GIANT-CELL TUMOUR (OSTEOCLASTOMA) OF BONE: ITS PATHOLOGIC DELIMITATION AND THE INHERENT CLINICAL IMPLICATIONS

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by

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THE SUBJECT OF giant-cell tumour of bone is a familiar one, but one approaches it with interest because it still presents challenging complexities. Let us begin with a few general facts about giant-cell tumour as a clinico-pathologic complex. In the great majority of the cases, the patient is between 20 and 40 years of age and the lesion is in an end of a long tubular bone. Roentgenographically, the affected bone part usually shows up as a rather large, more or less circumscribed, area of striking radiolucency, with little if any suggestion of so-called " trabeculation." Cytologically, the pattern of the lesional tissue in characteristic areas is that of a vascularized network of plumpish spindle-shaped or ovoid stromal cells, heavily intermingled with multinuclear giant cells. As to its clinical behaviour, giant-cell tumour of bone is a lesion which not infrequently recurs and which may even metastasize, so that the use of the prefix " benign " as part of its name is inappropriate.

A bone lesion presenting the cytologic pattern outlined would, of course, have to be denoted as a giant-cell tumour even if it was uncharacteristic in all the other respects. However, we have not encountered a bone lesion conventional for giant-cell tumour in its cytologic pattern and aberrant in respect of all the other features of the total general picture. Indeed, the greater the extent to which a supposed giant-cell tumour is uncharacteristic in these other particulars, the greater the need for caution in interpreting the tissue sections as representing giant-cell tumour of bone.

Age Incidence.—Let us now consider briefly the facts on age incidence of the tumour. In our series of 60 cases, both the mean and the average age fell at about 33 years. About 75 per cent. of the patients were between 20 and 40 years, and most of the rest between 40 and 55 years of age. The condition is definitely uncommon in persons over 55 and under 15. Indeed, we have come to view with scepticism any conclusions about giant-cell tumour drawn from reports heavily weighted with cases in the age group below 20. This is not to deny the occasional occurrence of giant-cell tumour of bone in the young. However, what one encounters much more frequently in the young are lesions which merely mimic giant-cell tumour in one respect or another, and which, on critical evaluation, are found not to justify the diagnosis of giant-cell tumour of bone.

Localization.—When one turns to localization, the findings are again consistent enough to constitute a diagnostic support. In any large representative series of cases it will be found that the lower end of the femur, the upper end of the tibia, and the lower end of the radius are by far the most common sites of the lesion. Indeed, these three sites together are likely to account for about 65 per cent. of the localizations in the series. If one adds the localizations in other long bone ends, one will probably have accounted for 80 per cent. of the cases. In many of the rest, the site of the lesion will still be a limb bone—in our experience most often a phalanx. Localization of giant-cell tumour to a trunk bone or skull bone is thus definitely not common, though it does occur.

It is true that the frequency with which one encounters reports of giant-cell tumour in a skull bone might lead one to think that its occurrence there was not uncommon. However, in connection with supposed instances of giant-cell tumour of jaw bones, one must guard against misinterpreting as a giant-cell tumour a so-called " brown tumour " focus of hyperparathyroidism. It is likely that the relatively high reported incidence of giant-cell tumour of jaw bones in the older statistics can be explained largely on the basis of this error.

Actually, there is usually not too much difficulty in distinguishing between the two lesions even on a cytologic basis alone. In a " brown tumour " focus (whether in a jaw bone or in some other bone), the size and distribution of the multinuclear giant cells, and the character of the stromal cells, offer cues. Specifically, the giant cells are small and often clumped or bunched (especially about areas of haemorrhage), the stromal cells are delicate, and there is often evidence of osseous metaplasia of the stroma. What such a " brown tumour " focus apparently represents is a reparative scarring reaction associated with the presence of giant cells in an area heavily damaged by the local effects of hyperparathyroidism.

Independently of hyperparathyroidism, one also occasionally encounters a jaw bone lesion which, though commonly interpreted as a giant-cell tumour, likewise seems not to warrant this designation. The cytologic pattern presented by tissue removed from such a lesion is analogous, in a general way, to that of the " brown tumour " of hyperparathyroidism. The predilection of this lesion for the jaw bones, its preferential occurrence in young people, the peculiarities of its cytologic pattern, and the consistent innocuousness of its clinical behaviour, have led us to set it off from conventional giant-cell tumour of bone under the name of " giant-cell reparative granuloma of jaw bones."* Indeed, in our experience, conventional giant-cell tumour, in the sense of the tumour we know in relation to the ends of long bones, is rarely encountered in a jaw bone.

Elsewhere in the craniofacial skeleton, the giant-cell tumour of bone seems likewise to be rare. In relation to the calvarium, for example, it

* JAFFE, H. L. (1953) Giant-cell reparative granuloma, traumatic bone cyst, and fibrous (fibro-osseous) dysplasia of the jaw bones. *Oral Surgery, Oral Medicine, and Oral Pathology* **6**, 159.

is only as a complication of Paget's disease that we have ever seen a tumour whose tissue pattern satisfied us as being consistent with that of giant-cell tumour as seen notably in long bones.

In regard to localization of giant-cell tumour in a trunk bone, there can be no doubt that the lesion occasionally occurs in a rib or in a part of an innominate bone. In respect of vertebral localization, it is rather difficult to be sure how many of the reported instances actually represent the lesion, since the diagnosis in these cases is so often based on X-ray findings alone. It seems probable that the lesion does sometimes occur in this site, though I myself have not yet seen tissue from a vertebral lesion presenting unequivocally the pattern of a giant-cell tumour.

There is an expansile lesion which one not infrequently sees in relation to vertebrae and which undoubtedly accounts for many reported supposed instances of giant-cell tumour of vertebrae. This lesion (which occurs in long bones also) may be encountered in any of the segments of the column. Its subjects are mainly older children and adolescents. Tentatively, we refer to this lesion as an " aneurysmal bone cyst."* The term " aneurysmal " in the name relates to a sort of " blow-out " distension of part of the contour of the affected bone area, creating the striking roentgenographic picture so often presented by the lesion. The term " bone cyst " in the name relates to the fact that what one finds when the lesion is entered through the thin shell of the bulged area is so largely a blood-filled cavity. The tissue on its wall is usually meagre, and what there is of it is rather meshy and honeycombed by vascular spaces, and one certainly does not see any substantial tissue areas presenting the cytologic pattern of giant-cell tumour. Just what this total picture may represent is difficult to say, but the burden of proof is upon those who would maintain that the lesion is merely a modified or atypical giant-cell tumour—terms often applied to this lesion when it appears in relation to long bones.

Two additional points concerning localization may well be made. Once in a great while, one encounters, in the interior of a long bone of an adult, a giant-cell tumour which is limited to the shaft—that is, which lies distinctly away from the epiphysial end of the bone. The other point is that, very rarely indeed, one encounters a case of giant-cell tumour in multiple sites in a patient in whom the possibility of hyperparathyroidism has been carefully excluded. I have observed a case in point in which there were giant-cell tumours in four different bone sites (three of them proved by biopsy) and in which the serum chemistry findings repeatedly proved to be negative for hyperparathyroidism.

Roentgenographic Picture.—Let us consider next the roentgenographic picture of giant-cell tumour of bone. This picture is largely determined by the fact : that the tumour develops rather rapidly ; that the tumour tissue causes rapid lytic destruction of the osseous tissue at the site of its growth ;

* JAFFE, H. L. (1950) Aneurysmal bone cyst. *Bull. Hosp. Joint Dis.* **11**, 3.

that the tumour tissue itself possesses no osteogenetic capacity ; and that, even peripherally, as long as the tumour is in a dynamic phase, there is very little, if any, perilesional reactive new bone formation.

In relation to the lesion in its typical location (the end of a long bone) these facts are reflected roentgenographically in the following general picture : the epiphysial end of the bone, sometimes alone but most often with part of the adjacent metaphysis, shows a large and somewhat eccentric area of striking radiolucency, with little if any suggestion of trabeculation. The involvement may extend to the articular cartilage, and occasionally an intra-articular fracture line is visible. The bone cortex in the affected region is found thinned and expanded, and may even show fracture. Despite this, there is likely to be very little periosteal new bone formation over the thinned and expanded cortex. It is to be noted that, in this general picture of the X-ray findings, no stress has been laid upon trabeculation and the resultant multilocular cyst-like effect as being important in the roentgenographic pattern of the lesion. Actually, few giant-cell tumours show pronounced trabeculation. Certainly a giant-cell tumour which is highly vascular and expanding rapidly is likely not to show even a vestige of trabeculation.

In connection with the question of trabeculation, some interest attaches to the following case. The patient was a middle-aged woman presenting a strikingly trabeculated lesion in the lower end of the radius. The roentgenograph of this lesion might have been used to represent the classic text-book picture of giant-cell tumour. However, nowhere in the lesional tissue could we find the characteristic histologic pattern of giant-cell tumour. Instead, we found that the lesional tissue consisted essentially of intertwining bundles of rather drawn out, spindle-shaped connective-tissue cells, and that giant cells constituted no integral part of its tissue pattern. I am reluctant to designate as a giant-cell tumour a lesion presenting such a histologic tissue pattern throughout, in spite of the consistency of the other features of the case with that diagnosis. Instead, I think we are dealing here with a fibroma of bone, which is merely mimicking a giant-cell tumour.

Histologic Tissue Pattern.—Let us turn now to some questions raised by the histologic tissue pattern of the giant-cell tumour. As noted, this pattern consists, characteristically, of a more or less vascularized network of plumpish, spindle-shaped or ovoid stromal cells, heavily intermingled with multinuclear giant cells (Fig. 1). In this connection, it may be well to give some passing attention first to the matter of nomenclature. Over-emphasis on the giant cells has been reflected in the names " giant-cell tumour " and " osteoclastoma." It is true that the giant cells stand out in the cytologic picture because of their size and number, and hallmark it. However, it is the stromal cells, from which the giant cells are derived by fusion, that really determine the cytologic character of the lesion and that offer the better guide to its interpretation. Indeed, while resigning

oneself to the accepted terminology, one wishes that the crucial stromal cells had been given some recognition in the name of the lesion.

Over-emphasis on multinuclear giant cells in bone lesions has caused confusion in another direction, also. Specifically, it still often leads to the misplacement into the category of giant-cell tumour (sometimes as variant or healing forms) of various lesions, mainly of relatively minor clinical importance. Increasingly it is being recognized that a bone lesion should not necessarily be designated as a giant-cell tumour merely because it contains some multinuclear giant cells, to the neglect of the lesion's total histologic pattern.

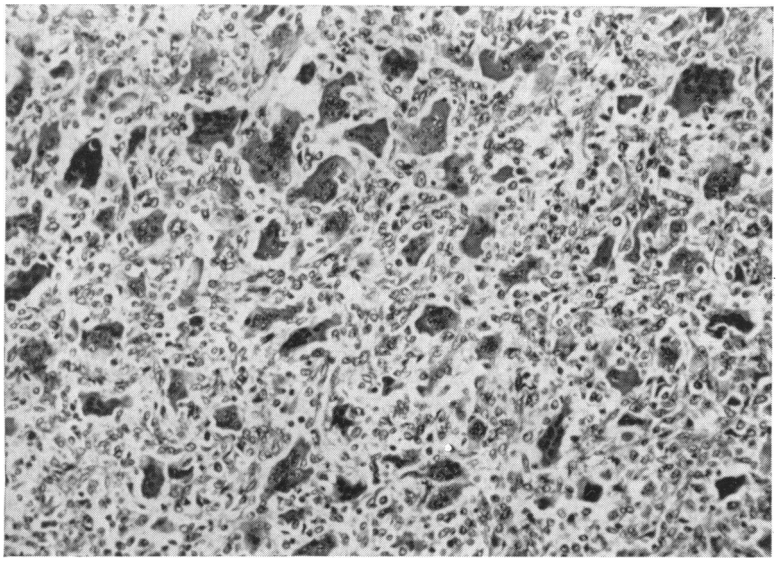

Fig. 1. Photomicrograph (× 100) showing the characteristic histologic tissue pattern of giant-cell tumour.

In this connection, it has already been pointed out that most of the supposed giant-cell tumours of jaw bones are apparently not giant-cell tumours at all, but represent instead the " giant-cell reparative granuloma of jaw bones " or else a " brown tumour " focus of hyperparathyroidism.

Another lesion which should be, and is more and more frequently being, detached from the giant-cell tumour category is the so-called Codman tumour, or, as we prefer to call it, " benign chondroblastoma of bone."* Specifically, this lesion used commonly to be denoted as the " calcifying " or " chondromatous " variant of giant-cell tumour. It is a lesion whose parenchymal cells are polyhedral rather than spindle-shaped

* JAFFE, H. L. and LICHTENSTEIN, L. (1942) Benign chondroblastoma of bone; a reinterpretation of the so-called calcifying or chondromatous giant-cell tumour. *Amer. J. Path.* **18**, 969.

or ovoid cells like those constituting the stroma of the giant-cell tumour. Histologically, this lesion differs from giant-cell tumour in that highly characteristic focal calcifications develop in relation to the parenchymal cells, and, as the calcification becomes more intense, focal necrosis becomes manifest throughout the lesional tissue.

Though the benign chondroblastoma usually takes its departure from an epiphysis (as does giant-cell tumour) it is a lesion which is rarely observed after 20 years of age, affects males almost exclusively, and has a practically uniformly favourable prognosis, almost always healing in promptly after curettement.

In relation to the shafts of long bones of children and adolescents, we encounter a lesion which again was forced into the category of giant-cell tumour, albeit as a variant. Specifically, we find it being interpreted as the " spindle-cell " or " xanthic " variant of giant-cell tumour, and even as the giant-cell variant of bone cyst or of osteitis fibrosa. To our mind, this lesion, too, should be held completely apart from giant-cell tumour. Actually, it is a fibromatous scar or a fibroma of bone, having merely a sprinkling of giant cells in a stroma of attenuated spindle cells, often containing haemosiderin-bearing phagocytes, and sometimes showing areas having groups of lipophages.

Now let us go back to the histologic pattern of the actual giant-cell tumour. In a particular case, even a virgin giant-cell tumour usually shows, here and there, some areas modified by haemorrhage, necrosis, cystification, and reactive scarring. In evaluating the lesion, one naturally discounts such areas and concentrates upon the viable and not otherwise modified tumour tissue. Finding the relational pattern of giant cells and stromal cells to be the one expected for giant-cell tumour, one fixes attention upon the stromal cells.

In most cases, one finds that the stromal cells are numerous and tend towards plumpness, and that no more than an occasional stromal cell shows mitotic division. Deviating from the majority, there are, on the one hand, cases in which the stromal cells are relatively elongated, sparse, and passive, more or less throughout the viable lesional tissue. At the other extreme, there are the rare cases in which so many of the stromal cells are large and atypical and so much mitotic activity is going on that the virginal lesion already has a definitely sarcomatous character (Figs. 2 and 3).

Clinical Behaviour.—As to clinical behaviour, one must, of course, expect an unfavourable outcome in the case of a giant-cell tumour whose stroma has a sarcomatous cast. However, in the vast majority of cases, as already noted, the stroma of the virginal lesion is clearly not sarcomatous. Nevertheless, even among these cases, there will be a good many in which the tumour will recur after surgical intervention (perhaps more than once) and even some in which, sooner or later, it will metastasize to the lungs. Unfortunately, one really cannot predict from the histologic

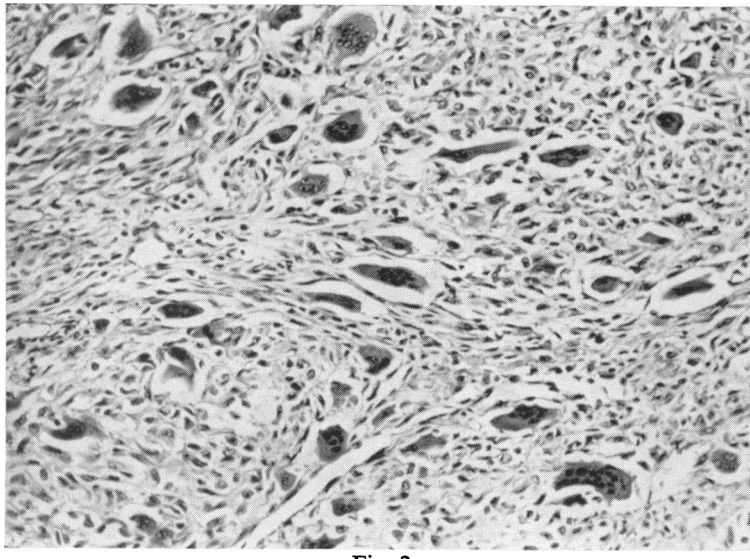

Fig. 2.

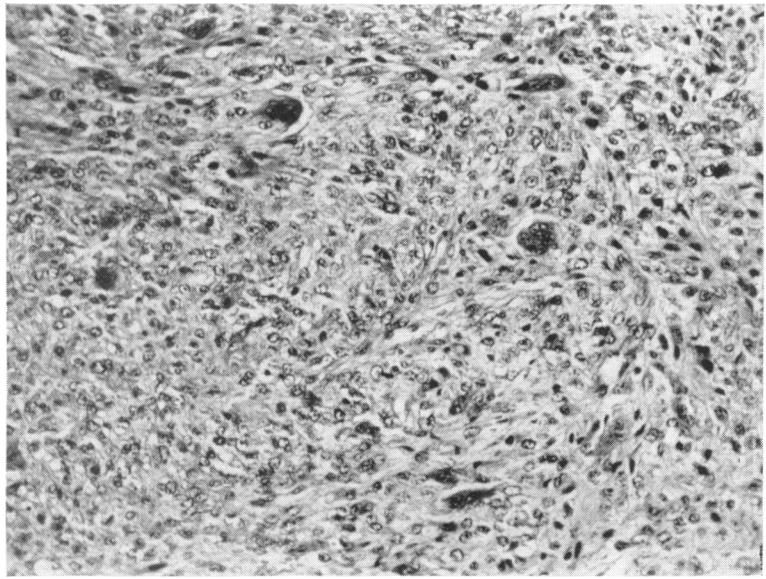

Fig. 3.

Fig. 2. Photomicrograph (×100) showing the histologic tissue pattern of a giant-cell tumour in which the stromal cells are numerous. Pulmonary metastases developed.

Fig. 3. Photomicrograph (×100) showing the histologic tissue pattern of a giant-cell tumour in which the stromal cells are so numerous that they warrant designating the lesion as already malignant.

pattern which cases these will be. On the other hand, in a lesion representing a recurrence of a giant-cell tumour, one is likely to note that the stromal cells are more crowded and plumper than they were in the original lesion. Still, this does not signify that the recurrent lesion will necessarily metastasize or take on locally the histologic feature of a frankly malignant giant-cell tumour.

In connection with the question of metastasis, it is clear that one can often find giant-cell tumour plugs in venous channels at the periphery of the tumourously involved bone site. There can also be no doubt that some of these tumour plugs become detached and reach the lungs as emboli. Undoubtedly, the story usually ends there, the tumour emboli being destroyed, but sometimes the emboli do become established as metastatic tumour foci, and grow in the cytologic pattern of the original giant-cell tumour.

Indeed, we have seen four cases in point. In none of these cases did either the metastatic tumour tissue or the tumour tissue at the original site acquire a frankly malignant giant-cell tumour pattern. In one of these instances, the patient was a man of 27 who had a giant-cell tumour at the lower end of a femur (Figs. 4 and 5). Interestingly enough, even before his femoral lesion was biopsied and curetted, a small, abnormal shadow was visualized in the middle lobe of the right lung (Fig. 6). At that time, the pulmonary lesion was not believed to be related to the femoral lesion, and the latter was curetted and filled with bone chips. In the course of a number of months, the pulmonary lesion enlarged somewhat, and subsequently the femoral lesion recurred. About a year after the original curettement, a mid-thigh amputation was done, and the solitary tumour nodule in the right lung was resected. The tissue pattern of the pulmonary lesion was that of a conventional giant-cell tumour, not differing from the pattern of the tissue originally curetted from the femur or that found in the femoral recurrence (Fig. 8).

In another instance of giant-cell tumour metastasizing to the lungs and retaining its " innocent-looking " tissue pattern, the pulmonary metastases nevertheless grew to massive size, and led to the patient's death. In this case, the patient was a man of 22, and the primary lesion was in the proximal phalanx of a finger. At the time of the original local intervention, difficulty was encountered in resecting the affected phalanx, and therefore the entire digit and part of the related metacarpal bone were amputated ; a local recurrence appeared fairly promptly, and more of the hand was amputated about a year after the original intervention. Locally, there was never any difficulty after this, and it was complaints from the pulmonary metastases that led to further hospitalization and to the patient's death three years after the original surgical intervention. Autopsy failed to disclose any other metastases than those in the lungs.

However, there are also cases in which a giant-cell tumour undergoes progressive cytologic changes in the direction of frank malignancy locally and, in its metastases, even fails to show the histologic pattern characteristic

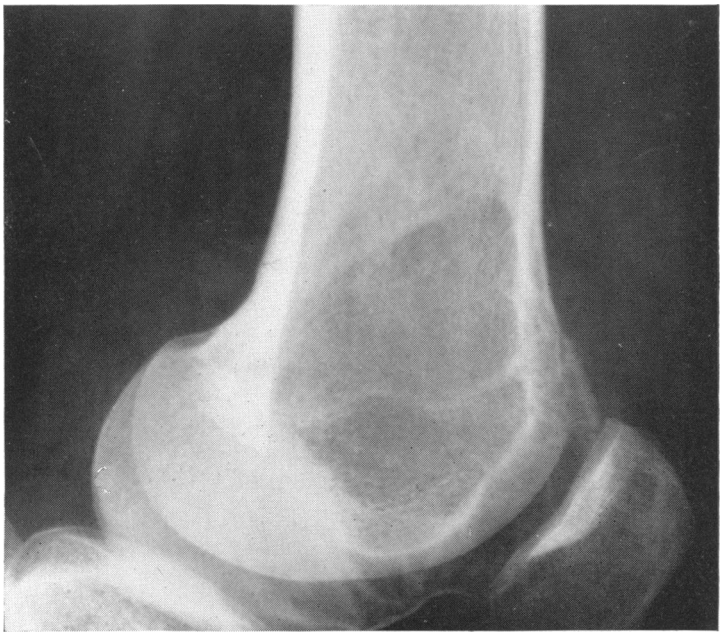

Fig. 4.

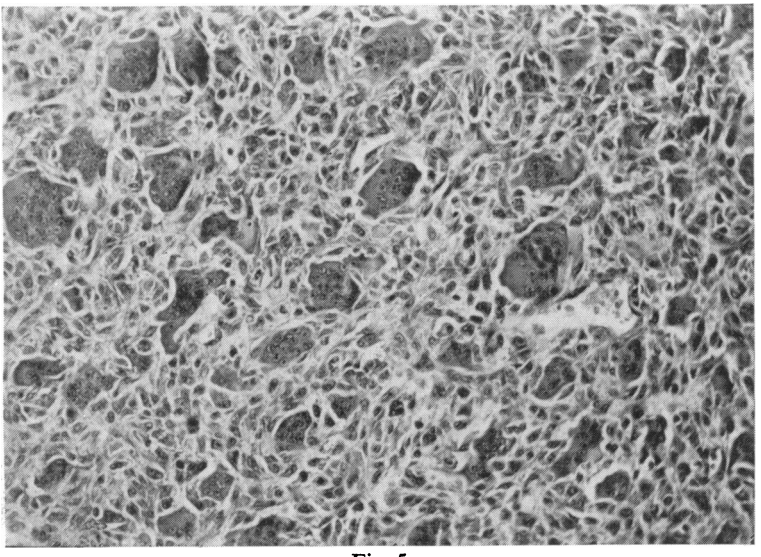

Fig. 5.

Fig. 4. Roentgenograph of a giant-cell tumour of the lower end of a femur, which metastasized to the lung. (See Figs. 6, 7 and 8.)

Fig. 5. Photomicrograph ($\times 100$) of tissue removed from the lesion shown in Fig. 4.

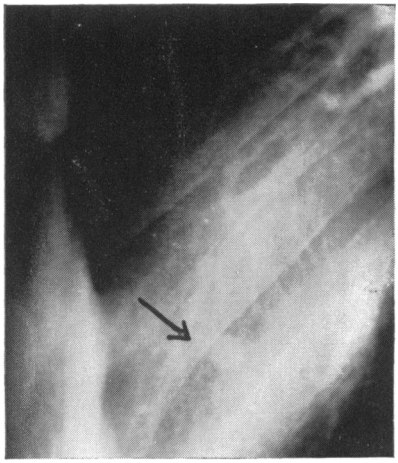

Fig. 6.

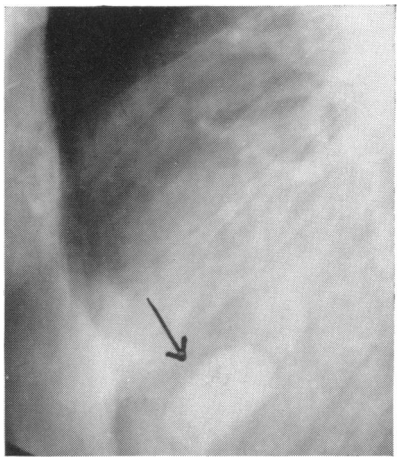

Fig. 7.

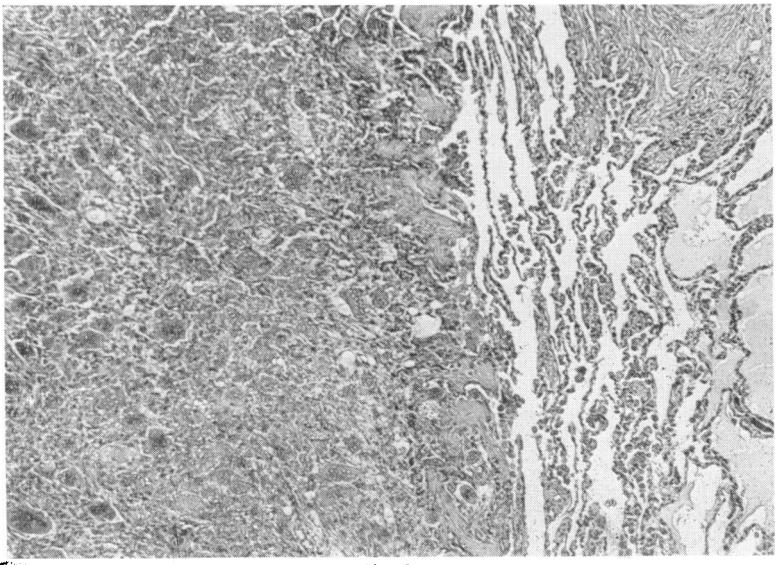

Fig. 8.

Fig. 6. Roentgenograph showing the small, round lesion which was visualized in the middle lobe of the right lung in the case illustrated in Fig. 4. This lesion was already present before the femoral lesion was curetted.

Fig. 7. The appearance presented one year later by the pulmonary lesion shown in Fig. 6.

Fig. 8. Photomicrograph ($\times$ 50) showing the histologic tissue pattern of the pulmonary lesion shown in Fig. 7. The pattern is that of a conventional giant-cell tumour.

of a giant-cell tumour at all. In a case in point—that of a woman of 35—the site of the giant-cell tumour was the ascending ramus of a pubic bone. The cytology of the tissue removed at biopsy in this case was that of a conventional giant-cell tumour with a rather succulent but not frankly malignant stroma. Subsequently, the tumour showed widespread local extension, and also metastasized widely. In the metastatic foci, the tumour tissue had completely lost its giant-cell tumour pattern and presented the pattern of a spindle-cell sarcoma.

Post-Irradiation Sarcoma.—Finally, we come to the matter of a malignancy appearing at the site of an irradiated giant-cell tumour. That this occurs is probably no longer open to question, and the happening is probably not even rare. The interval between the irradiation and the appearance of the sarcoma in the original giant-cell tumour site is usually five to eight years, but may be shorter or much longer. The sarcoma formation in such cases is to be interpreted as a noxious effect of the irradiation upon the bone area as a whole, rather than upon any residual giant-cell tumour tissue *per se*.

In the relevant case which I am demonstrating, the patient was a man of 28 who was treated in 1928 by curettage and irradiation for a giant-cell tumour at the upper end of a tibia (Fig. 9). He was free from complaints for the following 23 years, during which time he went about his duties as a police officer. In 1951, he developed pain in the upper part of the leg and a sarcoma was found to have developed in the upper part of the tibia, in the area where the giant-cell tumour had been present (Fig. 10). An amputation was done, and the malignant tumour was found to be an osteogenic sarcoma of a rather complex pattern. Some evidences of residual radiation osteitis could still be noted. The patient succumbed to metastases about a year after the amputation.

Summary.—Giant-cell tumour of bone continues to be a " problem child " among tumours of bone. This is true even though, in accordance with recent knowledge, the term " giant-cell tumour " is generally being used rather strictly. Specifically, it is no longer being made a catch-all for various other tumorous lesions formerly included among the giant-cell tumours, albeit as variants, merely because they contain some multinuclear giant cells. The genuine giant-cell tumour remains a lesion difficult to assay in respect of its clinical behaviour. In general, it can be said, however, that it very frequently recurs after any form of local therapy against it, and that instances of metastasis from giant-cell tumour are increasingly being recorded.

Whether a particular giant-cell tumour will recur cannot necessarily be predicted from the histologic pattern of the lesional tissue. Indeed, it may recur or even metastasize when the pattern is not in itself such as to create uneasiness. Thus, an occasional giant-cell tumour runs a malignant course without presenting, even in its metastases, an obviously

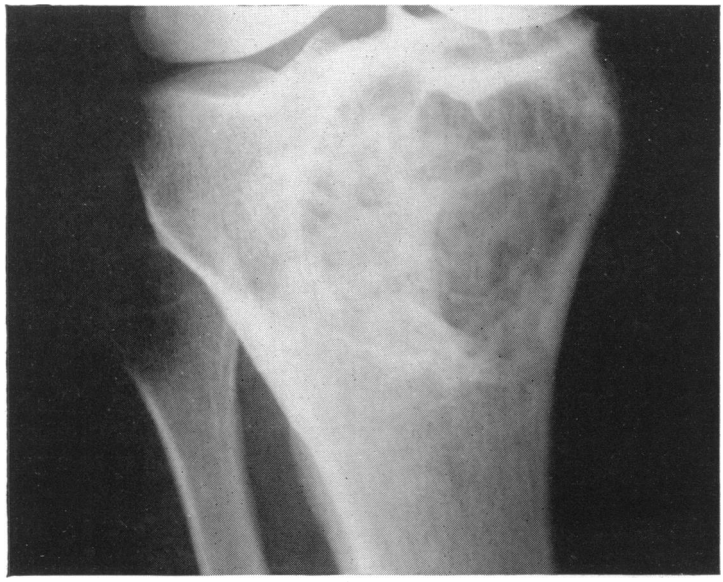

Fig. 9.

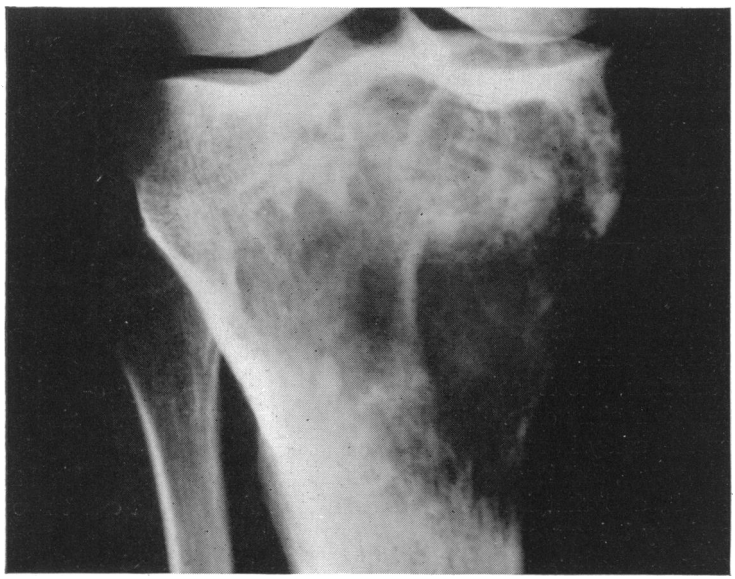

Fig. 10.

Fig. 9. Roentgenograph of the upper end of a tibia which had been curetted and irradiated on account of a giant-cell tumour.

Fig. 10. Roentgenograph of the upper end of the tibia in the same case, 23 years later, a sarcoma having developed where the giant-cell tumour had been present.

malignant histologic pattern. However, in most cases of malignant giant-cell tumour, the stromal tumour tissue does present a sarcomatous appearance. Sometimes this appearance is already manifest in the original local tumour, and sometimes it does not become so until after repeated local recurrence.

Altogether, the giant-cell tumour is a rather treacherous lesion, in regard to which the term " benign," still often made part of its name, conveys a false conception of its potentialities. The treatment of choice for giant-cell tumour is radical surgical excision, if the lesion is in any site accessible to this form of treatment. It is not necessarily contra-indicated as an initial procedure even if it should entail surgical fusion of a joint.

RESTORATION AND REBUILDING OF THE COLLEGE

THE SLATE ROOF over the Wellcome Museums has been completed and now that is is completely waterproof, progress can be made with the interior finishings beneath.

The plaster of the coffered ceiling in the Great Hall is being set in position and should be completed when this article appears in print, by which time the glazing of the windows should be well in progress. The Council is deeply grateful to Sir Archibald McIndoe for the gift of the oriel window, which is to be executed in stained glass with the Arms of the College as the outstanding feature of the design. The artist is Mr. H. Warren Wilson, A.R.C.A. Meanwhile, the panelling for the Great Hall is being prepared by Messrs. J. P. White & Sons, of Bedford, and will be erected early in 1954. It is to be of English chestnut veneer on block boards.

In the Exhibition Hall the plaster of the walls and of the curved ceiling has been completed.

For the new Council Room there has been selected oak panelling, taken from a tree planted in the reign of Queen Elizabeth I at Lilford Park, near Kettering, and later grown into a magnificent tree, 40 feet to the break and 124 inches in girth. In this panelling there is to be set a small bronze plaque of the present Queen, designed by Mr. Donald Gilbert, F.R.B.S., for buildings erected in coronation year. In the arrangement of the room there will also be incorporated a fine carved wooden fireplace removed from No. 44, Lincoln's Inn Fields.

Preliminary work has now started in connection with Phase II of the rebuilding (The Nuffield College of Surgical Sciences) and it is hoped that a contract will be placed within the next few weeks.