DIFFUSE TUMORS OF THE MENINGES *

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One of the most remarkable examples of tumor formation is that known as diffuse sarcomatosis of the meninges. Elsewhere in the body, as implied by its very name, a tumor is made up of cells or fibers collected together to form a mass. That mass, it is true, may be flattened and widespread, as in endothelioma of the pleura or the peritoneum, but even there flat elevations or multiple nodules may be recognized.

In the leptomeninges, however, there occasionally occurs the curious condition of a neoplasm which does not give rise to a mass. A considerable number of cases of this disease have been described, but many interesting points in the pathology of the condition still remain to be cleared up.

Such terms as diffuse sarcomatosis of the meninges are somewhat misleading for they give one the conception of a pathologic entity which does not really exist. There are indeed three ways in which the condition may arise: (1) it may be secondary to some tumor outside the central nervous system; (2) it may be secondary to a tumor originating in the central nervous system; or (3) it may (possibly) exist as a primary lesion of the meninges.

Many forms of neoplasm may occasionally set up metastases in the brain, and those most prone to do so are the most likely to give rise to diffuse involvement of the meninges. The tumor may be a carcinoma or a sarcoma. Judging from the recorded cases the latter is much the more common, although it is more than probable that very many of the cases of sarcoma have no real claim to be included in this class of neoplasm. Carcinoma of the lung is perhaps the form of cancer most frequently associated with cerebral metastases. In 105 cases of carcinoma of the lung Dosquet [1] found metastases in the central nervous system in 31.4 per cent. Morse [2] has recently described an interesting case of diffuse involvement of the meninges

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in which the primary tumor was an unsuspected carcinoma of the lung only discovered at necropsy. In this and in the other instances where diffuse meningeal involvement was observed, there was a definite tumor of the brain which, as will presently be seen, probably constituted the focus from which the meninges were involved. Although the relative incidence of cerebral metastases is not so high in cancer of the stomach and of the breast, yet these diseases on account of their great frequency are those most likely to be responsible for secondary growths in the brain.

Before discussing the various forms of sarcoma which may be found in a diffuse form in the cerebral meninges and the paths by which the tumor cells gain access to the subarachnoid space, it will be convenient to present the details of a case which recently came under my observation.

Clinical History

The patient was a Galician, 41 years of age, who commenced to suffer from headaches about the middle of December, 1923. The pain came on every few hours and lasted for from ten to twenty minutes. As the headaches increased in frequency and in severity he came to the hospital on December 19th. The pain at the beginning of an attack was first felt in the forehead, but presently it passed over the top of the head and down the back of the neck. Soon the pain became constant, but still much worse in spells during which he groaned and held his head between his hands. At no time did he complain of any dizziness or tinnitus.

On admission he appeared to be in a lethargic condition, manifesting a listlessness which increased in intensity so that he lay quietly as if asleep most of the time. He could be easily aroused, however, and then answered questions quite intelligently. At this time a provisional diagnosis of encephalitis lethargica was made. The cranial nerves appeared to be normal. The eyes reacted to light and accommodation. There was no optic neuritis. The deep reflexes were unimpaired. The plantar reflex was flexor in type. The abdominal and cremasteric reflexes were present. Owing to the mental condition it was not possible to make a satisfactory examination of the sensory functions.

On the back and the anterior abdominal wall there were several small, firm, painless, non-pigmented nodules. In the right lumbar region there was a pedunculated fungating mass about 2 cm. in diameter, which had apparently been present for a number of months and which had increased considerably in size during the last few weeks.

Soon after admission to the hospital he developed stiffness of the neck and a double Kernig's sign. A lumbar puncture was done in order to exclude the possibility of syphilitic meningitis. The spinal fluid, which was not under increased pressure, was clear, showed a marked increase in globulin and contained 280 cells per c.mm. The Wassermann test was negative both in the blood and in the spinal fluid. The cells in the spinal fluid were peculiar and quite unlike any

which I had seen hitherto. They were large and pale, with a large oval nucleus and abundant cytoplasm. The sugar in the fluid was 0.05 gm. per 100 c.c.

A portion of the fungating tumor of the skin was removed and was found to be a pigmented melanoma showing numerous mitotic figures and evidence of rapid growth. A diagnosis was then made of melanoma with cerebral metastases.

The lethargy increased and the headache became worse. On January 11th the patient developed a right-sided facial paralysis. He now lay in a semi-unconscious condition all the time, the head retracted and the knees drawn up. The plantar reflex showed an extensor response on the right side and occasionally a similar response on the left side. He commenced to vomit, gradually became completely unconscious and died on January 15th.

Necropsy Findings

The ***large nodule in the skin*** was removed and examined with greater thoroughness than had before been possible. Part of the nodule was deeply pigmented, even to the naked eye, but other parts were completely free from pigment. The tumor cells were large and spherical with very pale cytoplasm and an oval vesicular nucleus, were arranged in indefinite alveoli and could be seen to arise in the most unmistakable manner from the deepest layer of the epidermis. The other skin nodules were of similar structure, but they presented one important difference, namely, they were situated quite deep and separated from the epidermis by a considerable interval. It appears, therefore, that they were metastatic in origin, a point of considerable importance which will be referred to in the subsequent discussion.

The ***thoracic and abdominal organs*** were normal with the exception of the ***left kidney*** which presented a small circumscribed nodule in the cortex about 1 cm. in diameter. This nodule was composed of large spherical cells most of which were non-pigmented, but some of which were loaded with fine yellow granules. In the immediate neighborhood of the nodule the outline of several glomeruli packed with pigmented tumor cells could be made out. It appears certain, therefore, that emboli of tumor cells were being given off from the fungating nodule in the lumbar region and that some of these were arrested by the glomeruli of the kidney, while others formed secondary nodules in the deeper layers of the skin.

Brain. When the brain was removed in a somewhat poor light it seemed at first to be quite normal and certainly presented no gross tumor either to the sight or touch. Closer inspection in a good light, however, showed that there was a faint darkening of the pia-arach-

noid in certain regions and associated with the darkening there was a slight thickening. What appeared to be a thin film, yellowish brown and adherent to the underlying structures, covered the greater part of the cerebrum, the brain stem and the cerebellum. The condition was most marked over the left cerebral hemisphere involving the frontal lobe as far back as the fissure of Rolando and commencing again in the occipital region; it was difficult to determine with accuracy the exact limitation. The left frontal lobe was involved to a less degree. A distinct thickening and opacity were found in the interpeduncular space and over the brain stem and cerebellum.

The brain was opened by the usual incisions but, as these did not actually pass through the gray matter, no abnormality was revealed. When, however, the cerebrum was sectioned from before backward in a series of coronal sections, a very remarkable condition at once became apparent. The actual tip of the frontal lobe appeared normal, but on passing back for 2 or 3 cm., the sections showed the pia to be not only discolored but slightly thickened. It was firmly adherent to the cortex and could not be stripped off. A change was observed at the same time in the gray matter of the cortex, which also became distinctly discolored, the gray passing into a dirty brown in striking contrast to the pure white of the unaffected white matter. At the same time it was noticed that the cortical gray matter was slightly thicker than normal, averaging from 2 to 3 mm. in width. This thickening was seen in much the most striking manner not in the superficial cortex but in the folds of the convolutions surrounding the fissures. Here the gray matter was two or three times the normal thickness and appeared to be the seat of some kind of infiltration, an appearance which was particularly striking in the occipital lobe. Both surfaces of the cerebellum showed darkening of the pia, patchy rather than uniform in its distribution.

Further examination of the cut surface under the low power dissecting microscope showed that the pigmentation did not really penetrate into the full depth of the gray matter but only for about one third the distance. The apparent expansion of the gray matter surrounding the sulci was due to an infiltration of the pial prolongations with cells, thus producing a widening of the fissure. The cells, however, were packed with material which blended with the gray matter and thus gave rise to an appearance of spurious thickening.

The ventricles were not dilated nor did any part of their lining show tumor nodules. The choroid plexuses seemed normal. No tumors were found in any part of the brain substance.

The spinal cord was clothed with the same thin yellowish brown film which covered the brain. There did not appear to be an invasion of the cord itself.

Microscopic Examination of the Brain

Under the microscope it was at once seen that the discoloration of the surface of the brain was due to the fact that the subarachnoid space was filled with cells which infiltrated every nook and cranny of that space. It was as if molten wax had been poured into the space and had then been allowed to solidify. The cells were of the same type as those which constituted the skin tumors except that the nucleus as a rule was darker and more eccentric in position. A more striking difference lay in the fact that none of the cells was pigmented. Just as the discoloration of the surface varied in intensity in different places, so the degree of infiltration of the subarachnoid space varied in a corresponding manner. Although the picture in its general design was that which one associates with acute meningitis rather than cerebral tumor, yet there could not be the slightest doubt that the cells were tumor cells which, because of the special anatomic arrangements, spread out in a diffuse manner instead of forming a neoplasm.

In the cerebral cortex there were numerous masses of cells which at first sight appeared to be completely separated from those in the subarachnoid space and which were so markedly perivascular in their grouping as to suggest that they were derived from the vascular endothelium (Figs. 1 and 2). In occasional fortunate sections, however, it was clearly seen that these perivascular sleeves accompanied the vessels passing from the meninges into the cortex and that the cells were directly continuous with those in the subarachnoid space. That is to say, the infiltration of tumor cells had flowed along the perivascular prolongations of the subarachnoid space for a variable distance into the brain substance (Figs. 3 and 4). A remarkable feature of these perivascular masses was that the cells in many cases were loaded with yellow pigment, although those in the adjoining subarachnoid space were completely free from pigment.

This may possibly be accounted for by the more advanced age of the deeper cells.

The walls of both lateral ventricles (thalamus and caudate nucleus) were carefully examined but no tumor cells or any implants on the ependyma could be found. A number of large cells were observed in the choroid plexuses of the lateral ventricles. It was not possible, however, to decide whether these should be regarded as tumor cells.

Tumor cells were present in the subarachnoid space and in the subjacent brain tissue of the midbrain, pons and medulla. The cranial nerves issuing from these parts of the brain carried with them a sheath of tumor cells which penetrated between the main bundles of fibers.

The meninges covering the cerebellum were infiltrated with tumor cells but none was observed in the cerebellar cortex. The same was true for the spinal cord which was surrounded by a sheath of cells particularly thick in the anterior and posterior fissures. The substance of the cord and the central canal were uninvolved.

Summing up the necropsy findings, we may say that there were collections of tumor cells of the melanoma type in the skin, in the kidney and in the subarachnoid space of the brain and spinal cord; that these cells were continued into the perivascular and perineural continuations of the subarachnoid space; and that the cells in these latter situations were pigmented, whereas those in the subarachnoid space were not.

Discussion

It has already been pointed out that diffuse infiltration of the meninges, the condition commonly known as diffuse sarcomatosis of the meninges, may arise in one of three ways. It may be primary in the meninges, it may be primary in the brain and secondary in the meninges and finally it may be primary elsewhere and secondary in the meninges with or without involvement of the brain. In the first instance the tumor is a melanoma, in the second it may be a glioma or a melanoma and in the third it may be a carcinoma, a sarcoma or a melanoma.

True primary sarcomatosis (melanosis) of the meninges is probably a condition of great rarity. The term, however, must not be used in a loose manner. In a recent communication on "Primary

Sarcomatosis of the Leptomeninges," Ford and Firor [3] give details of four cases. In the first of these there was a tumor in the right hippocampus, in the second there was a tumor in the fourth ventricle and in the remaining two no necropsy was performed. Under those circumstances one is hardly justified in speaking of the meningeal condition as being primary.

Even in the absence of a tumor in the brain, caution must be observed before concluding that the condition originated in the meninges. The eyes must first be examined for the possible presence of a melanoma. As Bland-Sutton [4] points out, while melanoma of the choroid usually occurs as a discrete tumor, it may occasionally assume the form of a diffuse flat infiltration the quiet growth of which makes detection difficult. Some cases of melanosis apparently primary in the meninges may thus in reality be secondary to unrecognized tumors in the eye.

When all these possibilities have been excluded there still remains a small group of cases in which the condition appears to have originated in the meninges. The pia, especially that portion which covers the anterior surface of the medulla, contains many pigmented cells. In the negro, indeed, this part of the brain may present a darkening which can be recognized by the naked eye. From these cells a primary melanoma may take its origin.

While the possibility of a primary meningeal origin of these tumors must be admitted, it should not yet be regarded as proved. The anatomic findings in the supposed primary cases are exactly duplicated in cases which are undoubtedly secondary. This is well seen in a remarkable case recently reported by Weller [5] in which diffuse melanotic involvement of the meninges was associated with a recurrent melanosarcoma of the skin. In this case the body was simply riddled with metastases, nodules being found in the lungs, spleen, liver, kidneys, adrenals, bladder, prostate, testes, pancreas, intestinal wall and all the lymph glands, while the myocardium was studded with melanotic nodules. Melanomas were present in the floor of the fourth ventricle and in the choroid plexus so that either of these sites, both of which are exposed to the stream of cerebrospinal fluid, may have served as the invading points for the meninges. Our own case serves as an intermediate link between Weller's case and those of the supposed primary melanoses of the meninges.

There still remains to be considered a group of cases in which

melanosis of the meninges is associated with melanomas of the skin, but in which the two conditions are supposed to be quite independent. Rokitansky,[6] Oberndorfer,[7] Grahl [8] and Maclachlan [9] have described cases of extensive pigmentation of the brain associated with pigmented nevi in the skin. The cerebral pigmentation was confined to the meninges, the surface of the brain and the lining of the ventricles. The pigmented cells in the cerebral cortex showed a marked perivascular arrangement. None of these authors considers that the pigmentation of the brain was in any way secondary to the pigmented nevi in the skin. Berblinger [10] in a very careful study comes to the same conclusion. The title of his paper, "Multiple Melanomata of the Skin with Neurofibromatosis of the Cutaneous Nerves, Melanotic Tumor of the Cerebrum, Glioma of the Pons, Sarcomatosis of the Meninges, and High Grade Congenital Hydrocephalus in a Child of Nine Months," summarizes the pathologic lesions found. He considers that two separate processes were at work: (1) melanomas of the skin and (2) melanoma of the brain which was secondary to a primary melanosis of the membranes. The perivascular arrangement of the tumor cells in the cerebral cortex was identical with that of our own case.

The principal reason why Berblinger refuses to admit that the tumor in the meninges can have any relation to those in the skin is that no other secondary growths were found in the rest of the body. To this, two points may be raised in answer. First, Ribbert has shown that melanomas may metastasize while as yet the primary nodule shows no sign of malignancy. And second, if in our own case the nodule in the kidney which was undoubtedly metastatic in nature had either been overlooked or had not been present, the same argument could have been urged against a causal relationship between the meningeal and skin lesions; whereas there cannot be the slightest doubt that the one was directly dependent on the other. The matter is not susceptible of direct proof, but it appears much more reasonable to suppose that with occasional connecting links such as the metastatic nodule in the kidney the two conditions are related and not separate and distinct.

The second group of cases is that in which a primary tumor of the brain is associated with secondary diffuse involvement of the meninges. There is no occasion to say much on this subject. In all the cases we have found described in the literature, the primary tumor

has been situated in some part of the brain with direct access to the cerebrospinal fluid, usually in the wall of the third ventricle or the floor of the fourth ventricle. The tumor erupts into the subarachnoid space just as a carcinoma of the stomach or the ovary may erupt into the peritoneal cavity and scatter its cells broadcast throughout that sac. Small implantation growths may occur on the lining of the ventricles, as in a case described by Stanley Barnes,[11] in which a tumor of the frontal region had ruptured into the lateral ventricle and was associated with several small soft masses scattered throughout the lateral, third and fourth ventricles and the aqueduct of Sylvius.

With regard to those cases of evident metastases to the meninges from primary tumors situated outside the brain or spinal cord, sufficient reference has already been made in the opening pages of this paper. Although carcinoma, sarcoma and melanoma are the principal tumors recorded in the literature, there appears to be no reason why any type of malignant new growth should not behave in this manner.

Cells in the cerebrospinal fluid. In many cases of diffuse tumors of the meninges, including our own, peculiar cells have been found in the cerebrospinal fluid. These cells, sometimes of great size, may be multinucleated and even show mitotic figures. Usually they are taken for large lymphocytes or an endothelial type of cell. The cytoplasm is clear, often vacuolated and the nuclei are large and strongly basophilic. Some excellent figures of these cells appear in an article by Chatelin [12] in the Nelson Loose-Leaf Medicine. These cells must be regarded as true tumor cells. The fact that in melanomas they do not contain pigment must not be taken as an argument against their neoplastic nature, for we have already seen that the tumor cells in the subarachnoid space may be quite free from pigment as in our own case.

In conclusion, we may inquire what is the mechanism by which the tumor cells are distributed in such a case as that which has been described in this paper. It must at once be apparent that the cerebrospinal fluid is vitally concerned with this spread. Not only is the subarachnoid space both of the brain and of the spinal cord filled with tumor cells; not only are the primary tumors always situated in parts of the brain or cord readily accessible to the fluid; not only do the implantation growths occur solely in those parts which are

bathed by the fluid; but even the uttermost bounds of the subarachnoid space, even its farthest extensions along the vessels which penetrate into the brain and along the nerves which leave it, are permeated by the tumor cells. This permeation appears to be of a passive rather than an active character, for we could find little or no evidence of actual invasion of the brain substance. It is as if the tumor cells had been poured into the subarachnoid space as into a mould and had set there in the form of a jelly.

Both the gross and the microscopic appearance remind one of the picture of meningeal inflammation. Oppenheim[13] indeed speaks of a diffuse meningeal process rather than a true tumor formation. Lewkowicz[14] of Warsaw has pointed out in a recent paper that the prevailing views regarding meningeal infection fail to satisfy the needs of the case and that it is highly probable that instead of the infection commencing in the meninges it really originates in the choroid plexus as an ependymitis. The inflammatory cells, he believes, are carried by the flow of cerebrospinal fluid from the ventricles outward to the subarachnoid space and upward to that part of it in relation to the vertex of the brain. Some such mechanism may also be at work in cases of diffuse sarcomatosis of the meninges. From a focus in the choroid plexus, or in the case of a primary brain tumor in the cerebral substance, the tumor cells are carried outward by the flow of the cerebrospinal fluid and passively fill the subarachnoid space and all its ramifications.

Summary

Diffuse infiltration of the meninges with tumor cells, commonly known as diffuse sarcomatosis of the meninges, is in the great majority of cases a secondary condition. While the possibility of a primary meningeal origin must be admitted, this possibility is becoming open to doubt. The mechanism of the meningeal involvement is invasion of the cerebrospinal fluid with tumor cells from some focus standing in intimate relation to the fluid, such as the choroid plexus or the wall of the ventricles. A clinical diagnosis of the condition may be made from the discovery in the spinal fluid of large pale cells in considerable numbers.

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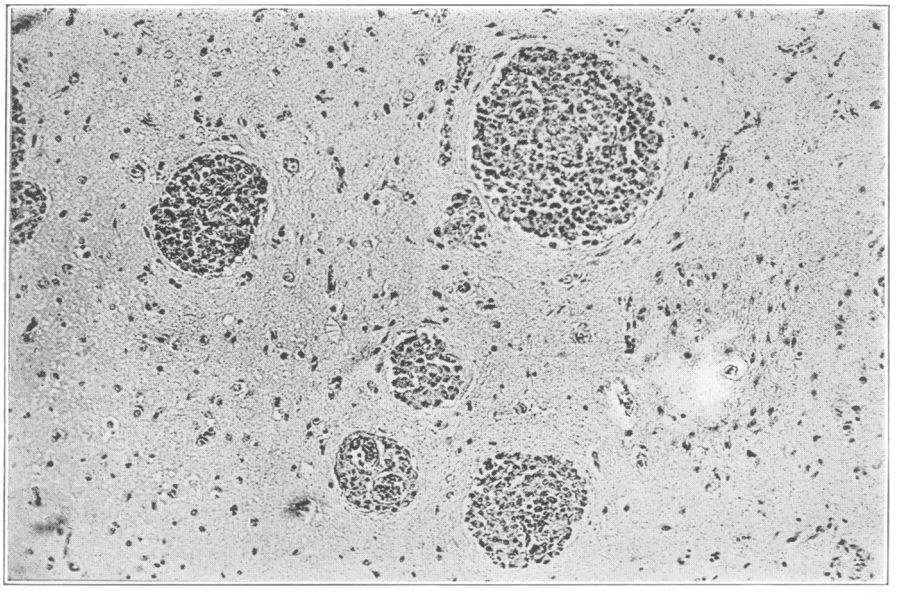
DESCRIPTION OF PLATES XCIV–XCV

FIG. 1. Groups of tumor cells scattered throughout the cerebral cortex and apparently not connected with the surface.

FIG. 2. Mass of tumor cells grouped around a small vessel.

FIG. 3. Showing the true method of formation of the tumor masses by extension of the cells along the perivascular prolongations of the subarachnoid space into the substance of the brain.

FIG. 4. The meninges in the fissures are infiltrated with tumor cells.



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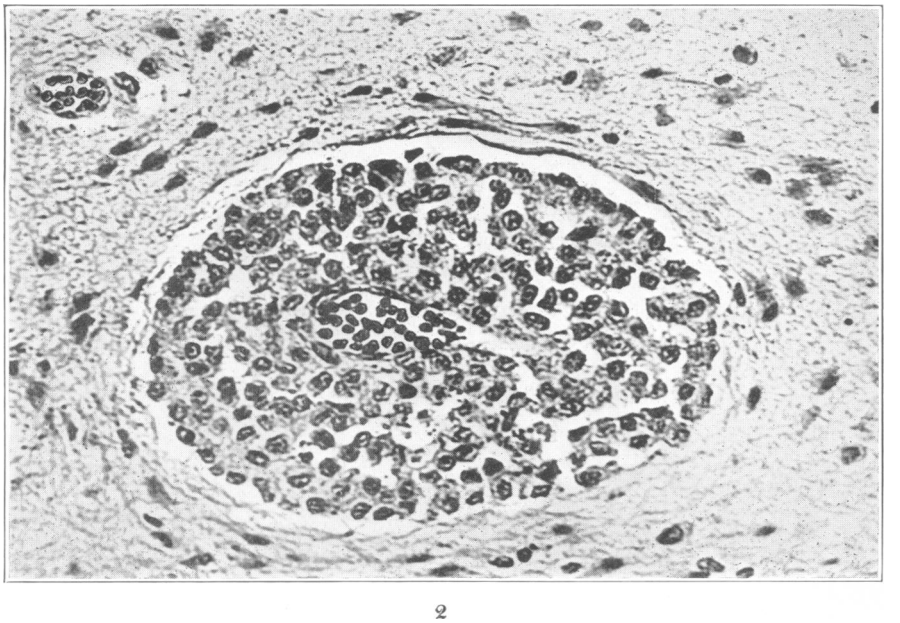

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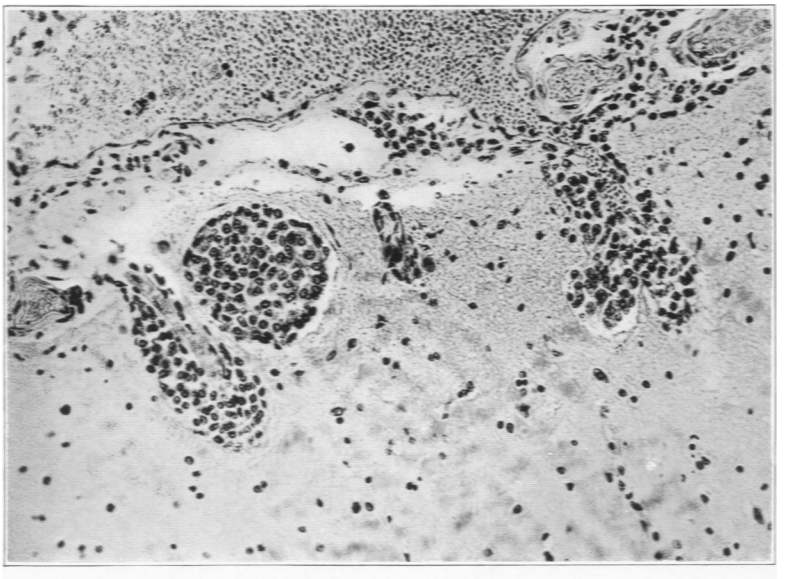

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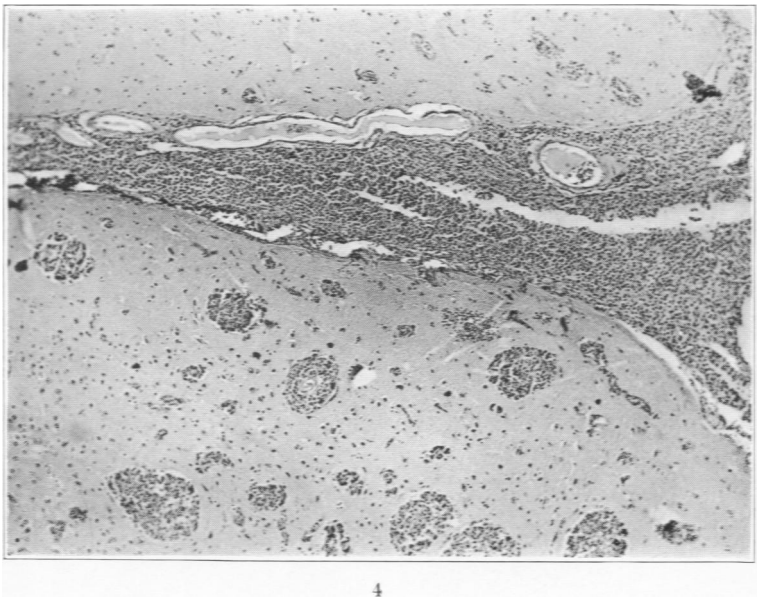

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