REPORT

of

COMMITTEE ON THESIS

The undersigned, acting as a Committee of the Graduate School, have read the accompanying thesis submitted by George J. Busman, for the degree of Master of Science in Dermatology and Syphilology. They approve it as a thesis meeting the requirements of the Graduate School of the University of Minnesota, and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science in Dermatology and Syphilology.

Albert C. Broders

Louis B. Wilson

H. J. Hoing

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THE UNIVERSITY OF MINNESOTA

GRADUATE SCHOOL

Report

of

Committee on Examination

This is to certify that we the undersigned, as a committee of the Graduate School, have given George J. Busman final oral examination for the degree of Master of Science in Dermatology and Syphilology We recommend that the degree of Master of Science in Dermatology and Syphilology be conferred upon the candidate.

Paul O'Leary
Chairman

W. P. Larson

H. C. Bodeen

H. G. Irving.

Date May 16, 1922

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THESIS

A CLINICAL AND HISTO-PATHOLOGICAL STUDY OF MALIGNANT ENDOTHELIOMAS AS EXEMPLIFIED BY THREE CASES WITH CUTANEOUS INVOLVEMENT.

George J. Busman, B.S., M.D.

Submitted to the faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Dermatology and Syphilology.

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The rarity of occurrence, the peculiarities of the clinical course, and the fact that the true nature of the tumor is often concealed because of early surgical or medical interference makes the malignant endothelioma peculiarly difficult to recognize from its clinical characteristics. Because of the difference of opinion regarding the actual existence of endotheliomata and because of the possibility of serious diagnostic error illustrated by our own experience, I am here undertaking to discuss the subject of malignant endothelial tumors in the light of three cases which clinically and histopathologically appear to allign themselves with this group.

The variability of the endothelial cell in neoplasms and the ability of endothelium to undergo metaplasia, simulating the epithelial type at one point and the connective tissue type at another has given rise to some confusion in the differential diagnosis of endothelial tumors. There is controversy as to the actual existence and the criteria for the diagnosis of endothelial tumors, in part because of the difficulty of obtaining material from the primary focus at a point where the structure still permits a demonstration that undoubted endothelial cells give rise to the tumor masses. Because of the relatively slow onset and low grade of malignancy of tumors from cells lining blood vessels, lymph vessels, lymph spaces and serous surfaces, the neoplastic change is usually well advanced before a diagnosis is even attempted. The size of the growth when then studied is such that it is practically impossible to trace the various cells through their transition stages to the original proliferating endothelium. This point among others is illustrated by my first case.

Case I. (This case was presented for diagnosis by the Section of Dermatology and Syphilology before the joint meeting of the Minnesota, Chicago and St. Louis Dermatological Societies at Rochester, Minnesota, August, 1921.)

No. A355289. Mr. J. C., male, age 34, when first examined April 10, 1921, presented a large ulcer on the left forearm, (Figure I). The ulceration

extended from three inches above the wrist to within two inches of the elbow. The borders were irregular, indurated, undermined, of a reddish to purple color, and were markedly hemorrhagic. Along the upper margin the border was slightly rolled and "pearly". The arciform configuration suggested a luetic lesion. The ulna was exposed, and although there was no evidence of a periostitis, there was necrosis of bone with partial destruction of the shaft. The extensors of the thumb and finger were destroyed. The elbow and lower third of the arm were swollen. There was a mass in the axilla and cord-like lines of infiltration extending from the broken-down tissue to the elbow flexure. There was also a nodule higher up the brachial lymphatics, with some diffuse infiltration of the surrounding skin. There was tumid induration of the tissues above the lesion.

The patient had enjoyed good general health except for the lesion described up to the time of his first examination in the Clinic. He stated that thirteen years previously he had been kicked on the forearm by a mule. The arm was not fractured and very little swelling or soreness resulted. A few days later he noticed a small lump on the forearm about 5 mm. in diameter. This small nodule gradually increased to 1.5 cm. in diameter during the course of a year. He had experienced practically no pain.

In 1914, five years after the onset of the lesion, the nodule which had grown to be about the size of a pigeon's egg without breaking down, was surgically removed. The mass recurred in situ, and a year later, April, 1915, a second operation was performed. An infiltrated mass which extended from three inches above the wrist to within three inches of the elbow was removed leaving a large granulating surface which healed partially. In October, 1915, the lesion was again explored and cauterized. Following this operation the wound remained open and gave off a continuous bloody discharge. At no time had there been much pain or tenderness, a remarkable fact in view of the size and nature of the lesion. The use of the hand was somewhat impaired because of the destruction of the long

muscles, but the patient's general condition was still excellent.

From October, 1915, to the date of admission to the Clinic the patient had received much local and systemic treatment with no benefit. This medication had consisted of six intravenous injections of arsphenamine; twelve intramuscular injections of mercury salicylate; potassium iodide, by mouth; two exposures to radium of two hours each, the number of milligrams not known; violet and x-ray exposures; various antiseptics including Dakin's solution; continuous wet dressings; and continuous local baths. The patient gave no history of syphilis and the blood Wassermann reaction had always been negative.

In investigating the possibility of syphilis in the Clinic the patient was given seven blood Wassermann tests following a provocative injection of three decigrams of arsphenamine (arsenobenzol) with negative results. A biopsy and culture were also taken. The provocative series was negative; the biopsy demonstrated subepithelial fibrosis with inflammatory changes; and the culture revealed an acid fast bacillus. On the hypothesis that the lesion might be an infectious granuloma allied to granuloma inguinale tropicum, the patient was given ten daily injections of from 3 to 10 cc. of a 10 per cent solution of tartar emetic. Local wet dressings of potassium permangenate solution 1-4000 were used. He also was given three exposures to Alpine sun lamp. The lesion became less hemorrhagic and there was less odor and sloughing. The edges of the ulcer were then painted with a 5 per cent scarlet red ointment; the base with a 10 per cent Balsum of Peru, and an aluminum acetate wet dressing used.

During the following three weeks an abscess slowly developed in the left axilla. Cultures from aspirated pus showed short chain streptococci. Three days after drainage a profuse hemorrhage occurred from the axillary wound requiring blood transfusion. The lesion on the forearm continued to improve very slowly under the local treatment and on July 30th a second biopsy was taken. The section revealed a very vascular inflammatory tissue, granulomatous, with marked plasma

cell infiltration about the vessels, no giant cells, no bacteria, no epithelial change except a moderate degree of acanthosis, inflammatory muscle tissue, and fibroblastic strands and septa. The lesion was then regarded as a granuloma of unknown type and anti-syphilitic treatment was again resorted to. The patient was given six intravenous injections of arsphenamine (arsenobenzol) at weekly intervals in conjunction with twenty intramuscular injections of mercury succinimide (grains 1/6) with no local improvement. Following this treatment radium was used on the nodules in the axilla and upper arm. The lesion in the forearm was exposed to x-ray.

On October 15th, six months after the patient was first seen in the Clinic, Dr. Stokes suggested the possibility of getting new light on the diagnosis by the removal of a small fresh nodule appearing near the older lesion (Figure II). This material was examined microscopically by Dr. A. C. Broders and diagnosed by him as an endothelioma. The importance of obtaining a specimen from an early nodule is here demonstrated in that two previous biopsies taken from the border of the old ulcer revealed only a vascular structure with inflammatory change (granuloma) and disclosed no evidence of the true character of the original process. After the diagnosis of endothelioma was made the arm was amputated at the junction of the middle and lower third of the upper arm. A small nodule from the inner side of the upper third of the arm was excised. The sites of possible metastases were then given repeated exposures to x-ray and radium until the patient was discharged, apparently in good health.

The histologic structure of the fresh nodule in this case is upon first examination rather unusual and complex. The most striking features when viewed with low power are an undifferentiated polymorphic-celled type of growth; a whorled arrangement of the cells; the formation of elongated cellular strands and narrow trabeculae; the close association of the tumor with blood vessels and the formation of channels which may contain blood cells (Figure III).

When studied with higher magnification many of the cell strands or trabeculae appear to be essentially ingrowths from or proliferations of the endothelial lining of the blood vessels and blood spaces. The cellular ingrowths by constant proliferation at first form the solid or whorled masses of cells. Vacuolization of the individual cells in the clumps and solid masses then occurs with the formation of loose trabeculated areas and an attempt at differentiation into capillaries and blood spaces takes place. The individual tumor cells are in general larger than the normal endothelial cell but vary enormously in size and shape and have no typical form. Although the majority are spheroidal; oval, cuboidal, spherical, flattened and long columnar forms also occur. In certain areas syncytial or branching forms are seen which resemble the true vaso-formative type of cell. These cells are a suggestion or an indication of the true nature of the growth. There are no characteristic tumor or foreign body giant cells seen. One constant feature of the tumor is the occurrence of what appear to be vacuoles in the cytoplasm of practically all cells. These vacuole-like areas which do not take a stain and which apparently contain neither fat, glycogen, hyalin or colloid material are of great importance for it is by their confluence that the lumina of the large characteristic sinuses and channels are formed (Figure IV). In the solid areas composed of whorls of cells the vacuoles in the individual cells are small but show evidence of coalescence with the resultant formation of larger spaces (Figures V-VI). In the less dense portions of the neoplasm the vacuoles displace almost the entire cytoplasmic content of the cells and by their confluence form much larger spaces. These parts of the tumor then represent, apparently, an attempt at differentiation into vascular structures. This differentiation, however, is incomplete as these spaces at best represent only rudimentary capillaries and blood spaces. In the walls the tendency of the cells to exhibit their true nature is easily seen. The cells bordering upon these spaces arrange themselves in rows, become elongated and form a rudimentary endothelial lining of the

spaces. The cells are thicker than normal endothelium, however, and the lining usually consists of several layers, although in some it may consist of a single layer and again it may be absent altogether (Figure VII). These lining cells also express the character of the tumor by the formation of new vacuoles in the cytoplasm. There is a suggestion of further proliferation of the lining with the formation of new cellular ingrowths into the new-formed spaces themselves.

The sinus-like spaces are occasionally found to be filled with red blood cells which apparently are extravasated into them following the rupture of true blood vessels in their vivinity (Figure vIII). There is no evidence of circulation nor can connection be demonstrated between the spaces and the true circulation.

The individual tumor cells have nuclei which are extremely variable in shape. They are larger than the nuclei of normal endothelial cells. Occasional multi-nucleated cells can be found. Mitotic figures were not found in this case. A delicate intercellular cement can often be distinguished. In certain regions free infiltration into the muscle tissue of the surrounding part is demonstrable and isolated muscle fibres can be found surrounded by tumor cells. There is moderate round cell infiltration. No involvement of the overlying epidermis is apparent. There is, however, moderate acanthosis. Slight plasma cell infiltration about the vessels occurs even in the early non-inflammatory nodule.

Case II. No. A43401. C. M., female, age 24, presented an ulcer on the left heel. At seven years of age the patient had a furuncle or abscess over the left Tendo-Achilles, and later an abscess on the same leg just below the groin. Ten years before entering the Clinic (1900) a nodule had developed on the inner side of the left heel. Six years later (1906) the nodule ulcerated and began to discharge. Four operations had been performed with no benefit. A contracture of the Tendo-Achilles resulted. Since 1908 the patient had been subject to severe hemorrhages from the bowels. These occurred at about six month intervals. Upon proctoscopic examination the lower bowel was negative.

On entering the Clinic (1910) a biopsy was taken from the ulcer on the heel. A diagnosis of either sarcoma or endothelioma was made. The lesion was cauterized and packed, but a recurrence developed as evidenced by a second operation and specimen examined on November 30, 1910. The lesion had again recurred and was re-operated upon January 20, 1911. Microscopic examination again revealed a malignant growth. A specimen removed February 23, 1911 presented the pathological picture of an oval-celled sarcoma.

On March 3, 1911 a new nodule which had developed on the ankle, together with the ulcer on the foot and the left inguinal glands were removed at the same operation followed by cautery. Specimens from all areas presented the same pathological picture. The patient then went home and on November 14, 1912, in reply to an inquiry she stated that she had recurrent lesions at the site of the former one and also five small tumors in various parts of the body. Determination of the exact character of these nodules was impossible, as she died May 4, 1913, three years after examination in the Clinic and thirteen years after onset of the lesion, without having returned for further examination or treatment.

The histo-pathologic findings in the lesions from this case varied considerably according to the time and place of removal of the specimens. Here again we find a polymorphic celled, undifferentiated type of growth (Figure IX). The cells at certain points in the tumor have a whorled arrangement and at other points are arranged in ropes or cords with the formation of trabeculae. There is no close association with blood vessels. When viewed with high power the cell strands and cell masses appear to have the characteristics of endothelium. The cells in general are,however, larger than ordinary endothelial cells. They vary from speroidal to cuboidal in shape. No giant cells are demonstrable. An occasional dividing cell and mitotic figure is seen. The conspicuous and constant feature is the occurrence of vacuoles in the cytoplasm of the cells. These vacuoles tend to coalesce with the formation of spaces and channels. The cells lining

these spaces are flattened and take on the character of true endothelial cells (Figure X). Red blood cells are found in some of these spaces but as in the preceding case no evidence of their connection with the true circulation could be demonstrated. The vacuolization, however, and the attempt at differentiation into vascular structures are much less evident than in the former case. The nuclei of the individual cells are large and extremely variable in size and shape. Only a delicate intercellular substance is present. There is free infiltration into the surrounding tissues. Examination of the overlying epidermis reveals no pathology. The tumor merges into a surrounding highly vascular granulation tissue (Figure XI). Specimens from the heel, ankle and groin all exhibit these same characteristics but in different degrees.

Case III. O. W. C., male, age 26. One year ago the patient received a slight injury to the hand by cracking a nut. A small growth appeared. There was no pain or soreness. Ten months later a glandular enlargement developed on the right side of the neck which grew to the size of a small hen's egg. Both nodules were surgically removed. Examination also revealed an enlarged gland in the right axilla. Microscopic examination of both these tumors revealed an almost identical picture in the two specimens. Examination with low power shows a cavernous type of growth in parts of which the cells show a whorled or solid arrangement (Figure XII). In the cavernous areas the cells are arranged in strands with the formation of trabeculae. The individual cellular elements vary again considerably in shape and size, but a common feature is the occurrence of vacuoles in the cytoplasm. It can be clearly demonstrated that it is by the coalescence of these vacuoles that the larger cavernous spaces are formed. The cells lining the lumina or spaces are flattened out with the formation of endothelium. The occurrence of the large spaces lined with flattened endothelial cells represents a more advanced attempt at differentiation into vascular structures on the part of the tumor than that present in either of the two preceding cases (Figure XIII).

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DISCUSSION OF THE HISTO-PATHOLOGIC AND CLINICAL PICTURES IN THE OBSERVED CASES.

It is interesting to note that in Case I an interval of six months (during which the patient was under observation in the Clinic) elapsed before the true character of the tumor was determined. The distorted picture with which we had to contend upon first examination made it almost impossible to recognize the character of the growth either by inspection or microscopic study. The history of a tumor of thirteen years' duration without definite metastasis suggested a benign rather than a malignant growth. No evidence of the original character of the lesion remained in the large ulcer. Repeated biopsies taken from the border of the lesion revealed no characteristics of a tumor of endothelial origin. In its place was a granuloma, probably the product of chronic infection. An imperfectly arciform configuration suggested the possibility of syphilis rather than malignancy. This diagnosis, however, was considered improbable because of the inability to confirm it serologically and the failure of the lesion to respond to treatment for syphilis. The distorted clinical picture is explainable on the ground that the lesion had been subjected to repeated surgical interference and that a large element of secondary pyogenic infection was present, as evidenced both by the purulent discharge and the metastatic abscess in the axilla. A culture from the lesion revealed a gram negative bacillus, probably saprophytic. The response of the lesion and the improvement in the general health of the patient under local medication is explained by the fact that the local infectious process was partially controlled. There was no effect, however, on the original neoplastic element as evidenced by the occurrence of new nodules in the upper arm. My first case is one then in which the original tumor is almost completely replaced by a secondary condition. In retrospect the hemorrhagic character of the tumor; the relatively benign course of the lesion; the good general condition of the patient; the long delayed metastasis which does not occur until the tumor has reached considerable size; and the appearance of the original lesion at a site of

a trauma are features of the case which might have led one earlier to suspect a malignant tumor of endothelial character.

Cases II and III also presented a clinical picture in many ways similar in character to Case I. Common features of both were the hemorrhagic character of the lesion; the onset following trauma; the relatively benign course of the growth; the late formation of metastases and the good general health of the patients. Histologically the tumors in all three cases presented essentially the same picture.

We are dealing then with three cases of tumor formation which because of their infiltrative and destructive growth, and the formation of metastases, must be regarded as malignant growths. Should they however, be designated as endotheliomata even though they reproduce the structure of the hyperplastic endothelial cell?

The inability to obtain an early nodule showing the actual beginning proliferation of the endothelial cells makes it of course, difficult to demonstrate beyond cavil that cells of undoubted endothelial origin give rise to the cell masses. However, the tumor cells in general exhibit so many characteristics of the endothelial cell that it seems justifiable to designate them as such. The undifferentiated polymorphic-celled type of growth; the appearance within the cells of vacuoles which in turn coalesce to form the rudimentary blood spaces; the syncytial or branching forms which resemble the true vaso-formative type of cells; and the differentiation of the cells lining the new-formed spaces into fairly typical endothelium, are all constant features which suggest endothelial origin. In Case II the differentiation into capillaries and spaces is the least complete and the tumor from its clinical behavior was the most malignant. In Case I the differentiation is more advanced and the malignancy less marked. Case III, however, shows almost complete differentiation into vascular structures and the tumor, to judge from its clinical behavior, is the least malignant. It seems evident, then, that the malignancy of the tumor depends in part upon the degree

of differentiation as in other neoplasms, the differentiation in this case being into vascular structures.

DISCUSSION OF THE CLASSIFICATION OF ENDOTHELIAL NEOPLASMS.

According to Ziegler[1], Delafield and Prudden[2], MacCullum[3] and others the classification of tumors depends upon whether their growth is typical or atypical, upon their morphology and upon their histogenesis. Two tumors may be the same morphologically and histogenically, but one may be benign and the other malignant, depending upon whether or not it is a typical or an atypical growth. We consider carcinoma as an atypical growth of epithelial origin. It is a malignant tumor derived from tissues which have their origin in the ectoblast or entoblast, the only exception being the lining of the genito-urinary tract whose epithelium as far as the bladder is of mesoblastic origin, and hence genetically closely related to the extensive mesoblastic group of tissues. In the same way a sarcoma is an atypical growth of connective tissue origin. It is a malignant tumor of structures which are products of the mesoblastic layer. Carcinoma and sarcoma differ then in both their morphology and their histogenesis. Their atypical growth characterizes them as malignant. According to Boehm, Davidoff and Huber[4], Prentiss[5], and others, the cells which constitute the endothelium that lines the serous surfaces including those of the pericardium, pleura, dura and peritoneum, together with those of the blood and lymph vessels and lymphatic spaces throughout the body, are modified cells of mesoblastic origin. The endothelial cell then belongs to the connective tissue group and is properly regarded as a modified element of that type of tissue. Endothelial cells resemble, however, those of squamous epithelium in that they are markedly flattened with faintly granular protoplasm, possessing flattened, oval, or nearly round nuclei; that they are of polyhedral shape and are united into a single layer by a small amount of intercellular cement substance; and that although the borders of these cells

may be quite regular or slightly wavy, more often they are serrated. The quantity of intercellular cement substances between endothelial cells is so small in amount, and the cell boundary so indistinct that it is necessary to resort to special staining methods to clearly bring out their outline. On the other hand in the connective tissues it is the intercellular substance and not the cells that gives character to the tissue, the cellular elements themselves forming the less conspicuous portion.[6] (Prentiss, Boehm, Davidoff and Huber[7], Piersol[8], and others).

An endothelioma then according to the interpretation which is placed upon the morphology and histogenesis of the endothelial cell may be either a tumor of mesoblastic or connective tissue origin, histogenetically a sarcoma, or it may be a tumor composed of cells resembling epithelium and hence morphologically a carcinoma. The material of the cases here presented does not permit of a decision of this interesting question. The term endothelioma must then stand essentially as a name representing a compromise between the histogenetic and the morphologic views of the classification of tumors. The endothelioma is histogenetically of mesoblastic or connective tissue origin but morphologically its cellular unit most closely resembles the epithelial cell of ectodermic or entodermic origin characteristic of the carcinomas.

DISCUSSION OF THE LITERATURE

In the past there has been much doubt regarding the actual occurrence of endotheliomata or endothelial tumors.[9] Maurer, in 1879, described two cases of malignant tumors of slow growth composed of ingrowths from the endothelial lining of blood vessels. The tumors exhibited an hemorrhagic tendency and also formed metastases. Microscopic examination showed cell masses arranged in whorls and trabeculae which grew by infiltration into and around nerves, ligaments and muscles. Many small round cells with large nuclei were present. The cytoplasm showed a tendency to disintegrate with the formation of vacuoles. By the coalescence of

these vacuoles distinct channels and blood spaces were formed, some of which contained red blood cells. Because of the tendency toward capillary and sinus formation he called the tumors angio-sarcomata.

In 1890, Franke[10] described a tumor the size of a goose egg, of five years' duration, consisting of a tissue containing blood spaces, lined by endothelial cells in which could be seen what he called "hyalin deposits" resembling vacuoles. The tumor was formed in the lumen of a vessel from its endothelial lining. He therefore suggested the name endothelioma rather than the former name sarcoma. Harris[11], in 1895, mentioned a case of primary cylindrical celled endothelioma of the pleura. In 1895 Volkmann[12] in discussing the endotheliomata characterizes them as tumors originating from endothelial cells lining blood vessels, lymph vessels and spaces, pleural and peritoneal serous surfaces. He states that the vacuole-like appearance is due to glycogen deposits in the cytoplasm as opposed to the idea of hyalin degeneration as expressed by former writers. The vacuoles or spaces in the tumor cells in the three cases which I have observed apparently contained neither hyalin nor glycogen.

Barth[13], in 1896, differentiated endothelial tumors from carcinoma and sarcoma in that they were new growths with the histogenesis of a fibroma or sarcoma and the morphology of endothelial structures. The case he described was that of a tumor composed of minute capillaries and blood spaces. The endothelial cells were thickened and contained large nuclei. Vacuole formation was a common occurrence in the cell cytoplasm. He traced his tumors to a definite proliferation of the endothelial cells of lymph vessels and lymph spaces.

Limacher[14], in 1891, described a tumor of the thyroid in which there was a distinct attempt at capillary formation. The cells of the tumor appeared to develop from the lining of blood vessels. Krompecher[15], in the same year stated that "tumors of the testicle of epithelial character (adenoma and adenocarcinoma) seldom have the histogenesis of epithelium". Testicular tumors of other than

epithelial origin usually develop in his opinion from lymphatic endothelium but occasionally from connective tissue. He stated that "the origin of lymph-endotheliomata in the large lymph spaces has been definitely demonstrated to be from endothelium; of those developing from the lymph vessels the origin has not been definitely proven to be from endothelium but everything suggests endothelial origin". The term endothelioma characterized the tumor histogenetically and angio-sarcoma morphologically. The statement that it is difficult to demonstrate that the tumors in blood and lymph vessels are directly of endothelial origin, although their structure strongly suggests it is entirely in accord with my observation.

Borrmann[16], in 1898, and Markwald[17], in 1899, report cases of endotheliomata of the scrotum and bone. The latter author does not state that he was able to demonstrate their origin from endothelium except in that their structures suggested it.

From 1900 to 1905 there was considerable difference in opinion as to the occurrence of endotheliomata and opposition to the granting of a definite identity to this group. Warthin[18], in 1901, reported a case of a tumor of the parotid which consisted of an overgrowth of the endothelial cells of the lymph spaces, lymph vessels and capillaries. The spindle shaped cells were directly traceable to endothelium through all their transition stages. Wolters[19], in 1900, reported the case of a patient with nodules having an endothelial structure on the chest. Coenen[20], in 1905, described the occurrence of similar lesions on the scalp. Colmers[21], in 1902, described a nodule in the penis with metastasis in the lymph glands, lungs and pericardium. Histologically a proliferation from the endothelial cells lining the cavernous spaces of the penis had occurred. Wood[22], in 1905, reported a case of an endothelial tumor of the testicle with metastasis in the kidney, liver and the lung. He stated that endotheliomas are directly related to the sarcomas.

Lazarus-Barlow[23], in 1903, in discussing the status of endotheliomata holds that the term includes a class of tumors which ontogenetically belongs to the class of sarcomata and yet so far as histological character is concerned bears a close resemblance to the carcinomata. He states that these tumors are composed of cells having the characteristics of endothelium and that they as a result must originate in structures in which these elements are present. Burkhardt[24], in 1902, declared that "histogenetically one cannot differentiate sarcoma from endothelioma". He suggested that the term endothelioma be dropped as confusing. If a tumor morphologically resembles an endothelioma it should in his opinion be called a sarcoma-endothelioma. He says further that "tumors of the same histogenesis may have a different morphology and that the morphology does not determine the type of the original cell". According to this writer sarcomas are derived from the various cells which go to form connective tissue. In the purest and least modified type of sarcoma, the spindle cell type, there is a definite participation of the endothelium of the lymph spaces. In such tumors the predominating type of cell and the endothelial cells respond to the same stimulus but in a different degree.

Zeit[25], in 1908, stated that those tumors which cannot from a pure histogenic and morphological point of view be classified as either epithelial or connective tissue tumors, should be called endothelial tumors. He explains their polymorphous structure on the supposition that the mesoderm comes from both the ectoderm and entoderm. Tumors of mesodermal origin then might at times have an epithelial character by reversion to their double embryonal anlagen, or again at other times might resemble connective tissue growths from mesoderm as such. Zeit described the clinical picture of endothelioma as differing from that of either carcinoma or sarcoma. Lazarus-Barlow[26], in 1906 and 1907, also expressed the belief that their supposed phylogenetic origin, combined with the method of arrangement of normal endothelium, should lead one to expect that endotheliomata

would show great structural variation ranging between that presented by a typical spheroidal celled carcinoma on the one hand to that of a typical sarcoma on the other. He contended that the group of endotheliomata in man must be enlarged to include certain growths of the breast, cervix, etc., which heretofore have been considered as carcinomata. He maintained further that the variations in certain growths in the human uterus and certain mouse tumors is explicable on the view that such growths are endotheliomata.

Ziegler[27] (1908) believed that we should consider the endothelioma as a special form of sarcoma and that endotheliomata in general often so closely resemble sarcomas that they cannot be distinguished from them. He remarks that "it is by no means determined that endothelial cells of lymph spaces and vessels do not take part in the formation of sarcomata". Delafield and Prudden[28], in 1914, state that the stroma of an endothelioma may become sarcomatous.

In 1908, 1909, 1910, Hanseman[29], Minne[30] and Lofaro[31] described tumors of endothelial origin occurring in the skin. These tumors presented malignant characteristics and the histology was that of endothelioma. Boerst[32], in 1913, reported similar tumors of the pleura, peritoneum, dura and skin and designated those occurring in the pleura and peritoneum as mesotheliomata.

A gradual change in the trend of opinion and a decline in the opposition to the concept of endothelioma has occurred during the past five years. Matheny[33], Frazor[34], Schöppler[35], Kren[36], Pernet[37] and Kettle[38] reported tumors, the structure of which characterized them as tumors of endothelial origin. Common features of all were the polymorphous celled type of growth; the whorled arrangement of the cells with the formation of elongated cell strands and narrow trabeculae; and the formation of vacuoles which coalesce to form sinuses and channels which contain blood. These authors define endotheliomas as tumors of mesodermal origin, the cells of which tend to differentiate into flat endothelial cells such as form the intima of blood and lymph vessels, and the inner surface of certain cavities or

spaces such as the pleura, peritoneum, and the arachnoid and subdural lymph spaces. They are characterized as hemangio-endotheliomata if the tumors arise from cells lining blood vessels and lymph-angio-endotheliomata if from cells lining lymph or serous spaces. The tumors are also classified into perivascular, endo-vascular and peri-endovascular tumors depending upon whether the original cells are in the perithelium, the endothelium or both.

CLINICAL SUMMARY OF REPORTED CASES

The literature thus reviewed in conjunction with my series yields a total of twenty-seven cases of endothelial tumors. A summary of the clinical characteristics of these cases is given in the following tables.

SEX INCIDENCE

Males	20 cases	73 plus per cent.
Females	5 cases	20 plus per cent.
Sex not given	2 cases	7 plus per cent.

AGE INCIDENCE

1- 5 years	1 case	3.7 per cent.
5-20 years	0 cases	
20-30 years	3 cases	11. plus per cent.
30-40 years	5 cases	18. plus per cent.
40-50 years	11 cases	40. plus per cent.
50-60 years	4 cases	14. plus per cent.

LOCATION OF INITIAL LESION

Lower extremities	6 cases	22 plus per cent.
Upper extremities	4 cases	14 plus per cent.
Skin (location not given)	4 cases	14 plus per cent.
Thorax (pleura)	3 cases	11 plus per cent.
Chest	1 case	3.7 per cent
Head	1 case	3.7 per cent.
Bone	1 case	3.7 per cent.
Lachrymal gland	1 case	3.7 per cent.
Thyroid	1 case	3.7 per cent.
Penis	1 case	3.7 per cent.
Testicle	1 case	3.7 per cent.
Scrotum	1 case	3.7 per cent.

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AVERAGE DURATION OF LESION

0- 1 year	1 case	3.7	per cent.
1- 2 years	4 cases	14.	plus per cent.
3- 4 years	1 case	3.7	per cent.
4- 5 years	4 cases	14.	plus per cent.
5- 6 years	2 cases	7.	plus per cent.
6- 7 years	1 case	3.7	per cent.
7- 8 years	3 cases	11.	plus per cent.
8-10 years	2 cases	7.	plus per cent.
10-13 years	2 cases	7.	plus per cent.
13-14 years	1 case	3.7	per cent.
15 years	1 case	3.7	per cent.

OCCURRENCE OF METASTASIS.

Metastases occurred in twenty-four or 89 plus per cent of the cases.

HISTORY OF AN ASSOCIATED TRAUMA OF THE ORIGINAL SITE OF THE TUMOR.

A positive history of trauma was reported in thirteen or 48 per cent of the cases. The clinical course in general in the reported cases is as in my own, that of a tumor of slow growth, developing at the site of a former trauma. The lesions in general do not produce metastasis until late when the tumor has reached considerable size. The tumors in all reported cases exhibit a marked tendency to bleed. A similar tendency was very evident in my series of cases. The late metastasis is in marked contrast to that of carcinoma. The results of early excision with thorough removal are good and the outlook for cure apparently is much better than in either carcinoma or sarcoma.

Various opinions are offered in the literature as to the etiology of endothelial tumors. Frazor expressed the belief that they are congenital in origin, supposedly developing from "rests" in the early formation of the vascular system. This question, however, is still as unsettled as in the case of the etiology of other malignant tumors. The development of the tumors takes place by endothelial cell proliferation with the formation of embryonic blood vessels. Further development may vary in different tumors. They may undergo arrest; again while retaining its capillary characteristics the tumor may grow by infiltration

into and between the surrounding tissues; it may change from a capillary to a cavernous structure; and it may become compact and solid. In the last mentioned type the endothelial cells form masses and whorls without capillary formation. This type probably is the malignant endothelial tumor which gives rise to metastasis.

Kettle has shown by cutting entire nodules in serial section that there is no physiologic connection between the blood spaces of the tumor and the vessels of the host. Small capillaries of the stroma rupture as a result of infiltration of their walls by the tumor and hemorrhage occurs into the surrounding tissues forming cisterns as it were from which oozing into the vacuoles already prepared in the tumor takes place. There is no true circulation of the blood in the growth. As Kettle remarks the condition is comparable to that seen in the early weeks of the development of the ovum where as a result of rupture of the maternal capillaries, blood is extravasated into the chorio-decidual spaces and so reaches the vacuolated spaces of the trophosphere. For this reason hemorrhage is a common incident in the development of these tumors. The blood-containing spaces in the malignant endotheliomata merely represent an attempt on the part of the tumor cells to perform their normal function. The spaces result from a degenerative process which has its counterpart in the physiology of the normal angioblast though it is quite uncontrolled in the malignant cell. The degree of malignancy of endotheliomas, as in carcinoma and sarcoma, depends first, not on the morphology, histology, or type of the original cell, but on the number and behavior of the individual cells. The higher the degree of differentiation the less the malignancy. The richer in cells and the more independent of intercellular substance the more malignant is the tumor. The second factor is the location of the lesion. The literature bears out the fact that if the tumor is situated in a highly vascular area or one rich in lymphatics metastasis occurs more readily.

SUMMARY

1. Three cases are reported of tumors whose cellular elements present the histologic characteristics of endothelial cells.

2. The clinical course of the lesions in general is that of tumors of slow growth often developing at sites of trauma. Metastases do not appear until late, when the tumor has reached considerable size. The tumors in all cases exhibit a marked hemorrhagic tendency.

3. Clinically the lesions must be differentiated from syphilis, carcinoma, sarcoma, sporotrichosis and the infectious granulomas. The hemorrhagic character of the tumor, the relatively benign course of the lesion, the long delayed metastasis, and the good general condition of the patient are features which should lead one to suspect a malignant endothelial tumor. Final diagnosis, however, is practically impossible without histopathologic study.

4. Because of the variability in arrangement of the endothelial cell; the ability of the cells to undergo metaplasia; the distortion of the original picture by secondary factors such as infection; and the difficulty of tracing the tumor cells through their transition stages to pre-existing endothelium, the earliest lesions obtainable should be employed in the histopathologic study.

5. The histologic structure of the tumors is that of an undifferentiated polymorphic-celled type of growth presenting a whorled arrangement of the cells with the formation of elongated strands and narrow trabeculae. There is definite evidence of an attempt at differentiation into vascular structures. A constant feature is the occurrence of vacuoles in the cytoplasm of practically all cells. These vacuoles coalesce with the resultant formation of large spaces. The cells bordering on these spaces arrange themselves in rows, become elongated and form an endothelial lining of the space. There is a close association of the tumor with blood vessels. Capillary and sinus-like channels are formed which may contain blood but which have no apparent connection with the circulation of the host.

6. According to the interpretation which is placed upon the morphology and histogenesis of the endothelial cell, the tumor may be regarded either as a structure of mesoblastic or connective tissue origin histogenetically a sarcoma, or it may be thought of as a tumor composed of cells resembling epithelium and hence, morphologically a carcinoma.

7. The term endothelioma as applied to my cases must stand essentially as a name representing a compromise between the histogenetic and the morphologic views of the classification of tumors.

8. Treatment consists of radical surgical removal of the original process followed by x-ray or radium applications to the site of the original lesion and all probable areas of metastasis.

9. A gradual change in current opinion and a decline in the opposition to the conception of endothelioma as a type of neoplasm has occurred during the past five years. The three cases which I have described help to substantiate the belief that a malignant endothelioma is an actual pathologic entity.

4-21 6M

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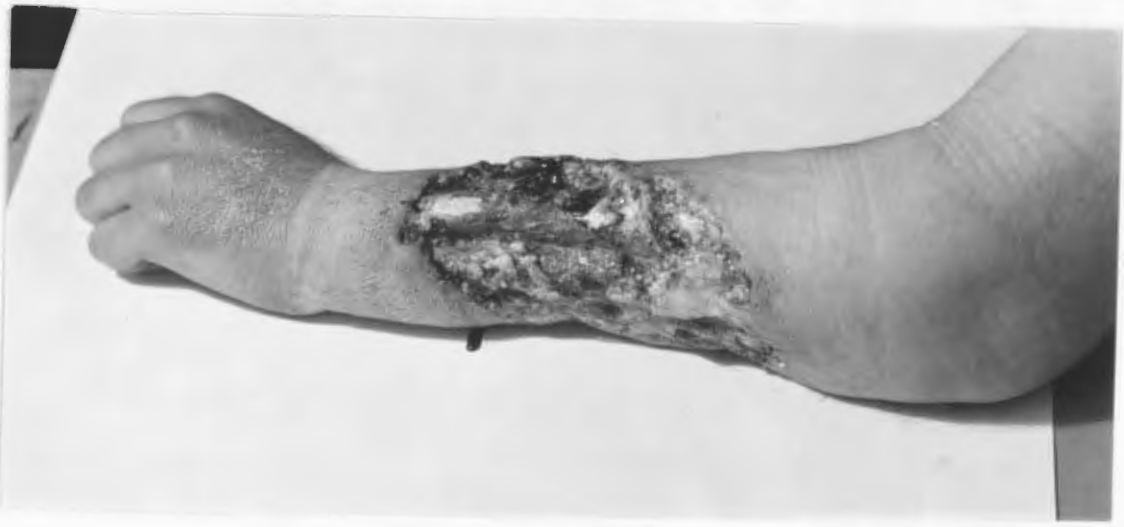

Figure I. Photograph of forearm in Case I showing the large ulcer.

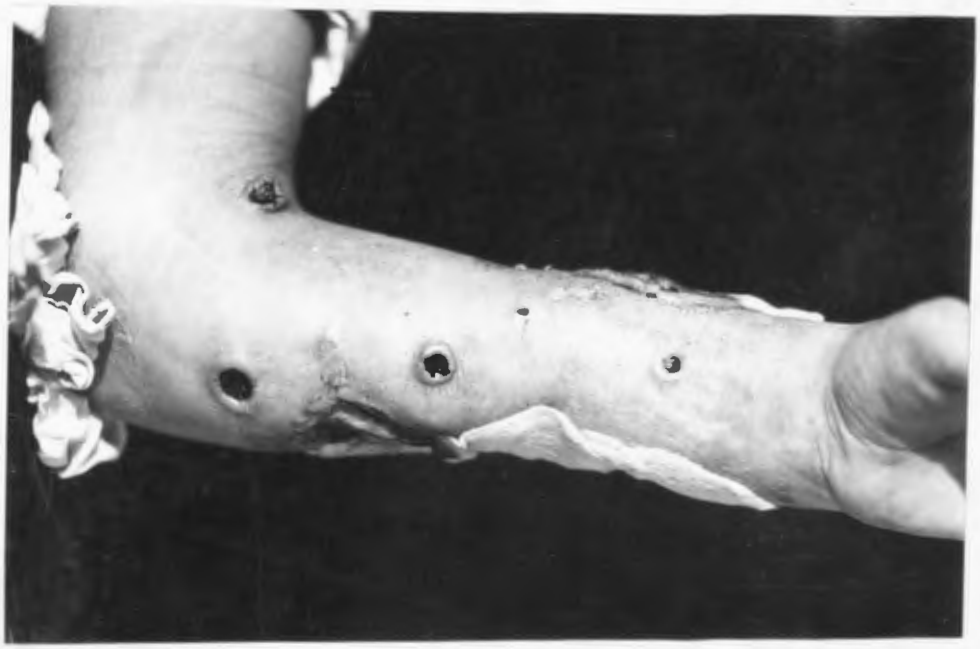

Figure II. Photograph of the undersurface of the forearm in Case I showing new nodules which developed and broke down while the patient was under observation.

Figure III. Low power photomicrograph of a specimen from a new nodule in Case I showing the two characteristic structures of the tumor; (a) A solid area in which the cells exhibit a whorled arrangement; (b) Area of more advanced differentiation into vascular structures (magnification 50 diameters).

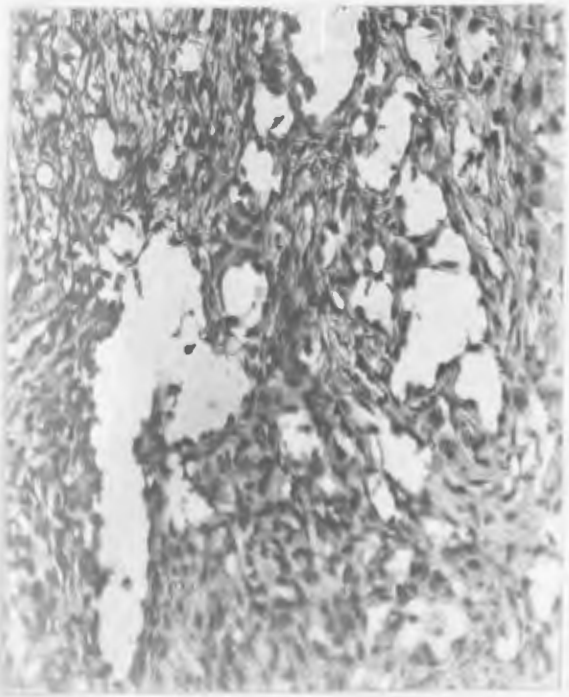

Figure IV. Photomicrograph (magnification 160 diameters) of the area of more advanced differentiation in Case I illustrating the arrangement of the cells into strands with the formation of trabecule; the occurrence of vacuoles in the cytoplasm in the individual cells; and the coalescence of these vacuoles with the resultant formation of large spaces.

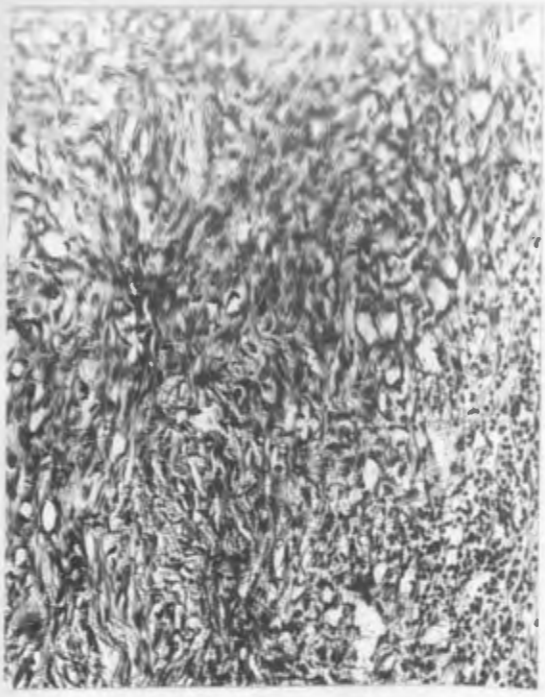

Figure V. Photomicrograph from the denser part of the tumor in Case I (magnification 160 diameters) showing early stages of vacuole formation.

Figure VI. (Case I). Photomicrograph (magnification 500 diameters) from the denser portion showing the various shapes and types of the cell elements with the occurrence of vacuoles in the cytoplasm of practically all cells.

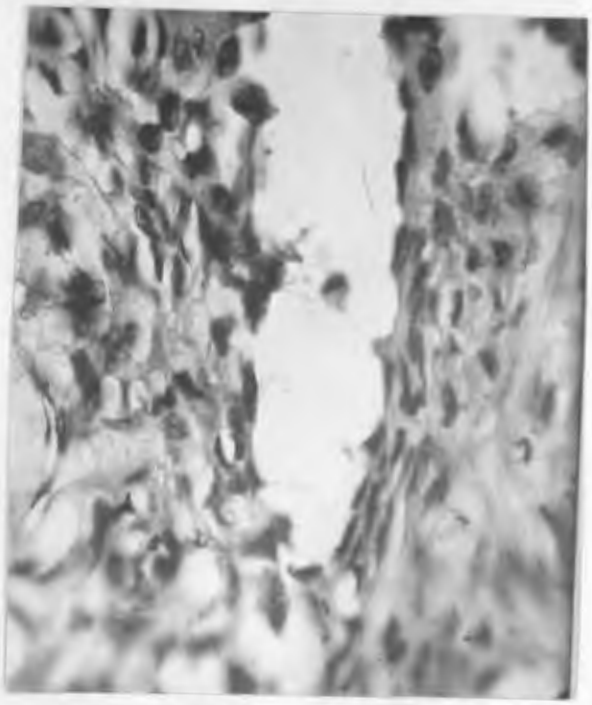

Figure VII. Photomicrograph (500 diameters) from the more differentiated portion of the tumor in Case I showing the tendency of the cells bordering on the spaces to arrange themselves in rows, to become elongated, and to form an endothelial lining for the space.

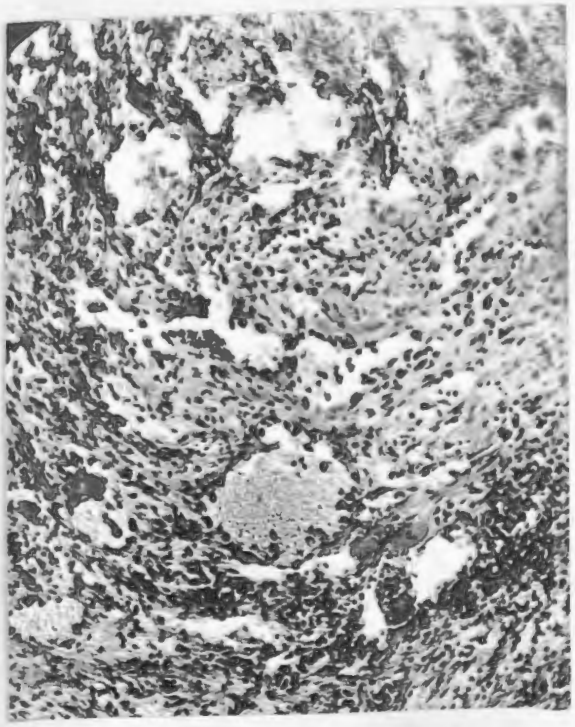

Figure VIII. Photomicrograph (100 diameters) showing the occurrence of red blood cells in some of the newly formed sinuses or spaces. (Case I).

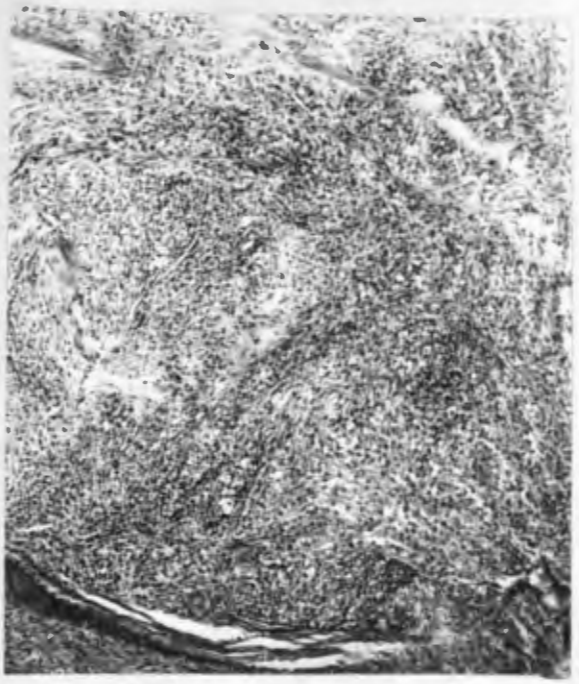

Figure IX. Photomicrograph (75 diameters) of a specimen from the tumor on the ankle in Case II exhibiting the polymorphic-celled, undifferentiated type of growth. In certain areas the attempt at differentiation into sinuses and spaces can be seen.

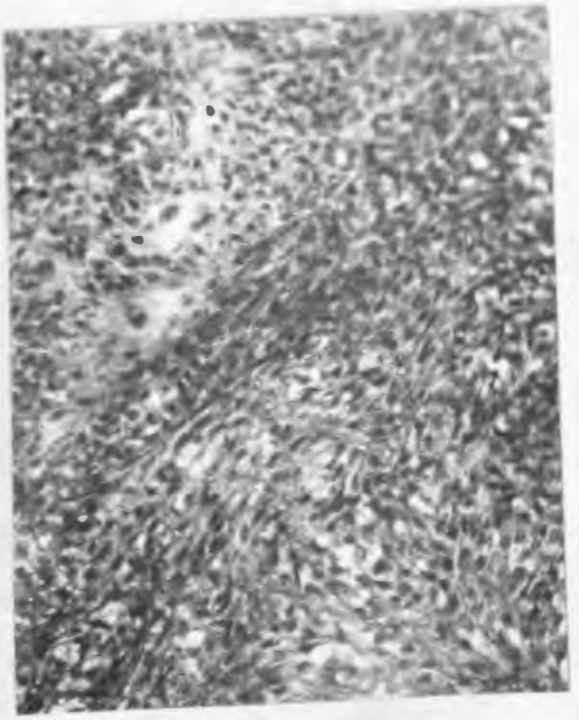

Figure X. Photomicrograph (150 diameters) showing vacuole formation in the cytoplasm of practically all cells (Case II). The coalescence of these vacuoles with the formation of larger spaces is also distinguishable.

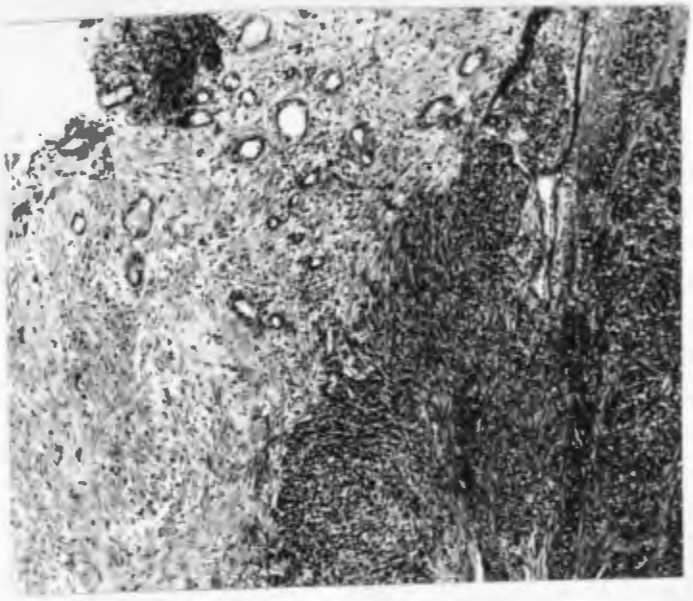

Figure XI. Photomicrograph (75 diameters) showing the characteristic masses of tumor cells in Case II in close association with a surrounding highly vascular granulation type of tissue.

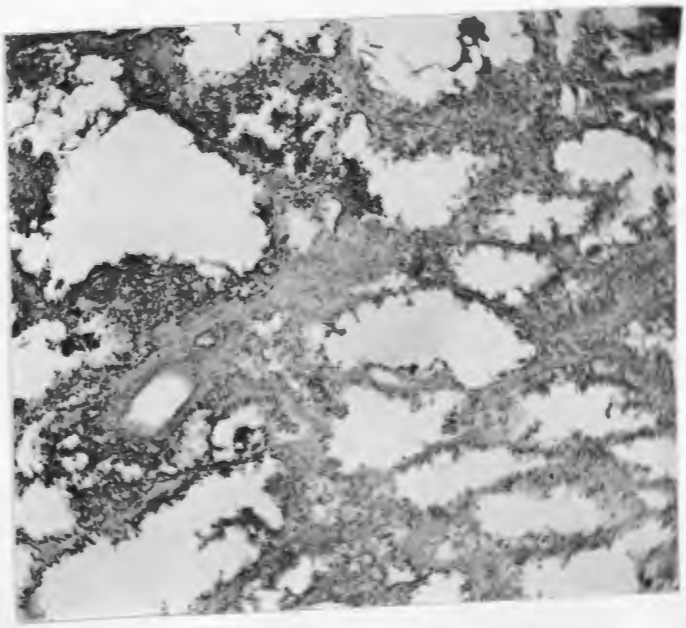

Figure XII. Photomicrograph (50 diameters) showing the cavernous structure characteristic of the tumor in Case III.

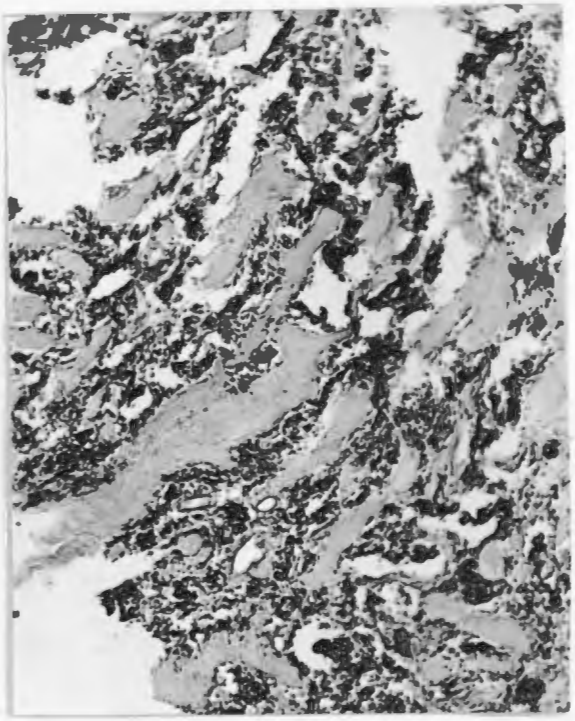

Figure XIII. Photomicrograph (75 diameters) of a specimen from the metastatic nodule in Case III showing the same cavernous type of growth as that in the parent tumor.