL CONSIDERATION OF THIS CASE

The pathologic anatomical findings in this case are, as described above, very much complicated and make the correct interpretation of the case extremely difficult. Among the remarkable findings, the universally appearing gliosis of the whole central nervous system, could reasonably be considered as the principal pathological feature of this case. But can the term "diffuse sclerosis" be applied and are those manifold symptoms covered by this diagnosis?

Before going into further discussion let us briefly state what is diffuse sclerosis. Macroscopically this disease is characterized by an abnormally firm consistency of the medullary substance. Chronic

internal hydrocephalus and the thickening of the pia mater are also frequent findings. Although the macroscopical findings are very characteristic, the histological substrata are rather vague in appearance. Some of the cases are classed as pseudo-sclerosis because of the negative findings, in spite of the macroscopical characteristics. In the histological findings the abnormal growth of the interstitial tissue is described as an essential anatomical factor. This process is, however, usually restrained in the medullary substance. Hyperplasia of the glia in the cortex has been heretofore very rarely observed and always accompanied by degenerative process of the nervous parenchyma. In the medullary substance most authors observed complete disappearance of the myelin sheaths with more or less decided demarcation against the normal tissue and with relatively well preserved axis cylinders. Infiltration of the peri-vascular lymph space with fat corpuscle cells and lymphocytes is observed by nearly all authors. Cyst formation, or softening, is reported very rarely. The polymorphous condition of the nuclei of the glia cells was observed only by Schilder. There is no case reported, showing an unusual growth of the rod cells, either in the cortex or marrow. The cerebellum is very rarely involved in the pathological processes, showing increase of the glia mostly in the medullary substance. In the spinal cord the sclerosis is very marked. Besides the gliosis in the pyramidal tracts the degeneration of the latter is observed as one of the most frequent findings.

In our case the macroscopical finding of abnormally firm consistency of the medullary substance corresponds exactly with the case of diffuse sclerosis. The pia mater is thickened, though there is no internal hydrocephalus. Microscopical findings are not exactly typical. At least they differ in certain respects considerably from those reported by Heubner or Haberfeld and Spieler. However, as was mentioned before, there are no definite microscopical findings for this disease and our case is reasonably grouped with this kind.

In the first place we have to differentiate our case from the diffuse glioma, with regard to the cyst formation, which is rather characteristic for the glioma, and also with regard to the extreme polymorphous condition of the nuclei of the glia cells.

The cyst formation, though it is very characteristic for the glioma, is not an absolutely new finding for the diffuse sclerosis. Rossolimo observed a large cyst in a case of the typical multiple sclerosis. Schilder found also small cysts in a case of the diffuse sclerosis, which he called *encephalitis periaxialis diffusa*. As for the polymorphous condition of the nuclei of the glia, our case cer-

tainly presents an astonishing example. Even in glioma, findings like this, except in the case of Lotmar, have not been described. But Schilder observed almost exactly the same condition of the nuclei in his diffuse sclerosis case. There are still quite a few points which lead us to consider this case as diffuse glioma. In the latter the boundary of the growth is indistinct and there is no change of the external configuration. Our case is similar to diffuse glioma and differs from the reported case of the diffuse sclerosis, since it shows no distinct demarcation between the degeneration and the normal parts. In the reported cases the axis cylinders of the focus remained in a relatively healthy condition, while in our case, as well as in diffuse glioma, the degeneration of the myelin sheaths is always parallel with that of the axis cylinders. The findings in the vessels, especially the infiltration of the adventitious cells into the brain matter, are very peculiar and these are described by Bonome, Bielschowsky and Ranke in glioma. Admitting all these similarities, our case, in which the increase of the glia element is universal and distributed equally over the whole central nervous system, can in no way be considered as a diffuse glioma.

In the second place general paralysis should be considered on account of the slight pial and perivascular infiltration and remarkable thickening of the fiber network of the border. The appearance of the abundant rod cells indicates also general paralysis. Blood serum was positive for Wassermann test though the spinal fluid was negative for ordinary laboratory tests. But one of the most important findings for the general paralysis, *i.e.*, the degeneration of the ganglion cells is not observed. Eighteen years duration of the mental disease does not indicate general paralysis. Negative laboratory tests of the spinal fluid together with above-mentioned circumstances will safely rule out general paralysis.

What is the etiology of this disease? Is it an exogenous or an endogenous disease of the central nervous system? Is the hyperplasia of the interstitial tissues secondary to the degeneration of the nervous parenchyma or is it a primary overgrowth of the sustaining tissue which in consequence causes the degeneration of the nerve element? This is a very difficult problem to answer.

Strümpell calls this pathological process "chronic interstitial encephalitis" on account of the inflammatory character of this disease. Weiss is of the same opinion. Rebizzi differing with these authors claims it to be a primary disease of the nervous element with consequent growth of the neuro-glia. In general, modern pathologists seem to have a tendency to deny the primary growth of the sustain-

ing tissue which is generally called "chronic interstitial . . . itis." Among the still obscure etiologies of this disease there are lues (both congenital and acquired), brain trauma, acute infectious disease, hereditary neuropathic taint and some unknown toxic agents, etc. But most authors are of the opinion that this disease is, in fact, only a terminal stage of various different diseases.

Let us first analyze, briefly, the pathologic anatomical findings of our case and go over the etiology of our particular case. In our case, there are a number of hypoplastic conditions of the brain and the body organs. The brain is abnormally small with apparently simpler convolutions. The heterotopia of the Purkinje cells is an unusual condition, which indicates a disturbance of development as does the high position of the left tube and ovary. Furthermore the swelling of the dendrites suggests, as was explained before, the congenital weakness of the nerve element. All these facts point to the congenital factors underlying in this case. The glia cells in this case seem to have had congenital predisposition, to be attacked by an external agent. Schilder's case showed also hypoplastic condition, such as chlorotic aorta and absence of the ovary on one side, though there were no abnormalities in the brain. Haberfeld and Spieler observed two brothers who died of this disease, which, in both cases, showed the same symptoms and ran the same course. All these suggest together with our case the endogenous component underlying in this disease.

In our case the newly formed glia cells are not uniform in character. The glia cells of the cell free border are apt to build more fibers. In the cortex layer, contrary to this, there are a remarkable number of rod cells of gliogenous origin with a small number of glia cells having large and small nuclei. In the medullary substance of the cerebrum there are more large nuclei than small ones. In the brain stem the proliferative process is most marked. Here there are almost all imaginable forms of the nuclei, suggesting direct division of the cells. The polymorphous condition of the nuclei in the cerebellum and the spinal cord is not so marked as in other parts, though there are a variety of forms and a considerable increase of the cells. In brief the newly formed glia cells show topic diversity which is not at all associated with the degenerative process of the nerve parenchyma. This topic diversity, with the exception of the active proliferative process in the brain stem, seems to express the different functions of the neuroglia cells. But these functions are performed only in an exaggerated manner, the glia cells of the border, for example, producing luxurious fibers, and the cells of the cortex ex-

hibiting peculiar shapes of the rod cells, etc. There is no reason, therefore, in our case, to consider that the general gliosis is a secondary process due to a primary nerve degeneration. It is more probable to presume that the proliferative process is a primary one. Our case, in this sense, is neither a terminal stage of the disease of the nervous parenchyma nor a chronic interstitial inflammation. It is rather to be grouped with neoplasma such as diffuse glioma.

CLINICAL CONSIDERATION IN REVIEW OF THE PATHOLOGIC ANATOMICAL FINDINGS

The diffuse sclerosis which has been reported is a disease occurring in young individuals. With the exception of Strümpell's case (sixty-six years of age) all cases began in childhood or at least in the beginning of puberty. Schupfer's case is nine years of age; Rossolimo's case, sixteen; Ceni's case, nine; Beneke's, one and three-fourths; Habermeld and Spieler's, seven; etc., etc. Both sexes seem to be attacked equally.

The clinical symptoms which have been reported, consist of spastic paralysis and progressive dementia. The disease is fatal, the duration being only several years. The cause of death is usually malnutrition and decubitus.

Our case is clinically as well as pathologically considerably different from those already reported. The onset of the disease is very late. The duration of the disease is eighteen years. She did not show typical spastic paralysis, though she showed oftentimes disturbance of the gait and evidences of hemiplegia. The most apparent symptom, especially in the former half of the course, was a manic depressive manifestation. The hemiplegia is explained by the softening of centrum semiovale and the internal capsule. But how is the manic depressive condition explained? The writer presumes an intermittent growth of the neuroglia, as in cases of glioma. And this intermittent growth seems to be expressed clinically in alternating symptoms which in the later half become very much more prominent, the cyst and the softening of the centrum semiovale, especially in its anterior part, will give the satisfactory explanation. The fainting spells with unconscious periods are explained easily by so marked a change in the cortex.

CONCLUSION

The writer presents a case of diffuse cerebro-spinal sclerosis, which both clinically and anatomically considerably differs from the cases already reported.

It showed in the beginning almost typical manic depressive manifestations, but later, the constantly progressing dementia was in the foreground. The patient showed evidences of hemiplegia, but the spastic paralysis was not as marked as in a case of Heubner form.

The principal pathological anatomical findings are: abnormally firm consistency of the medullary substance with softened and cystic areas, diffuse increase of neuroglia element in various forms, diffuse degeneration of the myelin sheaths and axis cylinders of the white matter, etc.

As for the etiology of this disease the writer assumes an endogenous factor, based on a number of hypoplastic conditions of the brain and the body organs.

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