SYNOVIOMATA *

LAWRENCE W. SMITH, M.D.

(From the Department of Pathology, Harvard Medical School, Boston, Mass.)

During the past few years there have accumulated in the pathological collection of the Harvard Medical School and the Peter Bent Brigham Hospital three rather unusual tumors, having too many points in common, both clinically and histologically, to be regarded as coincidental. In a fairly thorough search of the current medical literature of the past two decades, I have been able to find very few articles referring to similar tumors. For this reason, it is worth while calling attention to the existence of such a type of tumor. That I lay myself open to criticism in defending my thesis is apparent, but it is only by such wholesome difference of opinion that controversial points can be conclusively and ultimately settled.

The nomenclature which has been suggested in the title is a departure from the time-honored embryologic custom of designating a tumor by the type cell from which it is derived; and yet, such a term indicates obviously the tumor's origin, and conceivably offers a loophole of escape when the embryologic etiology is debatable, as in this case. Perhaps, and more correctly, one should use the term mesothelioma in this connection, for, like other serous cavities, the lining cells of the joint cavities and of the bursae are considered by most embryologists to be of mesothelial origin; or perhaps it would be more logical to utilize the much over-worked term endothelioma, and create an additional subdivision of that vast group of tumors of uncertain origin which are already included under that heading. It has seemed best, however, to classify this group with a name by which they may be easily identified, and which can readily be found in any published index. That there is a precedent for such a nomenclature is seen in the naming of other special types of tumors such as the hypernephroma, the meningioma and others.

CASE REPORTS

CASE No. 1. (P. B. B. H., Pathologic Report No. S-21-613.)

Gross specimen consists of three fragments of tissue, each measuring about 1 cm. in diameter, removed from the inner aspect of the

* Received for publication April 16, 1927.

thigh, apparently originating in relation to the fascia of Hunter's canal.

Microscopic examination: Sections stained with eosin and methylene blue, and phosphotungstic acid hematoxylin show an apparently definitely encapsulated tumor. This tumor is characterized by spaces in the form of anastamosing clefts lined in most instances by low cuboidal epithelial-like cells, and separated by compact cords of spindle-shaped cells which, in characteristic portions, seem to be devoid of intercellular substance and fibrils. There are mitotic figures in both types of cells, those lining the spaces and those composing the solid structure of the tumor. The cells lining the clefts in the preparation stained with phosphotungstic acid hematoxylin show a very delicate cuticular border, most evident in the form of terminal bars. Nevertheless, the impression is strong that these two types of cells have an identical origin. Parts of the tumor containing a small amount of fibrous tissue probably represent a stroma growth. Some of the clefts are dilated, filled with debris and cholesterin crystals. In some sections the intercellular substance is composed of a hyaline homogeneous material evidently derived from the connective tissue accompanying the growth. In cross-section this material is usually circular, in longitudinal section, elongated, giving rise to the appearance described in so-called "cylindromas."

It is impossible to assign a definite source to this growth. It agrees with the description of some endotheliomas, particularly the so-called *inter-fascial endotheliomas*. Dr. Wolbach has expressed the opinion that the tumor probably represents the type of cell lining tendon sheaths and bursae.

Subsequent history: Patient died about six months later, presumably of pulmonary metastases.

CASE No. 2. (P. B. B. H., Surgical Report No. 15615) (Pathologic Report No. S-21-813).

Abstract of clinical history: The patient is a well developed and nourished Jewess of 24 years, with a negative family and previous history. She complains of sharp, shooting pains radiating from the upper left thigh down the inner aspect of the leg to the ankle, and a mass in the upper and inner aspect of the thigh. The onset of the pain was rather insidious, beginning eight months ago. Three months before admission, the patient's sister noticed a mass in the upper left groin which has not appreciably increased in size.

Physical Examination: Negative except for an ill-defined, non-tender, hard mass 8 to 13 cm. in diameter, which extends just above Poupart's ligament and

curves downward and inward over the left thigh. On rectal examination, a round, hard, non-tender mass can be palpated which invaginates the rectal wall on the left side, and is apparently connected with the mass in the thigh.

X-ray Examination, November 21: Films of the pelvis and upper two-thirds of the femur, and the shaft of the left femur show no evidence of bone involvement.

Laboratory Examinations: Blood Wassermann; positive. On December 7, the patient was shown to members of the society of Clinical Surgery by Dr. Harvey Cushing, as a probable case of a semibenign growth of the nature of the desmoid tumors of Nélaton, although he was aware that such tumors are usually found in the abdominal wall.

Operation Report: Dr. Harvey Cushing, December 7. "Surface of tumor completely covered by the adducter group; the fibers split until the surface of what was evidently an enucleable, well encapsulated growth encountered. Surface was vascular and so elastic as to give impression of abscess or cyst. Growth large as two fists, many layers and bands of tissue over it. Tumor itself not vascular; contained many small cysts."

Pathologic report: The tumor is an unusual one, composed of spindle cells grouped in anastamosing cords and separated by endothelial-lined clefts. This is the typical arrangement of the tumor although large areas are seen where the growth is compact but in which new vascular channels although compressed can be made out. There are some areas where the tissue is compact and contains a small amount of collagen which is probably derived from an ingrowth of connective tissue cells. Mitotic figures are fairly numerous.

COMMENT: The tumor is one on which absolute classification remains suspended. The general arrangement is not wholly incompatible with a tumor of connective tissue origin, but the absence of fibrils and intracellular substance is against this diagnosis. There are similar tumors described as endotheliomas, and their origin attributed to fascia. The intimate relation of cell columns to endothelial-lined blood-containing spaces supports the diagnosis of endothelioma. Similar arrangements of tumor cells are found in solid tumors of the ovary, and it must be borne in mind that solid tumors of the ovary, regarded as epithelial in origin, are often composed of spindle-shaped cells. The possibility of the tumor originating in the pelvis from ovarian tissue must be borne in mind.

May 21, 1923. *Interval history:* Patient was well for two months after leaving the hospital, when she again began to have occasional sharp shooting pains in the left thigh. These have increased in frequency and severity during the past ten months.

August, 1923. Wassermann; positive. She was given 8 treatments with mercury succininide intramuscularly; however, the pain in the left leg continued. She noticed a small non-tender lump in left groin, but did not mention it at this time.

December, 1923. During the past few weeks the pain has extended down the leg to the ankle, with a drawing sensation in the groin. Appetite is good and there is no loss in weight. On physical examination, the outer aspect of the scar is tender. Palpation of the rectum reveals an elongated sharp-edged mass just outside the sphincter on the left side which feels adherent to the ascending ramus of the ischium and is slightly tender. A small mass is palpable in the right axilla.

X-ray Examination: A film of the patient shows a defect involving the ascending ramus of the ischium and descending ramus of the pubis, with several silver clips in position around this area. Bones elsewhere are normal.

June 8, 1924. The glands in the groin were excised because of recurrence.

Gross specimen: Circumscribed nodule 3 by 3 by 2 cm., surrounded by a thin fibrous capsule. It appears to be involved by tumor.

Microscopic examination: Dr. Hansman, "The nodule consists of a dense, rich, cellular tumor, made up of spindle cells with well defined nuclei, but a cell membrane is rarely seen. A few primitive blood vessels are seen as spaces lined by a single layer of endothelium, and containing red blood cells, lymphocytes and a few eosinophiles. There are numerous mitotic figures. The structure is identical with the first specimen."

March 16, 1925. *Interval history:* Patient remained entirely free from symptoms for two months, returning to the out-patient department for X-ray treatment every three weeks. In July she went to Omaha, and remained there six weeks. She had a recurrence of the same pain, two or three times a day, lasting five minutes. The left leg was slightly swollen, and she could feel several small lumps in her back just to the left and below the sacrum. Since that time she has had fairly intensive X-ray treatment, with intermittent relief of severe symptoms but persistence of transient symptoms. She was again seen in consultation by Drs. Cushing, Homans, and Sosman, all of whom advised strongly against further operative treatment and urged that X-ray therapy be given to the limit. At this time there was a large, firm, rounded mass to the left of the rectum extending from the symphysis to the sacrum, marked induration, discoloration and tenderness of the left labium majus and a small lump in the groin.

Through the courtesy of her attending physician, Dr. Thomas W. Leavitt, the subsequent history was obtained. She improved temporarily under intensive X-ray treatment but, after about two months had a further recurrence and progressively failed, dying of pulmonary metastases.

CASE No. 3. (Pathologic Reports Nos. H–24–30, H–25–296.)

This case is presented through the courtesy of the attending surgeon, Dr. James S. Stone.

Clinical history: The patient was a man 35 years of age, who had a swelling on the inside of the knee for about five months before admission to the hospital. This appeared to be under the vastus internus muscle, suggesting an origin from the synovial membrane. It did not appear to be connected with the bone. It was semifluctuant in places, but for the most part was fairly solid in consistence. The first operation consisted of an excision of the tumor mass with the surrounding tissues. The patient remained fairly well for a number of months, when a recurrence of the lesion was noted. He was treated by X-ray and radium for a period, without marked improvement. Fifteen months following the original operation, the leg was amputated 15 cm. above the knee joint. No nodes were palpable in the groin at this time. He showed, however, at the time of operation, definite metastases in the lung by X-ray, and proceeded to fail slowly during the next five months, dying two and a half years after the first appearance of the lesion.

Pathologic report: I: The original specimen consisted of a tumor mass measuring 8 by 6 by 3 cm., with considerable thickened synovial membrane and fascia attached. The tumor at one point contained a hard calcified irregularly outlined mass 3 cm. in its greatest extent. On section the tumor had a fairly well defined capsule which was extremely thickened. Centrally there were several foci of hemorrhage and necrosis, and cystic areas lined by smooth glistening walls. There was no gross evidence of invasion of this thickened synovial capsule.

Microscopic examination: Slides show a rapidly growing tumor with many mitoses. There is histologic evidence of infiltration of the capsule and the surrounding stroma. It is an unusual type of tumor microscopically, as the cells show a dual differentiation; some of them apparently forming synovial membrane, and resembling endothelial or almost epithelial cells, while the stroma is composed of the connective tissue type of cell. An exact diagnosis is not easily made, but a tentative one of mesothelioma or endothelioma is suggested. In view of the results in the other two similar cases which we have on record, the prognosis is presumably poor. Probably metastases have already occurred and for that reason amputation seems futile. Intensive radiation would seem to be the most logical form of treatment.*

* Personal communications. The sections were submitted to a number of pathologists and no absolute concurrence in diagnosis was made. Drs. J. Homer Wright and James Ewing made a tentative diagnosis of endothelioma. Dr. F. B. Mallory was in-

Pathologic report: II: The specimen consists of a leg amputated 15 cm. above the knee joint. The knee is swollen for some distance both above and below the patella, and in addition there is a definite tumor nodule on the lateral aspect of the knee just above the patella, which measures 4 to 6 cm. in diameter, and is elevated 2.5 cm. above the general surface. This has practically broken through the skin in one or two places. It is discolored by hemorrhage and necrosis. Two other smaller subcutaneous nodules are noted around the patella, the larger of these measuring 1 cm. in diameter, and being slightly elevated. The specimen is split longitudinally through the knee joint. The entire joint cavity is filled with tumor tissue which has infiltrated the patella, the tibia and the femur so that these bones around the knee joint can readily be cut with a heavy knife. The tumor is made up of very soft grayish friable tissue which grossly has no very definite structure or stroma. It is comparatively avascular. It is not unlike the appearance of a lymphoid or a neuroblastic round cell sarcoma in its consistence, but does not resemble it in other respects. The tumor involves the surrounding structures, including the fascia, muscles and subcutaneous fat. It has caused intense pressure on the sciatic nerve, which presumably accounts for the clinical pain.

Microscopic examination: Further histologic sections of the specimen present essentially the same characteristics as noted in the earlier specimen except that the spindle form of the cells is more uniformly present. Numerous mitoses and occasionally multiple mitoses are encountered. It suggests a very rapidly growing sarcoma, probably of synovial membrane origin.

Discussion

In reviewing the literature, two papers of particular value in respect to this group of tumors have appeared in the past few years; a brief discussion of the classification of the tumors of the knee joint by Züllig,[18] and a review of the reported cases up to 1923 by Faccini.[5]

clined to think that it was a fibrosarcoma with an inflammatory hyperplasia of the synovial membrane attempting to wall off the tumor, and felt that the prognosis was dependent on its connective tissue metastatic character. Dr. S. B. Wolbach concurred more definitely with me in the feeling that the tumor presumably arose from the synovial membrane, as both Wright and Ewing tacitly imply by their diagnosis of endothelioma.

The latter author refers to a monograph on tumors published by Barbacci [1] in 1915, in which several examples of this group of tumors allied to this type were recorded. Unfortunately, this volume has not been available, and the references as given by Faccini of the individual cases were inadequate for verification. In general, the tumors may be said to arise as follows:

1. In relation to the synovial membrane of the joint cavity itself; such as those reported by Rijssel,[15] Marsh,[11] Lockwood [9] and Faccini.[5]

2. From the synovial membrane of some of the overlying bursae, such as that reported by Smirnoff.[16]

3. From the fascial aponeurosis, of which a rather special variety seems to be the group occurring in relation to the rectus abdominis aponeurosis, and to which the same *desmoid* was given by Müller,[13] and which has been subsequently used quite generally. In addition to this rather limited type, the general term *fascial endotheliomata* has been applied by Ewing.[4] Gobbi [6] and Bolognesi [2] have reported typical tumors of this general variety.

4. Tumors arising in relation to the tendons and tendon sheaths. Buxton,[3] in reviewing the literature of this group of tumors, comes to the conclusion that there are probably no true primary tumors of the tendon itself, that the giant cell myeloma is the commonest tumor involving the tendon sheath, and that clinically they are particularly confused with simple inflammatory processes of the tendon sheath. McWhorter and Weeks [12] subsequently discuss the rather special group of tumors of the tendon sheaths usually described by the name *xanthoma*. They conclude that *xanthoma tuberosum multiplex* and all forms of xanthomas are the result of a systemic disease in which hypercholesterolemia is an essential feature. They feel that these nodules are not, strictly speaking, tumors, but are the result of an irritative connective tissue reaction to the deposition of cholesterin; and that, as recurrence follows the surgical removal of these nodules, surgery is indicated only in cases with pressure symptoms, because surgery does not affect the underlying etiologic process.

Accordingly, there is some relationship among the tumors of these various groups, although the last division of the xanthomas suggests an inflammatory reaction rather more definitely than do the others. Certain it is that the first two groups, the tumors arising directly

from the lining of the joint capsule and from the bursae, are essentially the same genetically, and differ only in their physical distribution. Clinically, there occasionally occur other tumors which may be confused with these groups. Of these, the rare cases of hemangioma of the joint may be cited. A recent case of this type was reported by Osgood.[14] Similarly, the fatty tumors of the capsule have frequently given rise to difficulties in differential diagnosis, particularly the type *lipoma arborescens*, which Züllig [18] discusses. And, finally, there are the sarcomas of fibroblastic origin, either in their simple fibrous tissue form, or differential chondroblastic or osteogenic forms. These are too numerous to cite in a paper which is limited, as this is. The essential pathology of these tumors has been brought out by many of the papers recorded above.

A recent paper by Zeckwer [17] from this department, has emphasized particularly the extreme variability of the cytology of this group of tumors derived from mesothelium. In the case which she presented of a tumor originating in the pleura, three distinct cell types were found, both in their fully differentiated forms and in their intermediate forms, which could be traced back to a common multipotential cell. This is obviously what one might expect in such tumors, in view of their origin from such a relatively undifferentiated cell type, and yet it is a fact which seems to have been overlooked or neglected by most of the contributors to this subject. In the three cases which are being presented, these same features of differentiation into two kinds of cells, the synovial lining type and the supporting stromal type, with intermediate forms between the two, are seen. This variation is illustrated by the drawings and photomicrographs appended. Particularly interesting is the point which she has made of the method by which lumina appear to develop as the result of vacuolization of the cytoplasm of certain of the cells which gradually become lined by additional cells formed by mitoses from the nucleus of the orginal cell. Similarly, the formation of pseudogiant cells in this manner is readily explained. By what influence the differentiation of the cell from the pure spindle-appearing type to the obvious endothelial cuboidal type is brought about is extremely difficult to explain.

SUMMARY

Three tumors of synovial membrane origin and presenting too many points in common, both clinically and histologically, to be regarded as coincidental, are presented as a type tumor. Their histology, as based on their embryologic origin from mesothelium, is discussed, the type cell showing multipotential characteristics comparable to other mesothelial tumors.

A review of the literature of the subject is presented.

REFERENCES

1. Barbacci, O. *Tumori*, 1915. (Cited by Faccini.) (Casa Editrice Francesco Vallardi, Milano.)
2. Bolognesi, G. Les tumeurs primitives des aponévroses. *Rev. de Chir.*, 1916, li, 876.
   Bolognesi, G. Nuovo contributo clinico sui tumorio primitivi delle aponeurosi degli arti. *Tumori*, 1919–1921, vii, 353.
3. Buxton, St. J. D. Tumours of tendon and tendon sheaths. *Brit. J. Surg.*, 1923, x, 469.
4. Ewing, James. Neoplastic Diseases, Philadelphia, 1922, Ed. 1, p. 306.
5. Faccini, U. Un caso di peritelioma sarcomatosa della capsula articolare del ginocchio destro. *Arch. Ital. di Chir.*, 1923, vii, 481.
6. Gobbi, L. Sarcoma fibroblastico primitivo della fascia lata. *Policlinico*, 1923, xxx, 1281.
7. Hardie, J., and Salter, S. C. A case of sarcoma degeneration of the synovial membrane of the knee-joint. *Lancet*, 1894, i, 1619.
8. Jolkwer, W. E. Cysto-endothelioma of tendon. *Zentralblt. f. Chir.*, 1926, liii, 1751.
9. Lockwood, C. B. A case of sarcoma of synovial membrane of knee. *London Chir. Soc.*, 1902, xxxv, 139.
10. Luijt, C. Van. Een Geval van Primair Sarcoom van de Knie. *Nederland Tijdsch. voor Geneesk.*, 1925, lxix, No. 2, 356.
11. Marsh, H. Primary sarcoma of the synovial membrane of knee-joint. *Lancet*, 1898, ii, 1330.
12. McWhorter, J. E. and Weeks, C. Multiple xanthoma of the tendons. *Surg. Gynec. Obst.*, 1925, xl, 199.
13. Müller. (Cited by Bolognesi.)
14. Osgood, R. B. Angioma of knee-joint. *Surg. Clin. N. Am.*, 1921, i, 681.
15. Rijssel, E. C., Van. Over Sarcoma van de Gewrichtskapsel. *Nederl. Tijdsch. v. Geneesk.*, 1917, lxi, No.2, 1143.
16. Smirnoff, A. S. Sur les tumeurs de bourses séreuses de l'articulation du genou. *Chirour. Arch. Vel.*, xxviii, 1912, 193. Abst., *J. de Chir.*, viii, 1912, 600.
17. Zeckwer, I. Mesothelioma of the Pleura. *Arch. Int. Med.*, 1924, xxxiv, 191.
18. Züllig, J. Tumoren der Kniegelenkkapsel. *Cor.-Bl. f. Schweiz. Aertze*, 1917, xlvii, 1368.

DESCRIPTION OF PLATES

PLATE 104

Case I

FIGS 1 AND 2. High power photomicrographs from different parts of tumor, illustrating multipotential differentiation, in Fig. 1, the spindle cell predominating; in Fig. 2 the synovial form well defined.

PLATE 105

Case II

FIG. 3. High power. Illustrates alveolar formation about fatty secretion.

FIG. 4. Oil immersion. Illustrates polypotentiality of cells, differentiating in both synovial and fibrous fashion.

PLATE 106

Case III

FIG. 5. Low power photomicrograph. Shows extent to which differentiation may be carried in these tumors, with development of well formed synovial lining cells.

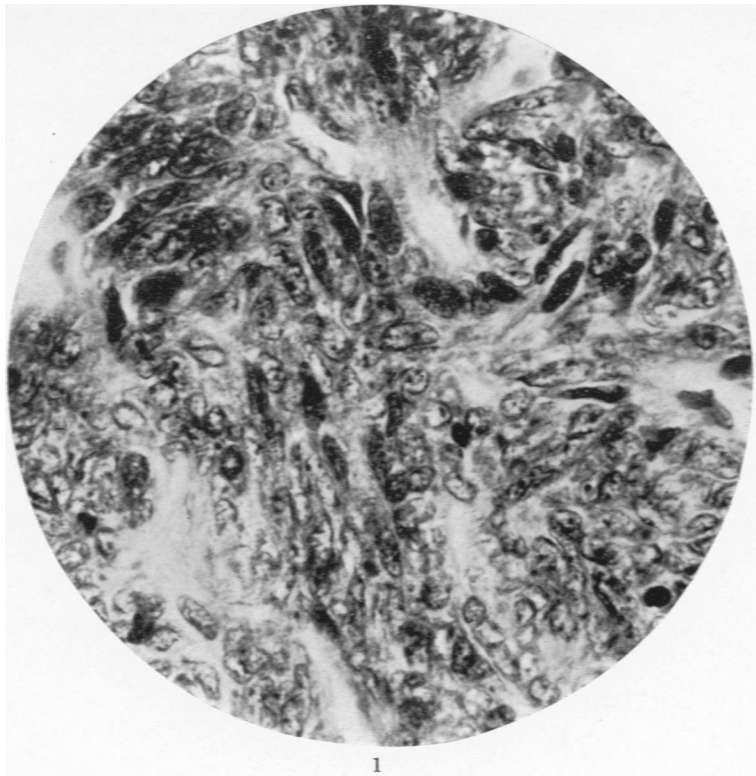
FIG. 6. Oil immersion. Same.

PLATE 107

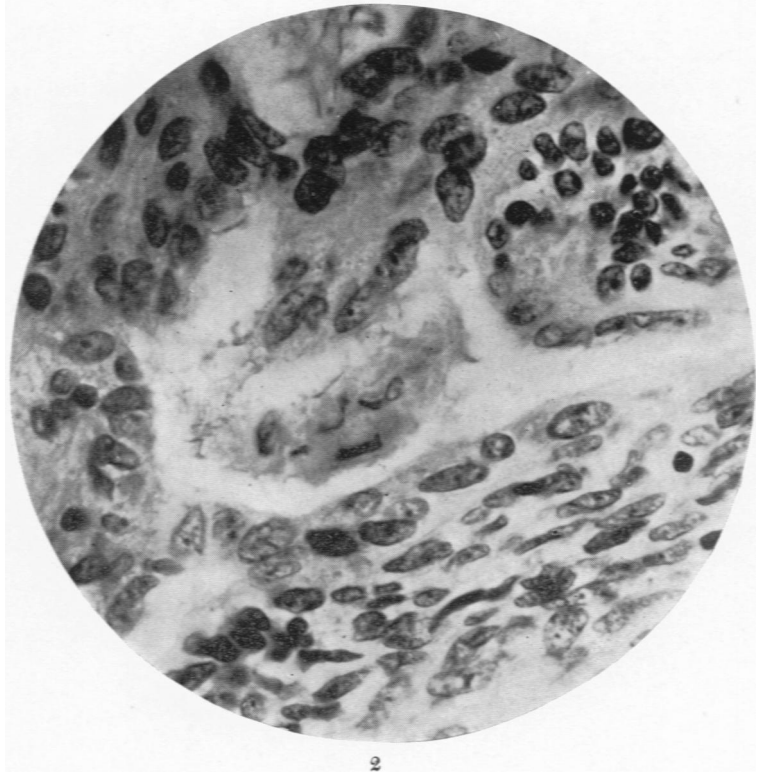
Case III

FIG. 7. Low power camera lucida drawing. Illustrates the dual differentiation of the cells into synovial and fibrous tissue.

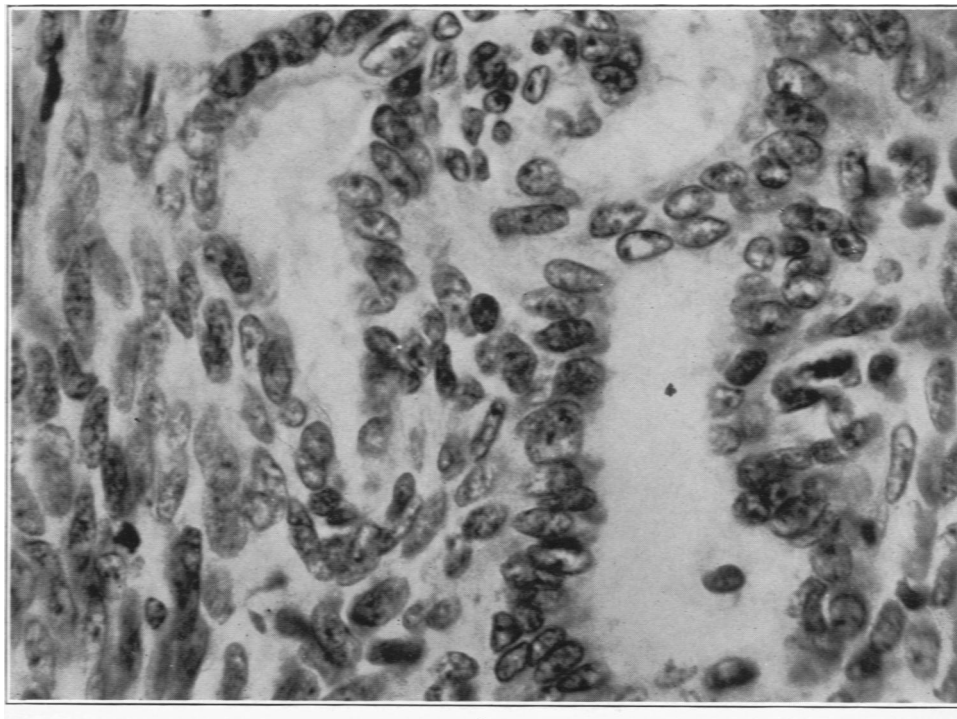
FIG. 8. High power camera lucida drawing. Illustrates the common parentage of the cells. Note mitotic figure centrally. Shows tendency of alveolar development from "signet ring." Vacuolization of cells.



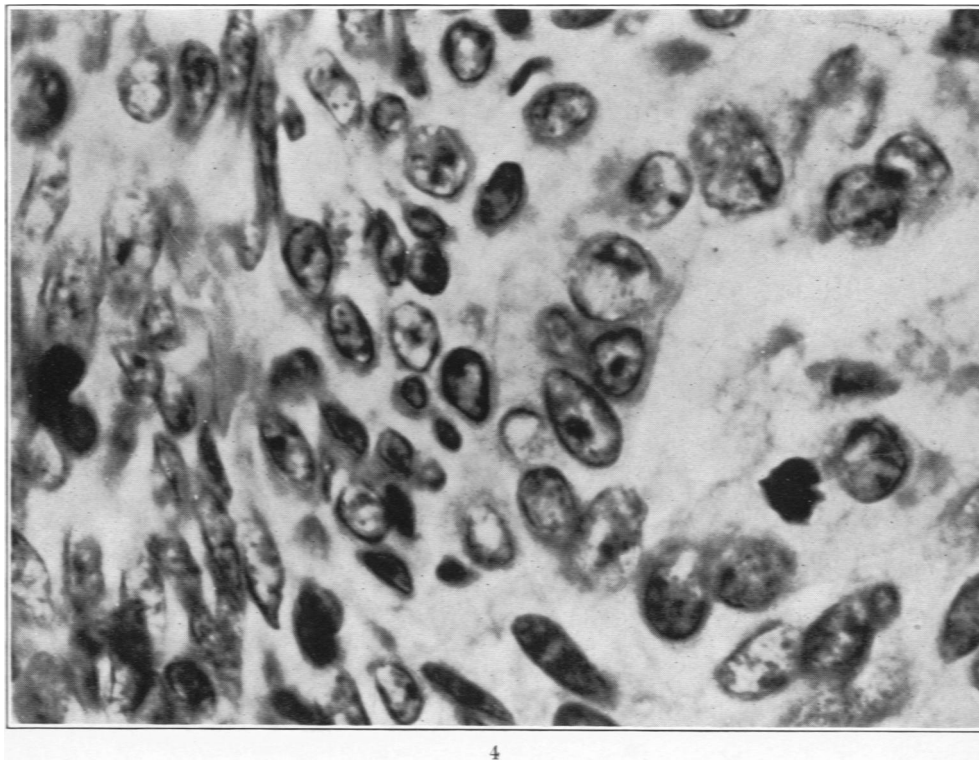
1



2

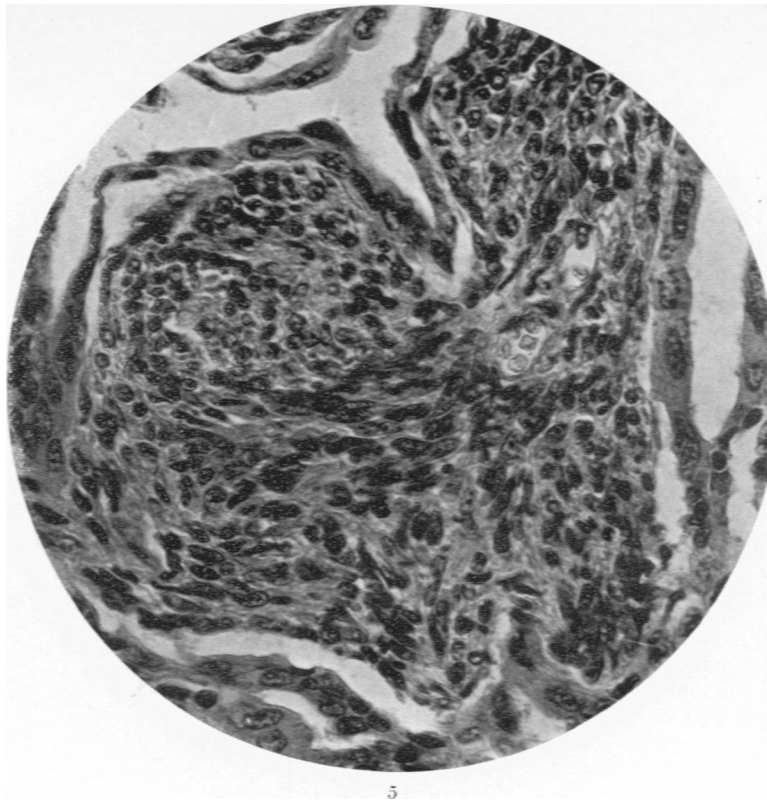


3

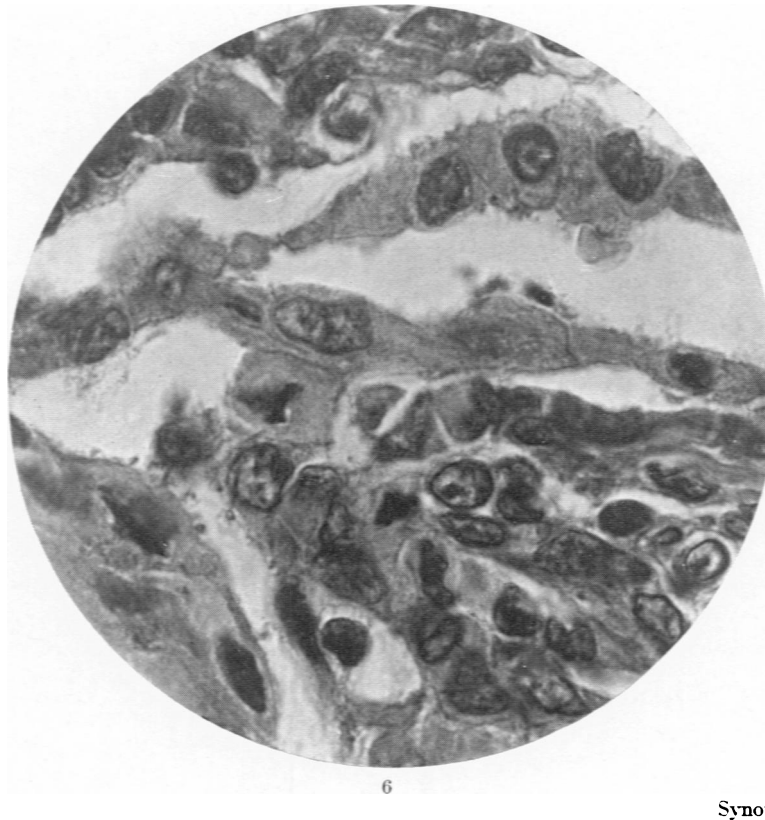


4

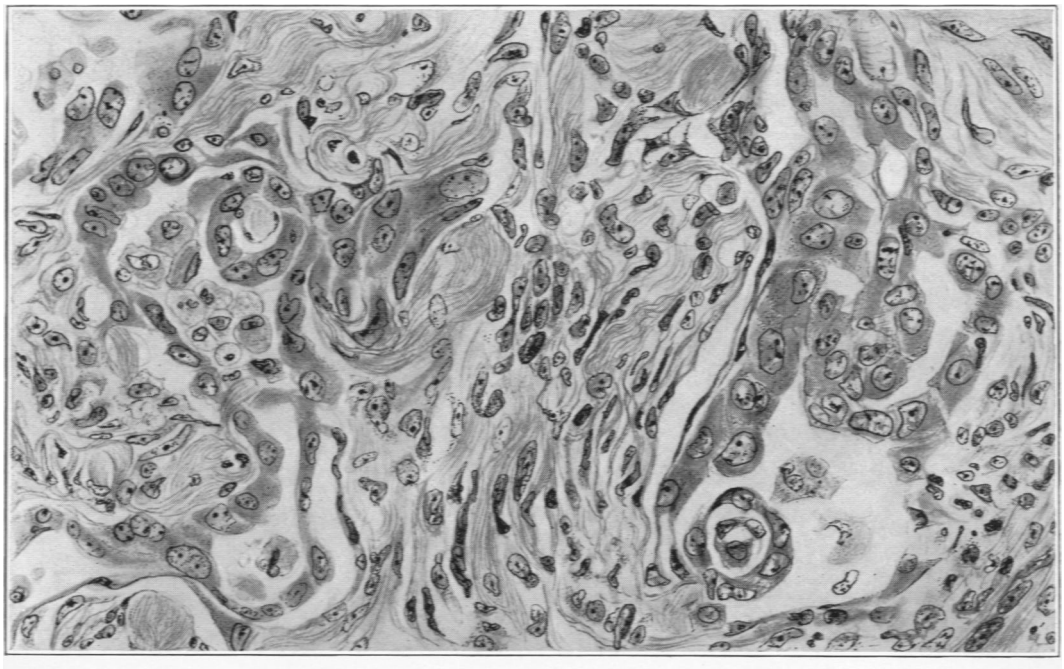
Smith Synoviomata



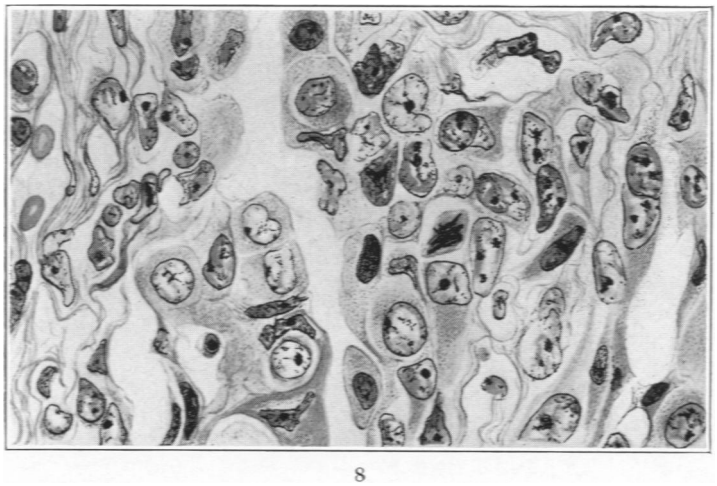
5



6



7



8