A PECULIAR FORM OF FIBROSARCOMA OF THE BRAIN.

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PLATES XXIX AND XXX.

Fibrosarcoma of the brain, though described with relative frequency by earlier writers, scarcely finds mention in later text-books of pathology, and though individual cases are still recorded in the current literature, they almost invariably come from observers who base their diagnosis chiefly upon the gross appearances, and whose description of the microscopic findings is far from satisfactory. A careful examination of the literature on the subject forces the conviction that the majority of tumors which have been classed as fibrosarcomata were in reality gliomata unusually rich in fibres. Indeed, the tendency of pathologists now is to regard as gliomata all tumors of the nervous system, which cannot be proven to have taken their origin either in the meninges or in the walls of the blood-vessels, in the latter case usually in the endothelium. It is, therefore, with some hesitation that I venture to give the name of fibrosarcoma to a primary growth in the cerebrum, a growth which cannot have originated in the meninges nor in the endothelium of the vessels. It seems, however, impossible to class it otherwise than as a connective-tissue tumor of a very peculiar type, originating probably in the outer coats of the blood-vessels.

The specimen was given me for examination by Dr. L. L. Skelton, of Chicago, to whom I am indebted for the following brief notes of the clinical history and autopsy. The patient was a married woman, twenty years of age. When seen by Dr. Skelton in consultation she was suffering from "terrific" headaches, and gradual impairment of vision. There were slight incoördination, hysteria, psychic changes

and intermittent albuminuria. Ophthalmoscopic examination showed choked disks. Dr. Skelton diagnosed a tumor of the brain, and advised operation. This was refused, and he did not see the patient again until after her death, when he was requested by the family physician to make an autopsy. This was done twenty-four hours after death. Upon removing the skull-cap the right cerebral hemisphere was seen to bulge a little, but the meninges and cortex were apparently unaltered. When, however, a shallow incision was made in the frontal region through the cortex, the latter peeled away, leaving exposed a spherical mass distinctly circumscribed and readily enucleated. This mass occupied the deeper parts of the three frontal convolutions and subjacent white substance projecting into the ventricle, but not involving the basal ganglia. No important changes were found in the thoracic or abdominal viscera; there were no new growths in any organ save the brain.

The specimen, when it came into my hands, had been for eighteen months in a four-per-cent solution of formaldehyde. Unfortunately the brain had not been preserved in toto, but the tumor had been removed with only that part of the tissues which directly surrounded it, so that the exact relation of tumor to brain could not be determined. The mass was about as large as a medium-sized orange and firm in consistence; its color was whitish with gray streaks. The cerebral tissue separated easily from the tumor; in no place was there any sign of infiltration, extension of the growth having evidently taken place by displacement of the normal tissue. Pieces from different parts of the tumor were hardened, some in alcohol, others in potassium-bichromate-chromalum solution according to Weigert's quick method for myelin sheaths, and others in picric acid and ammonium bichromate for Mallory's neuroglia stains. Sections were stained in the above-mentioned ways, and also with hæmatoxylin and eosin, with Van Gieson's picro-acid-fuchsin, and with Weigert's new fuchsin stain for elastic fibres.

The first sections examined were those which had been cut from the edges of the tumor, where the new growth seemed, to the naked eye, to be sharply divided from the uninvaded brain tissue; this im-

pression was confirmed under the microscope. The tumor was circumscribed, although not encapsulated, and there was no sign of a gradual infiltration of surrounding parts. Furthermore, the meninges were found to be uninvolved in the new growth. Often the normal tissue was separated from the tumor mass by a prolongation of the pia mater in between two convolutions, while the membrane itself was normal save for slight round-cell infiltration.

Examined under the low power of the microscope, the tissue of the tumor was seen to be exceedingly rich in cells, closely crowded together, and with very scanty intercellular substance. The cells were not evenly distributed, being often gathered together in clumps, which seemed composed of more or less circular elements, while bands of spindle-shaped cells occasionally ran across the field between the clumps. Spindle cells could also be seen near the blood-vessels, and these cells were possessed of processes, while the circular and oval cells were apparently devoid of processes. The intercellular substance had usually a granular appearance, but between the spindle cells it was delicately fibrillar. Under the high power the cells exhibited a great variety of shapes and sizes. So closely were they packed together in some places that it was impossible to distinguish their individual outlines, the appearance being that of a large mass of protoplasm with nuclei scattered through it. In thinner places, however, the cells stood out clearly, the protoplasm of the largest ones being granular, and taking the stain deeply. Mallory's phosphomolybdate stain brought out the cells most distinctly, and sketches were made of the different types in sections stained after this method (Plate XXIX, Fig. 1). The cell which seemed most widely distributed was the round, or irregularly oval, or angular cell of medium size, with lightly stained protoplasm and a single nucleus, the latter usually circular, staining deeply at the periphery and showing coarse chromatin granules. Apparently naked nuclei, singly or in clumps, occurred with great frequency, and occasionally very small cellular elements were found with a pyriform body and one delicate process. The spindle cells, mentioned above, occurred, not scattered among the other cells, but in slender bands or close to the blood-vessels. They

possessed but one nucleus, and one or more processes at each end. Some of them resembled the so-called brush cells. They lay with their long axes parallel, and their processes formed a fibrillar matrix, which was wanting elsewhere in the tumor. The larger cells were most irregular in outline and in the arrangement of their nuclei, which were sometimes as many as ten in number. The protoplasm was more granular than that of the other cells, and stained deeply; the nuclei were richer in chromatin. These cells were often found in groups, but no part of the tissue was totally devoid of them. They were frequently vacuolated, and this gave rise to appearances like those interpreted by some observers as intracellular parasites. Sometimes these cells would have one delicate process, rarely more, but the majority were altogether devoid of processes.

As can readily be seen from the foregoing description, the cellular elements demonstrated in this tumor are not those usually found in glioma, but suggest a connective-tissue growth. Gliomata containing irregularly shaped giant cells have been described by Fleischl,* by Klebs, by Stroebe, and by myself, but in all these cases the majority of the cells in the tumor were either spider, brush, or the so-called ganglion cells, all of which were furnished with processes, and the intercellular substance was rich in fibres. An attempt to stain sections of this tumor by Golgi's method failed entirely, but this may have been due to the length of time which elapsed before the autopsy was made, and perhaps also to the long immersion in formaldehyde.

The tumor was unusually rich in blood-vessels of all sizes, from capillaries to large vessels with several layers of elastic and muscular fibres in their coats. The smaller vessels presented no peculiarity in appearance, but in the larger ones the outermost fibres, which composed the wall, could often be seen passing out into the tissue to lose themselves among the cells at a long distance from their origin (Plate XXX, Fig. 4). These fibres had all the characteristics of elastic tissue. They pursued a wavy course, were curled at the free ends, and did not branch. Again, in other places, fibres exactly like these in character were found running between the cells, though they could

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

not be traced to any vessel, and had no apparent connection with the cells of the tumor. By Van Gieson's stain they came out in sharp contrast to the cells, staining pink or deep red (Plate XXIX, Fig. 2); by Mallory's phosphotungstate they stained a purple red (Plate XXX, Fig. 3); but it was in sections treated with Weigert's fuchsin stain for elastic fibres that they could most easily be traced (Plate XXX, Fig. 4). By this stain they appeared bluish-black, and therefore quite different from the delicate intercellular fibrils and processes from the spindle cells, which by all of the above-mentioned methods took the usual protoplasmic stain. The staining properties of these fibres forbade the supposition that they could be remains of medullated nerves. Sections were stained by Weigert's differential method for myelin sheaths, with the result that the medullated nerves were found to end abruptly at the edge of the tumor, no trace of such a structure being demonstrable within the new tissue. This absence of medullated nerves is regarded by Stroebe as one proof that a tumor is not of nervous origin.

Much more striking, however, than the single scattered fibres, were the thick circumscribed collections of coarse and delicate fibres which appeared everywhere throughout the tumor. These were dense masses lying among and on top of the cells, being sometimes long and spreading, sometimes round. They appeared in every variety of shape, from symmetrical rosettes to long irregularly branching masses. The fibres which composed them were usually delicate, and curved slightly, sometimes thick and bristling. In the larger masses, and in almost all the circular ones, the centre was composed of a granular material, the fibres appearing clearly only at some distance from the centre (Plate XXX, Fig. 3). Under the low power it often looked as if the fibres were processes of the surrounding cells, and passed from them into the centre, an arrangement suggesting that of the tails of the spermatozoa in a seminiferous tubule of the testicle. A close examination, however, under the oil immersion failed to show that these fibres were connected with the cell bodies; they seemed simply to pass among and over the cells. The cells directly surrounding them were usually spindle-shaped, sometimes with, sometimes

without processes. When present, such processes took the protoplasmic stain.

Although no part of the tumor was free from these masses, yet it was noticeable that the larger the number of blood-vessels, the fewer the fibrillar masses. Many of them occurred in close connection with the vessel walls, either entirely surrounding a small vessel, or covering one side, or, what was most common, scattered at intervals along the course of a larger vessel. Occasionally a rosette would contain in its centre a small collection of cells (Plate XXIX, Fig. 2).

A close connection between the fibrillar masses and the vessel walls suggested the idea that this connection might be invariable, and that in cases where the masses seemed independent, they were lying along the wall of a vessel which had not been included in the section. To prove this, serial sections were made, but with the result that by far the larger number of these masses were without demonstrable connection with the vessels.

In their staining properties these fibrillar masses corresponded with the single scattered fibres already described, and thus produced a very striking appearance, especially in sections stained by Van Gieson's method, where the deep pink rosettes stood out in sharp contrast with the yellowish background. By Weigert's elastic-fibre stain it was often possible to follow the single scattered fibres and see them end in a rosette, and also in many cases to find such fibres running from the wall of the vessel to lose themselves in rosettes at varying distances from the vessel (Plate XXX, Fig. 4). Though the fibrils composing the rosettes were usually much more delicate than the diffuse fibres, and stained a little lighter, yet there seemed no room for doubt that the two were of the same origin and character.

I can find in the literature no description of collections of fibres such as these in the case under discussion. Gliomata rich in fibrils are of frequent occurrence, but in these the fibres are never arranged in circumscribed masses, nor do they take the differential stains for connective tissue. By the kindness of Dr. Flexner I was enabled to compare with this tumor sections from an ependymal-celled glioma described by him a year ago. The arrangement of the fibres in his case on

first sight resembled somewhat the arrangement in the one I am describing. Here, too, there are long and circular collections of fibres surrounded by cells, but these fibres are processes from the cells from which they pass to the vessel walls; they stain as do ordinary glia fibres, and the cells are of the type of ependymal cells. The two specimens cannot, therefore, be regarded as belonging to the same class of growths.

The question then resolves itself into the following: Is this a glioma with a peculiar form of sclerosis, or a fibrosarcoma with masses of elastic fibres in the matrix? There are several arguments in favor of the former alternative. In the first place, it is unusual to find a connective-tissue growth in the cerebrum which has not sprung from the meninges, or from the endothelium of the vessels. The possibility that the connective-tissue elements in the outer and middle coats of the vessels might proliferate and form a true sarcoma cannot be denied, but this is not the usual form of connective-tissue growths in the nervous system. Upon the assumption that the tumor is a glioma, the apparent dissociation of fibres and cells might be explained by considering that this tumor represents the adult stage of neuroglia, when, according to Weigert, the fibres no longer have connection with the cells. Taylor argues in favor of this view, and has given a description of two specimens of glioma, the one representing the embryonic stage, the other the adult stage of neuroglia. In the former the fibres of the matrix proceed from the cell bodies; in the latter they are entirely independent of the small round cells. Maximilian Herzog also follows Weigert's view as to the dissociation of glia cells and fibres, but modifies it by regarding the fibres as cells which have undergone a senile change, analogous to the cornification of epithelial cells. He described an ependymal cyst lined with cubical epithelial cells. The cells became slender bipolar spindles as they approached the edge of the cyst, refractive granules appeared in the protoplasm, and finally the free edge was covered with stiff slender fibres, staining like cornified material. He argues that in this case the neuroglia cells, being of epithelial origin, reverted to the original type and formed a true epithelial growth, but that the process here

was in all essentials analogous to the formation of the fibres of neuroglia by gradual flattening and cornification of the cells. He might, therefore, consider the collections of stiff fibres in my case as analogous to the cornification of the cells in the centres of epithelial pearls in carcinomatous growths.

On the other hand, the arguments in favor of the connective-tissue nature of the tumor are many. In gross appearance it differs from a typical glioma, for it is circumscribed, firm in consistence and easily enucleated, while a glioma usually infiltrates instead of displacing the normal tissue, and is soft in consistence. Again, the characters of the cells and of the intercellular substance do not suggest a growth springing from the neuroglia. The entire absence of medullated fibres is another point against glioma.

The strongest argument, however, in favor of the connective-tissue origin of the growth is based on the chemical nature of the fibres, as shown by their reaction to differential stains. The distinctive chemical characteristics of neuroglia fibres, as evinced by their affinity for certain stains, is especially emphasized by Weigert in his exhaustive work on human neuroglia, and is made by him the basis for determination as to what does and what does not belong to this tissue. It is much to be regretted that the tumor was not obtained in the fresh condition, so that it could have been stained by Weigert's method for neuroglia fibres, but in the absence of this test the reaction of the fibres to the three stains mentioned above (Van Gieson's, Mallory's phosphotungstate, Weigert's elastic-fibre stain) would seem to prove conclusively that they belong to the connective tissues. The origin of the growth must be from the connective-tissue elements in the walls of the blood-vessels, and these elements, instead of producing a fibrosarcoma of the usual type, have gone on to the production of polymorphous cells with aggregations of elastic fibres within the matrix. That this is unusual must be conceded, but there is certainly an analogue to such a process in the formation of islands of hyaline cartilage in chondrosarcoma, and of bone in osteosarcoma.

I am unable to find descriptions of fibrosarcomata in which the fibres of the matrix were proven to be elastic fibres. It would seem that the

question as to the exact nature of such intercellular fibres in these tumors has not been systematically studied. The application of Weigert's admirable stain for elastic fibres to the study of tumors and of other pathological conditions gives promise of yielding interesting results. Melnikow-Raswedenkow in a recent article has described the distribution of elastic fibres in various organs in normal and pathological conditions. He notes especially the richness in elastic fibres of the walls of blood-vessels, particularly of the adventitia, and finds that the elastic fibres in healthy and diseased organs and tissues are derived mainly from the vascular walls. Within the central nervous system elastic tissue is scanty and present only in the walls of blood-vessels. He states that in tumors no new formation of elastic tissue occurs, a statement, however, contradicted by the presence of a large amount of elastic tissue in the tumor now under consideration. There is no other apparent source for the elastic tissue found in the present tumor than that in the walls, especially the adventitia, of the blood-vessels, and this conclusion is in accord with Melnikow-Raswedenkow's observations concerning the normal distribution of this tissue in the brain as well as with the relationship, already described, of much of the elastic tissue to the vessel walls. Where this relationship is no longer apparent, its disappearance may be attributable to obliteration of vessels or to the severance of the original connections.

The literature on the normal development of elastic fibres is most unsatisfactory. There seem to be two theories as to the origin of these fibres—the cellular and the intercellular theory—dating from Theodor Schwann's belief in the transformation of the cells into fibres and Max Schultze's view that the cells fused to form the fibrillæ. B. Lwoff believes that the fibres are formed by the outer part of the protoplasm of the cells, which becomes differentiated and lies as a sheath around the inner protoplasm and nucleus.

The later observers, almost without exception, hold that the fibrils are formed in the intercellular matrix, independently of the cells, or at any rate without visible connection with them. Henle, Kölliker, Ranvier, Schaefer, and Minot uphold this view. According to Ranvier, there appear in the gelatinous matrix between the embryonic

connective-tissue cells globules of elastin, probably deposited by the cells. These fuse and form fibrils. They appear late in embryonic life (fifth month in human beings), grow by thickening, and continue to form even after birth. According to Minot, the elastic fibres in the omentum develop thus: The connective-tissue cells become long and spindle-shaped, with oval nuclei. In between them appear fibrils which increase in length and number, and gradually form bundles, which take a wavy course. Throughout their development they have no apparent connection with the cells. Schaefer has observed that in the development of cœlenterates fibres appear in the matrix at a period when there is entire absence of cellular elements.

As regards the mode of development of the elastic fibres in the outer coats of the blood-vessels, the literature is even more scanty. The description of the formation of new blood-vessels may be followed with precision until we pass from the capillary tube with its simple endothelial coat to the arteriole with a fibro-muscular coat, where the subject suddenly becomes obscure. Most works on embryology ignore completely the question of the origin of these fibres. Minot says they are formed by the differentiation of the surrounding mesenchyma, while the pathologists seem to consider that, so far as concerns the newly-formed vessels in proliferating tissues, the outer coats are formed by multiplication and differentiation of the endothelium of the capillary walls.

So long as the whole subject of the normal development of elastic fibres is unsettled, it would be useless to attempt to explain their occurrence in a pathological growth. Whether, however, they are formed from the bodies of cells, or deposited by the cells in the matrix, or arise independently, it is certainly conceivable that a growth, originating in the connective-tissue elements of the vessel walls, might produce, in an abnormal and irregular way, the same kinds of fibres as its prototypes have produced in the course of normal development. As said above, the process would seem to be somewhat analogous to the formation of islands of cartilage or bone in mixed sarcomata.

In the tumor under discussion the steps in the process of fibre formation seem to be similar to those cited above as described by

Minot in the normal development of elastic fibres in the omentum. Spindle cells, like those which he describes as appearing before the fibres are found, occur in bands through the tissue of the tumor and, though furnished with processes, have no apparent connection with the real elastic fibres which are found between them. They would seem, however, to be in some way concerned in the formation of these fibres as they are present in greatest numbers in the neighborhood of the rosettes and the masses of fibrils which lie along the vessel walls.

DESCRIPTION OF PLATES XXIX AND XXX.

PLATE XXIX.

Fig. 1. Isolated tumor cells. Small, round and oval mononuclear cells. Small and large pyriform and fusiform cells. Giant cells with and without processes. One giant cell shows cellular inclusion. Leitz objective $\frac{1}{12}$ in. oil immersion, ocular 5. Mallory's phosphomolybdic acid hæmatoxylin.

Fig. 2. Typical field containing fibrillar masses of different shapes. One mass surrounds a small vessel almost completely. Two masses lie along the sides of vessels. One contains a group of cells in its centre. In one place scattered fibres pass between the tumor cells. Leitz objective $\frac{2}{3}$ in., ocular 3. Van Gieson's picro-acid-fuchsin.

PLATE XXX.

Fig. 3. One medium-sized rosette. The fibres can be seen passing over the cells. Large giant cells form a group to one side. Leitz objective $\frac{1}{12}$ in., oil immersion, ocular 5. Mallory's phosphotungstic-acid hæmatoxylin.

Fig. 4. Two small rosettes near a blood-vessel. Elastic fibres can be seen passing among the tumor cells to the rosettes, also from the vessel walls to the rosettes. Most of the cells are large, round and oval, but at one side can be seen a band of spindle cells. Leitz objective $\frac{1}{12}$ in., oil immersion, ocular 3. Weigert's elastic-fibre stain. Nuclei stained with lithium carmine.

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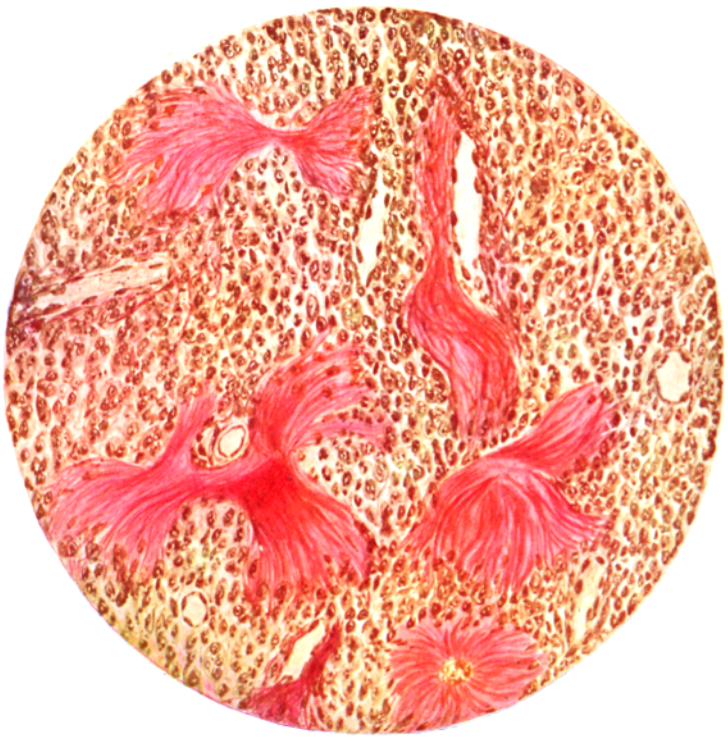

FIG. 2.

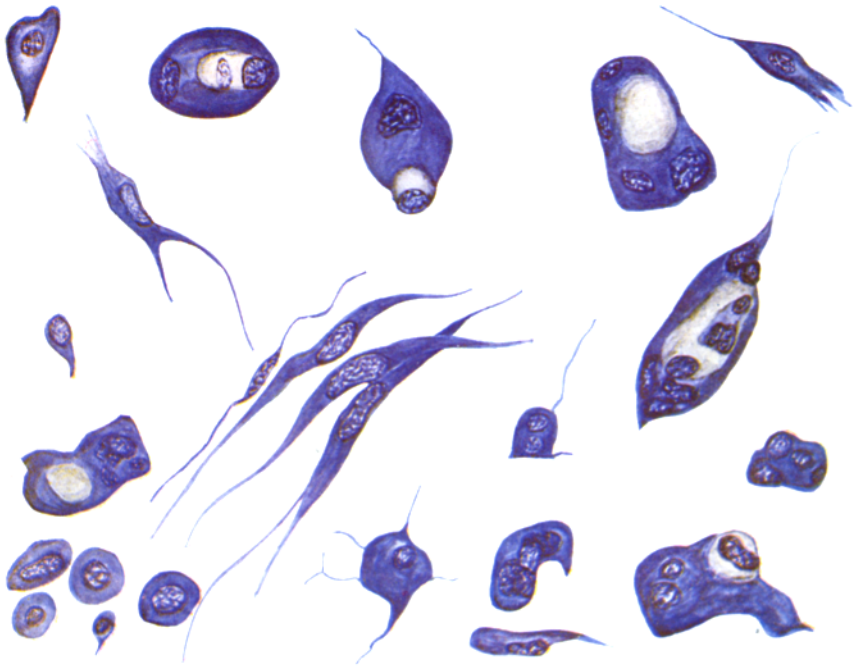

FIG. 1.

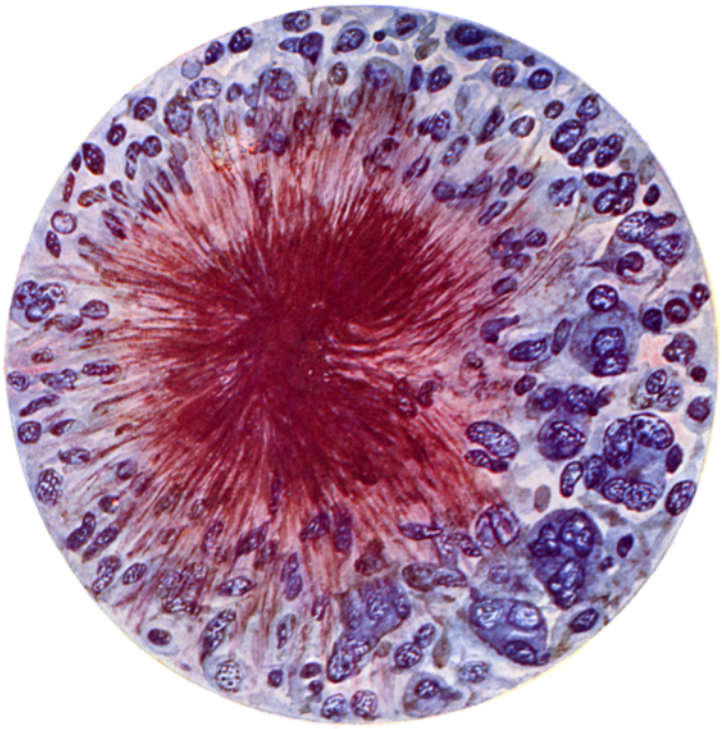

FIG. 3.

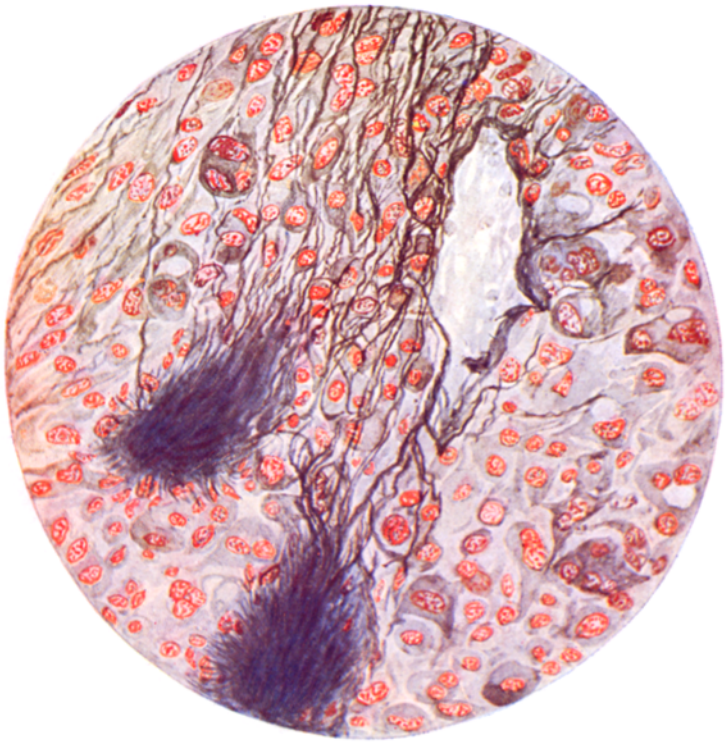

FIG. 4