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MALIGNANT GIANT CELL TUMOR OF BONE *

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INTRODUCTION

The question of the transformation of benign giant cell tumor of bone into sarcoma has been discussed for over 100 years. Lack of adequate pathological interpretation and especially adequate microscopy prevent modern evaluation of the statements of Cooper and Travers,[1] Lebert,[2] and Paget.[3] Much prominence has been given to Nélaton's monograph,[4] yet a careful perusal by Coley seems to show that Nélaton had but 6 cases of giant cell tumor which he personally treated, and that of 46 cases reported, mostly from the medical literature, but 14 were tumors of long bones. The follow-up of these cases was unsatisfactory; 4 individuals died postoperatively in the pre-Lister period, only 2 were traced for a 2 year period, 4 for a 1 year period, and the others were lost. Paget in 1853 called attention to the benign quality of giant cell tumor but left open an avenue of escape, apparently being by no means certain that some might not run a malignant course. In his Surgical Pathology, third edition, 17 years later, we find the same avenue open. One gains the impression that Paget may not have accepted the sarcomatous transformation of giant cell tumor but that he regarded the malignant tumors as something else. He states "nor have they, in general, any features of malignant disease, although myeloid structures have occasionally been found mingled with the ordinary structures of medullary cancer." He

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quotes instances in proof of the benign nature of myeloid tumors but draws his material entirely from tumors of the jaw. Pathological confusion appears obvious in one of Paget's cases — that of a farmer's boy with an enormous tumor of the calvarium, "believed to have originated in the effects of repeated blows on the head." From gross specimen, drawings of certain microscopic appearances, and from the clinical course, this tumor was clearly a meningioma which provoked much osteoplastic change.

Lebert first expressed himself of the view that all giant cell tumors were benign, but later altered his opinion. Virchow fully recognized the benign course of giant cell tumors of the jaw but agreed that giant cell tumors of long bones might yield highly malignant metastases. He calls attention to the fact that a tendency existed to regard such cases as complicated when viewed in retrospect, but incorrectly so. Virchow [5] himself discarded the case of Gerlach [6] in so far as to refuse to accept it as a tumor of medullary origin, but states that the case is nevertheless of value for the question of malignancy of myeloid tumors. Why he reaches that conclusion is not told us.

Virchow seems skeptical about Hutchinson's case.[7] In this patient the tumor is said to have consisted of a mixture of "myeloid" and "fibro-plastic" elements. The primary tumor was located in the upper humerus. Its definite onset followed 14 months after fracture dislocation but no surgical interference was permitted until nearly 5 years had elapsed. Resection and axillary dissection were followed by rather prompt recurrence, fungation, cervical extension — said to be in "glands" — and death. Metastases were found in the lungs. In the infra-axillary and supraclavicular "glands" (the present authors use glands in quotation marks because of a suspicion that the lesions were venous emboli), no giant cells were found and only "fibro-plastic" elements. The lung nodules contained giant cells with one to three nuclei. From the description these are probably malignant giant cells. The present authors see no reason from the available data to assume that this was other than a malignant change in a giant cell tumor. Virchow also doubts the case of Forster [8] which was indeed resurveyed with a follow-up by Wilks,[9] and classed as "osteoid cancer combined with myeloid disease."

Virchow has less doubt in accepting the case of Henry,[10] yet on

review of Henry's account the author himself seems to express misgivings for the first time as to the significance for prognosis of the myeloid cells. He writes that "the question now arises, whether they indicate anything more than that ossific changes are occurring in a tumor" and that "subsequent experience may enable us to determine the exact import of myeloid cells, but at present, it seems to me premature, to evaluate a characteristic which may after all only be accidental, into a test of a radical difference in the nature of a tumor." Finally, Virchow accepts without doubts the case of Wilks.[11] This seems strange for in this paper there is no evidence of microscopic examination of either primary, recurrent or metastatic masses. In fact Wilks stated that the naked eye characteristics of true myeloids were abundantly sufficient to distinguish them.

On reconsideration it would appear that the evidence on which Virchow based his acceptance of the occasional malignant course of giant cell tumors of the long bones is insufficient for present day standards of analysis although we do not doubt the truth of his conclusion.

Geschickter and Copeland [12] describe a case (JCB. N. 13714 — Dr. Dingman) where Bloodgood in 1924 had made a diagnosis of cellular but typical giant cell tumor on the basis of two curetted specimens, and of sarcoma with altered giant cells on the basis of an amputation specimen shortly thereafter. They regard the case as one of chondroblastic sarcoma of the femoral condyle rather than one of giant cell tumor. The patient rapidly developed pulmonary metastases and died within 6 months of the first symptom.

These authors similarly interpret the report of Stone and Ewing.[13] Here the diagnosis of chondrosarcoma is apparently reached from a perusal of microphotographs. We ourselves are in possession of the pathological material and cannot find evidence of a cartilaginous element. The bone shown in the published photograph is not tumor bone but bone in process of destruction.

Bone Registry case No. 68, patient Mrs. K., treated by Wilson and Simmons, is accepted by Geschickter and Copeland as benign giant cell tumor. They find on clinical analysis that the patient died of pneumonia and cardiac failure. However, Dr. Wilson, who actually cared for this patient, tells us he feels certain the patient had pulmonary metastases. Ultimate interpretation of the

case is dependent on facts no longer obtainable. Geschickter and Copeland interpret the changes in the recurrent tumor of this patient as a healing reaction. Others viewed them as evidences of malignant transformation. Although the process is not marked, we find in the initial tumor certain "stromal" areas of confluent, very cellular pseudosyncytial mesenchymatous appearing cells which remind us of features seen in other tumors that have run a malignant course, and though not denying that the tumor was a giant cell tumor, our initial prognosis would have been guarded. It is interesting to note that the periosteum was found broken through at first exploration, probably as the result of failure to regenerate at the patient's advanced age. Moreover, everything that might be supposed to excite into accelerated activity a borderline tumor seems to have been done — four curettages, packing with resultant fungation of uncontrolled growth, and intratumoral implantation of radium. Infection was inevitable.

The case described by Augé and Roux [14] was probably not a benign giant cell tumor. The patient was a male, aged 22 years. His initial symptoms were pain in the lower femoral region, relieved by rest. The pain was greatly accentuated by a fall 11 days prior to hospitalization. On admission the knee showed a rounded swelling, edema, local warmth, prominent veins, and a small effusion into the joint. The radiographic reports cannot be interpreted in terms of modern roentgen diagnosis. Fever was present and the process was thought to be osteomyelitis. After 9 days bed rest a pathological fracture occurred and amputation was performed. Within 2 months signs of pulmonary metastases appeared with pleural pain, "grippe," fever, emaciation, and bloody sputum; a scar recurrence grew rapidly, soft part metastases appeared and oliguria was noted. Autopsy showed pulmonary, pleuropericardial and renal metastases. Although the figures seem to show a primary benign giant cell tumor, the statement is made that it contained islands of cartilage and the pleural metastatic nodule is reported to have contained cartilage. The case is doubtless to be interpreted as chondrosarcoma with many epulis type giant cells. In a discussion, Delbet reaches a similar conclusion. At the same time he lays down certain rules for the diagnosis of benign giant cell tumors which, if followed literally, would surely make typical benign giant cell tumor a rare entity.

Geschickter and Copeland are probably correct in their interpretation of the case of Turner and Waugh [15] as an instance of femoral thrombosis by benign giant cell tumor and not one of malignant giant cell tumor in the usually accepted sense. This case is similar to one described by Coley [16] (J.McC., his case No. 11). We do not now regard this as a malignant giant cell tumor but as an example of local thrombotic recurrence of benign giant cell tumor. It is interesting to note that a radiologist skilled in diagnosis of bone tumors regarded this case as malignant from the beginning. Goforth's [17] case provides no data on which a diagnosis of primary benign giant cell tumor may be made. The case of Finch and Gleave [18] leaves much to be desired. The onset occurred with pain in 1915. Trauma was added in 1916, pathological fracture in 1917, which healed after exploration, and at that time a diagnosis of osteitis deformans was made. This is difficult to explain if the condition was a giant cell tumor. Pain recurred in 1919 and a diagnosis of giant cell tumor was then made. In 1925 a second fracture was followed by amputation, stump recurrence within a few months, and pulmonary metastasis. From the structure of the lung metastases an unqualified diagnosis of osteogenic sarcoma appears necessary. What the initial lesion was no one can say.

In Dean Lewis' case, reported by Geschickter and Copeland, all data on the original lesion were lost. Lewis is said to have believed the initial lesion to be a giant cell tumor. The metastases are described as bone-forming. One was curious in that it contained well developed marrow. This may be significant because of the fact that the present authors have twice noted evidence of hematopoiesis in areas of supposedly malignant giant cell tumors. We do not recall seeing such foci in osteogenic sarcomas, but this of course is not evidence. In a case to be discussed later King reports cells of "bone marrow type."

MacGuire and McWhorter [19] report 4 cases of giant cell tumor where the histology is atypical and where local recurrences or metastases or both occurred. The structure and behavior of their case No. 34 corresponds to what we regard as malignant "transformation" of giant cell tumor. We believe their case No. 35 is of the same nature but find difficulty in interpreting the microphotographs. In their other 2 cases we find the data, as presented, unsatisfactory for conclusions.

The case of Dyke [20] is somewhat similar to that of Augé and Roux in the distribution of metastases. The patella is a most unusual site for the common giant cell tumor, unless it be of the tendon origin type. The microphotographs are chosen from small fields and although they apparently illustrate benign giant cell tumor of the usual variety one would like to see more of it, or have a more elaborate description of the histology before drawing conclusions. Dyke's report is followed by one by Orr.[21] The latter publication is necessarily sketchy because the case is one resurrected from a museum specimen of 1898.

King [22] reports a very satisfactory case. The tumor was located in the lower end of the radius. It had been present for 4 to 5 years. The radiographs were typically those of giant cell tumor and roentgen therapy was given. On later examination there was evidence of partial sclerosis commonly seen in giant cell tumor but also of cortical erosion and soft part extension. The radius was resected and a graft inserted. Local recurrence led to absorption of the graft; epitrochlear extension was followed by amputation, clear-cut X-ray evidence of pulmonary metastases and death. No autopsy was performed.

Sections were at first interpreted as benign giant cell tumor. At a later review malignant appearing areas were found containing active spindle cells and giant cells of both tumor and foreign body type. The figures from the epitrochlear tumor show loss of all suggestion of giant cell tumor. King regards the case as an example of malignant giant cell tumor of bone and specifically states that the term refers only to a malignant form of benign giant cell tumor, and does not refer to obvious osteogenic sarcomas which contain giant cells. With King's interpretation and terminology we are in full accord. We believe that there are tumors which show malignant features from some relatively early period but which are to all intents and purposes identical in nature with the benign giant cell tumor and which are distinct from osteogenic sarcoma in the usually accepted sense. The existence of such tumors must necessarily throw more responsibility of proof on those who assert that surgical or radiological interference with a benign giant cell tumor, or even pathological fracture, are the cause of its assuming malignant characteristics. This matter will be discussed later in connection with individual case reports.

Some writers call attention to the fact that there exists no proved case of pulmonary metastases from benign giant cell tumor where the structure of the pulmonary metastases was that of giant cell tumor. The metastases are said to show always the structure of osteogenic sarcoma. The authors have not had opportunity to study pulmonary metastases from malignant giant cell tumors but would suspect, from the structure of the histologically malignant primary tumors, that the metastases would not resemble the usual osteogenic sarcoma. Although to date no acceptable case of pulmonary metastatic tumor has shown the structure of giant cell tumor, it should not be surprising if such were eventually reported. Giant cell tumors are known to invade veins, spread to adjacent bones, appear in adjacent or more distant soft part tissues, and may well go farther without assuming an appreciably altered structure. In this connection one might recall the curious metastases of chorioadenoma destruens, the growth of chondroma into veins, venous invasion by uterine myoma, and rare distant metastases. Through the courtesy of Dr. Paul Steiner one of the authors has had the opportunity to study a case with massive pulmonary metastases from a uterine myoma. In this case * neither the uterine tumor nor the pulmonary metastases could be regarded as malignant from their histology alone. Malignancy is an attribute. The expression may refer to behavior and may refer to possession by the tumor of certain characteristic histological features. These phenomena are not necessarily always parallel. To risk diverging one might cite the infantile nevus. Many infantile pigmented nevi cannot be distinguished from malignant melanomas, but clinically they are benign lesions.

Efforts have been made to minimize the occasional malignant character of giant cell tumor on the basis of (1) confusion in initial diagnosis, mainly between chondrosarcoma and giant cell tumor, and (2) the development of the concept that the malignant tumor which arose in an otherwise innocent giant cell tumor was a "secondary" osteogenic sarcoma. The first is valid. The second is a matter of philosophical discussion. Adopting the terminology of the Registry of Bone Sarcomas, a system of classification which has been useful, but which possesses some inconsistencies, one might safely state that the malignant giant cell variant was an

* To be published in full by Dr. Steiner.

osteogenic sarcoma —a sarcoma *arising* from bone. We cannot see, however, that it is any more "secondary" than are many other tumors where one never thinks of such designation. Every tumor is secondary to something. Actual histology would suggest that some malignant giant cell tumors had more the characteristics of granulation tissue sarcomas than anything else. This would fit well with various notions concerning the histogenesis of giant cell tumor, namely a peculiar reparative process following necrosis of cortical bone under specific conditions. Mallory's opinion [23] as to the essential reparative nature of the process designated as giant cell tumor has, we believe, received confirmation with the elucidation of the brown tumors of hyperparathyroidism. The mechanism of the radiation response of giant cell tumor is perhaps significant in this regard, for it is strongly suggested that radiation acts in these tumors toward reducing blood supply and permitting recalcification, rather than destroying tumor cells in the manner frequent in malignant tumors. It is also interesting that the last comprehensive study of the origin of the epulis type of giant cell in bone, that of Zawisch-Ossenitz,[24] reemphasizes the origin from penetrating endothelial sprouts. She reports solid endothelial sheets splitting off from invading capillary endothelium. Of course the interpretation is not new.

In a more recent single case report Puhl [25] attacks the theories of the essential reparative origin of giant cell tumor. He offers as substitute the statement that these tumors are dysontogenic lesions — tumors of embryonal mesenchyme, the mesenchymal cells being capable of differentiating in multiple directions, with the formation of giant cells, osteoid and cartilaginous tissue. Puhl is undoubtedly describing a case of chondromatous giant cell tumor. Admitting the possible correctness of his interpretation of the origin of chondromatous giant cell tumors, we question the advisability of assigning all giant cell tumors to similar origin. In several cases of malignant giant cell tumor we have noted resemblance of the tumor cells to condensed atypical mesenchyme. One must, however, consider the possibility of dedifferentiation and reversion in the production of such pictures as well as dysontogenesis. The exact mode of origin of the average giant cell tumor will probably await solution until opportunity arises, probably by accident, to see the lesion in its very early stages. It is difficult to

conceive of dysontogenic origin of the Brauntumoren of hyperparathyroidism.

Puhr [26] emphasizes a reticuloendothelial origin for benign giant cell tumors. We cannot see that the evidence is especially clarifying and quote the paper only because the theory is of interest in view of the structure of certain of the malignant tumors in our own series.

In selecting the following cases for detailed report, efforts have been made to exclude cases of doubtful significance. Only when material from the initial curettage and from subsequent specimens, in which no possible doubt can exist as to the malignant quality of the process, is available for review is the case regarded as suitable for presentation. If, however, the first material available for study comes from a *second* operative procedure, but still shows the lesion to be a giant cell tumor, subsequent course proving the lesion to be malignant and with histological proof of change of character, the case may still be included since it cannot be assumed that a recurrence of an initially malignant tumor will take the form of a benign giant cell tumor. Typical roentgen evidence of pulmonary metastases and the death of the patient are accepted as proof of malignant character and autopsy confirmation is not considered essential. Strict exclusion of certain material robs the series of several cases where no doubt exists in our own minds as to facts, but it is our feeling that the inclusion of such cases would add no information.

One case is included, although it is considered as malignant from the earliest available material. It is included because it is believed that, like King's case, it is a malignant giant cell tumor and not the usually accepted osteogenic sarcoma.

Case Reports

Case 1. H.C., male, aged 27 years, applied to the Memorial Hospital on June 1, 1929. He complained of pain largely confined to the popliteal region on the left, beginning 9 months prior to admission. There was no history of trauma. The joint had been swollen and inflamed. Motion was painful. The swelling and pain subsided at intervals only to recur. He walked with little difficulty. When the pain was severe, flexion was incomplete. On admission to the clinic no swelling was evident. Deep pressure failed to elicit pain but motion was limited. The patient presented radiographs which showed a large, multilocular cystic growth of the lower femoral region regarded as characteristic of giant cell tumor. The patient received X-ray treatment but since the

size of the portal is not mentioned the dose cannot be calculated. It was apparently not excessive. After treatment the early films are said to have shown improvement. The patient failed to report to the follow-up clinic until about 7 months had elapsed, when he returned with a pathological fracture which had occurred in bed. He was placed in a Balkan frame. Additional X-ray therapy was given and by April 30, 1930, the patient was using a walking Thomas caliper. Local swelling and tenderness following fracture had regressed. One month later radiographs were reported as showing suggestion of further decalcification and some reactivity of tumor. Thereafter films made about every 2 months were reported as showing little change. In October, 1931, the patient had a curettage with implantation of fat pad at another hospital. No drainage was done. About 1 month later the patient became febrile, the tumor showed marked evidence of local recurrence, and amputation was performed in January of 1932. The tumor rapidly recurred in the stump, pulmonary metastases were demonstrable, and the patient died on April 1, 1932.

Comment: It is difficult to assign the blame for the behavior of this tumor. Some would incriminate curettage, others the X-ray followed by curettage; some would suspect the influence of the fat pad, others the pathological fracture. We suspect the tumor itself, for reasons which will appear later. However there was rapid alteration after curettage and one may be justified in assuming the attitude *post hoc ergo propter hoc.*

Material from the curetted specimen (Fig. 1) comes from five different areas. The structure is essentially the same throughout. The giant cells are very large, some containing as many as 100 nuclei of uniform size and structure. They do not appear related especially to areas of blood pigment, hemorrhage or blood lakes. There are faint traces of dead bone in process of decalcification. No cartilaginous or myxomatous tissue is seen. In some areas the "stromal" cells are a trifle atypical, being more spindle shaped and less polyhedral than usual. No sharp demarcation can be made out, however, between these spindle cells, the polyhedral cells, and the smaller giant cells of probably recent formation. On long search, although mitoses are numerous in spindle and polyhedral cells, no atypical mitoses can be found. In some areas the spindle cells occur in hyaline areas no different from those of reactive fibrosis. A few well formed vessels are seen but for the most part the vascular channels are lined by single rows of endothelium. In some no endothelial lining can be made out. Hemorrhage has occurred in the interstices of the tumor and old blood pigment is found. There are occasional xanthomatous foci. In some areas

giant cells become sparse and spindle cells more prominent. There is a strong suggestion of vasoformative properties in these spindle cells and they appear inseparable from the capillary endothelium. Where the spindle cells are numerous they seem to grow in pseudo-syncytial fashion but cell boundaries are nevertheless present.

In the specimen obtained at amputation (Figs. 2 and 3) no cells of the epulis type are seen. Many giant cells occur but their nuclei are few in number, are very large, pale and vesicular, and some contain from seven to eight nucleoli. Where nucleoli are fewer they attain enormous size; some are as large as an entire normal plasma cell. Many atypical mitoses are seen. There are numerous degenerative mitoses where the cytoplasm is filled with coarse irregular chromatin granules. Some cells contain a single, large hyperchromatic nucleus, itself as large as a small epulis giant cell. Between the giant cells are large fusiform or polyhedral cells with rather clear cytoplasm, large vacuolated nuclei and giant nucleoli. Many show mitoses. All transitions between these fusiform and polyhedral cells and the tumor giant cells are found and there is a suggestion that the giant cells arise both by accretion and through multiple mitosis. Where the cells are more sparsely distributed a distinct endothelial character is noted. The tumor looks angioblastic, although this property is less marked than in other instances to be illustrated later on.

We can see no reason to call this tumor secondary. To do so arbitrarily creates division where none can be shown to exist. We believe the term "secondary" is a loose one. It might suggest that the lesion was of a fundamentally different histogenic type. This we do not believe. It is a continuation of the same underlying process in aggressive neoplastic form. "Secondary" might mean that a second cause or stimulus was operative. This may be quite possible. In fact, in most instances of malignant transformation of giant cell, tumor is strongly suggested.

CASE 2. L.S., male, aged 35 years, applied to the Memorial Hospital on Aug. 24, 1937. About 1 month before admission he began to experience discomfort about the left knee joint. Shortly thereafter he noted pain and swelling, and some tenderness on pressure. He consulted a physician who treated him under a diagnosis of arthritis, with no relief. Radiographs were then made and the patient was referred to the bone service at the Memorial Hospital. The lower end of the femur was involved by a destructive growth which extended from the articular surface of the right condyle upward for a

distance of 7 to 8 cm. The region was trabeculated. The cortex was thin and not perforated. The outer limits of the tumor were sharply demarcated, especially upward. It had the appearance of a giant cell tumor.

The patient was treated by curettage, washing out the cavity with zinc chloride solution in the usual manner, followed by Dakin's, and the wound was closed without drainage. Convalescence was at first uneventful but the patient complained of much more pain than usual about the time of his discharge. There was spasm of the hamstring muscles. On Oct. 10, 1937, blood was aspirated from the joint cavity. Roentgenographs at that time showed evidence of active extension of tumor accompanied by considerable increase in bone destruction. The lung fields were clear. Amputation was advised and accepted. On Jan. 10, 1938 the patient complained of pain in the chest. From then on, the downhill course was rapid; there developed metastases in the tenth thoracic vertebra, transverse myelitis, pulmonary metastases, and death occurred on March 14th.

Comment: The initial diagnosis of giant cell tumor was made by aspiration and from the aspirated material alone a note was made that the "stroma" was unusually cellular. From the curettings (Fig. 4), the tumor was reported as giant cell tumor with the reservation that its benignancy could not be guaranteed. There were numerous typical epulis giant cells with the characteristic, small polyhedral cell stroma. Hemorrhage had occurred with deposition of blood pigment. The blood supply consisted of widely dilated capillaries mostly with an endothelial lining of a single row of cells. Some vessels seemed to lack a complete endothelium and the tumor was telangiectatic. Hemorrhage had occurred in the interstices of the tumor quite recently but this was doubtless the result of the curettage. Old strands of fibrous tissue crossed the mass. There were traces of bone in process of decalcification. No cartilage or myxomatous tissue was seen. In one area (Fig. 5) the giant cells were scanty, nuclei less numerous, the cells were small, and there was a marked proliferation of cells of the "stromal" type, rather larger, slightly more ovoid, and slightly more hyperchromatic than the usual stroma cells. There mitoses were numerous but not atypical. These cells lined in part vascular channels without definite endothelial walls, although an occasional flattened cell resembling endothelium could be seen. Demarcations between individual cells were often indefinite. No tumor giant cells could be identified. On the basis of this area we refused to state that the tumor would run the course of the usual giant cell tumor but likewise refrained from calling it other than giant cell tumor. In examining the suspicious area Dr. Ewing stated that he

had previously seen such areas in giant cell tumors that had not run a malignant course. Nevertheless the atypical area fully justified our suspicions.

It is important to note that suspicious features in this tumor were found within a short time after known onset, prior to any interference, deliberate or accidental. In the amputated specimen we found an extremely destructive, soft, pulpy hemorrhagic tumor involving the lower end of the femur, including the epiphysis and lower 5 cm. of shaft. There was a pathological fracture, said to have occurred during or shortly after operative handling rather than prior to amputation. The tumor had broken through the cortex and a bulky soft part mass was present. The total bulk of tumor was about 13 by 13 by 10 cm. The joint cavity was invaded and filled with blood. There was an upward extension of tumor between the deep muscle planes. The gross diagnosis was aneurysmal giant cell tumor. In sections, only one area examined shows the characteristics of benign giant cell tumor. The others consist of tissue resembling the suspicious appearing area of the curettings. Cells are polyhedral or ovoid; nuclear-cytoplasmic ratio is disturbed, nuclei being unusually large. Growth appears to be largely syncytial and the tissue suggests a cellular, atypical condensed mesenchyme. The circulation is almost entirely telangiectatic. Giant cells of the epulis type are exceedingly rare. Mitoses are numerous; none appears atypical. The mode of growth varies from place to place. In some areas (Fig. 6) it is almost epithelial with cells appearing in sharply demarcated sheets. Such areas are also seen in endothelial tumors. Where hyaline fibrous tissue is being invaded it is impossible for us to separate satisfactorily the tumor cells from either fibroblasts or endothelium. Thus the tumor possesses characteristics seen in granulation tissue sarcomas. No tendency to form bone, cartilage or osteoid tissue is found. We class this case as one of primary, malignant giant cell tumor of bone.

CASE 3. G.G., male, aged 39 years, applied for treatment at Memorial Hospital on Feb. 15, 1929. He had had a curettage with packing of the cavity by gauze, at another hospital, of a typical giant cell tumor of the lower right femur, mainly the external condyle. Despite treatment, successive radiographs showed increasing destruction up to the time of the institution of X-ray treatment at the Memorial Hospital. From that time on, over a period of about 1 year, reports from radiographs indicated some increased bone

density, interpreted as a healing process. After about 1 year, however, films showed evidences of reactivated disease. Amputation was done on May 27, 1931. By September of 1932 a mass was palpable in the right groin. The mass extended into the abdomen. The patient complained of severe pain which finally necessitated chordotomy. On May 3, 1933, pulmonary metastases were found and on May 11th the patient expired.

Comment: Through the kindness of Dr. Jaffé we have reviewed the sections of the original tumor. Material from several different areas was interpreted by Jaffé and ourselves as typical benign giant cell tumor. There are no signs of bone production, atypical stroma, cartilage, or myxomatous areas. Sections from the amputated specimen 4 years later show a purely destructive, nonossifying, highly malignant appearing sarcoma. The cells are loose, round or ovoid, and contain one or more large hyperchromatic nuclei and giant nucleoli. Reticular structure is absent. There is no tendency toward the formation of long spindle cells and no epulis giant cells are seen. There are numerous mitoses, some atypical and multiple. The circulation is telangiectatic. An aspiration biopsy from the inguinal mass also showed a malignant tumor.

This tumor may have been malignant from its onset but the burden of proof must rest on those who refuse to accept the contrary evidence.

CASE 4. D.K., female, aged 28 years, was first treated by Dr. Lewis Gregory Cole in 1931 for what was regarded as a typical benign giant cell tumor of the right lower radius. She received sufficient radiation to control the usual giant cell tumor, but about 9 months later there was roentgenographic and clinical evidence of recurrence. More radiation was given but the process remained uncontrolled. Hence a curettage was performed and the cavity was swabbed out with carbolic acid. Within 4 months the tumor had again recurred and a second curettage was done. Altogether the tumor was curetted on six occasions (in 1931, twice in 1932, three times in 1933). Additional radiation was given between the fifth and sixth curettage and after the last curettage.

Comment: Material from the earlier specimens shows a typical benign giant cell tumor, containing numerous giant cells of the epulis type, without undue vascularity, and with no unusual alterations in the character of the tissues between the giant cells. Material from the fourth curettage is extremely vascular and the giant cells are less numerous.

For the first time a distinct alteration was observed in material from the last curettage and then, especially since the tumor had

fungated, an amputation was performed. The giant cells in the amputated specimen are of two types but suggestions of transition stages are observed. Large, typical epulis type cells predominate but there are numerous smaller giant cells with few nuclei, sometimes only two or three. In the intermediate type of giant cell can be seen in addition to the usual nuclei of the benign giant cell type, one and sometimes two very large, hyperchromatic nuclei with correspondingly large nucleoli. Malignant giant cells are of the usual type, with few large nuclei and with giant, atypical mitotic figures. Giant mitoses are found in the intervening tissue. In some giant cells there is a suggestion of growth by fusion of nuclei, the resultant nuclei resembling those of megakaryocytes. We can not be certain that some such cells are not megakaryocytes, especially since in addition to all of the features found in the last curettings, accentuated only in degree, in the amputated specimen there is distinct evidence of blood formation (erythropoiesis).

Were this tumor anything but a giant cell tumor it is most remarkable that six curettages were necessary before its malignant characteristics were detected. The patient has nearly passed the 5 year period of freedom from disease.

CASE 5. M.L., male, aged 44 years, applied to the Memorial Hospital on Nov. 8, 1933. His history stated that he had had pain of sudden onset in 1926, located just below the right knee. At that time the lesion was considered a tibial bone cyst. Operation was advised but refused. The pain lasted about 3 weeks and then subsided. It did not recur until about a year before admission to the Memorial Hospital. In August 1933 the lesion was curetted at another hospital. The material was diagnosed giant cell tumor. Pain persisted and 3 months later a second curettage was performed. At both operations the wound was closed tight, without drainage. Although the early radiographs were considered those of a bone cyst or giant cell tumor, later films taken in January, 1934, were considered as showing that the process had become malignant. Amputation was then done. Only 3 weeks after amputation, disease was evident in the stump and a mass was palpable over Scarpa's triangle. In May of 1934 evidence of pulmonary metastases appeared in chest films. The recurrent lesions resisted roentgen therapy. The patient died in July of 1934.

Comment: Sections from five different blocks of the curettings obtained at the second operation showed benign giant cell tumor. Review of these sections shows benign giant cell tumor. Giant cells are of the epulis type. Nuclei are small, uniform, and very numerous. The stroma cells are perhaps a trifle more spindle shaped than in some instances of giant cell tumor. Some appear

to line blood spaces, interrupting the continuity of the endothelial layer. The lesion is very vascular. It is impossible to separate the capillary endothelium and perithelial cells from other elements, and blood vessels, as is usual, form an integral part of the process. There are old areas of hemorrhage and masses of blood pigment which probably date from the first curettage. There is no evidence of cartilage or myxomatous tissue. After long search a single giant cell was found with a nucleus and nucleolus much larger than normal. The cell appeared, however, degenerated.

During the 2 months that elapsed between the second curettage and the amputation the curetted cavity had partly filled with fibrin, but a mass of recurrent tumor 6 cm. in diameter had developed in its anterior half. This mass invaded the soft tissues; an upward extension penetrated beneath the patella and extended on both lateral aspects nearly to the popliteal space. In a small area this upward extension invaded the cortex of the femur. The curious outlines of the recurrent mass suggested invasion of veins. There is a marked structural change in the tumor, a change of considerable significance. One portion consists of dilated blood vessels containing leukocytes but essentially no red blood cells. These vessels are surrounded by perithelial spindle shaped cells which merge gradually into sclerosing fibrous tissue without definite demarcation between the perithelial cells and the fibroblasts. It has many characteristics which would lead one to regard it as neoplastic granulation tissue. These capillary channels merge imperceptibly with channels lined by large, thick, irregularly fusiform, very hyperchromatic, malignant tumor cells (Fig. 7). The nuclei are large and mitoses are numerous. About some of the vessels the perithelial cells are arranged in whorls of malignant appearing cells inseparable from similar cells lining the channels. Where neoplastic vessels are less numerous the interstitial tissue shows fibrosing tendencies and ranges in appearance from cellular fibroma to spindle cell sarcoma. Epulis giant cells are no longer found. Taken as a whole the structure is that of malignant granulation tissue sarcoma.

The long history in this case is very much against the idea that there was anything malignant about the initial lesion. We cannot avoid holding the suspicion that this malignant tumor arose in a benign lesion after multiple curettages.

CASE 6. Material from the case of J.N., reported in detail by Stone and Ewing [13] is still available for study. We have reviewed this material in view of the assertion of Geschickter and Copeland that the tumor was not a giant cell tumor but a chondroblastic sarcoma. We are unable to find evidence that it was a cartilaginous tumor.

Comment: Since the case was reported in considerable length by Stone and Ewing we see no reason to duplicate the report. We find the early sections typical of giant cell tumor. The bone formation reported is a poorly developed calcification in an area of not very cellular hyaline osteoid tissue and is fully consistent with processes that may occur at the periphery of giant cell tumors or in pure inflammatory disease of bone. The "stroma" is not very cellular and the intercellular substance is quite fibrous, in some places almost keloidal in character. Although from the material remaining we are unable to trace the evolution of the malignant change in the recurrent tumor, material from the amputated specimen is still available. The malignant tumor present is similar to those described in other instances of this same change. The cells are loose, spindle or polyhedral elements, arranged in syncytial or pseudosyncytial fashion, rather delicate and hydropic appearing, and of an appearance suggesting that of condensing mesenchyme. Giant cells of the epulis type are absent. The tumor is quite different from known varieties of true osteogenic sarcoma.

CASE 7. E.M., female, aged 18 years, entered the Memorial Hospital on March 20th, 1928. Seven months prior to admission she first noted painful swelling of the right knee. This became progressively worse and she consulted a physician who performed a curettage after the roentgen diagnosis of giant cell tumor of the tibia. This curettage was not complete because of failure to secure hemostasis. Three weeks later a second curettage was likewise unsuccessful for the same reason. The patient was then referred to the Memorial Hospital. On admission the wound was found filled with gauze packing and was obviously infected. Radiographs taken after admission were indefinite; the tumor was considered malignant but it was also stated that an infected giant cell tumor, recurrent after curettage, could present the same features. Under external radiation, for a short period, the tumor fungated. Attempts to control growth by caustics failed, infection increased, and on May 26th, 1928, the leg was amputated despite roentgenographic signs of pulmonary metastases. The patient died 3 months later with extensive pulmonary disease.

Comment: The first sections show in our opinion a giant cell tumor, but like King's case and others of our own, we believe there were already definite evidences of malignant tendencies. In

fact there are areas in the first specimen that appear just as malignant as does the material from the amputation. Although the diagnosis of giant cell tumor is accepted we cannot say that it was ever benign. At the same time, in none of its characteristics does it resemble the usual osteogenic sarcoma. This case is carried in the registry of bone sarcomas as an osteogenic sarcoma but we feel that such tumors belong in a category by themselves.

Sections from the amputated leg show a tumor of pleomorphic structure (Fig. 8). There are large numbers of giant cells of the type seen in benign giant cell tumor. Some of these lie free in spaces. Some line vascular channels. Some lie free in vascular spaces. Many of the giant cells are continuous with reticular, loose, delicate appearing edematous tissue resembling mesenchyme. The reticular tissue passes, without lines of demarcation, over into small fusiform cells resembling fibroblasts. Some of the reticular cells are continuous with structures that resemble primitive vascular channels; the latter are lined by reticular tumor cells, interspersed with typical multinucleated giant cells. Maturation of fibroblasts and production of collagen are present to a very scanty extent. At intervals, among the loose reticular cells, a markedly hyperchromatic cell with a deeply staining ovoid nucleus is seen. Such cells are also found at intervals mingled with the reticular cells lining the vascular channels. Some contain central vacuolar spaces resembling those of primitive vascular channels. There is evidence that these hyperchromatic cells multiply by atypical multiple mitosis, producing large giant cells with several hyperchromatic, large irregular or giant lobular nuclei. Occasional cells of this type are seen in the vascular lumens. The tumor on the one hand definitely forms blood channels and, on the other, fibroblastic elements that are associated with the laying down of fine collagen fibers. Thus it resembles an angioblastic granulation tissue sarcoma of a peculiar type. In no areas are ossifying tendencies observed.

Discussion and Conclusions

We have been unable to arrive at a satisfactory descriptive term for these malignant giant cell tumors. It is perhaps best to retain the designation "malignant giant cell tumor" since it carries at least a definite connotation. Efforts to establish hard and fast lines

of distinction in cells involved in bone development have made the description of the histogenesis of bone most complex, and through the ultracytological analyses of various histologists cells have acquired individualities which they probably do not merit, or merit only in a transient sense.

We are unable to separate the cell elements of giant cell tumors from the connective tissue cells and vessels which are involved in the histogenesis of bone and which evolve in different directions dependent on the physicochemical conditions of the period. We feel much sympathy with the views of Moschcowitz,[27] as expressed in his paper on the relation of angiogenesis to ossification, and see many similarities in the development of malignant giant cell tumors. We venture to doubt that one can specifically state that a giant cell tumor is a tumor of giant cells, intervening connective tissue cells, or angioblastic elements, or that the malignant giant cell tumor is a sarcoma of giant cells, angioblastic elements, or an endothelioma or a granulation tissue sarcoma, since we find great difficulty in separating the elements of the tumor into permanent entities. In our own cases no true bone formation has been observed and yet it would surprise no one if a tumor with this evolutionary pattern should appear. Despite the tendency, which we also have followed, to reject as giant cell tumors of malignant type those tumors where cartilage has appeared in the metastases, still their rejection may not be necessarily warranted.

Thus the form assumed by the process known as giant cell tumor will be found to depend on the nature of the circumstances, physical and chemical, which have initiated the process, plus the extrinsic factors that interfere with its normal evolution. Until better understood, the interpretation of giant cell tumor and its malignant evolution must remain in a speculative phase.

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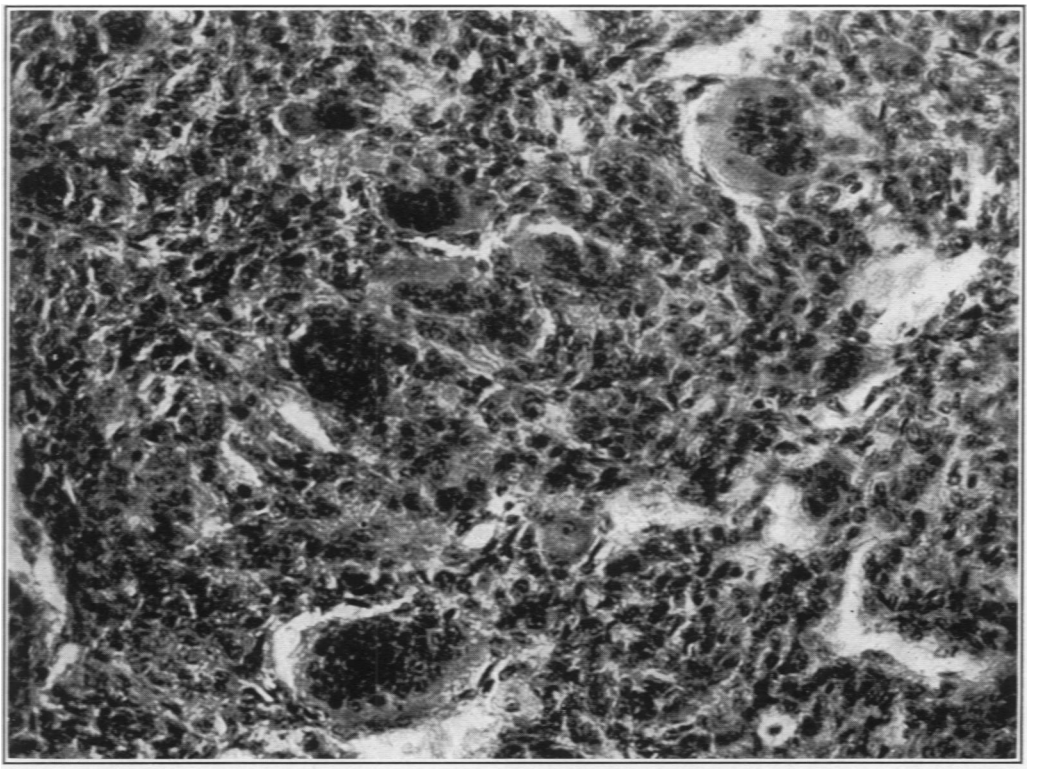
DESCRIPTION OF PLATES

PLATE 130

FIG. 1. Typical benign giant cell tumor.

FIG. 2. Malignant recurrence of the tumor illustrated in Figure 1.



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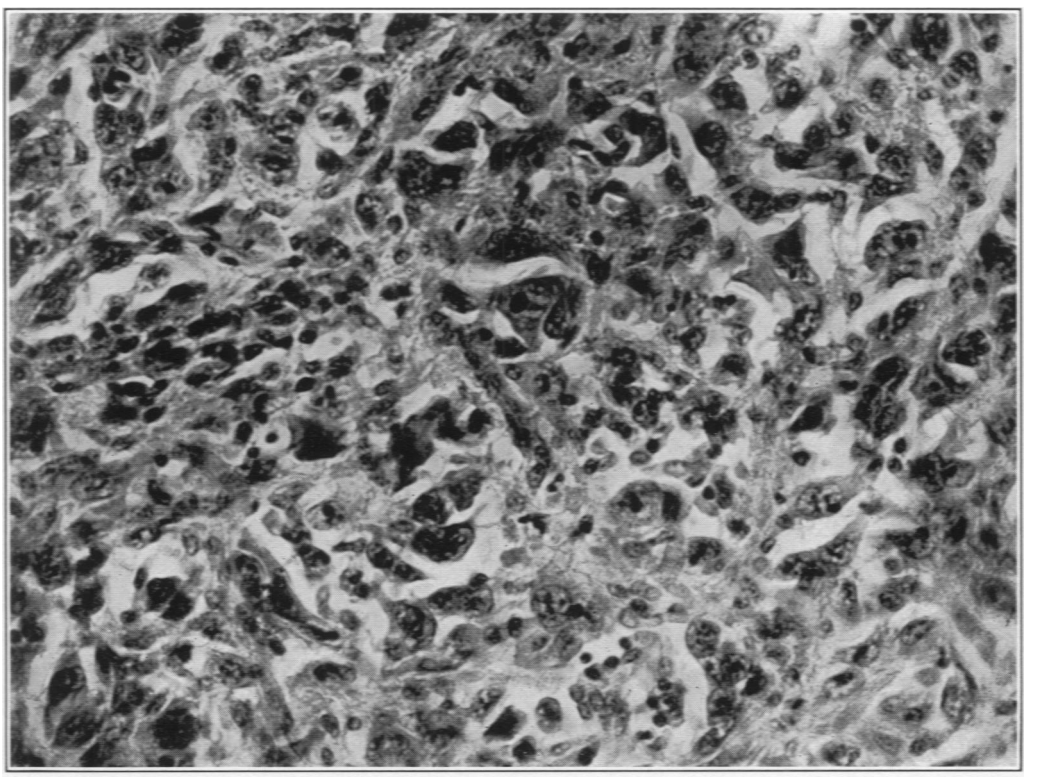

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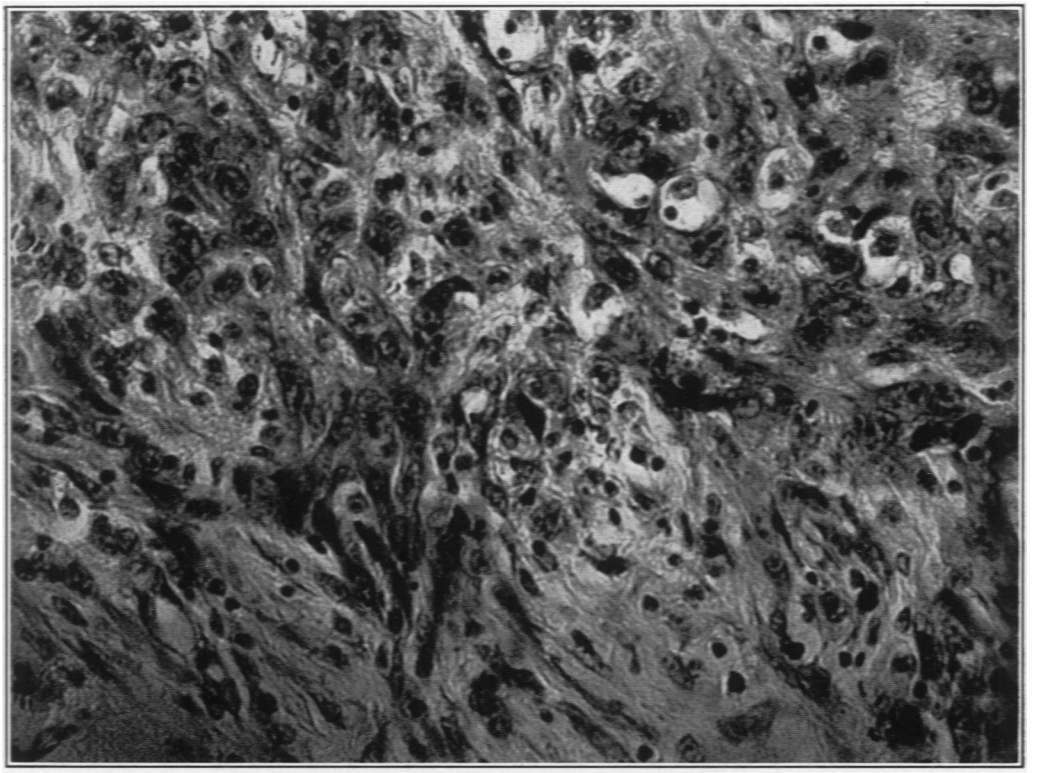
Stewart, Coley and Farrow Malignant Giant Cell Tumor of Bone

PLATE 131

FIG. 3. Malignant recurrence of the tumor illustrated in Figure 1. Syncytial cells growing in a manner suggesting the growth of endothelium.

FIG. 4. Typical benign giant cell tumor.



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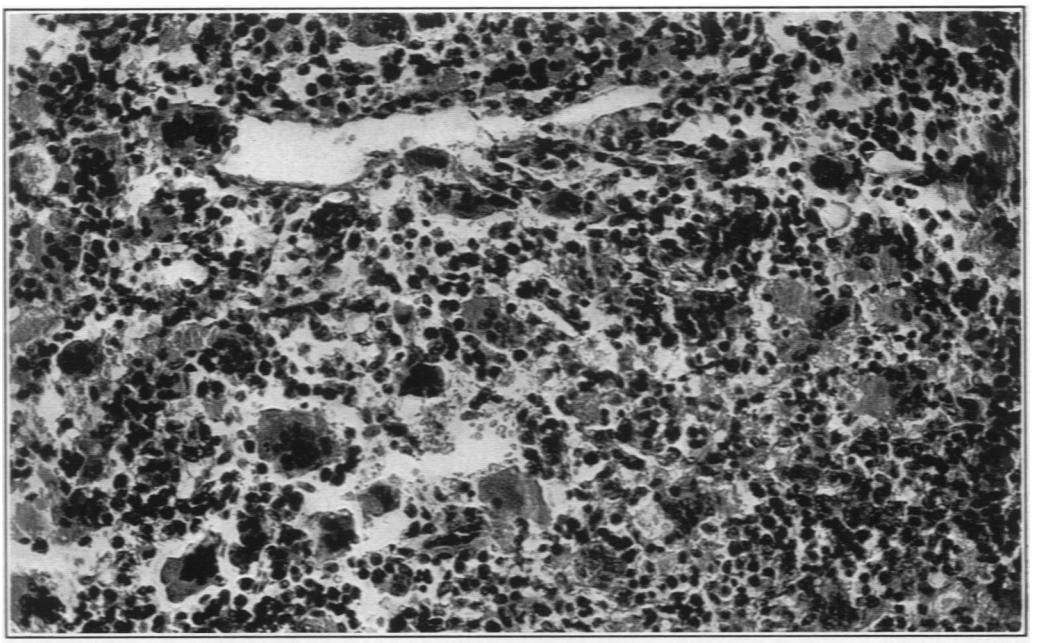

4

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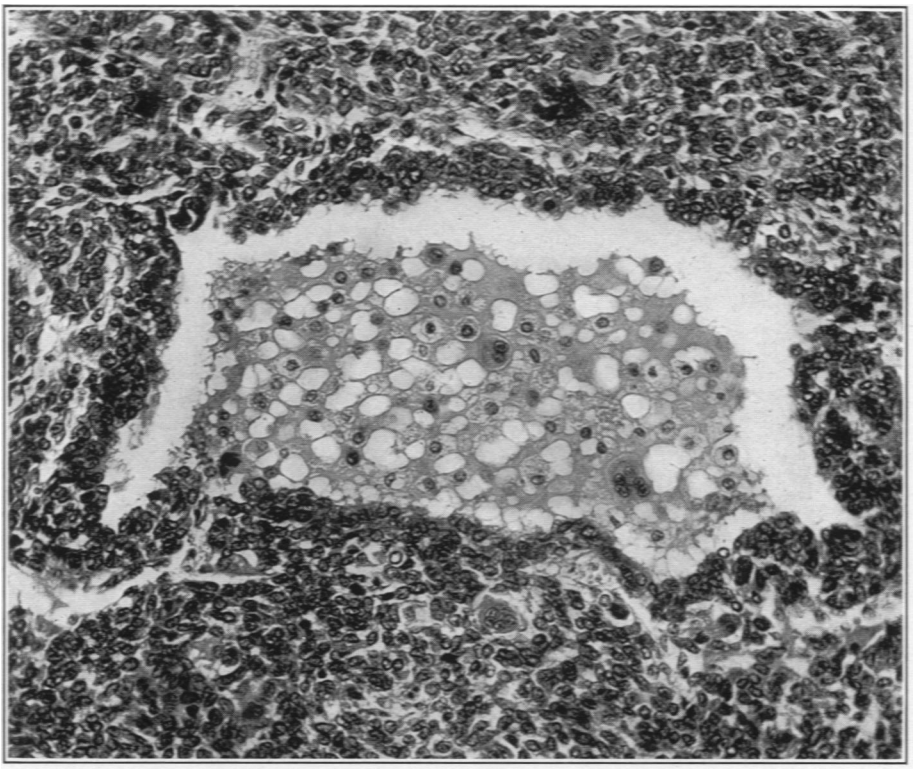
PLATE 132

FIG. 5. Area of peculiar small spindle cells resembling condensed pseudosyncytial mesenchyma. Malignant course suggested on basis of such area.

FIG. 6. Diffuse recurrent tumor. Growth in sheets of pale syncytial cells resembling an epithelial or a diffuse endothelial tumor.



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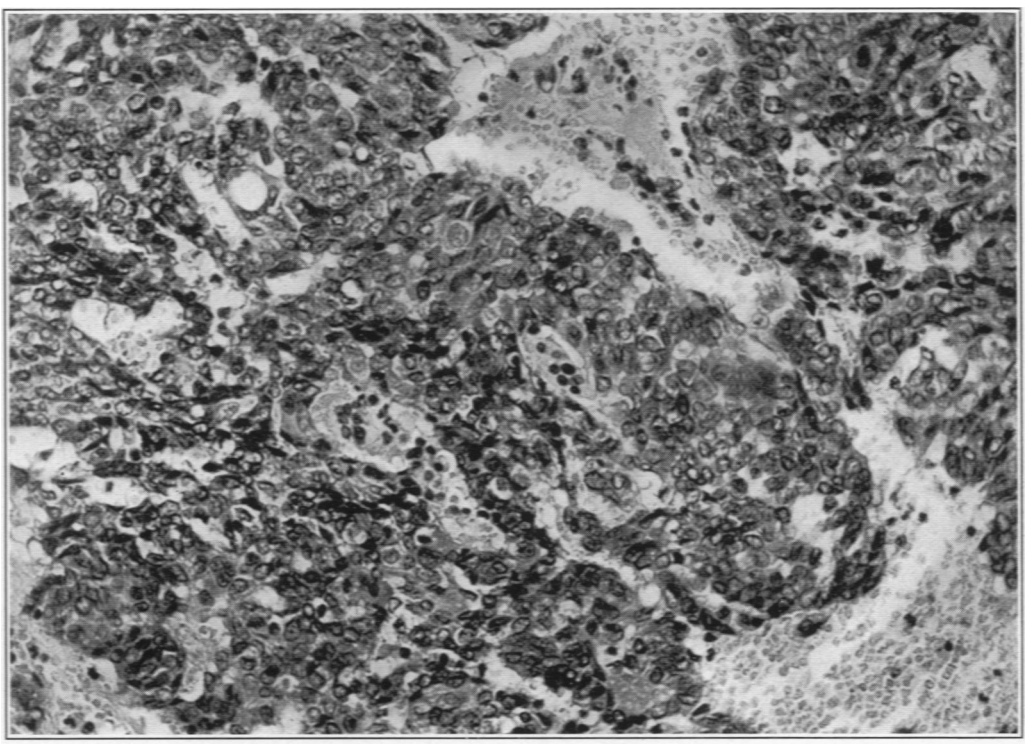


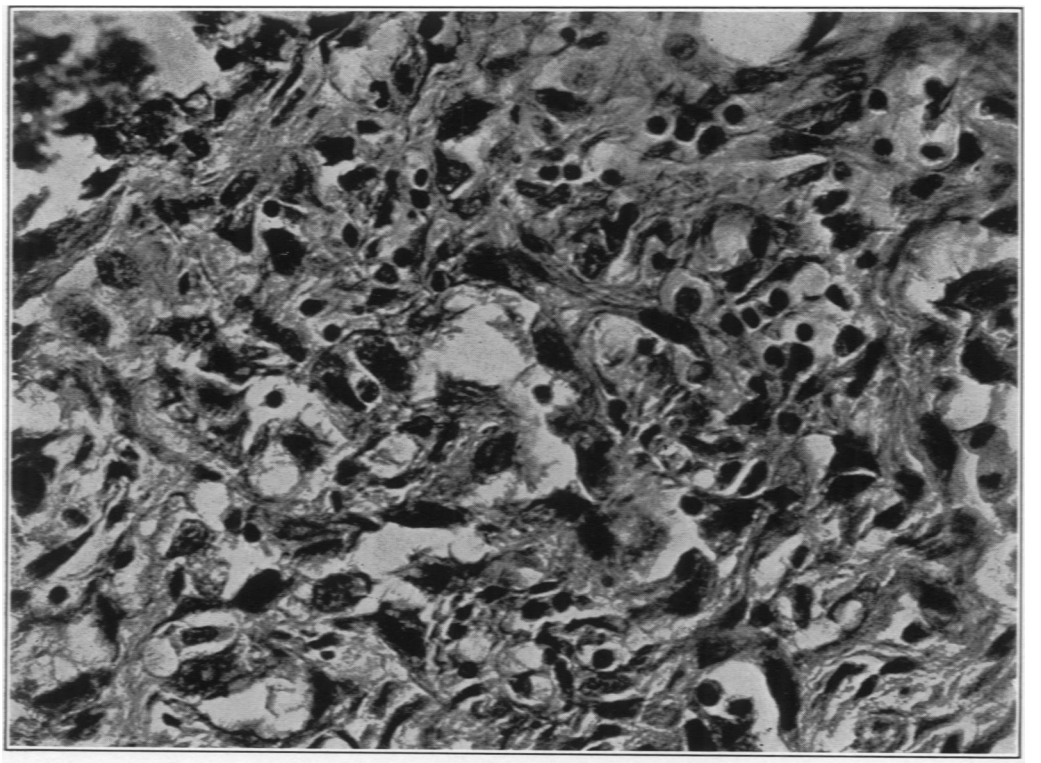
6

Stewart, Coley and Farrow Malignant Giant Cell Tumor of Bone

PLATE 133

FIG. 7. Marked angioblastic characteristics in the recurrence of a benign giant cell tumor.

FIG. 8. Malignant giant cell tumor. Distinct angioblastic characteristics.



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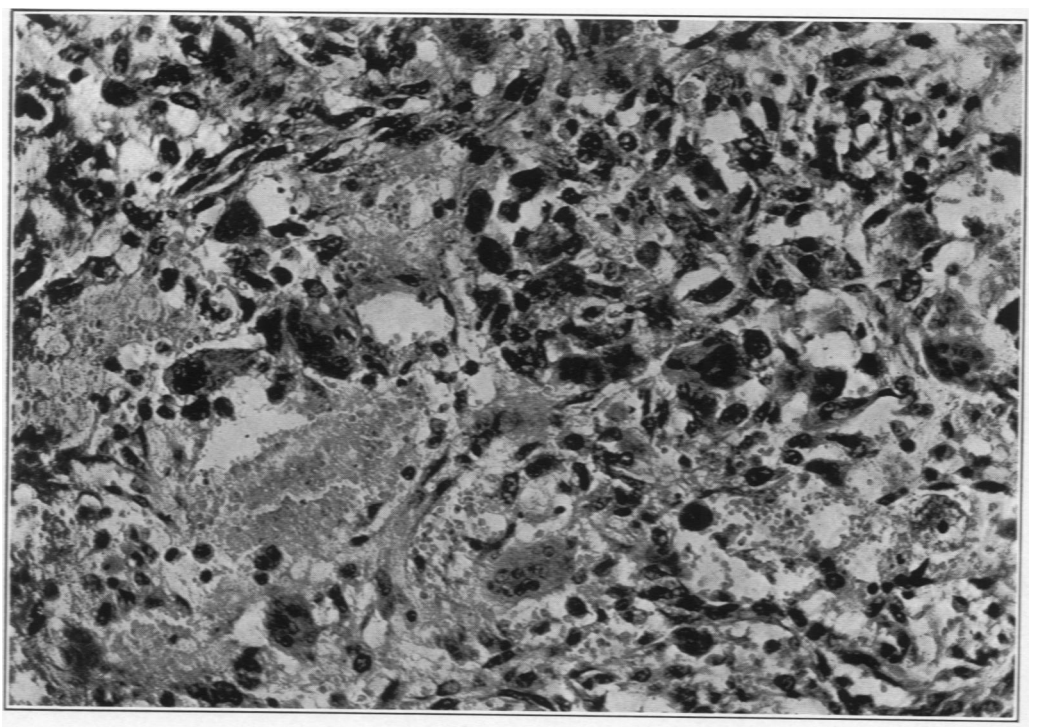

8

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Malignant Giant Cell Tumor of Bone