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A CONTRIBUTION TO THE STUDY OF GLIOMA

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INTRODUCTION.

One who engages in the study of glioma must necessarily encounter three important problems, which have been studied and discussed by a great many writers.

The first is the question of how to differentiate gliomata from sarcomata, and in association with this the arguments concerning gliosarcoma, and also the so-called glioma sarcomatodes. Golgi was the first to claim that the glioma is principally made of glia element, a simple fact known to all at the present time, but considered a great discovery at that time. Before that time, for a considerable period, Virchow differentiated gliomata from sarcomata as entirely independent tumors of the central nervous system, but he was unable to give definite histological criteria characterizing these tumors, because in those days the glia element was not known to be the derivative of the ectodermal system, and was not distinguished from the connective tissue element of the mesodermal origin. Among a number of authors, Stroebe is one who, after studying a great many cases of glioma, undertook to establish a definite differential diagnosis between glioma and sarcoma. Stroebe advanced the theory that the glioma is practically composed of astrocytes, and that "for the diagnosis of glioma not only the presence of the fibers among the cell elements is necessary, but also those fibers ought to be connected with cells in form of astrocytes." Since that time a great

many authors have proposed a number of criteria for this problem, but being based, as we know, on a defective knowledge of the neuroglia, it was always unsatisfactory. The rapidly growing glioma, at least in a part of the tumor, and a certain kind of glioma such as ameboid cell glioma, may not show any fibers at all, and the diagnosis cannot be made on the grounds of the formerly known characteristics of the neuroglia, but can be made only by the more profound recent knowledge of the latter element.

Since the classical study of Weigert (1895), our view of the structure and function of neuroglia has undergone a great change. Weigert demonstrated the neuroglia fibers by his own elective method, and considered them to be those executing the important and only function of the neuroglia, connecting and sustaining the tissue of the central nervous system. Shortly after that, Held (1909) approved Hardesty's idea of the syncytial nature of the glial protoplasm for the entire central nervous system, and still later (1903 and 1909) he pointed out that this syncytial protoplasm gives forth the characteristic fibers and cuticular membrane. Through the latter the ectodermal tissue of the central nervous system is separated from the genetically foreign substance of the pia mater and the blood vessels. He showed also that the fiber free cells of the glial origin, laden with waste product of the pathologic metabolism, could go through the limit membrane into the perivascular space, thus being set free from the syncytial union of the central nervous system. Bonome (1907) studied and showed how the early syncytial structure of the glial protoplasm metamorphoses into the complete syncytium of the mature central nervous system. According to this author, the metamorphosis taking place in this early period is not a simple developmental proceeding, but is a complicated process, in which chemically and morphologically different substances of various kinds are produced.

As for the pathological neuroglia, we owe our present knowledge to a great extent to Nissl, Alzheimer, and their pupils. Nissl described, while studying various diseases of the central nervous system, a number of different forms of progressive and regressive metamorphosed neuroglia cells. To those forms already known, he added a peculiar type of elongated rodshaped cell, which was called by the author *Staebchenzelle*, rod cell. Alzheimer's* (1899-1904) staining methods, by which he demonstrated the protoplasmic portion and products of metabolism within the cell, were better than any other methods. He pointed out clearly and precisely the scavenger function of the neuroglia element, and described a certain type

of glia cells as *amoeboides Gliazelle* (1910). He also noticed that under certain conditions, the protoplasmic syncytium proliferate without new formation of neuroglia fibers, and that primary existing fibers disintegrate occasionally into a peculiar substance amidst the altered syncytial protoplasm (Alzheimer's *Fuellkoerperchen*). Merzbacher, in his study of the morphology and biology of granule cells (1909), expressed his idea that neuroglia cells may have reparative or reconstructive and nutritive function, as well as scavenger function. Many authors support this latter conception. Marui, in his study of central neuritis, demonstrated a certain granule, which he called "Neucleoproteid like granule," in ameboid and preameboid cells of different cases, and in granule cells of a case of cerebral hemorrhage, and associated this granule with the constructive function of the neuroglia cells.

By these recent studies, our knowledge of normal and pathological glia is evidently broadened. The differential diagnosis between glioma and sarcoma has become much easier than it used to be. The glioma and sarcoma are genetically entirely different neoplasms, and therefore ought to be strictly distinguished from each other. The designation of gliosarcoma is to be avoided if possible, though there are rare cases of such combination.

The second problem is that of the pathogenesis of this tumor. The important arguments of this problem are: the question of congenital predisposition; possibility of the displacement of the embryonal sprout of tissue; the persistence of the embryonal cells; whether the fully developed glia cells are able to differentiate further into the lower type of neuroglia cells, etc. These have been much studied and discussed by various authors. Some support Cohnheim-Ribbert's theory of neoplasm, while others try to deny it.

The third problem encountered is regarding the relationship between the pathological proliferation of the neuroglia and the neoplasm of the neuroglial origin. Some consider them to be entirely different processes, while others do not find any fundamental difference between these two. In literature we find a number of different pathological conditions of abnormal neuroglia proliferations, namely, marginal gliosis, perivascular gliosis, ependymitis granulosa, diffuse sclerosis, multiple sclerosis, tuberous sclerosis, gliomatosis, neuroglioma ganglionare, glioma gangliocellulare, diffuse glioma, glioma, glioma sarcomatodes, etc. Are these entirely independent, or are they closely related, and to be explained under the same pathological process? This is an extremely difficult question.

With a few exceptions, former authors studied the tumor itself

and its immediate neighborhood more than the general glial condition of the individual, while the study of the latter is extremely important for the understanding and solving of the questions above mentioned, especially the last two. The writer has studied this in four cases of cerebral glioma, and found a number of interesting facts which may throw some light on the problems presented.

OBSERVATION I

Central Glioma of the Third Ventricle

This case was presented by Dr. L. G. Lowrey as, *Report of a Brain Tumor in a Case Clinically Considered to be Paresis*, in the *Journal of Nervous and Mental Disease*, Vol. 47, No. 5, 1917. After histological study he made a diagnosis of "Glioma, or at most a gliosarcoma." He reported this case, "because of the rarity of brain tumors among the insane, and because of the erroneous diagnosis of paresis made in this instance." As this was the nature of his purpose, he did not go into detail of general glial condition, although he noticed "the increase in the neuroglia in general, and a great many cells presenting themselves as long drawn out rods." The writer has studied this case from a different standpoint. The case history and general pathologic observation is abstracted from Dr. Lowrey's report.

The case is that of a male, D. S. H. Clinical No. 17643, Pathological No. 1764. This man was an illiterate French Canadian, with onset of mental trouble at age of forty-one. The family history was negative for nervous and mental diseases. Patient was married and had six children. There was no history of trauma or serious disease; no venereal disease. Onset of present trouble from 1911 to time of admission in October, 1913, at age of forty-three. He failed gradually, and did not work during this period. It was said he had a "shock" in 1912, following which he was unconscious for a few minutes. His speech was somewhat thick and indistinct for some months. He was never irritable, but became somewhat restless at night and memory gradually failed. For two weeks he was very weak and had to be cared for in bed. He complained of pains in head and all over body.

Physical Examination.—Well developed and nourished; mucous membrane pale; tongue tremulous; face, asymmetrical; lungs, negative; heart, normal except that sounds were distant; pulse, 82. There was moderate thickening of the peripheral vessels. Blood pressure was 135. Abdomen, negative. Wassermann on blood serum, posi-

itive, on spinal fluid, unsatisfactory. Fluid contained blood; hence, other laboratory tests were unreliable.

The patient complained of no pain or headache. The eye movements were normal. Arcus senilis. Pupils, irregular, unequal, react sluggishly to light and distance. Vision not determined. Co-operated poorly in sensibility tests, so that little was made out. No tenderness of large nerve trunks. Could not recognize objects, "due to dementia." Knee jerks absent. Arm reflexes, normal, Cremasteric and abdominal reflexes absent. Incontinent. Romberg, positive. Marked tremor of fingers and tongue. Somnolent.

Mental Examination.—Dull and stupid. Remained quietly in bed. Untidy. No spontaneous speech. Responses relevant and coherent. Some motor speech defect. Partially disoriented. No evidence of hallucinations. Memory much impaired. No tendency to fabricate. Could not be made to understand the association tests. Expressed no delusions. No insight. Thought he was sick, but mind all right. Indifferent.

Course of the Disease.—October 28, quiet, dull stupid; physical condition, poor. November 1, demented, speech defect, untidy. November 4th, brighter, more responsive, disoriented, memory impaired. November 12th, disoriented for place and partially for time; contented. November 14th, presented at staff meeting with a diagnosis of general paralysis, to which all agreed. December, difficulty in walking. Fell out of bed; staggering gait; headache and toothache. Eyesight dull. No delusions or hallucinations. January, 1913, convulsions. February, quiet, failing. No relevant responses. August, demented. Excited and angry at times. Marked expectoration. Spoon-fed. October 9th, gradually failed for two weeks. Had series of convulsions from which he did not rally. Died.

Autopsy.—One and one half hours post mortem. Contracture at hips and knees. Atrophy of calves. Tronchanteric and sacral decubitus. Pupils unequal. Axis of the eyes directed outward. Abdominal organs in good position. Adhesive pleuritis. Bronchopneumonia. Slight fibrosis of heart muscle. Fatty liver. Diffuse nephritis. Small colloid cyst in thyroid. Dura not thickened nor adherent. Pia not thickened. Considerable subpial edema. Basal vessel not sclerotic. Pituitary small and flat. Brain weight, 1560 g. Pons and cerebellum 180 g. Cerebellum slightly softer than normal. Sections negative.

Hemispheres.—Just in front of the anterior extremity of the corpus callosum there was, in the left hemisphere, a white, firm,

raised area of irregular shape. This was firmer than the surrounding tissue, whiter than the gyri, but had much of the same physical characteristics. Median sagittal section revealed a large irregular grayish mass, containing numerous soft, reddish, hemorrhagic areas. This had invaded the corpus callosum and both thalami. To a large extent it filled up the third ventricle, and more or less blocked the lateral ventricles, thus filling all apertures below the corpus callosum: The irregular mass observed on the median aspect of the left hemisphere was apparently not connected with the larger and deeper mass.

After the fixation, frontal sections were made. Tumor mass larger on the right than on left. In certain areas, as just above the thalamus, the entire right ventricle was filled by it. Where it invaded the ventricle walls, it was of looser texture. The corpus callosum was much corroded. On the right side, a whitish mass, rising behind the thalamus, extended for a short distance on the median surface of the hemisphere. The descending horn of the left lateral ventricle contained a large blood clot, in addition to bloody fluid. Gyrus dentatus poorly marked on left side. Above the posterior horn of the lateral ventricles the white matter was soft.

Microscopical Examination.—In addition to Dr. Lowrey's preparations which were stained with cresyl-violet, Weigert's iron hematoxylin and picro-fuchsin, phosphotungstic acid hematoxylin, Weigert's myelin sheaths method, and Marchi, sections were made from several parts of the tumor, both hemispheres, pons, cerebellum and spinal cord, and were stained by Weigert's neuroglia method, Cajal's neuroglia method, Alzheimer's methods for demonstration of protoplasmic neuroglia, Bielschowsky's method, and Herxheimer's for lipid substance.

The tumor consisted of glia cells, closely packed together, with a varying proportion of glia fibers. The glia fibers were demonstrated very well in all parts of the tumor, although they were rather thin and poorly developed, when compared with the abundance of cell element. In the periphery of the tumor, where the tumor tissue showed gradual transition into the normal brain substance, the glia fibers were thicker than they were on the surface or in the center of the tumor. A great many astrocytes or spider cells were observed in this region. The nuclei of the glia cells were of various shapes, some oblong, others oval and polymorphous. The staining quality of these nuclei also varied, the smaller ones being stained deeper than the larger ones. The chromatin substance and intranuclear network were well retained. The protoplasmic portion of the cells

were for the most part very small, but when demonstrated showed typical polyangular shape and direct connection to the fibers. Occasionally there were large cells, appearing like ganglion cells, scattered in various parts of the tumor. These were, apparently, the same cells described by Stroebe and others as, "Ganglion cell-like element within the glioma." Occasionally the cells had two or more nuclei, usually located in the periphery of the enormously large cytoplasm, with vacuoles of various sizes. The protoplasm of these large glia cells contained elements of various kinds, some possibly being phagocytic, while others were of regressive, character. These cellular contents showed various staining qualities, by which they could be separated into Marchi, fuchsinophilic, lipid granule, amyloid corpuscle, etc. In the study of pathological neuroglia these cells are known as granule cells, and their function as scavenger cells. Some of the tumor cells thus seem to function like the normal neuroglia.

In certain sections the nuclei of the glia cells aggregated into a sort of rosette formation. In none of the sections, however, was the writer able to find the cavities lined with epithelial or ependymal cells. Since Stroebe found a cavity lined with epithelial cells, and considered it to be a sprout of the embryonal neural tube, which gives rise to later development of the glioma, the like formation has been described by a number of authors. Some hold the same opinion as Stroebe, while others regard it to be a secondary formation from the tumor cells. The question arises, as to whether or not the glia cells are capable of transforming themselves to a lower embryonic stage of development. This question, and the relationship between the rosette and epithelial formations, will be discussed later.

Capillaries were markedly increased. Vessel walls were thickened, and showed occasional calcification and hyaline degeneration. Perivascular lymph space was widened, and in it some fat corpuscle cells were found. Throughout the tumor were hemorrhagic and necrotic areas.

The exact origin of this tumor cannot be definitely determined. The tumor cells did not show definite characteristics of ependymal cells, although most of the cells were more or less elongated in shape. The tumor filled most of the lateral ventricles posterior to the cut surface through the optic chiasm, involving the corpus callosum and invading the lateral walls of the third ventricle. From its location, it is most probable that the tumor originated from the ventricle wall, and belongs to the central glioma of cellular type.

Findings Outside of the Tumor.—In some parts, the tissue sur-

rounding the tumor showed rarefaction, the architecture being loosened. The cells were less numerous and intermingled with granule and fat corpuscle cells. This suggests that the tissue was degenerating by the expansive growth of the tumor. Beyond this area, the brain tissue showed some increase of neuroglia cells and fibers, but remarkably less than were found in the tumor tissue. In other parts, the tumor tissue showed gradual transition into the normal brain section, without any recognizable demarcation. The neuroglia cells diminished gradually and diffusely to the average number of the normal appearing tissue, but the writer failed to find a definite border between the normal and pathological; as the neuroglia cells, in this case, were generally increased, and no normal tissue, in regard to the neuroglia element, was found throughout the brain. The question arises as to whether the general increase of neuroglia cells was due to general paralysis, as was clinically diagnosed. There was no perivascular infiltration, no serious disturbance of the cytoarchitectonic and myeloarchitectonic picture, and no great changes in the nerve cells. The general gliosis is not to be considered a secondary reactive process to the general paralysis, or to the primary parenchymatous degeneration. The changes of the neuroglia consisted not only in the increase of the cells, but also in the deformation of the normal spheric type of the nuclei. Very few glia cells retained their original form, while the greater part of the cells showed more or less altered forms, ovoid, oblongate, rod shaped, irregular, polymorphous, etc. Most of the nuclei stained deeper than normal, some of them showing regressive changes, while a few of them stained pale. The satellite cells (*travant*) were not increased, but showed definite form anomalies, some even being transformed into long drawn out rods, *travant* rod cells. This change of the neuroglia in general indicated, apparently, the proliferative process of the preëxisting neuroglia by some primary cause, not as a result of the parenchymatous involvement. Has this general gliosis resulted from the infective proliferative stimulation given forth from the tumor tissue, or has it resulted from the common causative factor which originated the tumor? To find an explanation to this question the sections from different parts of the brain were comparatively studied. Contrary to the writer's expectation, the gliosis was not of a diffuse character, but showed considerable topic difference.

The left cornu ammonis, right posterior central convolution, and convolutions of both frontal lobes, showed most marked gliosis. In the left cornu ammonis the cells were extremely increased, being

packed closely together forming gliomatous areas. These areas were more or less diffuse, gradually transforming into the normal brain tissue. The cells were almost as polymorphous as those in the tumor tissue (Fig. 1). Nerve cells and myelin sheaths were observed among these areas, but they were more or less degenerated. Histologically, no distinction was noted between the tumor

FIG. 1. A gliomatous area found outside of the tumor.

and these gliomatous areas. Macroscopically, the cornu ammonis did not show any increase in volume, making it very difficult to classify this kind of process. Whether it is to be classed in the extremely advanced stage of the gliosis, or diffuse gliomatosis, cannot be positively determined. According to the histological picture, which is almost identical with the tumor itself, it ought to be called diffuse glioma, or, at most, diffuse gliomatosis, while, when the gross anatomy of this part is taken into consideration, it is more justifiable to classify it as diffuse sclerosis.

As Dr. Lowrey noted, there were a great many cells presenting themselves as long drawn out rods. These were the Nissl rod cells of the gliogenic nature (Fig. 2). The opinions of authors in regard to the rod cells differ; some propose the ectodermal origin, others insist on the mesodermal. The first theory is affirmed by Cerletti and Straussler, and the second by Nissl and Alzheimer. Ris, Achu-

FIG. 2. Rod cells found diffusely outside of the tumor in the normal brain tissue.

carro, and Ulrich, believe in both mesodermal and ectodermal origins.

The rod cells found in cases of multiple sclerosis, diffuse gliosis, diffuse glioma, and glioma, are believed by the writer to be definitely gliogeneous. The rod cells seem to indicate an abnormal proliferation of the neuroglia element, at least in the diseases above mentioned.

OBSERVATION II

Superficial Glioma of the Left Frontal Lobe

Case of a female, D. S. H. Clinical No. 17513, Pathological No. 2029. Patient's mother was said to have been nervous. Otherwise there is no history of mental or nervous diseases in the family. Patient was born in Ireland fifty-nine years ago, and at the age of twenty-nine came to Boston, where she worked as a waitress. She married and had three miscarriages. Her husband had syphilis some nineteen years ago, and the patient believed she had contracted it from him.

Onset of Illness.—Present trouble came on gradually for eighteen months. She became extremely irritable and showed marked impairment of memory. A year previous to admission she had an unconscious spell lasting two or three hours. Following this she was confused for several days, and from that time her speech became thick and incoherent; also her gait became unsteady. She was committed to Danvers State Hospital in August, 1913.

Mental Examination.—She was dull and stupid, and very untidy in her habits. She showed some speech defect which was more noticeable on repeating test phrases. She was confused and disoriented, and her school knowledge was poorly retained. Calculation ability was very poor. There was marked tremor of hands and writing was almost illegible. She had no hallucinations. Her memory was much impaired for both recent and remote events, and association of ideas was retarded. She seemed to have very little insight into her condition, and thought her coming to the hospital was due to some stomach trouble. She was apathetic, and showed slight motor restlessness.

Physical Status.—She was poorly nourished and developed. Slight asymmetry of face. Lungs, negative on auscultation and percussion. Cardiac dullness was not increased. No murmurs. Pulse, 84. Slight sclerosis of peripheral arteries. Abdomen, negative; genitourinary organs, negative; urine, negative; Wassermann test on blood serum, negative.

Nervous System.—Eyes, pupils equal, slightly irregular, react sluggishly to light. Hearing, apparently normal. Taste and smell not determined. Cutaneous sensibility localized poorly. Position sense fair. Stereognostic sense unimpaired. Vasomotor condition: No cyanosis or edema. Knee jerks exaggerated and equal. Marked clonus on right; less marked on left. No Babinski. Gait, ataxic. Marked swaying of Romberg's position. Marked tremor of extended fingers.

Course of Disease.—August 16, 1913, patient remained quietly in bed; untidy; euphoric. August 20. Marked memory and speech defect. September 17. Presented at Staff Meeting with the diagnosis of general paralysis, to which all agreed. October 3, confused; delusions developed. December 1, 1914, was unable to stand. Complained of drawing sensation and pain in left leg, also a twitching, as if her side and hip were drawn up. November 30, 1916. Patient gradually failed and was unable to walk. Was markedly demented and confused. July 13, 1917. Patient had continued to fail more rapidly during the last seven days and died, the cause of death being given as cerebral tumor. Like the previous one, this case was erroneously diagnosed as general paralysis, possibly because she had an indefinite history of syphilis, and because she had both mental and physical syndromes, similar to those of general paralysis. For some reason the spinal fluid was not examined, an unfortunate oversight, since the spinal examination on all suspected cases has been one of the routine tests of our laboratory.

Autopsy.—Six hours post mortem. Pupils were equal and regular. There was a deep sacral decubitus. Heart showed patent foramen ovale and fibrous myocarditis. Lungs were slightly adherent to the thoracic walls. There was chronic passive congestion of liver and chronic cholelithiasis. Kidneys showed chronic diffuse nephritis. Appendix contained a small calculus. There was fibrosis of uterus and cystitis.

Everywhere the dura was adherent to the calvarium. The brain weight with fluid was 1320 g. The dura was adherent to the brain on the left frontal region, and could be removed only by dissecting with scissors. The brain in the left frontal region showed a neoplastic area measuring 6x5 cm., and extending back from the frontal pole almost to the junction of the anterior central convolution. This area was very hard, somewhat elevated, nodular, and irregularly firm. Posterior to this mass the tissue was softened, almost gelatinous in consistency. The pia mater over this tumor mass measured three mm. in thickness, but elsewhere there was no thickening, nor adhesions, of the pia mater. The right frontal lobe showed nothing of note, the gyri being fairly well formed. The convolutions of both hemispheres were generally flattened. The rest of the left hemisphere, exclusive of the area in the frontal region mentioned above, showed nothing of note. Basally, the left olfactory bulb was small and densely adherent to the hemisphere. The right was negative. The circle of Willis showed slight thickening and irregularity in the region of the anterior communicating artery. No granulations on the floor of the fourth ventricle.

The *spinal cord* showed nothing unusual. Middle ears were negative. After fixation, frontal sections were made according to Dalton's method.

Left Hemisphere.—Cut surface through frontal lobe in front of the corpus callosum showed the tumor occupying the anterior pole of the centrum semiovale. The neighboring medullary substance was softened. Cut surface through the anterior border of the corpus callosum. The tumor was situated in the larger part of the centrum semiovale and in the anterior part of the corpus striatum. In consistency the tumor mass was partly soft and partly firm, the softening suggesting secondary degeneration. Cut surface through the corpus callosum and corpora striata. The centrum semiovale and medullary substance of the third frontal convolution was softened. On macroscopical observation no more tumor substance was to be seen. Cut surface through the corpus callosum and lenticular nuclei, in front of the anterior commissure. The lower part of the centrum semiovale and a part of the corpus striatum still showed softening. In the surfaces through the posterior to anterior commissure there were no apparent gross changes.

Right Hemisphere.—The lateral ventricles were somewhat dilated, while the cavity of the left side showed flattening. In the white substance of the right occipital lobe there was a small cavity, suggesting pocket formation of the lateral ventricle, but without any connection with it. The area surrounding this small cavity was somewhat soft in consistency. Cut surfaces of the white matter as well as the gray matter were firm throughout both hemispheres, with the exception of the above mentioned softened areas. The surface of the ventricular walls was smooth on both sides.

Microscopical Examination.—Examination of the cerebral cortex and spinal cord failed to reveal any evidence of a paralytic process, there being no lymphocytic infiltration in the meninges nor in the perivascular lymph spaces, and no plasma cells. The cyto-architectonic picture of the cortex was fairly well retained, there being no marked parenchymatous degeneration. In addition to these findings the negative spinal tests on fluid, which was taken post mortem, affirmed this case was not general paralysis, as was diagnosed clinically.

The tumor consisted of glia cells and fibers. The cells showed two different types, one being small with spheric nucleus and small protoplasmic bodies, more like normal glia cells, while the other was larger in size, appearing more like ganglion cells of the cortex, or of the anterior horn of the spinal cord. The smaller were more

numerous than the larger ones. The latter, however, were fairly abundant, and seen throughout the tumor. The protoplasmic body of these giant cells was extremely large, the whole cell being larger than the Betz cells of the motoric center, and when stained by Alzheimer's method showed a granular aspect, infringed by numerous vacuoles of various sizes. By application of light green fuchsin

FIG. 3. Giant cells or granule cells found in the tumor tissue. Sudan III.

stain, on sections treated with osmic acid, various chemical stages of fat bodies, both on septi and in vacuoles, were revealed. In some cells the fat bodies were uniform, while in others the sizes varied. Debris of the nerve element and amyloid corpuscles were observed in the cells, particularly in those having various forms of fat bodies. The cells with more uniform fat corpuscles may be regarded as the result of the regressive metamorphosis, while the others may be the result of phagocytic function. The giant cells possessed, not rarely, two, three, or more nuclei with various forms, located mostly in the

periphery of the protoplasm. The nuclei of the giant cells stained paler than those of the smaller (Fig. 3).

The giant cells showed characteristics of the granule cells of Merzbacher, which appear in the pathological processes of the central nervous system functioning as scavenger cells. These cells were very precisely described by Lotmar, in the *Beiträge der Histologie des Glioms*. The same cells were apparently observed by Pels-Leuden, Redlich, Borst, and others, in multiple sclerosis. Stroebe called the glioma, consisting of these cells, "Glioma gangliocellulare." To the writer, the designation of gangliocellulare seems undesirable, as this ganglion cell like form is only one of the manifestations of the various forms of the neuroglia, and has nothing to do with the ganglion cells of the cortex. It is better to call it granule cell glioma, or giant cell glioma.

The neuroglia fibers were very well demonstrated, especially those given off from the small neuroglia cells. In the central part the thick fibers were the only constituents of the tumor forming a dense network. In the periphery the fibers were finer, and the network was looser than in the central part. In the periphery the neuroglia cells were increased, occasionally showing mitotic figures.

The blood vessels were sparse in the tumor, showing more or less regressive changes. The neuroglia figures seen formed a thick envelope around the vessels, strengthening the *membrana limitans*. The perivascular lymph space was slightly enlarged with a few fat corpuscle cells. A few necrotic areas and hemorrhagic spots were observed, especially in the central parts. Degenerated nerve fibers were seen in the periphery, but none in the center.

Findings in the Immediate Neighborhood of the Tumor.—Forward and upward the tumor showed very gradual transition, both by gross and by microscopical observation. Posterior to the tumor the brain substance showed a large softened area, in which the tissue was rarefied with very loose neuroglia fibers and occasional fat corpuscle and granule cells. The granule cells, the same as were found in the tumor tissue, were more abundant than the fat corpuscle cells. The neuroglia cells in this region were laden with various lipoid substances and debris of the nervous element. Beyond this softened area, in the white substance of the parietal region, the neuroglia cells were still noticeably increased with various form anomalies, such as giant and small cells with irregular forms of nuclei. These were the same in quality as those of the tumor tissue, but less in quantity. Toward the occipital lobe the cells gradually decreased in number, and merged into the normal appearing tissue without any demarcation.

Neuroglia Element in General.—As in the preceding case, this case showed a marked general gliosis, not only in the cerebrum, but also in the cerebellum, pons, peduncles, medulla oblongata, and spinal cord. In the spinal cord, however, the gliosis was less marked than in the rest of the central nervous system. In this case also, the general gliosis was not found in the same intensity throughout, but showed considerable local difference. The pons and the medul-

FIG. 4. Gliosis in the pons.

lary substance of the occipital pole of the right hemisphere (contralateral to the tumor) presented the most marked gliosis. In the pons the large, pale stained, irregularly formed nuclei were very numerous, while the small spheric nuclei were less in number (Fig. 4). The cells appeared more abundantly in the ganglions than in the nerve tracts. The neuroglia fibers in this region were unusually well demonstrated, marginal glia being remarkably thickened.

The small cavity, in the white substance of the right occipital

lobe mentioned above, was lined with cubic epithelial cells throughout the entire dimension. In certain areas the ependymal cells arranged themselves in a single cell layer, while in other parts they presented four, five, or more cell layers (Fig. 5). This cavity, studied by serial section method, proved not to be connected with the lateral ventricle in any way, but in general appearance it was exactly similar. Since Stroebe found small cavities lined with epi-

FIG. 5. A cavity lined with epithelial cells in the white substance of the right occipital lobe.

thelial cells in the tumor tissue, the same formations have been described by a few authors, but as to the nature of the formations opinions differ. The ventricle like cavity in this case, though it was not in the tumor tissue, as in other cases, cannot be considered as anything else than the displaced or invaded neural canal, *i.e.*, lateral ventricle.

In the immediate neighborhood of this epithelial formation, a

great many cells were found from which parallel running fibers were given off, resembling connective tissue (Fig. 5). The nuclei of these cells were more or less elongated, some showing evidence of direct dividing. These elongated cells with parallel running fibers, when studied carefully, proved to be neuroglia cells of ependymal character. As is known, the ependymal cells give off fibers in one direction only, in this differing from other forms of neuroglia cells.

FIG. 6. Gliosis and giant cells with multiple nuclei.

Thus, this case indicated abnormal proliferation of the ependymal cells of the neural canal, evidently pointing to the embryonal factor in the sense of Cohnheim's theory. On the outside of this peculiar tissue of ependymal character was considerable gliosis. Not only increase of neuroglia cells was found but these cells showed an immense variety of forms (Fig. 6). Some were small and stained deeply, while others were large, very irregular in form, and with rather faint staining. Many of the giant cells, described previously,

were shown with less corpuscular and lipoid contents. Mitotic figures occasionally were seen. In short, the whole picture resembled that of the tumor tissue, probably with less cell element. The whole area showed very gradual transition into the apparently normal tissue of the occipital lobe. The neuroglia fibers were well demonstrated in this gliomatous area, as well as in the surrounding tissue. Both frontal lobes and cornu ammonis also showed well marked general gliosis. More rod cells were observed in the cortex than in the white matter. Particularly in the cornu ammonis considerable satellitosis and perivascular gliosis were observed. The marginal network of glia fibers was prominent throughout, but especially in the frontal lobe of the left side, corresponding to the tumor.

OBSERVATION III

Superficial Glioma of the Left Temporal Lobe

This case is that of a male, D. S. H. Clinical No. 21305, Pathological No. 2110. When admitted to this Hospital patient was forty-nine years of age. Mother died at age of seventy-two of goitre. One brother was a patient in this Hospital, his case being diagnosed as taboparalysis. Personal history showed no important diseases during infancy and childhood. Married at age of twenty-one, having one child. Until about five years ago he drank a great deal. No history of venereal diseases. About twenty years ago he got into a fight with a man in a billiard room, and was hit over the head with a billiard cue, but there were no serious after effects.

Onset of Disease.—About three or four weeks before admission he visited his brother, and at that time appeared exhilarated, grandiose, and talkative. About a week before admission he was taken sick in Providence, Rhode Island, and his brother was called to take care of him. He had been in a confused state of mind for three or four days, and was unable to take care of himself. He complained of headache, buzzing in his ears, and pains in his eyes. In moving about he would tumble and fall over things. He was removed to his brother's home where he remained ten days. He would not eat, was constipated, had frequent periods of confusion, and fainting spells; gait was unsteady. He was sent to this Hospital in December, 1918.

Mental Status.—He was aphasic, unable to comprehend questions, and could not recognize objects placed before him. Speech was incoherent and irrelevant. He was completely disoriented in all spheres. Memory was completely gone for both recent and re-

mote events. Association of ideas was very much impaired. No delusional formations could be obtained. He had no insight into his condition and was apathetic. There was no motor excitement.

Physical Examination.—Well nourished, well developed. Face asymmetrical; left nasal labial fold deeper than that of right. Hands cyanotic. Respiration, 18. No abnormalities were shown by auscultation and percussion. Heart sound somewhat irregular, but no definite murmur. Pulse, 80; rather high in tension and irregular. Blood pressure, 120-100. Considerable fetor. Stomach and abdomen negative. Genitourinary tract negative. Urine showed no sugar; no albumen. Wassermann on blood serum negative. Spinal fluid: Wassermann, negative. Gold, 3222221000. Globulin, faint ring. Albumen, 7 in 30.

Nervous System.—No nystagmus. Pupils, unequal and irregular, moderately dilated, reacted well to light test. Ophthalmoscopic examination was not done. Hearing, good. Taste and smell could not be tested. Reflexes. Deep reflexes practically abolished on both sides. Motility of facial muscles unimpaired. Tongue protruded somewhat to right. There was some loss of power in the right hand. Romberg, positive. There was a marked tremor of fingers. Slept well.

Course of Disease.—January 1, 1919. Confused, restless at times. January 20. Patient remained in bed for ten days on account of his confusion. At 9:30 P.M. he had a series of slight twitchings of the muscles and hands which lasted a few minutes. January 21. At 3:05 A.M. he sat up suddenly, and fell back dead.

Autopsy.—Seven hours post mortem. Small scar on right arm, also one on left leg. Acneform eruption over the back. Right nasolabial fold not as deep as left. Nose seemed somewhat deviated to left. There was profound hemorrhage from the nose. No adenopathy. The organs of the body were not taken out. Spinal cord was not removed.

The scalp was thick, but there were no adhesions or scars. Calvarium was dense, diploë was not visible. Grooves for middle meningeal arteries were deeper and wider on the left. Dura mater was neither thickened nor adherent. Pia mater was not clouded, but was remarkably congested. On removing the brain the left temporal tip was firmly adherent to the dura mater of the middle cerebral groove. Convolutions of both hemispheres were flattened. Basilar artery, carotids, and major cerebral arteries were not sclerotic. Cranial nerves, negative. A tumor, about the size of a hen's egg, was found over the lower surface of the left temporal lobe,

involving the uncus, anterior one third of the fusiform gyrus, and anterior two thirds of the second and third temporal convolutions. The first temporal convolution was considerably pressed down by the tumor mass. In consistency the tumor was fairly firm, but the brain tissue around it was somewhat soft. Within the tumor, and located above the uncus, was a nodular hemorrhagic area, about the size of a walnut, and of softer consistency than the surrounding tumor tissue. Brain weight, 1610 grams.

Vertical sections were made according to Dalton's method. The tumor occupied the greater part of the white matter of the left temporal lobe, extending from the cut surface through the corpus callosum and anterior commissure to the vertical section through the anterior pair of tubercula quadrigemini. The cut surface showed several hemorrhagic and softened areas. A certain part of the tumor showed a fairly well pronounced demarcation from the surrounding brain tissue, but the largest part of the tumor passed gradually into the normal brain substance.

Apart from the tumor, in the centrum semiovale and on the vertical section through the optic chiasm, a small hemorrhagic area was found. The centrum semiovale of the left hemisphere was found to be firmer in consistency than that of the right.

The right hemisphere was negative, except for the general flattening of the convolutions due to the increase of the intracranial pressure.

Microscopical Examination.—The tumor tissue consisted of a great many large and a smaller number of small spheric cells of neuroglia fibers. The large cells were the same as found in the preceding case. The small were more like normal neuroglia cells of the white matter. In the central part, the fibers were found thickly interwoven into a dense tissue. In the periphery they were finer and looser, and more in the form of prolongations of astrocytes.

Throughout the tumor the blood vessels were extremely increased, showing mostly regressive changes, while some indicated progressive processes. Most of the walls were thickened, calcified, or showed hyaline degeneration. In some places, however, the endothelial cells were shown proliferating and invading the surrounding tissue through the *membrana limitans*. Perivascular lymph spaces were dilated, and filled with cells laden with catabolic elements. Necrotic areas with coagulated albuminous substance, and many hemorrhagic areas were observed (Fig. 7).

The tumor tissue showed gradual transition into the normal substance, except in a certain area where there was more or less

definite demarcation, and where the tumor tissue compressed the surrounding substance. It is to be mentioned that this pronounced demarcation has nothing to do with the nodular area as found in a case of Stroebe's study, which he believed to be a regional metastasis. To the writer, the glioma seems to show expansive proliferation, in addition to infiltrative process.

FIG. 7. Necrotic areas with coagulated albuminous substance.

The Neuroglia in General.—The neuroglia cells were generally increased in the cortex, as well as in the white matter. Differing from the two preceding cases, the forms of the nuclei were not so variable, being more or less spheric. In the cortex, however, many rod cells of typical form were encountered. These were more numerous in the cornu ammonis than in other parts. Like the preceding cases, this case presented an extreme local gliosis. In the part of the centrum semiovale, where a small hemorrhage was observed, the gliosis was most pronounced. The forms of nuclei were

manifold, varying as much as in the tumor tissue. Here the question may arise as to whether or not the gliosis of this part is secondary reactive process to the hemorrhage, trying to repair the place destroyed. The area of this extraordinarily pronounced gliosis extended over the whole dimension of the centrum semiovale of this plane, and it seemed to be too large an area for the reactive secondary gliosis. Moreover, a fine network of neuroglia fibers was found inside the hemorrhagic area, suggesting, by their manner of proliferation, a primary process. Also, the hemorrhagic area appeared to be a recent occurrence, for the red blood cells retained their form and pigment. Landau found considerable alteration in the walls of the vessels inside the tumor, but none in those outside. In this case the vessel walls in the tumor showed, as described above, remarkable changes, with some progressive ones. The centrum semiovale vessels were also more or less sclerotic, walls were thickened, partly calcified, while in the remaining normal tissue there was no apparent alteration in the vessels. Therefore, it is more reasonable to regard the hemorrhage as being a secondary process, in consequence of gliomatous changes of the tissue.

Special attention should be paid to the fact that there was no histological connection between the tumor and the gliomatous area of the centrum semiovale. These two were independent, insofar as the formation was concerned. The glia fibers were unusually well demonstrated throughout. The marginal neuroglia network was extremely thickened, especially over the left temporal lobe, and immediately above the tumor.

OBSERVATION IV

Central Glioma of Left Hemisphere

This case is that of a male, D. S. H. Clinical No. 20818, Pathological No. 2087. Mother of patient had locomotor ataxia; otherwise the family history is negative for nervous and mental diseases. Patient was born in Nova Scotia fifty years ago. He received a grammar school education, and always worked as a lobster packer. Married at the age of twenty-seven; two children; no miscarriages. He denied venereal diseases. Had good disposition and excellent habits.

Onset of Illness.—About a year previous, while loading a boat, the derrick broke and a heavy beam came down on his head, rendering him unconscious for several minutes. He returned to his work the same day, but remained only a few moments as he became

unconscious again. He was taken home but returned to work in a few days. He continued work until January of the following year, although he was gradually failing. On January 4th, 1918, he had a severe attack of vomiting, with pains in his forehead, which lasted for three days, after which he returned to work. He worked for three days and had another attack, duplicating the previous one. These spells continued until May 2nd, when he was taken to the Massachusetts General Hospital, and there operated upon for brain tumor. The usual decompression was made, but brain did not appear to be under pressure, and there was no evidence of tumor. On May 9th, 1918, he was discharged, "unrelieved," to this Hospital.

Mental Status.—Patient was quiet, tractable, indifferent, and had little to say. He was tidy in his habits, and was partially oriented. He showed slight speech defect, which was more pronounced on repeating test phrases. His school knowledge and calculation ability was good. Memory was much impaired for both recent and remote events. He had no hallucinations or delusions. He realized his condition. He said his memory had been bad ever since he received injury, and could not recall when operation occurred, but remembered being operated on at the Massachusetts General Hospital. He said his head felt better, and things were beginning to come back to him. Emotional tone was one of indifference. There was no motor disturbance.

Physical Status.—Fairly well developed and fairly well nourished. Had a scar on right side of head in the temporal region, the result of operation for decompression. There was some facial asymmetry. Slight sclerosis. Chest, poorly developed and narrow, with sharp costal angle. Lungs showed nothing remarkable on percussion and auscultation. Heart, negative. Pulse, 72. Blood pressure, 140-70. Abdomen, somewhat tense, otherwise nothing remarkable. Genitourinary organs, negative. Wassermann on blood serum, negative.

Nervous System.—No localized pains or headaches. Conjunctivæ somewhat congested. Pupils, equal, slightly irregular, reacted well to light and distance. Hearing, good. Cutaneous sensibility unimpaired. No edema; no cyanosis. Arm reflexes present and equal. Knee jerks exaggerated and equal. No clonus. Babinski, both sides positive. Gait; somewhat unsteady. Romberg, positive. Some tremor of extended fingers. Patient slept well.

Course of Disease.—May 9, 1918. Patient quiet and tractable. dull and indifferent. Memory defective. Had insight into his condition. May 13th, continued quiet and tractable. Slight speech de-

fect. May 20th, no change. May 22nd, patient presented at Staff Meeting and diagnosed as traumatic psychosis. June 23rd, patient died, cause of death being given as bronchopneumonia.

Autopsy.—Extending from right ear upward and backward to the lambdoid suture was a linear scar. Beneath the temporal muscle was a circular area, six cm. in diameter, where the calvarium was removed, and the brain substance was palpable, but there was no bulging. There was another pale white scar, 4x6 cm., about two cm., in front of the right ear. The nasal septum was moderately deflected to the right. There was no malformation of xyphoid process. Fine omental adhesions around spleen, gall bladder, and cecum. Slight adhesive pleuritis. Early bronchopneumonia. Chronic passive congestion of liver. Cloudy swelling of kidneys. Slight hypertrophy of prostate.

The dura was not adherent to the calvarium. There were a few minute depressions along the superior sagittal sinus. The meningeal grooves were shallow. There was no evidence of fracture anywhere in the skull. Brain weight, 1500 g. Capillaries of pia mater were greatly injected everywhere. The convolutions were prominent but seemed to be flattened over the entire brain. On the inferior surface near the midline, the convolutions near the optic chiasm of the left temporal lobe were edematous, and fluctuated on palpation. The inferior surface of the left temporal and frontal lobes was broader and somewhat more flabby than on the right. The basilar vessels were not sclerotic. There were a few fresh fibrinous adhesions about the basilar vessels. The cord was not remarkable.

Sections of the Brain.—When the brain was sectioned, a soft, fairly well circumscribed brain tumor was found in the left hemisphere. This involved a large part of the internal capsule, a small part of the corpus striatum in the region of the caudate nucleus, and a large part of the central region of the frontal and temporal lobes. This tumor began about two cm. from the tip of the frontal lobe, and extended backward six cm. into the temporal lobe, barely reaching the main part of the internal capsule and the occipital lobe. It encroached upon the lateral ventricle, which was enlarged behind the tumor mass compensatorily. Also, there was some evidence of internal hydrocephalus in the right lateral ventricle. The mass forming the tumor was rather soft and structureless, and did not seem very necrotic. It was not especially rich in blood supply. In some parts it was fairly well circumscribed, while in other parts it invaded the brain substance. The choroid plexus seemed edematous and enlarged.

Microscopical Examination.—This tumor consisted of more cells than fibers. Toward the center the cells were very closely packed, and there were almost no fibers. The small cells were more numerous than the large. In the periphery the number of cells was noticeably diminished, with an increase of neuroglia fibers. Where the neuroglia cells were seen closely packed together, epithelial formations of various forms and sizes were encountered. These were found not only around the vessels but free in the tumor tissue, not, however, lining the vacuoles of large cavities. The forms were very irregular, and when seen under low power they appeared to be of glandular structure. By higher magnification these cells of epithelial formation were shown displaying the character of ependymal cells, being more or less cubic in form, and from one end of which fine fibers were given off toward the periphery (Fig. 8). The ependymal structure differed from the one observed in the white matter of the occipital lobe of the second case, in that the cell order was more irregular and was not related to the cavity, but found amidst the tumor tissue. However, this epithelial formation was the same as has been observed and described by many authors. In this case the tumor was located near the lateral ventricle, and the epithelial formation might be regarded as the remains of the embryonal tissue which may have given rise to the later development of the tumor. But on the other hand, the epithelial formation in this case, being an incomplete one, might be regarded as secondary formation of the neuroglia cells. The neuroglia cells in the tumor had a tendency to arrange themselves into an epithelial like structure. The irregular forms of the structure and its objectless arrangement would suggest that the formation was secondary, and made from younger proliferating neuroglia cells. Occasionally mitotic figures were observed.

Contrary to macroscopical observation, the vessels were found to be fairly abundant in the tumor, and showed fatty and hyaline degeneration, and a few calcified ones. The perivascular lymph spaces were enormously dilated, and contained granule and fat corpuscle cells. The neuroglia proliferation was especially marked around the vessels.

As has been described in the microscopical observation, the growth of the tumor was not absolutely infiltrative. In some parts, the tumor showed a pronounced line of demarcation against the normal tissue, the latter showing more or less marked rarefaction. Therefore, the tumor suggests, in these parts, a definite expansive growth. Heretofore the infiltrative growth of the glioma has been

considered as a chief characteristic, and little attention has been given to its expansive growth. In most parts, however, it showed diffuse infiltrative or infective growth (Stroebe). The transition into the normal appearing tissue was diffuse and very gradual with-

FIG. 8. Epithelial structures within the tumor tissue.

out noticeable demarcation. In front and behind the tumor mass, almost all areas of the centrum semiovale were occupied by considerably increased neuroglia cells, and the definite border of the tumor could not be determined.

Neuroglia Cells in General.—As in the other cases, in this case also a considerable general gliosis was discovered. This condition was found not only in the left hemisphere but also in the right hemisphere, cerebellum, and spinal cord. The glia cells were noticeably increased, both in the cortex and medullary substance. The forms of the nuclei were more or less altered, normal spheric cells being rarely observed. Rod cells were abundant in the cortex, and less in number in the white substance. The frontal convolutions and cornu ammonis presented a more marked gliosis than in the other parts. The centrum semiovale of the right hemisphere and lenticular nuclei of the same side displayed the most marked gliosis. Among these areas of gliosis, the ganglion cells and myelin sheaths were more or less degenerated, the ganglion cells revealing considerable fat deposit, which was granular in appearance, and occupied most parts of the cell body. The nucleus of these ganglion cells was seen pressed to the side of the cell body. The ganglion cells of the cortex showed some degeneration, which, however, is to be expected in most brains. The neuroglia fibers were demonstrated everywhere, the marginal network being remarkably increased. In most parts of the cortex and medullary substance perivascular gliosis was encountered.

SUMMARY

The recent study of the normal and abnormal neuroglia has shown that this element is more than a mere connective tissue of the central nervous system, and that it has a reconstructive and nutritive, as well as scavenger, function. There is even a hypothesis that the neuroglia cells may excrete a certain hormone, which is related to the development of the central nervous system. Thus, the glioma being of neuroglial origin, and the neuroglia being a specific and peculiar element of the central nervous system, the study of the general condition of the latter, in cases of glioma, is quite necessary.

One of the most important findings in this present study is the general gliosis associated with gliomata. In each case, herein observed, the writer found a well pronounced general gliosis, though each differed more or less in intensity. So far, in the search in literature, the writer has not been able to find that general gliosis, in cases of glioma, has ever been thoroughly described. It has been described by a few, but has attracted little attention.

How is the Diffuse Gliosis to be Explained?—The glioma, when proliferating, does not progress in the direction of the least resistance, as most other tumors do, nor does it grow by way of the lymph

channel or blood stream, but in most cases there is very gradual transition into the surrounding brain substance. Storch noticed this condition, and pointed it out thus: "It gives an impression as though all the glia cells of the peripheral part and the surrounding tissue begins to proliferate by some stimulus cast forth from the tumor. This, I might say, proliferative stimulus reaches to the neuroglia cells at a considerable distance." Thus Storch called attention to the gliomatous transformation of neuroglia cells of the normal brain tissue, even at a "considerable distance" from the tumor substance.

Does this So-called Infective Stimulation cause the Diffuse Gliosis?—The writer does not think so, for the stimulation is only around the tumor, and cannot explain the diffuse gliosis of the glioma, which is general in character.

The writer also studied the general glial element in two cases of endothelioma, in one case of metastatic carcinoma, in one case of metastatic sarcoma, and in two cases of internal hydrocephalus. In all of these the writer failed to find any noticeable general gliosis. By this comparative study the increase of the intracranial pressure can be safely ruled out from the etiology of the general gliosis. The sarcoma and carcinoma are tumors which are supposed to produce some toxic agent, but neither can this be responsible for the above mentioned condition. In the case of metastatic sarcoma, which had been provisionally diagnosed as glioma, the writer studied the brain tissue first, in the anticipation of finding the same general condition of the neuroglia, which condition, however, he did not find. But, this negative finding was later justified, as a careful study of the tumor revealed it to be a sarcoma, and not glioma.

Although Ranke admits Storch's infective theory, he gives another possibility for the explanation of the gliosis or gliomatosis of the surrounding areas of the tumor. Ranke says that some of the tumor cells, set free from the syncitial union, may wander into the normal surrounding tissue, especially around the ganglion cells, and may give the appearance which was noted by Storch. This explanation of Ranke sounds more reasonable than the infective theory, but is still insufficient, especially for the explanation of diffuse gliosis. Although Storch's theory is not available for the explanation of this question, we can still accept the idea of proliferative stimulation, which, however, does not directly execute its influence upon the surrounding tissue, but performs its action indirectly through the blood stream, although nothing definite is known.

Possibly there is another explanation for the general gliosis, *i.e.*

an assumption of a common causative factor for both general gliosis and tumor formation. The general gliosis in these cases of glioma showed a great resemblance to that of diffuse sclerosis. In the diffuse sclerosis, as in the cases discussed, the genesis and the character of the gliosis is not well known. Whether this is an exogenous or endogenous disease of the central nervous system has not been determined, nor is it known whether the hyperplasia of the neuroglia is secondary to the degeneration of the nervous parenchyma, or whether it is a primary overgrowth of the glial element, in consequence of which degeneration of the nervous element is caused. Strümpell called this pathologic process a chronic interstitial encephalitis, claiming it to be of an inflammatory character. Rebizzi, differing from Strümpell, declared it to be primary disease of the nervous element, causing the proliferation of the neuroglia.

In a study of a former case of diffuse sclerosis, the writer expressed the view that this diseased condition was probably brought about by a primary unknown biochemical stimulation, which worked upon the endogenous congenital factor, and therefore is to be classed as gliogenous neoplasma, such as diffuse glioma. The writer is of the opinion that in cases of glioma, diffuse gliosis is the same in character as diffuse sclerosis, being a primary process caused by the same etiological factor as that of the tumor. Yet, so far as the etiological or stimulative factor is concerned the writer has indefinite conception. It might possibly be caused by something related to a disturbance of the internal secretions. Some cases showed a positive Wassermann test on blood serum, as in those of diffuse sclerosis, while others presented neither clinical nor serological evidence of luetic infection.

In addition to diffuse gliosis, focal gliomatous areas were found in the first three cases. The glioma has been said to be a solitary tumor which is unable to form any metastasis, except regional nodular ones. How, then, can these gliomatous areas outside of the tumor be explained? Landau reported a case of diffuse glioma in which he observed two entirely separated areas of gliomatous alteration. Not rarely gliomata of the stem of the brain are found associated with gliomatous areas of the spinal cord, which show the clinical syndrome of syringomyelia. In regard to the difference of such gliomatous areas and the glioma, Landau concludes: "While the glioma, being originated from the displaced embryonic sprout, gives the impression of a circumscribed tumor which has started from a single predisposed area, and the regular form is only slightly impaired by its infiltrative proliferation, the diffuse gliomatosis

arises from innumerable points or, sometimes, even from macroscopically distinguishable spots which are of congenital abnormal predisposition and distributed over the large area of the cerebral tissue." In regard to the gliomatous areas and the tumor the writer cannot agree with Landau, for no fundamental difference could be seen between the two, except in external appearance. Both formations, probably, have resulted from a congenital basis and the same causative stimulation, the only difference being that the glioma appears more circumscribed and compact in cellular and fibrous element, while the diffuse glioma or gliomatous area is more irregular and diffuse. While the glioma shows a change of external configuration, the gliomatous area shows no changes of gross anatomy. Both processes are abnormal proliferation of neuroglia cells with congenital predisposition. The very rapid and luxuriant proliferation of the glioma gives the impression of the infiltrative or so-called infective progress, while the gliomatous areas present a picture of appositional growth.

Therefore, the gliomatous areas seen in these cases of glioma seem to the writer to be caused by the same etiological factor, acting on the congenitally displaced or agenetic tissue, and have only a quantitative difference between them and the tumor proper.

The epithelial formation in the glioma, and in diffuse glioma, has been described by many. The same structure was found by the writer in both the first and last cases discussed, and in the second case a displaced neural canal in the center of the gliomatous area was seen.

Stroebe was the first to describe this structure, and to regard it as a displaced neural canal which had taken place during embryonal life. This is an evident support of Cohnheim's hypothesis of superfluous or displaced embryonal cells, who states that: "Cells or tissue which in the course of the development of the body may be displaced or do not undergo the normal differentiation, may remain for long periods unaltered, but liable in later life, by some cause or other, to proliferate with all the potencies of the lowly organized cells, in the midst of the mature tissue."

Storch also observed ependyma-like element and cell groups scattered through the tumor. In one case he noted a splitlike cavity half lined with ependymal cells, and situated in the neighborhood of the ventricle. Storch admits the possibility of the displaced lateral ventricle being the cause of the glioma. "Theoretically," he said, "there is nothing to oppose the assumption that displaced embryonal neuroglial cells are responsible for the later development

of the glioma." But on the other hand Storch remarks, "Stroebe's findings of ependymal structure can be explained in another way, that is, the part of the lateral ventricle may be taken into the tumor tissue while the latter is proliferating, and on account of its irregular growth the cavity may be found at quite a distance from its origin." Storch also admits the possibility that the fully developed glia cells may be able to metamorphose themselves into the ependymal cells, just as the contrary is the fact, *i.e.*, the ependymal cells produce neuroglia cells physiologically.

Saxer does not believe in the congenital nature of the epithelial formation, but he says that the neuroglia cells being of ectodermal origin have a tendency to form an epithelial arrangement when proliferating. Bonome, agreeing with Saxer, does not regard it as always being a displaced neural canal, but differs from Saxer in that he considers it to be caused by embryonal undifferentiated cells. Ribbert, in studies of two cases of glioma, observed the same structure, and claimed it to be the displaced embryonal tissue. Podomaniczky also described the same structure and expressed the same idea as Ribbert. Landau agrees with Ribbert in that he does not regard the epithelial formation as a congenital malformation. "When the glioma is growing," he says, "one may find at the part of the most active proliferation, a formation which is identical with the embryonic neuroglial element, and the youngest stage of these proliferated glia cells corresponds to the epithelial formation."

The opinions of the different writers can be grouped under two hypotheses,—1. Primary existence of the epithelial structure as such, *i.e.*, a displacement of the embryonal cells.

2. Secondary development of the epithelial arrangement from proliferating neuroglia cells.

Under the second theory we find two varied opinions. Bonome regards epithelial formation as formed secondarily from embryonal cells, while Saxer asserts that the mature glia cells, when rapidly proliferating, form the embryonic type which are known as ependymal cells.

In all research literature which the study of epithelial formation has produced it is evident that the writers observed two different structures, one an ependymal cavity with typical cuboid cells, and the other of a rosette or irregular band form arrangement. In the case of Observation I the writer found a rosette formation, and in Observation II, in the center of the gliomatous area, was found a real ependymal cavity, while in Observation IV a bandlike arrangement of cells was seen. This last was described by Wintersteiner in his monograph on "das Neuroepithelioma retinae."

The atypical epithelial structure, as the rosette or bandlike arrangement of the cells seems, to the writer, to be a secondary formation caused by the proliferating neuroglia cells. The typical ependymal cavity lined with cuboid cells, found in the center of the glioma or in the gliomatous area, may be regarded as having primarily existed as a malformation, which later gave rise to development of the tumor. It will be very difficult, in some cases, to decide whether or not the structure found is primary or secondary.

The writer cannot agree with the assumption that the typical ependymal cavity is an accidental finding having nothing to do with the tumor formation. Not only Stroebe's case, and the case discussed in Observation II, but the findings of many support Cohnheim's hypothesis for the glioma. In most cases of syringomyelia Hoffmann regards the formation to be of the same origin. Glioma, on the other hand, presents an imposing array of instances in which tumors are found in conjunction with other congenital malformations, such as encephalocele, spina bifida, and syringomyelia. Another formation is the neuroglioma ganglionare, which is to be considered as a congenital heterotopia, and is occasionally found associated with glioma. Congenital malformations of other organs of the body have been observed by many writers. In the study of Observation II a patent foramen ovale was found, and in the last, Observation IV, was seen a malformation of the xyphoid process. All these facts lend considerable possibility to Cohnheim's hypothesis, and to the writer it appears to be applicable, at least in certain cases.

In connection with epithelial formation the question arises as to whether or not the mature neuroglia is able to form ependymal cells of a lowly organized type. According to Lenhossek, the gliomatosis is developed from the cells, *i.e.*, developed from undifferentiated neuroglia cells which retain their embryonal character, while the neighboring neuroglia cells differentiate farther to their mature form. He does not put great stress on the idea of the displacement of the cells, in this respect differing from Cohnheim. Landau, believing as Lenhossek, states that the epithelial cells and the ependymal formation of the tumor can be explained by the assumption of agenetic cells. Saxer is of the opinion that the mature neuroglia cells, being ectodermal in origin, have a hidden power to form epithelial structure when proliferating rapidly. In accordance with which of these opinions or theories are the observations of this study?

As has already been described, diffuse gliosis of cases of glioma

was not only expressed by an increase in number of cells, but the individual element showed very marked change in form. The first case showed hardly any normal appearing neuroglia cells either in the cortex or white matter. There were abundant satellite cells of rod shape, called satellite rod cells. These of abnormal form cannot be considered to have existed as such from the beginning. The facts that the transition between the normal part of the cerebrum and the tumor tissue is very gradual and that the neuroglia cells in general present remarkable abnormalities point to the hypothesis that the mature neuroglia cells are able to transform into a lower embryonic type.

If, however, the normal neuroglia cells are able to develop glioma cells, the congenital theory of Cohnheim and Lenhossek seems to be disproved. Is then, the congenital theory for the development of the glioma to be discarded? No. A whole array of facts suggesting congenital factor, which cannot be denied, has been pointed out by the writer. That the two apparently different hypotheses of Cohnheim and Saxer can be associated, is the opinion of the writer. The reaction of the neuroglia for the stimulus seems to be different in each individual. For example, Merzbacher's case showed gliomatosis, reacting to sarcoma and to local softening, but, few known cases of sarcoma are accompanied by secondary gliomatous formations, and no other case has ever been reported, in which the simple area of softening is considered to be the origin of the glioma. The congenital predisposition is not only to be expected in the form anomalies, such as displacement or agenesis, but is also to be expected in the character of the neuroglia cells, which may react easily to the external stimulus. In the present study neither metastatic carcinoma nor sarcoma showed recognizable general gliosis or gliomatous formation, except the normal reactive gliosis around the tumor. Merzbacher's case must then be considered as one with congenital predisposition, in which normal mature neuroglia cells have an abnormally exaggerated reaction to the external stimulation. The abnormally labil character of the neuroglia cells is naturally to be expected in brains with congenital predisposition,—thus finding an association between the hypotheses of Cohnheim and Saxer.

As to the proliferative modus of the glioma opinions differ. Storch added to the theory of infiltrative growth, to which most writers agree, a new proliferative process known as *inficierendes Wachstum*. As has already been mentioned, the proliferating picture around the tumor gave the author the impression that the neu-

roglia element in the neighborhood had been infected by some proliferative stimulation, produced from the tumor and gradually absorbed by it. Like Storch, and most authors, the writer observed a remarkable proliferative process of the cells in the cortex neighboring the tumor, especially those accompanying ganglion cells. Storch's theory at first seemed plausible to the writer, but when the diffuse gliosis was taken into consideration it was no longer sufficient explanation for this condition. Storch's idea that the normal cerebral tissue is readily transformed into tumor tissue is far fetched, and to the writer seems improbable.

The writer believes that the tumor is formed by a group of neuroglia cells of unstable character, or by displaced embryonal tissue, which reacts with the same abnormal proliferative process. By the assumption of a general stimulation, the coexistence of the general diffuse gliosis, proliferative process of the surrounding tissue, gliomatous areas, and the glioma itself can be explained.

Associated with the proliferative modus of the glioma there arises a question as to the difference between reactive gliosis and gliomatosis. Stroebe says that in gliosis the cells are more uniform and like normal neuroglia cells, while in glioma there may be found manifold varieties of the histological picture in the same process. Storch called attention to the secondary degeneration of the glioma, which is not found in the reactive or reparatory gliosis. Rossolimo thinks that the appearance of the cells with large thick prolongations, and the tendency for forming cysts, are characteristic of the gliomata. Weigert pointed out that the characteristic of the gliosis is in the luxuriant formation of the neuroglia fibers. Lenhossek and Storch are of the same opinion. According to Bonome, both irregular and polymorphous large cells and small, with scant protoplasmic portion, may be found in the areas of gliosis. Hertwig and Roessle think that the disproportion between the size of the nucleus and protoplasm is characteristic of tumor cells, and by this the tumor cells can be differentiated from reactive neuroglia cells. Ranke is of the same opinion, but says that the more important fact than this is the ependyma-like formation of the tumor, for by this the real tumor formation can be decidedly differentiated from the reactive gliosis. By him a part of the luxuriant proliferation of the tumor tissue was considered to be a reactive gliosis of normal neuroglia cells existing in the tumor tissue.

To the writer, it seems that many characteristics of the reactive gliosis and gliomatosis described by the authors cannot be applied in all cases. In fact, when studying cases of glioma and allied diseases,

transitional forms are, not rarely, encountered, making differentiation almost impossible. Henneberg, like the writer, could not see any absolute difference between the secondary gliosis and glioma. Merzbacher and Uyeda's case is also an example that there is no fundamental difference between the two.

Theoretically, the reactive gliosis and gliomatosis is distinctly separated, in spite of the fact that histological differentiation is sometimes almost impossible. Reactive gliosis is proliferation of the neuroglia, reacting secondarily to a certain condition; hence, it is an appropriate hyperplasia, showing some functional characteristics of neuroglia. These characteristics are filling spaces, encapsulating foreign bodies, strengthening the *membrana limitans*, deporting waste products, transporting nourishment, etc. In the reactive process the neuroglia cells may appear in various forms showing very active proliferation, sometimes as active as in the abnormal neoplastic proliferation, but always having a certain purpose; whereas, the hyperplasia of the tumor cells is entirely independent and egoistic in its way of proliferation.

Another fact that makes the differentiation between gliosis and gliomatosis difficult is, that the tumor cells execute, to a certain extent, the physiological function of the normal neuroglia. The scavenger function, luxuriant fiber formation, etc., seen in the tumor, have been attributed by many to the function of the abnormally proliferating tumor cells. Thus, in one way, the gliosis appears more like gliomatosis, while, on the other hand, gliomatosis has the appearance of gliosis.

Between the simple reactive gliosis and gliomatosis of decidedly neoplastic nature there are a number of diseases, which are known under the names of diffuse sclerosis, lobar sclerosis, tuberous sclerosis, multiple sclerosis, etc. Many claim predisposition of the individual for these diseases, while others propose that these diseases are exogenous, and result from an inflammatory process of the nervous element. Already the writer has expressed his idea as to the congenital nature of diffuse sclerosis and allied diseases. If these are, as presented, a primary development from some etiology acting on congenital basis, there is no fundamental difference between the glioma and these diseases mentioned above. The difference is in the various resultant forms, and not in the nature or genesis of the process.

Further discussion of these diseases individually is not the purpose of this study, and would lead beyond the limit of this article.

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