TUMORS OF BONES AND JOINTS*

HENRY LEWIS JAFFE
Director of Laboratories, Hospital for Joint Diseases, New York City

and

GOLDEN SELIN
Associate Pathologist, Hospital for Joint Diseases, New York City

THE tumors of the bones and of the joints make up a large and intriguing group of lesions. In their clinical investigation, the disciplines of pathology, roentgenology, and surgery converge and reinforce each other—perhaps more strikingly than in most other fields of medical practice. These tumors have been the subject of innumerable published reports, but the possibilities of additional knowledge about them, even in regard to the practical problems relating to them, still remain considerable.

In view of the variety of tumors which one encounters in connection with the bones, it seems advisable first to have in mind a very general orienting classification of them, such as is presented in the following table. This allows for the easy pigeonholing of all the possible bone tumors into a few very general categories.

GENERAL CLASSIFICATION OF TUMORS OF BONES

TUMORS DEVELOPING AS PRIMARY LESIONS IN BONES
TUMORS INVADING BONES FROM OVERLYING SOFT PARTS
TUMORS METASTATIC TO BONES
TUMORS DEVELOPING AT SITES OF PREEXISTING BONE DISEASE
TUMORS DEVELOPING AT SITES OF DAMAGE TO BONE FROM NOXIOUS AGENTS

It would obviously be impossible here to discuss fully even the first of these categories—that is, the tumors developing as primary lesions in bones. Our comments will be along the lines of general orientation, with emphasis on a few special points in each connection.

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TUMORS DEVELOPING AS PRIMARY LESIONS IN BONES

The tumors primary in bones comprise, of course, benign and malignant tumors. Some of the malignant tumors (notably malignant giant-cell tumor and chondrosarcoma) usually develop out of benign ones. As to the benign ones, these include not only indubitable tumors (such as giant-cell tumor) but also some (such as osteocartilaginous exostosis), which arise through maldevelopment, and still others (such as osteoid-osteoma), which for other reasons belong only on the periphery of the tumor field. The benign tumorous lesions to be encountered in bones are many. Some (such as neurilemoma and neurofibroma) are rare. Others (such as benign chondroblastoma and chondromyxoid fibroma) have only recently been delimited as entities. The ones which we have chosen for consideration here are giant-cell tumor, benign chondroblastoma, aneurysmal bone cyst, and chondromyxoid fibroma. The primary malignant tumors of bones are considerably less numerous than the primary benign ones. In connection with the malignant ones, we shall consider only osteogenic sarcoma – the most common of them. Familiar as it is, this lesion still raises some interesting general questions relating to its definition and differential diagnosis.

Giant-Cell Tumor.—This lesion continues to be the "problem child" among the benign tumors of bone.[1] This is true even though, in accordance with recent knowledge, the term "giant-cell tumor" 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 tumors, albeit as variants, merely because they contain some multinuclear giant cells. The genuine giant-cell tumor remains a lesion difficult to assay in respect to its clinical behavior. 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 tumor are increasingly being recorded.

Whether a particular giant-cell tumor 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 tumor runs a malignant course without presenting, even in its metastases, an obviously malignant histologic pattern. However, in most cases of malignant giant-cell tumor, the stromal tumor tissue does present a sarcomatous

appearance. Sometimes this appearance is already manifest in the original local tumor, and sometimes it does not become so until after repeated local recurrence.

Altogether, the giant-cell tumor 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 tumor is radical surgical excision, if the lesion is in any site accessible to this form of treatment. It is not necessarily contraindicated as an initial procedure even if it should entail surgical fusion of a joint.

Benign Chondroblastoma.—The lesion which has been delimited under the name of "benign chondroblastoma of bone"[2] was, and still occasionally is, referred to as the "calcifying" or "chondromatous" variant of giant-cell tumor. Though the idea that the basic cell of the tumor is the chondroblast is certainly implied in the name "chondroblastoma," we are unwilling to commit ourselves unequivocally to this idea. At any rate, it is increasingly being recognized that the lesion is a distinctive one, to be held completely separate from giant-cell tumor of bone. Growing experience with the lesion has abolished the idea that it predilects the upper end of the humerus, but has reinforced the idea that it strongly predilects males. The treatment of choice is curettage. Growing experience seems to indicate also the possibility that, in rare instances, this tumor undergoes malignant transformation.

Aneurysmal Bone Cyst.—As a descriptive term, the name "aneurysmal bone cyst"[3] is meant to convey the idea of a sort of "blow-out" distension of part of the contour of the affected bone area as presented roentgenographically, and the fact that when the lesion is entered, the affected area is found to be largely a blood-filled cavity. The lesion seems to represent a radiologic-pathologic complex sufficiently striking to merit independent consideration. In the past, the lesion has usually been conceived as representing some variety of giant-cell tumor or else a peculiar hemangioma of bone. On the basis of its roentgenographic picture, it may also easily be mistaken for a malignant tumor. While aneurysmal bone cyst may represent a primary disease entity, one should allow for the possibility that it may have developed in consequence of hemorrhage in the course of which some established benign lesion has been destroyed. At any rate, the original lesion is probably neither a giant-cell tumor nor a hemangioma. Despite its ominous

roentgenographic appearance, the lesion is benign. Therapeutically, all that is usually necessary is to curette the wall, collapse the cyst, and, if it is large, fill the cavity with bone chips.

Chondromyxoid Fibroma.—There can be no doubt that, in the past, the lesion which we call chondromyxoid fibroma of bone[4] has commonly been included among the chondrosarcomas or even been designated as myxosarcoma. The tendency to interpret the lesion as a malignant rather than a benign tumor on the basis of its cytology is understandable. In fact, there is almost a paradoxical incongruity between its superficially ominous cytologic appearance and its benign clinical course. However, experience with the lesion will lead one to recognize that its tissue pattern as a whole permits one to state that the lesion is benign, even though one may not be able to support this statement with histologic details. Indeed, this is the kind of lesion for whose identification one has to call upon a sort of sixth sense to amalgamate a number of minute, evanescent impressions into a distinctive whole.

The treatment of choice for chondromyxoid fibroma is curettage of the affected bone area, after which no further trouble is to be expected, even if the curettement has not been thorough.

Osteogenic Sarcoma.—The use of the term "osteogenic sarcoma" to include also chondrosarcoma of bone has, to a large extent, been abandoned. Indeed, "chondrosarcoma" is now almost universally recognized as an entity distinct from osteogenic sarcoma. On the other hand, fibrosarcoma primary in bone is as yet not generally separated off from osteogenic sarcoma. However, if one defines an osteogenic sarcoma of bone as a malignant connective-tissue tumor in which the sarcomatous stroma forms osteoid and osseous tissue in the course of the tumor's growth, it follows that the connective-tissue sarcoma of bone which does not lay down osseous tissue (that is, the fibrosarcoma) should also be placed in a separate category.

Likewise bound up with this definition of osteogenic sarcoma are certain other questions relating to designation and nomenclature. In speaking of osteogenic sarcoma, one usually has in mind the cases in which the tumor begins in the medullary cavity of the affected bone site and eventually extends through the cortex and even into the overlying soft parts. In these typical cases, the sarcomatous stroma may lay down large quantities of tumor osteoid and bone (sclerosing osteogenic sarcoma) or, relatively little tumor osteoid and bone (osteolytic osteo-

genic sarcoma), or, on the other hand, show extensive hemorrhagic and telangiectatic areas (telangiectatic osteogenic sarcoma). In all these cases, the prognosis is poor, the 5-year survival rate averaging about 5 per cent and certainly not exceeding 10 per cent, and the general prognosis is not really influenced by the extent of ossification of the sarcoma or by the other pathologico-anatomic qualities just mentioned.

However, there is a form of osteogenic sarcoma which has a much higher survival rate, and which in other respects, too, stands out from those cases just delimited. This is the form which we choose to designate as "juxtacortical osteogenic sarcoma."[5] It is a rather distinctive bone-forming tumor which develops in relation to the periosteum and/or immediate parosteal connective tissue. It is a tumor which, at least at first, is merely oriented to the regional bone in the sense of starting just beyond the confines of the cortex. Ultimately, the tumor may come to erode the cortex of the regional bone and even invade the marrow cavity, but these facts may not invalidate its more favorable prognosis.

It should be noted that, as a rule, this lesion is not sorted out from among the conventional osteogenic sarcomas. It is very likely that in the Bone Tumor Registry's classification (1939) of the bone sarcomas, the categories of capsular and parosteal osteogenic sarcoma and the category of periosteal osteogenic sarcoma comprise mainly instances of what we call juxtacortical osteogenic sarcoma. Possibly, juxtacortical osteogenic sarcoma represents the parosteal counterpart of the much rarer, malignant form of myositis ossificans.

TUMORS INVADING BONES FROM OVERLYING SOFT PARTS

A tumor developing in the soft tissues overlying a bone area not infrequently comes to erode the regional bone cortex and may even break through into the marrow cavity. That this may happen in cases of juxtacortical osteogenic sarcoma has already been pointed out in connection with osteogenic sarcoma in general. When a juxtacortical osteogenic sarcoma is seen for the first time at such a late stage in its evolution, it may indeed be difficult to decide from the x-ray pictures at that stage whether one is dealing with this soft-part osteogenic sarcoma or with an osteogenic sarcoma of the conventional type which has begun in the interior of the affected bone and broken out into the soft tissues.

Fibrosarcomas developing in the soft parts adjacent to a bone may likewise come to erode the bone cortex and even invade the marrow cavity. A rapidly growing anaplastic fibrosarcoma which is found involving both soft parts and bone sometimes likewise raises the question of whether the tumor began in the bone and extended into the neighboring soft parts or vice versa. Even a rather slowly growing, well differentiated fibrosarcoma of soft parts may come to erode the neighboring bone. When it does, however, the x-ray picture generally gives the cue that one is dealing with a tumor invading the bone from the outside, since where the tumor is irrupting into the bone the latter tends to show a margin of sclerosis.

A muscle tumor, also, may erode into the bone, and we have even seen a remarkable instance in which a malignant granular cell myoblastoma growing in the back of the thigh had extensively invaded the femur. Finally, it may be pointed out that if, in a soft-part tumor encroaching upon a bone, one sees small, roundish radiopacities scattered through the x-ray picture of the part, one can be fairly certain that the tumor is a vascular tumor—most probably a hemangioma.

TUMORS METASTATIC TO BONES

An appreciable number of cases of cancer first attract clinical attention through the appearance of a destructive bone lesion which turns out to represent a metastasis. As a rule, study of a biopsy specimen from the bone lesion reveals clearly that this is a metastatic cancer, and often the site of the primary lesion can be deduced from the cytologic pattern of the metastasis. On the other hand, this pattern may be ambiguous because the cancer cells are undifferentiated. In such a case, it may even be difficult to decide whether one is actually dealing with a metastatic carcinoma or, for instance, with a malignant lymphoma of bone.

Search for the primary cancer in cases in which the presenting difficulty is caused by a metastatic bone lesion is by no means always promptly rewarded. Indeed, it is striking how often such initial clinical search fails, leaving the question of the primary lesion still unsettled. In the course of time, the clinical progress of the case may disclose the primary site. Occasionally, however, it is still clinically obscure even at the time of the patient's death, and in rare instances it may even be overlooked at an autopsy.

Why the first site of metastasis from a cancer is so often one or another bone is an interesting question. Furthermore, one wonders why, in some cases, much of the skeleton may eventually be found heavily riddled by cancer, while visceral metastases (and notably hepatic and pulmonary metastases) are entirely lacking. To explain this apparent shunting of the metastases to the bones, Batson[6] has worked out the concept of the "vertebral vein system." Specifically, injection experiments have led him to the conclusion that there is a network of valveless veins around the spinal dura mater and the vertebrae which also has cranial and body-wall connections and even connections with the veins in the walls of the blood vessels of the extremities. He holds this vertebral vein system to be an independent one, existing in addition to the already recognized caval, portal, and pulmonary vein systems but connecting with these and providing by-passes for them.

This so-called vertebral vein system is conceived as a venous pool or lake in which the flow is very sluggish and subject to arrest and even reversal. It provides a series of passage-ways by which cancer emboli can be seeded directly into the bones, by-passing the liver and lungs. In particular, Batson was able to show by injection experiments that the prostatic vein plexus can be made to drain into the vertebral vein plexus. The possibility of such a drainage path, leading to by-passing of the caval system, would explain the early and sometimes exclusive lodgement of remote metastases from cancer of the prostate in the skeleton. Also, injection of breast venules demonstrated the vertebral vein pattern by which cancer emboli from the breast can likewise, as they so often do, spread first to the bones of the trunk and skull.

TUMORS DEVELOPING AT SITES OF PREEXISTING BONE DISEASE

The development of a squamous-cell carcinoma in a sinus wall of a bone affected with chronic osteomyelitis was never common and is now hardly ever encountered. The occurrence of an exuberant mass of granulation tissue (the so-called granulation tissue sarcoma) in a bone heavily affected with chronic osteomyelitis has likewise become rare. That a sarcoma may develop in one or another affected bone in a case of fibrous dysplasia has recently come to be recognized,[7, 8] but the incidence of this complication seems to be very low.

In connection with Paget's disease of bone, however, tumor development in affected bones is not at all unusual, though its actual incidence

is not clearly established. One can rate the incidence of this complication as being between 5 and 10 per cent among those cases in which the skeleton is heavily involved. However, one must not lose sight of the fact that it is found occasionally even when the Paget's disease is of rather limited extent.

The tumor itself is not necessarily a bone-forming sarcoma—that is, a straightforward osteogenic sarcoma. It may be of the nature of a fibrosarcoma, the tumor not infrequently being quite anaplastic and the stromal cells strikingly polymorphocellular. Occasionally, however, especially when it develops in an affected calvarium, the tumor may present the cytology of a giant-cell tumor, and furthermore even of one without ominous histologic characteristics. The development of a tumor in one bone site in a case of Paget's disease is soon followed by the appearance of tumors in other affected bone sites. This multicentric occurrence apparently represents the development of independent lesions in the various sites. In general, the appearance of a clear-cut sarcoma in a case of Paget's disease is an ominous prognostic indication. The course in those cases in which giant-cell-tumor-like lesions appear in the calvarium in single or even multiple foci seems to be much more favorable, so far as we know at present.

TUMORS DEVELOPING AT SITES OF DAMAGE FROM NOXIOUS AGENTS

In relation to the bones, there have been many clinical and experimental observations of both the immediate and remote harmful effects of the external application of roentgen and radium rays. It has been clearly established that if, for therapeutic purposes, one or more long bones, for instance, of a young child have been irradiated with too large a single dose, or at too frequent intervals, the bone or bones in question may become stunted because of damage to the epiphysial cartilage plate areas.[9] In a child, or in an adult, in whom, of course, the plates no longer exist, intensive external radiation is known to induce injury to the other bone elements also. That is, it may damage the periosteum, bone marrow, spongy bone, and cortex. The complex of changes which may appear under these conditions is usually designated as "radiation osteitis."[10] Specifically, this involves necrosis and sclerosis of the osseous tissue and fibrosis of the bone marrow. The bones so affected also become brittle and highly susceptible to fractures (which are also slow in uniting) and to infection.

That a sarcoma may develop in a bone which has been heavily irradiated has become increasingly evident as experience accumulates.[11, 12, 13] There is quite likely to be a lag of five years or so between the time of the intensive radiation and the appearance of the malignant tumor. The latter has been known to develop in a bone which had been heavily irradiated in the treatment of an infection (tuberculosis, for instance), a non-malignant tumorous bone lesion (such as a giant-cell tumor or a bone cyst), and even in an originally sound bone which had been within the field of irradiation. Though the incidence of post-irradiation sarcoma is apparently not high, its occurrence can not be doubted, and should be a deterrent to irradiation of benign bone lesions which could be treated by surgery instead. These experiences are in line with the earlier observations on the development of bone sarcomas in persons who, years before, had either ingested or inhaled salts of radium or mesothorium, the salts having lodged in the bones and first induced a radiation osteitis.[14]

TUMORS OF JOINTS

When thinking of tumors of joints, one usually has in mind the tumors developing in relation to the synovial membrane. However, the tendon sheaths and bursae mucosae have linings which closely resemble the synovial membrane of joints. Hence, it is not surprising that entirely analogous lesions should develop in the lining membranes of these various structures.

These lesions include the so-called "synovial sarcoma" or "synovioma." This is a relatively rare, highly malignant tumor, of specialized cytologic architecture. The histologic diagnosis of synovioma may present some practical difficulty, however, since much of the lesional tissue may show the pattern of a spindle-cell sarcoma. Thus, one may have to search the tissue to find, in the sarcomatous stroma, the characteristic clefts bordered by synovial lining cells which establish the diagnosis of synovioma.

More frequently, one encounters, in relation to the lining of articular capsules, bursae mucosae, and tendon sheaths, the lesion which has been designated as pigmented villonodular synovitis, bursitis or tenosynovitis respectively.[15] This lesion is at most only a quasi-tumor and apparently represents some local proliferative reactive process. When the villi and nodules of the lesion become matted together, as they so

often do, the cytologic pattern may be such as to invite confusion with synovioma or with some other form of malignant tumor. Safe guides in the histologic differentiation from the synovioma include the absence of a spindle-cell sarcomatous stroma and the presence of numerous phagocytes containing hemosiderin pigment and lipid which is mainly cholesterol.

In relation to clinical diagnosis, it is worth noting that, in the roentgenograph, a synovioma not infrequently presents spotty radiopacities, while the shadow cast by a villonodular lesion of large size presents a sort of lobulated configuration.[16]

REFERENCES

1. Jaffe, H. L., Lichtenstein, L. and Portis, R. B. Giant-cell tumor of bone; its pathologic appearance, grading, supposed variants, and treatment, *Arch. Path. 30*:993-1031, 1940.
2. Jaffe, H. L. and Lichtenstein, L. Benign chondroblastoma of bone; a reinterpretation of the so-called calcifying or chondromatous giant-cell tumor, *Amer. J. Path. 18*:969-91, 1942.
3. Jaffe, H. L. and Lichtentein, L. Solitary unicameral bone cyst, with emphasis on the roentgen picture, the pathologic appearance, and the pathogenesis, *Arch. Surg. 44*:1004-25, 1942. (See "Aneurysmal bone cyst", p. 1021); and Jaffe, H. L. Aneurysmal bone cyst, *Bull. Hosp. Jt. Dis. 11*:3-13, 1950.
4. Jaffe, H. L. and Lichtenstein, L. Chondromyxoid fibroma of bone; a distinctive benign tumor likely to be mistaken especially for chondrosarcoma, *Arch. Path. 45*:541-51, 1948.
5. Selin, G. Juxtacortical osteogenic sarcoma. (*Unpublished material.*)
6. Batson, O. V. The function of the vertebral veins and their role in the spread of metastases, *Ann. Surg. 112*:138-49, 1940.
7. Coley, B. L. and Stewart, F. W. Bone sarcoma in polyostotic fibrous dysplasia, *Ann. Surg. 121*:872-81, 1945.
8. Jaffe, H. L. Fibrous dysplasia of bone, *Bull. N. Y. Acad. Med. 22*:588-604, 1946.
9. Récamier, D. and Tribondeau, L. A propos de l'action des rayons x sur l'ostéogenese, *C. R. Soc. Biol. 59*:621-22, 1905.
10. Ewing, J. Radiation osteitis, *Acta radiol. 6*:399-412, 1926.
11. Jaffe, H. L. Giant-cell tumor of bone, *Bull. Hosp. Jt. Dis. 5*:84-91, 1944.
12. Hatcher, C. H. The development of sarcoma in bone subjected to roentgen or radium irradiation, *J. Bone Jt. Surg. 27*:179-95, 1945.
13. Cahan, W. G., Woodward, H. Q., Higinbotham, N. L., Stewart, F. W. and Coley, B. L. Sarcoma arising in irradiated bone; report of 11 cases, *Cancer 1*:3-29, 1948.
14. Martland, H. S. A general review of data gathered in the study of the radium dial painters, with special reference to the occurrence of osteogenic sarcoma and the interrelationship of certain blood diseases, *Amer. J. Cancer 15*:24-35, 1931.
15. Jaffe, H. L., Lichtenstein, L. and Sutro, C. J. Pigmented villonodular synovitis, *Arch. Path. 31*:731-65, 1941.
16. Lewis, R. W. Roentgen diagnosis of pigmented villonodular synovitis and synovial sarcoma of the knee joint, *Radiology 49*:26-38, 1947.