THE CLINICAL COURSE AND PATHOLOGICAL HISTOLOGY OF A CASE OF NEURO-GLIOMA OF THE BRAIN.

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Plates L–LIII.

Part I.

The Clinical Course.

By H. M. THOMAS.

Clinical Summary. Male; aet. 38; unmarried. Excellent family and personal history. Syphilis denied. Onset in 1890. Convulsive seizures, beginning in toes of right foot, followed by loss of consciousness. Attacks every few weeks for six years, all beginning in right foot and often involving right arm. Loss of consciousness, common at first, was absent during the last three years. Gradually increasing weakness of right leg for two years. Paralysis of arm during observation. No headache, vomiting or other general symptoms. Examination, autumn, 1896. Hyperæmia of the optic discs (no neuritis). Altered percussion note over left parietal region. Distended veins on left side of forehead. Slight weakness on right side of face. Distinct paralysis of right arm and leg. Increased reflexes and marked muscular atrophy in right limbs. Disturbance of temperature sense in right lower leg. Exploratory operation. Bone meninges normal; cortex inexcitable by strong faradic current. Death twelve days after operation.

The patient was an unmarried man, 38 years old,* who complained of weakness of the right leg, and of convulsive attacks, localized in this leg. The family history contained nothing of significance. In the personal history there was nothing that seemed to stand in a causal relation to the trouble from which he was suffering. The only injury that he had received was at the age of eight years, when he fell ten feet, striking the

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back of his head. He was not unconscious, but was able to get up immediately. He denied ever having had any venereal disease.

The trouble for which he sought relief had its onset in May, 1890, *i. e.*, six and a half years before his first visit to the Dispensary. For a year previous to this time he had been very much confined by his work, which was that of a book-keeper, and had suffered more or less from headaches which he attributed to constipation and to lack of outdoor exercise. He considered himself, however, in good health. In May, 1890, during a vacation of a week, he had his first attack. This occurred while he was at work painting the mast of his sailboat. At this time he had a sense as if something were going to happen, and he felt that it would be better for him to get down and work upon the bottom of the boat. He thought he had been dizzy, and soon forgot about it; in about half an hour, however, he began to have a sensation of numbness in the great toe of the right foot. This increased until it felt as if some one had hold of the great toe. He then became unconscious. He was alone in the boat, and was unable to tell how long the attack lasted. Upon regaining consciousness he discovered that he had bitten his tongue. He went to the club house, dressed, dined with a friend, and felt in no way incapacitated. The next morning, after a good night's rest, he returned to work on his boat, but upon lifting a heavy weight he became unconscious and fell. In this attack there seemed to have been no premonitory symptoms. He was told by his friends that during the same day he had had three or four convulsions. Of these he had no clear recollection. The next morning he had a slight attack in which he did not lose consciousness. This one began in the toes of the right foot, and later affected the leg. After this he went away to the mountains and was quite free from attacks until August, when he had, after the exercise of climbing a mountain, another convulsion. This also began in the right foot, which he stated was contracted for at least a minute before he lost consciousness. That same evening he had another attack, beginning in the same way. After this there was another interval of three months in which he had no convulsions. They then recurred, and he had several within a few hours. From this time on he had an attack on an average of about once every three weeks, during the years of 1891, '92, '93 and '94. In 1895 and '96 they became somewhat less frequent, occurring at intervals of about a month.

All the attacks began in the same manner, that is with a sensation of constriction of the toes (usually the great toe) of the right foot, then a contraction of the toes and foot, gradually involving the rest of the leg. During the first three years he usually lost consciousness, but after that

this symptom became more and more infrequent, and for two years before we saw him it had not occurred at all. At first the convulsions were confined almost entirely to the leg, and it was only during the last years that the right arm had become affected. After each convulsion, even at the beginning of his illness, the right leg was weak and numb for a longer or shorter period. At first this weakness was only of an evanescent character and quite completely recovered from, but for about two years before we first saw him the right leg had gradually become permanently weak and the numbness constant. His general health was good; he did not complain of headache, sick stomach, or difficulty of sight.

The examination on August 26, 1896, showed the patient to be a somewhat spare, but fairly well-developed man; his intelligence was good, his speech was rather thick and guttural, but showed no actual defect; there was no aphasia. The cranial nerves performed their functions normally; there was in particular no noticeable weakness of the right side of the face. The right arm was fairly strong, although somewhat weaker than the left, which was normal. The walk was typically hemiplegic, the weakness being of the right leg. The movements of the right ankle were almost completely lost, as were those of the toes; whereas those of the knee and hip were retained, although they too showed great loss of power. The left leg was normal. The right leg was smaller than the left, the difference of measurements of the thighs being about three cm. The deep reflexes were exaggerated on the right side, and were normal on the left. There was, however, no well-marked clonus. No abnormality was discovered in the sensory condition of touch, pain and temperature. An electrical examination showed that the muscles of the right leg required a somewhat stronger faradic or galvanic current to cause them to contract than did those of the left side. An ophthalmoscopic examination, made by Dr. Theobald, showed that there was well-marked hyperæmia of the optic discs (no neuritis). A low grade of choroido-retinitis existed, "such as occurs in consequence of eye-strain, and the hyperæmia of the disc, I take it, is only part of this condition."

The patient was seen from time to time, and on September 29 he reported that on the morning of that day he had had a convulsion, which affected particularly the arm, but also had involved the face, the latter for the first time. At the time of his visit to me the right arm was powerless. He entered the hospital on October 7.

The examination, after his entrance to the hospital, differed from that given above, in that it revealed a slight weakness of the right side of the face. The right arm had regained a certain amount of power, but was

still very weak. It was also discovered that the right arm was smaller than the left by nearly four cm. in the measurements of the upper arm, and that the right foot was colder to the touch than the left. A careful examination of the sensory functions showed that the condition of touch, pain, heat and cold was normal throughout the body, except on the anterior aspect of the right leg below the knee. Between the knee and ankle the patient was unable to distinguish accurately between hot and cold stimuli, and on the foot, heat and cold produced no sensation. The muscular sense was completely lost in the right arm and leg.

The head having been shaved, three lineal scars were detected above the occipital protuberance, the longest, 4 cm., and the smallest, 1 cm. in length. The scalp was freely movable in this region, as it was everywhere over the head. Dr. Camac * discovered by auscultatory percussion that there was an area on the left side of the mid-parietal region in which the note was of a lower pitch than that over the rest of the head. It was also noted that while the veins over the left temporal region were very prominent, those over the right were not to be seen.

I had informed the patient before he entered the hospital that it was probable that there was some growth which was gradually involving the brain, but that it was impossible to determine its precise nature. The supposition that it was some chronic, syphilitic meningeal growth was entertained, and, in spite of the fact of his having denied any infection, he was put on increasing doses of iodide of potassium. After the arm had become paralysed, and the convulsions begun to involve the face, the advisability of an exploratory operation was suggested to him. A week after his entrance to the hospital he was transferred to the surgical ward, the operation being performed on October 23, 1896. Previous to the operation he had two or three convulsions of the usual character; in one of these, however, he thought that the left side of the face was going to be affected.

The operation was performed by Dr. Bloodgood, who has kindly allowed me to use his notes. The upper half of the fissure of Rolando was exposed, the object being to examine the centres both of the arm and of the leg. The surface of the brain cortex appeared somewhat different from normal; the sulci were less distinct, and the surface of the convolutions presented a finely granular appearance. The difference, however, was not great, and neither Dr. Halsted nor I considered it remarkable. I attempted to stimulate the cortex with a faradic current, but was unable to evoke any muscular contraction, even with a very strong current. No

* I am indebted to Dr. Camac's careful notes for the description of the patient's condition upon entrance to the wards of the Hospital.

gross lesion having been found, the wound was closed, and the patient returned to the ward. Upon recovering from the ether it was noted that there was complete paralysis of the right arm and almost complete of the right leg. The face was not paralyzed. On the following day the patient's mind was clear, he spoke normally and complained of no headache. He did very well for four days, his pulse falling from 136 to 92 and his temperature from 101° to about 99° F. In the early morning of October 28 he began to complain of severe pain in the head. He became dull and somewhat delirious, refused nourishment and objected very much to being disturbed. On the 29th it was noticed that he had difficulty in chewing and swallowing, and on the 31st he was hardly able to speak. On November 1 he was better, more rational and talked with less difficulty. This improvement lasted for two days, but on November 3 the pain in the head, which had somewhat lessened, returned with its old severity, he became unconscious and died on the following morning. The temperature and pulse were normal for several days before his death; in the last twenty-four hours the pulse fell from 76 to 58 per minute, and an hour before he died it was 68. The degree of paralysis varied from day to day, but no careful examination was possible on account of the condition of the patient.

After the patient's death the body was removed to his home, where an autopsy, which was confined to the head, was made by Dr. Livingood, on the evening of the same day.

The clinical aspects of the case justify a few remarks. An accurate diagnosis during life was difficult, perhaps even impossible, and was at least not made. The patient presented himself with the history of having for six years been subject to convulsions, beginning in the right foot, and stated that for the last two years this foot and leg had become weak. The examination in the dispensary, besides weakness and atrophy of the right leg with exaggerated deep reflexes, revealed nothing of importance.

That there was some irritative lesion of the left motor region was evident, and the fact that the epileptic attacks preceded any permament paralysis by four years seemed to indicate that it was the cortex rather than the subcortical region which was primarily involved. The absence of choked discs, headache and vomiting, and the long duration of the symptoms made the presence of a growth in the brain itself appear improbable. The surmise that there was a chronic

meningeal process which had involved the motor cortex secondarily was believed to agree more nearly with the symptoms. That the lesion might be of syphilitic origin was considered, and the appropriate treatment given. The occurrence of paralysis of the right arm and the beginning involvement of the face made an exploratory operation seem advisable. The discovery post-mortem of a neuro-glioma, situated for the most part in the white matter beneath the motor cortex, which apparently had arisen in this locality, showed, however, that our assumption was incorrect. It is, to say the least, remarkable that such a growth should have existed in the brain for so long a time without causing the characteristic general symptoms.

The occurrence of Jacksonian epilepsy, followed at a later time by paralysis of the affected limb, in connection with a subcortical tumor, had been observed more than once before.* That the motor cortex would be inexcitable at the time of the operation is what one would expect from the lesion found. This lesion also explains the loss of the muscular sense in the arm and leg, and the disturbance of the temperature sense in the lower part of the leg, in accordance with our present conception that the central convolutions are the centre both for sensation and motion.

The altered percussion note over the region of the tumor, which was discovered by Dr. Camac on the day before the operation, is particularly interesting and emphasizes the importance of this sign as a help in the local diagnosis.†

The muscular atrophy of the right arm and leg is of particular

* Oppenheim, Die Geschwülste des Gehirns, in Nothnagel's Spec. Path. u. Ther. ix, I, 3, p. 73, Wien, 1896.

† See Bruns in Eulenburg's *Real-Encyclopädie*, viii, 658, 1895.

This sign was present in two cases of tumor of the frontal lobe which were operated on for me. In the first case it was pointed out by Dr. Allen Starr [*Jour. of Nerv. and Mental Dis.*, Oct., 1896, p. 660], and in the second case, in which it was very evident, the frontal bone, at the time of the operation, was found to have been reduced to the thinness of paper. In a third case I believed the sign to be present, but at the autopsy no tumor or other condition was found to explain it. From my own experience I should say that the sign is one about which it is easy to be deceived, and upon which reliance should be placed only when the difference in the percussion note is well marked and constant.

interest. It was of the nature of a general diffuse atrophy, involving all the muscles of the limbs; these muscles responded normally to the electric currents, although they required a stronger current to produce a response than is usual. That muscular atrophy does at times follow a lesion of the brain has been known for many years, but only recently has particular attention been called to the condition. Steiner* collected and analyzed the published cases and reported a personal observation, making in all eighteen cases. Since that time a considerable number of additional cases have been published. The subject is a most interesting one, and has given rise, in the attempt to explain the occasional occurrence of muscular atrophy associated with lesions of the brain, to several theories. These differ widely from each other, and involving, as they do, important physiological problems, their detailed consideration is beyond the scope of the present article. From a study of the cases it appears that muscular atrophy may follow any sort of lesion, situated anywhere in or near the motor path, within the brain. The lesion may be such as to destroy the continuity of the motor neurones, and thus be followed by secondary degeneration of the pyramidal tract; or there may be no evidence of such degeneration, and, indeed, the motor paralysis itself may be a very inconspicuous symptom.

In our case, Dr. Hamilton was unable to discover, even by the use of the newer methods, any secondary degeneration, and it is remarkable that in two of the cases in Steiner's list (Case VII, Roth and Muratow, and Case IX, Quincke), in which muscular atrophy followed the growth of a tumor in the motor region, the pyramidal tracts were normal. Finley† has very lately reported two instances of tumors of the brain in which secondary degeneration was absent. In one the growth was of the optic thalamus, and in the other it was of the crus cerebri.

* *Deutsche Zeitschr. f. Nervenheilk.*, lii (1893), 280.

† *Montreal Medical Jour.*, xxv (1896), 208.

PART II.

THE PATHOLOGICAL STUDY.

BY ALICE HAMILTON.

The histological study was limited to the cerebrum and medulla. It may be regretted that the spinal cord was not available also; but it is believed that the conclusions arrived at regarding the absence of secondary degenerations in the pyramidal tracts would not have been altered by an examination of the cord in its lower levels.

The seat of the operation was immediately around the Rolandic fissure. The meninges covering the affected area were dark in color and hæmorrhagic. In the formalin-hardened hemisphere the region of more or less involved tissue is composed of the ascending frontal, the ascending parietal and the third frontal convolutions. Externally the involved area occupies a smaller volume than the parts beneath the cortex. The immediate site of disease is indicated by a softened and depressed focus 2 to 3 cm. in width, from the centre of which projects, in the form of a hernial protrusion, a shaggy mass of brain tissue as large as a walnut, covered by membranes. The posterior superior tip of the third frontal convolution is impinged upon by the hernia and is pressed forwards, giving rise to a crescentic excavation 1.5 cm. long. A part of the hernia is derived from this convolution, which is softened. The cortical upper surface of the ascending frontal convolution is free from any gross lesion; on the other hand the surface within the Rolandic fissure projects forward, forming a distinct tumor-like bulging, which extends quite to the base of the convolution. On separating the ascending frontal from the ascending parietal convolution, the central portion, corresponding to the softened area, is occupied by a pulpy mass, which is found to be continuous with the surface of the latter. The cortical surface of this convolution in its entire length, except for the slight bulging in the lower part, appears normal; but on its Rolandic surface, in its lower half, there is a tumor-like projection, the cortical surface of which is firm, the interior softened.

A close study of the distribution of the diseased area made from time to time during the progress of the work shows that, while the foregoing description is accurate as far as the appearances seen on the surface are concerned, a section of the hemisphere and the gradual removal of more and more tissue from the affected convolutions made evident a tumor

invasion through the bases of these convolutions, extending into the centrum semi-ovale backward so as to involve the beginning of the optic radiation and forward within the area of the termination of the white matter in the frontal region. Below, it extends into the corpus callosum in its median and anterior portions, the posterior third seeming to escape. The softening extends to but does not enter the thalamus. There can be no doubt now that the softening is not post-operative, but due to the tumor.

From all parts of the tumor small portions were taken and transferred, some to alcohols of increasing concentration, others to Müller's fluid. The specimens hardened in alcohol were stained with Upson's carmine, hæmatoxylin and eosin, Van Gieson's picric-acid-fuchsin, Mallory's phospho-molybdic-acid hæmatoxylin and Nissl's methylene blue, while those hardened in Müller's fluid were treated by Marchi's and by Weigert's (medullated nerve) methods. Other specimens were treated by Golgi's silver chromate method and, finally, the attempt was made to demonstrate the neuroglia by Mallory's method, but without success, probably because the tissue was not fresh enough or handled exactly in the prescribed manner.

The results obtained by these different methods when combined give a very clear picture of the elements composing the tumor. Those specimens which were stained by Mallory's phospho-molybdic stain were perhaps the most valuable, as this stain shows with great clearness the cell processes and the outlines of those cells which have invisible cell membranes, and whose protoplasm is therefore difficult to see unless treated by so intense a staining agent as this.

A great variety of cells is seen, some typical examples of which are shown in the figures of Plates L-LIII. It would, however, have been necessary to draw a very great number of cells in order to show all the types, so great is their diversity. It would therefore be very difficult to classify them according to shape, but when one examines the character of the nuclei and of the protoplasm, the cells seem to fall into two quite distinct classes. Of these one is characterized by an invisible cell-membrane, protoplasm that stains faintly and processes which, if present, are exceedingly delicate. The nuclei in these cells are often slightly stained, but have a dark periphery and exhibit threads and granules of chromatin. The other class is distinguished by granular protoplasm, distinct outline, thicker processes, and usually a deeply stained nucleus. These two classes are not absolutely distinct, they merge into each other in some cases, but on the whole the two types are well separated. One may therefore say that all the cells with granular protoplasm are furnished with

distinct processes. Besides these, many normal neuroglia cells are present in addition to those which vary somewhat from the normal type.

Spindle cells are found in great numbers, some with single small nuclei, but a far greater number with two or three nuclei or with one large irregular nucleus. These cells are quite large and are furnished with remarkably long processes at one or both ends, or with a brush of many fibres, when they correspond with the so-called brush cells (*Pinselzellen*). The processes are seen sometimes to branch after leaving the cell (Plate L, *A*, *B*, *C*).

Of the same class, *i. e.*, with lightly staining protoplasm and dark nuclear membrane, are certain very large cells, usually more or less triangular in shape, provided with projecting nuclei numbering sometimes as many as eight in a single cell. These give rise to appearances very like that of giant cells in certain sarcomata (Plate L, *F*, *H*). At times the nuclei are grouped in a wreath around the periphery of the cell. Other large cells have very little protoplasm and look often like masses of naked nuclei grouped in clumps, some of them taking the stain deeply, and others only slightly (Plate LII, Fig. 1). Again, a clear vacuole may appear within a cell, pushing some of the nuclei to the edge of the cell and altering their shape. Even with Mallory's phospho-molybdic acid stain it is impossible to demonstrate with absolute certainty the presence of protoplasmic processes for these large cells; and in specimens stained by other methods there is absolutely no suggestion of such extensions. A notable absence is the large neuroglia cell with numerous radiating processes, the spider-cell (*Spinnenzelle*), which is nowhere to be seen.

Among the spindle cells described above are some which have granular protoplasm, like that of ganglion cells, and thick and coarse processes. The same is true of certain of the large triangular cells. But by far the greater number of the cells whose protoplasm is of this character impress one as being atypical ganglion cells. They assume various shapes and sizes and may be multinucleated. In no case, however, was pigment found in them and their nuclei are devoid of nucleoli. Yet they have the general character of ganglion cells. Still other cells look like neuroblasts, except that their protoplasm is more abundant and their nuclei stain more deeply and uniformly than is the case with the normal embryonic cells. These cells have distinct processes often thick and long and branching at a distance from the cell-body.

The blood-vessels are not especially numerous in any part of the tumor. In some parts they appear normal, but usually the walls are thickened by spindle cells (Plate LII, Fig. 1). These cells differ in no way from the

spindle cells throughout the tumor, they have processes at one or at both ends and usually lie close to the vessel wall with the long axis parallel to the course of the vessel. In some places these accumulations of spindle cells are very thick and in carmine specimens they stand out as deeply stained masses, always arranged evenly around the vessels and never under any circumstances pushing their way into the surrounding tissue.

Medullated nerve fibres are found in all parts of the tumor, also many devoid of the medullated sheath (Plate LIII, Fig. 4).

As the tumor, beginning with those sections nearest the cortex and going in to the centre of the tumor, is examined, the elements described above are found in varying abundance and arrangement (Plate LI). In the more superficial sections the ground substance is the usual fibrillar neuroglia network. Here are found the round cells with small nuclei, the spindle and brush cells whose processes begin, as one penetrates further down, to give to the ground substance a different appearance. Sections which approach the centre show the large multinucleated cells with clear, light protoplasm or with almost no cell body at all. The first cells of the second class to appear are the irregular spindle cells and those resembling neuroblasts; and finally the centre of the tumor is composed of irregular ganglion cells whose processes form a thick felt-work surrounding the cells. Comparatively few of the cells with clear protoplasm are found here except around the blood-vessels.

This, however, is only the general arrangement of the tumor; there are deviations from this type in some places. For instance, there is found in one place just below the cortex a nodule about the size of a hazel-nut, which macroscopically seems to be quite circumscribed and distinct from the rest of the tumor. Under the microscope this nodule is found to be composed of cells of the smaller type, round or slightly oval, usually with but a single nucleus, and very much more closely packed together than elsewhere in the tumor (Plate LII, Fig. 2, *B*). The appearance presented by this mass is quite different from that of the surrounding tumor tissue, especially in specimens stained with carmine or with hæmatoxylin, for in these the cells seem entirely devoid of processes. Only by using Mallory's phospho-molybdate stain could the presence of numerous very delicate processes be demonstrated. Near the edge of this mass the cells grow larger and more spindle-shaped (Plate LII, Fig. 2, *A*), but are still very densely packed together, and there is a sharp line of demarkation between them and the loose, large-celled tissue surrounding the mass (Plate LII, Fig. 1).

The tumor is for the greater part of its extent confined to the white matter, involving the cortex only in a few places. But the latter in this

situation, even when uninvaded by the new growth, is nowhere entirely normal. There is a decided increase in the number of small round cells; in one place karyokinetic figures were seen near the surface of the cortex within what were apparently neuroglia cells. In other places scattered tumor cells are found extending even up to the outer surface and, in one spot, a mass of closely packed round cells fills all the extent of the cortex. These are unquestionably tumor cells, not polymorphonuclear leucocytes. The latter are found penetrating here and there among the cells of the cortex and the upper part of the new growth, but they are few in number and always lie singly. There is therefore no evidence of any considerable inflammatory reaction, not even along the cortical surface and in the membranes.

In the lower layers of the cortex, near the new growth, there begin to appear round and spindle cells and giant cells. The normal pyramidal cells are still present, but there is no evidence of proliferation on their part. Here also, in the large-celled layer of the cortex, are found certain remarkable cells which look like enormous multipolar cells of the anterior horns (Plate LIII, Fig. 3).* They are normal in shape and structure, furnished with processes and with a single nucleus containing a distinct nucleolus. They are much larger than any pyramidal cells normally found in the cortex and they do not belong to the type of pyramidal cells, but resemble the largest of the multipolar cells of the cord, some even exceeding the latter in size.

Sections passing through both cortex and tumor, which have been stained by Weigert's hæmatoxylin method, show the medullated fibres passing down from the cortex to enter the tumor and, some of them at least, to pursue their course and emerge below to pass on to the internal capsule (Plate LIII, Fig. 4). The fibres seem to be simply pushed apart by the tumor cells, or sometimes when these cells lie closely packed together, as in the nodule described above, most of the fibres are forced to each side, curving around the mass to meet below. Examination under the higher powers brings to light many fibres which seem to lose their myelin sheaths on entering the tumor. The denser parts of the tumor especially show many such non-medullated fibres. That not many nerve fibres have undergone degeneration as a result of their passage through the new growth is shown by specimens from this same region stained by Marchi's method. Here can be found scattered single degenerated fibres, but never large tracts of such fibres.

Beginning with the internal capsule and passing down through crus,

* These cells resemble the "Betz cells" of the paracentral lobule, and doubtless are homologous with them.

pons and medulla as far as the decussation of the pyramids, serial sections were made and stained by Weigert's method. These gave very surprising results, for nowhere could any degeneration of the fibres of the motor tracts be discovered. Even a part of the crus prepared by Marchi's method failed to give any decided result, the isolated fibres, which gave the reaction, being too few and scattered to be of any significance.

In considering the nature of this tumor and the class of neoplasms to which it belongs, one finds that the question resolves itself into that of neuro-glioma or glio-sarcoma. A study of the literature on the pathology of brain tumors shows that either one of these two positions could be supported by many and eminent authorities. Perhaps it will be well at this point to review briefly what have been and are the opinions held by various authors on this subject.

The literature on glioma* begins, of course, with the appearance of Virchow's "Die krankhaften Geschwülste." Virchow separates gliomata from sarcomata and makes the separation depend on the character of the cells. In glioma the cells are of the type of neuroglia cells, they have always processes, which form an essential part of the ground-substance, and nerve cells and nerve fibres are always absent. The cells are proportionally few in number, the ground-substance is the more prominent part. Sarcoma, on the other hand, consists, of course, of polymorphous cells devoid of processes, and very numerous, while the granular cement substance is relatively scanty.

This classification was first objected to by Klebs, who maintains that nerve cells form a large part of some gliomata and are the only constituents of others. Following his well-known theory that in a new growth all parts of the tissue proliferate, Klebs asserts that there are tumors in which all nervous elements including axones are represented, yet which may resolve into gliomata. The character of the cell therefore, according to this view, does not determine the nature of the tumor.

Golgi, on the other hand, follows Virchow in basing the distinction between glioma and sarcoma on the characters of the cells, laying special stress on the cell processes. According to him a glioma must consist essentially of cells with radiating fibres, *i. e.*, spider cells. Jastrowitz describes as the typical elements, cells with scanty protoplasm, large clear nuclei and numerous processes. Hektoen follows Virchow and Golgi in

* References to literature are at the end of this article.

considering the presence of fibres the most important distinguishing point. He calls the tumor he reports a glio-sarcoma because it consists of cells furnished with processes similar to glia-cells, and also of round cells which seemed to be devoid of processes.

Practically all of the earlier writers accept this classification, though some lay more emphasis on the relative number of cells in the tumor than on their character. The results are therefore very confusing, for two cases which seem by the descriptions essentially alike, are classed, the one among the gliomata, the other among the sarcomata, according as they seemed more or less rich in cells. The conception of a glio-sarcoma is even more vague, the term being usually applied to a glioma composed of two or more different kinds of cells. In Lemcke's very exhaustive article 97 cases are collected from the literature up to 1881, 17 of which are reported as glio-sarcoma, 80 as pure glioma, but the description of the microscopic appearances is essentially the same in all and it is impossible to see why certain ones were supposed to belong to the mixed type and others not.

However, not all of the earlier authors accept the dictum that a tumor composed of cells with processes must be a glioma. Marchi considers the number of cells more important and classes among the sarcomata a tumor consisting of cells resembling neuroblasts and spindle cells with many fibres. The cells in this case were very numerous and the cement substance slight in amount. Fenoglio does the same. Indeed his typical sarcoma cell is exactly like Jastrowitz's typical glioma cell. Even down to the present day there are authors who still base their classification of brain tumors upon the character of the constituent cells, as Birch-Hirschfeld in his "Allgemeine Pathologie," 1892. A case described by Galavielle and Villard in 1895 is unhesitatingly denominated sarcoma because of the richness and variety of its cellular elements.

In the case of the earlier authors it is easy to understand why this should be so. The neuroglia was at that time looked upon as one of the forms of connective tissue, mesoblastic in origin, and a glioma therefore belonged to the connective tissue tumors, differing from sarcoma only in having its starting place in the modified connective tissue of the nervous system, and therefore resembling neuroglia, but capable of passing gradually over into pure sarcoma. This is very clearly expressed by Gowers, who puts glioma and sarcoma as subdivisions of the general class, mesoblastic new growths. Fleischl goes still further and proposes abandoning the term glioma, since it simply means a sarcoma which had its origin in the neuroglia and which, elsewhere in the body, would be called fibro- or myxo-sarcoma. Even a tumor consisting entirely of elements resem-

bling ganglion cells he calls a sarcoma originating from the pyramidal cells of the cortex.

After the establishment of the epiblastic origin of the neuroglia the distinction between these two classes of growths could be much more distinctly made, as also the close connection between glioma and neuroglioma. The only mesoblastic tissue in the brain being now known to be in the sheaths of the blood-vessels, it followed that any connective tissue tumor in the brain must originate either in the brain membranes or in the vessel walls. Thus Ziegler in his last edition limits the term glio-sarcoma to gliomata in which the connective-tissue cells of the vessel walls also undergo increase and form an integral part of the tumor. Stroebe and Oppenheim give the same definition of glio-sarcoma. Von Lenhossék inclines to the belief that all new growths occurring in the central nervous system are gliomata or neuro-gliomata. He admits the possibility of a mixed growth in which the cells of the vessel walls participate and would call such a tumor glio-sarcoma, but he refuses to accept as such any of the cases which have up to this time been described.

It seems therefore most logical to restrict the term glio-sarcoma to a tumor of undoubted mixed origin, yet the difficulty of applying this rule is great. Almost all authors speak of a thickening of the vessel walls as being present in gliomata; the cells lying near the vessels become more spindle-shaped and group themselves around the vessel in several layers. In most cases these cells do not differ in any way from the other spindle cells occurring in the tumor, but the latter are too evenly scattered to be regarded as having any connection with those around the vessel. In other gliomata the cells are all round with the exception of those in the vessel walls, and this has in some cases led the author to consider the growth a mixed one. It would seem, however, that as long as these cells are grouped evenly around the vessels and show no tendency to form masses pushing out into the surrounding tissue, as long as they do not, as Ziegler says, form an integral part of the tumor, they should be regarded simply as a proliferation of the cells of the vascular wall, due perhaps to the irritation of the neighboring tumor.

Still another view as to the part played by the blood-vessels is emphasized by De Beauclair, who describes three cases of "sarcoma" of the brain and gives as the most distinguishing feature of these growths their naked vessels, which lie directly in contact with the tumor cells, being without any limiting membrane. As this is characteristic of the vessels in sarcoma elsewhere in the body, the point is not an unimportant one. Buchholz wishes to establish as an important characteristic of glio-sarcoma the fact that many glia cells near the blood-vessels are furnished

with a long process which passes to the vessel wall and ends there in a triangular swelling. This peculiarity I do not find mentioned by any one else.

On the whole the term glio-sarcoma has been, even up to the present time, very loosely applied, and while accepting the definition of the later writers as probably correct, one is inclined, after studying the literature, to agree with von Lenhossék that no undoubted case of glio-sarcoma has yet been reported. Indeed, in the absence of drawings it would be hard to prove such a case in the literature.

Admitting the purely ectoblastic origin of all the cells in a neuro-glioma, there is still a difference of opinion as to the ganglion cells in such a growth, whether they are to be regarded as arising from the pre-existing ganglion cells or from the glia cells. Klebs holds that either may be true, that a new growth may have its starting point in the neuroglia and go on to the production of ganglion cells, or that it may start in the pyramidal cells of the cortex and also produce both neuroglia and ganglion cells. Golgi doubts the possibility of any proliferation on the part of the real nerve elements and prefers to regard those present in the tumor as pre-existing cells modified by the pathological process. This, however, would not apply to those cases in which the ganglion cells are enormously increased in number and found in situations where no ganglion cells exist normally, as in several of the cases reported by Klebs, in Osler's case, in the present case, and in others.

Both Klebs and Fleischl claim that they find ganglion cells in the act of unequal division, this division taking place simply by cleavage of the protoplasm, the nucleus seeming to take no active part in it. Their drawings show large irregularly shaped, multinucleated cells with one or two furrows or clefts in the protoplasm dividing them into unequal parts, one of which may be without a nucleus. In some cases cleavage seems to be not yet complete. Therefore these two authors consider the ganglion cells composing a neuro-glioma to be produced by the splitting of pre-existing pyramidal cells. This question I will return to later on; although appearances identical with those just described are found in my case (Plate L, *D*), they are capable, I think, of another interpretation.

The possibility of a proliferation of the pyramidal cell of the cortex has indeed been lately held by Vitzou and by Tedeschi. These two observers have, independently of each other, arrived at the conclusion that after extirpation of part of the cortex the nerve elements may proliferate. The great mass of opinion, however, is still against this position, and as regards the ganglion cells in a neuro-glioma the view most generally held is that all the elements in such a growth are derived from

indifferent embryonic cells, which may develop into neuroglia cells, or go on to the production of ganglion cells, or both. This view is held by Stroebe, by Raymond, by Tedeschi, by Fenoglio, by von Lenhossék, and by Lesage and Legrand. These two last-named authors found in a congenital tumor in a new-born child cells which represented all stages of development, none of them varying in any way from the types of normal embryonic cells. Hartdegen also finds only normal embryonic cells, though in abnormal situations. His case was also one of congenital tumor. Stroebe found, besides typical embryonic cells, many abnormal elements in several of his cases; irregular ganglion cells and multinucleated giant cells, but he considers them all to have originated in the neuroglia.

Raymond claims that he could in his case trace the development of the ganglion cells, which filled the centre of the tumor, from their earliest stage to complete development. He begins with the small round cell, which lies in the pericellular space around a ganglion cell and which, though in appearance just like a neuroglia cell, is capable of replacing the ganglion cell, if the latter perishes. This cell proliferates and in the next stage the space formerly occupied by the ganglion cell is found filled with small round cells. These take on the character of neuroblasts, often becoming multinucleated and sending out processes. The protoplasm increases and they reach the stage of atypical ganglion cells. The first stages are found near the edge of the tumor, the last in the centre. The drawings which accompany his article show examples of all these different stages, but hardly establish his first point, the starting of the process in the small cell near the ganglion cell. Nor can I find any authority for assuming the existence of such an *Ersatzzelle*. A small round cell is frequently observed in the pericellular space of a nerve cell, but I cannot find that it is considered by anatomists as a cell capable of developing into a true nerve element.

Renaut lays more stress upon the reversion of the cells in a neuroglioma to the type of those in the lower animals, and draws his comparisons from ganglion cells of the lower invertebrates, rather than from human embryonic cells. Fenoglio is unwilling to regard these so-called ganglion cells as in any sense true nerve elements, while Klebs and Fleischl consider them really nerve cells, and Renaut insists that he has even found some of the glia cells sending out true axis cylinders, which entitles them also to be regarded as nerve elements. This last seems somewhat doubtful, especially when one considers that he bases his assertion on appearances found in specimens stained only by the usual methods, hæmatoxylin and carmine. Osler, who found many ganglion cells in his case, does not consider them true nerve elements.

Probably a distinction should be made here between growths which occur in adult life and those which are congenital; the latter, being caused by misplacement or irregular development during fœtal life, would be composed of cells more like the normal.

To sum up then, briefly, the conclusions that may be drawn from the literature on this subject, it will be seen that the older view, which held that the nature of a new growth within the brain depended on the number and character of the cells composing it, has been abandoned. All new growths in the brain, being epiblastic in origin, are to be regarded as gliomata, unless they are proved to have as starting-points the membranes or the walls of the blood-vessels. A mere thickening of the vessel wall is not to be so interpreted. The term glio-sarcoma is to be limited to those tumors which show pathological increase both of the neuroglia on one side and of the connective tissue belonging to the vessels on the other, the latter being considerable enough to form an integral part of the tumor. Neuro-gliomata have the same origin as other gliomata, there being probably no proliferation on the part of the pre-existing ganglion cells, but all the cells of the tumor representing earlier or later stages of development of the original indifferent embryonic cells in which the process started. These cells are often far from any normal type and may not resemble either neuroglia cells or nerve cells. Such atypical ganglion cells are not true nerve cells and are probably not furnished with genuine axis cylinders.

Returning now to the tumor described above and considering it in the light of these conclusions, one cannot do otherwise than class it among the neuro-gliomata. Were one to judge simply by the characters of certain of the cells or by the richness in cellular elements, one would undoubtedly pronounce it a sarcoma. The great variety of cells, the presence of giant cells, some even devoid of processes, the absence of typical spider cells, and the fact that the cells sometimes lie in direct contact with each other, have all been taken as grounds for such a diagnosis. Or admitting that the mass of the tumor consists of cells which are epiblastic in origin, the increase of spindle cells in the walls of the vessels might lead to its being considered a

mixed growth, a glio-sarcoma. As we have seen, however, this increase is too slight to be considered sarcomatous in character, and as the mixed nature of the tumor cannot be sustained, it must be considered as belonging to the neuro-gliomata.

As to the question whether the irregular ganglion cells composing a large part of the tumor arise from pre-existing ganglion cells or merely represent the latest stage of development of the tumor cells, the appearances in this case seem to bear out the latter view. It must be admitted that ganglion cells are to be found which present appearances interpreted by Klebs and Fleischl as evidences of cell division, some of which are shown in the plates. But it seems far simpler and less presumptuous to suppose that these are cells in close apposition, whose shape has been altered by pressure, or, if there really is a beginning and still incomplete division, that it is of the nature of a degenerative change and not a true cell division. There is, besides, no evidence of the multiplication of pyramidal cells in the cortex, and the ganglion cells of the tumor are found, not in the cortex, but in the centre of the mass, in the white matter.

Karyokinetic figures were found only in the glia cells. The cells on the outer edge seem to represent earlier stages of development, those in the centre, later. Yet they do not represent merely different stages in the development of adult ganglion and neuroglia cells from indifferent embryonic elements. Many, indeed almost all, of the cells are atypical, some of them hardly resembling at all their prototypes, and are recognized as belonging with them only because transition forms between them and normal ganglion or neuroglia cells can be found. The cells first described, which have light, clear protoplasm, nuclei with dark periphery and delicate processes, seem to be products of cells which took the character of neuroglia, while those with granular protoplasm, dark, uniformly stained nuclei, and thick processes seem to belong to the types of nerve cells. That the latter are not true nerve elements seems proved not only by their deviating from the normal type in shape and in the structure of their nuclei, but also by the fact that Nissl granules cannot be demonstrated. They also failed to react to the Golgi method, but I am inclined to attribute

this to the imperfect preservation of the tissue, although Tedeschi and Osler, almost the only ones who have used this method in the examination of gliomata, state that the ganglion cells in their cases did not take the silver chromate. Osler, indeed, considered this an additional proof that they were not true nerve elements.

As regards the absence of degeneration of the motor tracts below the centrum semi-ovale, the cause is made clear by examining those sections of the tumor which were stained by Weigert's method, and where the fibres can be seen entering the mass, some losing their medullary sheaths, others persisting unchanged and emerging below. This appearance is very similar to that found in the so-called insular sclerosis (Charcot) of the cord, when, as is well known, the naked axis cylinders are found pursuing their course through the sclerotic patches, and the tract below shows no secondary degeneration. It is even conceivable that those fibres which lost their myelin sheaths in their passage through the tumor may have regained them on emerging. This interruption in the myelin sheath of a nerve is seen in the nerves in the mesentery of some of the lower vertebrates, and in the sensory nerves in man in their passage through a Pacinian corpuscle (Schiefferdecker). Also, as von Recklinghausen first pointed out, in neuro-fibromata of the skin the nerves take their course through the fibrous tissue partly as medullated fibres, partly as naked axis cylinders, and in all probability the latter were formerly also furnished with myelin sheaths.

I am glad to take this opportunity to express my gratitude to Dr. Flexner for his kind direction and assistance throughout this investigation; and also to Dr. Barker for many helpful suggestions.

DESCRIPTION OF PLATES L-LIII.

Plate L.

Isolated tumor cells. *A*, *B*, *C*, various forms of spindle cells. *D*, dividing (?) ganglion cell. *F*, *H*, non-branching giant cells. *E*, *G*, *I*, glia and neuroblastic elements. Phospho-molybdate stain.

Plate LI.

Vertical section through the affected motor convolutions. *A*, meninges; *B*, cortex showing invasion of tumor; *C*, white matter containing the main growth. Phospho-molybdate stain.

Plate LII.

Fig. 1. Typical field showing multinucleated and branching (ganglion?) cells, brush cells, etc. Same staining as previous ones.

Fig. 2. Two fields from the circumscribed nodule (page 645). *A*, spindle and branching cells; *B*, round and oval cells devoid of branches. Phosphomolybdate staining.

Plate LIII.

Fig. 3. Large multipolar (Betz) cell among pyramidal cells of the cortex and small tumor cells.

Fig. 4. Invasion of tumor cells between the medullated nerve fibres, some of which show varicosities. Weigert's myeline stain.

BIBLIOGRAPHY.

Baumann.—Inaug. Diss., Tübingen, 1887.

De Beauclair.—Inaug. Diss., Freiburg, 1891.

Birch-Hirschfeld.—Lehrb. d. allg. path. Anat., Leipzig, 1892.

Bramwell.—Intracranial Tumors, Edinburgh, 1888.

Buchholz.—*Arch. f. Psychiatrie*, xxii (1890).

Carrara.—*Giornale d. r. Accad. d. Med. d. Torino*, 1895, 270.

Ernst.—Ziegler's *Beiträge*, ii (1892).

Fenoglio.—*Gazz. delle Cliniche di Torino*, 1876.

Fleischl.—*Wiener med. Jahrbüch.*, 1872.

Francis.—*Am. Journ. Med. Sciences*, 1895.

Galavielle and Villard.—*Arch. de Neurologie*, 1895, xxx, 1.

Golgi.—*Rivista Speriment. di Freniatria*, 1875, 1.

Gowers.—Diseases of the Nervous System, 1892.

Hartdegen.—*Arch. f. Psychiatrie*, 1881.

Hektoen.—*Journ. Am. Med. Assoc.*, 1893, 20.

Jastrowitz.—*Arch. f. Psychiatrie*, iii.

Klebs.—*Prager Vierteljahresschrift*, 1877, 138.

Klebs.—Die allgemeine Pathologie, Jena, 1889.

Laveran.—*Bull. et Mém. d. Soc. Méd. des Hôp. d. Paris*, 1893.

Lemcke.—Langenbeck's *Archiv*, xxvi (1881).

Von Lenhossék.—Der feinere Bau d. Nervensystems, Berlin, 1895.

Lesage and Legrand.—*Arch. de Physiologie*, 4. Sér., ii (1888).

Marchi.—*Rivista Speriment. di Freniatria*, ix (1883).

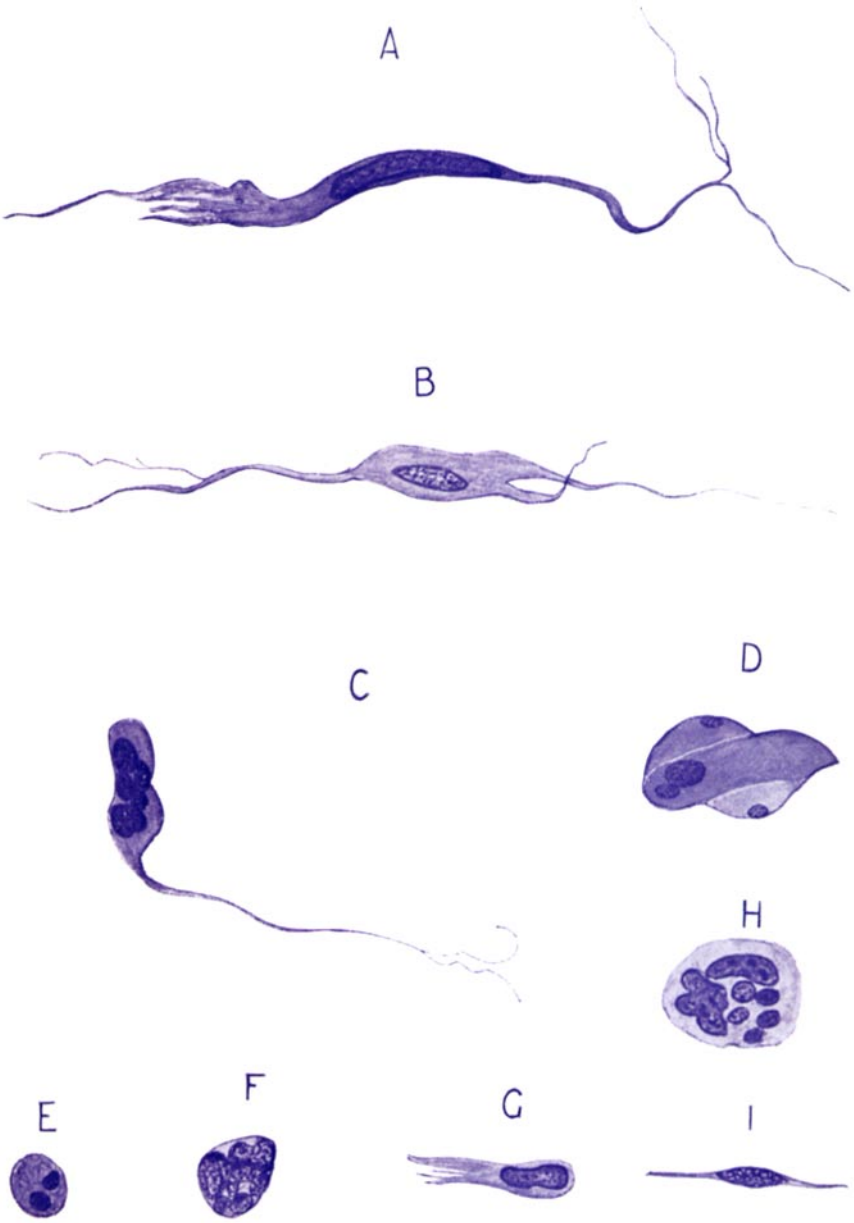
Neumann.—Virchow's *Archiv*, lxi.

Oppenheim.—*Arch. f. Psych.*, xxi (1889-90).

Oppenheim.—Die Geschwülste des Gehirns, in Nothnagel's Spec. Path. u. Ther., ix, I, 3, Wien, 1896.

Orth.—Lehrbuch d. spec. path. Anat., 1894.

Osler.—*Medical News*, 1886, 48.
Perls.—Lehrb. d. allgemeinen Pathologie, Stuttgart, 1877.
Pfeiffer.—*Deutsche Zeitschft. f. Nervenheilk.*, 1894.
Prautois and Étienne.—*Arch. de Neurol.*, 1894, 270.
Raymond.—*Arch. de Neurol.*, 1893, 26.
Renaut.—*Gaz. Méd. de Paris*, 1884.
Schiefferdecker and Kossel.—Gewebelehre d. menschlichen Körpers, Braunschweig, 1891.
Simon, Th.—Virchow's *Archiv*, lxi.
Sokoloff.—*Deutsch. Arch. f. klin. Med.*, xli (1897).
Stroebe.—Ziegler's *Beiträge*, xviii (1895).
Tedeschi.—*Rivista Speriment. di Freniatria*, 1894.
Tedeschi.—*Centralbl. f. allg. Path.*, vii (1896).
Virchow.—Die krankhaften Geschwülste, Berlin, 1863.
Vitzou.—*Arch. de Physiologie*, 5. Sér., ix (1897), 29.
Ziegler.—Lehrbuch d. path. Anat., Jena, 1895.


A
B
C
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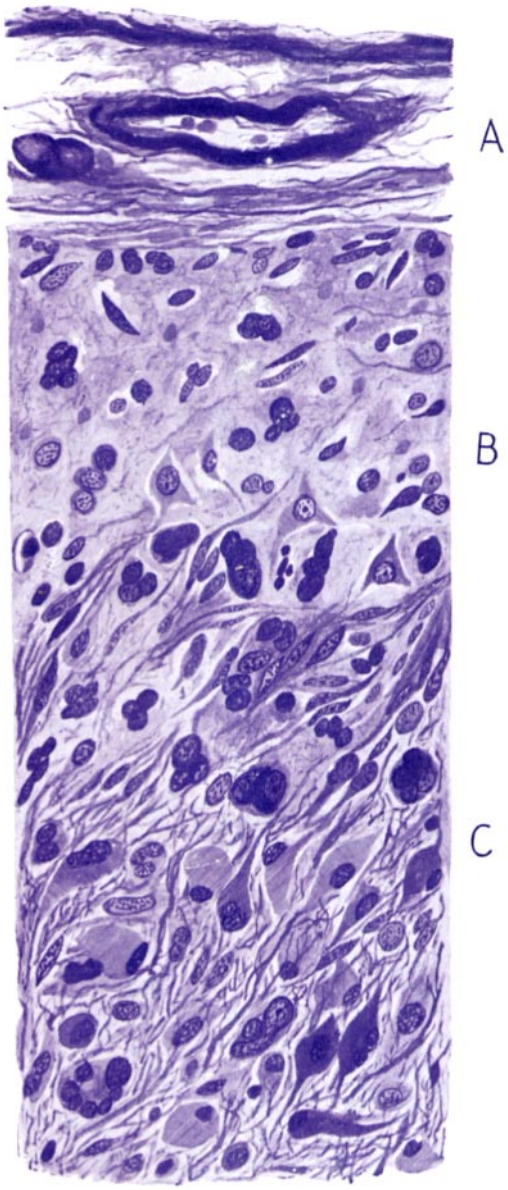
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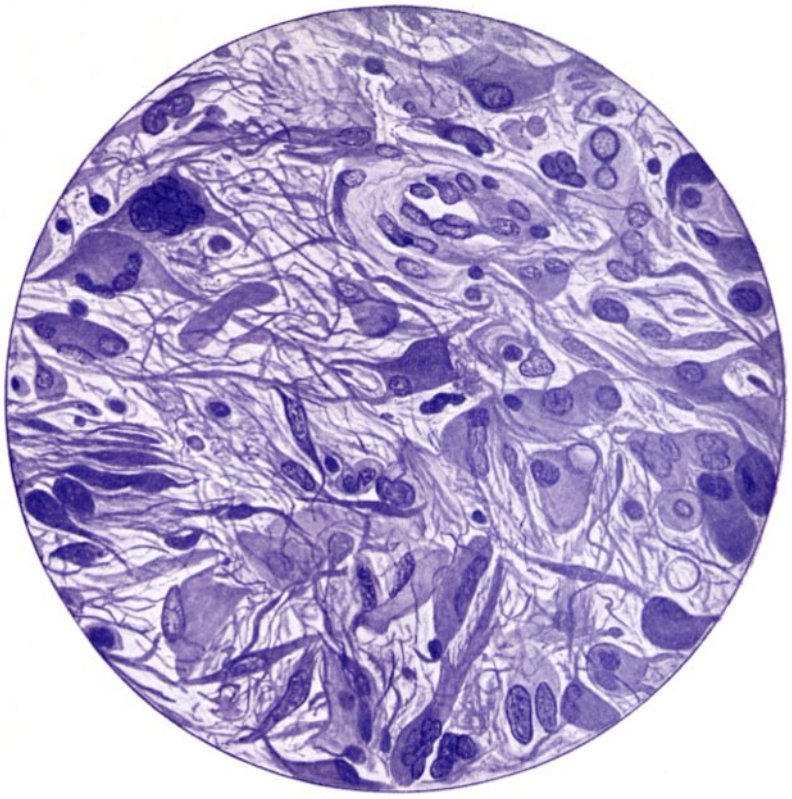

FIG. 1.

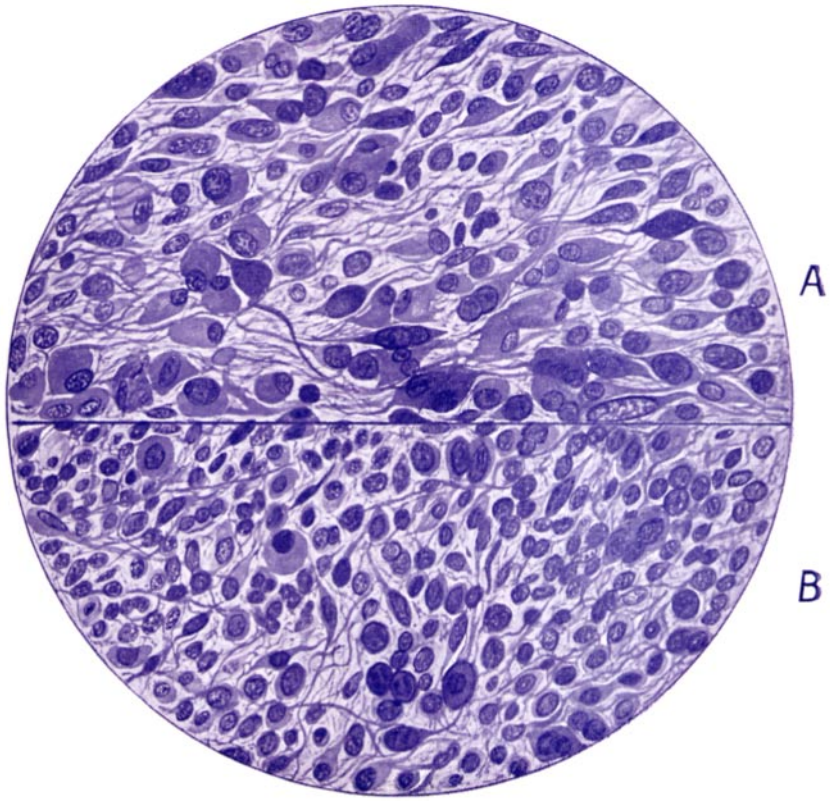

FIG. 2.

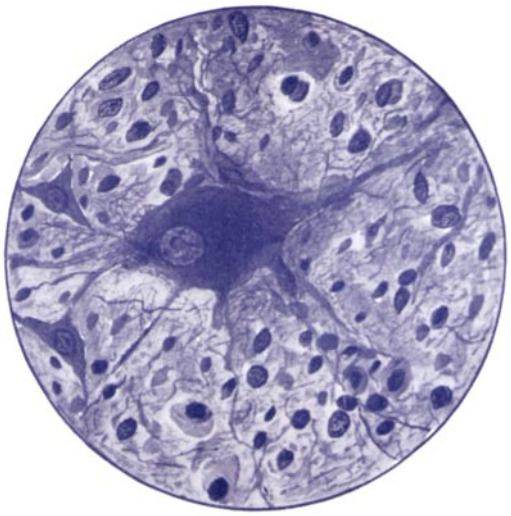

FIG. 3.

FIG. 4.