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Giant-Cell Tumors of Bone (Osteoclastoma)

A PATHOLOGICAL AND HISTOCHEMICAL STUDY

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The ontogeny of giant-cell tumors of bone still remains the subject of considerable controversy, and many important questions remain unanswered in connection with the histogenesis and clinicopathological diagnosis of these tumors. The separation of the true giant-cell tumor of bone from the group of so-called variants and from the other dysplastic or dystrophic bone lesions, with which it has been confused in the past, is still not accepted by all authors. True giant-cell tumors can no longer be considered innocent growths; on the contrary, they represent a progressive process which can recur, undergo sarcomatous transformation in about 10 per cent of the cases, and even produce metastases without apparent previous malignant alteration. The alleged variants, on the other hand, usually have a favorable evolution, and can be cured with curettage or roentgen therapy in low doses.

Many bone lesions are classified as giant-cell tumors merely because of their roentgenographic appearance or because of the presence of giant cells in the histological preparations, when actually the lesions so classified are really of minor clinical importance. This loose method of classification has contributed to the prevailing confusion and has prevented the establishment of uniform criteria for the therapy of giant-cell tumors.

One of the most important questions, which is raised in nearly all papers concerning this subject, is the reliability of grading of giant-cell tumors as a guide to prognosis, that is, is it possible to predict with any assurance the ultimate outcome of a given case on the basis of the initial histology of the tumor? Grading of these tumors was proposed many years ago by Stewart [91] and Ewing [20] and especially emphasized by Jaffe, Lichtenstein, and Portis [39] who separated benign, aggressive, and malignant types. Meyerding and Broders [55], the Bone Sarcoma Registry, and many others, distinguish a benign and malignant form.

On the other hand Geschickter and Copeland [23,24], Willis [100], Russell [71], and lately Williams, Dahlin, and Ghormley [99] have contended that giant-cell tumors which prove to be aggressive or frankly malignant are not initially distinguishable histologically from those with a benign course. Recently, Jaffe [36] called the giant-cell tumor a rather treacherous lesion and Coley, Higinbotham, and Kogure [14] termed it an unpredictable neoplasm.

Jaffe [38] mentioned four cases in which pulmonary metastasis occurred without the original tumors or their metastases ever developing frankly malignant histological characteristics. He stated that unfortunately one really cannot predict from the histological pattern which cases will metastasize. A small number of similar cases have been reported by other authors [19,24,41,46,59,65,71].

In the present paper a series of eighty-five giant-cell tumors studied in the course of the last twenty years are reviewed. On the services where these tumors were treated, the treatment of choice for a giant-cell tumor is segmental resection, followed by massive bone grafts [96]. This procedure has made possible the gross examination of the complete tumor in a great number of cases (forty-one), most of them unchanged by previous treatment. A great part of this material was received fresh or under conditions of preservation which allowed tissue cultures to be carried out in some cases, as well as a systematic histochemical study. Early in this investigation we studied the acid mucopolysaccharides, glycogen, lipids, and alkaline phosphatase [78], and later studied the acid phosphatase [81,82], and more recently, the beta-glucuronidase [8] and succinic dehydrogenase [84]. The results of these studies in normal bone during ossification were compared with those in a large series of pathological processes characterized by bone reabsorption and remodeling or by the presence of giant cells of the osteoclastic and chondroclastic types. Intense enzymatic activity of acid phosphatase, beta-glucuronidase, and succinic dehydrogenase with no evidence of alkaline-phosphatase activity was regularly demonstrated in the normal chondroclastic and osteoclastic cells. The multinucleated giant cells of the giant-cell tumor of bone and of the so-called variants exhibited identical histochemical behavior. Thus, it seems evident that the histogenetic and physiological characteristics of these different cells are similar in many respects.

There have been very few histochemical studies of giant-cell tumors. The phosphatases were investigated by Gomori [27,28,29], Changus (cited by Boyd [5]), Gilmer [25], and Pepler [69]. Non-specific esterases were studied by Pepler in a limited number of giant-cell tumors, but the results were contradictory. Pais and Baruffaldi [67] investigated the polysaccharides, alkaline phosphatase, lipases, and beta-glucuronidase in fifteen giant-cell tumors and compared the results in these tumors with those in the osteoclastic elements of normal tissue and of certain pathological tissues, including tissues containing tuberculous and foreign-body giant cells.

The extensive histochemical studies on the series of giant-cell tumors reviewed here may serve to clarify some of the disputed aspects of the histogenesis and behavior of this tumor.

MATERIAL AND TECHNIQUE

This series, which includes all cases studied up to January 1959, consists of eighty-five true giant-cell tumors of bone. Reports of forty-six of them were published previously in 1951 [87]. At that time fifty-seven cases were reported but on careful re-evaluation eleven were reclassified as so-called variants.

In many cases abundant material for histopathological study was available from tissue obtained at surgical biopsy or curettage. In forty-one cases the complete specimen was available since thirty-five segmental resections and six amputations had been performed. The amputations had been performed in the earlier cases. In forty-eight of the eighty-five cases, aspiration biopsy had been performed before the tumor was explored surgically. The diagnoses, based on the aspiration biopsy, were proved to be correct in the vast majority of cases. Smears of the aspirated material were stained with hematoxylin and eosin and with the May

Grünwald-Giemsa technique. The remainder of the material was embedded in paraffin—thus permitting a comparative cytological and histological study of the lesion [76].

In addition to the ordinary staining techniques used on the surgical material fixed in 10 per cent formalin and embedded in paraffin, Del Rio Hortega's silver method for reticular fibers and occasionally that for reticulo-endothelial elements were used on frozen sections.

For histochemical study, fresh material was used which had been fixed in 10 per cent formalin, or neutral formalin, and in 80 per cent alcohol (both at 5 degrees centigrade) as well as in Rossmann's fluid.

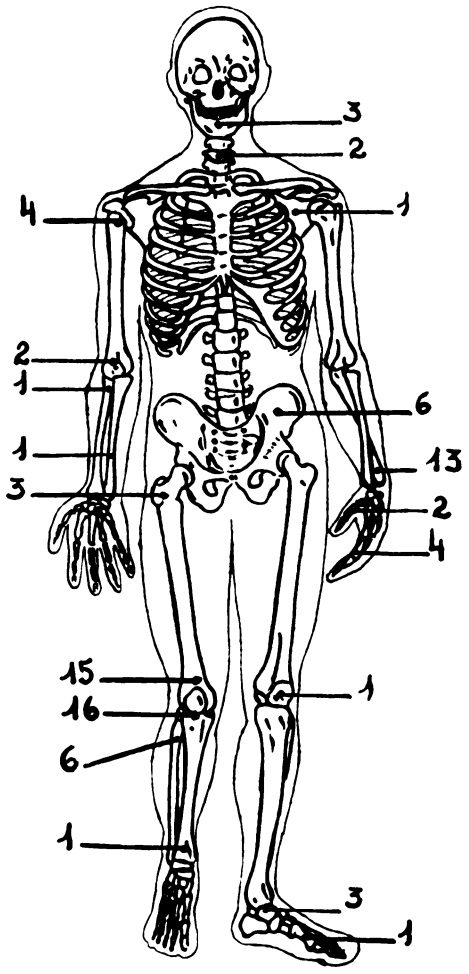

FIG. 1

Skeletal distribution of eighty-five cases of giant-cell tumor.

Glycogen, mucoproteins, acid mucopolysaccharides, lipids, and alkaline phosphatase were investigated in thirty-two cases, acid phosphatase in eighteen, beta-glucuronidase in ten cases, and succinic dehydrogenase in the last six.

Glycogen and mucoproteins were stained by McManus or Hotchkiss periodic acid-Schiff technique after fixation in 80 per cent alcohol at 5 degrees centigrade and in Rossmann's fluid. These preparations were controlled by ptyalin digestion at 37 degrees centigrade for two to three hours or by exposure to takadiastase at room temperature for from one-half to one hour. Lipids were studied using Sudan

IV and Sudan black B on frozen sections. Acid mucopolysaccharides were stained by the Lison-Sylvén method (0.5 per cent toluidine blue), by Hale's colloidal iron method, and by alcian blue (at pH 2.7) according to Mowry's modification [58].

Alkaline phosphatase was demonstrated by Gomori's technique [78], using different incubation periods (ten minutes, thirty minutes, three hours, and twenty-four hours) at pH 9.2. Acid phosphatase was studied in eighteen cases on frozen sections of tissue fixed in neutral formalin at 5 degrees centigrade, using Gomori's technique [28]. For comparison, eight cases were studied with Burton's azo-dye coupling method [7]. Times of incubation varied between five minutes and twenty-four hours.

Fishman and Baker's method [22] was used to demonstrate beta-glucuronidase. This method uses 8 hydroxyquinoline-glucuronic acid as a substrate and can be prepared biosynthetically at low cost.

The histochemical distribution of succinic dehydrogenase was studied by Rosa and Velardo's technique [70], which uses neotetrazolium chloride on fresh, unfixed, frozen sections (twenty to fifty micra thick). In some recent cases the new nitro-blue tetrazolium technique of Nachlas and his associates [61] was used. This technique provides a better visualization of the sites of enzymatic activity in thinner tissue sections under aerobic conditions, after relatively short incubation periods.

A large number (seventeen) of the so-called variants of the giant-cell tumor, aneurysmal bone cysts (six), epiphyseal chondroblastomata (two), chondromyxoid fibromata (one), and non-osteogenic fibromata (eight) were also studied with the same histochemical techniques, as well as solitary bone cysts (eighteen), benign osteoblastomata (two), and giant-cell tumors of the synovial membrane (twenty-three). The results obtained in this material and in the experimental foreign-body granulomata which are now being studied in collaboration with Dr. Cabrini will be the subject of a future publication.

CLINICAL CHARACTERISTICS

It is not the purpose of this paper to present in detail the clinical and roentgenographic features of this tumor. Only a few data concerning the age incidence and the location of the tumor in this series will be given.

Age Incidence

Fifty-eight cases (68 per cent) occurred in patients between twenty and forty years of age; the largest number (thirty-seven) occurred in patients during the third decade, which agrees with the statistics of the majority of authors [13,14,38,48,59,99]. Only nine patients were between the ages of fifteen and twenty years, and none was under fifteen. These authors also noted that giant-cell tumors are rarely found in adolescents and children. In a series of 101 cases Williams and his associates [99] found only ten cases in young people between ten and twenty years and none in patients under ten years; the youngest patient in the series reported by Coley, Higinbotham, and Kogure [14] was eleven years old, and Jaffe [38] mentions an exceptional case of a ten-year-old child.

It is noticeable that some European authors [26], and especially the French [31,94], report a large number of cases of giant-cell tumor in children. Of the eighty-nine cases in Trifaud and associate's series [94], ten were in children under ten years of age and forty-two were in patients younger than twenty years. These figures should be taken with some reservation because from the illustrations published it would appear that several of the tumors represent so-called variants and not true giant-cell tumors. In a recent revision of the material of the Children's Hospital in

Buenos Aires, carried out with Dr. Derqui, fifty tumors or pseudotumors, simulating giant-cell tumors, in children under twelve years were studied and not one case of genuine giant-cell tumor was found.

Localization

As shown in Figure 1 the most frequent site of the giant-cell tumors in this series is the lower epiphysis of the femur (fifteen cases), upper end of the tibia (sixteen cases), and lower end of the radius (thirteen cases). The relative frequency in this series of lesions in the phalanges, metacarpals, and metatarsals (seven cases) is quite remarkable, since these are considered rather rare locations. These tumors are exceptional in the patella and scapula and they are found only very rarely (two cases) in the spine. In this series there were three cases in the mandible. These figures agree with other published statistics [13,14,17,38].

Only a few authors mention multiple sites [13,38,45]. These can only be accepted as giant-cell tumors after hyperparathyroidism has been definitely excluded.

I have seen one patient in whom giant-cell tumor was found in three locations simultaneously—the iliac bone, femur, and tibia. Muscolo and Cabrini [60] reported a case of giant-cell tumor with one focus in the radius and another, which appeared later, in a metacarpal. They considered this to be a metastasis but in my opinion it is probable that this case belongs to this exceptional group of giant-cell tumors with multiple foci.

PATHOLOGICAL ANATOMY

Gross Pathology

The tumor presents, on section, a very characteristic appearance. Although there is considerable variability, all specimens show extensive soft fleshy areas which alternate in color from gray to a light red or dark hemorrhagic hue. The gray zones are of a somewhat firmer consistency, but are friable. The tumor is situated eccentrically in the epiphysis (Fig. 2), extending toward the articular cartilage and toward the metaphysis. In the more advanced stages, these tumors may occupy the whole metaphyseal and epiphyseal region. These extensive tumors are observed usually in the upper extremity, especially in the lower end of the radius. The explanation for this high incidence of extensive tumors in the upper extremity would appear to be that these tumors do not cause symptoms when they are located in non-weight-bearing bones (Fig. 4). As a result patients do not seek medical care until their tumors are far advanced. In the phalanges or metacarpals the tumor may occupy nearly all of the bone (Fig. 4).

The tumor is traversed by thin septa of connective tissue or bone and is surrounded by a thin bone shell which in the more advanced cases is distended beyond the surfaces of the adjacent normal bone as if it were inflated (Figs. 3-A, 3-B, and 5). This thin shell of bone does not represent the expanded cortex. Rather, it is a new displaced cortex formed by osteoclastic absorption of the endosteal surface and constant periosteal-bone deposition, a mechanism which has already been well described by Virchow [97].

In advanced tumors hemorrhage is more abundant, and small bright red or brownish cystic cavities are present. Never found are the large spaces and cystic cavities traversed by thin septa that are seen in aneurysmal bone cysts. Yellowish grey necrotic areas or zones of a sulphur-yellow color typical of xanthoma are often seen in advanced tumors; however, such zones are found only in limited areas and do not constitute a major portion of the lesion, as is the case in a histiocytic xanthogranuloma (non-osteogenic fibroma) which on rare occasions may be located in the epiphysis and simulate a giant-cell tumor roentgenographically (Fig. 7).

FIG. 2

Photograph and roentgenogram of a giant-cell tumor, in the lower end of the femur of a woman, forty-nine years old, localized eccentrically in the epiphysis and the adjacent metaphyseal region. Nine months previously the patient suffered a spontaneous fracture which consolidated after conservative treatment. In the months following, the lesion became evident and after a histological diagnosis of malignant giant-cell tumor was made, an amputation was done. After a review of all the pathological material, the tumor was reclassified as an aggressive giant-cell tumor. (Reproduced with permission from "Tumores a células gigantes de los huesos." By Fritz Schajowicz and S. Mondolfo. Rev. Ortop. y Traumatol., **21**: 3–34, 1951.)

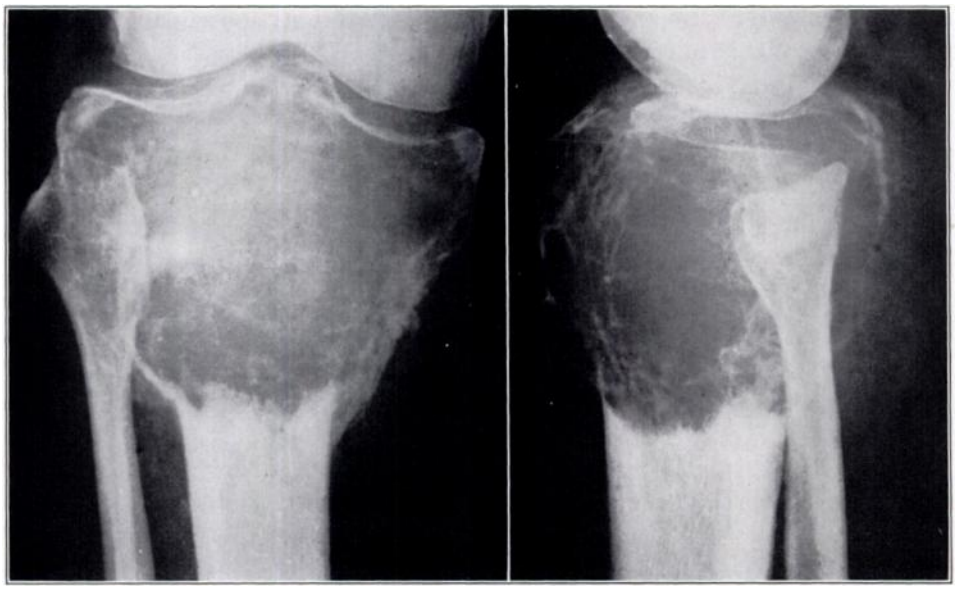

FIG. 3-A

Roentgenograms of a giant-cell tumor, in the upper end of the tibia of a woman, fifty-two years old, which involves the epiphysis and the adjacent shaft. The cortex is expanded, reduced to a thin newly formed bone shell partially destroyed by the tumor.

A giant-cell tumor, even in its more advanced stages, respects the articular cartilage, which is only rarely perforated (Fig. 6). Invasion of the joint space by the tumor is somewhat more frequent by way of the synovial and capsular tissues after the thin newly formed bone cortex has been destroyed. Perforation of the cortex occurs quite often and does not indicate that the tumor is malignant. The margins of the tumor within the metaphyseal spongy tissue are not well defined; there is no delimiting fibrous or bone membrane. This explains the frequency of recurrences after curettage (Fig. 8).

Microscopic Pathology

The histological diagnosis should be based on a study of those areas which have not been modified by extensive hemorrhage and such phenomena as necrosis or cicatricial fibrosis. In well preserved areas the histological structure is characterized by a great number of multinucleated giant cells which are uniformly distributed in the tumor. These cells are irregularly delimited and have prolongations

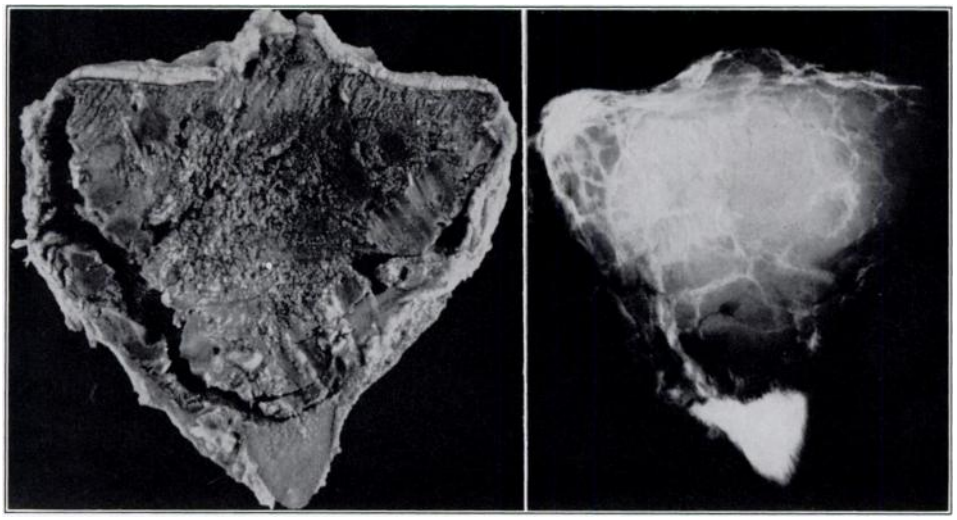

FIG. 3-B

Photograph and roentgenogram of the resected specimen. The large space (visible in photograph) is an artefact.

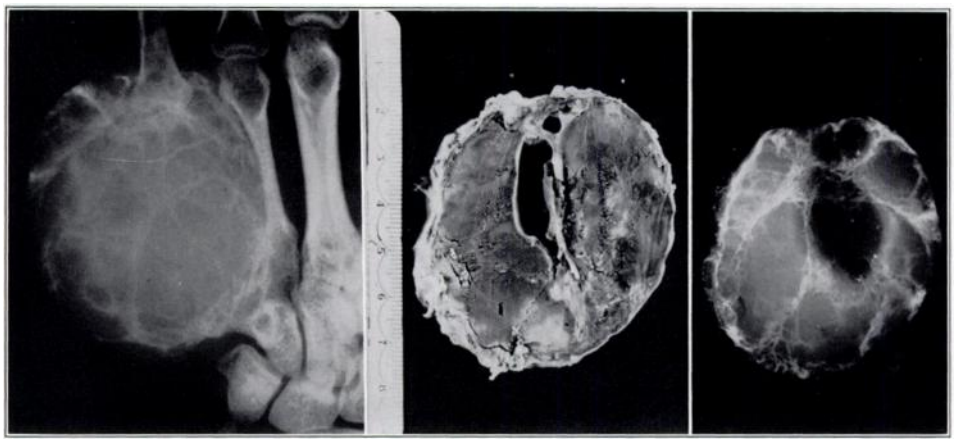

FIG. 4

The roentgenographic and gross pathological appearance of a giant-cell tumor involving the whole extent of the fifth metacarpal of a woman, twenty-two years old. The bone contour is very much distended and the tumor has caused compression atrophy of the adjacent fourth metacarpal bone. The treatment consisted in resection and bone-grafting.

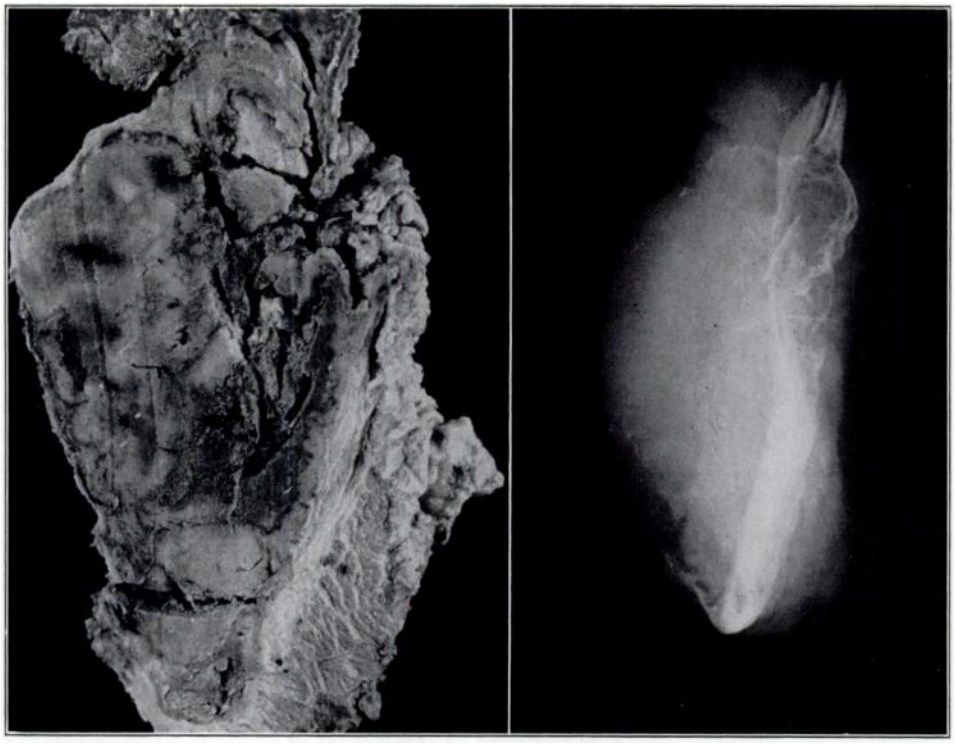

FIG. 5

Photograph and roentgenogram showing the typical aspects of a giant-cell tumor in an exceptional site in the scapula in a thirty-six-year-old man. The bone contour is very much expanded and the newly formed fine bone shell has been destroyed throughout an extensive area.

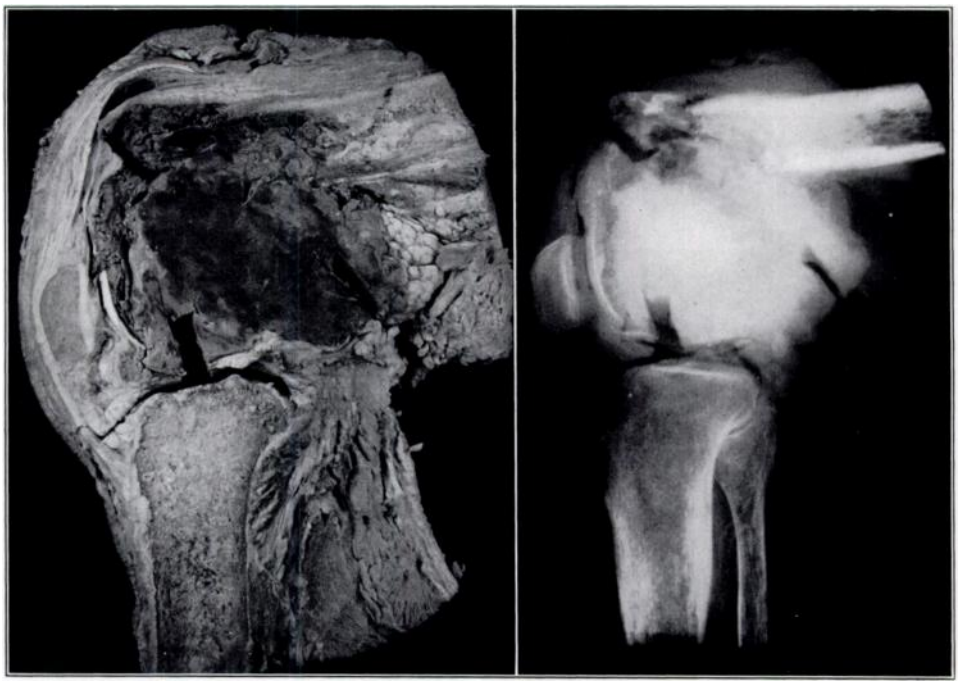

FIG. 6

Photograph and roentgenogram of the amputation specimen of a very advanced giant-cell tumor in the lower end of the femur in a fifty-two-year-old man. This specimen (histologically not malignant) demonstrates the extension of the lesion with complete destruction of the cortex and a great part of the articular cartilage, with invasion of the joint space after a long period without treatment. (Reproduced with permission from "Tumores a células gigantes de los huesos." By Fritz Schajowicz and S. Mondolfo. Rev. Ortop. y Traumatol., **21**: 3–34, 1951.)

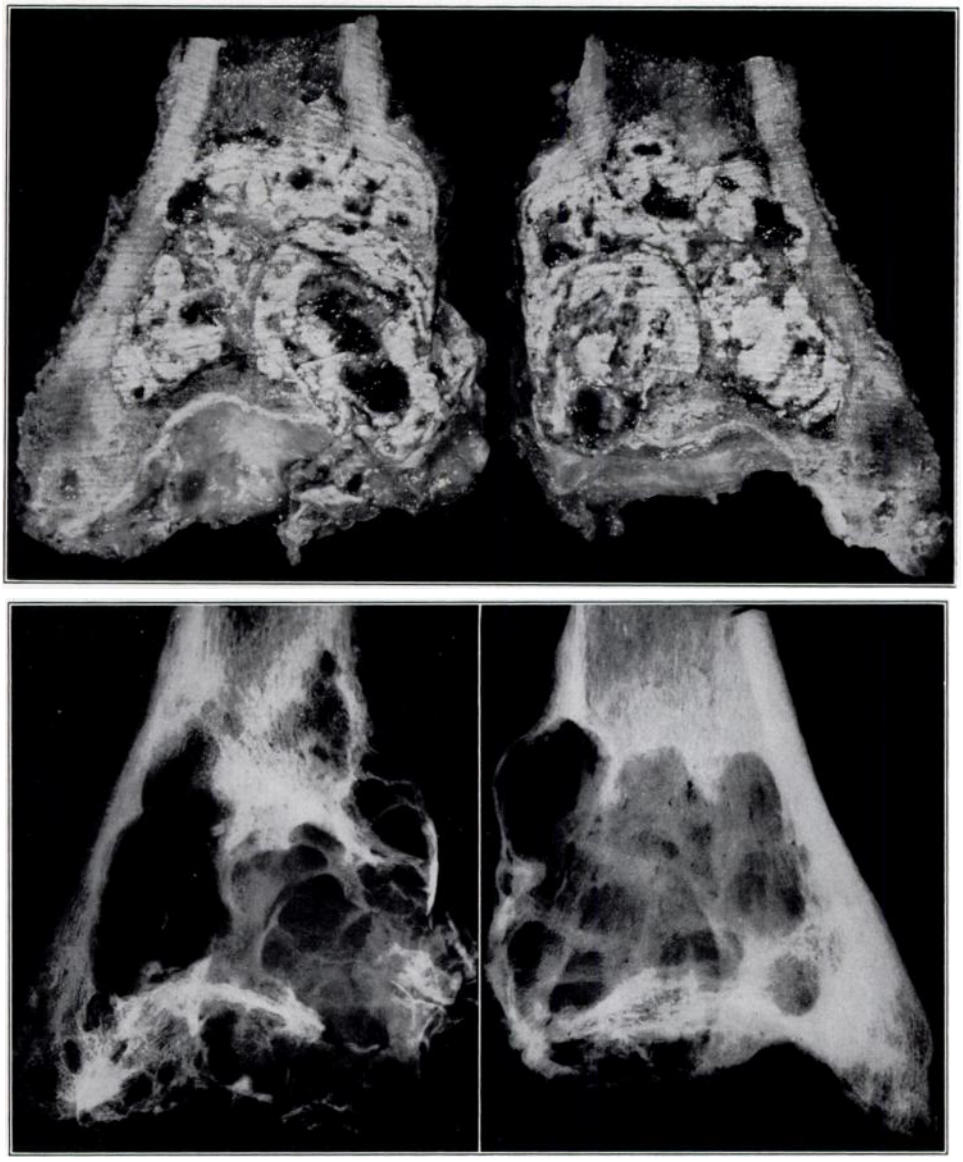

FIG. 7

Photograph and roentgenogram of a recurrent lesion in the distal end of the tibia of a thirty-year-old man. The roentgenographic appearance simulates a giant-cell tumor, but the gross pathological appearance, with predominance of the yellowish xanthomatous tissue and the histological pattern characterized by fibrous tissue, abundant lipoid-bearing foam cells, and sparse giant cells, indicate that it is a histiocytic xanthogranuloma (non-osteogenic fibroma) and not a genuine giant-cell tumor. This lesion had the same microscopic appearance when it was treated by curettage ten years previously.

of their abundant cytoplasm which is more or less basophilic and homogenous, or slightly granular. Sometimes, there are numerous vacuoles of different sizes in the cytoplasm. The size and number of nuclei are variable, but usually there are more than fifteen to twenty, and there may be hundreds. The appearance of the nuclei is identical to that of the nuclei of the mononuclear stromal cells which constitute the other essential element of the tumor. These cells are round, oval, or fusiform in shape and generally have large nuclei with little chromatin and only one or two inconspicuous nucleoli; there are only a few typical mitoses to be found (Figs. 9-A, 9-B, and 9-C).

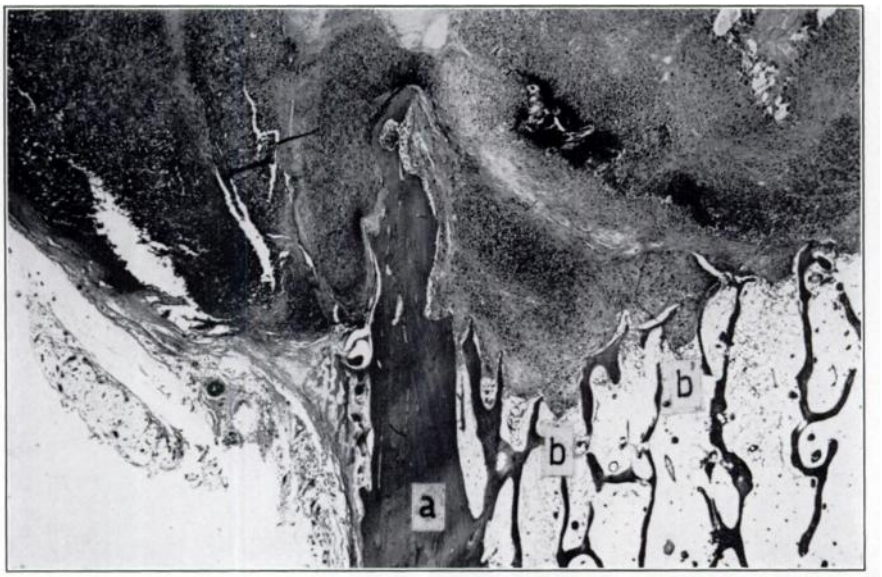

FIG. 8

Photomicrograph at low magnification, showing the destruction of the bone cortex *a* and the extension of the tumor into the extra-osseous tissues and into the marrow spaces *b*, *b'*. In the marrow spaces there is no bone or fibrous membrane. This explains the frequency of the recurrences after curettage. (Reproduced with permission from "Tumores a células gigantes de los huesos." By Fritz Schajowicz and S. Mondolfo. Rev. Ortop. y Traumatol., **21**: 3–34, 1951.)

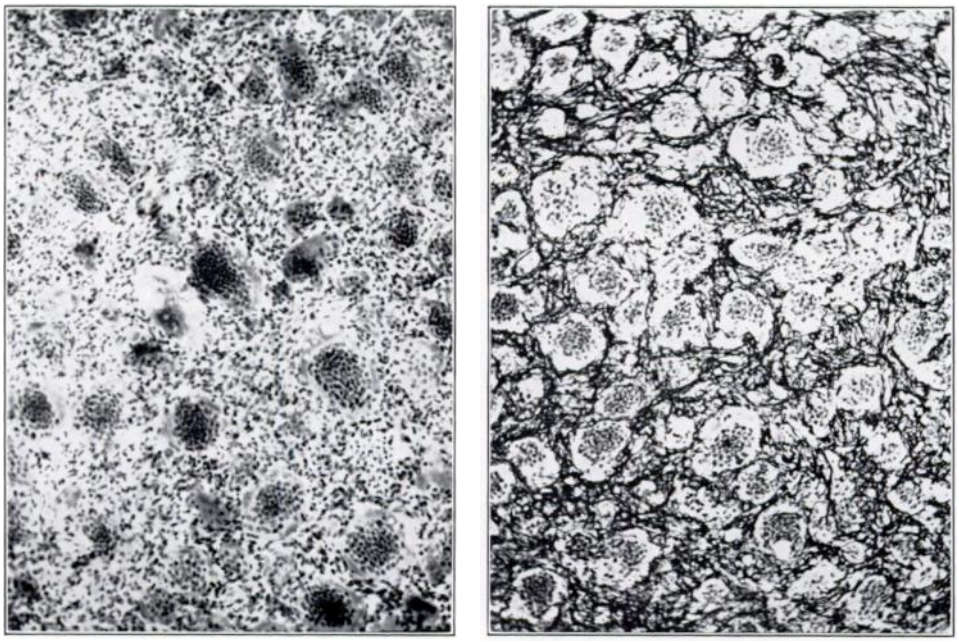

FIG. 9-A

FIG. 9-B

Photomicrographs (Fig. 9-A, × 70; Fig. 9-C, × 440) showing the characteristic histological pattern of a giant-cell tumor, with numerous multinucleated cells, the nuclei of which have a great similarity to those of the mononuclear stromal cells (hematoxylin and eosin).

Fig. 9-B: Reticulum stained with Del Rio Hortega's silver-impregnation technique. Numerous reticulin fibers, forming a dense network, surround individual cells and encircle the giant cells (× 70).

With the usual staining technique, the tumor shows very little collagenous stroma in the zones of active growth; nevertheless, with silver stains, a very dense network of reticular fibrils is seen surrounding the individual cells without pene-

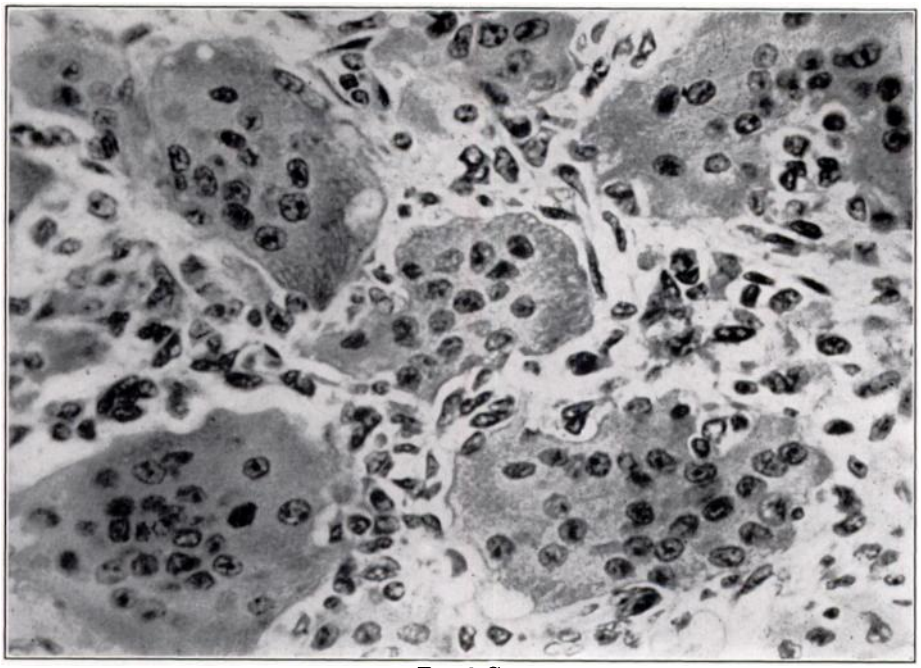

FIG. 9-C

trating the giant cells (Fig. 9-B). The tumor is rich in newly formed blood vessels, with walls composed only of endothelial cells, and in vascular channels which are lined by tumor cells themselves or by an endothelial layer. This vascular pattern would explain the presence of abundant hemorrhages, both recent and old, with phagocytosis of blood pigment by the mononuclear cells of the stroma. In all tumors there are some areas which are composed of spindle cells of a fibroblastic type with abundant intercellular collagenous substance; occasionally, groups of lipoid-bearing foam cells (xanthomatous cells) are present, particularly in the vicinity of necrotic foci. In these areas the giant cells are moderate in size and few in number, or there are none at all. According to Jaffe [38], this pattern reflects spontaneous regression and healing in the tumor. In an occasional giant-cell tumor this healing reaction may be predominant over the characteristic tissue, a histological pattern which indicates a favorable prognosis, as proposed by Scaglietti and Mondolfo [73] many years ago. Several epiphyseal lesions have been observed in which the whole specimen showed this fibroxanthomatous portion with only scattered giant cells. These cases were interpreted as examples of histiocytic xanthomatous granuloma or non-osteogenic fibroma [39,86,87]. They have a naturally favorable prognosis and do not constitute a healing reaction in a genuine giant-cell tumor. One of our cases showed the same predominant fibroxanthomatous appearance, both macroscopically and microscopically (Fig. 7) when the tumor recurred ten years after curettage.

The collagenous septa, of variable thickness, which traverse the tumor, frequently contain trabeculae of reactive new bone. I have not seen any convincing evidence of new-bone formation by the mononuclear tumor cells [59,88,99].

Histochemical Studies

1. *Enzymes*

In the giant-cell tumors there was intense alkaline-phosphatase activity, which was confined to the vessels (Fig. 11-A, *a*). The multinucleated giant cells (Fig. 11-A, *d*) and the mononuclear stromal cells did not contain alkaline phos-

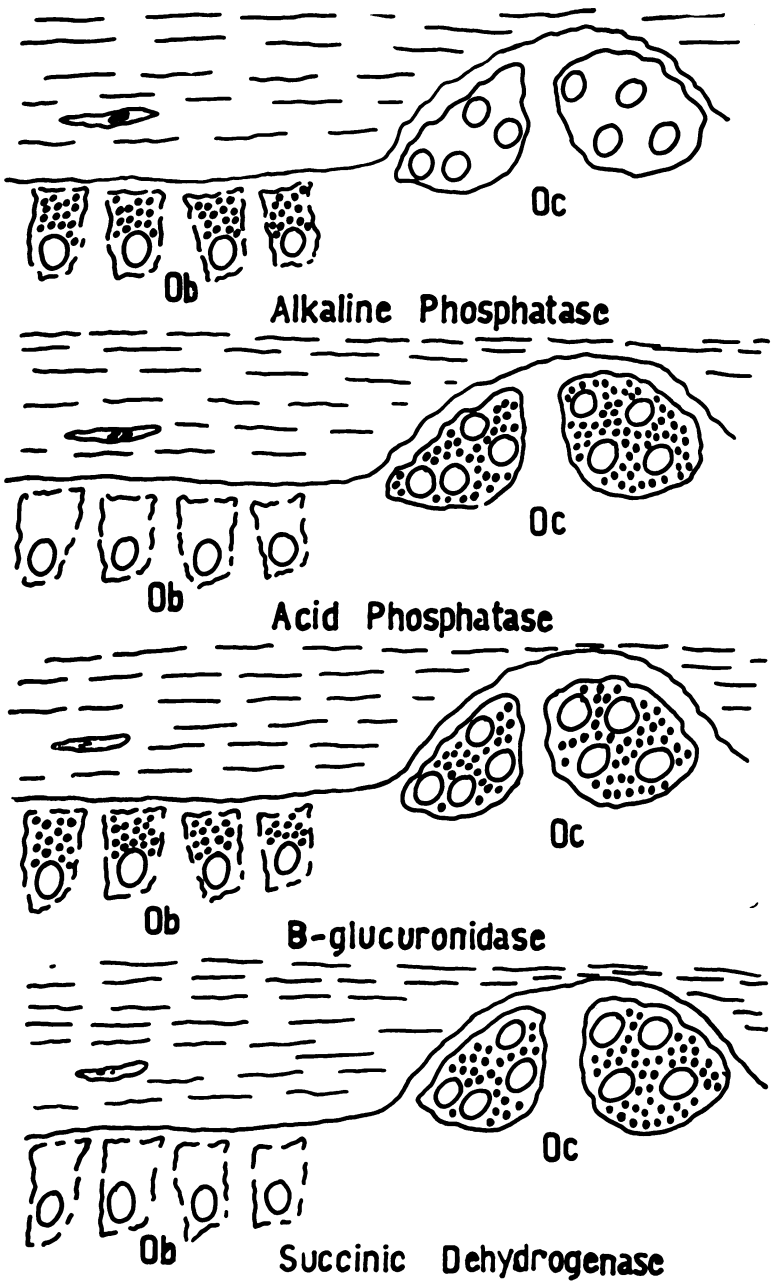

FIG. 10

Schematic drawing showing the intracellular distribution of different enzymes during normal bone formation and destruction. Osteoblasts: *Ob;* and Osteoclasts: *Oc.* Enzyme activity is represented by black dots.

phatase, in contrast to the highly positive osteoblasts surrounding the new-formed subperiosteal bone trabeculae (Fig. 11-B, *b*). The osteoclastic giant cells showed no activity (Fig. 11-B, *d*).

The multinucleated giant cells exhibited a strong acid-phosphatase activity which appeared after five to ten minutes of incubation, whereas the mononucleated cells only commenced to react after more than three hours' incubation.

Topographically, the results obtained by Gomori's method and Burton's azo-dye technique are identical, but the two techniques showed differences in

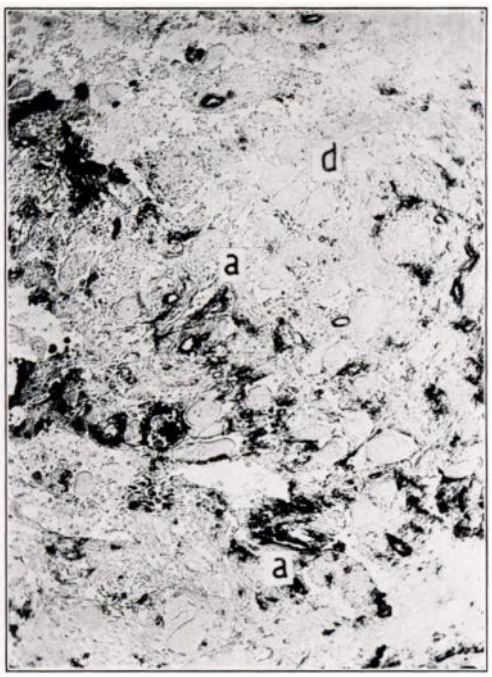

FIG. 11-A

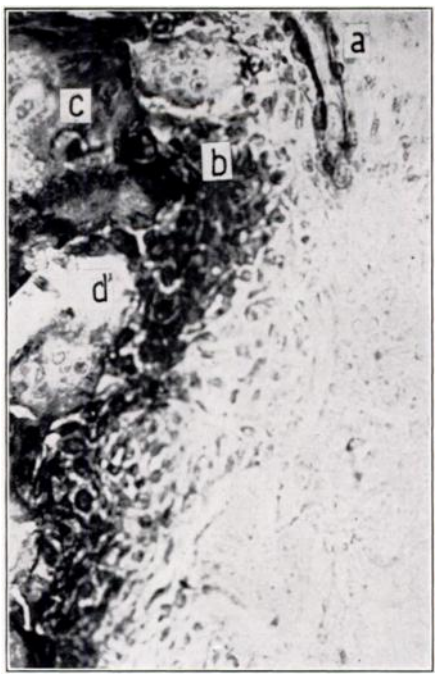

FIG. 11-B

Giant-cell tumor of the femur stained for alkaline phosphatase (Gomori's technique, incubation time, thirty minutes). The enzyme is localized in the blood vessels *a*, osteoblasts *b*, and some young cells included in the trabeculae *c*. The multinucleated giant cells of the tumor *d* and the osteoclasts *d'* are lacking in enzyme (Fig. 11-A, × 80; Fig. 11-B, × 360).

FIG. 12-A

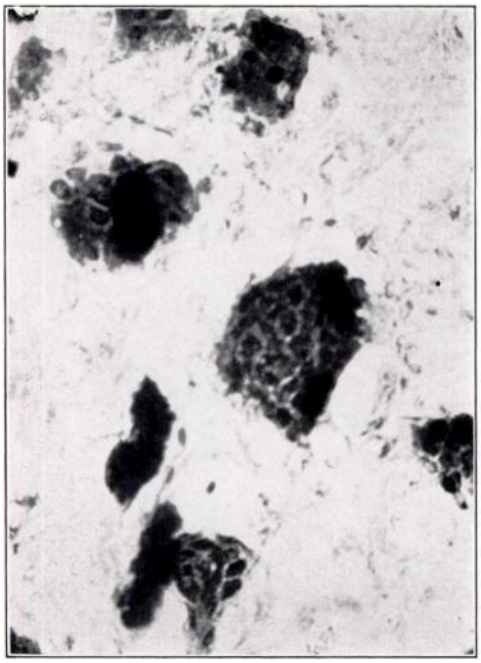

FIG. 12-B

Giant-cell tumor of tibia stained for acid phosphatase (Gomori's technique, frozen section, incubation time, thirty minutes: Fig. 12-A, × 175; Fig. 12-B, × 345). Intense enzymatic activity is observed in the multinucleated giant cells localized predominantly in the nuclei; it is lacking in the mononuclear stromal cells.

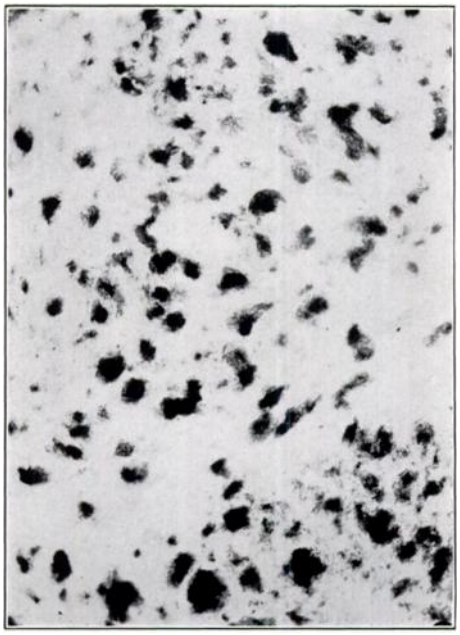

FIG. 13-A

FIG. 13-B

Giant-cell tumor of femur stained for acid phosphatase (Burton's azo-dye technique, frozen section, incubation time, two hours: Fig. 13-A, × 75; Fig. 13-B, × 345). Intense enzymatic activity is shown, localized predominantly in the cytoplasm of the giant cells.

cytological details. Gomori's method gave predominantly nuclear images (Figs. 12-A and 12-B), whereas Burton's azo-dye coupling method showed staining of the cellular cytoplasm, the nuclei remaining almost negative (Figs. 13-A and 13-B).

Burton's method gave precipitates after incubation for several hours; this makes it very difficult to detect small amounts of enzymatic activity.

The multinucleated giant cells present in aneurysmal bone cysts (Fig. 14)

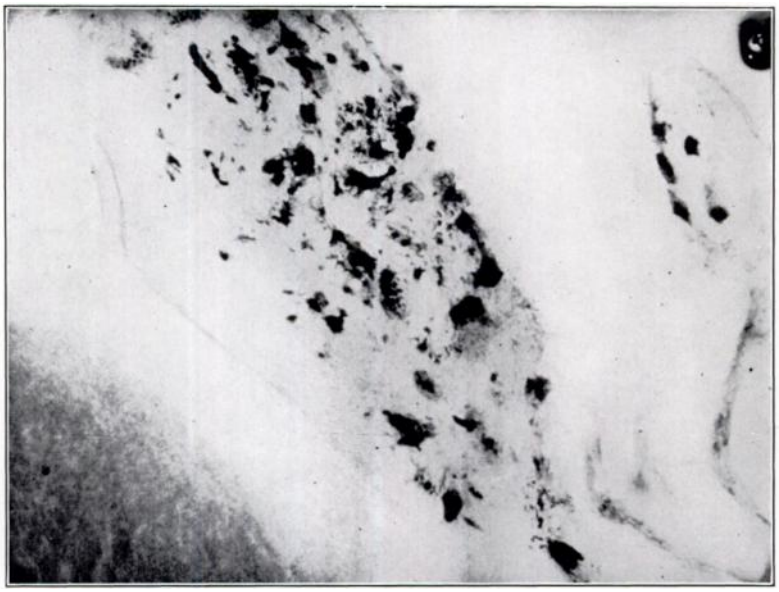

FIG. 14

Aneurysmal bone cyst stained for acid phosphatase (Gomori's technique, frozen section, incubation time, one hour, × 90). Strong enzymatic activity is observed in the numerous giant cells of different sizes present in the septae surrounding the blood spaces.

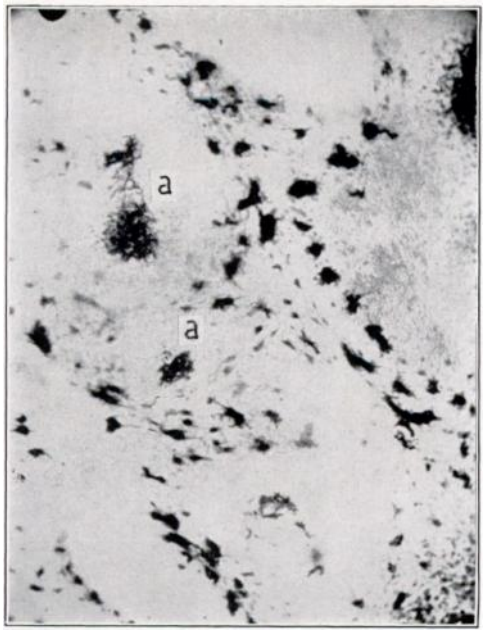

FIG. 15-A

FIG. 15-B

Osteogenic sarcoma of humerus stained for acid phosphatase (Gomori's technique, frozen section, incubation time, thirty minutes: Fig. 15-A, × 73; Fig. 15-B, × 310). Intense activity in the numerous multinucleated giant cells of osteoclastic type is observed. Some calcified bone trabeculae also appear black, *a*.

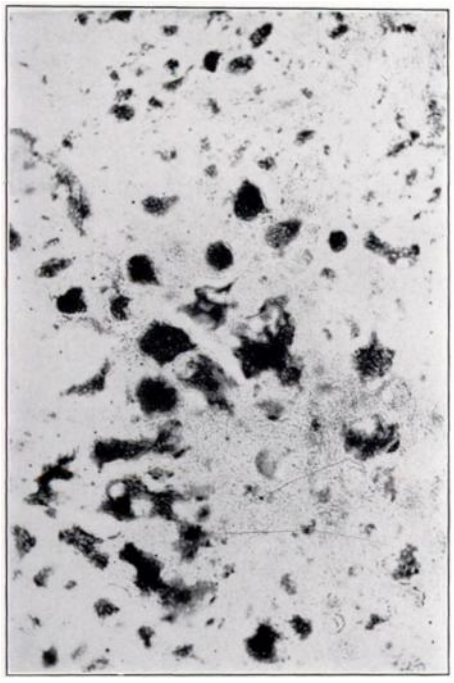

FIG. 16-A

FIG. 16-B

Giant-cell tumor of tibia stained for beta glucuronidase (Fishman and Baker's technique, frozen section, incubation time, one hour: Fig. 16-A, × 80; Fig. 16-B, × 360). The enzymatic activity is localized, especially in the cytoplasm of the multinucleated giant cells in different stages of evolution.

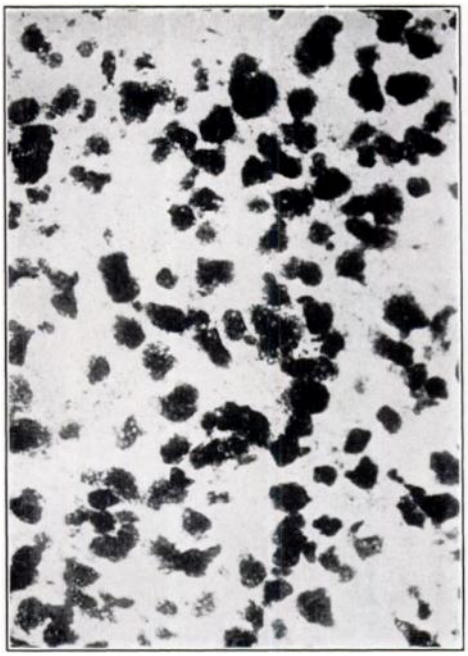

FIG. 17-A

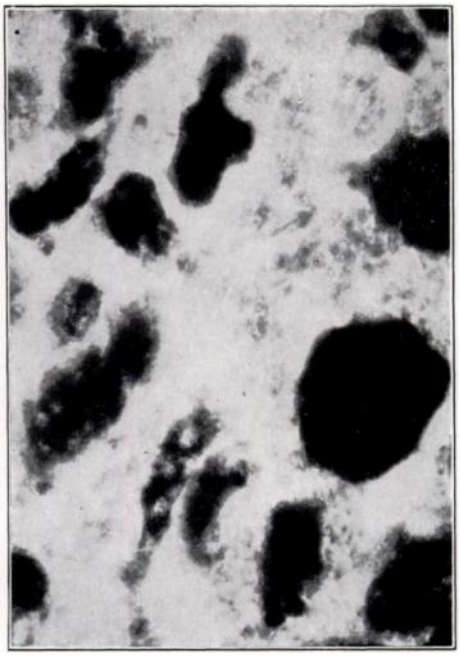

FIG. 17-B

Giant-cell tumor of tibia stained for succinic dehydrogenase (nitro-tetrazolium technique of Nachlas and associates, incubation time, thirty minutes: Fig. 17-A, × 75; Fig. 17-B, × 340). Strong enzymatic activity is localized, especially in the cytoplasm of the giant cells, the nuclei appearing as blank discs.

epiphyseal chondroblastoma, non-osteogenic fibroma, fibrous dysplasia, Paget's disease, solitary bone cysts, osteogenic sarcoma (Figs. 15-A and 15-B), and the like, also reacted very intensely, but I have not, as yet, established whether any quantitative difference exists.

In fourteen cases of pigmented villonodular synovitis, a positive reaction was observed in the multinucleated giant cells, but this activity seemed to be somewhat weaker than in the other lesions studied.

An abundant quantity of beta-glucuronidase which appears as a compact mass of blue granules in the cytoplasm was demonstrated in the giant cells after thirty minutes of incubation, while the nuclei remain negative (Figs. 16-A and 16-B). The enzymatic activity in mononuclear cells was much less, appeared as a weak reaction after three hours, and became somewhat more intense at twenty-four hours, although it never reacted with the same intensity as in the giant cells.

Intense succinic-dehydrogenase activity was observed after short incubations (ten to thirty minutes) in the giant cells of the six tumors studied; the activity was located primarily in the cytoplasm. The mononuclear cells did not show any enzymatic activity (Figs. 17-A and 17-B).

A case of osteogenic sarcoma also showed intense enzymatic reaction in the numerous giant cells of the osteoclastic type present in this tumor. There was only weak or no activity in the other tumor cells (Figs. 18-A and 18-B).

2. *Carbohydrates and Lipids*

With the McManus' method of periodic acid-Schiff staining, most giant cells showed diffuse reddish colored cytoplasm or more often fine reddish granules distributed in an irregular manner, sometimes in one and sometimes in both poles of the cell, and more rarely in the whole cytoplasm, but not in the nucleus (Figs. 19-A and 19-B). The cells of the stroma rarely took the stain. Staining remained after

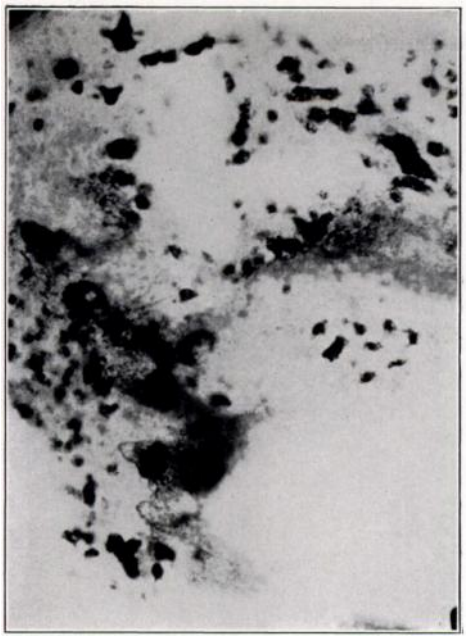

FIG. 18-A

FIG. 18-B

Osteogenic sarcoma of humerus, stained for succinic dehydrogenase. There is intense enzymatic activity in the multinucleated giant cells of osteoclastic type (nitro-tetrazolium technique, incubation time, one hour). Same case and magnification as Figs. 15-A and 15-B.

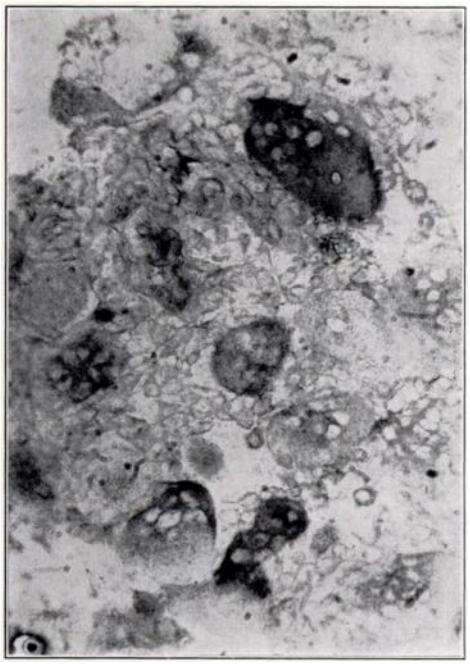

FIG. 19-A

FIG. 19-B

Fig. 19-A: Giant-cell tumor of radius. Periodic acid-Schiff positive substances in different amounts are shown in the cytoplasm of almost all giant cells, appearing as dark stained zones in the photomicrograph. The nuclei appear as blank discs since no counterstain has been used (McManus stain, × 310).

Fig. 19-B: Sudan black-B positive granules are shown in the cytoplasm of the giant cells; the nuclei are unstained (frozen section without nuclear counterstain, × 320).

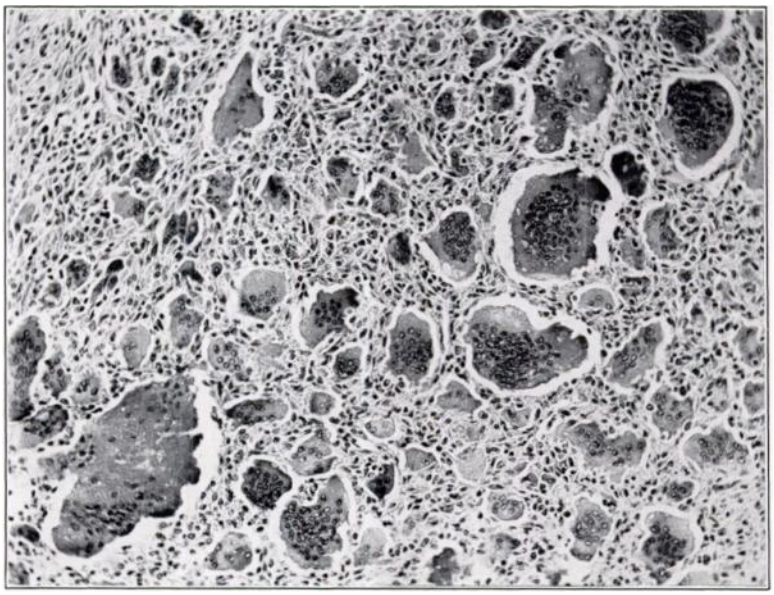

FIG. 20

Giant-cell tumor of tibia. Acid mucopolysaccharides are shown with Mowry's modification of the alcian-blue technique, and appear as diffuse dark-staining zones in the cytoplasm of most giant cells (× 122).

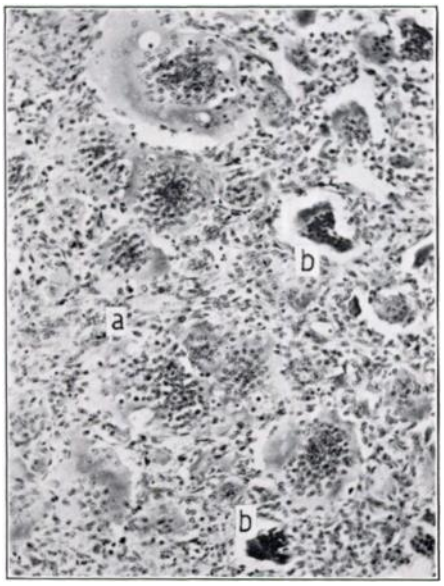

FIG. 21-A

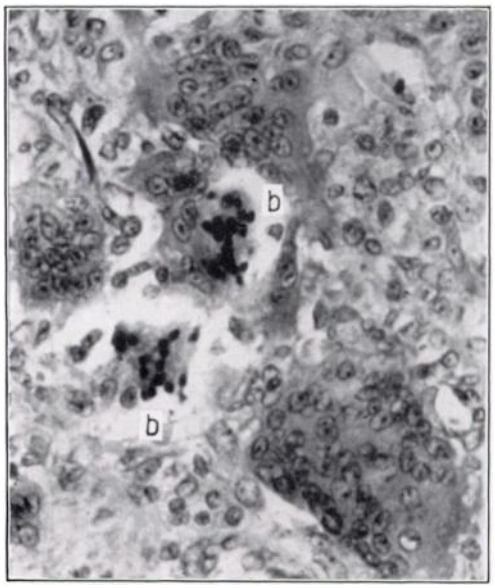

FIG. 21-B

Regressive changes, consisting in vacuolar degeneration of the cytoplasm *a* and pyknosis of the nuclei of the giant cells *b*, are frequently observed in giant-cell tumors (hematoxylin and eosin: Fig. 21-A, × 105; Fig. 21-B, × 390).

digestion with ptyalin and takadiastase, proving that it is not glycogen but some other type of carbohydrate.

The results with metachromatic staining with toluidine blue were not very clear as the basophilia of the cytoplasm of the giant cells impeded the demonstration of discrete metachromasia. Nevertheless, by use of alcian blue 8 GS (pH 2.7) with a short staining time and in acid solution, a technique which appears to be selective for acid mucopolysaccharides, a pale blue color was seen in the cytoplasm

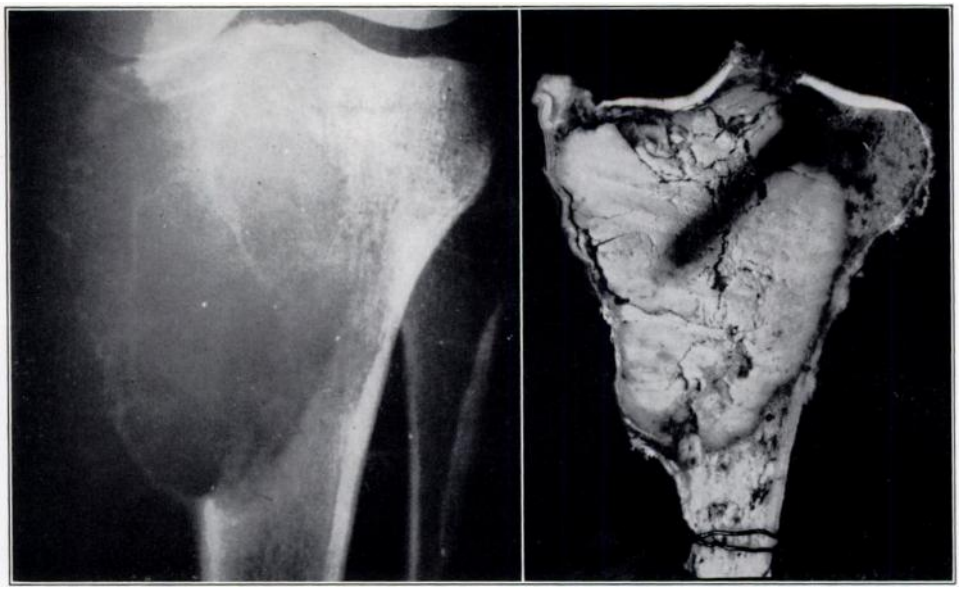

FIG. 22-A

FIG. 22-B

Malignant giant-cell tumor of the proximal part of the tibia. The specimen shows the grayish color of the tumor; the dark zone corresponds to a local hemorrhage in the tract of an aspiration biopsy. The photomicrograph shows the sparsity and smaller size of the giant cells and the polymorphism of the numerous stromal cells. The nineteen-year-old patient was treated with resection of the upper end of the tibia followed by bone-grafting and arthrodesis of the knee. She was alive twelve years later.

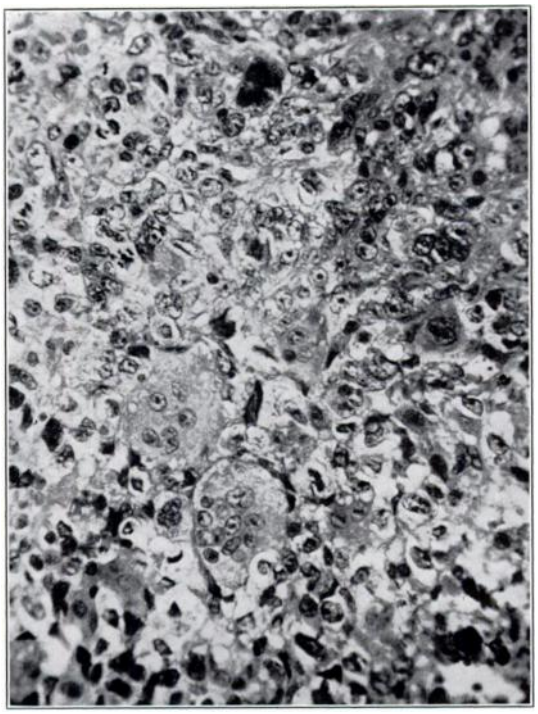

FIG. 22-C

of many of the giant cells. The distribution of the cytoplasmic staining was irregular and, like periodic acid-Schiff, generally more intense in the cell poles. Only rarely was a positive reaction obtained within the stromal cells (Fig. 20).

Material stained with Hale's colloidal-iron technique showed a similar distribution with positive staining of the giant cells, primarily their cytoplasm, and almost complete absence of staining in the stromal cells. The specificity of this method is not yet clearly defined and it is probable that proteins and mucoproteins give positive staining reactions, as well as the acid mucopolysaccharides [49,68].

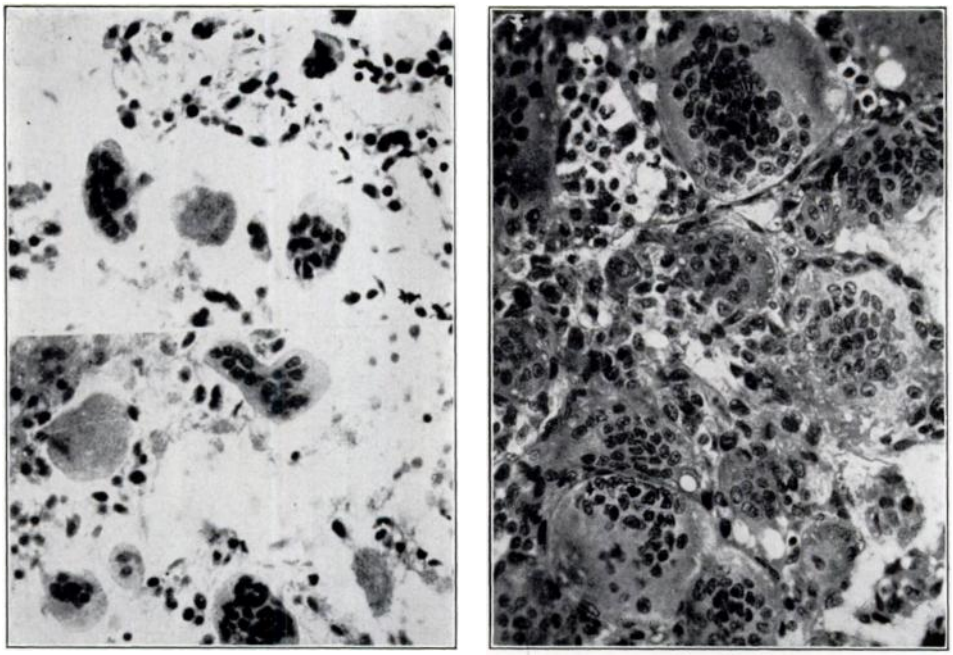

FIG. 23-A FIG. 23-B

Photomicrograph showing pulmonary (Fig. 23-A, × 275) and subcutaneous (Fig. 23-B, × 345) metastasis of a giant-cell tumor of the lower end of femur in a twenty-nine-year-old woman, treated with curettage and roentgen therapy, followed by resection. Histologically, the appearance is benign. (Fig. 23-A reproduced with permission from "Su di un caso di tumore giganto-cellulare con metastasi". By C. E. Ottolenghi, Fritz Schajowicz, and S. Mondolfo. Arch. "Putti", 4: 111–124, 1954.)

Only rarely was positive staining of the giant cells observed in formol-fixed frozen sections, stained with Sudan IV. This reaction was more frequent in the mononuclear cells, especially the foam cells adjacent to necrotic foci. In frozen sections stained with Sudan black B nearly all the giant cells presented an abundance of small granules which were distributed both diffusely and irregularly in all the cytoplasm, often being more intense in the vicinity of the cell poles (Fig. 19-B). The reaction is much less or absent in paraffin-embedded material. The mononuclear cells, which are positive to the Sudan IV method, present an intense bluish black coloring, which disappears entirely in paraffin-embedded material.

The presence in the cytoplasm of giant cells of substances which are positive to periodic acid-Schiff and Sudan black B and negative to Sudan IV indicates the existence of complex lipids, probably glycolipids (cerebrosides) or phospholipids. I have observed very similar histochemical reactions in Gaucher cells which contain cerebrosides of the abnormal kerasin type [63].

Histogenesis

Only a very few modern authors [98] still accept regeneration or inflammatory hyperplasia as the etiology of giant-cell tumor. This explanation was proposed a long time ago, especially by Looser [50], Konjetzny [44,45], and Haselhofer [34] in Germany, and by Barrie [3] in the United States.

I agree with the majority of authors that the giant-cell tumor is a neoplastic process and that the origin of the mononuclear stromal cell is from the undifferentiated mesenchymal cells of the bone marrow, interpreted by some authors as reticulohistiocytic elements.

From these same immature mesenchymal cells, with their tendency toward

fibroblastic differentiation, come the multinucleated giant cells, either by agglutination or conglomeration of the stromal cells, as held by the majority of authors [1,17,23,24,47,48,57,99,100] or by repeated division of the stromal-cell nucleus with-

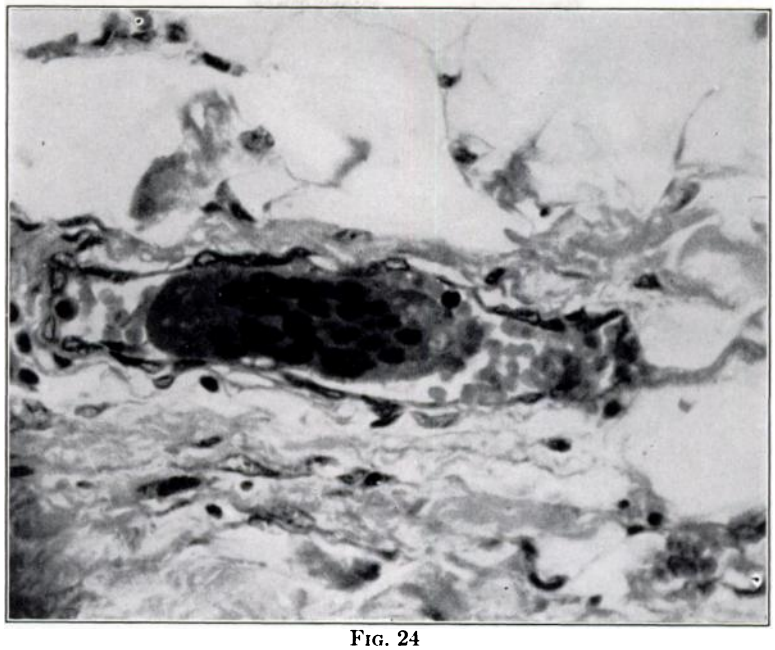

FIG. 24

A multinucleated giant cell is observed in a capillary blood vessel of the parosteal fibro-adipose tissue, adjacent to a giant-cell tumor.

FIG. 25

Sarcomatous transformation of a benign giant-cell tumor of the lower end of the femur, eighteen years after curettage and roentgen therapy in a twenty-year-old woman. *A:* roentgenogram of July 1938 before treatment; *B* and *C:* roentgenogram and photograph of the amputation specimen (Case of Dr. I. Slullitel). The patient died six months later with pulmonary metastases.

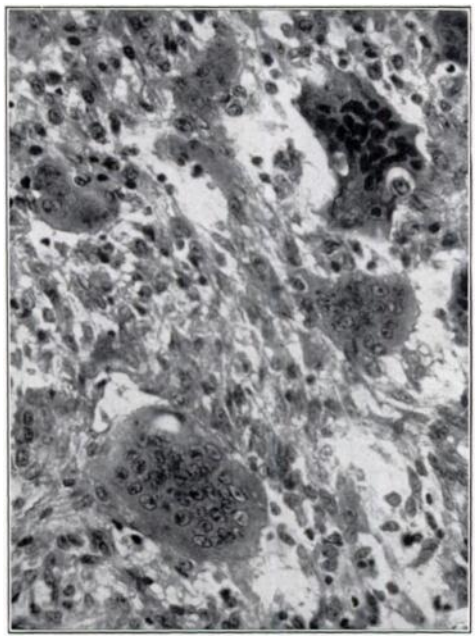

FIG. 26-A

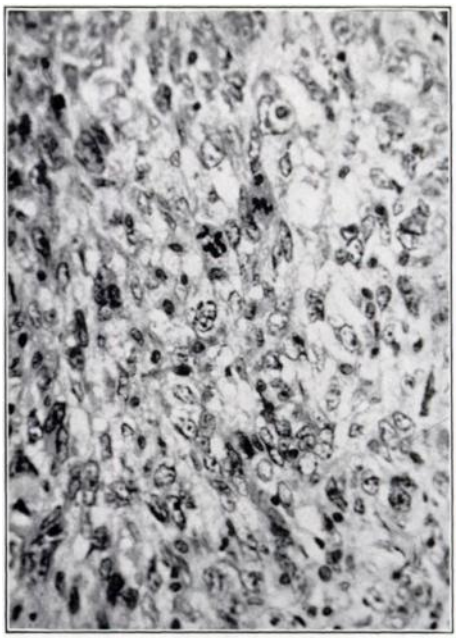

FIG. 26-B

Figs. 26-A, 26-B, and 26-C: Microphotographs of the same case as Fig. 25, showing in Fig. 26-A (× 330) the characteristic microscopic pattern of a benign giant-cell tumor before treatment and the appearance eighteen years later, after sarcomatous changes had appeared. In Fig. 26-B (× 330) the histological appearance is that of a fibrosarcoma but in Fig. 26-C (× 450) some scattered multinucleated giant cells of moderate size are still present. Atypical mitoses are frequent (hematoxylin and eosin).

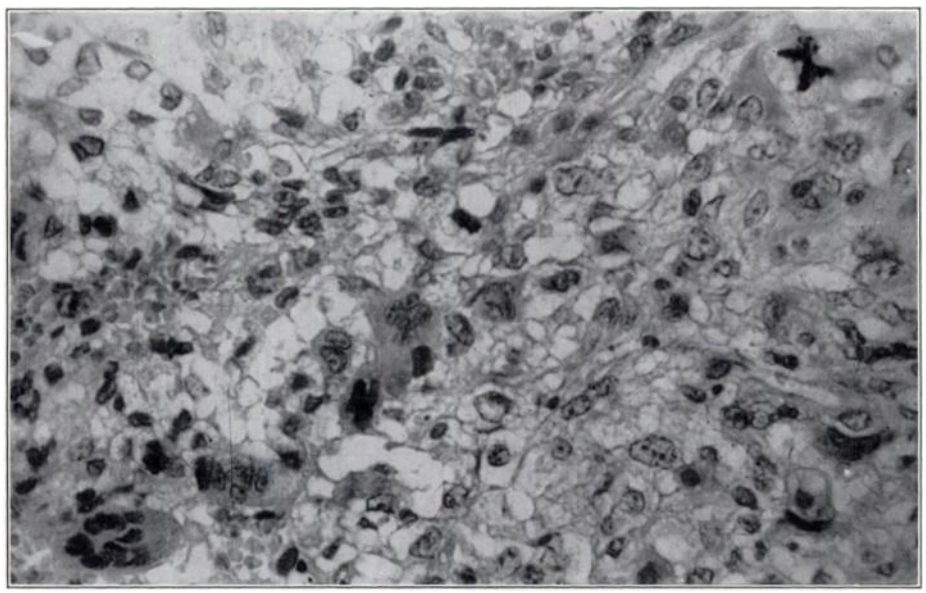

FIG. 26-C

out the corresponding cytoplasmic division, as suspected by Virchow [97] and reiterated by von Albertini [2]. Studying the cytological details of smears from numerous giant-cell tumors and tissue cultures Lustig and I [51] have been able to prove the existence of this last mechanism. Although we could not define the exact details of the cellular division, it seems to be amitotic. Brachetto-Brian [6] confirmed this finding in a solitary bone cyst.

In a systematic study now in progress with Montes de Oca and Cabrini, tissue cultures from forty cases of different types of bone tumor are being grown. Four of these are giant-cell tumors and in these we have observed a series of fields which would apparently indicate that the giant cell is formed by division of a mononucleated cell of the fibroblastic type, either by amitotic division or, as we have observed with great frequency, by nuclear segmentation. These findings must be confirmed by the study of more extensive material in order to exclude the possibility of their being degenerative cellular phenomena related to the type of culture medium used [56].

Owing to the great resemblance between the histochemical behavior of the osteoclast and the giant cell, the giant cell can be considered as a neoplastic deviation of the osteoclast. This would explain certain morphological differences between the two, such as the larger size and greater number of nuclei of the giant cell and the great abundance of these cells in a giant-cell tumor which far surpasses any functional requirement.

For these reasons I do not oppose the designation *osteoclastoma,* which has been used by most British authors from Stewart [91] to the present time. It seems quite clear that the multinucleated giant cell of the giant-cell tumor belongs to the same family as the normal osteoclast and that, even though it is a neoplastic element, it would be expected to exhibit a bone-destroying function.

Until these new findings are confirmed and the histogenesis of this tumor better defined, I shall continue to use the neutral term *giant-cell tumor of bone.*

The giant cell appears to have a limited life span, for in tissue cultures degenerative phenomena appear after three days while the fundamental mononuclear cell is still actively growing. These regressive changes are also often seen in histological specimens of giant-cell tumors and consist of nuclear pyknosis and karyorrhexis or karyolysis, which are generally combined with vacuolar degeneration of the cytoplasm (Figs. 21-A and 21-B). These phenomena correspond to different phases of the involutional cycle of the giant cell and were described in detail by us in 1943 [85] and by Brachetto-Brian [6] in 1946.

CLINICAL-HISTOLOGICAL CORRELATION

A careful histopathological review of our material and correlation of these findings with the clinical features of our cases showed that even in the cases with no previous treatment variations of the histological pattern exist, characterized principally by a more or less active proliferation of the mononuclear stromal cells. However, I believe that only striking histological evidence of malignancy can be considered of prognostic value (Jaffe and Lichtenstein's Grade III). Evidence of malignancy is a pronounced atypism of the stromal cells with frequent typical mitoses, often accompanied by atypical mitoses, and generally a diminution in the size and number of the giant cells.

These exceptional cases of which there were three in our series, have a more rapid evolution, a greater recurrence rate, and a greater frequency of metastasis, all of which agree with their ominous histological appearance. They should not be confused with osteolytic osteogenic sarcoma. The presence of areas showing neoplastic new-bone formation, sometimes difficult to perceive with the usual histological techniques but easily demonstrated by the presence of intense alkaline-phosphatase activity, makes differentiation of the two processes possible.

In benign (Grade I) and aggressive (Grade II) forms, no exact correlation exists between the histological picture and the clinical evolution, although it is perhaps more common for the histologically aggressive tumor to grow more rapidly, to be more destructive, and to be more apt to recur. On the other hand,

both types of histological pattern, as well as intermediate stages, may exist in different areas of the same tumor and pulmonary, bone, and cutaneous metastases of the same type may occur in both benign and aggressive tumors, as was observed in one of our cases (Figs. 23-A and 23-B) and has been described in the literature.

This complication may be explained in part by the fact that giant cells and small groups of tumor cells are often found in blood vessels near the tumor [6,38,85,89] (Fig. 24).

Sarcomatous Transformation

It is an indisputable fact that a benign giant-cell tumor may transform into a sarcoma. This generally occurs after roentgen therapy, whether associated with conservative surgical intervention or not. A considerable number of such cases have been published in detail. This complication occurs in about 10 per cent of cases [9] although some statistics [38,93] go as high as 15 per cent.

In this series, six cases of sarcomatous transformation occurred and all had been previously treated with roentgen therapy alone or in combination with curettage. The majority (five) of the sarcomata were fibrosarcomata. This agrees with other published cases, which include only very few osteogenic sarcomata [10,16,72].

The interval between commencement of roentgen therapy and the appearance of sarcoma has generally been between five and eight years; in our series it was between three and eighteen years, but other authors [10,16,38] mention cases in which the sarcoma appeared twenty-two and twenty-three years after roentgen therapy. Whether the action of the roentgen rays on the tumor cells is the cause of this late transformation, due to biological changes in the stromal cell, demonstrable as cytological changes [74], or whether it is the harmful effect of irradiation on neighboring healthy tissue [35], is still an unsolved problem.

The finding in one of our cases of fibrosarcomatous areas alongside areas showing the histological pattern of a malignant giant-cell tumor, and the same findings reported by Jaffe in some of his cases, appear to argue in favor of a true sarcomatous transformation of a pre-existent, apparently benign giant-cell tumor (Fig. 25).

DISCUSSION

It has become evident that the concept held by Nélaton [62], Gross [30], and Bloodgood [4] that the giant-cell tumor is a uniformly benign lesion is no longer valid. The estimation of different degrees of malignancy, although of use in some cases, has lost a great part of its value during recent years, since it is now known that with the exception of the frankly malignant forms, no good correlation exists between the histological picture and the clinical evolution. An increasing number of cases of benign or aggressive giant-cell tumors are being reported which have produced metastases with identical histological patterns. These are the main reasons which led us to resort to a more radical form of therapy, consisting in total resection of the tumor followed by bone-grafting in all instances in which the diagnosis of true giant-cell tumor is positive [96]. We have found no metastases or recurrences in those cases in which an adequate resection was performed as the first treatment. During the last few years an increasing number of surgeons have adopted this form of radical surgery [14,40,53,74].

Therefore, after almost 100 years, we are returning to the concept held by Virchow [97], who, in spite of calling the tumor a myelogenous giant-cell sarcoma (myelogenes Riesenzellsarkom), stated that in the majority of cases when the

tumor is completely removed in time it has such a good prognosis that it can almost be considered benign.

I consider that it is sufficient to make a histological diagnosis of true giant-cell tumor without necessarily giving the exact grade. The diagnosis can be made from an aspiration biopsy which enables material to be obtained from multiple areas. When performed prior to excision of the lesion, aspiration biopsy has given a correct diagnosis in 85 per cent of cases [64,76].

Our histochemical studies indicate that the histochemical behavior of the multinucleated giant cells of the giant-cell tumor and of the normal osteoclasts and chondroclasts is identical. This finding, in our opinion, indicates a close relationship and similarity in the physiological behavior of these cells.

The few papers published on this subject agree that there is a strong reaction for acid phosphatase in the multinucleated giant cells of the true giant-cell tumor, as well as in the giant cells of the so-called variants [5], the granulomatous lesions of tuberculosis, tuberculoid leprosy, and foreign-body reactions [67,69]. But Boyd [5], who bases his assertion on the studies of Changus and Gilmer, which have not been published in detail, also mentions the presence of acid phosphatase in the stromal cells of the giant-cell tumor and its absence in the variants and in other similar bone lesions, such as bone cysts, non-osteogenic fibromata, and fibrous dysplasias. Boyd considers these findings to be of value as a method of differential diagnosis.

Like Gomori, I have found intense acid-phosphatase activity but no alkaline phosphatase in the multinucleated giant cells and no alkaline or acid phosphatase in the stromal cells. Identical results were obtained in the so-called variants of giant-cell tumor and similar lesions. These findings have been confirmed by Pais and Baruffaldi [67]. The alkaline-phosphatase activity described by Boyd [5] in the stroma is due, in my opinion, to areas of reactive or metaplastic osteogenesis which are very common in these lesions. I do not think, therefore, that these histochemical methods can be of any use for diagnostic purposes.

The systematic biochemical studies carried out by Woodard [101] confirmed that the acid-phosphatase content of the giant-cell-tumor tissue is considerably higher than that of most other lesions in the osseous system, but the highest value found was only two units per gram. Since 200 units per gram are often seen in carcinoma of the prostate, it can not be expected that the presence of a giant-cell tumor will cause changes in the serum acid phosphatase comparable to those produced by metastatic prostatic cancer. Nevertheless, Lasser and Tetewsky [46], on two occasions, found in a case of metastasizing giant-cell tumor slightly elevated acid-phosphatase levels in the serum and suggested that these elevated levels may represent an abnormal amount of this enzyme released from the giant cells in the metastatic lesions. This problem requires further study, as other authors have also found a significant increase of acid phosphatase in bone and serum, both in experimental hyperparathyroidism [43], and in humans with the disease [32,42]. When the parathyroid tumor was removed, the serum-acid-phosphatase levels promptly fell to normal, coincident with the fall of the serum calcium, indicating that the serum-acid phosphatase in hyperparathyroidism is derived from an osseous source [32].

Histochemical studies have also shown the presence in giant cells, of the enzymes, beta-glucuronidase and succinic dehydrogenase. The giant cells also contain a periodic acid-Schiff positive substance in their cytoplasm which is either diffuse or finely granulated. This is not glycogen and is positive with Sudan black B and negative with Sudan IV. We have observed similar histochemical reactions, as have others [63] in Gaucher cells. These reactions evidently indicate the presence of complex glycolipids or phospholipids.

The various histochemical reactions for acid mucopolysaccharides did not give consistent results, and those obtained with Hale's colloidal-iron method are of rather questionable significance due to their apparent lack of specificity [49,68]; the metachromatic stain, toluidine blue, gave indefinite results due to the masking effect of the basophilia of the cytoplasm of the giant cells. Far more convincing results were obtained using alcian blue, which stains connective-tissue mucin and most epithelial mucins in acid solutions, with very little staining of the background proteins [58]. Using this technique, fine blue granules were found distributed in the cytoplasm in a very irregular manner in the majority of the giant cells. Differences in quantity of staining of benign and malignant cells, as found by Pais and Baruffaldi [67], could not be proved.

Osteoclasts and chondroclasts showed similar histochemical behavior in both normal and pathological conditions, but so did the giant cells present in pseudoneoplastic processes of the synovial membrane and granulomatous diseases [67,69], which are not related to bone and cartilage resorption.

Although Pepler [69] stated that granulomatous giant cells contain a nonspecific esterase, not present in giant-cell tumors of bone, these differences do not appear to be of fundamental importance.

In our present state of knowledge it would appear that this metabolic and enzymatic activity of the multinucleated giant cells is related to the digestion, solution, and elimination of several classes of substances.

SUMMARY

1. A series of eighty-five cases of giant-cell tumors of bone studied in the course of the last twenty years is reviewed. Comparative clinical, roentgenographic, pathological, and systematic histochemical studies have been carried out.

2. The clinical and pathological findings confirm the necessity of treating these tumors as an entity, because they are neoplastic processes capable of progressive growth, recur in a large percentage of cases, and, in 7 to 15 per cent of cases become transformed into sarcomata. They may produce metastases without visible malignant transformation. The so-called variants, which in general have a favorable prognosis, are easily distinguishable from true giant-cell tumors.

3. With the exception of a few rare cases showing a frankly malignant microscopic structure, there was no evident correlation between the histological appearance and the clinical and roentgenographic features. For this reason, grading of this neoplasm is now considered of little value. It is sufficient to establish a diagnosis of true giant-cell tumor to justify complete resection of the lesion. This diagnosis can be made by aspiration biopsy.

4. I believe that the giant cell derives from the mononuclear cell of the stroma and is thus of mesenchymal origin. I think that it is formed not only by agglutination and conglomeration of these cells, as is maintained by the majority of writers, but also by repeated division of the stromal-cell nuclei, without corresponding cytoplasmic division. This is probably accomplished by amitosis or nuclear segmentation, which has been observed in tissue cultures.

5. Systematic histochemical investigations of normal tissues, true giant-cell tumors, and many bone lesions and extra-osseous lesions, which are characterized by the richness of multinucleated giant cells, were done. The giant cells in these tissues have a very similar histochemical behavior. A close physiological and histogenetic relationship is thus established between normal osteoclastic and chondroclastic giant cells and those of giant-cell tumor.

6. Giant cells are characterized by an abundance of acid phosphatase, beta-glucuronidase, and succinic dehydrogenase; the absence of alkaline phosphatase;

and the presence in their cytoplasm of non-glycogen carbohydrates, principally acid mucopolysaccharides, and complex lipids. The stromal cells of giant-cell tumors do not generally show enzymatic reactions, nor do they possess glycogen, mucopolysaccharides, or glycolipids in significant amounts.

7. Histochemical study is of no diagnostic value when differentiating the giant-cell tumor from its so-called variants.

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