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Giant cell tumor of bone

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GIANT-CELL TUMOR OF BONE

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After a cursory perusal of any textbook or monograph, I have always read the introduction before making any concentrated effort to digest the contents. The incentive prompting an individual to write any document is most interesting to me, and this usually manifests itself in the author's explanatory introduction or preface. Many times it is because the author sorely feels the need of a more comprehensive work on a particular subject, other times because he desires to incorporate for posterity certain observations and facts noticeably omitted by other authors, or even, perhaps, to give vent to a literary inclination. I must confess that none of these reasons prompted my work. This paper is required - but I have attempted to present a none-to-well understood subject, in as complete a manner as is possible under existing conditions and restrictions. None of the material included herein is original, but numerous references to journals, textbooks, and monographs have assisted me in familiarizing myself with the countless sources of information at the disposal of one imbued with the scientific curiosity and ambition which if exercised, will elevate the "symptom-treater" to a more scientific student of medicine.

I am grateful to the office of Drs. Lord, Schrock and Johnson, and the University Hospital, for the use of their files and the roentgeno-gram photographs used herein.

Pare (75) in the 16th century described benign tumors of the maxilla
which were cured by excision, Beclard (7) in 1827 a medullary, vascular, "not
cancerous" bone tumour, and Warren in 1837 a benign central tumor of the femur.
Lebert (58) in 1845 recognized giant cells in certain medullary tumors, and
described yellow deposits in these masses as xanthosis, but did not differ-
entiate them from malignant sarcoma. Robin (81) in 1849 described two
cellular elements of the medulla of bone which he called "cellules medullaires"
and "cellules myeloplaques". The former were spherical or polyhedral, 0.015-
0.018 mm. in diameter, with a single nucleus of 6-7 microns, the cytoplasm
granular. They were more abundant in the young than in the old in the inter-
stices between the fat cells and vessels of the bone marrow. The latter type,
"cellules myeloplaques", he thought were a minimal normal constituent of adult
and aged bone, becoming tumorous when in abundance. They are described as
polygonal or irregular spheroids, 0.05-0.08 mm. in diameter, with finely granu-
lar cytoplasm containing six to ten nuclei, each of whicy had one or two
nucleoli in their center. This is described first in a case of supposed
"spina ventosa", an expansile tumor of the tibia. The term "spina ventosa"
had been used also by Dupuytren for a similar lesion along with "fongus hema-
toids". Eugene Nelaton (71) considered that Robin deserved credit for the
real identification of the "myeloplaques" as normal minor constituents of bone
marrow. Lebert (58) and Muller (70) had called the giant cells "mother cells";
Kolliker (54) considered them osteoclasts.

Nelaton (71) in his thesis of 1860 offered a simple but none the
less adequate definition of this neoplasm - "tumeur a myeloplaxes" - a
particular kind of accidental tissue production whose fundamental architecture
is characterized, not by simple presence of, but by the predominance of the

anatomic elements called "myeloplaques".

From this point he proceeded to indicate four essential types of
this class of tumor:

> (1) The solid or meaty (typical);
>
> (2) The fibroid, with more fibroblastic proliferation
>   in the stroma;
>
> (3) The "graisseuse" or xanthoid;
>
> (4) The vascular.

The cystic changes not uncommonly seen were considered then as simple
degeneration of the tumor.   Such as showed hemorrhage into these cystic areas
were considered the result of natural extravasation from the new-formed vessels
of the tumor (probable so-called bone aneurysm).

Gross (41) in 1879 reviewed the history and morphology of giant-cell
sarcoma emphasizing, against Billroth's opinion, the benign prognostic import-
ance of giant-cell structure, and showing in four fatal cases that this tumor
might become malignant.   Gross' description of the origin, structure, clinical
characters, and treatment of bone sarcoma stands today as the classic contri-
bution on this subject.

v. Bergmann, Mickulicz and v. Bramann (9) recognized the benign nature
of giant-cell tumors during the remaining few years of the 19th century.

Hinds (47) in 1898, believing this tumor to be benign, successfully
treated it by scraping and reported no recurrences after eighteen years of
careful study.

Bloodgood (12), Mallory (64) and Coley (23) are especially identified
with the exhaustive study and recognition of giant-cell tumors, during the
first part of the twentieth century.

Various names have been given this lesion, beginning with tumeur a myeloplaxes by Nelaton (71), myeloid sarcoma - a name almost universally used from 1870 to 1910, and still used in British literature, hemorrhagic osseous dystrophia, giant-cell sarcoma, benign giant-cell sarcoma of the epulis type, giant-cell sarcoid, giant-cell tumor (Bloodgood (12) , osteitis fibrosa cyslica (von Recklinghausen), hemorrhagic osteomyelitis (Barrie (2), and osteoclastoma (32)(36). The term most generally used today is giant-cell tumor or giant-cell sarcoma of the epulis type. Bloodgood (12) in 1912, after many years of extensive study and analysis of the condition writes, "It is my opinion that it might be well to drop the term 'giant-cell sarcoma', as it gives a wrong impression of the malignancy of the lesion, and use, at least temporarily, the designation 'giant-cell tumor'." Mallory (64) also doubted the correctness of the term giant-cell sarcoma. Stewart (86) disagrees with Bloodgood who classifies them as benign giant-cell tumors, and also with Barrie who characterizes them as a type of hemorrhagic osteomyelitis. Stewart believes that the name myeloid sarcoma, as introduced by Paget (73) nearly seventy years ago, on account of the naked-eye resemblance of the tumor to red marrow, is the best name to apply to this group of tumors; and that since none of its constituent cells is derived from specific bone marrow cells, the name "myeloma" is inaccurate and should be dropped. As it stands today, however, the majority of authors are using the Bone Registry's Classification and refer to this lesion as the benign giant-cell tumor of bone.

The question of the etiology of giant-cell tumors is at first glance intricately interwoven with an academic question: Is giant-cell tumor a neoplasm or a product of inflammation and repair? The acceptance of the name giant-cell tumor as a substitute for all other names of this lesion is not to be looked upon as a proof of the neoplastic nature of the lesion; the term "tumor" is used here merely in a clinical sense, that is, to indicate a swelling, inasmuch as the pathological anatomical sense of this word is at present not entirely clarified. The question of whether a giant-cell tumor is a true blastoma or merely an inflammatory process follows an old trodden path of discussion. Alexander and Crawford (1) state that it has at various times been considered the result of bone destruction due to spirochaete, tuberculosis, infectious bacteria and parasites, trauma, malnutrition, and metabolic change. As it stands today, the concept of the disease known as giant-cell tumor divides investigators in two opposing classes. To one belong those who look upon giant-cell tumor as a true blastoma and to the other those who see in it merely a product of inflammation and repair in bone. Kolodny (55) believes that since the view upon giant-cell tumor as a true blastoma is supported by tradition, the burden of proof in this dispute lies on the promulgators of the inflammatory nature of giant-cell tumors. The leaders among these are Mallory, Codman, and Barrie in this country and Lubarsch and Konjetzny in Europe. Mallory (64) has long maintained that the giant cells of the giant-cell tumor are not an integral part of the lesion but only a biological reaction of the large mononuclears of the blood, the so-called endothelial leucocytes, which are found wherever retrograde changes are going on. As a reaction to calcium salts absorption, these endothelial leucocytes fuse and form the giant cells.

Aside from these giant cells, no cells occur in these lesions which are not met with in ordinary inflammatory processes.

Codman (21) sees in the giant-cell tumor a repair process following intra-osseous hemorrhages due to rupture of nutrient vessels. In Codman's opinion the tendency of this disease to form expansive tumors does not warrant considering it as a neoplasm any more than does the enlargement of an aneurysm. Barrie (6) contends that the giant cells encountered in these lesions must be disregarded in attempting to reach a decision whether a process in bone should be considered either neoplastic or inflammatory, from the microscopist's angle of investigation. "Such cells," he says, "are the known accompaniment both of inflammation and neoplastic disease; their presence, therefore, cannot be affirmative of tumor growth"

Early efforts at repair in any non-suppurative area of osteolysis exhibits a picture similar to the process termed hemorrhagic osteomyelitis or giant-cell tumor. The same type of hemorrhagic granulation tissue structure is beautifully illustrated in early efforts at repair in fractures in bone. These facts, Barrie believes, should have weight against a diagnosis of neoplasm.

Steward (86) critically attacks Barrie's theory and emphasizes that myeloid sarcoma (giant-cell tumor) is a specific tumor taking origin from the fibrous tissue framework of the bone, and characterized by the invariable presence of osteoclast-like giant cells in large numbers, the latter being an integral and essential part of the tumor, making it unnecessary to assume that some foreign substance must be present to account for them.

Strongly substantiated by results of special investigations are the opinions of Lubarsch (62) and Konjetzny (56). Years ago Lubarsch had pointed out that the new growths observed in the course of osteitis fibrosa are of purely inflammatory nature. On the side of histological preparations Konjetzny showed how an intermedullary hemorrhage calls forth a reactive proliferative process. The product of this proliferative of the bone-marrow which can be compared to granulation tissue, consists histologically of all the elements encountered in lesions known as giant-cell tumor. The clinical course and the radiological findings are very closely related to those of giant-cell tumors. In the course of the natural life of this granulation tissue there is a stage of differentiation when fibrous tissue, osteoid, and sometimes osseous tissue takes the place of the hemorrhage after it has subsided, the blood clot organized, and all the foreign elements removed. Thus, Konjetzny concludes that the apparent tumor is merely a "chronic resorptive process."

The opponents of the opinion that giant-cell tumors are true blasto-mota emphasize the following points of the histology of giant-cell tumors as supporting their views: the absence of pleomorphism of the cellular elements and of hyperchromatism of the nuclei and the absence of excess of mitoses; the differentiation of the cellular stroma into dense fibrous tissue poor in cells; the uniformity in the size, shape, and chromatin content of the giant cell nuclei; the relation of the giant cells to extravasations, indicating their role in resorption; and the constant presence of old blood pigment. All these features are not inconsistent with the probable inflammatory nature of these lesions. It is generally conceded how difficult it is to distinguish histologically between a new growth in osteitis fibrosa and

entirely independent lesions considered as giant-cell tumors. This fact
alone is sufficient evidence to raise doubt as to the right by which giant-
cell tumor is occupying its place in oncology. On the other hand, there is
no sufficient evidence accumulated to support the contention that in all
cases of giant-cell tumor the lesion is a process of inflammation and repair.

The etiology of the typical giant-cell tumor is readily understood
if one accepts the new-growths observed in the course of osteitis fibrosa
cystica as giant-cell tumors. The main complex of osteitis fibrosa is the
disappearance of haemotoblasts and fat cells from the bone-marrow with a
subsequent overgrowth of the fibrous stroma and lymphoid elements. This is
accompanied by a simultaneous resorption of bone and new formation of osteoid
tissue, and this leads later in the course of years to fractures and de-
formities. Frequently, in the course of the disease, one encounters for-
mation of cysts. Hemorrhage into the cysts may lead to an overgrowth of
masses, resembling granulation tissue, which may enlarge and finally be
recognized as giant-cell tumors. The frequent history of an antecedent mild
trauma in giant-cell tumors has led to the recognition of trauma as an im-
portant etiological factor.

Barrie (6) reports that in all of twenty-eight cases one could
elicit a history of recent or ancient trauma. Geschickter and Copeland (39)
on the grounds of embryologic observations show how trauma acts in produc-
ing the bone cyst and giant-cell tumor. They maintain that trauma, in
disrupting the cortical blood supply produces an imbalance between osteo-
clastic proliferation in the medulla and relative compact bone in the cortex.
This osteoclastic activity to be of clinical significance, must be engrafted
upon a normal histogenic process. It must be superimposed upon osteoclastic

resorption of calcified cartilage in the metaphysis in young patients to
cause a bone cyst, and upon a similar in the epiphysis in adults to produce
a giant-cell tumor. That additional metabolic factors may enter into the
production of this imbalance is shown by the analysis of multiple giant-
cell tumors and bone cysts and the studies on the serum calcium and phos-
phorus in parathyroid disturbances. The work of Jaffe has shown that in-
crease in parathyroid hormone alone does not produce true tumors of this
type although giant-cell areas and osteitis fibrosa-like tissue may be
formed in the bone in animals fed with an excess of this substance. It is
apparent, however, from the studies recorded by Geschickter and Copeland
(39) that the age of the patient, the site of the injury, the rate and
extent of cartilagionous ossification at the end of the bone and the nature
of the blood supply in the affected regions are the predominant factors in
the development of bone cysts and giant-cell tumors.

Much depends upon the individual concept of trauma. Hemorrhage
into the bone-marrow may lead to cyst formation. Organization of the intra-
medullary hematoma with the appearance of the peculiar medullary granulation
tissue and expansion of the bone will then form the giant-cell tumor. Very
slight traumatization is frequently sufficient for the appearance of medullary
hematomata. While it is usually thought that fractures are not the cause
but merely a complication of giant-cell tumor and osteitis fibrosa, it is
probable that fissure fractures or, better, infractions with the rupture of
nutrient vessels may lead to the formation of giant-cell tumor.

Kolodny (55) gives a most complete description of the anatomical consideration of giant-cell tumors. The gross anatomy of giant-cell tumors depends largely upon the destructive and productive processes of the involved bone. The tumor tissue during its period of growth constantly destroys the bone while the periosteum lays down an advancing shell of new bone, thus preventing the tumor mass from an early perforation of the bone and an involvement of the adjoining structures. It is due to a combination of these two opposing reactions of the involved bone that the giant-cell tumor is an expansible but not infiltrative or invasive lesion encapsulated in a bone shell. Eating its way into the bone, the tumor tissue destroys the bone from within the medullary cavity, gradually expanding the old cortex, while a few more or less thick bony trabeculae running in various directions line the cystically expanded bone shell simulating beans, supporting the whole structure. It is this structure that causes the most characteristic "soap bubble" appearance in the roentgenogram. The investing capsule of the giant-cell tumor is furnished by the new formed bone shell and the periosteum. Ewing (35) shows that with the increasing growth of this reddish jelly-like tumor mass, the bony shell may eventually become thin and allow passage of the tumor tissue, but there is seldom any tendency toward invasion of the soft parts. Long after the bone shell is thus perforated, the periosteum still continues to envelop the tumor until a very advanced development of the tumor or a pathological fracture hastens the perforation of the periosteal capsule. This is in marked contrast to a malignant bone tumor where the perforation of the bone and the periosteum occurs very early.

The articular cartilage is very resistant in giant-cell tumor as it is in osteogenic sarcoma. It is most unusual to see the articular

cartilage destroyed by tumor tissue even in the advanced stage. An actual direct involvement of the joint cavity by tumor tissue is even less frequent than in osteogenic sarcoma; it occurs in pathological fracture and in very advanced cases. However, Gross (41) reported that the cartilaginous surfaces of the joint may be reached and absorbed and the joint surfaces may collapse from simple absorption, but without infiltration. Indirect involvement of the joint cavity may occur by tumor tissue spreading along intra articular ligaments, or from bone to bone along ligamentous attachments.

The gross appearance of the giant-cell tumor depends greatly upon the phase of the lesion. The typical giant-cell tumor consists of solid portions and numerous small cysts. The solid portions are very friable, crumbly, somewhat granular masses, varying in color from yellow and light brown to dark red. On incision, the tumor tends to extrude like granulation tissue. The texture of the growth becomes more dense with the approximation to the periphery and capsule. This vascular, soft, readily oozing, and frequently profusely bleeding tumor, resembling currant jelly, is entirely confined within the bone shell, it lies there loosely and can be easily scooped out by a curette. With the aging of the tumor or after radiation therapy, the tumor mass enters a cicatrizing phase. The reddish jelly-like tumor mass changes gradually, beginning at the periphery, to a more opaque and firm mass, while in the central portion the old juicy stroma prevails. Some varieties of giant-cell tumors may be solid and firm throughout from the commencement and because of their frequent peculiar yellow color due to the presence of lipoid material, they have been designated as anthomata. The various phases of giant-cell tumor are a result of advanced differentiation of the soft immature tumor tissue. All successive processes of repair can be traced here.

An attempt has been made to differentiate several varieties of giant-cell tumors which differ from the typical tumor grossly as well as histologically. Xanthoma is designated a variant of giant-cell tumor in which the presence of considerable fatty detritus lends the tumor a yellow appearance. Ewing (35) believes that the tumor may exhibit the features of a myxoma or myxosarcoma, being more or less translucent and elastic. It seems probable that the so-called myxomas of the marrow cavity have mainly this origin (57). The white giant-cell tumor is a rare but well recognized variation. Stewart (87) reports a case and in his discussion states the sarcomas of bone, which are white in color, are almost invariably highly malignant. He regards the maroon color as a secondary, even accidental characteristic, due partly to increased vascularity and partly - and more especially - to extravasation of blood.

While practically all the modern descriptions of myeloid sarcoma insist on the constancy of this color characteristic, and only admit at most that portions of the tumor may be white, Sir James Paget (73) in 1853 states quite unequivocally that "the tumor may be all pale - - - ". His description reads: "On section, the cut surfaces appear smooth, uniform, compact, shining succulent, with a yellowish, not creamy fluid. A peculiar appearance is commonly given to these tumors by the cut surface presenting blotches of dark or livid crimson, or of a brownish or a brighter blood colour, or of a pale pink, or of all these tints mingled, on the greyish-white or greenish colour basis. The tumour may be all pale, or have only a few points of ruddy blotching, or the cut surface may be nearly all suffused, or even the whole substance may have a dull modena or crimson tinge, like the ruddy colour of a heart or that of the parenchyma of the spleen."

Giant-cell tumors in whose texture islands of cartilage are encountered, are said to arise from absorption of misplaced islands of cartilage, when the released cartilage cells acquire a neoplastic character. When the vascularity of the tumor is not confined to the central portion, but is present in the largest portion of the tumor, it then represents the telangiectatic variety of giant-cell tumor. The clinical importance of such a differentiation of variants of giant-cell tumor is questionable, since there is no sufficient evidence accumulated to support the contention that these variants differ greatly in their clinical course. Furthermore, such variants cannot be distinguished before the tumor is submitted for a pathological examination, gross or histological. The appearance of cysts in an advanced giant-cell tumor is not uncommon. This also occurs after radiation therapy, where in the central portion extensive necrosis and cyst formation filled with blood clot and serous fluid occurs.

The cysts are filled with blood or chocolate-colored fluid, or an opaque, brownish, or greenish mucinous mass, a greenish or grayish serum, evidently the product of various stages of decomposition of blood extravasations.

Kolodny (55) reports that the histological structure of the typical giant-cell tumor consists of two leading elements: the giant-cells, and the stroma. The latter consists of numerous various sized blood spaces and exceedingly thin walled capillaries suspended in a very loosely woven net of spindle, round or polygonal cells with large vesicular nuclei. One of the most characteristic features of a giant-cell tumor is the absence of pleomorphism of the cells of the stroma. Geschickter and Copeland (39) report that the round cells outnumber the spindle cells in every instance in this typical tumor. This small round cell has a relatively large nucleus and a small amount of cytoplasm. There is a definite nuclear wall and a nucleolus. There is, apparently, a definite relationship between the round cell of the stroma and the giant cell. In the first place, when the giant-cells predominate in the tumor the round cell prevails in the stroma. More-over, the nuclei of the giant cell always have the same general form and staining characteristics as the nuclei of the round cells. The only impor-tant variation is the tendency for the giant cells to have a more acidoph-ilic cytoplasm with occasionally a greater concentration of chromatin in the nuclei and other signs of early degeneration. This could be accounted for by the age of the giant cell, the inference being that the giant cells are formed by agglutination of the round cells in the stroma (39)

In the central portion of the tumor, fresh extravasations of blood as well as hemosiderin can be found near the periphery of the bone shell. Geschickter and Copeland (39) also report that red blood cells in a well preserved state are scattered through the tumor more often unenclosed than enclosed by endothelial walls. The typical giant-cell tumor is thus both

hemorrhagic and vascular, newly formed vessels being by no means rare. Areas of organizing hemorrhage are frequent, and bordering on these is loose edematous tissue intermingled with areas like those of osteitis fibrosa. The giant cells average over 30 per field under the low power, with the number of nuclei in each cell varying from fifteen to two hundred. The cells range in size from ten to one hundred microns and may or may not have distinct borders to the cytoplasm. Kolodny (55) states that the histogenesis of this peculiar cell is still a subject of discussion; the theory in vogue at present is that these cells originate from the endothelium. Barrie and his associates (2,3,4,6,42) regard giant-cell tumors as a chronic, hemorrhagic, non-suppurative osteomyelitis, probably of traumatic origin and consider that the histological structure is indistinguishable from that of granulation tissue and that the giant cells, of endothelial origin, are scavengers formed for the purpose of absorbing and removing the detritus resulting from bone destruction.

According to Mallory, there are two types of giant cells, a tumor giant-cell and a foreign body giant-cell. The former are large, clear, bladder-like cells, with distinct outline but staining faintly, within which are multiple nuclei, which stain deeply and are situated in the center of the cell. They are true tumor cells resulting from multiple mitosis and signify rapid growth. The second type are as a rule smaller, their cytoplasm fairly abundant, sharply defined and staining deeply with acid dyes. The nuclei are smaller, uniform, without mitosis, and are often in clusters near the periphery of the cell. They resemble osteoclasts and are merely a reaction to the presence of foreign bodies and are due to the fusion of endothelial leucocytes.

Stewart (86) agrees with Schafer (82) that the specialized fibrous
tissue framework also provides the multi nucleated osteoclasts, whose func-
tion is bone absorption, and that they probably represent a specific form
of giant-cell. Goforth (40) believes that two mesoblastic tissues, the
osteoblastic or osseous tissue proper, and the fibroblastic, or specialized
fibrous tissue framework intimately associated in bone structure, are the
elements composing giant-cell tumor. Carnegie Dickson (31) and others,
think it probably arises from the reticulum of the marrow. Kolliker (54)
and Gross (41) believe it originates from the osteoblast. Jordan (50) who
has made a very careful study of this subject believes it may arise in either
of the last two ways.

No conclusive work has been universally accepted as to whether the
giant cell is an integral part of the tumor, or as Barrie (3) believes, a
cell attracted to the tumor to remove the numerous particles present, due
to extensive disintegration. Whatever opinion one may hold, one cannot deny
that the structure of a typical giant-cell tumor with the abundant giant
cells tied up like knots at the junctions of the endothelial strands suggests
that the giant cells play an important role in the composition of the tumor.
It is true that, when needed, the giant cells take up the function of scaven-
gers and it is not uncommon to find, in giant cells, fatty detritus, remnants
of blood cells, blood pigment, and even small spicules of bone.

Geschickter and Copeland (39) are of the opinion that giant cells
with few nuclei, relatively small and sparsely distributed, are not typical
of the benign giant-cell tumor, but are more characteristic of osteitis
fibrosa and osteogenic sarcoma.

Ewing (34), in describing the giant-cell tumor and its variants, emphasized that a study of the stroma offers a standard for differentiating between giant-cell tumor and medullary osteogenic sarcoma, secondarily containing giant cells, and is inclined to restrict the importance of the giant cells themselves.

Spicules of bone, some undergoing destruction and others representing a healing reaction, are frequently found near the margin of the tumor or its capsule. Kolodny (55) believes that to avoid errors in diagnosing a giant-cell tumor from the histology, one has to keep in mind the various deviations from the typical giant-cell tumor structure. In the so-called xanthoma, the resorption of a considerable amount of fatty detritus leads to an impregnation of the phagocytozing cellular elements with lipoids. Typical giant cells are few here, and their place is taken by aggregates of endothelial leucocytes which are peculiar here because of the fairly granular cytoplasm resulting from the lipoid inclusions. These are the so-called "foam cells". In the myxomatous type, the peripheral portion consists of spindle cells, with a large chromatin content of the nuclei, embedded in a mucinous mass.

The type of giant-cell tumor originating in connection with an absorption of misplaced islands of cartilage, presents a marked deviation from the normal structure. Numerous imperfect cartilage cells are seen and are called "epithelioid cells", because of their resemblance to epithelial cells. Unlike malignant bone tumors, in which the destruction of the involved bone is accomplished by both osteoclasts and tumor cells, in giant-cell tumors the task of destruction of the cortex is taken over by giant cells.

When a recurrence has taken place in a giant-cell tumor, the histology shows a variable picture and is always of an altered character. Cicatrization of a giant-cell tumor may be hastened occasionally by incomplete curretage and sometimes even by an exploratory incision, provided infection does not set in. Frequently, however, infection is not avoided and the infected fungating pulsating masses of the tumor acquire an appearance of a malignant new growth. Histologically, such a giant-cell tumor is greatly changed by the admixture of a reaction to infection and by stimulation to active growth.

The clinical incidence of giant-cell tumors is apparently lower than that of primary malignant bone tumors. According to the report of Codman (21) from the material of the Registry of Bone Sarcoma, the relative frequency of giant-cell tumors as compared with malignant bone tumors is about 1:2. Kolodny (55) believes this ratio is probably an exaggeration of the frequency of giant-cell tumors, since the Registry material counts many cases in which the patients were alive at the time the Registry began, while the average life duration of a patient with a malignant bone tumor is about twenty months. The giant-cell tumor is more frequently met with in the female than in the male; the ratio 6:5 is probably a fair expression of this frequency. Kolodny (55) believes it is in the decade between sixteen and twenty-five that most giant-cell tumors occur, an age considerably higher than for osteogenic sarcoma and Ewing's sarcoma. In 28% of females the disease occurred after the age of thirty, as against 41% in males. The youngest patient was a girl of six, and the oldest a man of sixty-eight. Platt (80) reports that over half of the cases in his series have been patients in the fourth or even fifth decade of life. "Indeed", he writes, "the surprising incidence of this tumor in the middle aged occasionally leads to difficulties in the differential diagnosis of solitary secondary malignant tumors of the long bones, where the primary growth is latent. Geschickter and Copeland (39) report that forty per cent of all cases are in the third decade of life.

Peirce (76) reporting the incidence of giant-cell tumors in the last eight years from the University of Michigan, excluding involvement of either maxilla or mandible, gives the age variation from four to forty-nine.

There were two in the first decade, eight in the second, four in the third, three in the fourth, and two in the fifth. Of the nineteen cases, eleven were male, eight female.

The location of the giant-cell tumor is in marked contrast to that of osteogenic sarcoma as far as the bone and the site of involvement is concerned. The bones of the lower extremity were involved in 56% of all cases of the Registry (21), while those of the upper extremity were involved in 23% of all cases; in 21% of all cases the bones of the trunk, including the pelvis and the shoulder girdle and the jaws, were involved. Of all the cases of involvement of the upper extremity, the radius was involved in 40%, all in the lower end of the bone. The femur was involved in 57% of all cases of giant-cell tumor of the lower extremity and the tibia in 36%. The lower end of the femur was, as a rule, involved, with very few exceptions, when the tumor was situated in the upper third of the femur about the trochanters. The lower end of the femur is involved much more frequently in the male than in the female, while an involvement of the upper end of the tibia, which is three times as frequent as that of the lower end of this bone, is seen more frequently in women than in men. In general, in about 47% giant-cell tumors were situated in the lower end of the femur and the upper end of the tibia. The jaws were the seat of the tumor in about 9% of all cases, the spine following closely with 8% of all cases of involvement. Involvement of the jaws, which is equally distributed between the upper and lower jaw, is apparently rare after the age of 25. The shaft of the long bones was involved in two cases, while in both these cases there was place for doubt as to the accuracy of the diagnosis, since a cyst complicated by a fracture could not be ruled out. Giant-cell tumor is situated in the small bones of the extremities more

frequently than osteogenic sarcoma. In contrast with osteogenic sarcoma, in

which the epiphysis frequently escapes involvement because of the epiphyseal

cartilage serving as a barrier to the spreading tumor, in giant-cell tumor the

epiphysis is involved in a large majority of cases. Here the epiphyseal carti-

lage does not seem to exert any influence upon the spreading of the tumor and

the latter frequently extends from here into the diaphysis. As a rule the

giant-cell tumor appears as a solitary lesion, and it would seem probable that

in some of the cases of multiple giant-cell tumors, one is dealing with a

proliferative osteitis fibrosa.

Alexander and Crawford (1), Kanavel (51), Martland and Haussling (42)

and Barrie (5) have reported what they have believed to be multiple giant-cell

tumors of bone. In a recent communication from Crowell to Alexander and

Crawford (1) five additional cases are given which were presented to the

Registry of Bone Sarcoma. It is interesting to note that no cases of multiple

giant-cell tumors have been accepted as true entities by the Committee on Bone

Sarcoma. Codman, in communication with Alexander and Crawford (1) states that

he is skeptical about the existence of the condition. Giant-cell tumors have

been found in almost every bone in the body.

Geschickter and Copeland (39) report from the records of the surgical

pathologic laboratory of the Johns Hopkins Hospital for a period of over thirty-

five years, only twenty-two cases of giant-cell tumor occurring in the head,

excluding the epulis of the alveolar border. Two of the giant-cell tumors were

found in the temporal fossa, six are recorded in the upper, and fourteen in

the lower jaw. All of these have been found in sites of bone formed from car-

tilage and none from the purely membranous portion of the calvarium (the

frontal and parietal bones). Dean Lewis (60) in 1924 reported a case of primary

giant-cell tumor of the vertebrae and reviewed sixteen cases from the literature.

Cotton (27) in 1928 reported a similar case. Kraft (57) described a case of giant-cell tumor of the patella and Mathews (67), one of the clavicle. The giant-cell epulis of the jaws is quite frequently met with. It is outside of the scope of this paper to deal with them specifically and the reader is referred to excellent discussions by Geshickter and Copeland (39), Bloodgood (11) and Scudder (83) for more detailed information regarding them.

Beekman (8), Broders (17), Garrett (37), and Mason and Woolston (66) have recently reported cases of giant-cell tumors of the tendon sheath, and emphasize the propensity for these tumors to occur on the hand about the fingers, and on the foot and about the ankle. Geschickter and Copeland (39) support the view that the giant-cell tumor of the tendon sheaths arise in the sesamoid bones.

The usual clinical history given by these patients has a sequence of trauma, pain, tumor and fracture extending over a period of from two to fourteen months. Pain in these cases is usually more severe than in bone cysts, but of less severity than in osteogenic sarcoma, of a more constant nature, and is sufficient to cause disability.

Pain is frequent and early complained of by a patient afflicted with giant-cell tumor. The pain, however, is of less severity than in osteogenic sarcoma, and it is more persistent after radiation therapy is begun. The patient's general condition usually remains good unless an exploration or incomplete curettage was done, accompanied by infection. Infection is very persistent in giant-cell tumor, and it may lead to sepsis in a brief period of time. The skin frequently lacks the dilated veins commonly seen in osteogenic sarcoma. When the skin is very distended by the large tumor, it may resemble pig skin, be edematous and cyanotic. Ulceration of the skin

occurs apparently only in the very far advanced cases which have long gone without medical attention. In the chapter on diagnosis I have discussed more completely the physical findings.

As a rule, giant-cell tumor is of long duration and slow growth; notable exceptions are known, however. At the present day, advanced stages of giant-cell tumors are seldom seen since their growth is interrupted by surgery or radiation. Occasionally, in long standing tumors, attempts at spontaneous healing occur, - cicatrization with ossification of the peripheric portion and cyst formation in the center. When infection takes place fatal hemorrhage and sepsis may ensue. After breaking through the investing capsule, the tumor travels along the intermuscular and fascial planes but does not invade the muscle tissue. Orthopedic problems arise from tumors of the spine. Infraction is almost a rule in giant-cell tumor, especially in the weight-bearing bones, where also complete pathological fractures are frequent. Geschickter and Copeland (39) report that pathologic fracture occurs in about 14% of these cases, or about one third as often as in the bone cysts. This fact again emphasizes the necessity of splintering and recumbency. The pathological fracture of the lower extremity is usually of the telescoping variety, with one end of the bone projecting into the cystically dilated other end. Joint involvement is exceedingly rare.

While some experienced observers maintain that it is always possible
to arrive at a diagnosis in giant-cell tumor from a microscopic examination
of the section alone, and others claim that the clinical history together with
the physical findings and roentgen-ray features will suffice for diagnosis
without an exploration of the tumor. Kolodny (55) believes that there are
times when neither method of examination, clinical and radiological, or mi-
croscopic, nor both of them combined will suffice for an accurate diagnosis.
These cases are rare, frequently they are complicated by previous surgical
treatment. These are the cases referred to by Ewing (34) as the "borderline"
giant-cell tumors, with a wide destruction of bone, with an absence of bone
shell, with smaller than usual giant cells containing larger and more hyper-
chromatic nuclei; they present a difficult task for the pathologist, especially
when diagnosis is requested from small curetted pieces of tissue. Kolodny
(55) believes that to the careful observer a complete history and thorough
physical examination, supplemented by satisfactory roentgenograms, will suf-
fice for an accurate diagnosis in the majority of cases. According to
Kolodny (55) palpation is an important diagnostic aid in the examination of
a giant-cell tumor. Frequently, one is able to palpate the bony capsule of
the tumor and its borders at the junction with the uninvolved diaphysis. The
bulky spheric shape feel of the tumor contrasts it from the fusiform shape
of the osteogenic sarcoma. It is much easier to palpate in giant-cell tumors
because of relative absence of tenderness. When the bone shell of the tumor
becomes very thin, egg-shell crackling can be made out. In the very vascular
variety of giant-cell tumors one occasionally feels a bruit.

Herendeen (44) believes that the location of the tumor is one of the
most important points in the diagnosis of giant-cell tumors. Although they

may occur in any bone in the body (they have been found in the skull, vertebrae, ribs, pelvis, upper end of femur and humerus, lower end of the ulna and radius, tibia and fibula), the most common sites are in the ends of the bones at the knee joints, and a tumor in the medullary portion of the distal end of the radium is nine times out of ten a giant-cell tumor. Giant-cell tumors may occur in the shaft or at some distance away from the end of the bone, but in these instances the diagnosis is more uncertain and the chances are greater that the tumor is a malignant one, as purely benign processes, other than giant-cell tumors such as chondromas and cysts in the medulla of bones are comparatively rare.

Morton and Duffy (69) of Yale University Medical School published an article on Bone Sarcoma in which they stated: "We are impressed with the difficulties which confront the average surgeon in arriving at a correct diagnosis and in deciding on proper treatment in any group of bone tumors. There are so many exceptions to the rule, that each case must be most completely studied and weighed before action is taken. Were we to trust to the Rontgen-ray picture for diagnosis we would in many instances be wrong. Were we to depend upon the microscopic sections alone, especially at the time of operation, we would be often misled."

Robert Osgood and his collaborators (72), in an editorial note following a review of Tumors of Bones, say : "Differential diagnosis of bone tumors is far from certain by any known method, particularly rontgenoscopy. This is altogether natural when we remember that even with the gross specimen before him and the slide under the microscope, the pathologist is often uncertain as to its character. Often there is such widespread involvement of the bone that it is impossible to determine the point of origin or the invasion. While in sympathy with any effort to systematize the diagnosis, we are under the impression that the one point of importance is whether the

growth is benign or malignant, and that the best way to determine this is by immediate exploration and pathologic examination. The relation of the region to be examined is also of importance, and occasionally the surgeon well trained in gross appearances in malignant disease must be governed by his finding quite as much as by the report of the pathologist, made necessarily somewhat incompletely at the time of operation."

Bost (16), in an excellent article on differential diagnosis, writes that giant-cell tumor must be differentiated from the following single osteolytic bone tumors: (1) bone cyst, (2) osteolytic sarcoma, (3) Brodie's abscess, (4) chondroma, (5) latent bone cyst, (6) single metastatic tumors, and (7) osteitis fibrosa cystica. It must also be differentiated from latent osteomyelitis and tuberculosis. Bone cysts involve mainly the diaphyses of the long bones and occur in the early epiphyseal age, from 5 to 15 years of age, and most often in the upper humerus, lower tibia, and upper femur. This tumor expands the bone only slightly. The cortex of the bone at both ends of the cyst is thinned out so that there is a gradual thinning of the cortex from the middle of the cyst to the poles, and not the abrupt transition of the normal cortex frequently seen in giant-cell tumor.

Osteolytic sarcoma is a malignant tumor occurring in patients from 10 to 20 years of age and involving the upper tibia, lower femur, and upper humerus. The point of differential diagnosis in this tumor is the fact that the tumor is medullary and rapidly destroys the cortex without expansion. This differentiates these tumors from benign lesions.

Brodies abscess may resemble a giant-cell tumor, but as a rule this condition involves the shaft of a long bone with no expansion or destruction of the cortex.

Chondroma may resemble a giant-cell tumor. However, these growths usually occur in the phalanges of the hands and feet, and in the sternum, where the giant-cell tumors rarely occur.

Latent bone cyst originates at any age, and is usually discovered accidentaly in the third decade. This cystic disease differs very little from the usual bone cyst, except that the condition has existed from childhood, being in a quiescent state without extension of the process.

Metastatic carcinoma to bone should rarely be confused with giant-cell tumor. It usually occurs in the bone near the nutrient artery, the mid-portion of the bone. The cortex is entirely destroyed without any evidence of its expansion. Metastatic carcinoma occurs usually after the age of 40, and more frequently in females. The disease is rare in bones below the elbows or the knees.

The benign giant-cell tumor may at times simulate a latent osteomyelitis. In these cases, a complete clinical history is of greatest value, and should always be secured in cases of doubtful diagnosis.

Tuberculosis gives a fairly definite clinical history. Joint involvement with subsequent disability is always an early feature, whereas in giant-cell tumor the joint is not usually involved. When this does occur, it is always late in the history of the case. The distinguishing factor is that in giant-cell tumor the enlargement is asymmetrical, whereas in tuberculosis there is symmetrical enlargement.

Osteitis fibrosa cystica with bone destruction and thinning of the cortex often resembles giant-cell tumor. However, in osteitis fibrosa cystica we find no expansion of the cortex, so typical of giant-cell tumor. Giant-cell tumor involves the epiphysis after ossification, while osteitis fibrosa cystica is present in the shaft of the bone before ossification.

Early osteogenic sarcoma may at times be difficult to distinguish from giant-cell tumor. However, giant cell tumor is always present in the epiphyseal area of the bone. New bone is produced in osteogenic sarcoma and is laid down in radiating lines perpendicular to the shaft, whereas new bone is never produced in giant-cell tumor.

Radiological examination is of outstanding diagnostic importance. Repeated radiological examination of skeletal tumors from many angles is indispensable for an accurate diagnosis. The roentgenogram is frequently of more importance than a microscopic examination when a variant of giant-cell tumor is dealt with.

The radiological appearance of a giant-cell tumor is most characteristic. It usually casts a bulky spherical shadow, showing a multicystic appearance as a result of the osseous trabeculation in the periphery. The shaft of the bone is absent and it appears as if the cortex is blown out from within the medullary cavity so as to form the thin bone shell, which sharply limits the tumor from the surrounding soft tissues. A continuation of the bone shell is seen limiting the tumor from the adjoining unaffected medullary cavity. When in advanced cases of giant-cell tumor, the bone shell is destroyed, in some areas the roentgenogram will simulate an invasion of the tumor into the soft tissues in spite of the intact periosteum. This should not confuse the reader from diagnosing giant-cell tumor. When the adjoining periosteum and cortex remain unaffected, this points strongly against osteogenic sarcoma. The shaft is absent in giant-cell tumor, but may be seen running through the osteogenic sarcoma. In giant-cell tumor, the tumor is in direct contact with the articular cartilage, while in osteogenic sarcoma a thin layer of spongiosa remains between the tumor and the cartilage.

Nichols (71) in an endeavor to simplify the roentgenologic diagnosis of bone tumors suggests a differential method based on the observation of four fundamental points: (1) their origin, whether medullary or cortical; (2) whether or not they are characterized by bone production, by bone destruction, or both; (3) the resultant condition of the cortex, whether expanded or destroyed, and (4) whether the growth is invasive or non-invasive.

When combined with the clinical history, physical findings and radiological features, the data of a pathological examination are of valuable diagnostic importance. To one experienced in the pathology of bone tumors, the gross anatomy of a giant-cell tumor will frequently mean more than the histology. It is well to remember that an occasional tumor can resemble grossly or histologically a giant-cell tumor and not be one. The histology is frequently misleading in giant-cell tumor, especially so when a frozen section is relied upon, as often happens. The diagnosis of giant-cell tumor from the section must not be based upon the presence of giant-cells alone; the type of supporting tissue is most important, although the giant cells are said to be an integral part of the giant-cell tumor they are occasionally encountered also in typical osteogenic sarcoma where lime salts are set free by rapid erosion and disintegration of bone. The very vascular, so-called telangiectatic osteogenic sarcoma may resemble grossly vascular giant-cell tumor. The histology is often misleading in the variants of giant-cell tumor. In the myxomatous variation the histology may suggest malignancy while the clinical findings and radiological features clearly indicate the benign nature of the lesion. In cartilaginous giant-cell tumors in a few cases a diagnosis of myeloma has been returned by the pathologist because of the abundance of rounded cells of the stroma. Occasionally several variants may be found in

the same tumor. The histology is especially deceiving when the tissues are
taken from tumor masses fungating through a former exploratory incision.

Shall a biopsy be performed before any method of treatment is adopted?
Upon this point there is the widest variance of opinion. It would seem that
the whole question is merely a part of the general advisability of a biopsy
in bone tumors of doubtful nature, since the necessity of exploration indicates
that one is not certain whether the tumor is benign or malignant. The diffi-
culties encountered in a diagnosis from the histology in a doubtful giant-cell
tumor are great to those little initiated in the pathology of bone tumors.
Ewing (34) repeatedly stresses the importance or desirability of making a
diagnosis without biopsy. Kolodny (55) believes that as a general rule, when
the clinical findings and the roentgenogram are baffling to the clinician,
the histology is also distressing to the pathologist. Whatever one may say
about the increase of malignancy in giant-cell tumors, by an exploratory
incision, one cannot deny that the dangers of infection with which such ex-
plorations are entailed are very great. However, if a biopsy is done, the
curettage of the tumor should be completed because a following infection will
add greatly to the difficulties of radiation.

Bloodgood (14) suggests the following working rule for the diagnosis
and treatment of tumors of bone. If a patient is under fifteen years, it is
probable that sarcoma is not present, and the diagnosis rests between the
common bone cyst, the less frequent giant-cell tumor and the rare chondro-
myxoma. If the patient is over fifteen, sarcoma cannot be excluded. The
most common central lesion of bone is the benign bone cyst. In the majority of
cases, they recover without any treatment. The second is the giant-cell tumor,
which predominates in patients over fifteen. Myxoma may occur at any age.

Myxoma must be constantly borne in mind, and is the most difficult of all bone tumors to eradicate locally.

The location of the tumor is also important: whether in the end of the bone, in the joint, or in the middle of the bone near the nutrient foramen; the last being the favorite site of the metastasizing carcinoma. Malignant tumors do not cross a joint, so that a lesion involving both sides of the joint is always a benign process. Whether the tumor is single or multiple, is also important, as is also the age of the patient.

Geschickter and Copeland (39) are of the opinion that the adult age of the patient and the involvement of an epiphysis are the most important aids in making a differential diagnosis. The other common central bone destructive lesion occurring in an adult is a single focus of metastatic carcinoma.

Bost (16) believes that giant-cell tumor may often be positively diagnosed by the roentgen findings, but not always. He presents the following characteristics of giant-cell tumors from the roentgenologic standpoint: (1) the lesion is subcortical, beginning at one side of the epiphysis and gradually extending centrally, involving cancellous bone; (2) the lesion is almost always invariably single; (3) it is an epiphyseal disease, the lesions involving most frequently the upper end of the tibia, lower femur, and lower radius; (4) the tumor occurs usually between the ages of twenty and thirty years; (5) the tumor appears in the roentgenogram as a circumscribed bone destructive lesion, involving the epiphysis and diaphysis, the tumor being globular, trabeculated, and asymmetrical; (6) the growth is medullary, and of osteolytic character; (7) giant-cell tumor arises only in bone derived from cartilage, a fact which gives these tumors their characteristic location and age distribution.

Barrie (6) presents the following table covering the more important features pertaining to the solitary lesion in making a diagnosis of hemorrhagic osteomyelitis (giant-cell tumor):

Clinical Picture

Age of Patient - May occur at any age. Most frequent in first and second decades of life.

Duration of Lesion - Months - perhaps years before lesion attains large size.

Symptoms of Onset - Usually history of injury, recent or remote.

Pain - - - - Apparently never constant.

Inspection - - Usually some enlargement of site of lesion.

Palpation - - Tenderness and pain on pressure.

Joint movements Some limitation of motion in nearest joint. Limp with lesion in lower extremity.

X-RAY PATHOLOGY

Cancelli - - - Area of osteolysis rather clear cut, rounded or oval in shape.

Periosteum - - Usually intact unless lesion has attained large size, years after onset.

Gross Pathology Appearance of vascular granulation tissue sometimes interspersed with areas of fibrosis, or degenerated hyaline masses.

Microscopic Picture - Heterogeneous cellular picture of fibroblasts, scavenger giant-cells, endothelial and polynuclear leucocytes, lymphocytes, eosinophiles and red blood cells.

The theory that giant-cell sarcoma is always a benign lesion and never metastasizes dates back to the middle of the nineteenth century. In 1854 Sir James Paget (74), in his lecture on surgical pathology, gave Lebert full credit for being the first one to describe giant-cell tumors. After a study of Lebert's cases, as well as a few of his own, Paget very modestly concludes that his own observations are too few and too various to warrant many general conclusions. Those which he tentatively expressed, however, were:

"The tumor is single, occurs most frequently ih youth, rarely in adult age, is slow in growth, and without pain, and generally comes on without any known cause such as injury; has no tendency to ulcerate. - - - They may (but I suppose very rarely) cease to grow. They are not apt to recur after complete removal, nor have they in general any features of malignant disease."

And then, at the end, Paget very wisely adds, that while these and many other cases may be enough to prove that the myeloid tumors (giant-cell tumors) are generally of an innocent nature, "still, I suppose, cases may be found in which, with the same apparent structure, a malignant course is run." Further observations have shown some of Paget's conclusions to be incorrect. It is now known that injury is a very important factor as an exciting cause. Coley (24) reports that fifty-six per cent of his series of cases gives a distinct history of antecedent local injury, and also that pain is one of the earliest and most constant symptom.

Nelaton, in 1860, strongly advocated the view that giant-cell tumors are only locally malignant, and furnishing much new data in support of this view.

Bloodgood (10,12,13) for many years has upheld this doctrine and at present the majority of pathologists here and in Europe have accepted it. Coley (24) states that, "This view has been expressed so often and so emphatically that many surgeons have accepted it without a sufficiently careful or critical examination of the data upon which it is founded." Only in the light of data accumulated from the clinical history, physical and radiological findings and pathological examination may a prognosis be given.

When left alone, the giant-cell tumor may follow one of two ways. Advanced growth of the tumor may lead to fatal hemorrhage or septicemia. Occasionally, following a pathological fracture, such a tumor may enter a cicatrizing stage. The bony shell may become very thick.

The question of the prognosis of giant-cell tumor treated conservatively by curettage or radiation, forms a subject for ardent discussion. On one side many cases are cited of giant-cell tumor leading to pulmonary metastases, and death. Kolodny (55) reveals two sources of error of these authors by a careful study of their cases. The first is that not in all cases mentioned was the primary lesion a giant-cell tumor, and the second that not in all fatal cases are metastases proved to have been present. On the other hand, the authors believe that giant-cell tumors are always benign lesions lacking the ability to produce metastases. The exceedingly few cases of giant-cell tumor in which, after repeated surgical operations, pulmonary metastases and death occurred these authors explain by the fact that due to surgical insult and ill-advised therapeutic measures the giant-cell tumor becomes transformed into a malignant bone tumor which, as a malignant tumor and not as a giant-cell tumor, led to pulmonary metastases.

Gross (41) in 1879, for the first time, reported five cases of benign giant-cell tumors which underwent degeneration. From this time on,

the question of benignity or malignancy of the giant-cell tumor led to some

of the most passionate disputes ever known in medical literature. Thus,

while Bryant (18), Bloodgood (13, 15), Martland (65), Stone and Ewing (89)

Codman (20) and Meyerding (68) and others, considered the benign character

of the lesion as unquestionable, Stewart (88), Waugh and Turner (90),

Shattock (84), MacGuire and McWhorter (63), Finch and Gleave (36), King (52)

and especially Coley (24) repeatedly emphasized that some of the giant-cell

tumors are distinctly malignant and that they produce metastases. Not even

the Registry could settle the question definitely. While Codman (20) is

"convinced that they are benign", Kolodny (55) after analyzing the same

material says: "The question as it stands today is whether or not a giant-

cell tumor is always benign. From the evidence on hand, this question is

to be answered in the negative." At the same time Goforth (40) writes:

"Giant-cell tumors constitute a series. Those at the lower end of the scale

show relatively adult fibrous stromas, and are essentially benign. They

exhibit more cellular and active stromas, composed chiefly of relatively

immature fibroblasts cells, and become increasingly more locally aggressive

as the scale is ascended."

Evans and Leucutia (33) believe the giant-cell tumor is essentially

benign, but believe that such a differentiation as that of Goforth is of some

help from the therapeutic standpoint. It is comprehensible that a rather

cellular tumor with immature fibroblastic elements would show a great ten-

dency toward recurrence, especially if incompletely removed. Moreover, since

with each recurrence, the tumor is apt to become more and more virulent, it

is plausible that finally a malignant degeneration of the lesion should follow.

Stone and Ewing (89) described such a case. Evans and Leucutia (33) believe that the majority of cases described in the literature as primarily malignant giant-cell tumors are based on mistaken or incomplete diagnosies. Dr. Channing Simmons (85), in analyzing the cases of the Registry, concludes that there is no instance in which a proved giant-cell tumor formed metastases. He cites cases 295, 349 and 68 to show that the giant-cell tumor may change its character and become osteogenic sarcoma which metastasize in the usual manner and causes death. He states that giant-cell tumor is known to become an osteogenic sarcoma in about 3.7% of the cases. Crowell, (29) in presenting the 1933 report on the Registry of Bone Sarcoma, lists 272 cases of benign giant-cell tumor, and 14 cases of malignant giant-cell tumor.

The main factor in the clinical course of giant-cell tumor requiring one to be on guard in the prognosis is rapid growth of the tumor. The typical giant-cell tumor is of long duration and slow course. Rapidity of growth is a sign of aggressiveness of the tumor. Another reliable sign of aggressiveness is the destruction of a large portion of the bone shell of the tumor. A giant-cell tumor reaching a very large size is very apt to recur after curettage since the size of the tumor excludes the possibility of a complete removal of the tumor tissue. With each recurrence the prognosis becomes less favorable. Care should be exercised in the arrival at a prognosis based upon a recurrence, because with each recurrence the growth is apt to become more anaplastic and malignant. The high percentage of clinical recurrences after treatment in typical giant-cell tumor speaks for the progressive nature of this disease. Geschickter and Copeland (38) reviewed 222 cases of giant-cell tumor in the surgical pathological laboratory of Johns Hopkins Hospital and found that there were thirty-one recurrent cases following a primary curettement, and many of these showed repeated recurrences despite surgical

intervention. Recurrence was found to depend not on histologic structure,
but on a poor selection in the type of treatment applied in the individual
case or on an incomplete operation. Advanced destruction of the bone shell,
incomplete currettement, failure to use chemical or thermal cauterization
or needless sacrifice of cortical bone at the operation, as well as an age
over 35, were found to be factors predisposing to recurrence after curette-
ment.

In relation to a prognosis, the findings of a pathological exami-
nation are of outstanding significance. The giant-cells of epulis type, when
present in excess, are a true indication of the benignity of the lesion. The
typical giant-cell tumor where the giant cells form the bulk of the tumor is
of very slow growth, not aggressive, and easily eradicated even by incomplete
curettage. On the other hand, with the disappearance of the giant cells and
with an increase in the number of spindle cells of the stroma, the aggressive-
ness of the tumor increases. Viewed largely, the type of cells of the stroma
are of greater importance than the giant cells. Recurrence can be expected
when the hyperchromatism of the stroma cells occurs and also when the stroma
cells have become abundant and rounded. However, pleomorphism and cellu-
larity in the central portion of a giant-cell tumor are not of such unfavor-
able significance for the prognosis as their presence in the peripheric
portion of the tumor, where they notoriously mark aggressiveness. A guarded
prognosis is to be given also in the case of the very vascular, so-called
telangiectatic, giant-cell tumor which as a rule is more aggressive and
recurs more frequently than other types.

While in malignant bone tumors the problem of therapy today is to
find a way to relieve the sufferings of the patient for a longer period of
time, in giant-cell tumor, the whole crux of the question is as to choice
between various methods of treatment, each of which may lead to permanent
cure. The history of the therapy of giant-cell tumor is remarkable for the
continuous change from radical to more conservative methods of treatment.

Bryant (19) reports a case of a young woman treated in 1861 by
amputation of the thigh who was still alive after seventeen years. Dr.
Gross (41) in 1879 treated these tumors by amputation when permitted, and
occasionally excised when the more radical measures were refused. He con-
cluded that although surgical interference was followed by a mortality of
31.25%, it frequently succeeded in preventing local and systemic infection
as well as prolonging life. He was of the opinion that because of the diffi-
culty in determining the true nature of the neoplasm in its incipient stages,
delays were extremely dangerous, since, instead of having to deal with pure
myeloid sarcoma (giant-cell tumor), the disease might eventually prove to be
an osteoid sarcoma, or a small celled medullary sarcoma, in which events,
valuable time would have been lost, and the patients would have been exposed
to the dangers of local infection and general dissemination. Instead of am-
putation, excision of an entire joint, or of the affected epiphysis, along
with the shaft, of the more slender long bones were resorted to, particularly
if the tumor presented a uniformly smooth surface, and was of a firm, dense
consistence or was enclosed in an osseous shell. In cases of doubt, excision
was commenced, and removal of the limb was substituted, if the capsule of the
tumor was discovered to be perforated, and the soft parts infiltrated by the

morbid product. The mortality rates were high because of the profuse hemorr-

hage encountered near the seat of the tumor, the high percentage of post-

operative infections, and the number of malignant sarcomas which were diagnosed

as myeloid sarcomas (giant-cell tumors) with death ensuing from subsequent

lung metastasis. Towards the end of the ninteenth century the benign nature

of the giant-cell tumor became more widely accepted and the more conservative

resection method gained its group of supporters, headed by Drs. v.Bergmann,

Mickulicz and v.Bramann (9). Hinds (47) in 1898 reported a case of myeloid

sarcoma (giant-cell tumor) of the femur treated by scraping. The dark red

and firm growth was scraped out with a sharp spoon. The surface of the cavity

was scrubbed with chloride of zinc solution (grains twenty to the ounce), and

was packed with cyanide gauze. At the end of six weeks, because of unsatis-

factory granulations, the cavity was again scraped out and scrubbed with

zinc chloride solution. The patient made an uneventful recovery and was in

excellent general health, with a slight deformity of the knee, after a period

of three years. In 1916 Dr. Hinds (13) in a personal communication to Dr.

Bloodgood enclosed a letter from the patient written twenty-one years after

conservative operation. The patient had perfect function and worked as a

forester cutting down trees, carrying heavy weights, and walking from ten to

twelve miles a day. An x-ray print (12) was also sent, demonstrating that

the cavity was filled with bone. Dr. Bloodgood (10), in 1903, reported a case

of a medullary giant-cell sarcoma (giant-cell tumor) of the upper end of

the tibia in which the tumor was apparently completely removed by chiselling

without destroying the continuity of the tibia. The entire bone cavity was

curetted and swabbed with pure carbolic acid, followed by alcohol, then

irrigated with 1:1000 bichloride solution, followed by normal salt solution.

Horsely's wax was used to check the bleeding in the cavity. The patient was in good health and almost complete function was restored in 1903 - one and one half years later.

In 1891 the curative effect of accidental erysipelas in inoperable sarcoma was observed by Dr. Coley (22). In 1893 he began the use of toxins of erysipelas and Bacillus prodigiosus in the treatment of inoperable bone sarcoma, and soon after that used them in operable cases as a prophylactic against recurrence, after amputation. He reported in 1909 the successful use of the mixed toxins in 52 cases of inoperable sarcoma. With such excellent results in inoperable cases, the mixed toxins of erysipelas and Bacillus prodigiosus were used as an adjunct to treatment with gratifying results. Dr. Coley (23) says, regarding the use of mixed toxins in the more benign lesions of bone,"while good results have been obtained from operation alone in a limited number of cases in this group, I am convinced that the number of successes will be greatly increased by combining the toxin treatment with conservative operation". Dr. Bloodgood (12) agrees with Þ. Coley that his serum should be used in all inoperable cases, that it should also be used before and after operable cases when the sarcoma is of a type which experience has shown to be very malignant, and in which few, if any, cures have been accomplished. He cites twenty-six cases of giant-cell tumor in which there was no treatment other than removal of the tumor by curette, excision, resection, or amputation, and in no case was there a recurrence or metastasis of the disease. He is of the opinion that there is no more reason for giving a patient with a true giant-cell tumor Coley's serum, x-ray, or radium treatment, than to employ them for lipoma, exostosis or any other type of benign tumor. Bloodgood's (12) conclusions as to the conservative treatment are as follows:

1. Conservative treatment is justifiable. Curetting should in some localizations of the tumor, be the operation of choice. But in those localizations where resection in continuity does not interfere with function, resection becomes the operation of choice; for example, upper end of fibula, lower end of ulna.

2. It is justifiable to attempt curetting to preserve function even when conditions suggest a great probability of recurrence. There is no position where curetting is not justifiable as a first attempt. It has succeeded when the entire lower end of the femur was involved.

3. The number of successful cases of curetting will depend chiefly on the number of attempts.

4. After curetting or resection, the wound should be disinfected with pure carbolic acid followed by alcohol or chloride of zinc solution. Thermal cauterization may replace chemical cauterization. The operation should always be done, if possible, under an Esmarch. This procedure is not indicated because of the malignancy of the giant-cell tumor, but because in curetting disseminated cells are left, while in resection, cutting into the tumor may inadvertently be done. ~~[struck out]~~ Hitzrot (48) states that recurrences have been more frequent when this has been incomplete or has not been followed by cauterization.

5. It is not necessary to perform the bone transplantation at the primary operation unless a single bone like the humerus or femur is divided in its continuity. In simple cases there is no reason why the transplantation should not be performed at the same time, but in some cases the resection may be tedious and bloody, and the patient may not be in good condition. In such cases it will be safer to transplant at a second operation.

6. It is simpler, when possible, to get the bone for filling the defect by splitting the bone which has been resected. This can be accomplished through a single wound. When this cannot be done on account of a large defect, one can remove the upper third of the fibula without injury to the function of the limb, or chisel large pieces from the tibia without destroying the continuity of the bone. The treatment of giant-cell tumors of bone by means of the roentgen ray covers a period of at least twenty-five years. Dr. Pfahler (78) in 1906 was the first to treat such a case. A roentgenological diagnosis of osteo-sarcoma was made. A section removed for microscopical examihation was diagnosed as a round cell sarcoma. The patient was given intense roentgen ray treatment and was symptom free after three months. After a year and a half the bony tumor was only reduced to two thirds of its original size. This was reported as "the first case that has been observed Roentgenologically during the process of recovery from an osteo-sarcoma". Dr. Pfahler (79) reviewed this case in 1932 and reported that, "it showed beginning lime deposit at the end of a month, and progressive improvement from that time onward, during at least fifteen years, and is known to be well for twenty-five years. At the end of this time the bone completely recalcified but remained about 25% larger than normal". The clinical, roentgenological, and microscopical diagnosis was "sarcoma", but in retrospect these "cured sarcomata" are now recognized as having been giant-cell tumors.

Dr. Herendeen (43) in 1924 wrote his first of a series of articles dealing with the roentgen-ray treatment of bone tumors, recording the changes noted in giant-cell tumors following treatment with the roentgen ray or radium, and comparing briefly the value of these agents with the standard surgical methods of treatment.

The cases treated at the Memorial Hospital from 1919 to 1924 were grouped as follows: Group I, consisted of those cases in which no operation was performed. (In two or three instances incision for biopsy was done.) Group II, consisted of those cases referred for treatment on account of recurrence following operation. Group III, consisted of those cases referred for treatment to prevent recurrence after operation. In the majority of the cases representing Group I, the roentgenographic features were so characteristic that the diagnosis was made without the aid of a biopsy. The changes observed, following treatment, were largely in those cases in which there had been no incision into the tumor. In addition to the cases in Group I, seven cases were treated on account of a recurrence and five to prevent recurrence after curettage.

These figures emphasize two things: of the cases of giant-cell tumor admitted to the hospital, about 15% applied for treatment to prevent recurrence, on advice of their surgeons, who apparently realize the difficulty of removing all of the tumor tissue; about 20% applied for treatment for a recurrence – some cases having a recurrence after two or three curettements or attempt at local removal. Plates made from one to two months following treatment have revealed in almost every case the same reaction, which consists in rapid enlargement of the tumor, with expansion of the cortex and a thinning out of the bony capsule of the tumor, until hardly any of the outline is visible. Prior to the demonstration of these changes in the roentgenogram, the skin becomes reddened, and the parts swollen and soft or edematous to the touch. As time goes on the redness and swelling subside, the tumor becomes firm to the touch, and a roentgenogram then reveals a return of the outline of the tumor, with evidence of the production of bone or deposit of calcium in its capsule. The function of the part returns, pain

disappears, and the tumor feels firm or stony hard. A plate made later discloses increasing density and calcification, and later still the entire mass seems converted into almost solid bone.

During the stage of reaction - that is, a month or two after the first treatment is given - the tumor has all the appearance, both clinically and roentgenographically, of a rapid increase in growth. Most surgeons and others unfamiliar with the changes induced by the roentgen-ray treatment, assert that it is a failure, and the assertion is also made that it stimulates the activity of the growth, hence immediate operation is advised. If, however, at the end of another month or two, the patient is examined and a roentgenogram is made, it will be found that the reaction has subsided, that the tumor is becoming ossified, that pain is relieved and function is returning, and there is present a well-marked effort of a healing process. Up to the time of the writing of this article by Herendeen, sixteen cases of primary giant-cell tumor of the bone had been treated at the Memorial Hospital with the roentgen-ray or radium alone. All of these cases were filed at Boston in the Registry for Bone Sarcomas. The oldest case was treated in 1918 and was apparently cured in 1924. Eight of the thirty-six cases studied were classified as a typical, undetermined, or as tumors simulating giant-cell tumors. This figure emphasizes the frequency with which one encounters variations from the typical or characteristic giant-cell tumors. Herendeen summarizes his first article by saying, "It does not seem premature or too optimistic to say that it is believed that most of them can look forward to a complete cure and restoration of function. It may be that in some of the more advanced cases only a retardation or a halt in the growth with firm encapsulation and without dense ossification will result from the treatment; but if so, these cases will be in a much better position for curettage than they were prior to the

radiation, and it does not appear unwise, before advising a patient to submit

to an amputation on account of the size and location of the tumor, and the

fact that it may have broken through into a joint, to give roentgen ray treat-

ment a fair trial to obviate the loss of a limb by amputation."

A follow-up of Herendeen's cases, previously cited, shows that all

of those considered in the previous report continued to improve or have re-

mained free of any sign of recurrence or presence of actively growing tumor,

except two. One case developed a recurrence, but, on treatment, responded

favorably and the condition at this time is quite satisfactory. Another case

was treated under a mistaken diagnosis and came to amputation. This tumor,

when examined in the laboratory, was found to be locking in many of the

essential features of a giant-cell tumor and resembled considerably what Ewing

terms as a telangiectatic sarcoma. This patient is alive and well today with

no evidence of the disease present. It should be emphasized that the great-

est value of radiation in the treatment of giant-cell tumor appears to be in

those cases where the tumor has so destroyed the end of a weight-bearing bone

that the logical procedure is amputation. It is obvious that the value of a

simple curettement in such cases lies only in the ability to completely re-

move the tumor. This frequently cannot be, or is not accomplished. If, how-

ever, the tumor is completely removed, a shell-like cavity remains, so fragile

that the limb is of no value for weight-bearing purposes. A number of such

cases have been followed for a considerable period and it was only after a

lapse of years that it has been possible to demonstrate in the radiographs

the production of any considerable quantity of new bone. Furthermore, the

hazards of infection or destruction of the joint surfaces in such cases are

considerable. There are numerous instances where curettement of a small tumor

is the logical treatment, but even in these instances, it is doubtful,

according to Herendeen, if radiation cannot accomplish as much as curettage

in the relief from pain and saving of time in restoring the limb to usefulness
(44). Dr. Coley (25) believes with Dr. Herendeen that it is now possible to
state definitely that giant-cell tumor can be cured by radiation but disagrees
with him on the period of disability. Coley is of the opinion that the time
required to effect a cure by radiation is considerably longer than that re-
quired by operative treatment or by toxins, with or without curettage, and
hence the period of disability is prolonged. The chief disadvantage of radi-
ation as a routine, primary method of treatment of giant-cell tumor lies
in the fact that in a considerable number of cases the diagnosis of benign
giant-cell tumor cannot be made from clinical and roentgen-ray data alone.
Dr. Coley still firmly believes that it is possible to cure these cases of
giant-cell tumor most rapidly and certainly by surgery (curettage) followed
by toxins. "This method," he says, "requires a much shorter period of dis-
ability and is not associated with greater risk". Platt (80) and Cotton (28)
believe that operation is absolutely preferable to irradiation. Cotton says,
"I would go even further and say that irradiation usually acts to stimulate
the tumor growth, the curative effect beginning only later and at the expense
of unnecessary deformity from loss of bone. He believes that only when such
tumors are found in the spine (60) is the x-ray to be chosen as a means of
treatment.

Dr. Herendeen (45, 46) reports several cases in 1930 and 1931 to
substantiate his statements that roentgen-ray therapy is perhaps best suited
for the treatment of giant-cell tumors. Herendeen (46) states that there is
no standardized method of irradiating these tumors. There is no roentgen-ray
dose. The amount of radiation given to the tumor and the methods of deliver-
ing it vary with the case. Few of these tumors respond alike to the same
dose of roentgen-rays. Radiosensitivity varies, as does that of other tumors,

with the presence or absence of many factors, which include age of the patient,

location of the tumor, rate of growth, and the local effort at growth restraint.

It has been found that owing to the susceptibility of these tumors, they can

be destroyed through the application of lighter doses which are not followed

by an extreme degree of reaction. Bone regeneration seems to follow more

promptly when lighter doses are employed. Special care should be taken during

the early stage of the treatment of these tumors to protect the part from

injury, and especially to protect the tumor from pressure in a weight-bearing

limb, but it is seldom necessary to apply plaster splints, or to hospitalize

the patient.

In the knee joint cases, Herendeen (46) gives on the average of

eight or ten treatments, a series consisting of three exposures, the exposures

from three or four days to a week apart, the portals consisting in the exter-

nal, anterior and internal surfaces, using the so-called low voltage technic,

140 kilovalts, 4 milliamperes of current, 4 millimetres of aluminum filters,

12-inch target skin distance and from 12 to 15 minutes' exposure. An interval

of approximately six weeks to two months is allowed to elapse before these

treatments are repeated; but a great deal of variation occurs in the dosage

and methods of delivering it. The roentgenologist must himself determine the

amount to be given in each case at each treatment, and the decision as to how

much to give and when to give it can be arrived at only through careful

questioning of the patient, examining the part under treatment, and inspection

and comparison of the radiographs obtained from time to time.

Pfahler (79) recommends the use of high voltage roentgen rays and

filtration through 0.5 mm. Cu. When dealing with large bones, such as a

lesion in the upper extremity of the humerus or the lower extremity of the

femur in a large man, the 200 kv. technique is essential. His technique in

the treatment of giant-cell tumors consists of fractional cases. None of the

cases in Pfahler's series have shown the swelling, increased pain, and marked

increase in the decalcified area such as has been reported by Herendeen (46).

Pfahler and Parry (79) believe that such symptoms are due to the massive dose

technique. Pfahler emphasizes that, "In osteogenic sarcoma, rapid saturation

with radiation to the limit of normal tissue toleration is justified in order

not to lose the radiosensitivity, but in giant-cell bone tumors this is not

essential and one is less apt to interfere with the repair, or to set up an

osteitis. This fact makes an accurate diagnosis essential." In general,

Pfahler recommends treatment with high voltage roentgen rays, filtered through

0.5 mm. of copper, at a distance of 50 cm., 25% skin erythema doses given

successively through one, two, three or four fields of entry. If the case is

clearly a giant-cell tumor, these treatments need not be given more than three

times a week, but if there is any doubt, the treatment should be given daily

until the tumor area has been brought to 100% of a skin erythema dose accord-

ing to the "saturation technique" of Pfahler. If a satisfactory diagnosis

of giant-cell tumor is made, the treatment need not be crowded, but in all

cases one must keep account of the total dosage, and not give sufficient to

produce secondary degeneration. Degenerative effects are due to the total or

cumulative dosage and may occur when no erythema has ever been produced.

This amount varies with the location and condition of the soft tissues. After

the treatment during three weeks, one can allow an interval of about six weeks

to two months and then re-study the case and treat accordingly.

The most common site for giant-cell tumors is in the ends of long

bones, and therefore when they occur in young children they are in the

neighborhood of the epiphyses. For this reason, many physicians hesitate to

have these cases treated by irradiation. However, Borak, after reviewing all

of the records, concludes that no normal bone has been found damaged in any

of the cases unless there has been some damage to the overlying tissues.

Pfahler and Parry (79) have also found this to be true. Of the twenty-six

cases of giant-cell bone tumor which have been referred to them for treat-

ment between 1906 and 1931, all cases have shown a definite and satisfactory

response, more satisfactory in the young than in the adult.

In 1932 Dr. Carleton Peirce (76)(77) reviewed the nineteen cases

of giant-cell tumor which were diagnosed as such by the Department of Roent-

genology of the University of Michigan from 1924 to 1932. This group does not

include any with involvement of either maxilla or mandible. Fourteen of these

confirmed by histopathologic study are analyzed, ten considered clinically

cured, two presenting malignant features. They found that roentgen irradi-

ation in repeated relatively moderate doses offers the most for the patient,

except when for cosmetic or functional reasons better results could be ob-

tained with the addition of surgical intervention. Surgical intervention

should not follow roentgen therapy short of six weeks to two months. If

surgery is contemplated, thorough curettage and equally thorough chemical

cauterization of the cavity should be executed, followed immediately by a

consistent roentgen therapy program (74).

LeWold (59), Kraft (57), Evand and Leucutia (33) and Desjardins (30)

have also reported the successful use of roentgen ray therapy in these giant-

cell tumors. The use of radium in the treatment of giant-cell tumors has not

met generally with much success, however, Coley (26) reports a case success-

fully treated with a radium pack and Coley's toxins. The high cost of a ra-

dium pack makes its use almost prohibitive in the average institution.

Hitzrot (48) believes that the implantation of radium as a part

treatment in curettement is not advisable because of the delay in healing

produced by the action of the radium.

It is very generally believed that it is possible to make a correct diagnosis of giant-cell tumor from the clinical and roentgenologic evidence alone, but Coley (26) shows that records at the Memorial Hospital and the Hospital for Ruptured and Crippled have proved that to rely on such evidence alone results in error in about one out of every five cases, or, in twenty per cent. Inasmuch as such an error may result in the loss of life of the patient, it is not justifiable in taking such a risk if there is any safe way by which a correct diagnosis can be made before treatment is begun. While it has now been proved that giant-cell tumors of the bone can be cured by roentgen ray, by no means can all such cases be cured by radiation. The chief objection to radiation as the method of choice is that it is not always possible to be certain that a given tumor is a benign giant-cell tumor, and if radiation is continued indefinitely in such a case, metastasis may develop before the error is recognized. Hence, the importance of making a correct diagnosis early in all cases of central tumor of the long bones justifies an exploratory operation, and far outweighs all the disadvantages associated with such exploration.

This exploration should not be a mere biopsy, and should be undertaken only by the surgeon who is to have future charge of the patient, and who has had sufficient experience with bone tumors to enable him to carry out the most careful surgical technique. In all cases of giant-cell tumor, the entire tumor should be curetted down to healthy bone, and the cavity swabbed out with zinc chloride. Therefore, the so-called exploratory operation is not a biopsy but, is the method of choice to be employed in the treatment of giant-cell tumors. In this opinion of Coley's (26), Bloodgood (13) and most surgeons here and in Europe concur.

If the microscopic examination shows that the tumor is of a defi-
nitely malignant, metastasizing type, then amputation can be performed,
following this with prophylactic toxin treatment. The use of toxins after
curettage for giant-cell tumor is advocated by Coley but declared unnecessary
by Bloodgood.

To substantiate their procedure for treatment Coley offers a brief
resume of a series of cases, diagnosed as benign giant-cell tumor from clini-
cal and roentgen ray evidence, which later proved to be malignant. It is
interesting to note that one of these cases was selected from all the giant-
cell tumors observed at the Memorial Hospital, and included by Dr. Kolodny
(55) in his admirable and exhaustive review of the Bone Sarcome Registry data,
as a typical examination of giant-cell tumor.

CASE PRESENTATIONS

5-26-33

6-21-34

CASE I

Mrs. K.K., age 25, white, entered University Hospital on 3/12/33 complaining of:

(1) Pain below left knee for six months

(2) Gradually increasing tumor mass below left knee for six months.

History:- Trauma to left knee area in 1931 with considerable pain. Condition apparently cleared with no known complications. Trauma to same area in October 1932 with resulting fracture of upper portion of left tibia. Roentgenograms taken in December 1932 because of moderate enlargement at site of fracture. Diagnosis of bone cyst made at that time. This mass showed progressive enlargement with considerable pain in area even when leg immobile.

Examination:- Nodular enlargement on antero-lateral surface of upper left tibia about the size of half a walnut. Circumference below left patella - 14 inches. Circumference below right patella - 13 1/3 inches.

Roentgenography:- 3/13/33 Radiographic studies of the left knee demonstrates a large cystic area involving more than half the diameter of the upper end of the tibia which shows a pushing out of the cortex which is markedly thinned along the lateral and superior aspect of the external plateau. There is evidence of cellular partitions extending through portions of the cystic area. There has been no effort at new bone formation, the lesion being primarily a destructive lesion.

3/16/33 No evidence of metastasis involving the skeletal structures or the lung fields.

Operative procedures:-

3/14/33 - Drs. Lord and Johnson attending. Small incision made two inches laterally below patella and laterally. The tumor had practically eroded through the tibia wall and contained from 50-100 c.c. of

semi-liquid material with friable tissue which was removed. Cavity swabbed with iodine and packed with iodine saturated gauze.

3/23/33 - Dr. Lord attending. Incision made over the head of the fibula on the left leg. Tumor cavity opened and about 40 cc. of soft semi gelatinous tumor tissue was scooped out. This cavity connected with the primary cavity in the tibia. Both cavities swabbed with Tr. of Iodine and filled with Mosteg-Morhoff bone wax because of extensive hemorrhage. One container of radium was placed in the center of the wax in the tibial cavity and one in the fibular cavity. Wound left open.

Pathological report:

Gross: Several masses of red hemorrhagic tissue in which are seen yellowish-gray nodular pieces of tissue.

Microscopic: Extensive hemorrhagic areas, some areas showing giant-cell formation, other areas showing more fibrous tissue, with comparatively uniform sized spindle-shaped cells. In these areas giant cells are comparatively few in number. Giant cells much more numerous in areas showing degeneration and where hemorrhage is particularly extensive.
Diagnosis:- Osteogenic sarcoma.

4/25/33 - Microscopic sections reviewed by Dr. Bloodgood and Dr. Tollman - diagnosis changed to benign giant-cell tumor.

X-Ray Therapy:

3/26/33 - University Hospital - Dr. H. B. Hunt. Total 3000 mg. hours through 1 mm. Brass, 2 mm. Lead, and three-tenths Platinum was given through 2 Lead capsules in the head of the tibia.

3/30/33 - Methodist Hospital - Dr. H. B. Hunt. 5x100 R, ¼ Copper, 1 Aluminum, Ant., Post., Lat., and Med. of upper 1/3 tibia. Intensive x-ray therapy given over the lesion, directed through four parts.

Progress:

2/8/34 - Check-up x-ray taken:- Tumor has not increased in size following operation and radiation. Effort at bony repair seen.

The patient was up and about for over a year apparently symptom free, until May 1934, when this area again became painful. Re-admitted to University Hospital June 26, 1934 because of severe pain in knee area with profuse drainage.

3/26/34 - Biopsy taken - negative soft tissue.

7/12/34 - Amputation at lower third of femur.

7/12/34 - Biopsy taken - no evidence of tumor infiltration in section through skin, muscle and regional lymph glands.

Discussion: This case is unique in its completeness of complications, in spite of judicious treatment and observance of every precautionary measure. Trauma preceded the recognition of the tumor by over one year. Pain and enlargement with x-ray plates revealed the tumor. This case illustrates the difficulty in making proper diagnosis even with biopsy. The original biopsy report was osteogenic tumor, although clinical and x-ray evidence tended toward giant-cell tumor. This biopsy report was later changed after consultation with Dr. Bloodgood. The extreme hemorrhagic condition of the tumor necessitated the use of bone wax. This condition in itself makes curettement very difficult and because of the extreme danger of infection, under the most aseptic conditions, the use of roentgen therapy, in favorable cases, where diagnosis is evident, is to be recommended because it obviates these complications.

The recurrence of tumor tissue, well illustrated in this case, is probably due to incomplete curettage. With extensive involvement of the

tumorous area, and profuse hemorrhage at operation because of the telangi-
ectatic condition of the tissue, it is easy to realize the difficulties
confronting the surgeon in his attempt to completely eradicate all tumor
tissue.

This recurrence of tissue, loss of weight bearing due to extensive
involvement of the tibia and fibula, and possible local malignant changes,
made amputation above the knee a most advisable procedure.

The patient is in good general health at present, repeated roentgen
plates failing to show any metastatic nodules.

5-28-33   8-4-33

11-9-33   5-6-34

CASE II

Mrs. C.C., age 21, white,seen by Dr. Herman Johnson, presented

the following complaints:

(1) Progressive swelling of the lower forearm for twelve months.

(2) More rapid growth during the past five months while the patient

has been pregnant.

Physical Examination: Fusiform enlargement of the distal end of

the forearm on the ulnar side, firm to palpation.

Roentgenological examination: 5/9/33- Roentgenograms show a cystic

trabeculated expansion of the distal end of the ulna measuring 3x3½x7½ cm.

with very pronounced rarefaction of bone through the region of expansion.

Diagnosis: Giant-cell tumor of the distal end of the ulna.

Therapeutic procedure: It was decided to treat the case by radi-

ation and to allow the patient to return for surgery in case a satisfactory

result was not obtained.

Radiation therapy: 5/28/33 - 350 R- units of radiation was deliv-

ered into the tumor through ulnar, dorsal, radial and volar ports, delivering

about 1190 R- units into the tumor itself. The radiation was energized by

200,000 volts, filtered through ½ cu. and 2 mm. Al. at a distance of 60 cm.

The patient returned after one week for further radiation. (Re-

calcification is not to be expected for a period of about three months and

during the three weeks directly following therapy there may be slight further

lysis of bone)

11/20/33 - Patient returned showing a subsidence of the swelling

of the distal right ulnar region and showing slight brownish pigmentation in

the overlying skin. The circumference of the forearm at a level two inches
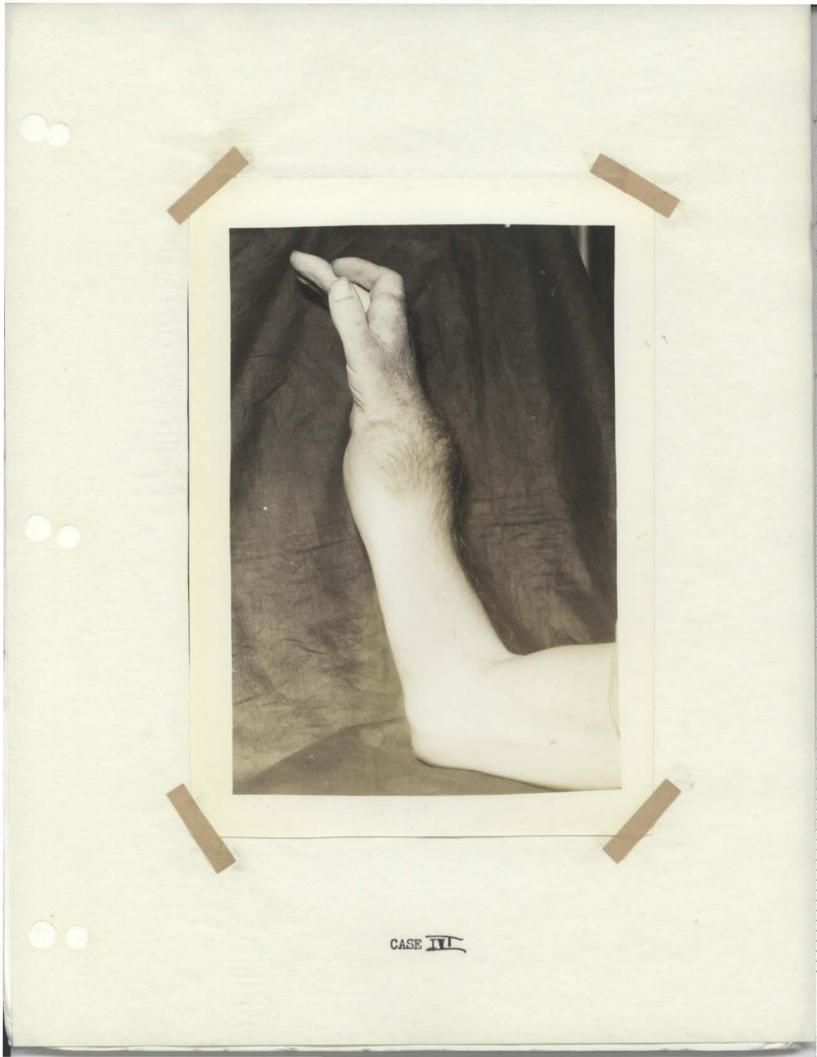
above the wrist measures 6½ inches at this time.

Further A.P. and lateral radiographs show the cyst to have shrunk to about half its previous total volume. It now measures about 2.3 mm. in diameter and is 7 cm. in total length. The cyst originally measured about 3.5 cm. in diameter and 7 cm. in length. In addition there has been a definite increase in calcification through the cortex and along the trabeculation within the cyst.

No further radiation was given.

Discussion: This case was included to illustrate the very satisfactory results obtained by radiation therapy in selected cases. Radiation therapy is indicated in clinical and roentgenological positive giant-cell tumors. Best results are obtained where radiation is given without the deleterious effects of surgical interference for biopsy.

The cosmetic effect is not as good as might be obtained by curettage, but radiation is preferable to this more radical procedure when the knee area is extensively involved, necessitating resection, bone grafting, prolonged disability and oftentimes loss of function.

Admittedly, each case is an individual problem and the innumerable factors involved call for different lines of attack.

CASE IV
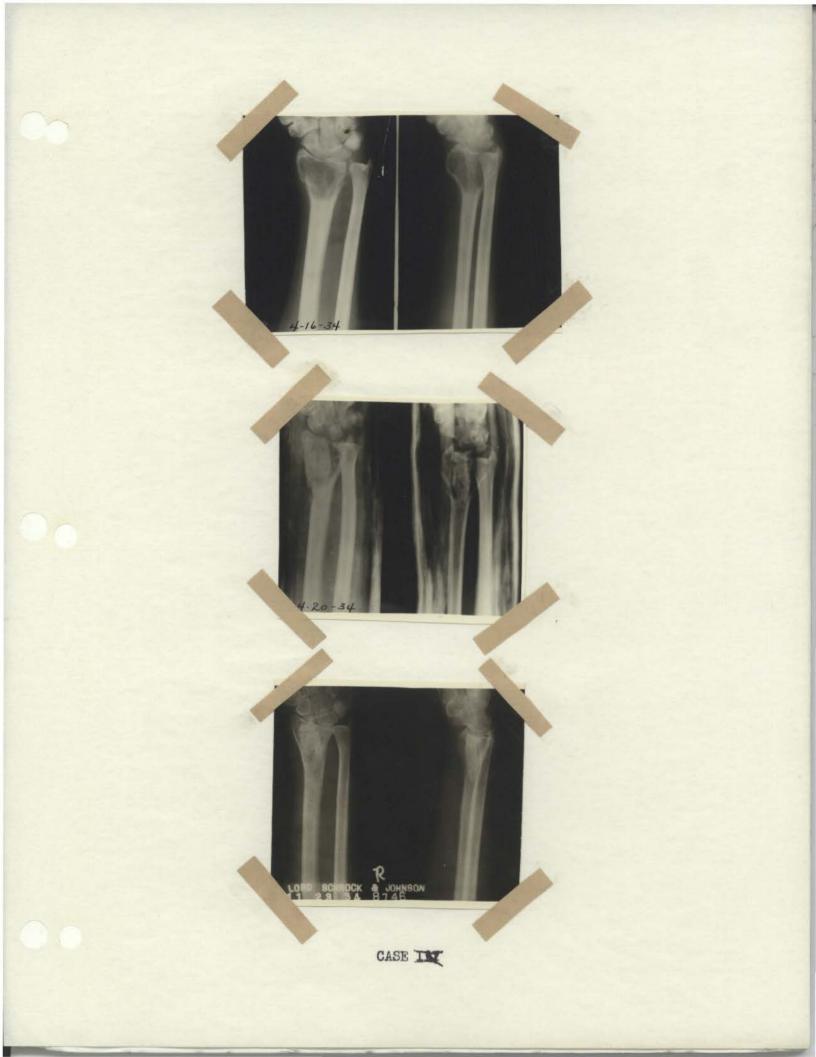
Mr. E. McL., male, age 60, seen by Dr. Robert D. Schrock.

History: Fracture at wrist in 1930. Wrist splinted. Patient went to work four months later. Swelling continued to slowly increase in size. Injury to this area again in 1933. No pain present except rheumatic pain, not confined to this area alone.

Symptoms: Progressive enlargement of distal third of right forearm on the radial side. Gradually increasing deformity and dysfunction. No pain.

Roentgenological examination: Roentgenograms reveal large, single, cystic trabeculated expansion of the distal end of the right radius, with very pronounced rarefaction of bone through the region of expansion. A very thin layer of increased density is seen surrounding the expansion on the ulnar side, and at the base of the radial side. This is probably a very thin cortical capsule. There is no evidence of the shaft seen through the expansion. The ulna is displaced medially and distally.

Diagnosis: Giant-cell tumor of distal third of right radius.

Discussion: This case was included to illustrate the simplicity of diagnosing a truly typical giant-cell tumor by roentgenological and clinical examination. The history is typical - trauma and slow progressive increase in size of the tumor, but the absence of pain and advanced age of the individual teach a lesson ih themselves, by illustrating that textbook symptoms and generalities must not be adhered to dogmatically. The absence of one or more typical findings must not overweigh the bulk of proof.

4-16-34

4-20-34

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CASE IV

Mrs. W.R.M., female, age 21, entered the offices of Drs. Lord, Schrock and Johnson on April 16, 1934 because of pain and swelling in the right wrist area.

History: Pain in right wrist since autumn of 1933. No history of previous trauma. Slight swelling in area.

Symptoms: Pain and swelling in right wrist. Some limitation of motion.

Physical examination: Enlargement of distal third of right radius.

Roentgenological examination: Radiograms show a cystic trabeculated area involving the epiphysial portion of the right radius. This area of expansion is surrounded by a thin line of dense material having the same density as the cortical bone. A fracture of the articular cartilage is seen.

Clinical and roentgenological diagnosis: Giant-cell tumor of radius.

Operative procedure: Dr. Schrock attending. Radial incision made. Egg shell cortex found surrounding single cavity containing jelly-like substance grossly resembling giant-cell tumor tissue. Cavity cleared, ether pack inserted. Articular cartilage and dorsum of cortex fractured to prevent radial deviation. An immediate bone graft from the ilium was transplanted to the defect, because of the insufficient strength in the cortex to maintain the proper position of the wrist upon the forearm. The graft was drilled ten or twelve times to permit early vascularization. The egg-shell cortex was then firmly collapsed upon this drilled, spongy bone. Moulded splint immobilization.

Microscopic examination: Specimen consists of light brown material from a bone cyst in the forearm. Several sections show numerous giant cells

containing large numbers of nuclei, an inflammatory reaction, and moderate mononuclear reaction. Some areas are typically inflammatory, while others are masses of giant cells in a fibrous matrix.

Gross pathology: Tumor showed characteristic thinning of cortex somewhat egg-shell in appearance, but a little more vascular than the true bone cyst. The contents were rather well organized granulation-like tissue, fairly vascular and with a definite limiting membrane. The articular cartilage of the radius showed nicely the fracture demonstrable in x-ray together with the fracture on the dorsal surface.

Pathological diagnosis: Giant-cell tumor of bone.

Progress:

11/23/34 - Roentgenograms reveal graft has healed. Position good. No signs of recurrence. Wrist tends to flexion. Placed in cock-up splint.

3/15/35 - Wrist coming into dorsi-flexion position nicely. Hand used actively and in excellent condition.

Discussion: This case is included to illustrate the excellent results obtainable in favorable cases by surgical procedures. It is well to add in this connection, that the surgeon should be well trained in orthopedic procedures, to transplant bone grafts if necessary, to maintain proper anatomical relationships or to provide the best functional position if permanent fixation is inevitable.

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