Acta Radiologica

ISSN: 0001-6926 (Print) (Online) Journal homepage: informahealthcare.com/journals/iaro20

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To cite this article: Sigurd Ry Andersen (1945) The Malignancy of Giant Cell Tumors, Acta Radiologica, 26:1-2, 11-35, DOI: 10.3109/00016924509176503

To link to this article: https://doi.org/10.3109/00016924509176503

FROM THE RADIUM CENTER, COPENHAGEN (CHIEF: JENS NIELSEN, M. D.) AND THE SURGICAL SERVICE OF THE FINSEN INSTITUTE (CHIEF: PROF. O. CHIEVITZ)

THE MALIGNANCY OF GIANT CELL TUMORS[1]

A Study on Giant Cell Tumors and Allied Affections in Bone, with Reference Specially to their Malignancy

by

Sigurd Ry Andersen

The malignancy of giant cell tumors is a controversial subject; which is not surprising, since the nature of these affections and their delimitation from a number of other benign and malignant affections in bone are still uncertain. In the last twenty years a great deal has been written about them: for particulars, GESCHICKTER & COPELAND's excellent: »Tumors of Bone» (New York, 1936) and HELLNER's: »Die Knochengeschwülste» (Berlin, 1938) may be referred to. Here, I shall call attention only to a few points of particular importance in connection with the subject.

The best known theory respecting the *pathogenesis* is the one advanced by GESCHICKTER & COPELAND, according to which the giant cell tumors and osteitis fibrosa are not true neoplasms, *but an abnormally highly developed phase of the normally occurring absorption of calcified cartilaginous tissue* which takes place during the normal endochondral growth of the bones preformed in cartilage. This absorption takes place by means of giant cells —osteoclasts — whose proliferation should be abnormally great owing to traumatically determined nutritional disturbances in the bone.

In the epiphyses of the long tubular bones, in which the vascular supply is poorest, there should, as a result of this, develop the more progredient forms, called *giant cell tumors;* histologically characterized by numerous giant cells with centrally situated nuclei and abundant hemorrhage, but only slight fibril formation and little, or no formation of new bone. The meta- and diaphyses, whose nutrition is better, should offer better conditions for a restorative reaction, resulting in the devel-

[1] Read, in a somewhat modified form, at the meeting of the Danish Radiologic Society, Feb. 9th, 1944. Submitted for publication, Aug. 25, 1944.

opment of *local osteitis fibrosa,* mostly in the form of an isolated *bone cyst* histologically characterized by a stroma rich in fibrils and with new bone formation, but only few giant cells and little hemorrhage; besides, there may be formation of cysts, because the bone tissue after resorption of hemorrhage cannot collapse. This restorative reaction, which is termed *fibro-ostosis,* should be furthered by the thicker cortex of the diaphyses, which forms a barrier against the abnormally proliferating tissue containing the osteoclasts; and the same should apply, though in lesser degree, to giant cell tumors in the head, vertebrae, ribs and fingers; which should explain the intermediate histologic forms often seen in those sites. According to GESCHICKTER & COPELAND, giant cell tumor and osteitis fibrosa should thus be two phases of the same disease, and in accordance with this conception they also term them respectively *progressive and regressive osteoclasia.*

According to this theory, the formation of giant cell tumors is connected with the development of the bones preformed in cartilage; and, in fact, they are found exclusively — or, at any rate, almost exclusively — in these. An exception to this are, however, the giant cell tumors — *epulis gingivae* — formed along the alveolar borders (which are preformed in connective tissue). GESCHICKTER & COPELAND consider these as entirely homologous formations, only connected with the normal resorption of the deciduous teeth by odontoclasts; and in support of this they point to the fact that epulis hardly ever occurs back of the first molar. With regard to the giant cell tumors that not rarely occur in, or near tendon sheaths in the hand and foot, they believe that they arise from sesamoid bones.

Generalized osteitis fibrosa (*Recklinghausen's disease*) is now held to be caused by hyperparathyroidism, most often a parathyroid adenoma, with secondary changes in the calcium- and phosphorus levels of the blood, and in the bones, where not only extensive halisteresis and multiple diaphyseal cysts are seen, but sometimes also epiphyseal giant cell tumors of a histologic structure similar to that of the solitary. It is even stated that the disease may begin with a giant cell tumor or an epulis. As a rule, removal of the adenoma will cure the disease, whereupon the changes in the bones disappear.

GESCHICKTER & COPELAND have, on the basis of a very large material, *maintained that a giant cell tumor always is benign,* and that in cases where metastases appeared and death supervened the diagnosis must have been wrong, in the sense that an original osteogenic sarcoma had not been recognized, or that the death was due to some other cause. In recent years they seem, however, to have had some doubts; and in the last edition (1936) of their work they relate a case which seems clearly to show malignant transformation of an originally benign giant cell tu-

mor. The theory proposed by the two authors seems very plausible and no doubt contains many correct observations; besides, it is the only one, so far, by which it has been possible to give a picture embracing both giant cell tumor and osteitis fibrosa. It has, therefore, also many adherents, though up to the present it cannot be said to have been proved.

While it is commonly agreed that osteitis fibrosa is not a genuine neoplasm, but always a benign affection (albeit from time to time cases of osteogenic sarcoma are reported, which have resembled benign bone cysts and have been treated as such), it is *maintained by many that giant cell tumors are true tumors, mostly benign, but in some cases malignant* (W. B. COLEY, J. EWING, F. W. STEWART). Others (H. L. JAFFE and co-workers) would among the epiphyseal giant cell tumors in long tubular bones recognize *a separate group, which they conceive as genuine neoplasms of varying malignancy.* They have even subclassified these tumors into three grades, according to the degree of their malignancy; rather on the line of BRODERS' system for grading of cancer. The weight is laid chiefly on the degree of differentiation of the stroma; the giant cells being considered as a more secondary phenomenon. Only typical giant cell tumors are recognized, while the numerous "variants" of such are left out. Their classification is as follows:

Grade I. Typical giant cell tumors of absolutely benign appearance, with numerous multinuclear giant cells with centrally situated nuclei and a »not compacted» stroma of chiefly round or oval cells with slight fibril formation; slight cellular atypism, no, or at most a few, normal mitoses. Furthermore, abundant hemorrhage and deposit of blood pigment, but only very slight new bone formation.

Grade II. Tumors with compacted stroma and marked atypism with rather frequent abnormal mitotic figures, perhaps also the giant cells somewhat atypical.

Grade III. Tumors with sarcomatous stroma with highly atypical cells and small giant cells.

Grade I corresponds to typical giant cells and are stated mostly to remain benign, but often to recur, and then to exhibit characteristics which put them in the next grade. The tumors of grade II correspond in appearance most nearly to the »malignant giant cell tumors», and are stated to have considerable tendency to recur, and in some cases to become malignant. The tumors of grade III are stated to be malignant, and to metastasise sooner or later.

The classification seems to me to be rather artificial, particularly as regards grade III, which in my opinion is only an expression for an osteogenic sarcoma with giant cells; a by no means uncommon finding. — The authors point out that the roentgenologic picture may be the same in all three grades, and stress the necessity of biopsy being performed in all cases.

As basis for their classification they have only a material of 14 sure cases of epiphyseal giant cell tumor, all in subjects above the age of 21 years. Of these, 3 are stated to have become malignant and ended in the patients' death. A closer scrutiny of the material shows, however that only with regard to the first of the cases is the documentation sufficient to make it acceptable as proof; and even so, the original microscopy classed it as grade II; that is as not indubitably benign.

Interesting, but somewhat lacking in clarity is a paper by F. W, STEWART & co-workers, relating some cases of so-called »*malignant giant cell tumor*», which clinically and roentgenologically resembled benign giant cell tumors, but in which the first microscopy nevertheless showed very slight signs of malignancy, mostly in the form of single abnormal mitotic figures; the malignancy eventually being confirmed by the appearance of metastases and the death of the patients from malignant sarcomas containing giant cells. Unfortunately, no photographs of the preparations are given. The authors do not themselves draw any final conclusions from the material. It is possible that these somewhat dubious »malignant giant cell tumors» were merely osteogenic sarcomas, perhaps of a special type. On this point, there is need of further investigations; but the cases may serve as a reminder always to make thorough histologic examination, and in case of doubt to repeat the biopsy. EWING concludes (with GOFORTH) that »there are all degrees of malignancy; each must be evaluated according to its particular structure».

In the course of years a number of cases have been reported, about which it has been *maintained that malignant transformation of benign giant cell tumors into sarcoma has been proved.* In hardly any of them the proofs are satisfactory. It must be an absolute requirement that the original tumor is beyond all doubt benign, not only clinically and roentgenologically, but also histologically. Especially must it be pointed out that both chondrosarcomas and osteogenic sarcomas may give an exactly similar roentgenologic picture. Furthermore, it would be best to require that some years shall have elapsed before the malignant process manifests itself; since otherwise it is difficult to exclude the possibility that the growth is a primary osteogenic sarcoma. In the malignant stage there must often be required the occurrence of metastases of indubitable histologically malignant character; because a giant cell tumor often, if it has become infected or has been the object of several operations or irradiations, gets another, seemingly more malignant appearance. Nor yet can invasion of giant cell tumor tissue into the surrounding soft tissues be taken as proof of malignancy, since such invasion often occurs also in the case of otherwise benign giant cell tumors. In going through a number of cases from the literature I have found at any rate three that seem rather convincing. The first is GESCHICKTER & COPELAND'S

case, already mentioned, of a giant cell tumor in the upper part of the tibia of a man, 45 years old, who three years after curettage and postoperative roentgen treatment had to undergo amputation for an osteogenic sarcoma. The other two — in which photomicrographs are lacking, though — are reported by W. B. COLEY (his cases no. 1 and 5). In the first, the growth was situated in the lower part of the femur of a man 39 years old, and had been treated by curettage and postoperative roentgen. In the other, it was situated in the upper part of the tibia of a man aged 19 years, and had been treated by curettage followed by radium (formerly published by STONE & EWING).

Besides, there are a number of cases in which the malignant transformation seems likely, but has not been proved. That such transformation may, in fact, occur, is also recognized by many writers (HELLNER, among others), though it is considered as very rare.

We do not know what causes a giant cell tumor to become malignant. W. B. COLEY, who believes that it is a genuine neoplasm, which in about 15 per cent of cases becomes malignant, has pointed out that the malignant mostly are those that have been subjected to postoperative radiation treatment, and he therefore deprecates such treatment, at least as postoperative measure. His material consisted of 23 patients treated by curettage followed by radiation treatment, and of these he states that in 7 cases the tumor became malignant, whereas this was only the case with 1 out of 31 that had been treated only surgically. Of the cases in which radiation treatment had been given, one had been treated with radium, the others with roentgen (dosage not stated). It cannot be seen from the material whether it had been in any way sorted before the choice of therapy was made, and most of the cases related do not seem convincing; so there is really no support for this hypothesis about the effect of postoperative radiation treatment in these cases. The procedure also still has some adherents (HELLNER); but on the whole the tendency in recent years is *to use either roentgen therapy alone* (as first proposed by HERENDEEN) *or surgical therapy;* whereas radium treatment seems to have been abandoned. The roentgen treatment is most often given serially, with fractioned doses considerably smaller than in the case of malignant tumors. SCHINZ and ZUPPINGER for example use doses of 2,400—3,600 r in all These series can be repeated, because *the giant cell tumors, in contrast to the malignant, do not become radioresistent* (LA CHARITÉ). HERENDEEN has called attention to the fact that giant cell tumors in the first month or two after the irradiation show a »*paradoxical reaction*» in the form of passing increase of the tumor and effacement of the bone contours. But after that length of time the reaction subsides, and instead there begins, in the cases where the irradiation has had a favorable effect, a reactive healing process in the form of increased

new formation of bone. American writers, especially, still recommend surgical treatment, however; mostly curettage, because they consider the results of irradiation as uncertain (GESCHICKTER & COPELAND). In this connection it may be mentioned that localized osteitis fibrosa nearly always is treated by curettage. In many cases this lesion subsides spontaneously, though; and, besides, an osteitis fibrosa is, on account of its histologic structure, very little radiosensitive. Epulis gingivae, which is always benign, seems to respond well both to roentgen and radium therapy (KJELLBERG) and to excision.

When a giant cell tumor has become malignant (or in a wrongly interpreted case of osteogenic sarcoma), radical operation is indicated unless there are distant metastases. These tumors are never radiosensitive.

In Denmark, only a few authors have written about giant cell tumors (FLEMMING MØLLER, FLEISCHER-HANSEN et al.), and no case of malignant transformation has been reported. COLLIN has recorded the cure of 10 cases of epulis by radium treatment; all recurrences after surgical operation. Besides, KREBS has reported the cure of 4 epiphyseal giant cell tumors by large doses of roentgen; most of them, though, with resulting ankylosis and destruction of the epiphysis.

As these lesions are very rare (the Mayo Clinic, for instance, has only 3 or 4 cases each year), I have thought it of interest, though the material is small, to *report the cases from the Radium Center in Copenhagen and the surgical service of the Finsen Institute.* All the cases from the period 1930 to 1943 are included, after elimination of a number not sufficiently examined. Of the 47 remaining, 43 were examined microscopically, and nearly all these preparations I have had an opportunity to study; in cases of doubt they have been submitted to Prof. J. ENGELBRETH-HOLM, M. D.

Where there has been doubt about the differential diagnosis between giant cell tumor and osteitis fibrosa in the long tubular bones I have rested my judgment on the clinical picture and the result of the roentgenographic examination rather than on the microscopy, which in these cases often is somewhat inconclusive, because the histologic picture of these lesions no doubt changes somewhat in the course of the disease and especially seems to depend on whether the microscopic examination has been made during the progressive or the regressive phase.

The material is no doubt to some extent a selected one, most of the cases having been referred to the Radium Center and the Finsen Institute from other hospitals; and a number of them are recurrences after previous treatment elsewhere. Though epiphyseal giant cell tumors are generally stated to occur most frequently in the third decade of life, the average age for the patients with this lesion is in my material 42 years; which

also seems to indicate its being more selected, containing a larger proportion of more serious cases; recurrences and malignant transformation being most often recorded in the older age-classes.

The Material from the Radium Center and the Finsen Institute, 1930—1943

Giant cell tumor in epiphyses of long tubular bones	11
(Probably primary osteogenic sarcoma, mistaken for giant cell tumor	1)
Giant cell tumor in short bones and in soft tissue	3
Localized osteitis fibrosa in long tubular bones	8
Generalized osteitis fibrosa	3
Giant cell tumor in upper jaw	1
Localized osteitis fibrosa in upper jaw	2
Epulis gingivae	19
	47 (+1)

The following is a brief summary of the different case histories.

Giant cell tumor in epiphyses of long tubular bones

Case 1. — K 7772. Commercial agent, aged 52 years. — Typical giant cell tumor in medial condyle of femur, verified by microscopy. Curettage, with insertion of radium, 480 mg/h. Since well, function good, no recurrence; followed for 11 years.

Case 2. — R 11572 (and K 11125). Hous wife, aged 34 years. — Giant cell tumor in medial condyle of femur. Microscopy: giant cell tumor with xanthomatous areas. Roentgen treatment, 150 r x 12, total, 1800 r., without effect. Two years later, curettage with good effect. Since well, no recurrence, but ankylosis of knee joint. Followed for 9 years.

Case 3. — K 10484. Housewife, aged 55 years. — Typical giant cell tumor in lateral condyle of tibia, verified by microscopy. Completely cured after curettage. Followed for $8^1/_2$ years.

Case 4. — R 13902. Farmer, aged 49 years. — Typical giant cell tumor in lateral condyle of tibia, verified by microscopy. Roentgen treatment, 4 series with resp. 800, 900, 900 and 900 r. total, 3,500 r, without effect; wherefore curettage. In the following year, recurrence with perforation to the skin; renewed curettage with good effect. Since well, function fairly good, no further recurrence. Followed 7 years.

Case 5. — K 12427. Bicycle-dealer, aged 59 years. — Typical giant cell tumor in medial condyle of femur, verified by microscopy. Curettage (Holbaek County Hospital); two years later recurrence and renewed curettage. Four years later again recurrence and curettage, this time with good effect. Since well, function fairly good, no further recurrence. Followed for $8^1/_2$ years.

Case 6. — R 16725. Housekeeper, aged 44 years. — Probably giant cell tumor in lateral condyle of tibia (no microscopy). Curettage and intense postoperative roentgen treatment, 10,500 r (Aalborg County Hospital). Five years later suddenly roentgen ulcer, but hardly recurrence; excision and curettage. Microscopy: cicatrix from irradiation (?). As there was no tendency to healing, resection; later amputation of femur. Func-

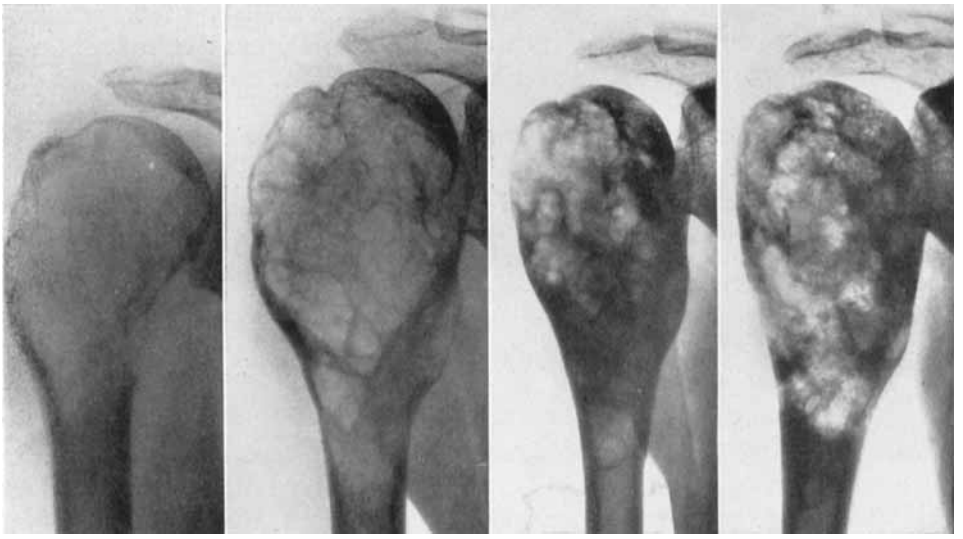


Fig. 1. Fig. 2. Fig. 3. Fig. 4.

Fig. 1. Benign-looking giant cell tumor in head of right humerus untreated. (April, 1940)

Figs. 2—3. Same tumor after roentgen treatment, resp. 2,400 r (Sep., 1940) and 5,600 r (Oct., 1941). After passing progression, considerable reparatory new bone formations. No signs of malignancy.

Fig. 4. Same tumor, Feb., 1943. In the lower part of the bone there is now considerable destruction with ill-defined limits, large perforation and spontaneous fracture. Strong suspicion of malignant transformation.

tion of stump good. Followed for $6^1/_2$ years, but only for six months after the amputation.

Case 7. — R 21715. Army officer, aged 28 years. — Clinically and roentgenologically typical giant cell tumor in medial condyle of tibia; *histologically of a type intermediate between giant cell tumor and osteitis fibrosa;* microscopy (twice) showing numerous large and small cysts with hemorrhages and blood pigment. In the walls of the cysts, many giant cells in a rather fibrillar stroma, peripherally, osteoid tissue. Roentgen treatment, 5 series: 600, 1100, 900, 900 and 1800 r, 5300 r in all, without effect. Curettage with good effect. Since well, function good, no recurrence. Followed for 4 years.

Case 8. — R 22255. Farmer, aged 20 years. — Formerly well. In 1937, uncomplicated fracture of right forearm; never injury to right shoulder. In January, 1940, suddenly pain in the latter while working, and, as pain persisted, referred to the Radium Center in April, same year. *Clinically*, general condition good; corresponding to right shoulder slight tumefaction, tenderness and restriction of movement; otherwise nothing objectively abnormal. *Roentgen examination* showed in head of right humerus a benign-looking giant cell tumor, the size of a duck's egg, occupying the whole of the epi- and metaphysis and extending for some distance into the shaft. It was delimited by a thin shell of bone without sure signs of perforation. No spiculae or other signs of malignancy (see Fig. 1).

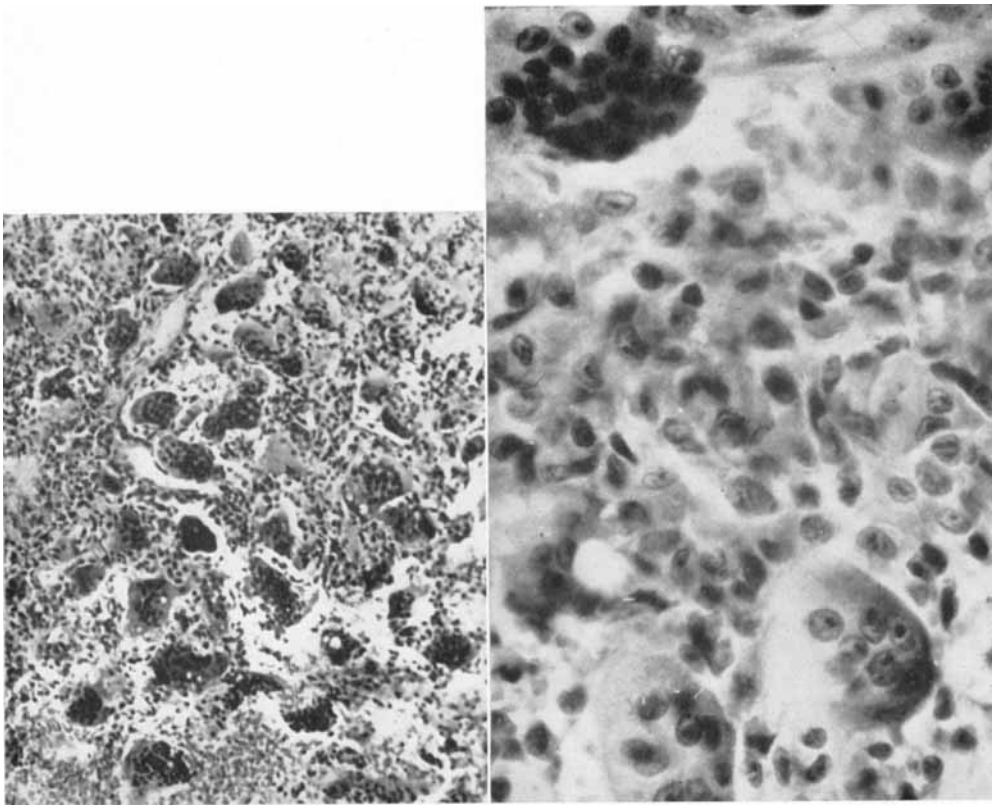


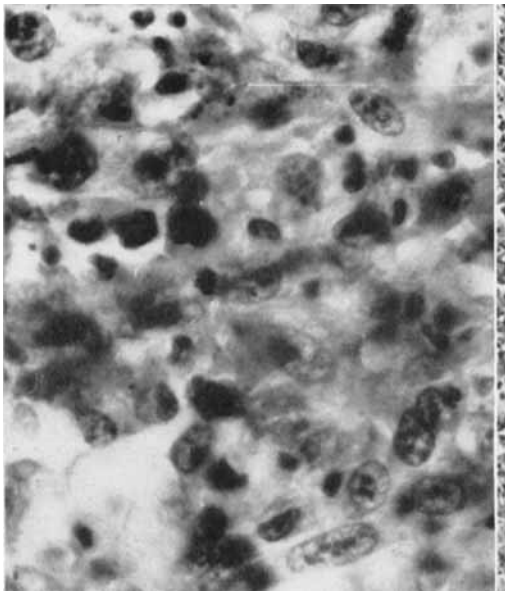
Fig. 5. Fig. 6.

Fig. 5. Biopsy specimen from head of humerus, April, 1940: Untreated, benign-looking giant cell tumor with multinuclear giant cells in typical, non-compacted, slightly fibrillar stroma with copious hemorrhage but no osteoid tissue and no signs of malignancy. (×96),

Fig. 6. Same preparation more highly magnified. No signs of malignancy. (×480).

Biopsy specimen taken with Christiansen's trephine, April, 1940: Rather thick column of tissue, about 1.5 cm. long, consisting of tumor tissue with numerous giant cells with many centrally situated nuclei in a typical, in places slightly fibrillar stroma with ovoid to spindle-shaped, often somewhat angular nuclei. A few, not tumorous mitotic figures, no cellular atypism and no invasive growth in the surrounding adipose tissue. Copious hemorrhage and a little bone tissue in the process of resorption, but no osteoid tissue. Histologic diagnosis: Benign-looking giant cell tumor. (Figs. 5 and 6.)

The patient was given *roentgen treatment* from April, 1940, to May, 1942, 6 series in all, of resp. 800, 1600, 800, 1200, 1200 and 800 r; total, 6400 r (180 kv.; 0.5 mm. Cu.; distance. 40 cm.; field, from 10×15 to 20×24 cm; 100—200 r per dose). Several controlling roentgen examinations showed in the beginning some progression of the tumor, later continued healing with considerable reparatory new bone formation both in the compacta and in the many sharply delimited trabeculae. No signs of malignancy. (Figs.



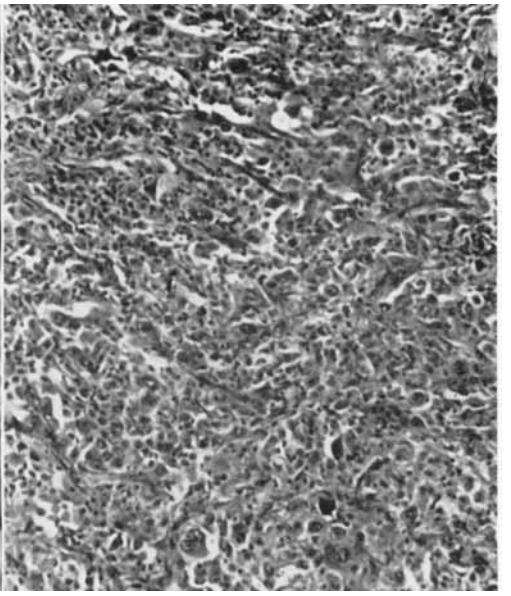


Fig. 7. Fig. 8.

Fig. 7. Tissue removed by curettage March, 1943: heaps of large cells, suspected to be sarcoma cells; with irregular, in many cases enormous nuclei with tumor-like mitotic figures.

Fig. 8. April, 1943: Polymorphocellular (osteogenic) sarcoma with close-set, mostly spindle-shaped cells with some fibril formation, enormously varied nuclei and abnormal mitotic figures.

2 and 3.) Also the subjective symptoms disappeared, and from May, 1942, the patient was in possession of his full capacity for work, with only a slight restriction of movement in the right shoulder joint. During this time no microscopic examination was made.

In January 1943, — that is about 3 years after the affection began, — he suddenly, while working, again felt a pain in his right shoulder. In February there was considerable restriction of movement, and a *roentgen examination* now showed in the lower part of the former giant cell tumor, over an area about the size of a tangerine, considerably increased destruction, with numerous vaguely delimited rarefactions; and, laterally, a large perforation and spontaneous fracture. Malignant transformation was strongly suspected (Fig. 4). *Biopsy* (Feb., 1943) showed necrotic tissue with infection. Here and there in the tissue there were a few heaps of cells, rather suspected to be sarcoma cells, with large, irregularly shaped, in some cases enormous, nuclei; but of the original giant-cell tumor tissue nothing was seen.

The patient was febrile, but his general condition otherwise good. As it was taken for granted that giant cell tumors always are benign, the changes were interpreted as being due to the spontaneous fracture, and the case for a time merely kept under observation. In March, 1943, *curettage* was performed. The *microscopy*, as the last time, concluded in: sarcoma suspected (Fig. 7). But the general condition gradually became affected, and renewed *biopsy* from the tumor now showed indubitable polymorphocel-

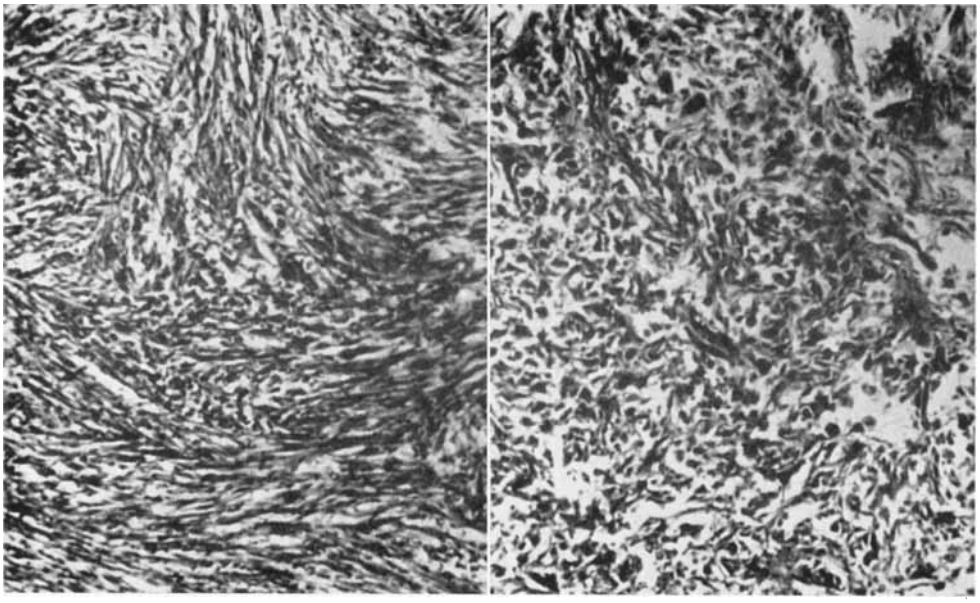


Fig. 9. Fig. 10.

Fig. 9. May, 1943: Tissue from the amputated tumor. Marked fibril formation and many mitotic figures.

Fig. 10. May, 1943: Another portion of the same tumor, with marked nuclear polymorphism.

lular (osteogenic[1]) sarcoma with numerous, mostly spindle-shaped, cells, lying close to each other, with greatly varied, enormously hyperchromatic nuclei and numerous abnormal mitotic figures. There was moderate fibrillation, but no osteoid tissue. (Fig. 8.)

In May, 1943, *interthoracoscapular amputation* was done, chiefly as palliative measure. Corresponding to the head of the humerus there was found a tumor, as large as the head of a child, filling the entire marrow cavity of the caput humeri, of which there remained only a thin shell, with invasion into the soft tissues on all sides; besides considerable inflammation with several abscesses. The joint was intact. *Microscopy,* both from the marrow cavity and from the masses of tumor in the muscles showed, as before, polymorphocellular (osteogenic) sarcoma. Large portions of the tumor tissue was built up of close-set fusiform cells with marked fibril formation (Fig. 9); in other places, polymorphous oval or round cell nuclei dominated (Fig. 10). Everywhere considerable cellular atypism and numerous tumor-like mitotic figures; besides, considerable infection in the tumor; but no giant cells or osteoid tissue.

In June, same year, *roentgen examination* at the Radium Center showed metastasis in the right lung, and in September, same year, it was reported from the hospital in Svaneke that the metastases had grown larger and were now giving marked symptoms, and enormous recurrences of the tumor had developed in the cicatrix from the

[1] The term osteogenic sarcoma is here everywhere used in the sense in which it was first used by EWING, of a malign bone tumor arisen from cells with the potential power of bone formation (CUTLER & BUSCHKE).

operation. *Microscopy* from one of these metastases (which was as large as a man's head) showed polymorphocellular sarcoma, exactly as before. The patient died in September, 1943, in a state of extreme cachexia, $3^1/_2$ years after the onset of the disease. Necropsy was not performed.

Epicrisis. — A farmer, aged 20 years, with a clinically, roentgenologically and histologically typical, benign-looking giant cell tumor in the head of the humerus was treated by roentgen irradiation 6 times in the course of 2 years, being given, in all, 6500 r, with good subjective effect and marked roentgenologic signs of healing. Three years after the onset of the disease, the condition suddenly got worse, with spontaneous fracture; and markedly malignant, osteogenic sarcoma was ascertained, which despite amputation led to enormous metastases in the cicatrix from the operation and clinical and roentgenologic signs of metastases in the lungs. Death supervened 9 months later.

Discussion. — The case seems to be a clear one of malignant transformation of a benign cell tumor into an osteogenic sarcoma. The only possibility of error is that there in some other part of the original tumor may have been sarcomatous portions which had not been reached in the trephining for biopsy sample. If that is the case, the growth would have been a primary sarcoma that had masked itself as a benign giant cell tumor — or a malignant giant cell tumor. Despite the rather large column of tissue from the trephining deep into the tumor, this possibility cannot be excluded, of course. Like the cases from the literature, this case can therefore at most be taken as support for the *probability* of giant cell tumors being capable of malignant transformation. For the clinician, this is, however of minor importance. The principle is the ascertainment of *the fact that a to all appearances benign giant cell tumor may eventually end as a malignant sarcoma,* which means *that it is impossible to be absolutely sure that an observed giant cell tumor may not become malignant,* though such a transformation undoubtedly is rare. I am inclined to believe that it would be very rare if a thorough examination were always made at once *of the whole tumor* — that is if curettage were always done to begin with; because thus the suspect cases would be eliminated.

Case 9. — R 27399. Workingman, aged 33 years. — Typical giant cell tumor in the head and neck of the radius, verified by microscopy. Roentgen treatment: 2 series, each of 3,000 r; 6,000 r in all; without sure effect. Followed for 16 months.

Case 10. — R 30120. Housewife, aged 47 years. — Typical giant cell tumor in lateral condyle of tibia, verified by microscopy. Roentgen treatment: 3 series, of resp. 1,000, 800 and 1,500 r; total, 3,300 r, without sure effect. Followed for 1 year.

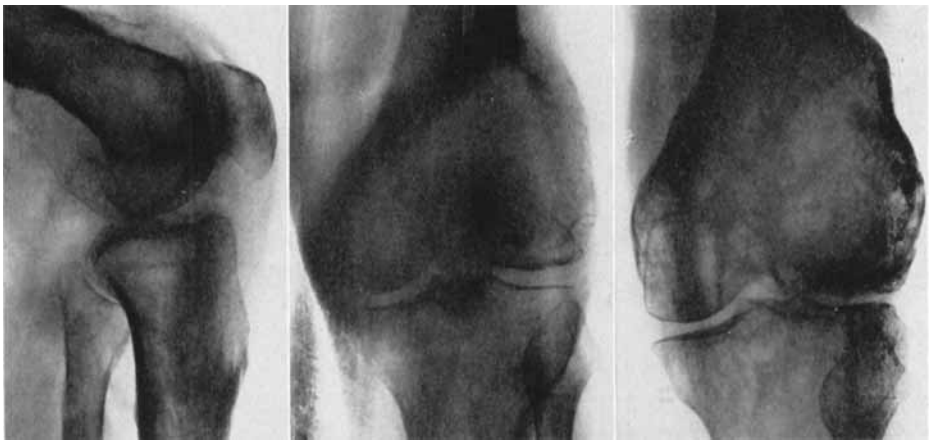


Fig. 11. Fig. 12. Fig. 13.

Figs. 11—12. Lateral and anterior views of right knee, untreated; Oct., 1935: Finely lobulated, orange-sized tumor in lateral condyle of right femur; some suspicion of malignancy, but not unlike a giant cell tumor.

Fig. 13. Same tumor, Oct. 1938, (3 years after intensive roentgen treatment): Marked consolidation of the compact tissue and the trabeculae more sharply defined. The growth now most nearly resembles a giant cell tumor in the process of healing.

Case 11. — R 31002. Housewife, aged 47 years. — Typical giant cell tumor in distal epiphysis of radius, verified by microscopy. Roentgen treatment; 1 series, 600 r, in all; without effect. Later, curettage, with good effect. Followed for 18 months.

To show what difficulties the differential diagnosis sometimes may present, I relate the following case, in which the tumor, from which the patient eventually died, for several years resembled a giant cell tumor.

Case 12. — K 17546. Coal merchant, aged 51 years. — Formerly well. Had for two years been complaining of pain in the right knee. No preceding trauma, but during the course of the disease several severe injuries. In October, 1935, *roentgen examination* showed in the right lateral condyle of the femur a tumor, the size of an orange, occupying the whole epi- and metaphysis and extending for some distance up into the shaft. The bone, which was somewhat puffed up, was by the very finely lobulated tumor reduced to a paper-thin shell. The delimitation upwards toward the sound bone tissue was a little vague, but there were no spiculae. There was some suspicion of the tumor being malignant, but it rather resembled a giant cell tumor (Figs. 11—12). He was in the course of 5 months, without preceding biopsy, given fractioned *roentgen treatment*, 200 r × 50; total, 10,000 r, to the right knee, with good effect on the pain; the condition otherwise unchanged.

In October, 1938, recurrence; and he was admitted to the Copenhagen County Hospital, Gentofte, Service H, where *roentgen examination* showed that the tumor had progressed a little, but now showed marked consolidation both of the compact tissue and of the trabeculae, with sharp delimitations; it now most nearly resembled a giant cell tu-

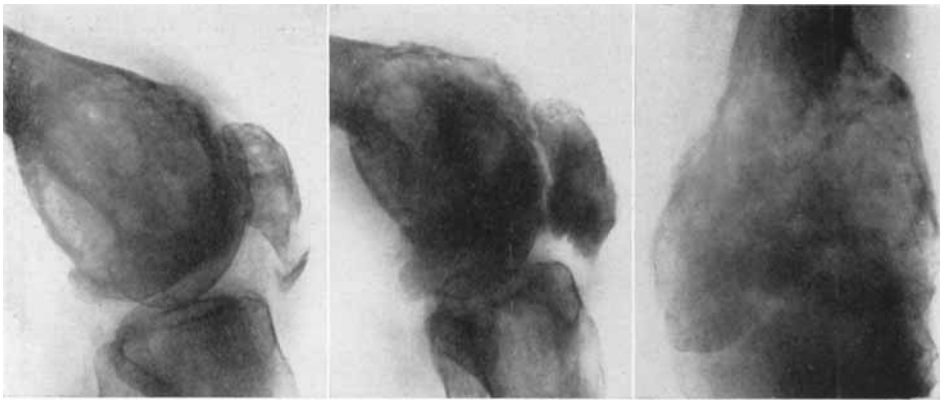


Fig. 14. Fig. 15. Fig. 16.

Fig. 14. Same tumor July, 1940: Further consolidation of the compact tissue, indicating continued progress of the process of healing. Besides, several strain fractures, but no signs of malignancy.

Figs. 15—16. Jan. 1941: Now unmistakable osteogenic sarcoma with effaced structure and large massive, cotton-woolly shadows.

mor in the process of healing (Fig. 13). *Curettage* was done, and masses of yellowish-white granulation tissue removed. *Microscopy:* osteitis (? osteitis fibrosa).

In 1940, there again came recurrence, and the patient was referred to the surgical service of the Finsen Institute, where *roentgen examination* (July, 1940) as before showed giant cell tumor, but now with a little better consolidation as expression for further healing. Besides, there were several strain fractures around the knee-joint; thus, in the patella; but no signs of malignancy (Fig. 14). The case was still considered as a giant cell tumor, and the patient was kept under observation, but no biopsy was performed.

In January, 1941, the pain became more intense, the knee became very much swollen, there were hard, prune-sized lymph nodes in the right crural region, and also the general condition was visibly affected. *Roentgen examination* now, — seven years after the onset of the disease, — showed an entirely different picture. The tumorously rarefied area had become larger, and the structure was very much effaced. In the distal half of the patella and in both femoral condyles there were considerable, massive, cotton-woolly shadows, as expression for new bone formation, and the interarticular space was almost entirely effaced. The picture was now clearly that of a sarcoma (Figs. 15—16). *Trial boring* from the tumor (Jan. 1941) showed unmistakable polymorphocellular (osteogenic) sarcoma with tissue rich in fibroblasts, marked cellular atypism, hyperchromatic nuclei and abnormal mitotic figures; but no osteoid or cartilaginous tissue, and no giant-cell tumor tissue (Fig. 18). After *preoperative irradiation* with roentgen (100 r × 10; total, 1,000 r), palliative high *amputation of femur*, with excision of the lymph nodes, was performed.

After the amputation, the patient went rapidly downhill, got pains in the abdomen and hemoptyses; and in August, 1941, he died at home, about eight years after the onset of the disease.

The *microscopy* from the curettage at the County Hospital in Gentofte, in 1938, was now revised. The tumor consisted for the greater part of highly fibrous tissue poor

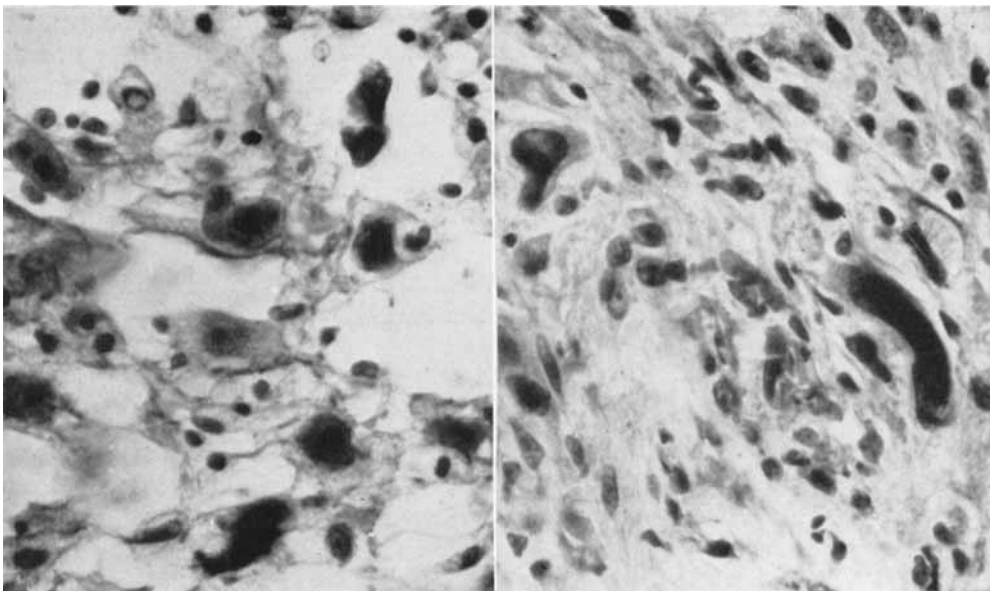


Fig. 17. Fig. 18.

Fig. 17. Tissue from curettage Oct., 1938: Loose tissue with polymorphous tumor-like cells with enormous irregular nuclei and large nucleoles; besides, a few mitotic figures and double nuclei, but no giant cells. Sarcoma, probably osteogenic.

Fig. 18. Biopsy specimen from tumor, Jan., 1941: indubitable polymorphocellular sarcoma (osteogenic); tissue rich in fibroblasts, with marked cellular atypism, hyperchromatic nuclei and abnormal mitotic figures.

in cells, which in some places was necrotic. In other places there were scattered hemorrhages, and, besides, there was some myxomatous tissue. In a few places there were areas with numerous polymorphous, tumor-like cells, some of them with large, irregular nuclei and large nucleoles, here and there double nuclei and a few mitotic figures; but no giant cells. There was no cartilaginous or osseous tissue, and no cysts (Fig. 17). On account of the tumor-like elements, *the tumor must be considered as having already at that time been a sarcoma, probably osteogenic.* The dominating fibrous portions may have been expression for a cicatrix from the intense irradiation three years previously.

Discussion. — Unfortunately no biopsy was made at the first treatment, in 1935, and the case is therefore not quite clear. From the microscopies it appears that the patient in all probability already at the time of the first recurrence, in 1938, has a sarcoma, though a slightly malignant one, but there is nothing in the microscopy to indicate that this sarcoma should have developed from a giant cell tumor; though this does not exclude the possibility that such may have been the case. Nor yet are the roentgenograms quite typical, since there at the first examina-

tion was some suspicion of malignancy whereas the later roentgenograms, on the contrary, pointed rather to a benign giant cell tumor in the process of healing. No doubt the patient in 1941 had a slightly malignant sarcoma, which eventuated in death. I should think it *most probable* that the tumor in this case has been *an originally only slightly malignant, osteogenic sarcoma, which for seven years has masked itself as a benign giant cell tumor and in that time gradually has become highly malignant.*

The case shows the necessity ot careful and repeated examination in all doubtful cases, and especially the necessity, in all cases, of immediate biopsy.

We thus have here *11 cases of epiphyseal giant cell tumors in long tubular bones*; Case 12 not being included. All except Case 6 were verified histologically. Six of the eleven were followed for over five years, two for over three years. *Of these 8, one (Case 8) became malignant and eventuated in death from osteogenic sarcoma.* Of course, conclusions respecting the frequency of malignant transformation of giant cell tumors on the basis of a numerically so small, and, moreover, selected, material are not warranted. Also Case 7 is interesting, histologically, as seeming to show *a transitional form between giant cell tumor and osteitis fibrosa.*

On the whole, the material corresponds well to the large compiled materials from America, but it is curious to note that though trauma is generally considered as an important factor for the development of these tumors, there was trauma in the anamnesis of only three, or, at most, four of our cases.

The roentgen treatment was in most of the cases given in several series, with intervals of some months between each; and each series fractioned, with daily doses of from 100 to 200 r. The doses were, however, considerably smaller than »cancer doses»; in most cases 800 to 1,200 r in each series; the maximum 1,800 r (180 kv.; 0.5 mm. Cu.; distance, 40 cm.; and rather small fields).

In 7 of the cases, roentgen treatment was given as the first therapeutic measure; but only in one case (Case 8) a positive favorable effect was observed, and this eventually showed malignant transformation. *In none of the cases observed for a longer period than 18 months after the roentgen treatment subsequent operation was avoided.* The material thus speaks against the efficiency of the roentgen treatment; but it must not be forgotten that the material probably is rather selected. As this therapy has given excellent results elsewhere, the services do not think of abandoning it, but will continue to use it, only with the employment of somewhat higher doses.

Giant cell tumor in short bones and soft tissues

Case 13. — R 23612. Boardinghouse keeper, aged 30 years. — Giant cell tumor in the talus, verified by microscopy. Curettage (Nykjoebing Sj. Hospital). Twelve years later, recurrence and again curettage, followed by roentgen treatment: 2 series, each of 600 r; total 1,200 r; with good effect. Since well, function good, no recurrence. Followed for 3 years after last operation.

Case 14. — K 11892. Domestic servant, aged 20 years. — Hazelnut-sized giant cell tumor in soft tissue radially to first phalanx of 3rd finger, verified by microscopy. Cured after extirpation. Followed for 5 years.

Case 15. — K 11975. Housewife, aged 50 years. — Bean-sized giant cell tumor adhering to extensor tendon of 5th finger, at level of ungual phalanx; verified by microscopy. Extirpation. No follow-up.

The microscopy showed in all three cases numerous giant cells in coarsely fibrous tissue, with many centrally situated nuclei. There were no signs of infection. The location of the two cases in the fingers makes it very likely that they may have arisen from sesamoid bones.

Localized osteitis fibrosa in long tubular bones

Case 16. — K 6543. Tobacconist, aged 34 years. — Probable bone cyst in medial malleolus. Roentgenologic diagnosis: ? osteitis; ? cyst. Microscopy: detritus-filled multilocular bone cyst with connective tissue walls and hemorrhage; but no giant cells or signs of infection. Complete cure after curettage. Followed for 7 years.

Case 17. — K 10284. Girl, aged 14 years. — Localized osteitis fibrosa in shaft of tibia. Microscopy: A few small giant cells in fibrillar stroma with osteoid tissue and bone in the process of resorption, but no cysts or hemorrhage. Roentgen treatment 4×5 Sabouraud (Bispebjerg Hospital, service A), with some effect. Five years later, spontaneous fracture, curettage, recurrence and renewed curettage, this time with good effect. Since well, function good, no further recurrences. Followed for 15 years; 6 years after the last operation.

Case 18. — K 11765. Nurseryman's apprentice, aged 16 years. — *Typical gigantocellular epulis gingivae + bone cyst in shaft of tibia* (of the latter, no microscopy). Serum calcium, normal. Serum phosphorus, 5—8 mg per cent. The epulis treated by curettage (Copenhagen County Hospital, Frederiksberg), postoperative roentgen treatment: total, 4,100 r, with good effect. Four years later, the cyst in the tibia spontaneously regressed. Since well, function good. Followed for 7 years.

Case 19. — K 12392. Girl, aged 1 year. — *Polycystic osteitis fibrosa in shafts of tibia and fibula*, verified by several microscopies. Serum calcium and -phophorus, normal values (several tests). Curettage, twice, of both bones; later, in spite of repeated operations, pseudarthrosis, but hardly recurrence. Followed for 7 years.

Case 20. — K 12404. Domestic servant, aged 22 years. — Clinically and roentgenologically, bone cyst in shaft of tibia; *histologically, type intermediate between giant cell tumor and osteitis fibrosa;* the microscopy showing a large, solid tumor with numerous typical multinuclear giant cells in a highly fibrillar stroma of fusiform cells, with copious hemorrhage, but no cysts or osteoid tissue. The histologic picture resembles the »spindle cell variant of giant cell tumor» described by GESCHICKTER & COPELAND. — Curettage (Aalborg County Hospital). There is still a fistula; but otherwise the patient is symptom-free, with good function. Followed for 9 years.

Case 21. — R 16497. Boy, aged 10 years. — Typical bone cyst in lower part of shaft of tibia, verified by microscopy. Spontaneous fracture. Curettage. Since well, function good, no recurrence. Followed for 5 years.

Case 22. — R 18601. Girl, aged 18 months. — Clinically and roentgenologically, bone cyst in upper part of shaft of humerus, with spontaneous fracture. No microscopy. Complete spontaneous healing. Followed for $5^1/_2$ years.

Case 23. — R 27143. Boy, aged 15 years. — Bone cyst, the size of a duck's egg, in upper part of shaft of humerus; verified by two microscopies. No histologic signs of malignancy. As the tumor progressed rapidly, primary resection was done, with transplantation of bridge from the fibula. Since well, function fairly good, no recurrence, but only followed for 15 months.

We thus have, in all, 8 fairly sure cases of localized osteitis fibrosa in long tubular bones; for two of which there is, however, no microscopic verification. None of the cases became malignant. In Case 18 there was a combination of epulis gingivae and bone cyst in the tibia. The serum calcium values were normal, but the serum phosphorus repeatedly increased. In Case 19 there were cysts both in the tibia and in the fibula, but the blood values were normal. Another interesting case is no. 20, which showed a type histologically intermediate between giant cell tumor and osteitis fibrosa. The material furnishes a good illustration of *the variegated picture of these lesions* and the difficulties which the differential diagnosis often presents both for the clinician and for the histologist.

Generalized osteitis fibrosa

The material contained 3 cases (nos. 24, 25 and 26) of *generalized osteitis fibrosa*, of which only the first is verified histologically, however; (it has formerly been published by O. CHIEVITZ & H. C. OLSEN). In two of the cases there were multiple cysts, in the third only general halisteresis with spontaneous fractures; in none of them there were giant cell tumors. In two of them there was renal calculus. In all of them, there were typical hematologic changes, and they were cured after removal of a parathyroid adenoma. The cases have been followed up for respectively 11, $2^1/_2$ and 8 years after the operation.

Giant cell tumor and osteitis fibrosa localized to bones of the head, inclusive epulis gingivae

Finally, I shall relate the cases *localized to bones of the head*, 22 in all; of which 3 were located in the upper jaw, while the others were cases of epulis gingivae.

Case 27. — R 8604. Housewife, aged 44 years. — *Giant cell tumor in the left maxilla*, with extensive destruction in the premolar region of the alveolar process, later also in the hard palate and the maxillary sinus. Microscopy: numerous giant cells in a moderately fibrillar stroma with chiefly spindle-shaped cells, but no bone- or cyst formation. *The tumor had perhaps arisen from an epulis gingivae.* Roentgen treatment: 2 series of resp. 2,400 and 3,200 r, total, 5,600 r, without effect; therefore curettage and insertion of radium, 1,350 mc/h. Microscopy now showed fewer giant cells and markedly fibrillar stroma (? radiation effect). Good effect of the operation and the radium treatment. No recurrence. Patient died from other cause, 10 years after the operation.

Case 28. — K 12023. Boy, aged 8 years. — *Benign tumor of left maxilla, probably osteitis fibrosa. Not arisen from any epulis.* By operation, a large, solid, firmly fibred, reddish brown tumor was extirpated, which had invaded the maxillary sinus, whereas the alveolar process was not involved. Microscopy showed an essentially fibrillar connective tissue with abundant collagenic, partly hyalinized fibrils and a quantity of osteoid tissue; besides, there were a few scattered heaps of large multinuclear typical giant cells and some little hemorrhage; but no cysts or signs of malignancy. The microscopic picture most resembled that of an osteitis fibrosa. The patient has since been well, there has not been any recurrence. Followed for $5^1/_2$ years.

Case 29. — R 33108. Domestic servant, aged 20 years. — *Benign tumor of the right maxilla, probably osteitis fibrosa; hardly arisen from any epulis gingivae.* Operated upon in the Nykjoebing (Falster) Hospital for »a large cyst in right maxillary sinus with progression to the sphenoid and the ethmoid bone; the tumor possibly arisen from the root of a tooth. Microscopy: dental cyst with chronic inflammation». Three years later, recurrence set in and the right maxillary sinus was resected (Copenhagen County Hospital, Gentofte, Service E). The orbital wall seemed to be eroded by the tumor; but, as previously, there were no signs of epulis gingivae. Microscopy: fibrillar stroma with numerous spindle-shaped cells and some osteoid tissue, but only here and there multinuclear giant cells, and no cysts. Copious hemorrhage and blood pigment; no signs of malignancy. The microscopic picture corresponds well to that of osteitis fibrosa. The patient was given postoperative roentgen treatment: total, 4,275 r; which seems to have arrested the growth of the tumor. Followed for $3^1/_2$ years.

Discussion. — Case 27 is perhaps one of the rare ones in which an epulis gingivae invades the bone. Otherwise it nearly always proliferates outwards. No. 28 and no. 29 are interesting, because they *both seem to be cases of localized osteitis fibrosa of the maxilla and at least one of them has no relation to an epulis.* The location is rare; among GESCHICKTER & COPELAND's 22 cases there is not a single one in this site. But, as a rule, these lesions will probably not be diagnosed, but will be called osteofibromas or something similar.

Epulis gingivae

The material consists of 19 cases, all verified histologically. Histologically, they fall into two groups: gigantocellular epulis (17 cases) and fibromatous epulis (2 cases). The angiomatous types, which by some are called angiomatous epulis (epulis being merely a regionally determined designation), are not included. A closer scrutiny of the preparations gives one the impression of *an even, gradual transition* from cases which histologically hardly can be distinguished from epiphyseal giant cell tumors, through the most common form, in which the stroma chiefly consists of spindle-shaped cells with considerably more fibril formation and osteoid tissue, while the giant cells and the hemorrhages become fewer, to cases in which there are no giant cells, but marked fibroostosis; — the type here called fibromatous epulis. Where the line of demarcation should be drawn must, I think, be a matter of opinion. Where it is a question of osteitis fibrosa, the histology is, in fact, quite uncertain. *Few diagnoses have probably in the course of time been so misused as this, which does not cover any precise, well defined pathologic field.* Almost any connective tissue reaction in bone has at some time or other been designated by that term. Too superficial biopsy is another source of error. The peripheral portions of a giant cell tumor usually contain a great deal of connective and osteoid tissue, but no giant cells; on the basis of such a preparation one is easily led to diagnose the case as osteitis fibrosa, whereas a later microscopy may show unmistakable giant cell tumor.

The age of the patients varied from 7 to 69 years; only three were under 20 years old. Roentgen examination showed in about half of the cases rarefactions corresponding to the alveole; in none of them there was invasion of any deeper seated bone. All the cases were followed for over 3 years, nine were observed for over 5 years. In none of the cases malignant transformation occurred (such transformation has never been observed). They all became entirely symptom-free, most of them after the first treatment; a few, however, were recurrent cases from other hospitals. Ten of them were treated surgically, by extirpation or excision with or without electrocoagulation of the base, one was a recurrence after operation elsewhere. Exclusive roentgen therapy was employed in 4 cases, two of them recurrences after surgical operation. The treatment was in most of them given as close irradiation in doses of 300 to 500 r. daily, total, 2,000. 3,000 to 5,000 r; with 60 kv., 4 ma. Combined surgical and roentgenologic treatment was used in 5 cases. Radium was not employed.

All the methods of treatment employed have given good results in this absolutely benign affection. I wish to stress this, because the advocates

of roentgen treatment of giant cell tumors emphasize the excellent effect in the treatment of epulis and on that basis often uncritically extend the same to apply to the far less tractable epiphyseal giant cell tumors in long bones. This is, for instance, the case with LACHARITÉ's report of 14 cases, of which 12 were epulis.

Conclusion

The present material corresponds on the whole fairly well to the large collected materials from the United States of America. *It illustrates the enormously variegated picture which these lesions present*, because it in spite of its numerical smallness contains many forms intermediate between the different groups and thus clearly shows the very near relationship between giant cell tumor and osteitis fibrosa.

My study of the cases, especially the histologic examination, has *not* enabled me to sort out from among the giant cell tumors a group which might be considered as genuine neoplasms, such as JAFFE and his coworkers have believed it to be possible. On the contrary, *there seems to me to be an even, gradual transition to osteitis fibrosa* (which certainly is not a neoplasm). For the same reason *I have not found it expedient to subclassify these tumors, of which by far the greatest part are benign, into different grades.*

The material does not tell us anything about the nature of the so-called malignant giant cell tumors. *Only one case* (no. 8) *underwent malignant transformation into an osteogenic sarcoma*, and in this case the original microscopy consisted only in examination of a specimen obtained by trephine biopsy, which showed benign-looking giant cell tumor. Thus, the possibility cannot be excluded that microscopy of the whole tumor would have shown malignant giant cell tumor (or osteogenic sarcoma). A couple of similar cases, with lethal isssue, one of which (no. 12) is related, proved on closer examination to have probably been primarily malignant, osteogenic sarcomas, which in the beginning had masked themselves as benign giant cell tumors. The same is indeed the case with the great majority, by far, of the cases published as examples of malignant transformation of giant cell tumors; though a few of them seem rather convincing. For the clinician it is important, however, to know *that an osteogenic sarcoma in the beginning not infrequently may to the point of deception resemble a benign giant cell tumor, and particularly that the roentgenologic pictures of the two conditions may be exactly alike; so that the possibility of the case being an osteogenic sarcoma cannot be excluded with certainty except on the basis of a histologic examination.* I also wish to emphasize that although a giant cell tumor in the overwhelming majority of cases will remain benign, *there is no absolute certainty that*

it may not eventually become malignant. In doubtful cases, — and among such are especially recurrences affecting the general condition and cases where the patient is in an advanced age, — renewed biopsy and revision of the original microscopy are therefore advised. On the other hand it is just as important that no unnecessary, mutilating measures are resorted to in these for the overwhelming part benign affections. Therefore, it must be remembered that their appearance when they recur, and especially if they have become infected or have been subjected to roentgen treatment, in most cases changes considerably; but that this does not mean that they have become more malignant.

The etiology and pathogenesis of these affections are still obscure; especially are biochemical and histologic examinations lacking. The present material gives no information in these respects, beyond the fact that none of the 47 cases either as regards the age of the patients or the site of the lesions are contrary to GESCHICKTER & COPELAND's theory, according to which they are an abnormal phase of the growth of bones preformed in cartilage, or of the deciduous teeth. It is worthy of note, though, that trauma was rare in the anamnesis of these cases, while American authors ascribe considerable importance precisely to preceding injury as determining factor.

In conclusion, I shall briefly touch on a few important questions respecting these lesions from the clinical point of view.

The giant cell tumors in the epiphyses of long tubular bones can be more or less defined by comparison of the clinical, roentgenologic and histologic findings, and can thus be distinguished from the forms localized to the meta- or diaphyses and termed localized osteitis fibrosa. In most cases, the latter consists in a solitary bone cyst; but sometimes the affection is polycystic, mostly in the same bone, more rarely in several. In short and flat bones, in facial bones preformed in cartilage, and along the border of the jaws, cysts are found which histologically mostly show forms intermediate between giant cell tumor and osteitis fibrosa. In all these cases, the serum calcium and serum phosphorus levels are normal, in contrast to what is the case in generalized osteitis fibrosa, which mostly (or always) is determined by a parathyroid adenoma and is cured by the removal of the latter. Since the last-named affection may begin as a giant cell tumor, a local bone cyst or an epulis, it is advisable always to make a serum calcium and -phosphorus analysis.

In all cases, the question between benign and malignant must be decided by a combination of all diagnostic aids; especially must the possibility of osteogenic sarcoma be considered. The disease is in the overwhelming majority of cases benign, though recurrence is frequent and the course mostly year-long. In epiphyseal giant cell tumor, the func-

tion of the joint is often compromised, even after healing; and on the whole this type is considerably more obstinate. It is also here that the possibility of malignant transformation must especially be borne in mind.

Before the treatment is instituted, biopsy should always be performed, either by excision or by means of trephine. Biopsy has formerly been hesitated from especially in the case of bone tumors, for fear of causing increased spread of the tumor cells. This fear seems to be groundless, though; and that metastasising should increase after biopsy has never been proved (ENGELBRETH-HOLM).

The treatment varies according to the site of the lesion and the other conditions in the individual case. The epiphyseal giant cell tumors are mostly treated either by curettage or by irradiation with roentgen. At present it is impossible to say which of the two methods is the best. In most cases I would myself prefer curettage also for the reason that it gives possibility for microscopy of the whole tumor, whereby one is enabled to recognize at once any possible existing malignant characters of an otherwise benign-looking growth. The combination of surgical operation and radiation therapy is by many deprecated as inefficacious or directly dangerous. At any rate it offers no advantages. In suspicious cases there may be question of resection or amputation. In case of osteogenic sarcoma radical operation is the only chance. In case of recurrence, the treatment may be repeated; but for the most part operation will be preferable; in obstinate cases perhaps resection.

It is difficult to give definite indications for the manner in which the roentgen treatment should be given. It is generally agreed, though, that the doses (given fractioned) should be considerably smaller than in cancer, and that any considerably cutaneous reaction should be avoided, so that the treatment may be repeated several times at intervals of a few months. Radium therapy seems to be of little effect.

Localized osteitis fibrosa is best treated by curettage; but there are many latent or slightly symptom-giving forms whose tendency to spontaneous healing renders treatment superfluous. If there is spontaneous fracture, bandaging in the usual manner will mostly be sufficient. In the cases which histologically resemble giant cell tumor, roentgen treatment may be tried, but is otherwise of little effect.

The numerous intermediate forms, for instance in vertebrae, ribs, pelvic or cranial bones, often have a considerable tendency to spontaneous healing. In many of these cases roentgen treatment will be preferred to the often risky and technically difficult operations in these regions. Epulis gingivae seems to respond well both to excision, roentgen and radium. In cases of generalized osteitis fibrosa, examination should be made for parathyroid tumor. The tumor can very rarely be palpated

in the neck; even if the objective finding is negative, operation should therefore be proceded to if there are typical hematologic changes. When the adenoma responsible for the condition is removed, the bone cysts usually regress spontaneously.

All in all, giant cell tumor and osteitis fibrosa are, despite the many unsolved problems, fields in which treatment is well repaid.

SUMMARY

The author reports 47 cases of giant cell tumor and osteitis fibrosa from the Radium Center in Copenhagen and the surgical service of the Finsen Institute. A case of clinically, roentgenologically and histologically benign-looking giant cell tumor in the head of humerus became 3 years after roentgen treatment transformed into an osteogenic sarcoma with lethal issue. A probably primarily malignant, osteogenic sarcoma in the condyle of femur, after masking itself for 7 years as benign giant cell tumor, led to the patient's death from osteogenic sarcoma. In contrast to curettage, roentgen therapy was found of little effect in epiphyseal giant cell tumors. Histologic scrutiny showed an even, gradual transition between giant cell tumor and localized osteitis fibrosa, and it was not found possible to subclassify these tumors into different grades.

ZUSAMMENFASSUNG

Verf. berichtet über 47 Fälle von Riesenzellentumor und Osteitis fibrosa aus der Radiumzentrale in Kopenhagen und der chirurgischen Abteilung des Finseninstituts. Ein Fall von klinisch, röntgenologisch und histologisch gutartig aussehendem Riesenzellentumor des Humeruskopfes ging 3 Jahre nach Röntgenbehandlung in ein osteogenes Sarkom mit tödlichem Ausgang über. Ein wahrscheinlich primär malignes, osteogenes Sarkom im Femurkondylus führte, nachdem es sich 7 Jahre lang unter der Maske eines gutartigen Riezenzellentumors verborgen hatte, zum Tode des Kranken an osteogenem Sarkom. Zum Unterschied von Auskratzung erwies sich Röntgenbehandlung bei Riesenzellentumoren der Epiphysen als wenig wirksam. Histologische Untersuchung ergab schrittweise alle Übergänge zwischen Riesenzellentumor und lokalisierter Osteitis fibrosa, und es gelang nicht, bei diesen Tumoren je nach dem verschiedenen Grade Unterabteilungen zu unterscheiden.

RÉSUMÉ

L'auteur relate 47 cas de tumeurs à cellules géantes et d'ostéite fibreuse provenant du Centre radiothérapique de Copenhague et du Service chirurgical de l'Institut Finsen. Un cas de tumeur à cellules géantes d'aspect bénin tant du point de vue clinique et radiologique qu'histologique, dans la tête de l'humérus, se transforma trois ans aprés un traitement aux rayons de roentgen en un sarcome ostéogénique avec terminaison mortelle. Un sarcome ostéogénique du condyle du fémur, de caractère malin probablement dès son début, après s'être masqué sept ans durant sous les apparences d'une tumeur bénigne à cellules géantes, fut cause de la mort du malade. La thérapeutique par les rayons de roentgen se montra peu efficace en comparaison du curettage dans les tumeurs épiphysaires à cellules géantes. L'examen histologique révéla une transition régulière, graduelle entre la tumeur à cellules géantes et l'ostéite fibreuse localisée mais il fut impossible d'établir des sous-classes où faire rentrer les diverses étapes du développement de ces tumeurs.

LITERATURE

1. CHIEVITZ, OLE & HANS CHRISTIAN OLSEN: Hosp. tidende, *75*: 1, 1932.
2. COLEY, WILLIAM B.: Amer. J. Surg. *28:* 768, 1935.
3. COLLIN, E.: Hosp. tidende, *72:* 521, 1929.
4. CUTLER, MAX & FRANZ BUSCHKE: Cancer. Its diagnosis and treatment. Philadelphia & London. 1938.
5. ENGELBRETH-HOLM, J.: Ugeskr. f. Læger, *104:* 1105, 1942.
6. EWING, JAMES: Neoplastic diseases. A treatise on tumors. Philadelphia & London. 1942.
7. FLEISCHER-HANSEN, C. C.: Nord. Med. Tid. *11:* 401, 1936.
8. GESCHICKTER, CHARLES F. & MURRAY M. COPELAND: Tumors of bone (including the jaws and joints). New York 1936.
9. GOFORTH, J. L.: Arch. Surg. *13:* 846, 1926 (cit. from: EWING 6).
10. HELLNER, HANS: Die Knochengeschwülste. Berlin 1938.
11. HERENDEEN, RALPH E.: Amer. J. Roentgenol. *12:* 117, 1924.
12. —: Ann. Surg. *93:* 398, 1931.
13. JAFFE, HENRY L., LOUIS LICHTENSTEIN & ROBERT B. PORTIS: Arch. Pathol. *30:* 993, 1940.
14. KJELLBERG, SVEN ROLAND: Acta radiol. *22:* 202, 1941.
15. KREBS, CARL: Ugeskr. f. Læger, *95*: 454, 1933.
16. LACHARITÉ, H.: Radiophys. et Radiothérap. *1:* 535, 1927—29.
17. MØLLER, P. FLEMMING: Fortschr. Röntgenstr. *53:* 465: 1936.
18. SCHINZ, HANS R. & ADOLF ZUPPINGER: Siebzehn Jahre Strahlentherapie der Krebse. Zürcher Erfahrungen 1919—1935. Leipzig 1937.
19. STEWART, F. W., B. L. COLEY & J. H. FARROW: Amer. J. Path. *14:* 515, 1938.
20. STONE, W. S. & J. EWING: Arch. Surg. *7:* 280, 1923 (cit. from GESCHICKTER & COPELAND 8).