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From the Codman Bone Tumor Registry at the Armed Forces Institute of Pathology, Washington, D. C., USA

Sarcomas Arising in Bone Cysts

By

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With 32 Figures in the Text

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Bone cysts have always been considered as benign and commonly as non-neoplastic. A review of the literature in 1931 by SCHINZ and UEHLINGER yielded five reports of sarcoma arising in a cyst, but only the case reported by HAENISCH was considered acceptable. This was a solitary radiolucent metaphyseal defect in the upper humerus of a 7-year-old child with a spontaneous fracture that healed following radiation therapy. Four and a half years after the fracture a fatal osteogenic sarcoma developed in the area of the lesion. No anatomic or histologic data on the nature of the original lesion or of the amputation specimen is mentioned. A sixth case was reported in 1936 by FRANCISCO et al. of a radiolucent defect in the upper end of the tibia of a 9-year-old child that gradually calcified under radiation therapy. Four and a half years later a sarcoma was found at the site of the original lesion. The amputation specimen showed no evidence of a cavity or residuals of a cyst; the medullary cavity and surrounding soft tissues were occupied by a solid sarcoma producing cartilage and hence diagnosed as a chondrosarcoma. Thus, the literature contains no anatomically and histologically verified case of a bone cyst with a simultaneous or subsequent spontaneous sarcoma.

A major problem in such cases is proof of the cystic nature of the original lesion. In virtually all instances the original lesion was diagnosed because of a sharply defined roentgenographic defect in the normal structure of calcified bone. Such defects can be produced by giant cell tumors, enchondromas, fibrous dysplasias, fibromas, angiomas, and lipomas, as well as by bone cysts. Therefore proof that the lesion is a cyst requires surgical verification. VIRCHOW described the first bone cyst in a humerus as a long, hollow cavity with a tough wall 3 to 8 mm thick, having a smooth glistening inner surface. Unless the structural nature of the radiologic defect is similarly verified it is impossible to be certain that the lesion is a cyst. Another problem is created by the ability of a number of bone tumors to undergo extensive cystic degeneration and to be mistaken for a primary cyst. Consequently, large microscopic sections (or multiple sections) of the entire tumor are necessary to establish the direct relationship of the sarcoma to a characteristically structured cyst wall. A third problem arises from the fact that x-ray therapy can induce sarcomatous transformation of certain bone lesions,

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including bone cysts (CAHAN et al., CRUZ et al.). Therefore, the third requirement for proof of the thesis would be the development of a sarcoma in association with an anatomically verified cyst that had not been subjected to radiation therapy.

The Bone Sarcoma Registry, located at the Armed Forces Institute of Pathology, contains over 300 cases of simple bone cysts and material from over 3,000 malignant primary bone tumors. Among these cases there are *four examples of large, untreated simple bone cysts with a sarcoma arising from the wall of each cyst.* It is the purpose of this communication to report these cases, together with a fifth case of a sarcoma of the wall of a cyst produced by infarction of bone marrow.

Biopsy material was fixed in 10 per cent formalin. Amputation specimens were dissected, sawed in half longitudinally, and fixed in formalin. Decalcification was in a special electrolytic bath utilizing 8 per cent hydrochloric acid, 10 per cent formic acid, and a special decalcifying vat designed at the Armed Forces Institute of Pathology. All materials were embedded in paraffin, including the large sections. Portions of the tumors were examined by frozen section and stained with Harris hematoxylin, oil red O (ORO), and sudan black B (SBB). Paraffin sections were stained with periodic acid-Schiff (PAS) reaction, the Rinehart-Abul-Haj modification of the Hale colloidal iron reaction for acid mucopolysaccharide (AMP), the Abul-Haj modification of this stain for sulphate radicals, alcian blue, phosphotungstic acid hematoxylin, and Wilder's reticulum stains. Portions of unstained sections were examined by ultraviolet and polarized light. Duplicate sections of AMP-stained material were prepared after digestion at 37° C with bovine testicular hyaluronidase ("Wydase", Wyeth Laboratories). Duplicate sections of PAS material were prepared after digestion with diastase. Only those results of special stains that are germane to this presentation are reported.

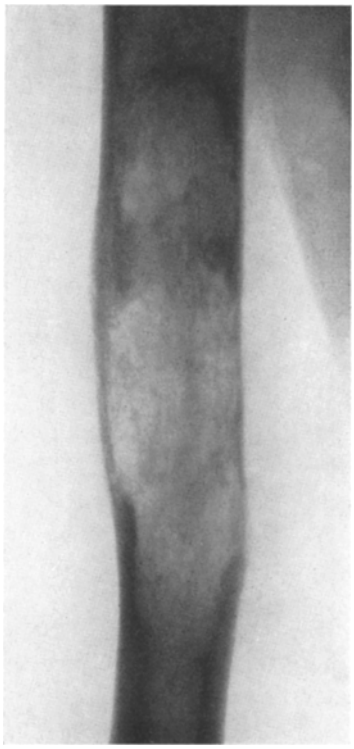

Fig. 1. Case 1. Roentgenogram of humerus showing destruction of midshaft cortex with a radiolucent defect extending upward toward head. AFIP Acc. 823205

Case reports

Case 1. AFIP Acc. 823205 (contributed by Dr. HANS VETTER, Aarau, Switzerland). A 25-year-old white man suffered immediate severe pain when struck on the left upper arm by a heavy wooden beam. The next day there was extensive swelling. The swelling persisted, and pain continued, with progressive difficulty in using the arm until the man was unable to work. Three weeks after injury a roentgenogram (Fig. 1) showed a fusiform swelling and destructive process involving the midshaft of the humerus. Biopsy demonstrated a malignant tumor, and shoulder disarticulation was carried out 36 days after the injury. The patient recovered rapidly from surgery but died of pulmonary metastasis 26 months after operation.

The humerus (Fig. 2) was deformed and distended in the midshaft area by a pathologic fracture and tumor tissue mushrooming into the soft tissue. The distention was due to a fusiform nodular tumor filling the medullary cavity. The adjacent cortex was perforated by tumor and laminated. In the marrow cavity proximal to the tumor was an 8-cm-long pear-shaped, smooth-walled cyst containing some slimy, gelatinous material. The cyst wall was greyish white, tough,

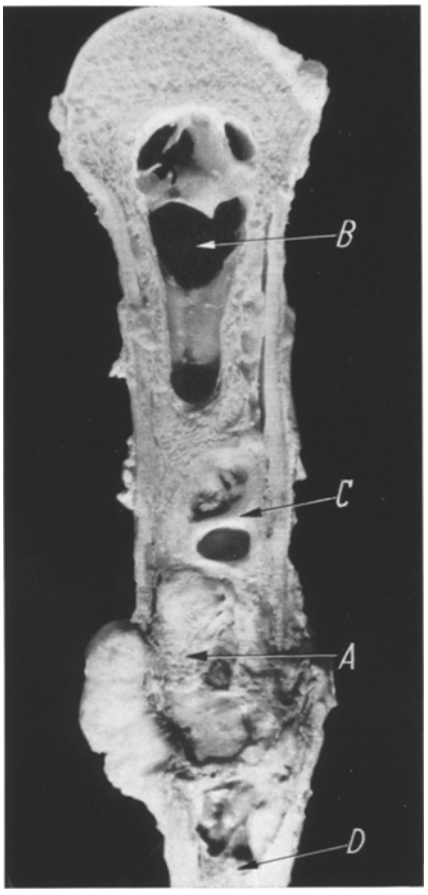

Fig. 2. Case 1. A longitudinal slab of humerus showing (*A*) neoplasm in the area of cortical destruction; (*B*) cyst filling upper end of humerus; (*C*) additional cysts adjacent to the neoplasm; (*D*) the region of histologically abnormal bone marrow. AFIP Acc. 823 205.

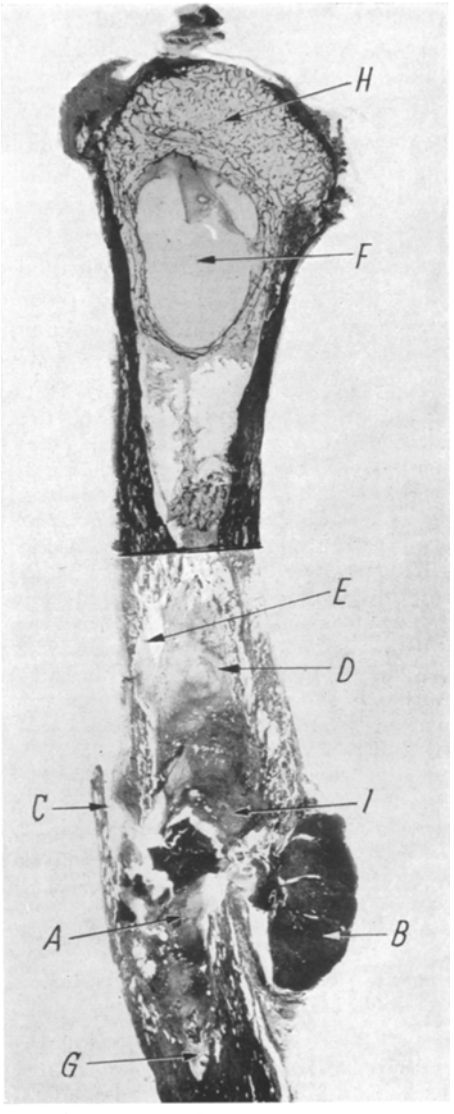

Fig. 3

Fig. 3. Case 1. Large off-center section of entire humerus showing (*A*) neoplasm; (*B*) extension of neoplasm into soft tissue; (*C*) fracture; (*D*) tangential cut of smaller cyst wall; (*E*) adjacent dysplastic fatty marrow; (*F*) upper portion of large cyst; (*G*) area of transition between abnormal marrow and neoplasm; (*H*) normal cancellous bone and bone marrow; (*I*) area of bizarre liposarcoma pattern. Hematoxylin and eosin. AFIP Acc. 823 205

and glistening. The lower end of the tortuous cyst was in immediate contact with the tumor.

Sections of the bone (Fig. 3) showed that the medullary cavity at the fracture site was filled with clotted blood. In the muscles and soft tissue about the fracture there was extensive benign bone and cartilage proliferation characteristic of callus. The cortex was expanded and perforated by many resorption cavities with numerous osteoclasts. Periosteal new bone was present on the surface. The tumor, where it extruded into the soft tissue, appeared as a dense mass of close-packed, small spindle cells with fine strands of collagenic matrix. The tumor filling the expanded marrow cavity was composed of spindle cells associated with some

collagen production (Fig. 4). Just above and below the fracture site there was an extensive region of much larger spindle cells associated with large polyhedral cells and massive giant cells, all having a vacuolated cytoplasm (Fig. 5). These cells stained heavily with ORO and SBB and also stained with AMP and alcian blue unless subjected to prior treatment with

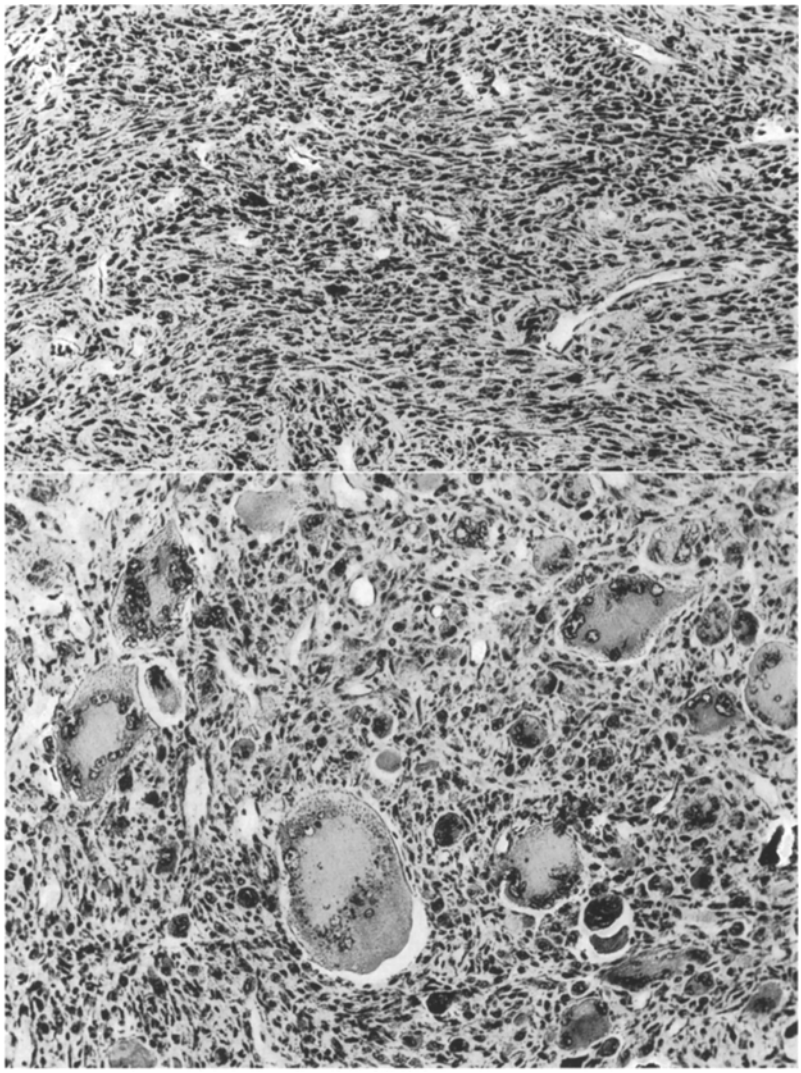

Fig. 4

Fig. 5

Fig. 4. Case 1. Microscopic pattern of area "A" of Fig. 3, showing tendency to spindling of undifferentiated sarcoma cells. Hematoxylin and eosin. Mag. 140 ×. AFIP Neg. 61—6723

Fig. 5. Case 1. Microscopic pattern of area "*I*" of Fig. 3, showing extremely large, bizarre giant cells with peripheral fine vacuolization and smaller polyhedral and spindled vacuolated cells. These cells stained heavily with ORO, SBB, and AMP. Hematoxylin and eosin. Mag. 110 ×. AFIP Neg. 61—6722

hyaluronidase. Superiorly the tumor merged with the lower end of the cyst. The fatty marrow about the lower half of the cyst was myxomatoid, with enlarged and irregularly shaped fat cells and foci of atypical metaplastic osteoid material. The cyst wall (Fig. 6) was a thick band of virtually acellular fibrillary collagen with a thin shell of bone in the outer layers of the collagen. Within the cyst were areas of poorly defined acellular, disintegrating myxomatous

fat associated with clusters of macrophages filled with mucoid granules staining with PAS. Myxomatous fatty marrow over the top of the cyst contained many dilated, blood-filled sinusoids. In some sections of the main tumor below the cyst there were segments of a dense acellular fibrous wall exactly like that which lined the cyst. Distal to the tumor a wide band of abnormal marrow with enlarged, irregularly shaped fat cells, telangiectatic sinusoids, and myxomatous and fibrillary changes shaded gradually into the lower end of the spindle cell fibrosarcoma (Fig. 7).

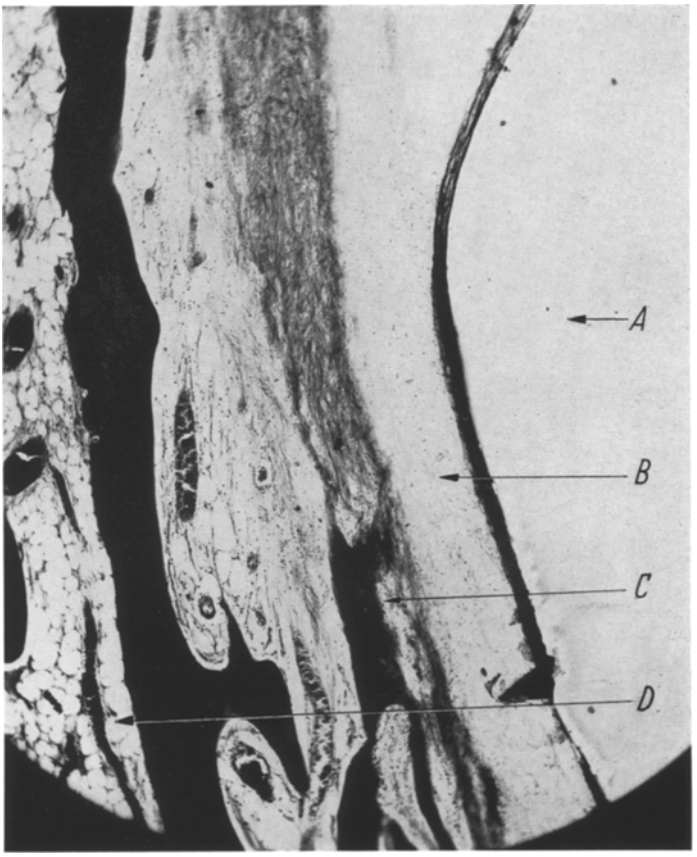

Fig. 6. Case 1. Microscopic pattern of area "F" of Fig. 3, showing a portion of cyst wall with (*A*) cavity; (*B*) fibrillary lining; (*C*) fibro-osseous metaplasia of outer portion of cyst wall; and (*D*) adjacent normal cancellous bone and bone marrow. Hematoxylin and eosin. Mag. 35 ×. AFIP Neg. 61—6719

Summary. The cavity was a classic simple bone cyst very similar to the original lesion described by VIRCHOW, with a highly specialized fibrous wall both grossly and microscopically, with fibrous, myxomatous, dysplastic abnormalities in the surrounding fatty marrow, and with slimy, gelatinous, degenerating myxoid and myxolipoid material in the cavity.

About the distal end of the cyst and surrounding a solid, rodlike extension of the cyst wall was a malignant tumor that had expanded the cortex and extended out into the soft tissue. The extraosseous mass and much of the intraosseous tumor was a spindle cell, collagen-producing fibrosarcoma. A substantial portion of the intraosseous tumor presented an additional pattern of vacuolated large

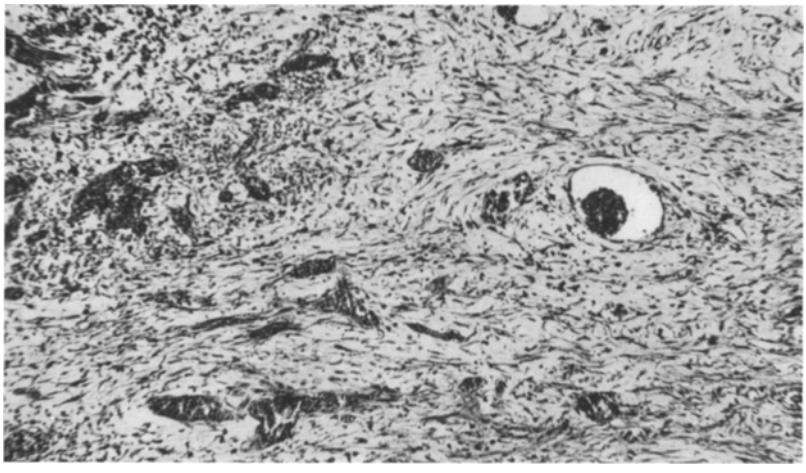

Fig. 7. Case 1. Microscopic pattern of area "G" of Fig. 3, showing abnormal fat with many proliferating elongated cells resembling the spindle cell sarcoma pattern of Fig. 4. Hematoxylin and eosin. Mag. 80 ×. AFIP Neg. 61—6720

spindle, polyhedral, and multinucleated giant cells that contained fat and stained with an acid mucopolysaccharide reaction that was abolished by hyaluronidase. The marrow cavity for a considerable distance distal to the tumor was the seat of myxomatous and myxofibrillary changes that gradually merged with the sarcoma.

Case 2. AFIP Acc. 970261 (contributed by Dr. Louis B. Thomas, Department of Pathology, National Institutes of Health, Bethesda, Md.). A 46-year-old white man had noted vague intermittent aching in the left shoulder and upper arm for 4 months, and on several occasions the arm had "given way". Because of increasing pain a roentgenogram was made that showed a pathologic fracture in the upper humerus (Fig. 8). Biopsy demonstrated a malignant tumor, and the limb was removed by transscapular amputation. The patient recovered and returned to work. Ten months after amputation asymptomatic, small metastatic nodules were noted on chest roentgenograms, and 4 months later he developed some cough, with blood-tinged sputum and pleuritic pain. Slowly the pulmonary nodules grew to a massive size, and the patient died about 18 months after amputation.

The amputated humerus (Fig. 9) showed a fracture about 3 cm below the neck, where the cortex was eroded and thinned. The surrounding muscles were hemorrhagic, but no recognizable tumor was noted in the soft tissues. The medullary cavity for 5 cm distal to the fracture was filled with soft, friable, necrotic appearing red-brown to grey-brown tissue. In the distal portion this material separated readily from a firm, partially calcified shell within the marrow cavity. Tumor also filled the medullary cavity for 3 cm

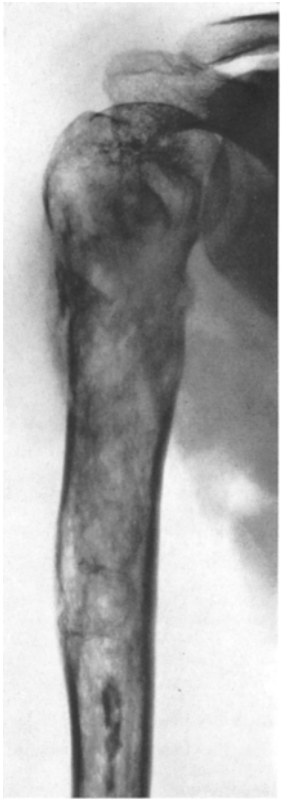

Fig. 8. Case 2. Roentgenogram of humerus showing destruction of surgical neck, radiolucency of the shaft, and a calcified rod in the lower third. AFIP Acc. 970261

proximal to the fracture, extending into the humeral head, where it was capped by a semilunar mass of yellow-tan tissue. Another yellow-tan rounded, sharply circumscribed 1 cm spherical mass with a rigid fibrous capsule was located distal

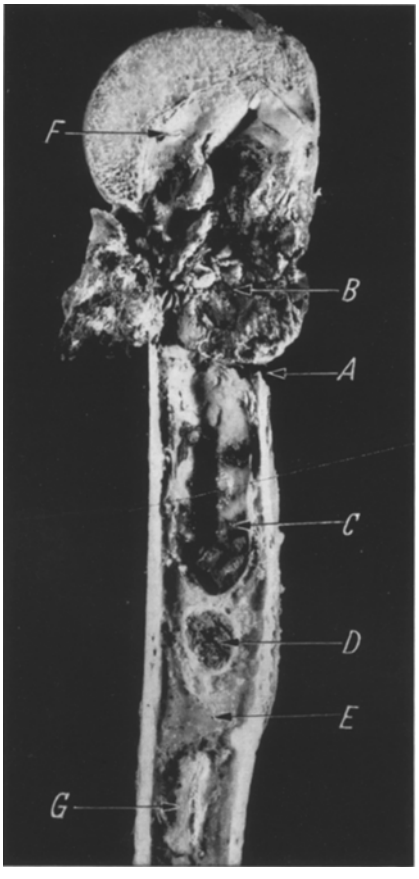

Fig. 9. Case 2. Longitudinal slab of humerus showing (*A*) fracture; (*B*) neoplasm filling upper end; (*C*) large cyst; (*D*) smaller cyst containing necrotic fat; (*E*) area of abnormal marrow; (*F*) cap of yellow-tan material above tumor; and (*G*) calcified rod.
AFIPAcc. 970261

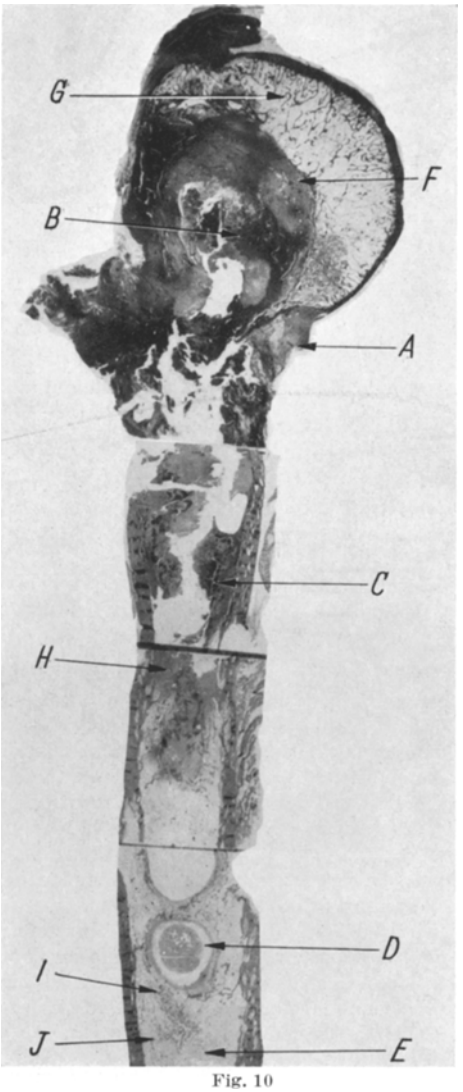

Fig. 10

Fig. 10. Case 2. Large section of humerus showing (*A*) fracture; (*B*) neoplasm; (*C*) cyst wall surrounded by tumor; (*D*) satellite cyst filled with necrotic fat; (*E*) area where calcified rod had been; (*F*) region of yellow-tan cap; (*G*) normal cancellous bone and marrow; (*H*) area of bizarre liposarcoma; (*I*) area of abnormal fat with osteoid metaplasia; (*J*) area of abnormal fat. Hematoxylin and eosin. AFIP Acc. 970261

Fig. 11. Case 2. Microscopic picture from area "B" of Fig. 10, showing undifferentiated spindle cell sarcoma with occasional strands of collagen. Hematoxylin and eosin. Mag. 100×.
AFIP Neg. 61—6709

Fig. 12. Case 2. Microscopic picture from area "H" of Fig. 10, showing large, bizarre giant cells with extensive vacuolization and numerous small globoid bodies in cytoplasm and large vacuolated spindle and polyhedral cells. They all stained heavily with ORO, SBB, and AMP. Hematoxylin and eosin. Mag. 150×. AFIP Neg. 61—6707

Fig. 11

Fig. 12

Fig. 13

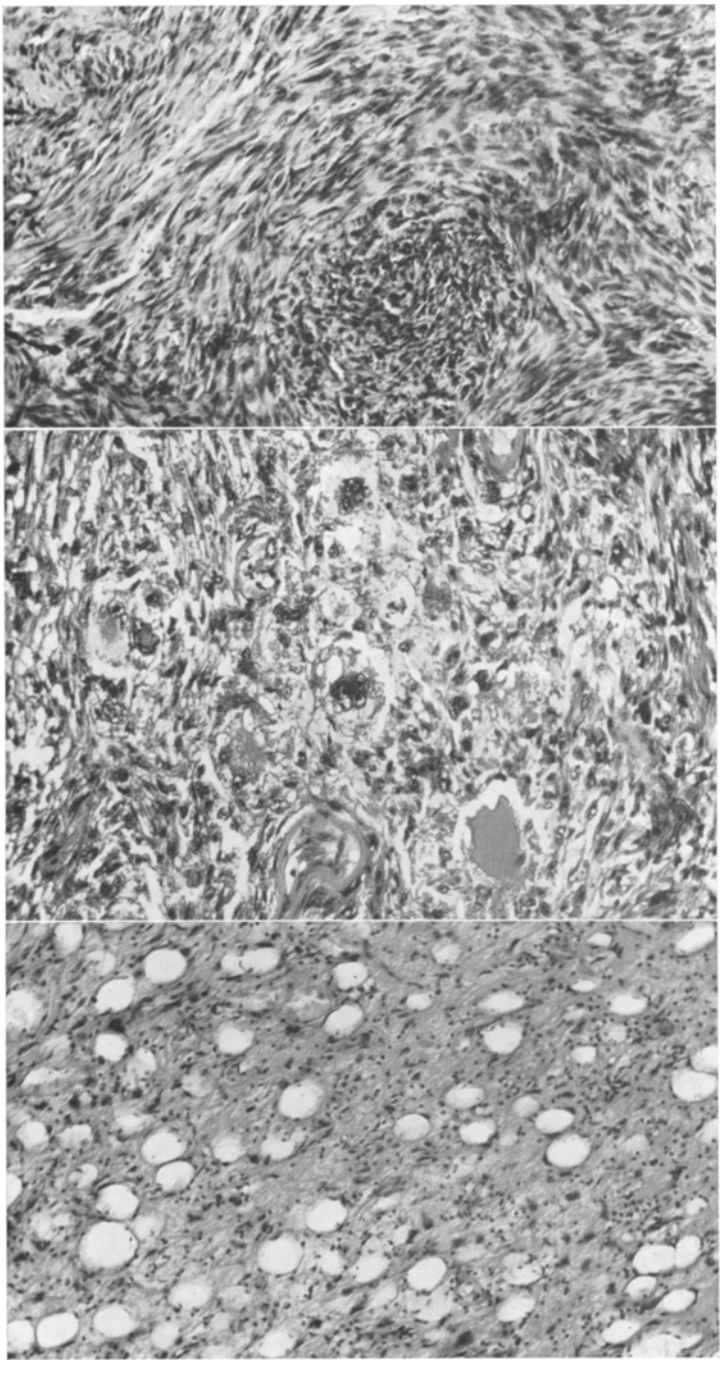

Fig. 13. Case 2. Microscopic pattern from area "F" of Fig. 10, showing myxomatoid fat with large, scattered proliferating cells beginning to resemble cells of the spindle cell sarcoma of Fig. 11. Hematoxylin and eosin. Mag. 100 ×. AFIP Neg. 61—6710

to the lower end of the tumor, and just beyond this a tan, linear 4 cm calcified core of tissue occupied the center of the medullary cavity surrounded by yellow fatty marrow. After fixation much of the contents of the lower end of the main cyst cavity and of the smaller distal cyst floated out or fell out and revealed a rigid, smooth, glistening cyst wall 1 mm thick.

Fig. 14

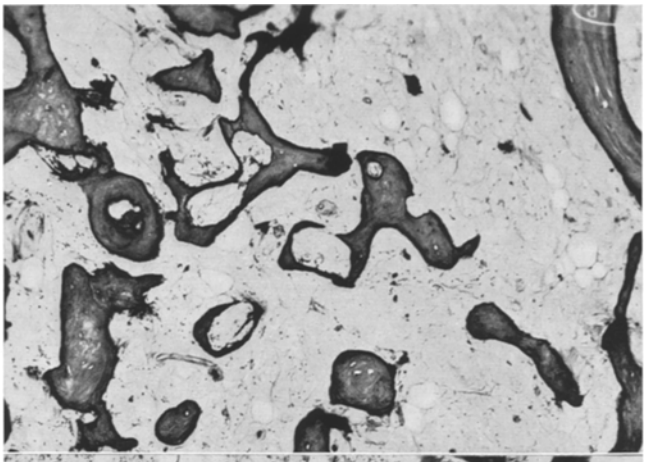

Fig. 15

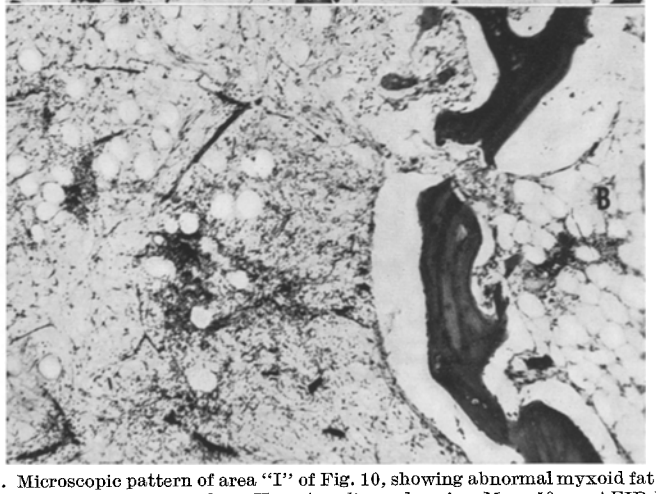

Fig. 14. Case 2. Microscopic pattern of area "I" of Fig. 10, showing abnormal myxoid fat with scattered abnormal metaplastic osseous trabeculae. Hematoxylin and eosin. Mag. 50 ×. AFIP Neg. 61—6706

Fig. 15. Case 2. Microscopic pattern from area "J" of Fig. 10, showing (*A*) abnormal fat with myxomatous change and variable cell size, and (*B*) normal fatty marrow. Hematoxylin and eosin. Mag. 50 ×. AFIP Neg. 61—6704

Microscopic sections showed the upper shaft to be filled with tumor over an 8 cm area (Fig. 10). The cortex adjacent to the fracture was thinned and riddled with resorption cavities containing numerous osteoclasts. Periosteal new bone and callus were present about the fracture. Some of the tumor cells were beginning to extend into the soft tissue. Most tumor cells were large spindle cells with a pale, abundant, vacuolated cytoplasm (Fig. 11). Between the cells were scattered irregular chunks of hyaline material and strands of collagen. Occasional clusters of multinucleated giant cells were seen, as well as large polyhedral cells that had a fine vacuolated cytoplasm (Fig. 12). These cells stained heavily with ORO and SBB, and also stained with AMP and alcian blue unless previously treated with hyaluronidase. Only a few

thin strands of osteoid were encountered. The yellow-tan cap noted at the proximal end of the tumor was a region of myxoid fat cells and fibroblasts that appeared to be undergoing transition to malignant tumor cells (Fig. 13).

Scattered through the body of the main tumor were elongated dense bands of acellular collagen having foci of calcification characteristic of a cyst wall. On reconstruction, most of the wall of a large cyst could be made out filling the upper end of the diaphysis. In many places the cavity circumscribed by these walls was filled by necrotic fatty marrow, cholesterol slits, foreign body giant cells, old blood pigment, and small spindle cells. In some places sheets of neoplastic cells had penetrated through the cyst wall and were present within the cavity, but most of the tumor was in the marrow spaces surrounding the fibrous cyst wall.

Below the tumor there was an oval extension of the cyst wall made up of acellular collagen with an outer margin of bone and scattered areas of deep basophilic collagen. In some sections the irregular wall projected forward into the cavity so that it was cut tangentially. The lower half of this cavity contained a peculiar myxoid fat with clusters of atypical short, stubby osteoid trabeculae. The spherical mass just distal to the main lesion had an identical fibrous wall with a bony rim in its outer portion. The cavity was filled with necrotic debris and numerous cholesterol slits. The fatty marrow surrounding the cysts was myxoid in character, with foci of ayptical bony trabeculae (Fig. 14). Similar abnormal fatty marrow extended down into the shaft around and below the elongated calcified core. In these myxoid areas (Fig. 15) the fat cells were larger and more irregular in shape than those in the normal ends of the bone.

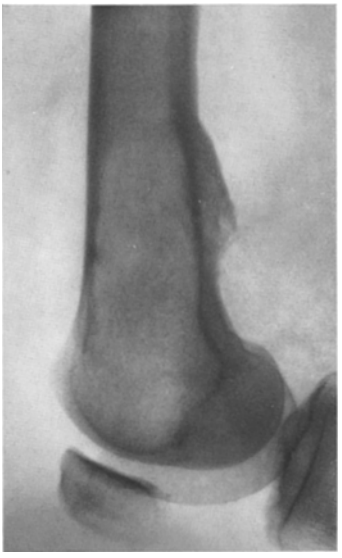

Fig. 16. Case 3. Roentgenogram of femur showing radiolucent mass on posterior surface of femur with elevated periosteum above it and ill-defined radiolucent defect of lower femoral shaft. AFIP Acc. 822818

Summary. A typical, characteristically differentiated cyst wall extended through two-thirds of the length of the diaphysis, intact although segmented in its lower half, and broken up and embedded in a malignant tumor in the upper half. Within the cyst wall was necrotic fat in various stages of disintegration and associated with a foreign body reaction. Surrounding the cyst wall was a spindle cell, collagen-producing fibrosarcoma with some foci of osteoid. An additional pattern of very large, vacuolated spindle and polyhedral cells with occasional multinucleated giant cells was prominent. These cells stained for fat and with an acid mucopolysaccharide reaction that was removed by hyaluronidase. Filling the lower half of the shaft and surrounding the cyst was fibromyxomatous abnormal fat tissue with foci of dysplastic osteoid. Capping the upper end of the tumor was a similar area in transition to malignant tumor.

Case 3. AFIP Acc. 882818 (contributed by Captain F. J. McMahon, MC, USN, Chelsea Naval Hospital, Chelsea, Massachusetts). A 64-year-old white woman, who had noticed some pain in the popliteal region for 6 months, was found to have a firm mass in this area associated with a radiologic defect in the underlying femur (Fig. 16). After biopsy had demonstrated a malignant tumor, the limb was amputated through the upper thigh. Four years later the patient was alive and free of any evidence of tumor.

The popliteal mass measured 6.5 × 5.5 × 4.5 cm, was soft, tan to grey-tan, and had a few 1 to 3 mm scattered foci of cystic degeneration and hemorrhage. In the femur (Fig. 17) was a hollow cavity 7.2 cm long filling the medullary space

and containing clear fluid. The lining of this cavity was smooth, glistening, moderately firm, and 1 to 2 mm thick. Posteriorly the cyst lining merged with the popliteal mass through a 3.5 cm defect in the cortex. Above the defect the periosteum was elevated and the cortex thickened as it merged with the outer fibrous portions of the extraosseous mass.

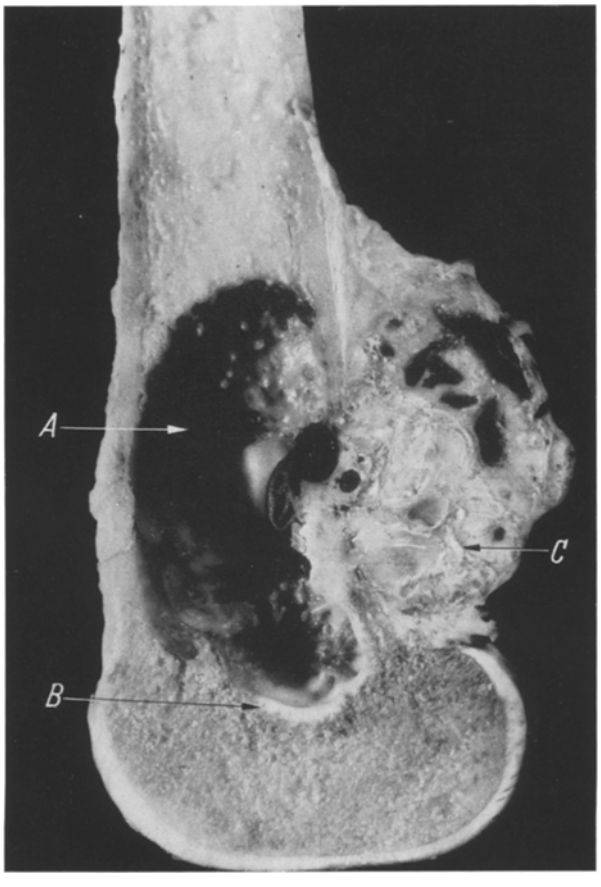

Fig. 17. Case 3. Slab of femur showing (*A*) cyst of femur; (*B*) nubbin of tumor at lower end; and (*C*) large tumor bulging into cyst and out into popliteal space. AFIP Acc. 822818

Sections (Fig. 18) demonstrated the cyst lining to be a thin wall of compacted fibrillary collagen of scant cellularity (Fig. 19). Where the cyst wall was close to the cortex, a layer of osteoclasts was resorbing the cortex along the endosteal surface. At the lower pole of the cyst was a nubbin (Fig. 20) of close-packed hyperchromatic spindle and polyhedral cells interspersed with multinucleated cells and small amounts of abnormal osteoid produced by the neoplastic cells. In places the entire thickness of the fibrous cyst wall was infiltrated by tumor cells. Between this nubbin and the large mass was another, smaller focus of anaplastic, closely packed cells in the outer layer of the cyst wall. Posteriorly, where the cyst wall merged with the popliteal mass, there were a number of lakes of blood, and a portion of the cyst extended in a tortuous manner about halfway into the extraosseous mass. The mass itself was composed largely of numerous multinucleated giant cells and associated large, polyhedral mononuclear cells similar to those seen in a giant cell tumor or osteoclastoma (Fig. 21). There was considerable variation in size, shape, and staining quality of both mononuclear and giant cells, and many atypical mitotic figures were present. Intervening strands of spindle cells producing collagen subdivided this mass into lobules. Along one side of the extension of the cyst into this mass was a band of neoplastic osteoblasts producing osteoid and bone. Where the mass bulged into the femoral cyst, tumor cells had invaded and destroyed large portions of the cyst wall. A few small areas of atypical fat with myxoid change and atypical metaplastic osteoid trabeculae were present in the fatty marrow adjacent to the upper and lower poles of the cyst.

Summary. A typical simple bone cyst with a 1 to 2 mm glistening, smooth fibrous wall filled the lower end of the femur. Arising in its posterior wall, bulging into the cyst, and extending out into the popliteal space was a sarcoma, much

of which had the pattern of a malignant giant cell tumor. At the lower pole was another small focus of malignant tumor with the pattern of an osteosarcoma. Between these two malignant masses was another portion of very early neoplastic cell development in the cyst wall.

Case 4. AFIP Acc. 991283 (contributed by Colonel JAMES E. ASH, MC, USA (Ret.), and Dr. LOUIS B. THOMAS, Bethesda, Md.). A 35-year-old woman who had noted vague

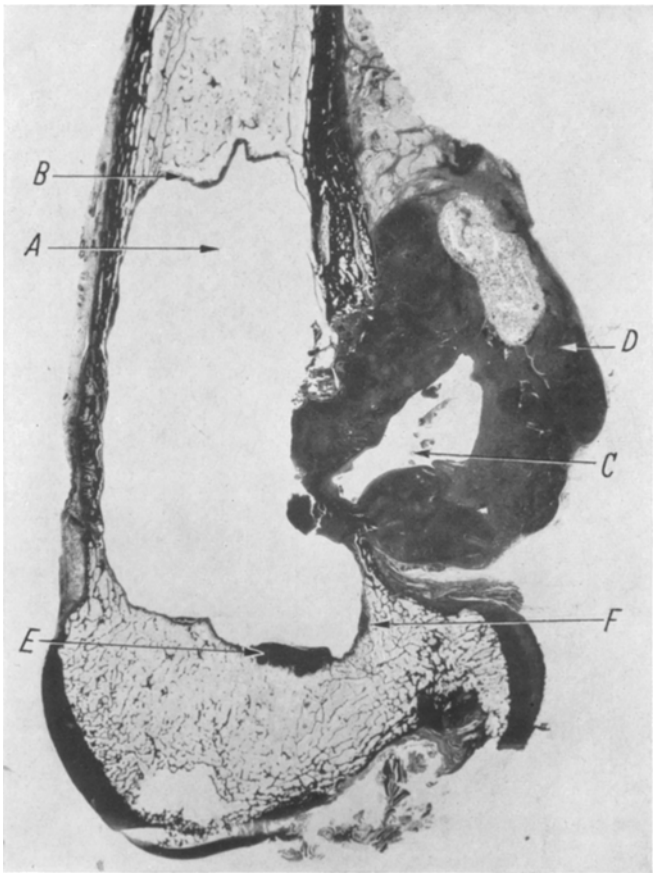

Fig. 18. Case 3. Large section of femur showing (*A*) cystic cavity; (*B*) fibrous cyst wall; (*C*) portion of cyst cavity in tumor; (*D*) tumor bulging into cyst and into popliteal space; (*E*) independent focus of tumor in cyst wall; and (*F*) small additional focus of tumor of cyst wall. Hematoxylin and eosin. AFIP Acc. 822818

twinges of pain in the right knee for 2 years stumbled, fell, and struck her right knee, causing it to swell to twice its normal size. Cortisone injections into the knee produced some decrease in size, but the pain gradually increased, particularly with exercise, and the patient began to notice difficulty in climbing stairs. Three months after the injury she noted a small mass in the popliteal space, which subsequently did not seem to enlarge. Six months after injury a first roentgenogram (Fig. 22) showed a lesion in the femur associated with the popliteal mass.

At biopsy the femur was entered through the lateral condyle, and the intraosseous lesion was demonstrated to be an empty, hollow, well-demarcated cavity that did not communicate with the medullary space above or below. The cavity was lined by thin, moist, pinkish-grey to white tissue with some polypoid thickening. The wall was easily peeled from an underlying shell of hard eburnated bone that separated the cyst from the adjacent marrow, except

at the distal end, where an extension of cyst wall tissue blended into the marrow of the lateral condyle. The cyst lining was demonstrated to be in direct continuity with the popliteal mass through a large defect in the posterior cortex of the femur. Following biopsy, a block excision of the mass, the adjacent cortex, and all of the lining of the cyst was carried out, and the cavity filled with a bone graft from the ilium. Two months after the block resection the limb was disarticulated at the hip. Six months following disarticulation the patient was in good health and carrying out her household activities, and a full investigation revealed no signs of metastatic growths.

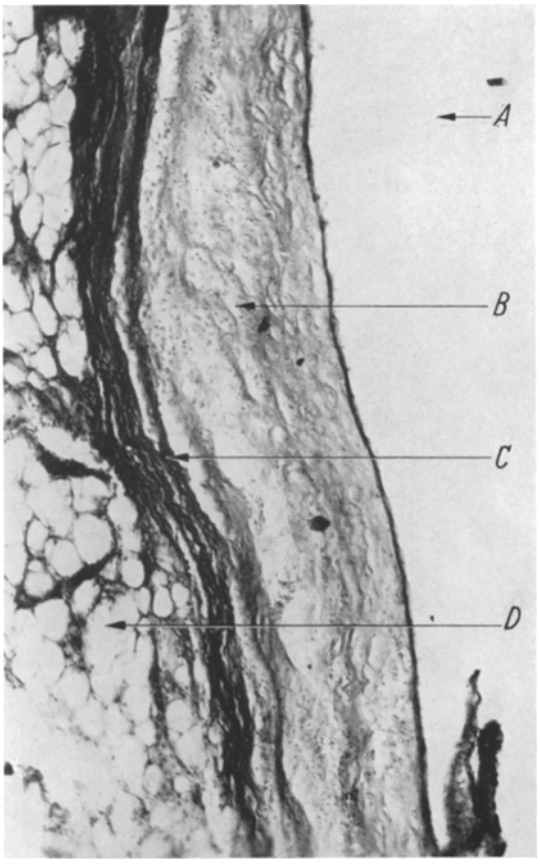

Fig. 19. Case 3. Microscopic pattern of area "B" of Fig. 18, showing (*A*) cavity; (*B*) delicate fibrous cyst wall containing abnormal fat and xanthoma cells with (*C*) calcified outer collagen strands; and (*D*) normal fatty marrow. Hematoxylin and eosin. Mag. 90 ×. AFIP Neg. 61—6732

Microscopic study of the initial curettings (Fig. 23) of the cavity showed a malignant tumor lining the cystic space. Broad bands of mature and immature chondroid material, scattered denser strands of osteoid material, and numerous large polyhedral cells with dense hyperchromatic nuclei and poorly defined cytoplasm made up the lining. Nowhere was a dense fibrous wall found, such as may be curetted from a simple bone cyst, although some areas suggested a fibrous wall infiltrated with tumor cells.

The resected popliteal mass was 6 × 5 cm, smooth, bosselated, almost stony hard, with a hard white cut surface showing scattered gritty flecks of calcium. Microscopically, it was composed for the most part of broad bundles and fascicles of dense collagen (Fig. 24) with focal areas of calcification adjacent to regions of faint mucoid staining of the collagen. There were a few foci of bone formation. Many areas were virtually acellular; most areas contained only a few small spindle or stellate cells. In only a few places there were clusters of large, hyperchromatic spindled and stellate fibroblasts, as well as occasional multinucleated tumor giant cells. Where the mass faced the cavity through the defect in the cortex, the collagen merged gradually and imperceptibly with the chondroid matrix of the cyst lining.

The distal one-fifth of the amputated femur (Fig. 25) and the lateral condyle contained a mass of abnormal firm white tissue measuring 6 × 3 cm, having a fairly sharply demarcated margin, and containing scattered cystic areas. In the center of this tissue was the large iliac bone graft. Microscopic sections showed the original cavity to be filled with the bone graft and granulation tissue (Fig. 26). The iliac graft was dead, avascular, and acellular except for the ghosts of cells with granular nuclear debris in the marrow spaces. The graft was locked in place by new-formed callus arising from the cancellous bone at both ends, and its marrow cavity at each end was penetrated for a short distance by viable capillaries and young fibroblasts. Surrounding the graft and filling the cyst cavity was a loose meshwork of fresh vascular,

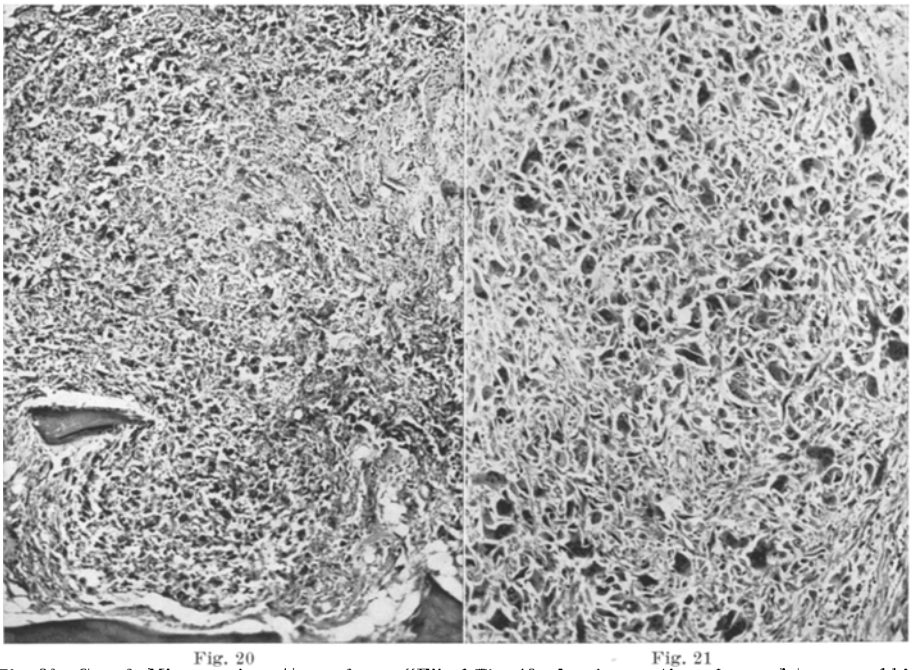

Fig. 20 Fig. 21

Fig. 20. Case 3. Microscopic pattern of area "E" of Fig. 18, showing portion of second tumor nubbin in cyst wall with numerous hyperchromatic cells and small, thin strands of abnormal osteoid material. Hematoxylin and eosin. Mag. 50 ×. AFIP Neg. 61—6730

Fig. 21. Case 3. Microscopic pattern of area "*D*" of Fig. 18 from popliteal mass, showing part of a lobule containing numerous giant cells in a background of mononuclear spindle and polyhedral cells with considerable variation of shape. Hematoxylin and eosin. Mag. 90 ×. AFIP Neg. 61—6733

areolar connective tissue with numerous normal proliferating fibroblasts and delicate reticulum strands. No neoplastic cells were present in this broad band of young connective tissue.

The margin of the cavity was marked by a rim of neoplastic tissue that came into contact with the articular cartilage at the lower pole and the femoral cortex at the upper pole. Where the neoplastic rim was thickest there was a residual cystic cavity with fragments of a thin fibrous wall. The neoplastic rim (Fig. 27) contained numerous clusters of highly abnormal osteoid amidst close-packed hyperchromatic cells. The cells were very large, polyhedral in shape, and had an abundance of pale-staining vacuolated cytoplasm.

Where the tumor approached the cortex there were broad sheets of osteoclasts applied to the endosteal surface, and numerous resorption cavities were present throughout the cortex. The larger resorption cavities were filled with cellular tumor. Fatty marrow between the neoplastic cells and the articular cartilage and adjacent to the intercondylar notch showed myxomatous change and telangiectasia of sinusoids.

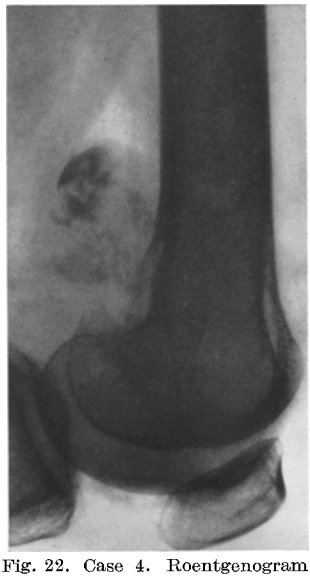

Fig. 22. Case 4. Roentgenogram of femur showing large, partially calcified mass on posterior surface and ill-defined radiolucency of lower part of shaft. AFIP Acc. 991283

Summary. The lining of the large cavity filling the lower end of the femur was entirely neoplastic, with considerable chondroid and some

osteoid production. Some chondroid areas suggested benignancy, with a scattering of cartilage cells in a poorly defined hyalinized material. Such areas could represent, and in fact in places suggested, infiltration of a hyalinized fibrous wall, but no clearly defined substantial benign fibrous wall was identified. Two months later osteoid-producing neoplasia predominated over the chondroid pattern. The large tumor arising from the cyst wall and extending posteriorly into the popliteal space was a dense, calcifying, collagenic mass with rare foci of fibrocartilage and calcifying bone and a few clusters of malignant fibroblasts.

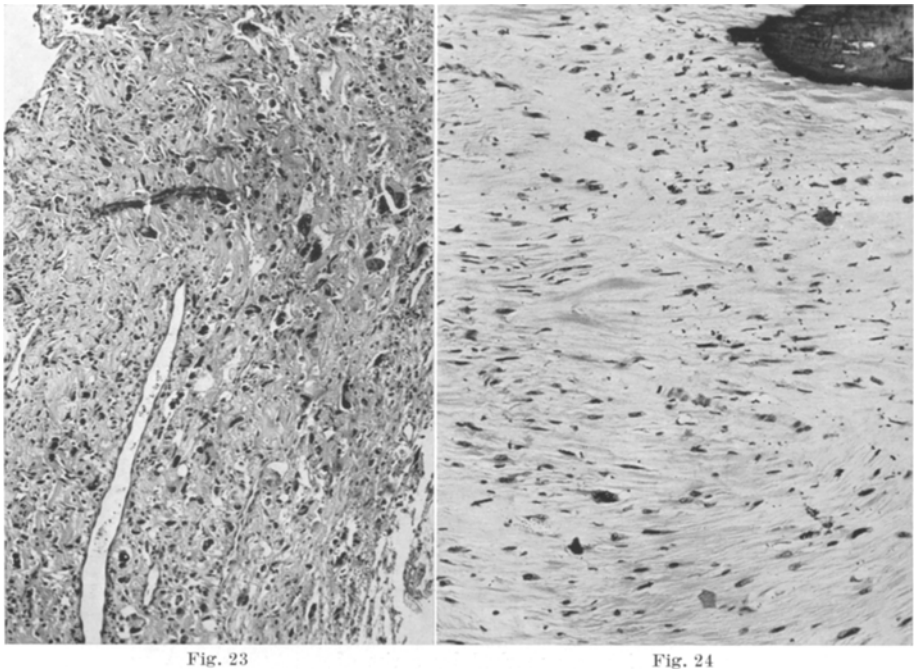

Fig. 23 Fig. 24

Fig. 23. Case 4. Section of curettings from cyst wall showing fibrous wall containing many large, bizarre neoplastic cells. Hematoxylin and eosin. Mag. 85 ×. AFIP Neg. 61—6717

Fig. 24. Case 4. Section of popliteal mass from an area of excessive cellularity showing large hyperchromatic fibroblasts and abundant collagen and portions of a calcified focus. Hematoxylin and eosin. Mag. 90 ×. AFIP Neg. 61—6712

No necrotic tumor was present within the original large cystic cavity. Fatty marrow in the lateral condyle adjacent to the bone was myxomatoid and excessively vascular.

Case 5. AFIP Acc. 88951. A 48-year-old Negro man had for a year noticed some difficulty with the right leg on climbing ladders, and had suffered pain in the leg for some weeks associated with the appearance of a soft mass over the lateral aspect of the right tibia. Roentgenograms demonstrated lesions characteristic of bone marrow infarction in both femora and both tibiae (Fig. 28) and in the phalanges. In addition there was a destructive lesion in the upper portion of the right tibia. Biopsy of the extraosseous mass demonstrated a malignant tumor. Despite irradiation the mass continued to grow, and 2 months after biopsy a midthigh amputation was performed. A month later metastatic growths in the lung were noted, followed by dyspnea, cough, bloody sputum, and pleuritic pain. The patient died 6 months later, 1 year after he first began to complain of pain.

The marrow cavity of the femur contained a tortuous cavity 9 cm long and about 1 cm in diameter, with an extremely dense calcified wall and a softer yellow necrotic material filling

the cavity. Sections (Fig. 29) show the cavity to be filled with infarcted necrotic fat and debris and separated from the surrounding normal marrow by a broad band of dense collagen. In many places this wall was calcified. In some places the residual outline of enlarged dead fat cells could be discerned in the midst of the fibrous wall. Associated with the outer portion of the wall were areas of deep blue-staining, atypical appositional bone that resembled bone produced under ischemic conditions (Fig. 30).

The amputated tibia showed an 8 cm hemorrhagic, necrotic mass on the anterior surface just below the knee. The tibia was filled with light grey glistening tumor in direct continuity with the external mass through a large defect in the anterior tibial cortex.

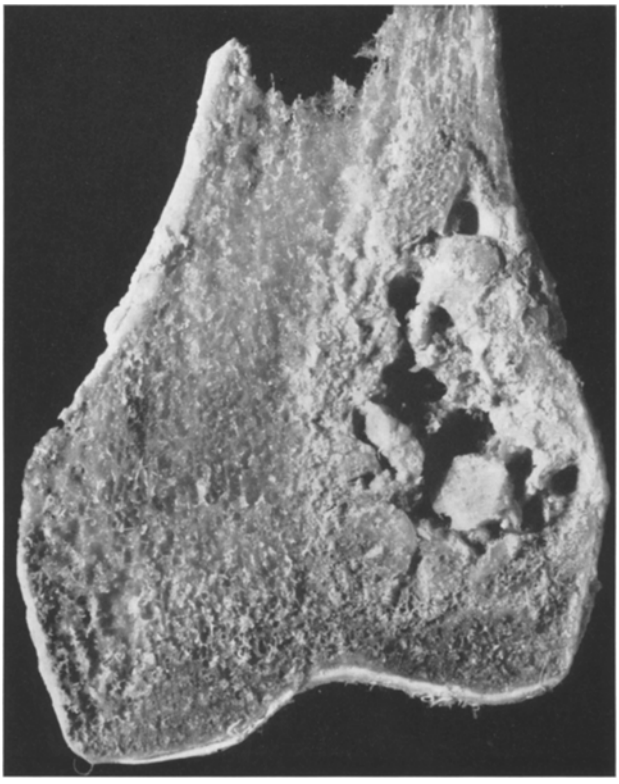

Fig. 25. Case 4. Slab of resected femur showing cavity filled with portion of bone graft and ill-defined cyst wall. AFIP Acc. 991 283

Multiple sections of the tibia showed portions of a cavity wall (Fig. 31) and some remnants of the cavity space embedded in the tumor. The cavity wall was a thick, dense layer of acellular collagen with areas of calcification, was lined by necrotic debris, and was similar to the cavity wall seen in the femoral cyst. Surrounding the cyst was a mass of hyperchromatic cells associated with the production, in various places, of dense collagen, of cartilage, and of osteoid. Where the tumor merged with the adjacent normal marrow, it was made up of very large spindle and polyhedral cells with an abundant, finely vacuolated cytoplasm and frequent bizarre multinucleated giant cells and strap cells with tandem nuclei. The foci of large, vacuolated spindle, polyhedral, and bizarre giant cells all stained heavily for fat with ORO. The cytoplasm of these cells was filled with AMP- and alcian blue-stained material unless subjected to prior digestion with hyaluronidase.

Summary. Multiple bone marrow infarcts were present in a Negro, who on careful questioning stated that he had never engaged in any occupation or activity

that might account for infarction. Sickling tests were not done. These infarcts produced cystic cavities filled with necrotic fat and lined by ghosts of ischemic and calcified fat cells associated with a dense hyalinized and calcified collagen wall. In the tibia, about the remnants of such a cavity was a sarcoma that variously produced collagen, osteoid, and chondroid materials to mimic fibrosarcoma, chondrosarcoma, and osteosarcoma. Arising from the cyst margin and fibrosarcoma, particularly at the periphery, was another pattern of large spindle,

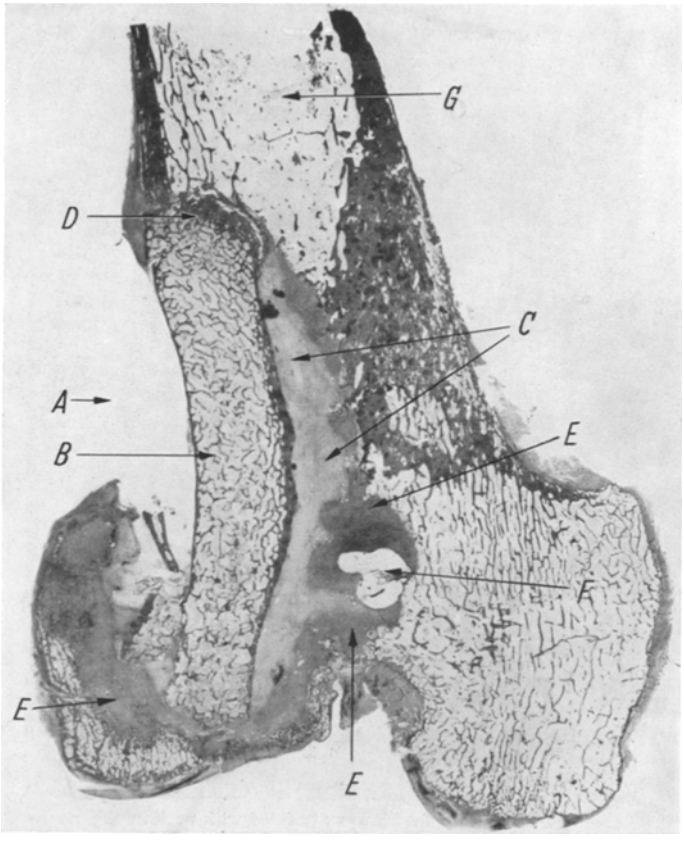

Fig. 26. Case 4. Large section of femur showing (*A*) defect created by removal of popliteal mass; (*B*) iliac bone graft; (*C*) young granulation tissue; (*D*) callus at end of graft; (*E*) neoplastic cyst wall; (*F*) remnant of cyst cavity in neoplastic wall; and (*G*) normal cancellous bone and fatty marrow. Hematoxylin and eosin. AFIP Acc. 991283

polyhedral, and giant cells, all richly vacuolated and filled with fat and hyaluronidase-digestible acid mucopolysaccharide. The extraosseous tumor was extremely anaplastic, with many bizarre cells resembling those of a rhabdomyosarcoma.

Discussion

The first four cases demonstrated the simultaneous presence of a well-defined large cavity, either completely empty or containing some fluid, and a sarcoma of the cyst wall. In each case the cyst was an old lesion and the sarcoma a recent development. Each cyst wall contained reactive bone in the outer layers of the

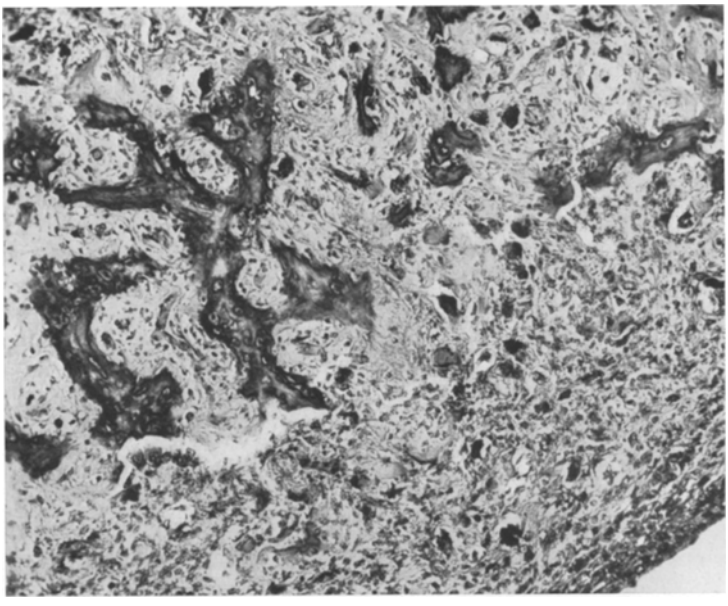

Fig. 27. Case 4. Microscopic pattern of areas "E" and "F" of Fig. 26, showing cavity of residual cyst and large numbers of hyperchromatic cells producing abnormal osteoid and bone. Hematoxylin and eosin. Mag. 90 ×. AFIP Neg. 61—6713

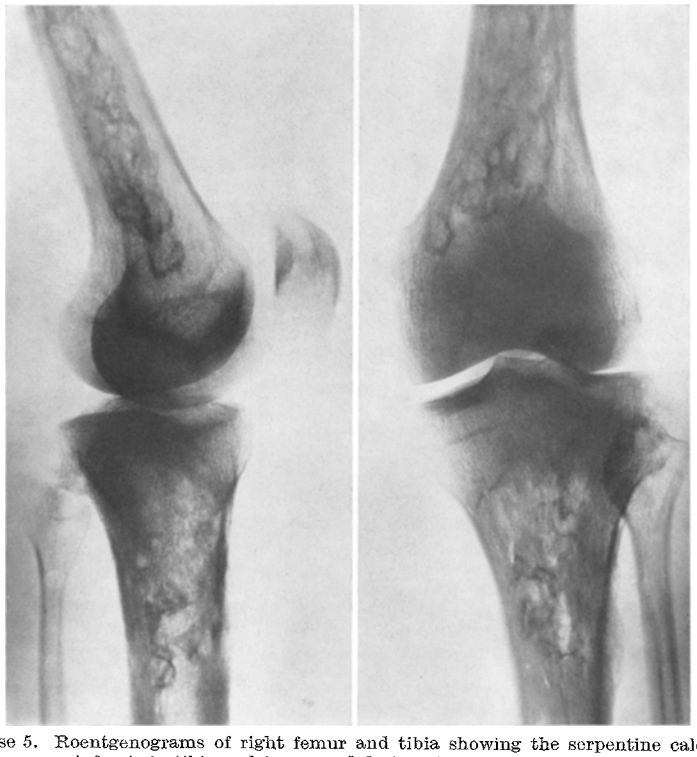

Fig. 28. Case 5. Roentgenograms of right femur and tibia showing the serpentine calcified margin of the bone marrow infarcts in tibia and femur and destruction of the tibial cortex. Hematoxylin and eosin. AFIP Acc. 88951

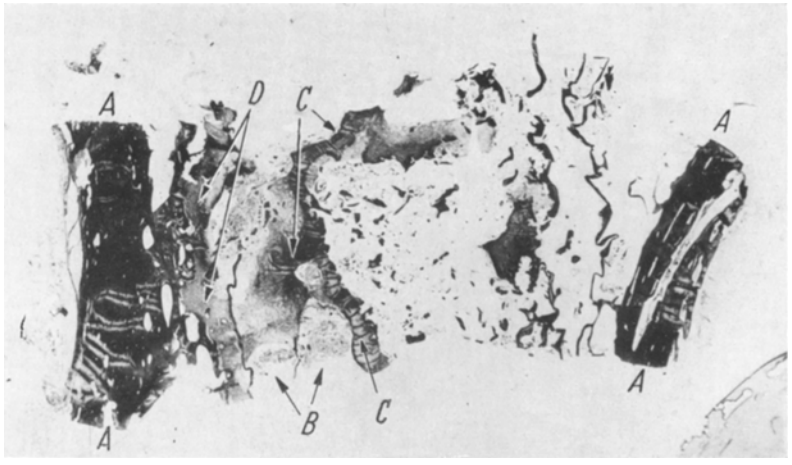

Fig. 29. Case 5. Cross section of femoral shaft in longitudinal plane showing (*A*—*A*) cortex; (*B*) cavity that was filled with oily liquid; (*C*—*C*) calcified margin of cavity; and (*D*) area of ischemic change of adjacent marrow. Hematoxylin and eosin. AFIP Neg. 61—6726

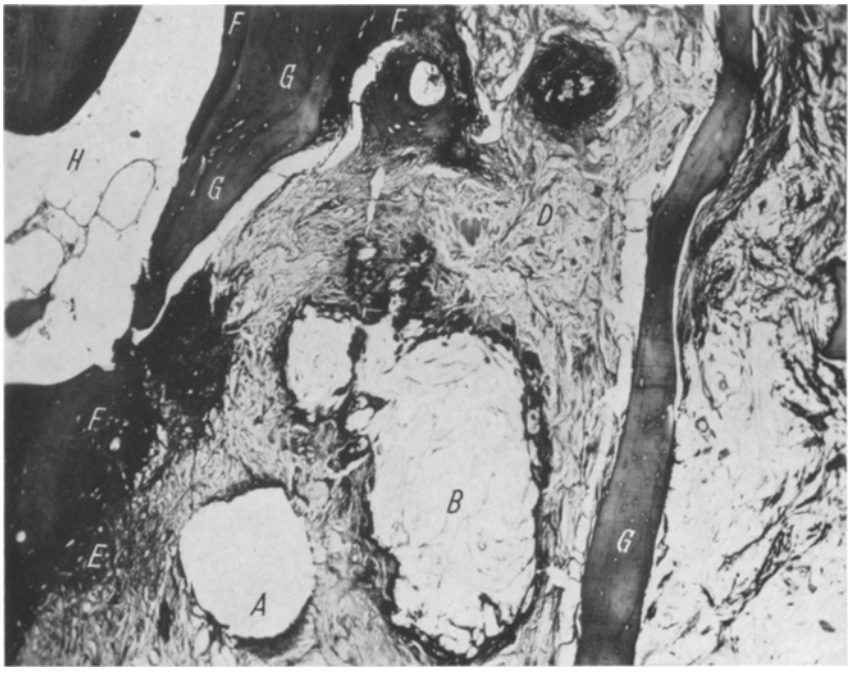

Fig. 30. Case 5. Microscopic pattern of area "*D*" of Fig. 29, showing (*A*) pool of liquefied marrow; (*B*) area of infarcted fat; (*C*) calcified wall about fat infarct; (*D*) fibrous marrow with (*E*) strands of calcified collagen; (*FFF*) woven basophilic appositional bone applied to original trabeculae; (*GG*) trabeculae of cancellous bone devoid of osteocytes; and (*H*) normal fatty marrow. Hematoxylin and eosin. Mag. 50 ×. AFIP Neg. 61—6728

fibrous wall. Fig. 32 is a reconstruction of these four cases based upon multiple sections. The first two cases, involving the humerus, each showed a large cyst at the proximal end, very similar to the one described by VIRCHOW. The cyst wall was a dense, rigid, smooth, glistening fibrous material with ossification of the outer layers. The cavities contained fluid or degenerated myxoid or fatty material, in

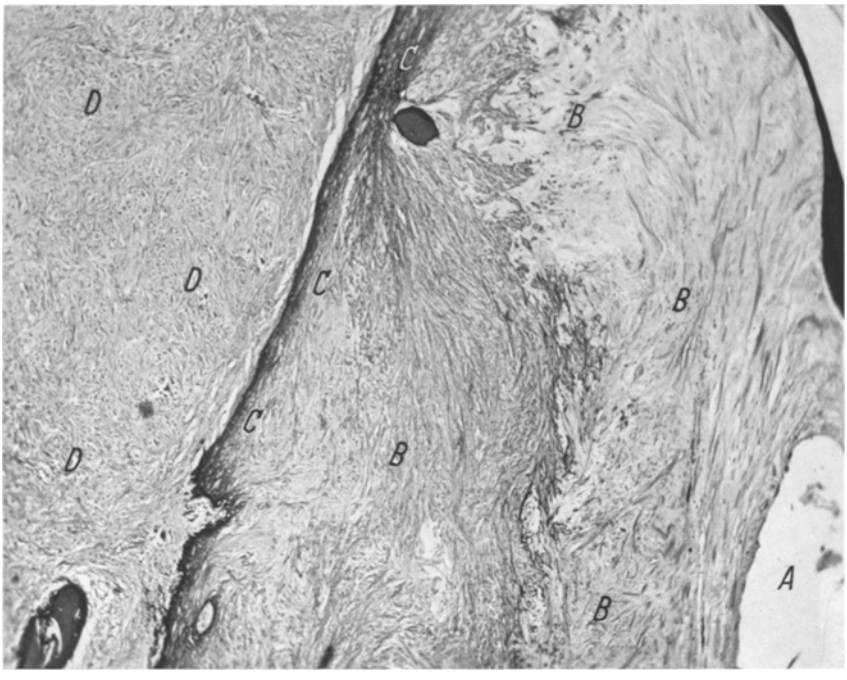

Fig. 31. Case 5. Portion of cyst wall and tumor from tibia showing (*A*) cavity; (*B*) acellular fibrous cyst wall with (*C*) calcification of outer layer; and (*D*) sheets of neoplastic cells. Hematoxylin and eosin. Mag. 50 ×. AFIP Neg. 61—6727

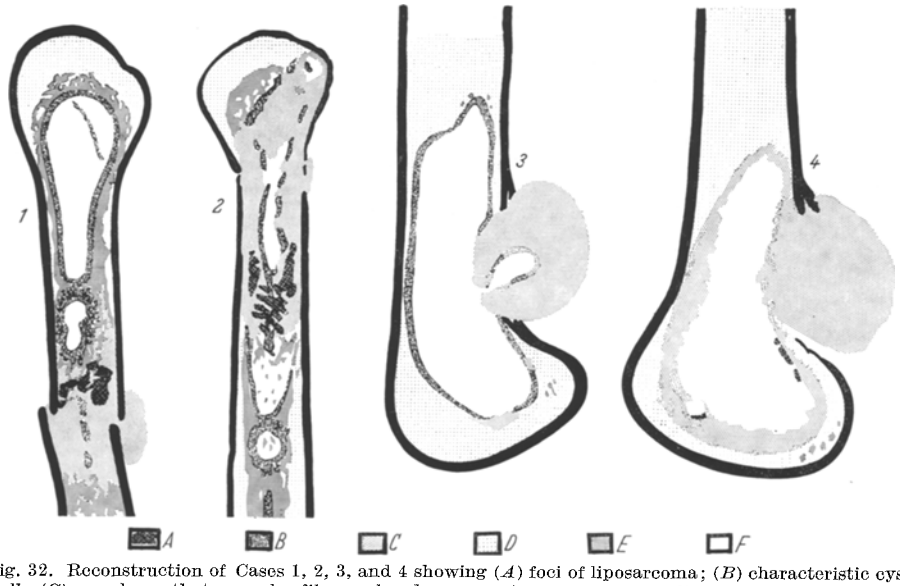

Fig. 32. Reconstruction of Cases 1, 2, 3, and 4 showing (*A*) foci of liposarcoma; (*B*) characteristic cyst wall; (*C*) neoplasm that may be fibro-, chondro-, or osteosarcoma or malignant giant cell tumor; (*D*) normal cancellous bone and bone marrow; (*E*) foci of abnormal fat resembling lipoma; and (*F*) cyst cavity

some places associated with foreign body reaction. In both cases large portions of the cyst and its walls were present through much of the length of the diaphysis, as in VIRCHOW'S case.

In the first case the sarcoma arose around the lower portion of the cyst and extended out into the soft tissue and into the cyst wall. In the second case a similar sarcoma developed around the upper end of the cyst, infiltrated the cortex to the soft tissue, and also penetrated the wall of the cyst. In both cases the marrow surrounding the cyst and its extensions was abnormal: the fat cells were somewhat larger and more variable in shape than normal, with frequent foci of mucoid and delicate fibrillary transformation associated with telangiectatic sinusoidal channels (resembling the pattern of an angioma) and scattered clusters of benign atypical osseous metaplasia. Capping the lower end of the tumor in the first case, and the upper end of the tumor in the second case, was a broad band of such abnormal fat where the fat cells appeared to transform to malignant tumor cells.

In case 3 much of the cavity is lined by a typical old acellular fibrous wall. About the lower end of this cyst were several areas of cellular proliferation that were beginning to invade the wall. At the lower pole this proliferation was sufficient to produce a recognizable nubbin of tumor tissue, while posteriorly a large mass bulged into the cyst and extended out into the popliteal space. A few small foci of abnormal fatty marrow with myxomatous and telangiectatic changes, together with some atypical osteoid trabeculae, were present adjacent to the upper and lower poles of the cyst.

In case 4 the entire lining of the cavity was neoplastic, and no typical benign bone cyst lining could be found, although several areas suggested cyst wall infiltrated with neoplastic cells. The thin outer shell of bone about most of the cyst lining, as described at biopsy, and the empty cavity identify the lesion as a pre-existing bone cyst. The main tumor mass invaded posteriorly into the popliteal area. The fatty marrow of the lateral condyle between the distal end of the cyst and the articular cartilage showed some foci of myxomatous and telangiectatic alteration.

In the first two cases much of the neoplasm was a recognizable spindle cell fibrosarcoma associated with collagen production. In the third case an abundance of blood lakes was associated with malignant giant cell tumor in the main mass, while osteoid production indicated an osteosarcoma pattern in the smaller nubbin. In the fourth case both cartilage and bone production were present — cartilage predominating in the resected material, and osteoid in the amputation material — to produce the patterns of osteosarcoma and chondrosarcoma.

In the first two cases there was an additional pattern characterized by very large spindle cells and polyhedral cells, both notable for an abundance of extensively vacuolated cytoplasm, and a varying population of large, quite bizarre multinucleated giant cells with a vacuolated or xanthomatoid cytoplasm and with globoid bodies. This was essentially the pattern described by DAWSON in her report on liposarcoma of bone. It was these cells that were packed with neutral fats stainable by ORO and SBB, and that stained heavily with AMP unless the material had been pretreated with hyaluronidase. WINSLOW and ENZINGER, in their study of soft tissue tumors, noted the same staining in liposarcomas of soft tissue and in embryonic fat and atrophic fat. Cells that stain heavily for hyaluronidase-digestible AMP and for fat are not found in the usual bone tumors. Fine, granular AMP staining of osteoclasts and of giant cells of osteoclastoma is the only other cytoplasmic AMP staining common in bone, and this is not altered

by hyaluronidase. Extracellular cartilage matrix may stain with AMP. Young cartilage cells may exhibit some staining, but neither the matrix nor cell staining is abolished by hyaluronidase digestion. Fibroblasts, normal fatty marrow, and osteoblasts do not show similar staining. Therefore, this bizarre pattern of unusual cells, abundant in the two humerus cases, is interpreted as the pattern of a liposarcoma.

The relationship to lipoid tissue was further re-enforced by the obviously abnormal fat surrounding these cysts, with a gradual transition from cells of the benign abnormal pattern to malignant tumor. This abnormal fatty tissue may be considered either as a dysplasia or as a lipoma, duplicating the patterns of the fibrolipoma, angiolipoma, and myxolipoma that may be seen in soft tissues.

The criteria for a liposarcoma involve the presence of (a) a lipoma pattern; (b) patterns that are clearly malignant, yet can be related to the lipoma; and (c) distant metastatic growths. DAWSON has described in exquisite detail the only reported case of a tumor primary in bone that meets all these criteria and duplicates the pattern of well-recognized liposarcomas of soft tissue. She noted the fibrosarcoma-like patterns of the extraosseous portion of the tumor and included an excellent review of the literature, with recognition of STEWART'S doubts concerning the cases he described. None of the other adequately reported cases in the literature seem to us free of serious doubt, either as to being primary in bone or as to being liposarcoma. The one exception is the case recently reported by RETZ (which also showed the same staining reactions as reported by WINSLOW and ENZINGER). LICHTENSTEIN'S "mesenchymoma" may be another case. In the cases here reported there were both the lipoma pattern and the liposarcoma pattern (with transitions between the two), and there were metastatic growths present in the lungs on roentgenograms of two cases. None of the metastatic material has been available for study, however, and it is therefore not yet possible to state whether the liposarcoma pattern appears in the metastatic lesions.

In the first four cases there are accordingly a variety of patterns that, if taken out of context, would result in a variety of diagnoses — as indeed occurred at the time of biopsy. PHEMISTER drew attention to this common variability when whole bone sections were studied, and JOHNSON attempted to assign meaning to such variability and to the further change in pattern that may occur when a tumor escapes from the bone into soft tissues. The significance of the variable patterns in these tumors associated with bone cysts is to be found in the nature of the bone cyst.

VIRCHOW carefully described in detail nubbins of abnormal tissue that extended from the cyst wall into the adjacent fatty marrow and pointed out that these nubbins were related to the histogenesis of the cyst. He regarded the cyst as a neoplasm that had liquefied centrally and referred to the myxofibrillary glistening, gristle-like wall and the adjacent nubbins as a peculiar mucoid-fibrillary chondroid substance quite different and distinct from the cartilage of an enchondroma. HASLHOFER and HERZOG presented excellent reviews of the various theories as to the nature and histogenesis of bone cysts, most of which ignore the implication of VIRCHOW'S findings. JAFFE and LICHTENSTEIN, in their study of bone cysts, expressed the belief that the cyst arose out of a dysplastic development of the fatty marrow of the metaphysis. A summary of the most recent study of cysts

by JOHNSON and KINDRED emphasized again the nubbins of abnormal tissue in the fatty marrow surrounding the fibro-osseous cyst wall and delineated four patterns: (a) a fibrillary pattern that may go on to osteoid production; (b) a myxoid pattern that may go on to chondroid production; (c) a telangiectatic angioma-like pattern that may be associated with cellular areas resembling giant cell tumor; and (d) the very frequent presence of areas of abnormal fat that they interpreted as lipomatous in nature. They drew attention to the parallel myxo-, fibro-, and angio-, lipoma patterns seen in soft tissue, and agreed with VIRCHOW'S interpretation of the cyst as a neoplasm that began as a solid lesion. In the sarcomas associated with the first four cases the same range of patterns is present, but in malignant form, viz., fibrosarcoma, chondrosarcoma, osteosarcoma, and malignant giant cell tumor in association with blood lakes. In addition, two tumors had patterns interpreted as liposarcomatous in nature. Thus the sarcomas associated with these four cysts duplicate the range of patterns seen in benign bone cysts.

The fifth case was another example of a sarcoma associated with a cyst, but in this case the cyst had a distinctively different pattern and origin. Fortunately, an intact benign cavity from the femur made it possible to clarify details. While the contents of the cysts were similar to those of the two humerus cases, the wall was more than merely a compacted fibrillary, collagenic structure. The wall contained the ghosts of fat cells with calcification in streaky patterns through these cells and calcification of much of the compacted wall. The general pattern was that of ischemic fat akin to the late stages of pancreatic fat necrosis. Furthermore, immediately adjacent to the wall, appositional bone laid down on the cancellous trabeculae had the pattern of bone produced under ischemic circumstances. The femoral lesion was quite characteristic of a bone marrow infarct, and the feature that distinguished it from the simple bone cyst was the ample evidence of ischemic change in the wall of the cavity.

In the tibia the same cavity contents and ischemic fibrous wall were seen, and in addition, an extensive sarcoma that reproduced the patterns seen in the tumors arising from the simple bone cyst; viz., fibrosarcoma, chondrosarcoma, osteosarcoma, and liposarcoma. FUREY et al. have described two other instances of sarcoma arising in association with bone marrow infarction. One was from a white man, the other from a Negro man. No occupational explanation for infarction was present, and results of sickling tests were not reported. DIGGS has reported typical multiple bone marrow infarcts of the type seen in these cases in association with sickling. It would seem to be of some significance that a cyst produced in this manner, with its attendant abnormalities of the fatty marrow, results in the same display of variable patterns that can be found in the sarcomas arising from simple bone cysts.

The areas of destruction of the antecedent cyst wall by sarcoma and the extension of tumor into the cyst cavity indicate that the sarcoma may eventually fill the cavity and obliterate the cyst wall, leaving little or no evidence of the antecedent cyst. This might account for the seeming rarity of the entity. Future study of appropriate cases will require a careful search for residuals of an old cyst wall in the midst of a seemingly solid tumor, and a careful distinction between a primary simple bone cyst and massive cystic degeneration of a primary neoplasm.

Summary

Four typical, large, hollow simple bone cysts with a sarcoma arising in the cyst wall are described. The range of patterns in the sarcomas duplicated the range of patterns that may be found in the walls of bone cysts. The same variation was present in another sarcoma arising from the wall of a cystic cavity that was produced by bone marrow infarction.

Zusammenfassung

Eingehende makroskopische und histologische Beschreibung von 4 Fällen von sekundärer Sarkomentwicklung auf dem Boden einer einkammerigen Knochencyste. Im Sarkom wird das Strukturprinzip der Knochencyste wiederholt. Die gleichen Veränderungen finden sich in einem 5. Fall von Knochensarkom, welches sich auf dem Boden eines cystisch umgewandelten Knochenmarkinfarktes entwickelt hatte.

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