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CONTENTS

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THE TREATMENT OF BONE TUMORS

Renewed interest in this subject has been brought about by the trial of various classifications, use of radiation and publication of end results. Will it be possible for us to determine our policy at this time?

I. Classification.

A. Bartlet, Edwin I.: The Treatment of Bone Tumors, California & West. Med. 33: 877, 1930.

Bartlet suggests the following classification of bone growths according to prognosis:

1. Benign---curable.

   (1) Osteogenic tumors.

   a. Exostosis.
   b. Osteoma.
   c. Chondroma of the phalanges.
   d. Fibroma (lipoma, fibrolipoma).

   (2) Inflammatory conditions.

   a. Osteoperiostitis.
   b. Osteitis fibrosa (bone cyst).

   (3) Giant cell tumor.

2. Malignant---incurable.

   Osteogenic sarcoma.
   Ewing's tumor.
   Myeloma.
   Angiosarcoma.
   Metastatic tumors.

3. Borderline---hopeful.

   Central chondromyxoma (except phalangeal).
   Atypical sarcoma.

Comment: Philosophical without publication of any figures.

B. Codman, E. A. (Kolodny, A., Bone Sarcoma; Surg. Pub. Co. of Chicago, 1927).

The classification accepted by the Registry Committee embrace all bone lesions under eight headings.

1. Metastatic tumors primary in tissues other than bone.
2. Periosteal fibrosarcoma.
3. Osteogenic tumors, (a) benign, and (b) malignant.
4. Inflammatory conditions.
5. Benign giant cell tumors.
6. Angiomata, (a) benign, and (b) malignant.
7. Ewing's tumor.
8. Myeloma.

Comment: An attempt to break away from "osteosarcoma" with probably too much simplification?

C. Fraser, J., Tumors of Bone, Edinburgh, M. J. 37:153 (Oct.) 1930.

Simple Tumors
arising from osteoblasts:
exostosis, osteomata;
arising from cartilage cells:
chondromata;
arising from marrow cells:
giant-cell tumors.

Borderline Tumors
arising from marrow cells:
myelomata.

Malignant Tumors
arising from fibrous tissue:
fibrosarcomata;
arising from osteoblasts:
osteogenic sarcomata;
arising from blood vessels:
malignant angiomata;
of doubtful origin but probably vascular: Ewing's sarcoma;

Secondary or Metastatic Tumors of Bone.

Comment: Developmental classification.

D. I. Tumors Related to Osteogenesis. (Geschickter and Copeland. Textbook Nov. 1931 A.J. of Canc.)

A. Tumors Derived from Precartilaginous Connective Tissue.

1. Osteochondroma or Benign Exostosis.
2. Chondroma or Benign Chondromyxoma.
3. Primary Chondromyxosarcoma.
4. Secondary Chondromyxosarcoma.
5. Osteoblastic Osteogenic Sarcoma.

B. Tumors Related to Subsequent Cartilaginous Growth.

1. Chondroblastic Sarcoma.
2. Osteolytic Osteogenic Sarcoma.
3. Bone Cyst and Osteitis Fibrosa.
4. Benign Giant Cell Tumor.

II. Tumors of Non-osseous Origin.

1. Primary Lymphoma of Bone (Endothelial Myeloma of Ewing).
2. Multiple Myeloma.
3. Metastatic Carcinoma.
4. Fibrosarcoma and Neurogenic Sarcoma.

Note: Approximately one-half of all primary neoplasms of the bone are related to pre-cartilaginous connective tissue. This includes all tumors containing cartilage and osteoblastic sarcoma. New growths observed in true bone tumors are never simple over-production of the cells of the same type. It involves, in addition, a step in cell differentiation which is not started or caused by the neoplastic processes. Instead, the histogenic transition is a normal occurrence, and the tumor occurs after it has been initiated. For this reason only those localities and age periods at which such normal histogenic steps occur in the skeleton are capable of giving rise to true neoplasms. This gives a new importance to the skeletal and age distribution of each form of tumor, and these two features together constitute a most important diagnostic aid. It justifies a new approach to the clinical study of the tumors of bone, giving a new significance to the pathology of these lesions. This differs somewhat from that of the Bone Tumor Registry, but it is essentially the same.

II. Tumors of Bone.

The following materisl in quotation marks is an excerpt from "Tumors of Bone by Geschickter, C. F., and Copeland, M. M.", published by the Amer. J. of Cancer, N. Y. 1931.

" 1. Exstosis:

The largest group of benign tumors arising from precartilaginous connective tissue in the skeleton are the benign osteochondromas or exostoses. These neoplasms are most frequent near the ends of the long bones of patients between ages of 10 and 25 years and form a bony skeletal outgrowth surmounted by cartilage. While a great number of these osteochondromas escape clinical observation, because of the absence of symptoms, the majority give evidence of their presence by painless swelling of the bone or by stiffness with rheumatic pains in the neighboring joint, the average duration of such mild symptoms being slightly over five years. The distinctive diagnostic features of this group of lesions are the base or pedicle of normal bone protruding through a periosteal gap, and the more or less overflowing neoplastic cartilaginous cap. This structure is visible in the x-rays as an osseous outgrowth differentiated into cancellous and compast portions which merge imperceptibly with identical zones in the normal bone beneath and as an overlying cartilaginous growth with varying degrees of calcification and an occasional superimposed bursa containing fluid or calcareous material.

A similar structure can be traced under the microscope. Going from the most outward layer to that next to bone, there is visible first an insignificant primitive connective tissue membrane merging with the adjoining tendons, second, a zone of cartilage of the normal adult type undergoing calcification in its deeper layers, and third, a zone of normal laminated bone, differentiated into cancellous and cortical zones enclosing islands of fatty bone marrow. Histogenetically, these tumors are considered to be an exaggeration of a

normal bony protuberance intended for the anchoring of an important tendon. At such a junction nature provides normally for a protuberance of bone bulging through a gap in the periosteum to meet an adjoining tendon, which cooperates in the formation of the attachment by cartilaginous ossification within the substance of the tendon. An exostosis represents a failure in the accurate approximation of the tissues entering into such a junction, the cartilaginous center in the tendon persisting in the form of primitive connective tissue, proliferating in excess, and the protuberance of normal bone beneath extending to form a pedicle or base.

Cases of single exostoses without symptoms may be left untreated but should be watched by repeated x-ray examination, since they may undergo secondary malignant change particularly after the age of 30. Simple excision usually suffices to cure those ostoochoncromas producing pain by dysfunction.

Treatment and Prognosis: The foregoing analysis of the histogenesis and etiology of exostoses has an important bearing onthe treatment and prognosis of the disease. Ordinarily these lesions are benign and represent merely a readjusted unbalance between two normal phases of growth. Operative intervention is not called for, since in the usual exostosis the periosteum and underlying cortical bone succeed eventually in "hemming in" the cartilaginous cap except at the point where the fibrous portions of the tendon or ligament perform an identical function. However, operative removal may become necessary because of the interference by the tumor with the function of the surrounding muscles in the use of the adjacent joint. When the location of the tumor is such that repeated injuries result in the formation of a bursitis, the consequent painful lesion warrants excision.

In the removal of such an exostosis, a more careful dissection is warranted than is usually given such tumors. The zone of periosteum overlying the adjacent normal bone about the pedicle or base should be carefully delimited and marked out by the knife and laid back. The base or pedicle should then be chiseled through and the tumor lifted off the underlying bone while it is still attached to strands of the adjacent tendon. The fibers of the tendon entering the tumor zone should then be partially dissected and clipped above the cartilaginous zones which are frequently embedded in them. After the growth has thus been removed, care should be taken to provide for the reanchoring of the strands of the tendon and to suture the adjacent fascia and muscles over the rift in the periosteum to aid in the restoration of the normal cortex when healing occurs.

Ordinarily the usual exostosis, when operated on, is accorded no such systematic treatment. The tumor is chiseled away piecemeal in a careless fashion, the surgeon neglecting the relationship of the adjacent tendons to the tumor. The result is that recurrences of such benign exostoses are by no means rare (5% of this series), and when recurrence does not take place, the adjacent cortex often reforms in an irregular and troublesome manner.

While many exostoses do not require operation and cures are commonly effected in those with aggravated symptoms by simple surgical removal, there is a third group in which both the prognosis and the treatment is an entirely different problem. This is the group of benign osteochondromas which undergo secondary malignant change. In the present series of cases, malignancy arose in over 7% of these benign exostoses or osteochondromas. This is a far higher percentage than is generally conceded, but the reason for this increase in the percentage of malignancy in the present series is due to the care with which they were studied.

It is not sufficient to follow up the cases of benign exostoses and to find out in which of them the patients subsequently die of sarcoma developing in the original lesion. The usual benign exostosis which comes under the observation of the physician or surgeon is removed, and this removal usually eventuates in healing so that the possibility of malignancy is obviated. In patients discharged without treatment or who have recurrence after removal there is, of course, the possibility of

malignancy. But there is also a still larger group of cases that never come under the observation of any physician until malignant change has occurred. To determine this third group and to isolate those cases which show evidence of arising in a previous osteochondroma. It is this third group of cases in which most of osteochondromas terminating in sarcoma were found.

In view of this fairly large percentage of cases with malignant change, the question arises whether or not the removal of an exostosis is warranted as a preventive measure. Such a wholesale removal of these growths is not favored, but attention is called to the need of following cases in which operation has not been performed and of informing the patient to return at once if he observes any unusual increase in the growth or an aggravation of symptoms. In addition, tumors which are discovered in the roentgenogram in and about the pelvis or about the spine should be removed or followed by repeated roentgen examinations twice yearly because their location makes any increase in size dangerous to the patient.

While transformation of these neoplasms, it does not serve as a guide in rendering of a prognosis. In persons between 15 and 20, the growth impetus following adolescence may stimulate these tumors directly, and in patients over 40 the loss of the proliferating powers in the periosteal regions of the exostosis makes stimulation by trauma or infection of the tumor more dangerous. This permits the malignant change to occur at almost any age.

2. Multiple Exostoses.

These multiple exostoses are usually known as hereditary deforming chondrodysplasia. This disease is a congenital disturbance in the perichondrium and hence affects markedly the growth of the bones derived from cartilage. Not only do the tags of the perichondrium in the tendon ends proliferate to form the cartilaginous caps covering the bony outgrowths described under single exostoses, but disturbances and deficiencies in the periosteum in the metaphyseal regions lead to widening of the metaphysis and inhibition of bone growth. For this reason the x-ray films taken of this condition disclose numerous typical osteochondromas involving the metaphyseal regions of the bones, and in addition, widening of the metaphysis and variation in the length of the bones. The regions most frequently and severely affected are those of the forearm and foreleg, the bones of which may be fused at one point. Bending in the extremities is frequent, and occasionally central chondromas may be formed in the metaphysis by ingrowth s of the cartilaginous areas which resemble bone cysts in the roentgenogram. Microscopically tumors excised from the bones in this condition are identical with those described in the chapter on exostoses or osteochondromas.

The prognosis as far as life is concerned is good in these cases, but there is no adequate form of treatment except operation for correction of deformities after the growth period has ceased. In two cases with such multiple skeletal involvement, we haveobserved secondary malignant change in these cartilaginous growths resulting in death from chondromyxosarcoma. Other such cases with malignant change have been reported from time to time in the literature.

3. Benign Chondroma.

A common type of cartilaginous tumor often classified with the benign exostosis is the benign chondroma. These tumors differ histologically from the osteochondromas in that the osseous material typically present in the latter is absent or sparse in these cartilaginous lesions andtheir location in the skeleton is most frequently central instead of periosteal. The chondroma is a benign lesion occurring in the small bones of the hands, feet, or spine and about the ribs and sternum in patients between the ages of 20 and 30 years. In the phalanges of the hand where this tumor is most frequently located, the growth produces a central rarefaction, visible in the roentgenogram as an expanded and cystic area within a shell of cortical bone. Contrary to the usual belief, the central chondroma is rarely multiple and rarely affects the long bones.

Clinically the symptoms are mild and protracted, extending on the average over five years and producing recurrent soreness in a swelling of stationary or slowly increasing size. Cures may be achieved by complete excision or curettement followed by cauterization, but because histologically there are strands of early connective tissue and mysoma associated with the adult cartilage which makes up the bulk of this tumor, these lesions are apt to recur if incompletely excised. In the prognosis of these tumors, it is a striking paradox that the more cellular chondral lesions in the small bones associated with fetal cartilage and myxoma are uniformly benign; whereas the less cellular tumors of larger size occurring in such bones as the sternum and ribs, although composed as benign adult cartilage, must be looked upon clinically as potentially malignant.

Histogenetically, these tumors represent supernumerary joint cartilages, derived from a prechondral connective tissue, which normally forms the joints of the body. This explains their occurrence in the small bones of the hands and feet and about the sternum and the spine where there are a great many articular surfaces. In these regions aberrant strands of primitive connective tissue traverse the axis of the future bone at right angles and become enclosed as development progresses, gradually giving rise to central chondromas.

Prognosis and Treatment. When these benign cartilaginous tumors are quiescent and give mild or no symptoms, they are best let alone and kept under observation by repeated roentgen examination. If because of their position they are frequently subjected to trauma, resulting in soreness and discomfort to the patient, there complete surgical removal should be undertaken, if this is feasible and the tumor is not too large. In the phalanges the lesion is usually small enough to permit preservation of the continuity of the bone after thorough curetting followed by cauterization. The case with which this tumor tissue is transplanted in the wound with resulting recurrence, however, should constantly be kept in mind.

Recurrence is not frequent following operation on chondromas in the small bones. Approximately one third of the cases in this series were treated by primary amputation or radical resection, and in all such cases a permanent cure was effected. When curettement is followed by adequate cauterization, either thermal or chemically with 50 per cent zinc chloride, permanent cures have been established in such lesions occurring in the bones of the hand or foot.

In the chondromas occurring in the large bones, recurrences have followed operation in approximately 25% of the cases. In some of these instances the growth returned after repeated partial excisions when the neoplasms, because of location, could not be completely removed. It is important to record here that patients followed from five to ten years after the first observation have remained well without treatment, although in some instances, there has been a gradual increase in the size of thetumor and recent evidence of malignant change.

When a previously quiescent tumor shows sudden signs of increased growth, with an exacerbation of symptoms, immediate and complete removal is indicated, as secondary malignant change is to be expected. In the instances in which the patient has been so unfortunate as to neglect the growth and allow the tumor to become of unusual size, or in which the location about the sternum or spine makes complete removal difficult or dangerous, partial excision followed by radium therapy should be attempted. The clinical follow-ups on the malignant cases arising from previous benign tumors of this group warrant a trial of thorough irradiation by means of radium. A favorable prognosis can usually be given unless the tumor is of the type just discussed and is too large or in too vital a location to permit complete removal.

In deciding whether a particular lesion in this group is to be treated from the benign or malignant standpoint, the location and not the pathologic changes must be given primary consideration. Chondromas occurring in the small bones of the hand or foot (the os calcis excepted), regardless of their pathologic appearance, may be looked on as benign

lesions, curagle by thorough extirpation (curetting and cauterization). True chondromas of large size occurring about the sternum and spine or in the long bones regardless of their microscopic appearance, must be looked on as potentially malignant, and their surgical removal, if indicated, should be followed by radium therapy.

4. Periosteal Osteogenic Sarcoma (Primary).

A periosteal osteogenic sarcoma containing cartilage and known as chondromyxosarcoma may arise primarily in young patients at the sites where tendons insert directly into bone. The most frequent ages for the appearance of the primary chondromyxosarcomas are between the years of 14 and 21. The favorite sites are about the knee, at the line of the insertion of the adductor magnus, in the lower femur, or in the upper tibia where the tendon of the quadriceps attaches. The symptomatology is brief--about six months in duration and is characterised by pain, tumor, and dysfunction. The neoplasm is composed of a cartilaginous mass, accompanied by ossification and a small amount of cystic degeneration. In the x-ray it is faintly visible as a subperiosteal shadow with an infiltrating outward margin which may be streaked by a few spicules of calcified or ossified material. The tumor does not involve the cortex or medullary cavity until late in the disease when it invades these areas and bone destruction is the result. Histologically these chondromyxosarcomas are characterized by a transition of connective tissue to myxoma and thence to fetal and adult cartilage followed by bone formation. Histologically, they represent abnormal proliferations of precartilaginous connective tissue which forms a tissue of union and a growth zone between the ends of tendon and normal bony protuberances and thus from an embryonic standpoint are closely allied to the benign exostoses. Permanent cures in the primary chondromyxosarcomas average about 5 per cent. Amputation, radical excision or resection followed by radium therapy is the method of choice in treatment. The usual clinical course of the primary form terminates fatally within 20 months.

Prognosis and Treatment: Permanent cures, even when amputation is performed promptly without a previous exploration, are rare in primary chondrosarcoma. In a fatal case the patient usually lives approximately fourteen and one-half months after operation. Since the average duration of symptoms prior to operation is five and one-half months, a case of primary chondrosarcoma can be expected to run its entire clinical course within twenty months. Neither the age nor the location of the growth greatly influences the ultimate results, although apparently the prognosis is somewhat worse for children and when the lesion is in the upper end of the humerus and of the femur. Delay with prolongation of symptoms previous to operation accompanied by destruction of medullary bone diminishes the prospect of a cure. Incomplete initial surgical treatment must be looked on unfavorably, but one cure was accomplished despite delay and recurrence after an initial operation.

If there is failure in the operative procedure, primary chondrosarcoma shows a marked tendency to recur locally as well as to metastasize. The total number of cures in the 42 cases followed in this series for more than five years was 2. In both cured cases amputation was performed, this procedure following after radium treatments in one. In both microscopic verification of the diagnosis is available in the laboratory.

Deep roentgen therapy, either preceding the operation or given postoperatively, has no influence on the results as far as can be determined from this series of cases. When the patient has refused operation deep roentgen therapy has apparently been helpful in alleviating pain, except in the more advanced stages of the disease. Its use, however, cannot be considered other than palliative in the dosages ordinarily administered. Radical resection, when used alone, has not been successful in accomplishing a cure and should be used in conjunction with a radium pack. In lesions of the skeletal trunk radical excision or resection, followed by thermal cauterization and radium therapy is worthy of a trial. The dosage in such

cases must be adequate (30,000 to 50,000 millicurie hours by external application at 10 cm.) and competently administered, at an institution where sufficient radium is available. Interstitial radium may be used inserting 100 millicuries of radium emanation.

5. Secondary Chondromyxosarcomas

may complicate a benign exostosis, a benign chondroma, or benign multiple skeletal diseases such as Paget's osteitis deformans or hereditary deforming chondrodysplasia. Most often the patients are between the ages of 35 and 55, but occasionally a person under 30 is affected. The location differs from the primary form of chondrosarcoma in that there is a greater tendency for the regions about the upper humerus, ribs, and heel to be involved. The total duration of symptoms averages over 6 years, the more recent and acute symptoms following upon a history of rheumatic pain for many years in the region of an osteochondroma or some permanent defect such as a crooked or a short arm. Although the actual onset of malignancy is difficult to establish, this change does not precede the onset of the acute symptoms by many months.

In the roentgenogram the most easily recognized secondary chondrosarcoma is that in which the superimposed malignant change is visible as a fuzzy infiltrating periosteal shadow. Where a previous osteochondroma is implicated, the evidence of this original lesion may remain in the form of a widened metaphyseal region or the more thoroughly ossified portion of the base or pedicle of the exostosis may persist. In advanced cases the entire tumor site becomes the seat of an infiltrating granular mass in which scattered elements of broken osseous material may be seen. Destruction of the cortical bone with invasion of the medullary cavity follows and pathologic fracture may occur.

Histologically, the malignant change giving rise to secondary chondromyxosarcoma bears out the connective tissue origin of this neoplasm. At the site where the sarcoma is arising there is, first, a proliferation of the connective tissue elements, which are present only in insignificant proportions in the benign cartilaginous group and always interspersed with chondral elements in the primary chondrosarcoma. This proliferation has a myxomatous character, and therefore Bloodgood originally called attention to it under the term "pure myxoma of bone".

Permanent cures in the secondary form of chondromyxosarcoma average about 25 per cent. Radical resection or amputation is the treatment of choice. Following this radical excision followed by the implantation of radium into the wound or external irradiation with the radium pack should be undertaken. The disease runs a chronic course even in fatal cases, some patients succumbing only after five to ten recurrences over a period of from 6 to 8 years. (Note: May be some of our late deaths).

Prognosis and Treatment: When a malignant change has occurred in secondary chondrosarcoma, the average duration of life does not exceed more than two or three years. In a small group of fatal cases, the duration may be from 4 to 8 years after many recurrences; there are 6 such cases in this series. In all probability the first recurrence in some of these was a benign growth, the malignant change following the recurrence. These secondary malignant tumors grow more slowly than primary chondrosarcoma and are probably influenced in this matter by the advanced age of the person. If such a tumor is explored and the microscopic section only is submitted for pathologic analysis and prognosis, it is practically impossible to render an accurate opinion because of the gradual gradation from the benign chondromas, on the one hand, and the close resemblance to primary chondrosarcoma, on the other. If an x-ray film is available however, the chances of a cure can be largely estimated by the amount of bone destruction and the extent of the invasion of the marrow cavity by the tumor. The greater the degree of medullary involvement, the worse is the prognosis.

The percentage of actual cures in this form of tumor not including 6 fatal cases terminating 4 to 8 years after treatment is 24%. Of the 12 patients living and well more than 5 years after treatment, 8 were treated by radical resection or amputation. In the other cases, curetting followed by cauterization with the soldering iron and subsequent

deep roentgen therapy or radium treatment accomplished a cure. In one of the cases in which a radical resection of the jaw was done after several recurrences following excision, radium was used following the resection.

The remarkable feature in these cases of cure is the occasional effectiveness of radium and the number of recurrences due to ineffective treatment before ultimate recovery was achieved. In one case, which must be looked on as a cure of 5 years' duration, amputation was performed 4 years after the original exploration. In 2 other cases there were numerous recurrences prior to the amputation or radical resection.

All the patients who were cured except 2 were over 25 years of age; in 2 the tumor was at the upper end of the humerus, and in 2 it extended above the midshaft of the femur. Cures in the upper portion of the humerus or femur speak for low grade malignancy in this type of tumor, since they are extremely rare in this location when the growth is primarily malignant. The actual role of the incomplete operation cannot be estimated in any of these cases, since it is possible that the original unsuccessful operations were performed on a benign tumor and a malignant change followed at a later date, closely preceding the final operative procedure. Unfortunately, exact microscopis studies on the tissue from each operation are not at hand to settle this point. However, in view of the many cases that have ultimately proved fatal after recurrences following incomplete operation, it is only fair to assume that radical operation is usually necessary at the onset of the malignant course to effect a cure. If biopsy is performed and not followed by immediate amputation, cauterization and irradiation is advised, because of the danger of transplanting tumor in the wound.

In deciding on the operative proce - dure, it is well to bear in mind that irradiation is not always effective in this form of sarcoma. Only when complete eradication of the tumor cannot be accomplished by radical resection or amputation does irradiation with radium present distinct advantages. However, if the tumor is cartilaginous and its benign or malignant nature is in doubt, it is best to excise with the cautery and follow with radium therapy.

6. Sclerosing Osteogenic Sarcoma (Primary).

This is a highly differentiated form of osteogenic sarcoma composed of osteoblasts and is sclerosing in type according to the terminology of Virchow. While this form of sarcoma does not ordinarily contain cartilage, it is derived from the primitive perichondrium after this structure has been transformed into periosteum and may rarely show cartilage formation.

This tumor is characterized in the x-ray film by dense radiating new bone in the periosteal zone in the metaphysis of the long bones of youthful patients, and is recognized as the "sun ray" of 15 and 25 years, predominates in the lower femur and in the upper tibia, and runs a fairly acute course, initiated by trauma and accompanied by pain, tumor, and dysfunction. The average duration of symptoms is under ten month. The tumor is essentially a proliferation of new bone proceeding from the subperiosteal region of the metaphysis, raising the periosteum on the outward side and infiltrating tne marrow cavity inwardly. Both the x-ray and the gross specimen depict this and have a characteristically sclerosed appearance.

Histologically, the tumor is composed of large osteoblasts derived from connective tissue with much intercellular osteoid substance scattered in a disorderly way throughout the growth. The neoplasm is an exaggeration of the function of osteogenesis which resides in the primitive connective tissue of the subperiosteum and arises during the age period and at the site where this subperiosteal tissue is active. This tumor is, therefore, characteristically limited to the postadolescent age period and to the metaphyseal region of the long bones. Permanent cures can be achieved in approximately 25% of these cases by prompt resection or amputation. Deep x-ray or radium therapy is not advised, as the tissue gives no evidence of being radiosensitive.

In elderly adults an unusual secondary form of sclerosing osteogenic sarcoma may occur. The preceding lesion is either the callus of a fracture or myositis ossificans. In pathology it

it resembles the more common primary form.

Prognosis and Treatment: Although the duration of the symptomatology is brief, averaging less than 10 months, and the post-operative duration of life in fatal cases averages only 14 months, the percentage of cures effected by radical operation is unusually great in this type of sarcoma. In 60 cases in which complete data were available, including follow-up study, extending over a period of five years or more, there were 16 cured patients living 5 years or longer. All these cures were effected by radical operation, amputation being performed when possible and radical resection in cases affecting the clavicle or rib. In all but 2 cases, the radical operation was instituted at once. In 2 of the living patients, however, there had been previous aspiration or exploration followed by amputation at an interval of weeks or months.

These data leave no question as to the procedure of choice in this type of sclerosing sarcoma of the bone. Radical amputation or resection should be performed at the earliest possible date, following an exploration under the tourniquet. Frozen sections should be made with an immediate and competent pathologic report, and the operation proceeded at once. If facilities for frozen sections are not available and consultation is required in the diagnosis, the roentgenograms and not the sections should be sent, as a diagnosis can usually be obtained roentgenologically without the necessity of exploration, if the proper authorities are consulted. This is the method advocated by Bloodgood.

Deep roentgen therapy does not result in cure in these cases and only restricts the rate of advance of the peripheral margin of the lesion. Two of the patients considered cured had received Coley's toxins in addition to radical operation. Three had also had the benefit of postoperative irradiation.

In regard to the prognosis, it is possible to state that in the patient with a sclerosing sarcoma of the bone, regardless of age, provided the lesion is situated where complete resection or amputation is possible, the chances of cure are more than 25 per cent, when primary radical operation is performed. This probability of a cure becomes less the longer the duration of symptoms prior to operation and the greater the interval of radical treatment. It can also be stated that patients surviving radical operation after 18 months, who show no signs of recurrence or metastases at that time, will, in all probability, remain free from disease.

This high percentage of 5 year cures in osteogenic sarcoma is unusual, and the better prognosis in patients with this sclerosing form depends on the state of differentiation of the malignant cells of osteoblasts which represents the apex of development in the derivation of bone from connective tissue. The better prognosis in these sarcomas is in keeping with the general rule that the higher the state of differentiation in the neoplastic tissue, the less malignant is the clinical course.

Secondary Sclerosing Sarcoma: The clinical data reviewed indicates that the usual sclerosing osteogenic sarcoma, whether microscopically typical or representing one of the variant forms described, arises de novo during the active period of growth. Practically all of the patients are between 14 and 35 years. There are, however, a few exceptions (4 among 78 cases), patients who are beyond the period of growth, and the inference is that the malignancy is secondary to an original primary and benign lesion.

This is definitely indicated by the data in one of the cases. In this instance, a white man, aged 67 had fractured his right elbow one year previously. The roentgenogram showed a distinct ununited fracture with diffused callus formation about the upper end of the ulna. In this callus formation a secondary malignant change occurred, and the patient died of metastases two and a half years after an amputation at the shoulder girdle.

In another case, a white woman, aged 38, complained of acute pain in the left side of the chest which was more intense on coughing. A brace was applied to the chest, roentgen therapy was given, and the lesion became apparently better. A year later the symptoms recurred, and a roentgenogram revealed an osteogenic sarcoma arising over the fourth rib in the axillary line. Although the examination was performed elsewhere and an inquiry was not made in regard to

trauma, the history suggests that this was apparently another instance of secondary sarcoma arising in the callus of a fracture.

Two other instances of secondary sclerosing osteogenic sarcoma in patients 28 and 34 years of age, respectively, are recorded in the laboratory. Both of these arose in a previously bening myositis ossificans.

These instances of sclerosing, osteogenic sarcoma arising secondarily to benign lesions are in keeping with the evidence studied in regard to the other forms of osteogenic sarcoma. Both chondrosarcoma and the osteolytic varieties may arise as primary or secondary lesions, and to the sclerosing form must also be ascribed such possibilities.

7. Malignant Giant Cell Tumors. (Osteolytic)

In the literature the conception is frequently put forth that malignant variants of the giant cell tumor arise by gradual transformation from benign giant cell tumor. This is erroneous. These malignant variants are nearly always forms of osteogenic sarcoma with giant cells that produce bone destruction. One of such forms, the chondroblastic sarcoma, arises from a proliferation of cartilage at the epiphyseal line during the age of puberty and is extremely rare. The tumor occurs most frequently in adolescence, in the region of the epiphyseal line in the upper end of the tibia, the lower end of the femur , and the upper end of the humerus. In the x-ray there is a mottled area of bone destruction with or without a slightly expanded bone shell and, in addition, a definite periosteal reaction. Under the microscope these lesions show a proliferation of chondroblasts which produce abortive fragments of calcifying cartilage. At the margin of these tumors, as a defensive reaction, giant cells proliferate and attempt to remove calcified products of the tumor. These tumors have a symptomatology prior to operation averaging only 5 months in duration and in the series of 24 cases, there were only two"5-year cures." In both, irradiation was used, once in conjunction with curetting, and the other in conjunction with amputation. It is to be concluded, therefore, that a combination of surgery and irradiation is the method of choice in the treatment of this tumor, unless an early amputation can be performed.

Prognosis and Treatment: The duration of symptoms and the clinical follow-up emphasize the malignant character of this calcifying form of chondrosarcoma. The usual duration of the disease from the onset of the first symptoms to death does not exceed two years. With present standards of diagnosis and methods of treatment, the outlook is not favorable. Of 14 cases in this series in which amputation was performed all but 1 terminated fatally. One patient survived the operation more than 21 months, only to succumb to metastasis.

Considering the malignancy of the growth, an unusual number of the patients were treated by curettment with or without cauterization, in most instances owing to faulty diagnosis. None of these patients were benefitted by this mode of therapy when used alone. Two patients curetted and treated by erysipelas and prodigiosus toxins (Coley's) died 3 and 9 months, respectively, after the procedure was instituted.

Although preoperative or postoperative irradiation failed in the majority of cases wherein it was used, the two five-year cures (10%) recorded in this series were obtained by this mode of therapy in addition to surgical measures. One, radium as well as deep roentgen therapy was employed, the radium being implanted directly into the operative wound after curettage. This patient also received Coley's toxins. In the other case, a thorough course of deep roentgen therapy followed curettment, and in addition, amputation was finally performed. While both deep roentgen therapy and radium have failed (one patient treated by direct radium implants died of tumor 19 months after treatment was begun), irradiation should not be neglected as a counterpart to operation in these cases on chondroblastic sarcoma. This is borne out by a follow-up study in nearly 200 cases of the various chondrosarcoma groups (primary, secondary, and chondroblastic). The conclusion seems warranted that unless an early amputation can be performed, operative intervention should always be followed by irradiation, preferably by competent radium therapy. The radium dosage, how-

ever, must be adequate and should not be attempted unless at least 120 mg. are available.

8. Osteogenic Sarcoma (Osteolytic)

The osteolytic form of osteogenic sarcoma is a destructive tumor arising in the region of the marrow cavity in the shaft of the long bones. Clinically the tumor which usually comes under treatment after about 1 year of symptoms shows a wide age distribution, being most frequent in young adults and becoming gradually less frequent with advancing age. The neoplasm shows an unusual tendency to produce a pathologic fracture. In the x-ray a central area of rapid bone destruction which dissolves the cortex without expansion and with definite periosteal involvement can be seen.

This type of tumor is related histogenetically to the formation of cancellous bone from the endosteum which normally follows in the wake of calcified cartilage. Since sufficient amounts of this calcified cartilage are absent at the site and the age when these tumors arise, ossification is incomplete and an osteolytic tumor is the result. Microscopically, this is characterized by large malignant spindle cells and round osteoblasts with numerous mitotic figures and a small amount of poorly formed intercellular osteoid tissue. The giant cells present in the lesion represent an attempt on the part of these phagocytes to remove the incompletely formed osteoid tissue. In these cases early amputation was found to offer the best chances for a permanent cure. All of the cases (6%) of 5 year cures in this group of tumors were achieved by this method. An examination of these cured cases shows that most of them presented exceptional features in that they occurred in patients over 30 with a long duration of symptoms suggesting that the sarcoma was secondary to some preceding chronic and benign lesion. (Important).

9. Bone Cyst.

The benign solitary bone cyst is a frequent lesion in children under 15 years. This lesion usually occurs in the shaft near the upper metaphysis of the humerus, femur, or tibia and runs a protracted and benign course with mild symptoms, averaging 2-1/2 years. Pathologic fracture is usually the only acute phase of the disease and is one of the most frequent reasons for consulting the physician. In the x-rays this tumor shows a central bone expanding defect, the contours of which are symmetrical and have a smooth and intact outline. The cavity in the bone may be traversed by lines of trabeculation. Pathologic fracture with tendency to unite may occur. In the gross and under the microscope the lesion shows a healing reaction of fibrous tissue and new bone formation about the cavity, which contains the remains of old hemorrhage or straw colored fluid.

Arrest of the lesion without obliteration of the cavity results in the latent bone cyst. Progression of the disease when the presence of the cyst is complicated by parathyroid tumor or general skeletal disease.

10. Osteitis Fibrosa Cystica.

Variants of the bone cysts and related forms of osteitis fibrosa include the acute bone cysts or giant cell variant of osteitis fibrosa which occurs on the shaft side of the epiphyseal line in young patients with a duration of symptoms under six months; progressive osteitis fibrosa which diffusely involves a single bone and pathologically is of the polycystic variety; multiple osteitis fibrosa which diffusely involves the skeleton with cystic changes and is associated with parathyroid tumor and disturbances in the calcium balance; and the latent bone cyst, a quiescent lesion which is usually accidentally discovered in adults.

The prognosis for life is unqualifiedly good in all forms of bone cysts and osteitis fibrosa. Permanent cures vary with the different types of lesions. The latent bone cyst does well without treatment. The acute bone cyst often responds to proper irradiation but may require curettment and filling of the cavity with bone chips. The typical bone cysts may be treated as a simple fracture, if such an accident has occurred, or curetted and collapsed at operation. Progressive diffuse and multiple forms of osteitis fibrosa should be carefully studied from a systemic and metabolic

viewpoint. Lowering of the serum phosphorus with hypercalcemia warrants exploration of the parathyroid glands. A diet rich in calcium, phosphorus and Vitamin D with ultra-violet therapy should be tried.

Prognosis and Treatment: The prognosis as to life is unqualifiedly good in all forms of bone cysts and osteitis fibrosa. The chances of permanent cure as well as the mode of treatment however varies with the type of lesion.

In the solitary latent bone cyst occurring as an accidental finding in an adult in which symptoms are absent no treatment is necessary. In the typical solitary type of cyst occurring in a young patient in which pathologic fracture has taken place with impaction and good position, a satisfactory result may follow a simple fixation. X-ray therapy, if the dose is not too high may be used to stimulate healing. Operation is not necessary. If there is any tendency, however, for the lesion to progress at the end of several months, an operation should be performed, the cavity curetted and its lining stripped from the cyst wall. Obliteration of the cavity should then be accomplished by filling with bone chips, or by crushing.

In the acute bone cyst, or giant cell variant occurring in the metaphysis x-ray therapy in moderate doses is the treatment of choice. In case of failure with irradiation operative interference such as recommended for the typical bone cyst should be employed.

In multiple osteitis fibrosa an attempt should be made to rule out the possibility of parathyroid tumor, and to determine the nature of the underlying systemic condition. Studies of the blood serum calcium and phosphorus values should not be omitted. Since most of these diseases contribute to the development of the cysts through their influence on the calcium-phosphorus metabolism it is important to provide a diet rich in calcium, phosphorus, and Vitamin D, and to give the patient the benefits of sunlight and ultra-violet therapy. If a parathyroid disturbance is suspected on the basis of the blood chemistry and urine studies these glands should be explored surgically.

While a permanent cure can be expected in the various forms of solitary bone cysts, progressive deformity in spite of treatment may result in the multiple varieties. Fortunately in most of these diffuse lesions there is a predisposition for the disease process to become ultimately arrested. This should be borne in mind before attempting to perform operations for the correction of deformities, and in young patients it is wise to postpone such measures until after bone growth has achieved its full maturity.

11. Giant Cell Tumor.

In adults benign giant cell tumor, an epiphyseal lesion closely related to the bone cyst may occur. This lesion is most frequent in the lower end of the femur, upper end of the tibia, and lower end of the radius and gives rise to a more acute clinical picture than does the bone cyst, the symptoms averaging 14 months. The usual sequence of events is trauma, pain, tumor, and pathologic fracture. In the x-rays the giant cell tumor shows a central defect situated asymmetrically in an epiphysis within a bone shell which is usually perforated. The lesion is progressive and unless surgical intervention is attempted, or proper x-ray treatment is instituted, arrest cannot be hoped for. Histogenetically, the tumor is related to the resorption of calcified cartilage by giant cells which occurs as a step in normal bone growth in the region of the epiphysis until late in life, and under the microscope that is shown by many large multinucleated giant cells predominating in a stroma of small round cells.

The occurrence of giant cell tumors in the skull follows the distribution of the cartilaginous centers of ossification supporting the view that these tumors are related to the normal process of ossification via cartilage.

In the etiology of giant cell tumor, trauma with interruption of the periosteal blood supply with inhibition of the normal reactive processes in cortical bone was shown to play a role in the production of these new growths.

The treatment of giant cell tumor depends upon whether the lesion is seen as a primary condition or whether it is recurrent. In a primary case, not too far advanced, curettment followed by

cauterization is advocated particularly for the lower femur and upper tibia. In advanced cases in the fibula, ulna, or radiu, resection is preferred. In early cases deep x-ray therapy may be given a trial. Once the giant cell tumor has recurred, resection is the treatment of choice, except in those bones where resection is equivalent to amputation of the limb. Here further curettment, cauterization, and filling the cavity with bone chips should be tried.

The Treatment of Giant Cell Tumor:

Since the contributions of Bloodgood to the American literature of giant cell tumor in 1910 and 1912, the treatment has been steadily increasing in conservatism. Amputation, then resection and then curettement have been the treatments of choice, and now roentgen therapy alone is being advocated by some. The 214 cases forming the basis of the present study indicate this evolution in treatment, these cases recording the various forms of therapy practiced since 1896.

Primary treatment:

Among the primary forms of treatment are listed amputation, resection, curettage, exploration and roentgen therapy only. Of these various forms, curettment has been used most frequently. Excluding the alleged metastatic group, and a few isolated giant cell tumors of the skull and vertebrae (dangerous because of location) mortality either from treatment or from the tumor itself has been exceedingly rare--less than 1%.

Amputation was the primary operation in 30 cases, and although one third of these cases were explored before amputation, and twenty had shown perforation of the bone shell prior to operation, there were no recurrences, no operative deaths and no patient diet of tumor. In half of these cases the patients have remained well from ten to 20 years and over, but in spite of these uniformly good results, the sacrifice of the limb at a primary operation is rarely justified. Hardly ever is the lesion so advanced that the function of the limb is beyond the restoration, and even when pathologic fracture has occurred, it must be remembered that the majority of these heal with appropriate treatment. Particularly in the upper extremity the conservation of the limb or even one of its minor members should be attempted.

Resection was performed as the initial procedure in 34 cases. There were no deaths from either the operation or the tumor, and if we except an excision of a tumor in the lower jaw, recorded as resection, and a similar case in the radius, there was not a single recurrence. In 5 cases a portion of the bony shell was destroyed before operation, in three pathologic fractures had occurred, and in three other cases, there had been a previous exploration. Here again the mode of treatment was usually needlessly radical, and in 5 cases involving the tibia and two involving the femur, in view of the functional results, curettage followed by cauterization would have been preferable. Preliminary roentgen therapy was not resorted to in a single instance in this group, and in many, the age of the patient and the extent of preservation of the bone shell favored treatment by curettage. Resection is permissible, it would seem, in advanced cases or in cases of elderly persons with involvement of the fibula, radius or ulna, although in eleven cases in the ulna, in which the patients were treated by curettment, there was not a single recurrence.

In 105 cases primary curettage was the mode of treatment. The tumor in 31 of these cases recurred. One patient died of a tumor in the vertebrae, and another grew progressively worse after partial curettment of a giant cell growth in the sphenoid bone. Seven patients became secondarily infected after the first or second curettement, necessitating amputation in three instances. Several of these infections followed radium implantation into the wound, a postoperative procedure which has been proved ill advised in this group of tumors. Although it cannot be determined from the records in exactly how many instances, thermal or chemical cauterization followed curettement, it can be safely stated from this study that recurrence was more frequent in the group in which no cauterization was employed. In view of this, and in consideration of the fact that the patients in 16 of the 31 recurrent cases were cured by a second or even third curettement, it may be stated that curettage properly performed in

carefully selected cases is unquestionably the treatment of choice.

Primary roentgen treatment without operation was employed in 5 cases--3 have been followed and are living less than 5 years. This therapy proved successful in certain cases (Herendeen) reported in the literature. The dosages however must not be of full strength, lesions in the long bones and in adults under 50 respond more favorably, and months are required to prove the effectiveness of the irradiation. When postoperative roentgen treatments have been given in certain instances, they have not prevented recurrence and would seem to be of no particular benefit. As Bloodgood has pointed out, roentgen therapy, when compared to proper curettement, is more uncertain, often more prolonged, and does not offer the benefits of microscopic diagnosis in doubtful cases.

Nine patients refused operative treatment, and of these, 7 have been followed: 2 are dead (1 of hemorrhage), 3 are living over 5 years, and 2 are well less than 5 years. Here there is a considerable risk of either crippling or death, and prompt treatment in view of the good results obtained in the majority of cases would have offered much to these misguided patients had they availed themselves of surgical advice.

Secondary Treatment:

When curettage or excision has been followed by recurrence, the problem of the secondary treatment of giant cell tumor arises. Experience shows that little can be expected from roentgen therapy and more undesirable results may follow radium implantation into the wound. If sections of tissue are available from the original operation, they should be submitted to a competent pathologist for confirmation and check of the diagnosis of the primary growth. If not, the recurrent tumor should be reoperated on when where is an opportunity for one familiar with the microscopic appearances of this group of lesions to pass on the frozen sections at the time of operation. In any event, an attempt should be made to recheck the benign or malignant character of the growth. If the recurrence is benign, further curettement may be tried if the lesion is in the femur or tibia, and if the age of the patient and the degree of preservation of the bone shall warrant it. In the fibula, radius, ulna, or humerus, resection is advised.

Should the lesion be sarcoma, amputation followed by deep roentgen ray is indicated, since one 5-year cure in this series was obtained under such conditions. The crux of the matter, of course, lies in an accurate pathologic diagnosis.

12. Giant Cell Variants.

Atypical cases of giant cell tumor include the spindle cell variant which is a healing form of giant cell tumor found usually in small bones. Clinical recurrences due to faulty selection of the type of operation in the individual case or to insufficient treatment because of an erroneous diagnosis are also included. The so-called malignant variant of giant cell tumor in which the microscopic picture, because of infection and necrosis approaches that of osteogenic sarcoma belongs in this group. Finally, so-called metastatic giant cell tumors which have been found upon analysis to be either benign giant cell tumors, dying of other causes, forms of osteogenic sarcoma erroneously diagnosed as benign in the first instance, or a chronic benign lesion of obscure nature ultimately leading to malignant change must be distinguished. In the treatment of these atypical cases the operative measures must depend upon a careful differential microscopic diagnosis.

The Metastatic Group: Recently there has been an attempt to show that the typical giant tumor called benign may occasionally metastasize and produce death. Stone and Ewing, Goforth, and Finch and Gleave are among others who have published reports on unusual giant cell tumors, apparently typical in structure, but peculiar in behavior. Goforth stated that "an occasional case is met with, which although locally malignant, and in a few instances actually metastasizing, apparently does belong to the giant cell tumor group." Similar statements are frequently found in the literature with illustrative case reports, and it would seem that

there is a tendency for the pendulum to swing away from the more fundamental contributions of Nelaton, Paget and Bloodgood on the benign nature of the giant cell tumor.

Eight such cases from the literature and from the records of the surgical pathological laboratory of the Johns Hopkins Hospital have been studied. Sections of all of these cases are in the laboratory and are available for study. The eight cases analyzed represent the unusual members of a much larger series from the clinics of New York, Philadelphia, Chicago, Baltimore, Canada and England -- in all a series of well over 500 cases.

Two important conclusions stand out in analysis of this material: First, in no cases has a nodule of typical giant cell tumor ever been found in the lung, for wherever these metastatic nodules have been examined, they have shown the histology of osteogenic sarcoma. Second, in no one case has the association of an originally benign and typical giant cell tumor in the bone with a secondary metastatic osteogenic sarcoma in the lung been proved.

These are the two fundamental points. On the whole, pathologists are agreed that regardless of their opinion as to the nature of the original growth, the actual metastasizing lesion is not giant cell tumor but an osteogenic sarcoma. It may be taken as proved that a giant cell tumor found to be typical by a competent pathologist is safely treated conservatively. The question, therefore, is not whether a giant cell tumor will metastasize--it never does--but whether these growths when they recur after improper treatment will undergo malignant change and give rise to osteogenic sarcoma. This question has not been settled, and while there is no denying this possibility, the evidence necessary to affirm it is still lacking.

The 8 cases considered have been presented in abstract elsewhere.

We may conclude from an analysis of these eight cases selected as metastatic from among hundreds of typically benign giant cell tumors that they are not strictly bona fide. In no case has transformation of giant cell tumor into sarcoma been proved and in no case have typical secondary giant cell tumor nodules been found in the lungs. In half of the cases a diagnostic error was made, either in ascribing death from other causes to metastases, or in failing to recognize the histology of the original lesion as sarcoma. In the other 4 cases, since material from the original lesion was not saved for confirmation of the diagnosis, there is no proof that the original tumors were typical giant cell tumors, and not a low grade malignancy from the start. Nor can it be contended that the giant cell areas in the final sarcomatous growths were other than a resorptive phase in osteogenic sarcoma without histologic connection with giant cell tumor. The only plausible deduction is that in a few isolated instances an apparently benign lesion of bone, when subjected to unsuccessful treatment and to trauma, may by its failure to heal, provide a fertile site for the subsequent development of osteogenic sarcoma. The unhealed area of bone, and not the nature of the original lesion is the important factor.

13. Related Giant Cell Growths.

Both giant cell epulides of the alveolar border and giant cell zanthomas of the tendon sheath are related histogenetically to the resorption of temporary bony structures, and hence despite their extra-skeletal location are closely akin to typical giant cell tumors of the bone.

The term epulis is applied to many varieties of lesions upon the gum, but amont this miscellaneous collection a clinical entity composed of a giant cell and fibroid type of epulis may be found. These lesions are common in patients between the ages of six and forty-five, are rare at the site of the molar teeth and generally correspond in location and incidence with the shedding of the deciduous teeth. Pathologically they resemble giant cell tumor or the giant cell variants of osteitis fibrosa. They are prone to recur after simple excision unless the excision has been thoroughly done and the region cauterized.

Giant cell tumors of the tendon sheaths are usually related to the development of sesamoid bones rather than to the tendon proper and hence the granulation tissue conception of these so-called xanthomatous lesions is an

erroneous one. These tumors are usually found in the tendons near the metacarpophalangeal joints but may be found periarticularly in any region where sesamoid bones occur. The patients are usually between the ages of 25 and 40. The tumors vary in size from a pea to an egg and the typical yellow color is due to old blood pigment. Microscopically fibrous tissue, the remains of white fibrous cartilage, giant cells, foam cells and old hemorrhage predominate. Complete excision usually suffices for a cure.

In the long bones the xanthoma variant of giant cell tumor is relatively rare. These tumors do not differ in their clinical behavior from typical giant cell tumor, but pathologically have a more yellow color, and are characterized by the presence of foam cells and other evidences of lipoid degeneration.

Most of the so-called giant cell tumors of the soft parts may be related to abberant sesamoid bones or to heterologous centers of ossification involving pre-cartilaginous tissue.

14. Ewing's Tumor: is a neoplasm occurring in the first two decades of life, involving most frequently the tibia and femur; and may metastasize late in the disease to other bones. The disease never primarily involves an epiphysis. It shows the usual symptoms of sarcoma of bone, of pain and tumor, followed by dysfunction. The duration before treatment is about 13 months. It may give the systemic reactions of fever and leukocytosis. In the roentgenogram the disease first widens the shaft of the bone by stimulating bone formation in parallel layers endosteally and subperiosteally, raising the periosteum in "onion peel" fashion. Later the tumor, which arises intracortically, produces areas of bone destruction in the medullary cavity and subsequently in the cortex. Histologically, the tumor is composed of small round cells with dense nuclei and scanty cytoplasm simulating a lymphosarcoma. Histogenetically, the growth appears to arise within the lymphatic channels of the bone. Combined surgery and irradiation gives the best results in treatment, yielding about 10% of permanent cures. The average duration of symptoms is 13-1/2 months and the postoperative duration of life 16 months in fatal cases. While a few cures may follow irradiation alone, this form of treatment should not be persisted in after 6 weeks if definite results are not achieved. Irradiation, however, provides a good therapeutic test.

Treatment and Prognosis: The treatment, as outlined, here, is based on the observations of Bloodgood and further supported by the analysis of the cases presented here.

In cases in which metastases have not occurred, amputation for lesions of the lower extremity below the upper third of the femur, and resection of bones for lesions in the upper extremity, following preoperative irradiation, offer more hope of cure than does irradiation alone.

If the lesion occurs in the upper part of the femur or has become so extensive in the upper extremity that the operation of choice is not warranted, irradiation should be resorted to and continued in therapeutic doses until amputation becomes necessary to relieve pain.

When the lesion is considered operable and the clinical picture, roentgenogram and other laboratory observations are such that sarcoma cannot be ruled out, irradiation as a therapeutic test is advised, since shrinkage of the tumor after two or three treatments is characteristic of Ewing's sarcoma.

At present, we have complete follow-up reports on 54 cases of Ewing's sarcoma. In 45 the patients are dead and in 8 cases the patients are living and apparently well at the time of writing. Every patient who is reported well in this series has a duration of life of more than 5 years since the onset of symptoms, and 6 are living over 5 years following an operative procedure.

We have divided the methods of treatment into three main groups for analysis: (1) amputation or resection with irradiation, (2) amputation or resection without irradiation, and (3) irradiation alone or with exploratory operation.

In group I there are 13 cases with a postoperative duration of life averaging 29.2 months. In 5 cases in this group (23%), the patients were found to be well with an average duration of life of 5 years and 7 months.

In Group II there are 24 cases with an average duration of life of 2 months. In one case of this group (12%), the patient is living 78 months after treatment. This patient's lesion was curetted prior to irradiation.

From a study of these three tabulations there is seen to be little choice between irradiation and radical operation. The evidence indicates that the patient should receive a combination of both forms of treatment when the tumor is observed prior to metastasis.

In selecting features in the clinical history which would be of value in making a prognosis, an analysis was made of the living cases. Their ages ranged from 12 to 30 years. The site of involvement was either the lower or the upper extremity, including the shoulder girdle. The x-ray picture showed either destruction of bone or formation of bone and sometimes both. It also disclosed diffuse involvement of the bone, and either a parallel or a right angle periosteal reaction. The gross clinical changes were not striking, and both normal white cell counts and leukocytosis with fever were observed. Radical operation with or without irradiation alone were among the methods of treatment.

All of the patients reported in this series as living today had a preoperative duration of symptoms averaging twenty months, as against 6 months for those who died within a year following operation. The shorter duration of symptoms apparently therefore, indicates a more rapidly growing tumor and is ground for a grave prognosis. This reflects seriously on the hope of cure through early diagnosis and early treatment in a definite group of these cases. Apparently, symptoms do not always precede the fatal stages of the disease by a sufficient margin for the purposes of therapeutics.

Exploration does not necessarily affect the prognosis in cases in which radical operation or x-ray treatment follows exploration. In 2 cases in which the patients are living over years, exploration was done before the operation of choice was performed. In one case of curettement followed by irradiation, the patient is living over 4 years after treatment. In 6 cases, in which an exploratory operation was performed without further treatment, death occurred in from one to twenty-two months.

15. Multiple Myeloma

is a rare form of tumor causing death and developing in many foci in the red bone marrow of adults. The ribs, spine, pelvis and upper ends of the femurs are most frequently affected and the patients are generally in the 6th decade of life. Clinically, in addition to the rheumatic pains, there are skeletal deformities, leading to pulmonary changes with emphysema and neurological manifestations such as radiculitis and paraplegia. A nephrosis with nonprotein nitrogen retention and a low blood pressure associated with an albuminous substance in the urine, known as Bence-Jones bodies, is present in from 65 to 70% of the cases. The plasma proteins may be markedly increased. The tumors in multiple myeloma are bone destructive and appear in the x-ray as multiple punched out areas, varying in size from that of a pea to that of an orange. The tumors produce pathologic fractures in 62% of the cases, a rib being the most frequent bone thus involved. Microscopically, the tumors are composed of a plasma-like cell with an eccentric nucleus containing a spoke-like arrangement of chromatin. There is a very scanty amount of intercullar substance. The tumor arises from the marrow tissue. The disease pursues a fatal course, the average duration of life being approximately two years. Occasional cases live 5 years or longer, but no method for establishing a cure in multiple myeloma is known and no proved cure case has ever been recorded. Deep x-ray therapy is the most valuable form of treatment in bringing about symptomatic improvement.

Prognosis and Treatment: The prognosis is uniformly unfavorable, the average duration of the disease being about 2 years. The longest duration of any proved case is five and one-half years. The duration of the disease appears to be uninfluenced by treatment, although roentgen-ray therapy has been reported asbringing about remissions; however, as we have pointed out, remissions occur spontaneously. With no proved case reported as cured it is evident that palliative symptomatic treatment only is available. Nursing care to avoid unnecessary pain on motion and pathologic

fractures is important. When fractures occur, the ordinary methods of treatment by fixation may be given, as pain is thus minimized and healing often accomplished. Morphine for pain, liver diet and tonics for anemia and inhalations for respiratory complications are help ful.

Among palliative measures, deep x-ray therapy is outstanding. Control of pain and acceleration of healing in pathologic fractures has been occasionally accomplished under such treatment. In recent years with improvement in the methods and technic of irradiation encouraging symptomatic improvement is the rule. It is important that the clinician assume an attitude that is not too pessimistic, since much can be done to add to the comfort and cheerfulness of these patients.

16. Metastatic Bone Tumors.

In 100 cancers of breast with secondary involvement of bone the primary lesions were found microscopically to be of the scirrhus type (58), with a few instances of adenocarcinoma (6 cases), medullary carcinoma (4 cases), comedocarcinoma (5 cases) and colloid carcinoma (2 cases). In one patient, the primary lesion was found to be fibrosarcoma.

The bones most often involved were, in the order of frequency: the spine, pelvis, femur, skull, ribs and humerus, while metastases in the forearm and the lower leg were of infrequent occurrence.

Clinically, pain of a severe rheumatic character was an important feature. When the metastatic foci were located about the spine, girdle pains and many other neurologic manifestations developed. Occasionally, pain preceded roentgenologic evidence of skeletal metastases from 3 to 18 months. The majority of the cases eventually showed a secondary type of anemia with its complications as the disease progressed. In an occasional case reported in the literature it was pointed out that a pseudo-pernicious type of anemia was present. The terminal phases of the disease were a progressive emaciation, usually with much pain. When the lungs were involved (19 cases), respiratory embarrassment with spitting of blood and paroxysms of coughing were added features of discomfort.

Pathologic fracture occurred in 15 instances, 13 being in the femur, one in the ilium and multiple fractures of the ribs in the other case.

As shown by the roentgenogram, metastatic lesions of the bone from carcinoma of the breast were found most often to be multiple, presenting themselves as a single focus in only 1/4 of the cases. The majority of the solitary foci were in the vertebrae or femur. Two types of metastatic lesions were discussed (osteolytic and osteoplastic). The osteolytic form of metastatic deposit appeared to be the more common, and in the long bones both types were often found well above the usual entrance of the nutrient artery in the case of the femur and above or below it in the case of the humerus. Mottling representing an increase in the density of the bone was often found within the areas of destruction, together with thickening of the cortex above or below the site of metastasis, and it was pointed out that microscopically this proved to be an attempt at osseous repair or fibrostosis.

Treatment has been emphasized, the patients being divided into three groups: (1) those who first had a radical amputation of the breast; (2) those who had only simple amputation or local excision; and (3) those on whom no operation was performed and who received only various forms of palliative treatment. The results obtained from roentgen therapy were relief from pain in many instances and a definite prolongation of life. Resection of the affected part apparently had no effect on the duration of life, but gave relief from excruciating pain.

Sixty-three cases of hypernephroma have been reviewed, and in 22 instances skeletal metastases were found. The bones usually affected, in the order of their frequency were: humerus, spine, femur, pelvis, ribs, bones of the feet, skull and sternum.

The lesions of the bone appeared in the roentgenogram either as single or multiple foci, located in one or more bones. There was a single focus in a long bone in the majority of cases (69%). It was pointed out that many of these lesions were at the site of the nutrient vessels, as well as in the heads of the femur and humerus,

together with associated metastases of the pelvis in many cases. Little evidence was found, in metastases of the bone from hypernephroma, of any attempt at formation of new bone within the area of destruction.

Evidence has been presented to substantiate a hematogenous route of metastatic invasion in hypernephroma. Irradiation alone offered as great a chance for the prolongation of life in this group of cases as did surgical intervention alone or surgical measures combined with roentgen or radium therapy.

Osseous lesions in carcinoma of the prostate were found in 134 of 1040 cases and involved most frequently the pelvic bones, vertebrae and femurs. The patients showed obstructive urinary symptoms and enlargement of the prostate at the time the metastases were noted, with a subsequent progressive emaciation, secondary anemia and excruciating pain in the affected bones. As depicted in the roentgenogram, the metastatic lesions in the bones were predominantly osteoplastic, a characteristic phenomenon in bony deposits from prostatic cancer. On gross examination, these metastatic areas were usually white or grayish nodules, surrounded and mixed with healing bone. This reaction was found to be quite the reverse of that usually seen in other metastatic lesions, and the possibility that the invasive powers of the metastatic tumor were of such moderate character that the bone was allowed to proliferate with sufficient rapidity to keep apace with the invasion of the tumor was set forth as an explanation of this phenomenon. Roentgen therapy offered relief from pain, but was not effective in eradicating the lesion or in greatly prolonging the life of the patient. Resection and amputation offered only comfort.

Malignant disease of other organs with metastases to bone was found to be rare.

It was pointed out that both an embolic and a lymphatic mode of involvement were responsible for metastatic lesions of bone.

17. Parosteal Sarcoma.

Two types of soft part sarcoma are prone to invade the bone by direct extension, fibrosarcoma and neurogenic sarcoma. Both of these forms of malignancy cast a soft-part shadow in the roentgenogram, and produce osseous destruction, eroding the bone from without, inwardly. Pathologically the fibrosarcomas may be divided into a fibro-spindle cell group containing differentiated elements of the fibroblastic series and an undifferentiated spindle cell group of the "oat shaped" cell type. In the fibrospindle cell group an attempt may be made to eradicate the disease by local operation to be followed by amputation in the advent of recurrence. Permanent cures are common in this group in spite of local recurrence. In the undifferentiated spindle cell group, primary amputation when possible is advocated.

In neurogenic sarcoma producing osseous involvement the prognosis is poor and even primary amputation does not often suffice to cure permanently. These tumors are not radiosensitive.

Angiomas, lipomas and rhabdomyosarcoma invading bone are mong the rarer tumors of the osseous system. The first two are benign and may be treated locally. The one myogenic tumor recorded died despite amputation."

III. Treatment of Osteogenic Sarcoma by Means of Irradiation.

Pfahler, G. E., and Parry, L. D., The Amer. J. of Roentgenology and Radium Therapy. XXV, 761-784 (June) 1931.

1. Diagnosis. The diagnosis and differential diagnosis of osteogenic sarcoma involves great difficulties. Yet, unless the diagnosis is accurately made, all other discussion is of no avail. The Registry of Bone Sarcoma demands a complete history, a complete set of roentgenograms (or a series of them) as well as pathological sections. Ewing states that roentgenograms are of equal or greater importance than microscopical sections. When the expert radiologist is in doubt, the pathologist is also often in doubt. If microscopical slides are sent to several equally expert pathologists, the opinions are often different. Kolodny finds that with a good clinical history and roentgenograms, one can be as sure of a

diagnosis as from seeing the patient, the lesion, the gross specimen and numerous sections, and adds, "Not infrequently a roentgenogram is more decisive than a number of microscopic sections."

2. Biopsy. This naturally raises the question as to the advisability of doing a biopsy preceding operation or radiation treatment. There has been no definite proof that biopsy is detrimental, but on theoretical grounds, it is thought inadvisable by a number of observers. The authors believe that this objection can be over - come by previous irradiation with operation immediately following. In addition, this would help in determining the radiosensitivity of the tumor. "Round cell sarcoma" and "giant cell tumor" are thought to be more radiosensitive but the final test is the irradiation itself. Each patient should be considered individually, and from this standpoint it would seem that a biopsy should be reserved for the cases in which malignancy cannot be determined, and in which operation depends upon such a diagnosis. From the standpoint of science and for the sake of determining the relative value of any therapeutic measure, it is desirable to have a biopsy in every case. Twenty or more years ago, many cases of bone tumors were reported histologically as sarcoma that are not considered malignant today.

3. Classification: The authors accept the Registry of Bone Sarcoma classification, and class under the heading of osteogenic sarcoma, all solitary malignant tumors of bone. They are not equally radiosensitive. Those studied microscopically and reported as "round cell sarcomas" are generally considered the most sensitive; periosteal sarcomas are the most radioresistant. From the standpoint of the radiologist, the more slowly growing and the more bone productive, the more radioresistant is the tumor.

4. Previous reports: Holfelder reports 25 cases treated with deep roentgen therapy during the 5 years preceding July, 1926. Of these, 16 have been under observation more than 3 years, and the other 9 more than two years since the conclusion of treatment. 6 out of the 16 have been well over three years, and 3 of the 6 have been well over 5 years. Of the 6 well cases, 3 were confirmed by microscopical examination. Of the 25 cases, 10 have died. Of the 9 cases under observation less than 3 years, 7 are clinically well from 1 to 2 years, and of these 7 cases 6 had histological examination. There was 1 other case which recurred after 5 years. Holfelder believes the chief value of histological examinations is for statistical purposes. He has not found it of assured value in determining the sensitivity to irradiation, nor in making a prognosis.

Evans and Leucutia have reported on 12 cases of osteogenic sarcoma. Ilium, death, 2-1/2 years; frontal and sphenoid, well, 5 years; ilium, well, 6 years (plus lung metastases); fibula, well, 5 years; osteogenic sarcoma, well, 5 years; Ewing's tumor, well, 1 year; palate, well, 3 years; multiple chondrosarcoma, stationary, 4 years; metocarpal myxoma, well, 5 years; ilium, well, 2 years; giant cell, well, 4 years. Excellent reports have also been made by Herendeen, Soiland, Borak, Kienbock, and others (America and Europe).

5. Author's Series. 58 cases of osteogenic sarcoma, 64% males and 36% females (usual ratio). The average duration before treatment was 1.4years. Of the 58 cases of osteogenic sarcoma 41 were confirmed by microscopical examination. The other 17 were so far advanced as to need no such confirmation. Of the 58 cases, 16 were treated by deep roentgen therapy or radium packs (alone) and of the 16 cases, 7 have been symptom-free from 1 to 9 years (1, 1-1/2, 2-1/2, 3, 6, 8, 9). Of these 16 cases, 9 died from 2 months to 7-1/2 years after treatment (1/6, 1/2, 1, 2, 3, 6, 7-1/4 years). Note: 31% 5-year living and dead. Combined surgical and x-ray treatment in 39 cases of osteogenic sarcoma (with histological report), 14 (36%) are symptom-free from 1 to 10 years (of these 30% are symptom-free 3 years and 19% are 5 years or more). Of those diagnosed by clinical and roentgen evidence only 3 out of 17 recovered (17%), which suggests that they were of a more advanced type.

6. Treatment. Authors believe that heavy radium packs (300 to 400 mg.) are more effectual than roentgen rays, but they are generally not used because of the increased expense. They agree with Holfelder that all cases of osteogenic sarcoma should be given a trial by irradiation, since the results are at least as good or better than those following the most radical operation. Holfelder now advises a biopsy in all cases in which the patient will consent, but only after preliminary irradiation over a period of a month. (Also the Author's recommendation). The lungs should be examined roentgenologically, and such examinations should be made from time to time during the treatment. In a number of cases, they have been able to trace metastatic lesions although at the beginning they were too small to be recognized as such. In response to irradiation in osteogenic sarcoma is remarkably slow. While other tumors show a response after a few weeks, the bone sarcomas may seem to be getting worse for from 1 to 3 months, and then show improvement. At this stage authors have been generally recommending amputation, but perhaps more patience would have made the amputation unnecessary. Holfelder had seen cases in which no improvement was recognized clinically until after 8 to 10 months. He says "In some cases of giant cell, round cell and spindle cell sarcomas, improvement has been noticed after four weeks while in exactly similar histological cases no improvement has been noticed until after 8 to 10 months." Improvement is indicated by a smooth and even deposit of calcium in the areas previously shown to be destroyed. Theoretically, if amputation is chosen preliminary irradiation is useless. Previous records, however, of primary amputation are very poor. From practical observation, it seems therefore that preliminary irradiation is useful even though when an operation at a later date is to be done.

7. Technique. Authors state that they keep 100% effect on tumor for a period of one month. Pause 2 to 4 months and repeat. Great care must be taken in the treatment but even so some damage may be unavoidable. Even the bone structure may be damaged, but it usually occurs when there has been damage to the overlying soft tissue. No interference with growth has occurred unless the soft tissues were damaged or the affected extremity has been kept at rest.

7. Case Histories: then follow: Tumors according to location, occiput 1, zygoma 1, inferior maxilla 2, clavicle 2, ribs 1, radius 3, ulna 2, ilium 6, sacrum 1, femur 15, tibia 13, fibula 1, calcaneum 1. Youngest patient was 1-1/2 years and oldest 78; average age 31.5 years. Of the 58 cases, 24 tumors were excised, 18 were amputated, and in the others no operation was done (all radiated). Metastases were present in 40 cases. Tumors of the zygoma, clavicle, rib, radius, fibula, ulna, sacrum, and ilium are all dead with the exception of 1 which is symptom-free after three months (ilium). Tumor of occiput, living, 3 years, inferior maxilla 6 years, 4 of femur, of fifteen cases 2-1/2, 3, 9, 10 years. Of the 13 cases of the tibia, 10 are living, 3 months, 6 months, 1 year, 1-1/2, 3, 4, 5, 6, 8 and one up to 5 years no trace since 1910. This is remarkable when compared with the previous reports on femur, 1 calcaneum symptom-free five years.

8. Summary and Conclusions:

1. Based upon a study of 58 cases of osteogenic sarcoma treated by irradiation, together with review of similar work done in other clinics, authors feel justified in concluding that the only two methods of treatment for this disease are irradiation or surgery, or the two combined.

2. The results from irradiation seem to be at least equally as good as, and they believe better than, those obtained by surgery alone.

3. Preliminary irradiation of the tumor area and irradiation of the pulmonary area followed by amputation, has given us the best results to date, but based upon Holfelder's observations, it would seem that we may not have waited long enough for the full

beneficial effect of the irradiation.

4. A biopsy for diagnosis is desirable but should be preceded by a preliminary thorough course of irradiation by deep roentgen therapy for a month preceding the biopsy.

5. An accurate diagnosis is still the most important single element in the therapeutic management of osteogenic sarcoma.

Impressions:

1. 5% of all surgically removed exostoses recurred, 7% become malignant. In view of this, all exostoses giving symptoms should be carefully removed. All not so treated (no symptoms) should be followed and asked to return for repeated x-rays (after 30).

2. There is no adequate form of treatment for multiple exostoses. They occasionally become malignant (2 cases).

3. Benign chondromas are apt to recur if incompletely excised. Those with mature features are more malignant than those with a cellular structure. Recurrence is not frequent following operation on chondromas in small bones. Primary amputation, radical resection, curettement and cauterization all result in permanent cure in the bones of the hands and feet.

4. Chondromas occurring in large bones, recur after removal in approximately 25% of the cases. Many of these large tumors have been followed from 5 to 10 years and remain well without treatment, although in some instances there has been a gradual increase in size and in some recent evidence of malignant change. When previously quiescent tumors show sudden signs of increased growth immediate and complete removal is indicated. When the location makes this difficult, partial excision followed by irradiation may be attempted. Radiation should always be tried in this group of large tumors.

5. Permanent cures in primary chondrymyxosarcomas (periosteal osteogenic sarcoma) average about 5%. Amputation, radical excision or resection followed by radiation therapy is the treatment of choice. The usual clinical course of the primary form is to terminate fatally within 20 months. Prognosis is worse in children and when the lesion is in the upper end of the humerus and femur. The tumor shows a marked tendency to recur locally as well as to metastasize.

6. Secondary chondromyxosarcomas (after benign chondroma, Pagets disease, etc.) have a longer average duration (6 years). Permanent cures in the secondary form average about 25%. Radical resection or amputation is the treatment of choice. Following this, implantation of radium or external irradiation should be undertaken. The disease runs a chronic course even in fatal cases (with many recurrences).

7. Sclerosing osteogenic sarcoma is a highly differentiated form resulting from faulty osteogenesis at the post-adolescent age (15-25) in the metaphysis of long bone. Permanent cures can be achieved in approximately 25% of these cases by prompt resection or amputation. Deep x-ray or radium therapy is not advised as the tissue is not radiosensitive. Secondary sclerosing osteogenic sarcoma may occur in elderly adults. As a general rule, all forms of sclerosing sarcoma show 25% cures with primary radical operation. Probability of cure becomes less the longer the duration of symptoms prior to operation, and the greater the interval between incomplete and radical treatment. If the patient survives 18 months without signs of recurrence or metastasis, cure will probably result.

8. Malignant giant cell tumors are often chondroblastic sarcomas with giant cells present. Two 5-year cures resulted in a series of twenty-four cases (10%). Because of the cartilaginous element, radiation should not be neglected pre- and post-operatively if early resection is not done.

9. The osteolytic form of osteogenic sarcoma is a central lesion with a frequent tendency to pathologic fracture. Early amputation offers the

best chance for permanent cure (6%). Cured cases are usually over 30 with long duration of symptoms (secondary degeneration?).

10. Benign solitary bone cysts usually come in because of pathologic fractures. The tendency to unite spontaneously and to heal is evident in most. Prognosis is excellent in osteitis fibrosa but varies with the type of lesions. Latent cysts do well without treatment. Acute bone cysts respond to radiation but may require curettement and filling in with bone chips. Diffuse types require investigation of the parathyroid gland.

11. The best treatment of giant cell tumor is curettage. Radiation may be used (but is longer). So-called metastasizing giant cell tumors usually prove to be something else.

12. Epulides tend to recur after simple excision unless thoroughly done and the base cauterized. Giant cells of tendon sheath are cured after complete excision.

13. Ewing's tumor may be irradiated or amputated. Radiation is a good diagnostic test. (6 weeks). Only cures followed combined radiation and amputation (10%).

14. The prognosis in multiple myeloma is unfavorable as the disease runs a fatal course. Occasionally cases live 5 years or longer. Tumors are radiosensitive and symptomatic improvement results from this form of treatment.

15. X-ray treatment of metastatic breast lesions results in relief of pain in many instances with suggestive prolongation of life. Resection of single lesions does not have any effect on duration of life, but gives relief from pain.

16. Radiation offers as good a chance for prolongation of life in metastatic hypernephroma as surgical intervention alone or surgical measures combined with roentgen or radium therapy.

17. Roentgen therapy of lesions of prostate to bone offers relief from pain but is not effective in eradicating the lesion or greatly prolonging life.

18. Parosteal sarcomas are usually fibro-sarcomas or neurogenic sarcomas. Both may produce osseous destruction by eroding the bone from without. Permanent cures are common in the fibro-sarcoma group when amputation follows local recurrence. In the undifferentiated spindle cell group, primary amputation when possible is advocated (more malignant).

19. The outlook in neurogenic sarcoma producing osseous involvement is poor and even primary operation does not suffice to cure. These tumors are not radio-sensitive. Other tumors near the bone should be treated in the usual way, according to tumor type.

IV. Diagnosis and Therapy of Tumors in the Long Bones. (B.J.Pearson)

Ivar Behring, Acta Chir. Scand. LXVI, 197-250, (May 30) 1930.

1. Material: 384 cases that received a diagnosis of bone sarcoma in the hospitals. Representing most of Swedish Hospital from 1900-1926.

Divided into four groups:

Group I. Contains 246 cases in which the diagnosis of primary malignant bone tumor (including giant cell tumor) was definitely made by microscopic examination.

Group II. 48 cases where the clinical investigation consisted of x-ray and operation.

Group III. 43 cases where the diagnosis is probable.

Group IV. 47 cases doubtful.

The following results were based on 246 cases, including 27 cases of giant cell tumor (definitely diagnosed cases). 32 patients died in the hospitals (48 hospitals) either before or after operation or later.

Sex and age: 219 cases of osteogenic sarcoma. 131 men, 88 women. Ratio 3:2. Youngest patient 4 years, oldest 84 years.

2. Pathology: According to Codman's classification:

(1) Metastatic bone tumors.
(2) Periosteal fibrosarcoma.
(3) Osteogenic tumors, benign and malignant.
(4) Inflammatory conditions.
(5) Benign giant cell tumors.
(6) Angioma, benign and malignant.
(7) Ewing's tumor.
(8) Myeloma.

The giant cell sarcoma one finds in the register as giant cell tumor. (X-ray central localization, and local extension, histologically typical and benign prognosis).

Localization:	Osteogenic Sarcoma	Giant Cell
Femur	99	11
Tibia	88	9
Humerus	35	3
Fibula	17	2
Ulna	3	2
Clavicle	2	0
Radius	2	0

Of 89 osteogenic femur sarcoma 59 (70%) occurred in distal femur (metaphysis). Whereas, 27 cases (30%) had other locations in femur. In 11 giant cell sarcoma 9 (82%) occurred in the lower femur while (18%) occurred in upper femur. 76 osteogenic tibial sarcomas 61 (80%) proximal tibial metaphysis 15 (20%) localized in other places in tibia. Of 9 giant cell sarcoma, 8 proximal, 1 distal.

Humerus sarcoma. 23 cases (74%) proximal and 8 (26%) in distal; 3 giant cell sarcoma in proximal part of humerus.

Fibial sarcoma. 15 cases. 9 (64%) proximal. (Metaphysis and caput), and 5 (36%) distally. 2 giant cell sarcoma localized in caput.

Clavicullar sarcoma. 2 cases. 1 in acromial, other in sternoclavicular end.

Radius sarcoma. 1 case in distal (diaphysis), 1 in upper portion.

Ulnar sarcoma. 1 osteogenic sarcoma localized in proximal (metaphysis) 2 giant cell sarcoma in distal part of ulna.

3. Length of History - (duration).

Of 205 cases of osteogenic sarcoma disease lasted from 2 weeks to 15 years. Of 4 cases with long duration, 15 years to 11 years, and 2 cases with 10 years slowly growing circumscribed tumor which grew fast after trauma. Microscopic examination was chondrosarcoma and result after operation was good. 80% of osteogenic sarcoma duration was shorter than 1 year before operation.

4. Trauma: 144 of 210 patients with osteogenic sarcoma gave no history of trauma. 31% (66 patients) gave trauma as a causative factor. Symptom-free interval after trauma in 19 cases of osteogenic sarcoma was 3 months or less in 12. In 9 of 27 cases of giant cell sarcoma, 33% gave trauma as a causative factor.

5. Symptoms: First symptom of osteogenic sarcoma in 103 of 210 patients (49%) was pain while in 87 (41%) it was a palpable tumor without pain. This last figure is remarkable as 4% of this group had first noticeable symptoms after fracture.

TABLE I. (See next page)

TABLE I.

	OSTEOGENIC SARCOMA								GIANT CELL SARCOMA						
	Pain	Tumor	Sensitiveness	Weak Tired	Stiffness	Limping	Spontaneous Fracture	Total	Pain	Tumor	Sensitiveness	Weak Tired	Limping	Spontaneous Fracture	Total
Femur	50	28	-	-	1	3	2	84	9	2	-	-	-	-	11
Tibia	38	31	2	1	1	1	2	76	3	4	-	1	1	-	9
Fibula	2	12	-	-	-	1	-	15	2	-	-	-	-	-	2
Clavicle	1	2	-	-	-	-	-	3	-	-	-	-	-	-	-
Humerus	12	11	-	-	1	-	5	29	2	-	-	-	-	1	3
Radius	-	2	-	-	-	-	-	2	-	-	-	-	-	-	-
Ulna	-	1	-	-	-	-	-	1	-	2	-	-	-	-	2
Total	103	37	2	1	3	5	9	210	16	8	0	1	1	1	27
Percentage	49%	41%					4%		59%	31%					8%

Further Course of Disease: Spontaneous fracture occurred in 26 cases of 210 osteogenic sarcomas, 6 in 27 giant cell sarcomas.

FEMUR

	Total	Spontaneous Fracture	%
Osteogenic Sarcoma	84	12	14.
Giant Cell Sarcoma	11	3	27.

TIBIA

Osteogenic Sarcoma	76	6	8.
Giant Cell Sarcoma	9	2	22.

HUMERUS

Osteogenic Sarcoma	29	8	28.
Giant Cell Sarcoma	3	1	33.

Impression: Spontaneous fracture from giant cell sarcoma occurs oftener than osteogenic sarcoma.

General Condition: General condition of these patients on the whole was good---only 1 of outspoken cachexia.

6. Palpable Lymph Nodes: Only in 65 cases were the regional lymph nodes examined. In 29 of these cases were they positive, in 36 negative. Of 29 cases of osteogenic sarcoma with palpable regional lymph nodes, 17 cases were histologically examined and only in 6 cases was there tumor infiltration. One case of giant cell sarcoma with palpable lymph nodes. Histological examination negative.

7. Operation:

A. Osteogenic Sarcoma of Femur.

(1) Biopsy.

In 10 cases biopsy was done to establish diagnosis. 1 case died as the result of operation - bleeding. The others lived after operation, 1 to 15 months, average 6-1/2 months. The longest was 13 years

old (15 months) diagnosis was chondro-myxofibrosarcoma osteoides - highly differentiated tumor. The origin of the tumor was periosteal.

(2) Curettment.

8 cases, only 1 operative death; 7 average life 3.9 months. 6 metastasis to lungs and bones. 1 (?). One case lived 3.5 years.

(3) Extirpation (5 cases)

5 cases including periosteal extraperiosteal, or peripheral origin. Of these only 1 died before November 1928. (Died 3-1/2 years later. Diagnosis - Fibromyxoma periosteal).

(a) Cases living.

Periosteal spindle cell sarcoma with giant cells. Condyle of femur free from disease 8 years.

(b) Fibromyxosarcoma -- trochanter majus entirely subperiosteal. Living and well, 4 years.

(c) Fibrosarcoma femur -- periosteal. Well 2 years 7 months, then died of cerebral hemorrhage.

(d) Femur (anterior infiltrated muscles). Extirpation - osteochondroma-osteiodes sarcomatosum, living 1 year.

The good prognosis in these cases is due to localization, well circumscribed and relative histological benignity.

(4) Resection of femur (9 cases).

Operations.

Arthrectomy + resection of condyle femur.	1	case
Resection of distal femur end with implantation of shaft in tibia, according to Mickulicz.	1	"
Resection of knee	2	"
Resection of femur + osteoplastic	4	"
Resection of femur, according to Sauerbruch	1	"

The primary operative mortality is high. 2 patients died at the end of operation. 1 died, one month after of infection.

(5) Amputation of Femur (24 cases)

No operative deaths. 1 died 14 days after operation. 16 patients died of their sarcomas, average 10 months after operation. 1 patient died 1 month after of pneumonia. 1 case 6 years after operation (chondrosarcoma) of diabetes. 5 patients living sound and well from 7 - 16 years after operation. If one counts the case living 6 years, well and dying of diabetes, then we have a 25% cure. The age of these 5 averaged 24 years and duration before operation 4-1/2 months. The tumor in 2 cases was central and in 3 peripheral. Well differentiated tumor 1, spindle cell sarcoma 1, chondrosarcoma 2, and fibrosarcoma 1.

(6) Exarticulation coxae (33 cases).

33 cases- 9 in proximal metaphysis, 3 diaphysis, 20 distal end femur. All of these cases were disarticulated at the hip. Of these 1 patient died (15 year old girl) during operation; 55 year old male, 5 days postoperative of lung gangrene; and 60 year old male 2-1/2 months afterward of a paralaryngeal phlegmon. 33 patients died later of sarcoma, postoperative life 8-1/2 months (average). (3 lived) 13 years, 2 years and 1 month, and 1 year and 8 months. If we call only the first case 13 years a cure, then we have 3% cure. Histological examination shows a relative benignity. The first was fibrosarcoma of marrow. The other 2 fibrosarcoma with partial sclerosis - connective tissue with few cells. Of the 27 cases of sarcoma that died, the origin could be determined in 21 cases. 9 were central and 13 peripheral sarcoma. 14 of 27 cases showed undifferentiated sarcoma. The late results of disarticulation are worse than those of amputation.

Late Result for operated cases: Sarcoma femuris.

Operation	Number operated cases	Operative Deaths	Died of Intercurrent disease within 4 yrs. after oper.	Died of Sarcoma		Free from Recurrence	
		No.	No.	No.	Length of life post-oper.	After 4 years	
						No.	%
Resection of femur	9	3	1	4	18.5 Mos.	1	11%
Amputation of femur	24	0	2	16	10 Mos.	6	25%
Disarticulation of hip joint	33	2	1	27	8.5 Mos.	1	3%

2 Cases ?

Amputation Cases of Sarcoma Femur.

	Number	Average Age Yrs.	Duration of the disease (before oper.)	Origin of Tumor			Histology	
				Central	Peripheral	Not determined	differentiated.	Not differentiated
Died of Sarcoma	16	24	3.5 Mos.	4	9	3	6	10
Free from recurrence after at least 4 yrs.	6	29	4.4 Mos.	3	3	0	6	0

Disarticulation for Sarcoma of Femur.

	Number	Duration of disease (before operation)	Origin of Tumor			Histology	
			Central	Peripheral	Not determined	Differentiated	Not differentiated
Died of Sarcoma	27		8	13	6	10	14
Free from recurrence after at least 4 yrs.	1		1	0	0	1	0

Of 66 radical operations femur sarcoma (9 resections, 24 amputations, 33 disarticulation) that were examined later. 8 were free from recurrence at least 4 years after operation (resection 1, amputation 6, disarticulation 1). (12%).

B. Sarcoma of Tibia.

(1) Biopsy (1 case).

1 case, 13 years old, history of 3 months. No permission for operation from parents. Biopsy periosteal osteiod sarcoma. Died in 2 months.

(2) Curettment (7 cases).

5 central, 1 not determined. All except 1 died, average 8-1/2 months, average history 5 months, average age 28.3 years. One patient lived 6-1/2 years- 49 year old male. First symptoms began with a fracture of tibia and fibula 6-1/2 months before operation. Histology - spindle cell sarcoma with epithelioid tubule-like structure.

(3) Extirpation (2 cases).

2 patients, age 20 and 46 years. First, 2 year history, died 2 yrs. 1 mo. Second, died 4 yrs. 1 mo. Pathology - round cell sarcoma and spindle cell sarcoma with connective tissue.

(4) Resection of tibia (3 cases).
Resection + osteoplastic.

(a) Male, 34 yrs. 4 mos. history. Central sarcoma. Pathology - osteoid sarcoma. Secondary amputation antecrural 1 month later. Six weeks more amputation - recurrence. Metastasis in inguinal region. Died 3-1/2 months after operation.

(b) 30 years, male, 5-1/2 months history. Died 4 months after of lung metastasis. Diagnosis - sarcoma with many giant cells, lung metastasis.

(c) 16 year old female, 2 months history. 6 weeks later new recurrence and secondary amputation. Pathology - chondrosarcoma. Well after 15 years.

(5) Amputation of femur (64 cases) and antecrural (2 cases) for sarcoma of tibia.

Of 66 amputations for sarcoma of tibia, 64 had amputation of femur or Grittis operation and 2 amp. anticruralis. 44 cases died of sarcoma. 1 died of leptomeningitis (tuberculosis). 20 patients lived free from recurrence-- 17, 4 years or more; 3 (2-1/2, 2, 1 yrs). 27% cure. Note difference that bone location makes.

Late Results after Resection and Amp. Sarcoma Tibia.

Operation	No. operated	Died of Sarcoma		No. Free from Recurrence	
		No.	Post. oper. life	After 1-4 years	After 4 years
Resect. Tibia and osteoplastic	3	2	4.5 Mos.	0	1
Amp. Femur or Gritti or Amp. antecruri	66	44	16. Mos.	3	18

1 Died of Intercurrent Disease.

Amp. Femur. (Gritti, Amp. Antecrur) Sarcoma Tibia.

	No.	Aver-age Age	Dura-tion	Origin			Histology		
				Cen-tral	Peri-pheral	Not Deter-mined	Diff.	Not Diff.	Not Described
Died of Sarcoma	44	23	12	17	12	15	16	18	10
Free from Recurrence after 4 Yrs.	18	31	12	10	2	6	10	4	4

Post-Operative Average Life of 44 Sarcoma Tibia (Dead)

1st Decade		2nd Decade		3rd Decade		4th Decade		Later Decade	
No.	Post-Oper. Life	No.	Post-oper. Life	No.	Post-Oper. Life	No.	Post-Oper. Life	No.	Post-Oper. Life
2	6 Mos.	26	14 Mos.	9	22 Mos.	3	22 Mos.	4	25 Mos.

Of the 44 patients who died average age 25 yrs. average history 11 mos. Of 69 "radical operations" of sarcoma tibia (3 cases of resection and 66 amputations) which were examined later 18 were free from recurrence after 4 years.

C. Sarcoma fibulae.

(1) Extirpation or resection of fibulae (10 cases).

No operative deaths. 1 patient died 14 days after operation of phlegmonous enteritis. 4 patients died of sarcoma, 9-1/2 months after operation (average), average age 20 years. History 6-3/8 months. Of these cases, 2 were histologically well differentiated (1 spindle cell sarcoma). 5 cases live. 3 of these can be considered definitely cured and have lived from 7-15 years. 2 cases are free from recurrence. 2 yrs. 9 mos. and 2 yrs. 1 mos. Of these 5 cases, tumor was well circumscribed and had not broken through the capsule 2 central, 1 periosteal, 3 unknown. Average age 29.6 years. History 4-2/3 mos.

(2) Amputation Gritti - amputation of femur and disarticulation.

Sarcoma fibulae (5 cases). 5 cases of fibilar sarcoma, local recurrence after local excision. All died, 6.6 months postoperatively.

Late Results for Operated Cases Sarcoma Fibula

Operation	No. Op.	Died of Intercurrent disease	Died of Sarcoma		Free from Recurrence	
		No.	No.	Post Op. Life	After 1-4 Years	After 4 years
Extirpation and Resection Fibulae	10	1	4	9 Mos.	2	3
Amp. Femur Gritti and Disarticulation	5	0	5	7 Mos.	0	0

Extirpation and Resection Fibulae

	No.	Avg. Age	History	Origin			Histology		
				Central	Peripheral	Not Det.	Diff.	Un-Diff.	Not Described
Died of Sarcoma	4	20	6 Mos.	0	1	3	1	2	1
Free from Recurrence 4 Yrs.	3	30	5 Mos.	1	0	2	2	1	0
Seemingly Free from Recurrence	5	33	11 Mos.	2	0	3	3	2	0

Of 15 sarcoma fibulae operated (10 resections or extirpations, 5 cases amputation femur or disarticulation) 3 cases, 20 years old, after at least 4 years were free from recurrence.

D. Sarcoma of the Humerus.

(1) Resection of humerus and osteoplastic (12 cases).

In 12 cases of sarcoma of the humerus resection and osteoplastic. No operative deaths. 9 died from sarcoma from 2 months to 5 years and 9 months. 1 patient lives at 1-1/2 years with pelvic metastasis. 2 patients live, 7-1/2 and 13-1/2 years, free from recurrence. 16% definite cure. Of the 9 cases who died, tumor was in the proximal portion of the humerus or in the middle of the diaphysis -- 8 were central. 7 of these sarcomas at operation had broken through the cortex and infiltrated the muscles. 2 are periosteal. 6 cases had no local recurrence but metastasis. 6 cases strongly undifferentiated. 1 case angiosarcoma. 2 spindle cell sarcoma.

(2) Amputation of Humerus. (2 cases).

2 cases of sarcoma of the humerus with high amputation. First patient died 2 months of metastasis, other 3 months. Both tumors morphologically undifferentiated.

(3) Disarticulation in humero-scapular joint. (10 cases).

3 patients of which 2 children (ages 8 and 13 years) died during operation (30% mortality). Of the remaining seven, 6 died of the disease, average 9 months after operation. One patient lived 2 yrs. 11 mos. with manifest lung metastasis. In the 7 cases that overlived the operation, the tumor was situated in 4 cases in the proximal portion of the humerus and in 3 distal.

(4) Amputation of interthoraco scapularis (7 cases).

No operative deaths. In 5 of 6 cases, the tumor is in the upper portion of the humerus. In the 7th case in the distal 2/3 of the humerus. 4 tumors undifferentiated. One patient lived 7-1/2 years after operation. 55 year old male who for 15 years had a tumor of the humerus, slow growth for 9 years. Histology - chondrosarcoma.

Late Result of Operative Cases Sarcoma of the Humerus.

	No.	Operative Deaths		Died of Intercurrent Disease	Died of Sarcoma		Free from Recurrences	
		No.	%	No.	No.	Post-Oper. Life	1-4 Yrs.	More than 4 Yrs.
Resection of the Humerus	12	0	0	0	9	19 Mos.	0	2
Amputation Humerus	2	0	0	1	1	2 Mos.	0	0
Disarticulation Humerus	10	3	30	0	6	9 Mos.	0	0
Amp. Interthor-Scap.	7	0	0	0	6	9 Mos.	0	1

2 living with Metastasis.

Resection Humerus and Osteoplastic.

	No.	Avg. Age	History	Origin		Histology		
				Central	Peri-pheral	Diff.	Undiff.	
Died of Sarcoma	9	34.9	9 Mos.	8	1	5	3	1 ?
Lived over 1-1/2 Yrs. free from Recurrence & Met.	1	20	8 Mos.	0	1	1	0	
Free from Recurrence at least 4 Yrs.	2	32	4 Mos.	0	1	1	0	1 ?

Disarticulation of Humerus.

	No.	Avg. Age	History	Origin			Histology	
				Central	Peri-pheral	Not Det.	Diff.	Undiff.
Died of Sarcoma	6	43	4 Mos.	1	2	3	1	5
Living with Metastasis Lungs.	1	30	6 Yrs.	0	1	0	0	1

Amp. Interthoraco-Scapularis

	No.	Avg. Age	History	Origin			Histology	
				Central	Peri-pheral	Not Deter-mined	Diff.	Undiff.
Died of Sarcoma	6	24	6.2 Mos.	0	4	2	4	2
Free from Recurrence more than 4 Yrs.	1	55	15 Yrs.	0	0	1	1	0

Of 31 sarcoma of humerus (12 resections, 2 amp., 10 disarticulation, 7 amp. interthoraco-scap.) 3 were free from recurrence 4 years.

E. Sarcoma of Clavicle. (2 cases)
Aged 77 and 63 years. 1 tumor of acromial, other localized at sternal end. Resection of clavicle. 1 died of sarcoma, recurrence 5-1/2 mos., other 7-1/2 mos. Pathology - small round cell sarcoma, first. Sarcoma, second.

F. Sarcoma radii (2 cases)
Extirpation (1 case). 53 years old female. 10 year history. Fibro-sarcoma. Well after 15 years.
Amputation antibrachii. (1 case)
74 year old female. History 8 mos. Died 3 years after operation "old age". Chondroma with chondrosarcoma.

G. Sarcoma of ulna. (1 case).
23 year old male. History 10 years. Well after 15 years. Pathology-malignant chondroma.

H. Giant cell sarcoma. (27 cases).
(1) of femur (2 cases)
1 case curettment only. 5 cases curettment followed by amputation of femur. 3 cases exarticulation coxae. 1 disarticulation with transplantation fibula. 1 knee joint resection. 9 of these 11 were free from recurrence after 4 years. 1 died of metastasis 10 mos. This tumor discharged and perforated pelvic bone so quickly that it was thought to be a sarcoma but microscopic picture showed giant cells. 1 died 7 mos., recurrence.

(2) Giant cell of tibia (9 cases)
2 curettment. 6 curettment with secondary amp. Gritti. 1 amp. secondary. 6 free from recurrence, 4 years. 1 free from recurrence 2-1/2 years. 1 died 2-1/2 mos. of multiple metastasis. 1 died 3 mos. lung metastasis.

(3) Giant cell sarcoma fibula (2 cases).
2 patients with proximal fibula (localized giant cell). Resection of fibula. 7 and 10 yrs. free from recurrence.

(4) In the Humerus (3 cases).
1 curettment. 2 disarticulation. These last 2 died, 3 yrs. 9 mos. and 4 yrs. 10 mos. of multiple bone metastasis. 1 patient living 15 years, no recurrence.

(5) Of Ulna (2 cases).
With resection. Several years, no recurrence.

CONCLUSIONS:

1. Osteogenic sarcoma occurs oftener in males 3:2.
2. Disease most frequent in young age group with greatest frequency in the second decade. (41%).
3. The frequency curve for giant cell sarcoma is in the 3rd decade.
4. Osteogenic sarcoma as well as giant cell tumor has predilection for the long tubular bones, especially femur. Then follows tibia, humerus, fibula, ulna, clavicle, and radius respectively.

5. (a) Most cases of sarcoma of emur are localized at the distal femur nd (70%).

(b) In tibial sarcoma it is ost frequently localized in the proximal ibial end (80%).

(c) Sarcoma of humerus - proximal nd (74%).

(d) Fibular sarcoma - proximal nd (64%).

(e) Femur giant cell sarcoma - listal end (82%).

(f) Tibial giant cell - proximal nd (89%).

(g) Humerus giant cell - proximal nd (100%).

(h) Fibula giant cell - proximal nd (100%).

6. 65% of osteogenic sarcoma have a shorter history than 6 months and 82% have a shorter history than 1 year prior to operation.

7. In 32% of osteogenic sarcoma, the patient associates the beginning of disease with trauma. In only 18% does the trauma seem to be of significance.

8. The same is present in giant cell sarcoma in 33% and 19% respectively.

9. The first symptom of osteogenic sarcoma is pain 49%, tumor 41%. In 4% a spontaneous fracture is a heralder of the disease.

10. The most frequent initial symptom of sarcoma of femur is pain. In fibula, clavicle, radius and ulna, tumor as a rule comes before pain. In tibia and humerus both.

11. Sarcoma of humerus has the greatest tendency to spontaneous fracture.

12. Spontaneous fracture is more frequent in giant cell sarcoma (22%), osteogenic sarcoma (12%).

13. In 65 cases osteogenic sarcoma, a palpatory examination of regional lymph nodes was done and these were enlarged in 29 cases (45%).

14. Of 29 cases of osteogenic sarcoma with palpable regional nodes, 17 were subjected to a histological examination and 6 cases (35%) showed tumor metastasis.

15. Biopsy and curettment alone for osteogenic sarcoma gives a bad prognosis. The post-operative course of curettment cases is on the average shorter than if only biopsy was performed.

16. Resection with or without osteoplastic operation in tibia, femur and humerus with periosteal origin and central sarcoma with extension through capsule and periosteum gives small chances of cure.

17. Good results are obtained from resection of fibula for osteogenic sarcoma. Free from recurrence for at least 4 years (33%).

18. Good result also for femur (distal) or tibia with amputation at joint in osteogenic sarcoma. Free from recurrence at least 4 years (27%).

19. For femur and humerus with high localization (proximal) or infiltration locally disarticulation coxae and interthoraco-scapular amputation, the operative mortality is high (10%), and late results are poor, 4% free from recurrence after 4 years.

20. The average length of history is longer for the cases free from recurrence after certain operations than those in a similar group that died of sarcoma (less malignant?).

21. Peripheral sarcoma gives a worse prognosis than central.

22. The histo-pathological examination of sarcomas in patients free from recurrence shows a higher per cent differentiation than for those who died 86% - 44%.

23. If there is histological evidence of tumor infiltration of regional nodes, then the prognosis is very poor.

24. Exploratory osteotomy makes the prognosis worse.

25. The postoperative life of patients in osteo-sarcoma averages 2-1/2 months.

V. Martland, H. S., The Occurrence of Malignancy in Radio-active Persons.

A. J. of Cancer, XV, 2435-2517 (Oct.) 1931.

Summary:

1. Martland and Humphires in 1929 reported two osteogenic sarcomas among 15 deaths in dial painters from a New Jersey plant using luminous paint. They attributed the development of the sarcomas to chronic irritation caused by a radiation osteitis, produced by internal bombardment from deposits of radio-active substances in the bones, thus establishing a definite cause for

sarcoma of the bone for the first time. On account of the small number of cases covered, this was regarded at the time by some as "an alluring theory, not yet subject to proof."

2. This paper reports an additional number of bone sarcomas occurring among dial painters. There have been five deaths from osteogenic sarcoma in a total of 18 originating in occupational poisoning by radio-active substances in former dial painters from the New Jersey plant, an incidence of 27 per cent.

As the incidence of the ordinary variety of primary osteogenic sarcoma is only about 0.07 per cent, this is overwhelming evidence that the radio-activity of these dial painters is the true cause of the sarcomas.

3. In addition, three cases of former dial painters from the same plant still living are reported. In one of these there is undisputable evidence of osteogenic sarcoma of the femur. In the remaining two there is strong presumptive evidence that such a lesion is developing.

The report of a death from osteogenic sarcoma of the rib, occurring in a dial painter employed in New York and Connecticut clock factories, is also included, to show that radium poisoning is not indigenous to New Jersey, but has occurred in other states where luminous watch dials have been manufactured. The number of dial painters dying in other states has never been determined, as radium poisoning was never heard of, or recognized, until the New Jersey cases were described.

4. A short sketch, or résumé of the author's interpretation of so-called radium poisoning in the watch dial industry has been given to facilitate an understanding of the occurrence of the bone sarcomas. The extensive literature should be consulted for more detailed description of this disease.

5. The osteogenic sarcomas in the radium dial painters undoubtedly develop in areas which have previously been the seat of a radiation osteitis. We have also to consider the possibility that the alpha particle may have a more direct action in producing malignancy by speeding up somatic cell division as a result of its destructive ionization.

The term "radiation osteitis" was first used by Ewing to describe changes taking place in bones which received large external doses of irradiation for therapeutic purposes, usually adjacent to a malignancy. He found that the marrow had been replaced by a loose, non-cellular, fibroblastic tissue in which there was considerable fat. His lesion never showed, however, the intense inflammatory character seen in the dial painters, the process always being of a sclerotic nature.

6. The author's interpretation of the radiation osteitis seen in dial painters may be summed up as follows: In a radio-active dial painter who has, for example, 10 micrograms of radio-active substances deposited as insoluble sulphates in the entire skeleton, there are constantly being ejected about 370,000 space-occupying alpha particles a second, with a speed approximating 18,000 miles per second. This bombardment, which I have designated as an internal bombardment, is continuous, and will last for an indefinite period. For instance in the year 3491 A. D., the skeleton will still be giving off 185,000 alpha particles per second.

The tremendously disruptive effect of ionization produced by this bombardment causes atomic and molecular disintegration. In time, a hyperplastic, red marrow results, due to compensatory stimulation. Such a marrow is characterized by a packing of the marrow spaces with primitive stem cells, which I have interpreted as promyelocytes, proerythroblasts, and hemocytoblasts.

The ability to form cells of the granulocyte series, with the exception of the eosinophil myelocyte, is practically lost. As these cells are chiefly extravascular in location, very few immature cells escape into the circulating blood; hence the leukopenia with a tendency toward an agranulocytic blood picture.

The power to form red cells is retained, but greatly reduced, and reverts to an embryonal, megaloblastic type of production. As the formation of the red cells is chiefly intravascular, many immature cells are washed into the blood stream, especially macrocytes. Hence the resemblance of the blood picture to that of addisonian anemia. This hyperplastic, irritative, embryonal marrow I have designated as

the first stage of radiation osteitis.

The process now subsides in patchy areas over the skeleton. A very cellular replacement fibrosis, of an intense, inflammatory character, develops, with numerous eosinophil myelocytes, lymphocytes, and plasma cells. Many of the fibroblasts show mitotic figures and hyperchromatism, and these areas can be distinguished from sarcoma only with great difficulty. It is in these areas that sarcoma arises. On account of their wide distribution over the skeleton, it is easily seen how multiple primary sarcomas may occur in the same individual. I have called this the second stage of radiation osteitis.

In the final stage of the process of radiation osteitis the marrow is entirely replaced by an old, non-cellular fibroblastic tissue. The bones become soft, partially decalcified, and deforming lesions occur, particularly in areas subject to a great deal of weight or trauma. Coxa vara, deformities of the spine, spontaneous fractures, etc., are likely to occur.

7. Attention is called for the first time to the difference in biologic effects on the human bone marrow of external penetrative irradiation and internal alpha radiation as seen in these cases. In this respect attention is called to the fact that the anemias developing from undue exposure to external radiation (gamma rays of radium and x-rays) are considered by most authorities as of the aplastic type, although anatomical proof of this is woefully lacking. On the contrary, the anemias caused by internal alpha bombardment, as first described in the radium dial cases, are of the regenerative , hyperplastic, or megaloblastic type.

8. Attention has also been called to the occurrence of bone sarcoma in Paget's deforming osteitis and its rare occurrence in the osteitis fibrosa cystica of von Recklinghausen, showing that the literature already records instances of malignancy developing in bones which were the seat of chronic inflammatory lesions which were not nearly as severe and intense in character as the radiation osteitis in the dial painters.

9. That radio-activity in the human body may play an important part in the production of other forms of malignancy in no way connected with radium dial painting is suggested, the high incidence of primary carcinoma of the lungs in the cobalt miners of Schneeberg and in the pitchblende mines of Joachimsthal being noted.

10. The multiplicity of lesions and diseases produced by irradiation from external exposure to radium and x-rays, and radiation from internal bombardment by the alpha particle, such as occurred in the dial painters, is noted.

We may encounter: leukopenias; mild anemias; local skin lesions such as x-ray dermatitis, radium burns, epidermoid cancers, etc.; fatal anemias of the aplastic or aregenerative type; fatal anemias of the regenerative or pernicious type; panmyelosis and leukemoid bone marrows; myelogenous leukemias, in acute and subacute forms; radiation osteitis with jaw necrosis; radiation osteitis with crippling bone lesions, such as coxa vara, deformities of the spine, and spontaneous fractures; radiation osteitis with skull lesions; radiation osteitis with the development of osteogenic sarcomas, and primary carcinomas of the lung. All are produced by practically the same tiologic agent, either by light waves (gamma rays of radium and x-rays) or by bombardment of space-occupying masses (alpha particles and negative electrons).

Such a variety of lesions produced by a single agent might indicate that many of these lesions are closely interrelated and are only manifestations of various degrees of injury to, or stimulation or exhaustion of, certain normal body tissues.

Conclusions:

1. These studies indicate that it is important to have proper medical supervision over the use of radium and x-raus for therapeutic purposes, and governmental control over industries and occupations in which exposure to radio-active substances takes place.

It would seem that the use of radiations for therapeutic purposes should be confined to hospitals and institutions specializing in and competent to handle such treatments, and that the indiscriminate use of radium and x-rays should be in some way controlled.

All occupations in which the

handling of radio-active substances occur should be under strict governmental control and supervision. Rules and regulations covering the dangers of exposure should be outlined. Technical methods should be devised in specific industries so that exposure is reduced to a minimum. In the refining of radio-active substances, for instance, Schlundt is of the opinion that this can be accomplished.

If in a certain industry the exposure cannot be reduced to a safety minimum, the procedure in use should be given up for some other method; if this is not possible, the industry should be discontinued. In this respect it is interesting to note that the U. S. Public Health Survey, which shows that the habit of licking brushes in the watch dial industry has been stopped and that various mechanical methods have been devised to apply lyminous paint, states that, in spite of the utmost care and precautions against undue exposure, girls who work under the new methods still become radio-active and show an average of one half a microgram of radio-active substance in their bodies. It is a question whether under these conditions we should be satisfied to regard the industry as a safe one.

The above arguments apply also to the sale of radio-active waters, emanators, activators, etc. The sale of all such commodities should be stopped until it is definitely established that they are harmless. The indiscriminate sale of these waters and apparatus by laymen and quacks is criminal. Their therapeutic effects are nil if we exclude the psychic effects produced on the patient. The human race would not suffer by eliminating them.

2. These studies, aside from drawing attention to the occurrence of malignancy in radio-active persons and giving another cause for osteogenic sarcoma, may be of importance in the experimental study of cancer. It may be possible to show new methods by which malignant tumors may be produced in animals. Recently, in Germany, bone sarcoma has been produced in the rabbit by means of irradiation from implanted radium.

3. The question arises, may not other forms of malignancy depend upon the presence in the human body of increased amounts of radio-activity too small, perhaps, to detect by our present methods?

This question will be harder to answer than appears at first thought. While the amounts of radio-active substances in the dial painters are extremely small, being measured only with great difficulty, they must be very much greater than one would ever expect the normal individual to acquire. Unfortunately, at the present time, we are unable to estimate much smaller quantities. A great deal less might produce malignant changes over a longer period of time. Some have thought that 10 micrograms of radium deposited in the tissues of the body is probably just within the limits of tolerance of the average person. From my experience, it is impossible to state what is the greatest amount of radio-activity the body can safely carry. My idea is that less than one half of a microgram is dangerous. Theoretically the exposure to, or the use of any radio-active substance that will increase the normal radio-activity of the body is dangerous. At the present time I can only suggest that some other types of malignancy may be caused by minute amounts of radio-active substances to which the human body, in its normal environment, is exposed.

VI. Coley, B. L., and Sharp, G. S., Paget's Disease - a Predisposing Factor to Osteogenic Sarcoma. 23:918-937 (Dec) 1931.

The frequent association of Paget's disease and osteogenic sarcoma in patients over 50 years of age as attracted attention. It seems that this group may be important in giving a clue to one of the etiologic factors of osteogenic sarcoma. No instance is known of the development of a benign giant cell tumor or endothelial myeloma occurring in a bone that was the site of a preexisting Paget's disease.

1. Description: Sir James Paget, in 1877, first described the disease that bears his name. It is apparent that it is a constitutional disease, although it may manifest itself in a single bone;

.t more commonly involves a number of ›ones, and of these the skull is a favorite ;ite. The condition is considered rare, ılthough most writers agree that it pro-›ably occurs more frequently than is gen-›rally recognized, for it seems likely ;hat it is often overlooked, especially ;hen it attacks only the skull.

2. Etiology: Probably the most engaging theory is that it is due to a defective metabolism of calcium, having as its underlying basis a faulty function of the parathyroid glands. Further investigation is needed along these lines and may be productive of real information.

3. Gross Appearance: The changes in the bone seen in Paget's disease are characteristic and are the result of a combination of destruction of bone and formation of new bone. The latter, however, does not consist of normal bone, but of osteoid tissue. Changes in the shape, size and structure of the bone occur. The medullary cavity is encroached on, and in advanced cases it is often impossible to state where the cortex ends and the medulla begins. The skull, spine and the long bones of the lower extremity are most frequently affected.

4. Symptoms and Signs: Bowing of the lower extremities occurs, due to the effect of the bearing of weight, and the resulting deformity is one of the characteristic features of the disease. In other cases, however, the increase in the size of the head is the first symptom noted. Pain in the legs is an inconstant and often transitory symptom; it may disappear entirely as the disease progresses. Fractures sometimes occur in bones affected by the changes of Paget's disease, but union generally results.

5. Diagnosis: The diagnosis is not difficult if the condition is suspected and roentgenograms are made, because the changes in the bone as revealed by x-ray films are rather characteristic. Occasional cases of metastasis to bone from carcinoma are seen in which the picture of Paget's disease is closely simulated; of these, prostatic carcinoma is apt to be the most confusing. In the absence of a demonstrable primary growth elsewhere, the diagnosis of Paget's disease is rendered more certain.

It is the author's belief that if roentgenograms of the skull were made more generally of patients over 50 years of age it would be found that osteitis deformans is much less rare than it is thought to be. We now make a practice to obtain films of the skull on all patients in the Bone Tumor Clinic over the age of 50.

6. Paget's Disease Associated with Sarcoma of the Bone.

In his earliest communication concerning the disease that bears his name, Paget mentioned the tendency in patients with osteitis deformans to develop neoplastic conditions. In his twenty-three personally observed cases, we learn from a subsequent report that of the eight patients who were traced to their deaths, malignant diseases developed in no less than five.

Packard, Steele and Kirkbride reviewed the literature up to 1901 and collected 66 cases of undoubted osteitis deformans in which there was an associate sarcoma in 5, or 7.5 per cent. DaCosta, in 1914, assembled 213 cases in which sarcomatous diseases of some form developed in 9.5 per cent. Gruner, Scrimger and Foster reported that in about 9 per cent of their cases of Paget's disease this condition was associated with sarcoma.

When a condition as relatively rare as Paget's disease comes to be associated with a second condition as uncommon as osteogenic sarcoma, one cannot but seriously consider that this association is more than one of mere chance or coincidence. In one year Camp observed 2 cases of sarcoma in Paget's disease at the Massachusetts General Hospital. Locke found that 4 of his 65 patients with osteitis deformans had osteosarcoma or fibrosarcoma (6.2 per cent).

Bird studied the records of four large Boston hospitals with some interesting results. He was able to collect records of 64 patients with osteitis deformans, in 7 of whom (approximately 11 per cent) sarcoma occurred.

Study includes a total of 71 cases of osteogenic sarcoma in patients over 50 years of age. Twenty cases

were collected from the records of the Memorial Hospital and 51 were from the Bone Sarcoma Registry. As shown, the association of osteogenic sarcoma and Paget's disease is relatively the same in the two series.

Association of Osteogenic Sarcoma and Paget's Disease*

	Memorial Hospital	Bone Sarcoma Registry	Total
Number over 50 Yrs. with Osteogenic Sarcoma	20	51	71
Number over 50 Yrs. with Osteogenic Sarcoma and Paget's disease	6	14	20
Percentage of cases with 2 diseases associated	30	27.4	28.1

* Case E.S. in the series from the Memorial Hospital is also included with the cases from the Bone Registry.

*There are, however, four cases in the Bone Sarcoma Registry of osteogenic sarcoma associated with Paget's disease in patients under the age of 50. Three of the patients were men and one was a woman. Their ages were 35, 37, 42 and 47.

Conclusions:

1. From a study of cases of osteogenic sarcoma in Memorial Hospital, it was found that in no patient was this condition associated with Paget's disease prior to the age of 50.

2. In a collected series from Memorial Hospital and the Bone Registry of seventy-one cases of osteogenic sarcoma in patients over 50 years of age, Paget's disease was found to be a predisposing factor to osteogenic sarcoma in 29 per cent.

3. Of patients with the two diseases associated, men are affected five times more frequently than women.

4. In general, it may be said that osteogenic sarcoma in patients over 50 has the same sites of predilection as in younger persons.

5. A patient over 50 with osteogenic sarcoma of the skull presumably has Paget's disease.

6. When osteogenic sarcoma is associated with Paget's disease, it invariably develops in a bone showing the characteristic changes of Paget's disease rather than in an otherwise normal bone.

7. Evidence is presented to show that Paget's disease is present from ten to fifteen years or more prior to the development of a complicating osteogenic sarcoma.

8. The duration of life is shortened by the association of osteogenic sarcoma with Paget's disease, as determined by a comparative study of a group of patients of the same age without osteogenic sarcoma.

9. No record has been found of the survival for five years of a patient with osteogenic sarcoma and Paget's disease under any method of treatment.

10. Paget's sarcoma has proved to be relatively resistant to radiation.

11. Preliminary radiation by intensive exposure to radium pack and high voltage x-rays and, following amputation, the use of prophylactic constitutional therapy with the mixed toxins are suggested as a method worthy of trial.