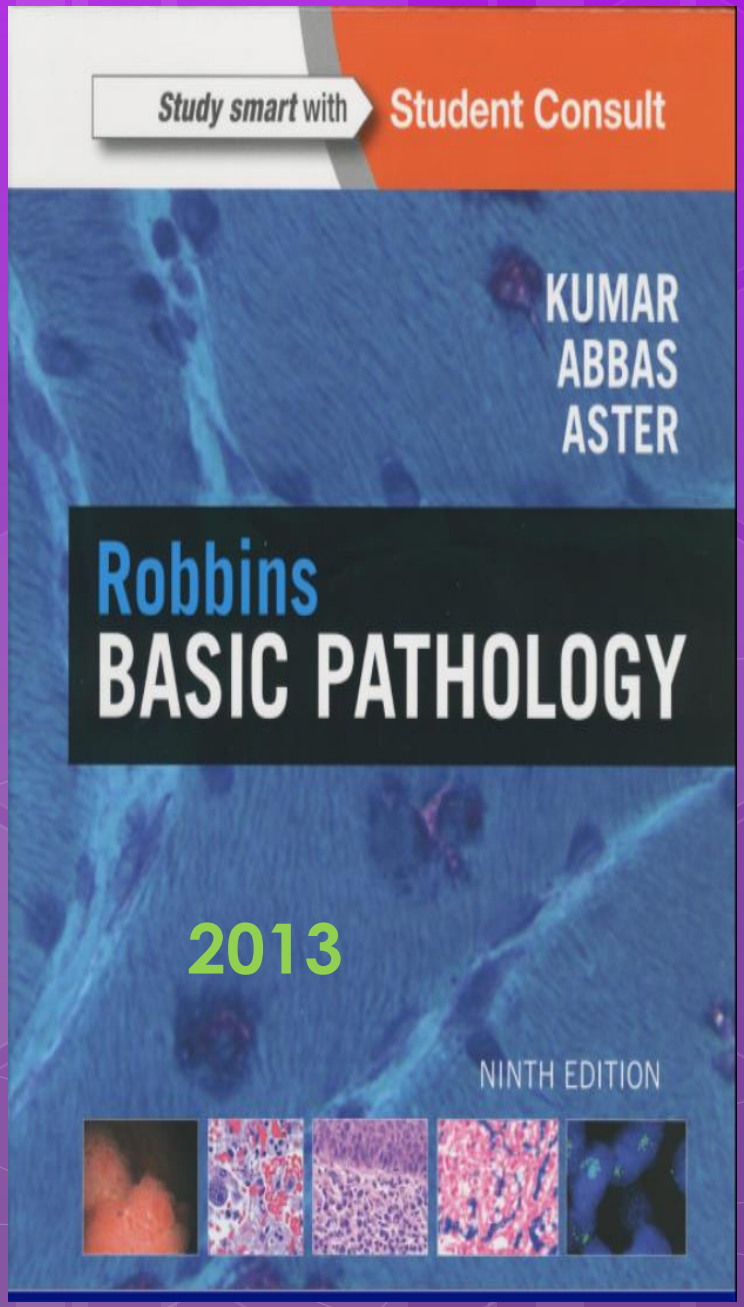
IN THE NAME OF GOD



chapter 20, pp 765-781

BONE PATHOLOGY

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- Rickets and Osteomalacia
- Hyperparathyroidism
- FRACTURES
- OSTEONECROSIS (AVASCULAR NECROSIS)
- OSTEOMYELITIS
- BONE TUMORS
- Bone-Forming Tumors
  - Osteoma
  - Osteoid Osteoma and Osteoblastoma

Rickets and Osteomalacia

- Both rickets and osteomalacia are manifestations of vitamin D deficiency or its abnormal metabolism
- The fundamental defect is an impairment of mineralization and a resultant accumulation of unmineralized matrix.

Rickets and Osteomalacia

- This contrasts with osteoporosis , in which the mineral content of the bone is normal and the total bone mass is decreased.
- Rickets refers to the disorder in children, in which it interferes with the deposition of bone in the growth plates.
- Osteomalacia is the adult counterpart, in which bone formed during remodeling is undermineralized , resulting in predisposition to fractures.

Hyperparathyroidism

parathyroid hormone (PTH) plays a central role in calcium homeostasis through the following effects:

- Osteoclast activation, increasing bone resorption and calcium mobilization.
  - PTH mediates the effect indirectly by increased RAN KL expression on osteoblasts.

Hyperparathyroidism

- Increased resorption of calcium by the renal tubules
- Increased urinary excretion of phosphates
- Increased synthesis of active vitamin D, 1,25(OHh-D, by the kidneys, which in turn enhances calcium absorption from the gut and mobilizes bone calcium by inducing RANKL on osteoblasts .

Hyperparathyroidism

- The net result of the actions of PTH is an elevation in serum calcium, which, under normal circumstances, inhibits further PTH production.
- However, excessive or inappropriate levels of PTH Can result from autonomous parathyroid secretion (primary hyperparathyroidism) or can occur in the setting of underlying renal disease (secondary hyperparathyroidism).

- In either setting, hyperparathyroidism leads to significant skeletal changes related to unabated osteoclast activity.
- The entire skeleton is a ffected, although some sites Can be more severely affected than others.

- PTH is directly responsible for the bone changes seen in primary hyperparathyroidism, but additional influences contribute to the development of bone disease in secondary hyperparathyroidism.

- In chronic renal insufficiency there is inadequate 1,25-(OHh-D synthesis, which ultimately affects gastrointestinal calcium absorption.
- The hyperphosphatemia of renal failure also suppresses renal α-hydroxylase, further impairing vitamin D synthesis; additional influences include metabolic acidosis and aluminum deposition in bone.

- As bone mass decreases, affected patients are increasingly susceptible to fractures,bone deformation, and joint problems.
- Fortunate!y, a reduction in PTH levels to normal can completely reverse the bone changes.

MORPHOLOGY

- The hallmark of PTH excess is increased osteoclastic activity, with bone resorption.
- Cortical and trabecular bone are diminished and replaced by loose connective tissue.
- Bone resorption is especially pronounced in the subperiosteal regions and produces characteristic radiographic changes, best seen along the radial aspect of the middle phalanges of the second and third fingers.

- Microscopically, there are increased numbers of osteoclasts boring into the centers of bony trabeculae (dissecting osteitis) and expanding haversian canals (cortical cutting cones) (Fig. 20-6, A).

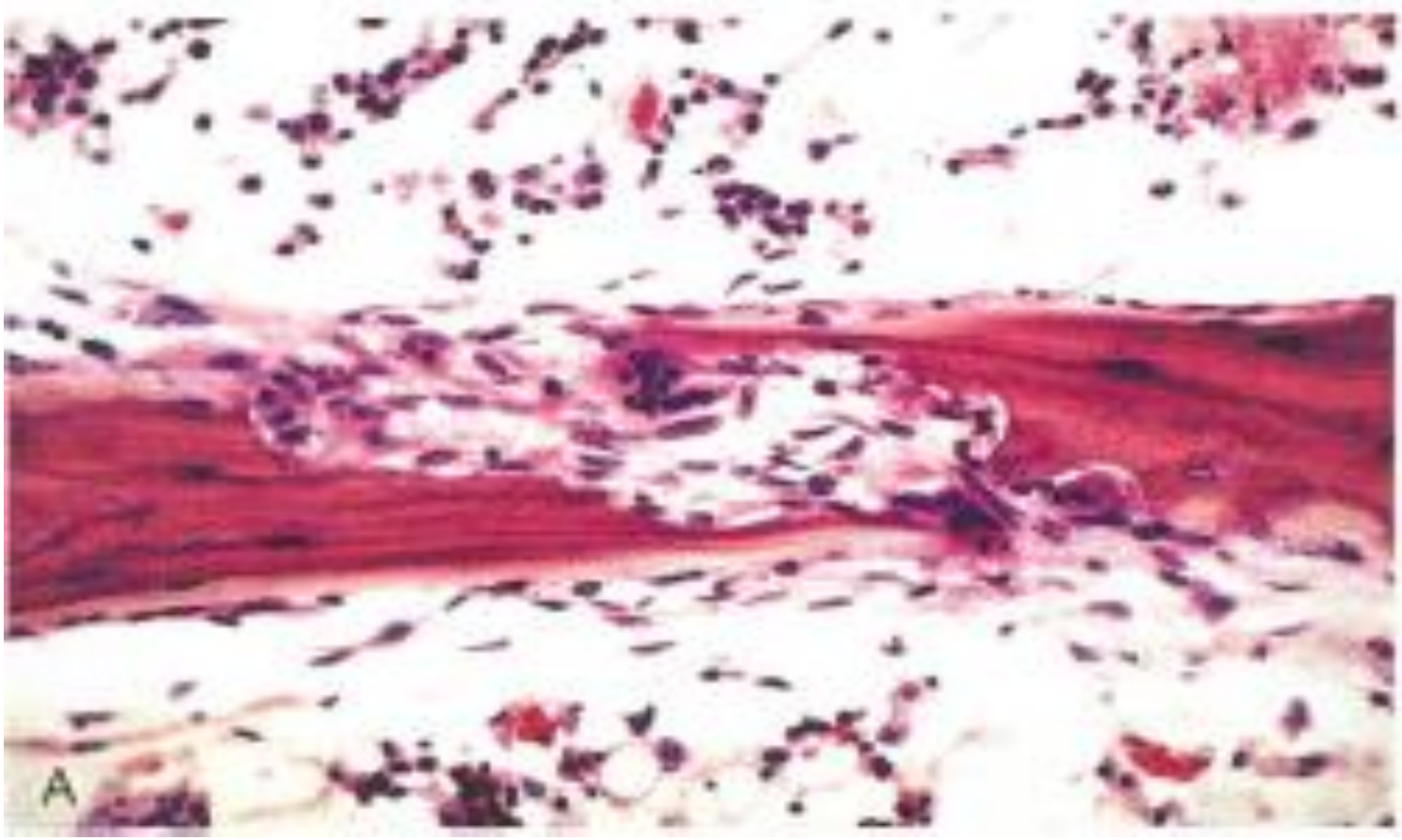


Figure 20-6 Bone manifestations of hyperparathyroidism.
A, Osteoclasts gnawing into and disrupting lamellar bone.

- The marrow space contains increased amounts of loose fibrovascular tissue.
- Hemosiderin deposits are present, reflecting episodes of hemorrhage resulting from microfractures of the weakened bone.
- In some instances,collections of osteoclasts, reactive giant cells, and hemorrhagic debris form a distinct mass termed a brown tumor of hyperparathyroidism (Fig. 20-6, B).

Figure 20-6 Bone manifestations of hyperparathyroidism.
B, Resected rib, with expansile cystic mass (so-called brown tumor).

- Cystic change iscommon in such lesions (hence the name osteitis fibrosa cystica), which can be confused with primary bone

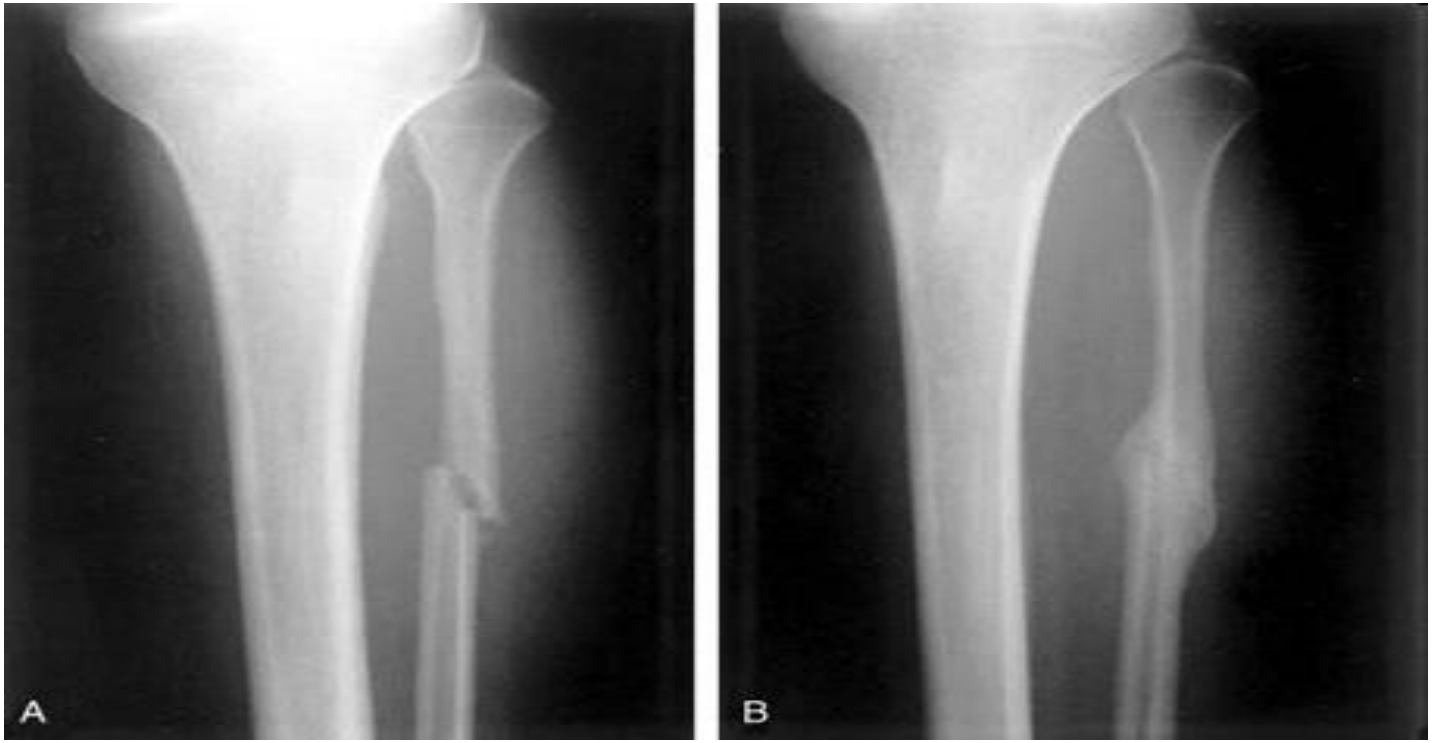
FRACTURES

- Fractures rank among the most common pathologic conditions of bone.
  - Complete or incomplete
  - Closed, in which the overlying tissue is intact,
  - Compound, in which the fracture extends into the overlying skin
  - Cominuted, in which the bone is splintered

- Displaced, in which the fractured bone is not aligned .
- If the break occurs at the site of previous disease (a bone cyst, a malignant tumor, or a brown tumor associated with elevated PTH), it is termed a pathologic fracture.

- A stress fracture develops slowly over time as a collection of microfractures associated with increased physical activity, especially with new repetitive mechanical loads on bone (as sustained in military bootcamp activities).
- In all cases, the repair of a fracture is a highly regulated process that involves overlapping stages:

FRACTURES



- The trauma of the bone fracture ruptures associated blood vessels; the resulting blood clot creates a fibrin mesh scaffold to recruit inflammatory cells, fibroblasts, and endothelium.

- Degranulated platelets and maraudina inflammatory cells subsequently release a host of cytokines (platelet-derived growth factor, fibroblast growth factor) that activate bone progenitor cells, and within a week, the involved tissue is primed for new matrix synthesis.

- This soft tissue callus can hold the ends of the fractured bone in apposition but is noncalcified and cannot support weight bearing.

- Bone progenitors in the periosteum and medullary cavity deposit new foci of woven bone, and activated mesenchymal cells at the fracture site differentiate into cartilage-synthesizing chondroblasts.
- In uncomplicated fractures, this early repair process peaks within 2 to 3 weeks.

- The newly formed cartilage acts as a nidus for endochondral ossification, recapitulating the process of bone formation in epiphyseal growth plates.
- This connects the cortices and trabeculae in the juxtaposed bones.

- With ossification, the fractured ends are bridged by a bony callus.

- Although excess fibrous tissue, cartilage, and bone are produced in the early callus, subsequent weight bearing leads to remodeling of the callus from nonstressed sites; at the same time there is fortification of regions that support greater loads.
- This process restores the original size, shape, and integrity of the bone.

- The healing of a fracture can be disrupted by many factors:
- Displaced and comminuted fractures frequently result in some deformity; devitalized fragments of splintered bone require resorption, which delays healing, enlarges the callus, and requires inordinately long periods of remodeling and may never completely normalize.

- Inadequate immobilization permits constant movement at the fracture site, so that the normal constituents of callus do not form.
- In such instances, the healing site is composed mainly of fibrous tissue and cartilage, perpetuating the instability and resulting in delayed union and nonunion.

- Too much motion along the fracture gap (as in nonunion) causes the central portion of the callus to undergo cystic degeneration; the luminal surface can actually become lined by synovial-type cells, creating a false joint, or pseudoarthrosis.

- In the setting of a nonunion or pseudoarthrosis, normal healing can be achieved only if the interposed soft tissues are removed and the fracture site is stabilized

- Infection (a risk in comminuted and open fractures) is a serious obstacle to fracture healing.
- The infection must be eradicated before successful bone reunion and remodeling can occur.
- •.

- Bone repair obviously will be impaired in the setting of inadequate levels of calcium or phosphorus, vitamin deficiencies, systemic infection, diabetes, or vascular insufficiency

- With uncomplicated fractures in children and young adults, practically perfect reconstitution is the norm.
- When fractures occur in older age groups or in abnormal bones (osteoporotic bone), repair frequently is less than optimal without orthopedic intervention.

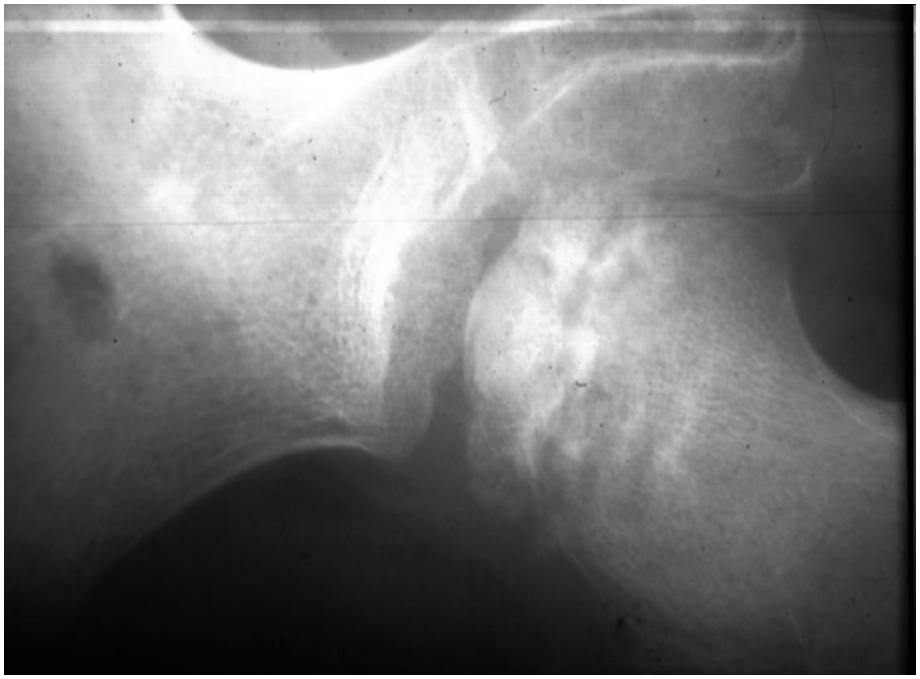
OSTEONECROSIS (AVASCULAR NECROSIS)

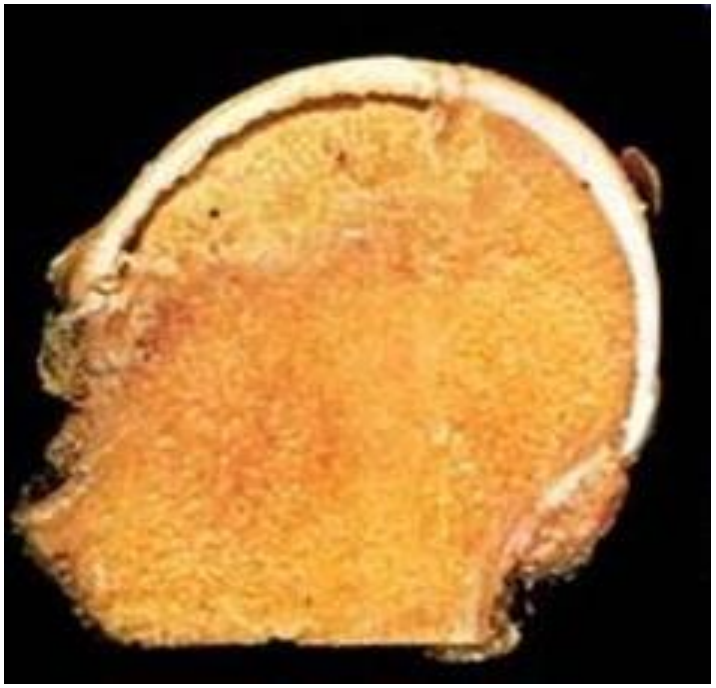
- Ischemic necrosis with resultant bone infarction occurs relatively frequently.
- Mechanisms contributing to bone ischemia include
  - Vascular compression or disruption (e.g., after a fracture)
  - Steroid administration
  - Thromboembolic disease (nitrogen bubbles in caisson disease)
  - Primary vessel disease (vasculitis)
  - Sickle cell crisis
- Most cases of bone necrosis are due to fracture or occur after corticosteroid use, but in many instances the etiology is unknown.

MORPHOLOGY

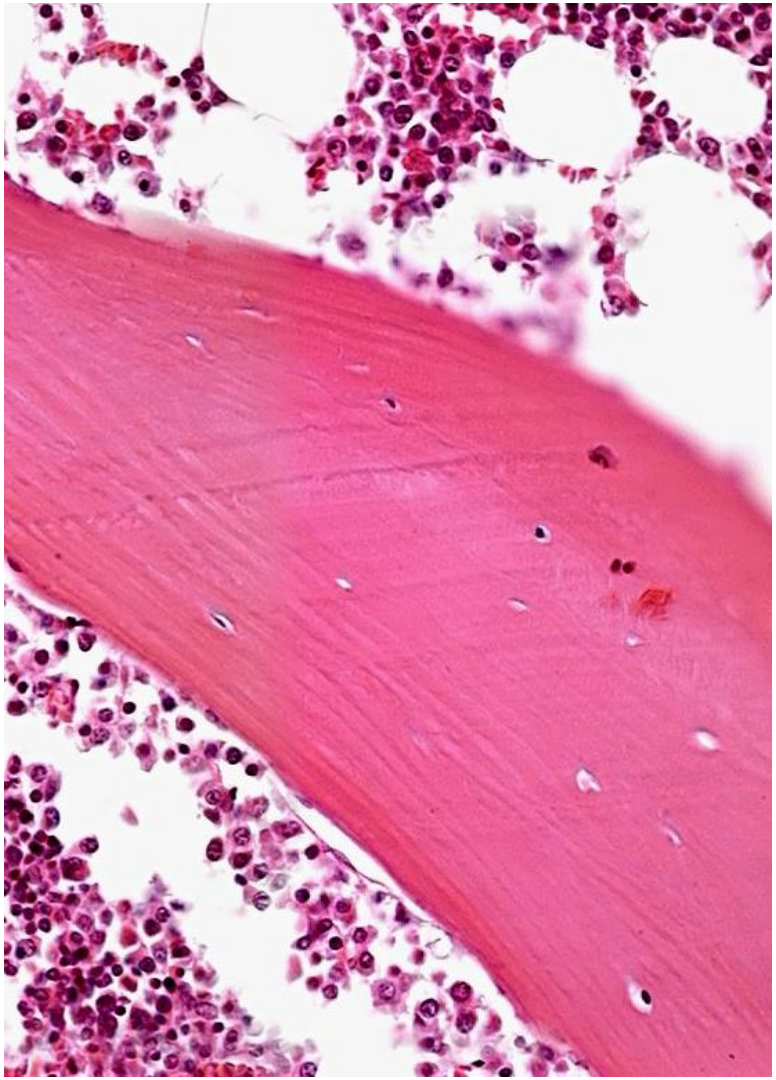
- The pathologic features of bone necrosis are the same regardless of cause.
- Dead bone with empty lacunae is interspersed with areas of fat necrosis and insoluble calcium soaps.

OSTEONECROSIS

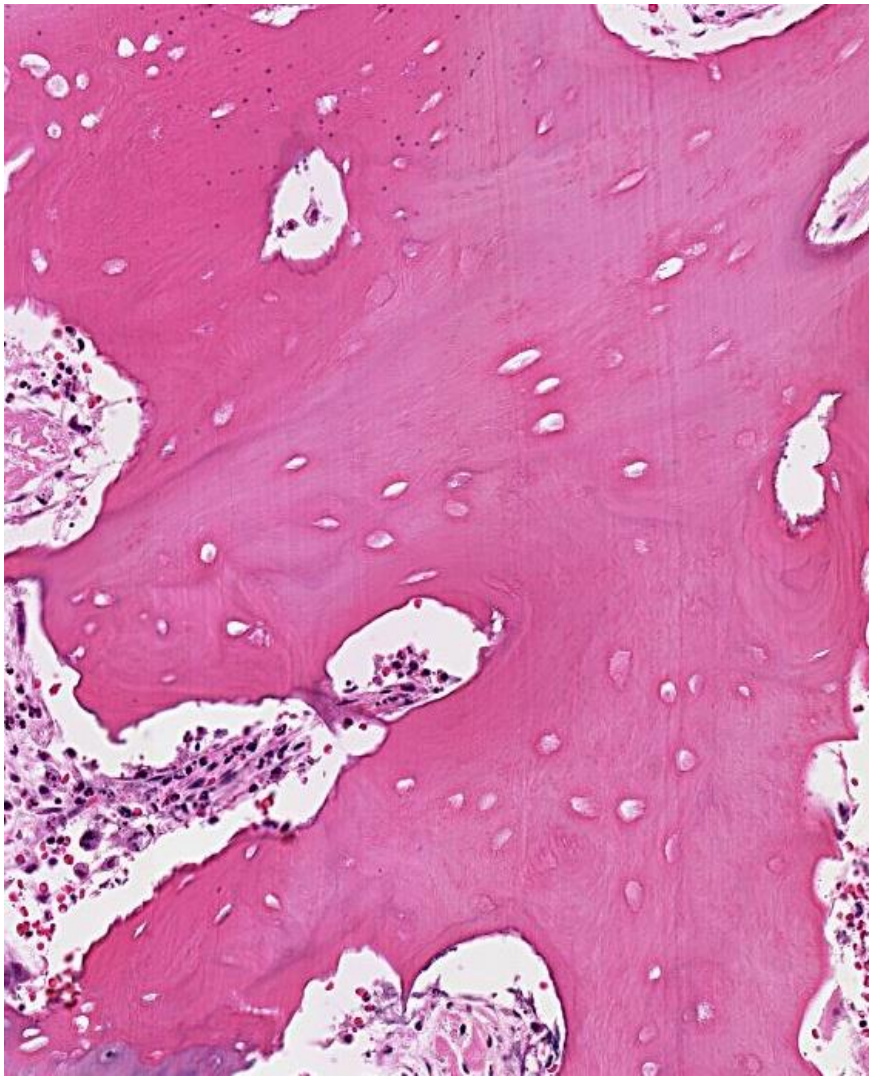




NORMAL



OSTEONECROSIS



- The cortex usually is not affected, because of collateral blood supply; in subchondral infarcts, the overlying articular cartilage also remains viable because the synovial fluid can provide nutritive support.

- With time, osteoclasts can resorb some of the necrotic bony trabeculae; any dead bone fragments that remain act as scaffolding for new bone formation, a process called creeping substitution.

Clinical Course

- Symptoms depend on the size and location of injury. Subchondral infarcts initially present with pain during physical activity that becomes more persistent with time.
- Medullary infarcts usually are silent unless large in size (as may occur with Gaucher disease, caisson disease, or sickle cell disease).

Clinical Course

- Medullary infarcts usually are stable, but subchondral infarcts often collapse and may lead to severe osteoarthritis.
- Roughly 50,000 joint replacements are performed each year in the United States to treat the consequences of osteonecrosis.

OSTEOMYELITIS

- Osteomyelitis is defined as inflammation of bone and marrow, but in common use it is virtually synonymous with infection.
- Osteomyelitis can be secondary to systemic infection but more frequently occurs as a primary isolated focus of disease; it can be an acute process or a chronic, debilitating illness.

- Although any microorganism can cause osteomyelitis, the most common etiologic agents are pyogenic bacteria and Mycobacterium tuberculosis.

Pyogenic Osteomyelitis

- Most cases of acute osteomyelitis are caused by bacteria.
- The offending organisms reach the bone by one of three routes:
- (1) hematogenous dissemination (most common);
- (2) extension from an infection in adjacent joint or soft tissue;
- (3) traumatic implantation after compound fractures or orthopedic procedures.

- Overall, Staphylococcus aureus is the most frequent causative organism;
- its propensity to infect bone may be related to the expression of surface proteins that allow adhesion to bone matrix.

- Escherichia coli and group B streptococci are important causes of acute osteomyelitis in neonates, and Salmonella is an especially common pathogen in persons with sickle cell disease.

- Mixed bacterial infections, including anaerobes, typically are responsible for osteomyelitis secondary to bone trauma.
- In as many as 50% of cases, no organisms can be isolated.

MORPHOLOGY

- The morphologic changes in osteomyelitis depend on the chronicity and location of the infection.
- Causal bacteria proliferate. inducing an acute inflammatory reaction. with consequent cell death.
- Entrapped bone rapidly becomes necrotic; this non-viable bone is called a sequestrum.

MORPHOLOGY

- Bacteria and inflammation can percolate throughout the haversian systems to reach the periosteum.

- In children, the periosteum is loosely attached to the cortex; therefore. sizable subperiosteal abscesses can form and extend for long distances along the bone surface.

- Lifting of the periosteum further impairs the blood supply to the affected region. and both suppurative and ischemic injury can cause segmental bone necrosis.

- Rupture of the periosteum can lead to abscess formation in the surrounding soft tissue that may lead to a draining sinus. Sometimes the sequestrum crumbles , releasing fragments that pass through the sinus tract.

- In infants (and uncommonly in adults). epiphyseal infection can spread into the adjoining joint to produce suppurative arthritis.
- sometimes with extensive destruction of the articular cartilage and permanent disability.

- An analogous process can involve vertebrae, with an infection destroying intervertebral discs and spreading into adjacent vertebrae.
- After the first week of infection. chronic inflammatory cells become more numerous.
- Leukocyte cytokine release stimulates osteoclastic bone resorption. fibrous tissue ingrowth. and bone formation in the periphery.

- Reactive woven or lamellar bone can be deposited; when it forms a shell of living tissue around a sequestrum, it is called an involucrum (Fig.20-7).
- Viable organisms can persist in the sequestrum for years after the original infection.

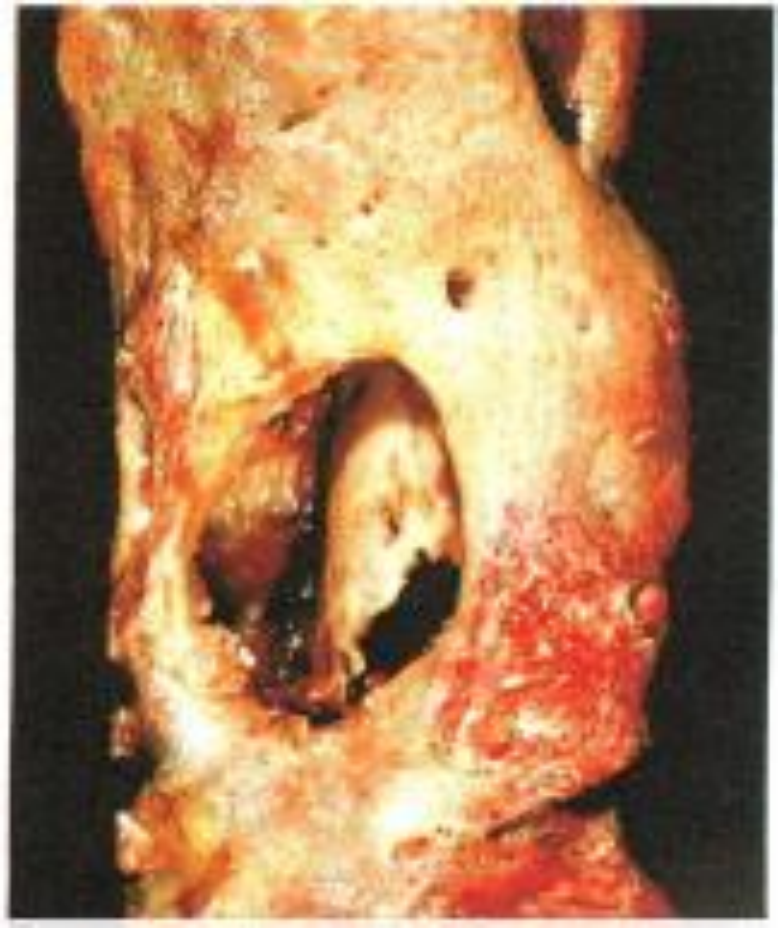
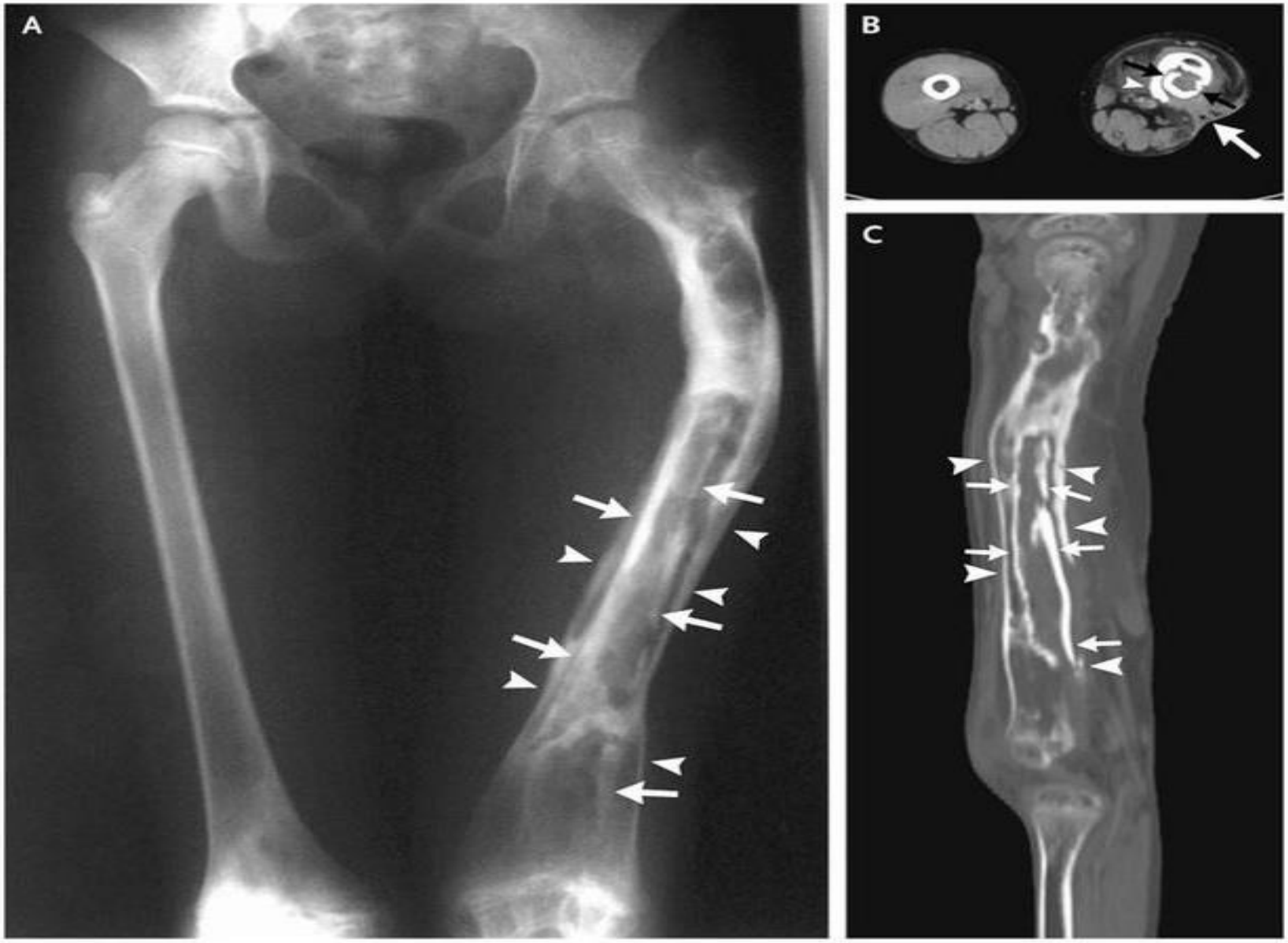


Figure 20-7 Resected femur from a patient with chronic osteomyelitis.Necrotic bone (the sequestrum) visible in the center of a draining sinus tract is surrounded by a rim of new bone (the involucrum).



Sequestrum (dead bone, arrowheads) Involucrum (new bone, full arrows)

Clinical Features

- Osteomyelitis classically manifests as an acute systemic illness, with malaise, fever, leukocytosis, and throbbing pain over the affected region.
- Symptoms also can be subtle,with only unexplained fever, particularly in infants, or only localized pain in the adult.

- The diagnosis is suggested by characteristic radiologic findings: a destructive lytic focus surrounded by edema and a sclerotic rim.
- In many untreated cases, blood cultures are positive, but biopsy and bone cultures are usually required to identify the pathogen.

- A combination of antibiotics and surgical drainage usually is curative, but up to a quarter of cases do not resolve and persist as chronic infections.
- Chronicity may develop with delay in diagnosis, extensive bone necrosis, abbreviated antibiotic therapy, inadequate surgical debridement, and/or weakened host defenses.

- Besides occasional acute flareups, chronic osteomyelitis also may be complicated by pathologic fracture, secondary amyloidosis, endocarditis,sepsis, development of squamous cell carcinoma if the infection creates a sinus tract, and rarely osteosarcoma.

Tuberculous Osteomyelitis

- Mycobacterial infection of bone has long been a problem in developing countries; with the resurgence of tuberculosis (due to immigration patterns and increasing numbers of immunocompromised persons) it is becoming an importan disease in other countries as well.

- Bone infection complicates an estimated 1% to 3% of cases of pulmonary tuberculosis.
- The organisms usually reach the bone through the bloodstream, although direct spread from a contiguous focus of infection (from mediastinal nodes to the vertebrae) also can occur.

- With hematogenous spread, long bones and vertebrae are favored sites.
- The lesions often are solitary but can be multifocal, particularly in patients with an underlying immunodeficiency.
- Because the tubercle bacillus is microaerophilic, the synovium, with its higher oxygen pressures, is a common site of initial infection.

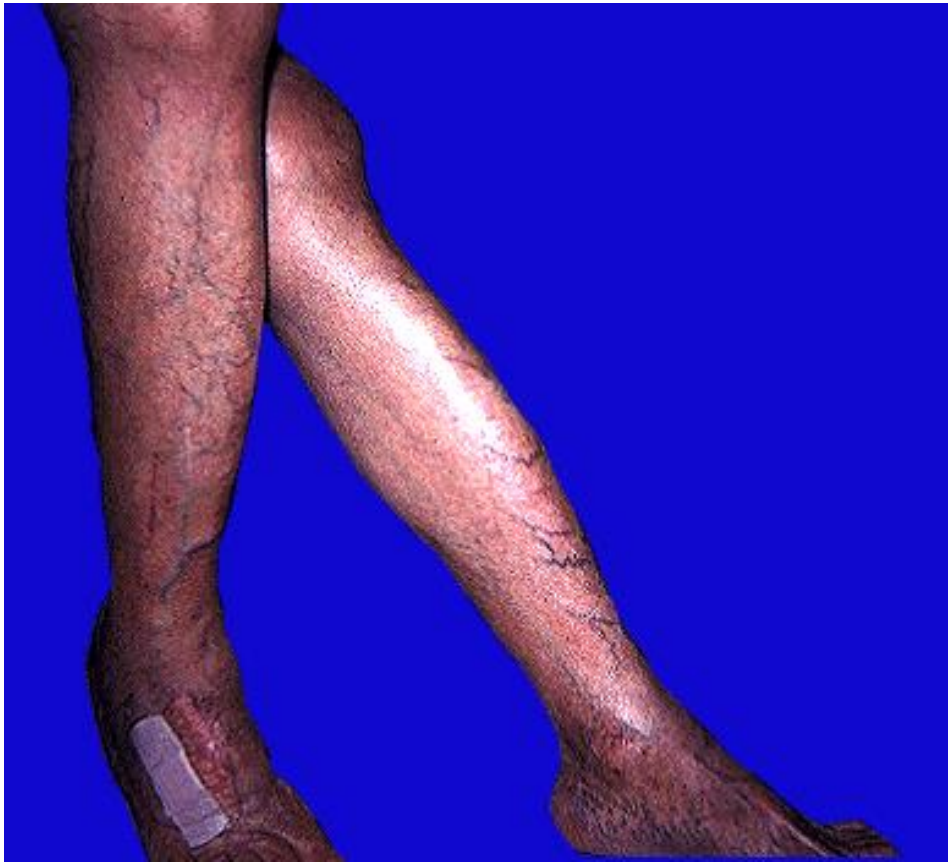
- The infection then spreads to the adjacent epiphysis, where it elicits typical granulomatous inflammation with caseous necrosis and extensive bone destruction.
- Tuberculosis of the vertebral bodies is a clinically serious form of osteomyelitis.
- Infection at this site causes vertebral deformity, collapse, and posterior displacement (Pott disease), leading to neurologic deficits.

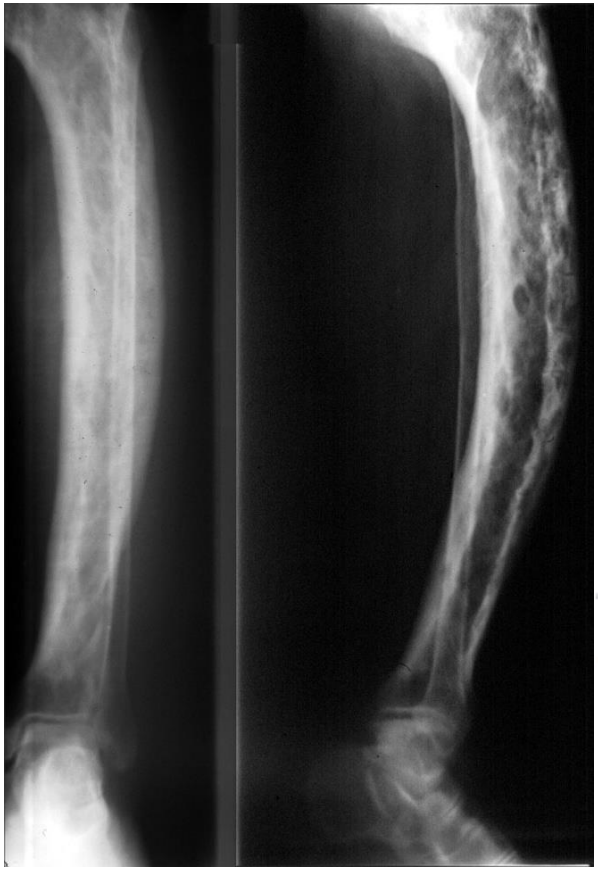
POTT's DISEASE

Syphilis

CONGENITAL

TERTIARY, “SABRE” shins



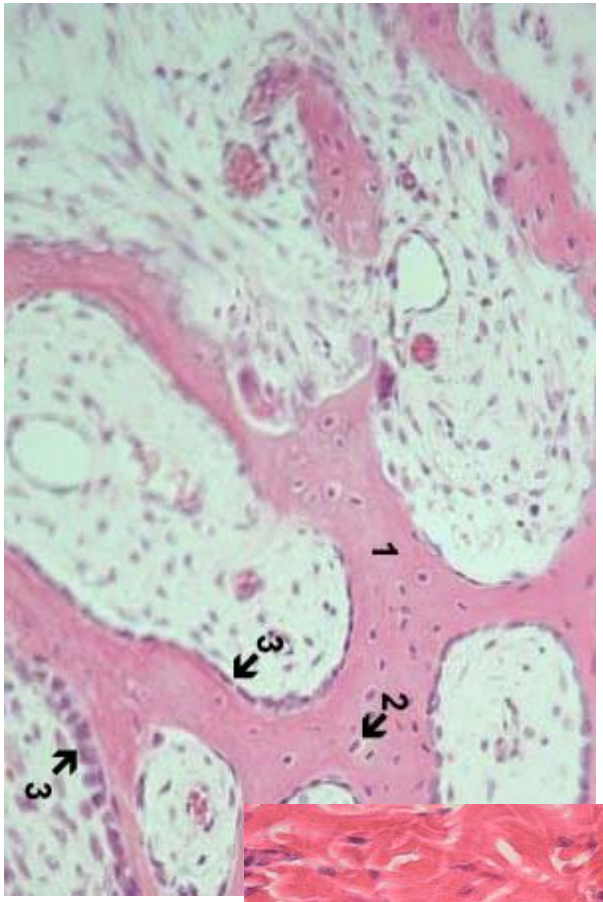


- Spinal deformities due to Pott disease afflicted several men of letters (including Alexander Pope and William Henley) and likely served as the inspiration for Victor Hugo's Hunchback of Notre Dame.
- Extension of the infection to the adjacent soft tissues with the development of psoas muscle abscesses is fairly common.

BONE TUMORS

- Primary bone tumors are considerably less common than bone metastases from other primary sites; metastatic disease is discussed at the end of this section.
- Primary bone tumors exhibit great morphologic diversity and clinical behaviors -from benign to aggressively malignant.

- Most are classified according to the normal cell counterpart and line of differentiation; Table 20-2 lists the salient features of the most common primary bone neoplasms, excluding multiple myeloma and other hematopoietic tumors,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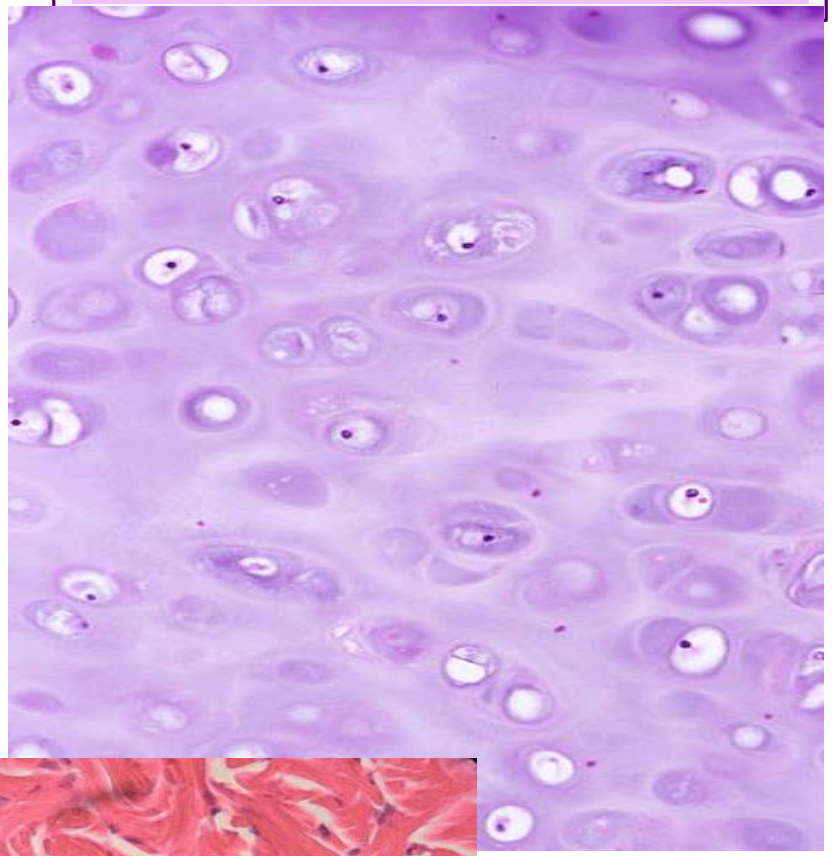


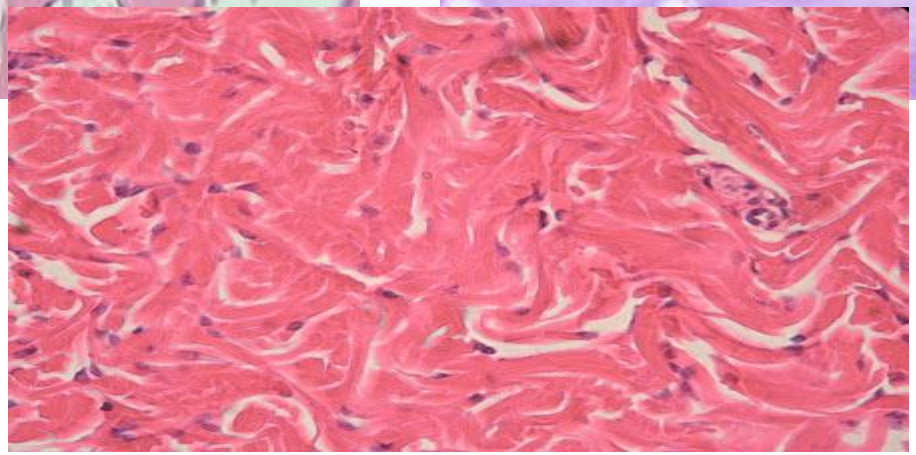


Table 20–2 Tumors of Bone

Tumor Type	Common Locations	Age (yr)	Morphology
Bone-Forming			
Benign			
Osteoma	Facial bones, skull	40–50	Exophytic growths attached to bone surface; histologically similar to normal bone
Osteoid osteoma	Metaphysis of femur and tibia	10–20	Cortical tumors, characterized by pain; histologic pattern consisting of interlacing trabeculae of woven bone
Osteoblastoma	Vertebral column	10–20	Arise in vertebral transverse and spinous processes; histologically similar to osteoid osteoma
Malignant			
Primary osteosarcoma	Metaphysis of distal femur, proximal tibia, and humerus	10–20	Grow outward, lifting periosteum, and inward to the medullary cavity; microscopy shows malignant cells forming osteoid; cartilage also may be present
Secondary osteosarcoma	Femur, humerus, pelvis	>40	Complications of polyostotic Paget disease; histologically similar to primary osteosarcoma
Cartilaginous			
Benign			
Osteochondroma	Metaphysis of long tubular bones	10–30	Bony excrescences with a cartilaginous cap; may be solitary or multiple and hereditary
Enchondroma	Small bones of hands and feet	30–50	Well-circumscribed single tumors resembling normal cartilage; arise within medullary cavity of bone; uncommonly multiple and hereditary
Malignant			
Chondrosarcoma	Bones of shoulder, pelvis, proximal femur, and ribs	40–60	Arise within medullary cavity and erode cortex; microscopy shows well-differentiated cartilage-like or anaplastic features
Miscellaneous			
Giant cell tumor (usually benign)	Epiphysis of long bone	20–40	Lytic lesions that erode cortex; microscopy shows osteoclast-like giant cells and round to spindle-shaped mononuclear cells; most are benign
Ewing sarcoma	Diaphysis and metaphysis	10–20	Arise in medullary cavity; microscopy shows sheets of small round cells that contain glycogen; aggressive neoplasm

- Overall, matrix-producing and fibrous tumors are the most common, and among the benign tumors, osteochondroma and fibrous cortical defect occur most frequently.
- Osteosarcoma is the most common primary bone cancer, followed by chondrosarcoma and Ewing sarcoma.

- Benign tumors greatly outnumber their malignant counterparts, particularly before the age of 40 years; bone tumors in elderly persons are much more likely to be malignant.

- Most bone tumors develop during the first several decades of life and have a propensity to originate in the long bones of the extremities.
- Nevertheless, specific tumor types target certain age groups and anatomic sites; these associations are often helpful in arriving at the correct diagnosis.

- For instance, most osteosarcomas occur during adolescence, with half arising around the knee, either in the distal femur or proximal tibia.
- By contrast, chondrosarcomas tend to develop during mid- to late adulthood and involve the trunk, limb girdles, and proximal long bones.

- Most bone tumors arise without any previous known cause.
- Nevertheless, genetic syndromes (e.g., Li-Fraumeni and retinoblastoma syndromes) are associated with osteosarcomas, as are (rarely) bone infarcts, chronic osteomyelitis, Paget disease, irradiation, and use of metal orthopedic devices.

- In terms of clinical presentation, benign lesions frequently are asymptomatic and are detected as incidental findings. Others produce pain or a slowly growing mass.
- Occasionally, a pathologic fracture is the first manifestation.
- Radiologic imaging is critical in the evaluation of bone tumors; however, biopsy and histologic study and, in som cases, molecular tests are necessary for diagnosis.

Bone-Forming Tumors

- The tumor cells in the following neoplasms all produce bone that usually is woven and variably mineralized.

Osteoma

- Osteomas are benign lesions most commonly encountered in the head and neck, including the paranasal sinuses, but which can occur elsewhere as well.
- They typically presentin middle age as solitary, slowly growing, hard, exophytic masses on a bone surface.
- Multiple lesions are a feature of Gardner syndrome, a hereditary condition discussed later.

- On histologic examination, osteomas recapitulate corticaltype bone and are composed of a mixture of woven and lamellar bone.
- Although they may cause local mechanical problems (obstruction of a sinus cavity) and cosmetic deformities, they are not locally aggressive and do not undergo malignant transformation.

Osteoid Osteoma and Osteoblastoma

- Osteoid osteolllas and osteoblastomas are benign neoplasms with very similar histologic features.
- Both lesions typically appear during the teenage years and 20s,
- with a male predilection (2: 1 for osteoid osteomas).
- They are distinguished from each other primarily by their size and clinical presentation.

- Osteoid osteomas arise most often beneath the periosteum or within the cortex in the proximal femur and tibia or posterior spinal elements and are by definition less than 2 cm in diameter, whereas osteoblastomas are larger.

- Localized pain, most severe at night, is an almost universal complaint with osteoid osteomas, and usually is relieved by aspirin.
- Osteoblastomas arise most often in the vertebral column; they also cause pain, although it often is more difficult to localize and is not responsive to aspirin.

- Local excision is the treatment of choice; incompletely resected lesions can recur.
- Malignant transformation is rare unless the lesion is treated with irradiation.

MORPHOLOGY

- On gross inspection, both lesions are round-to-oval masses of hemorrhagic, gritty-appearing tan tissue.
- A rim of sclerotic bone is present at the edge of both types of tumors; however, it is much more conspicuous in osteoid osteomas.
- On microscopic examination, both neoplasms are composed of interlacing trabeculae of woven bone surrounded by osteoblasts (Fig. 20-8).
- The intervening stroma is loose, vascular connective tissue containing variable numbers of giant cells.

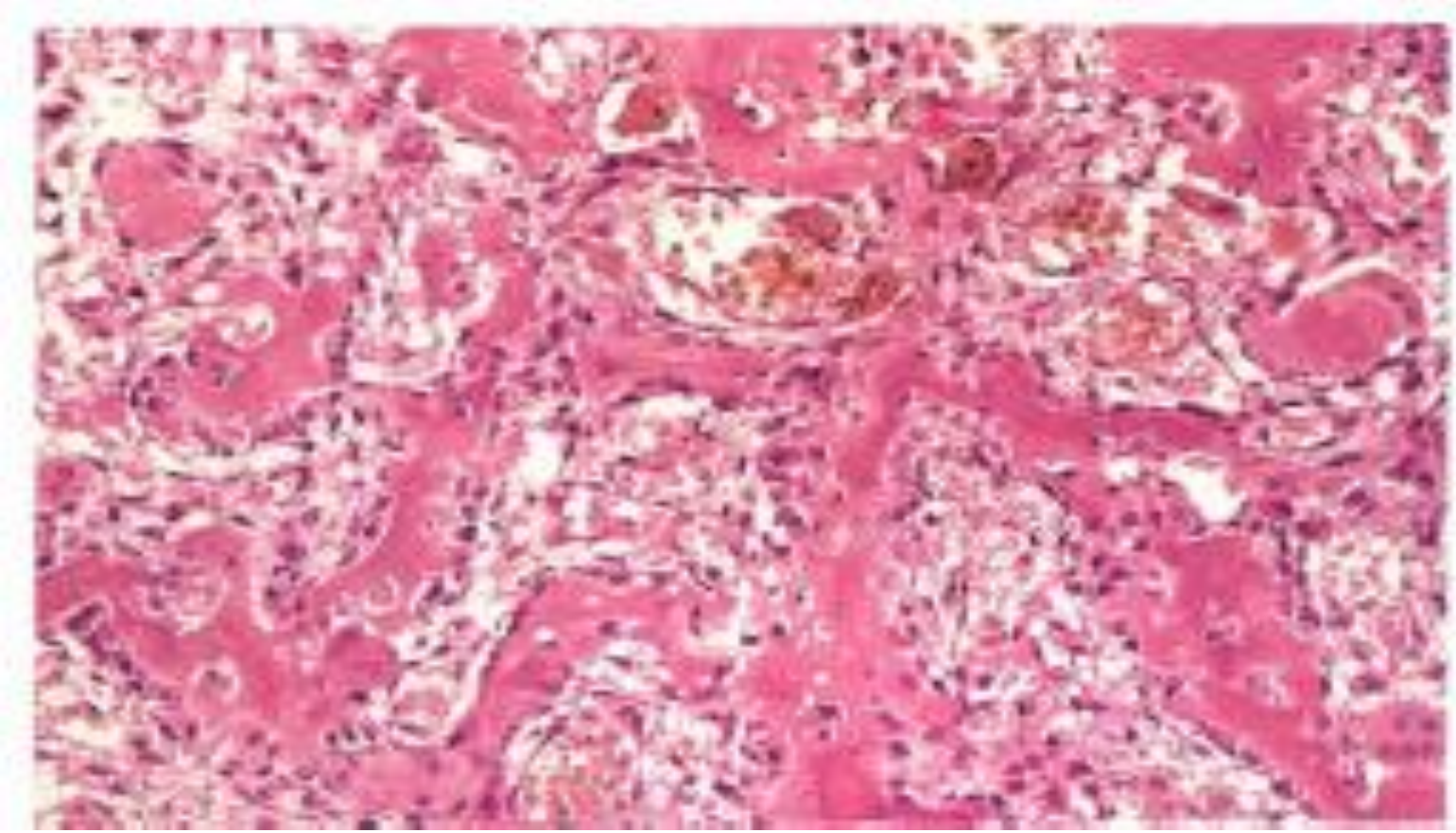
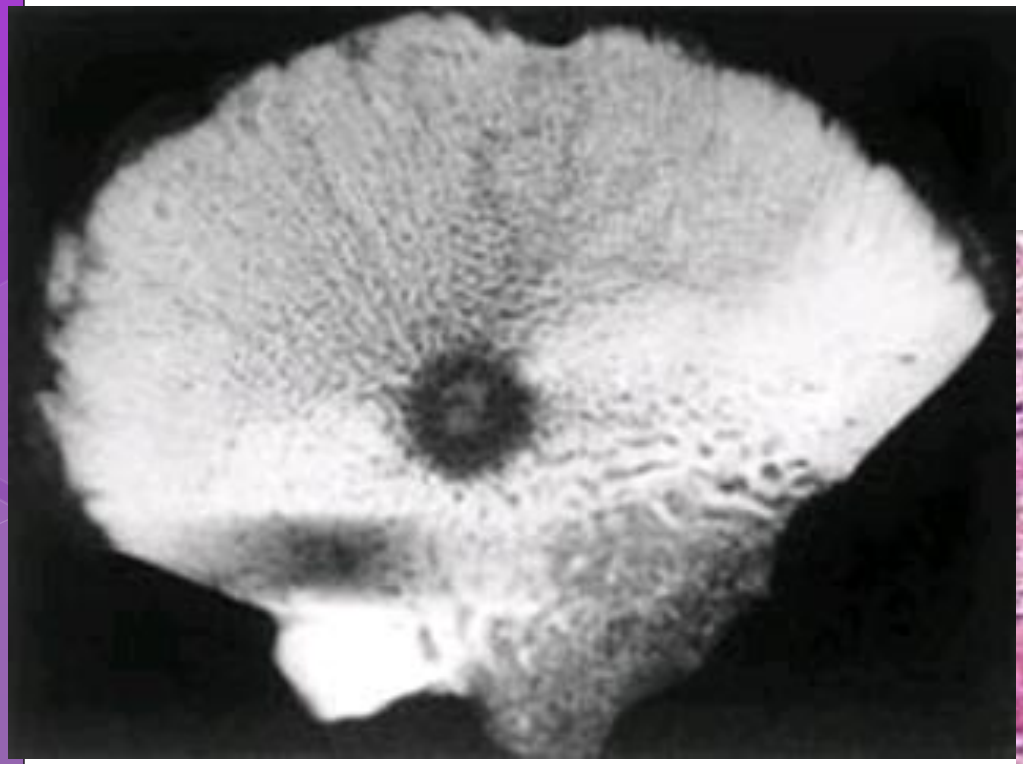
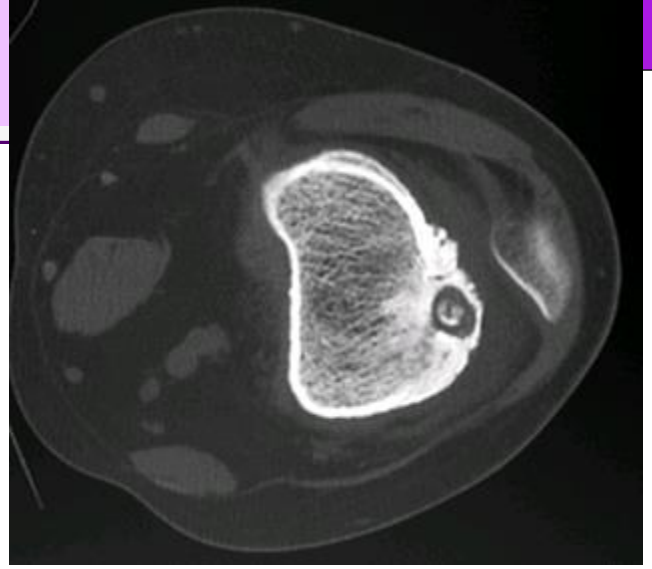
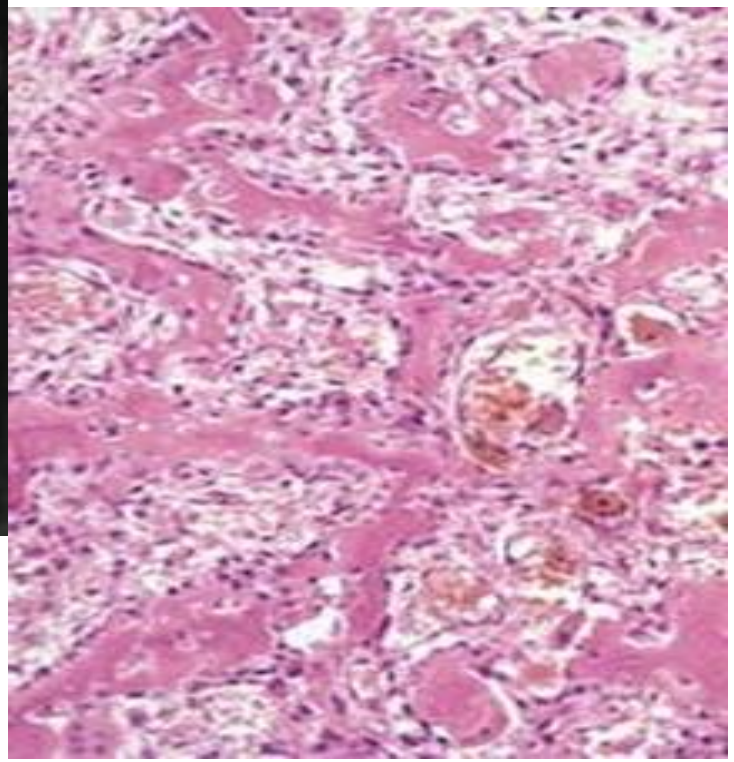


Figure 20-8 Osteoid osteoma showing randomly oriented trabeculae of woven bone rimmed by prominent osteoblasts. The intertrabecular Spaces are filled by vascularloose connective tissue.

NIDUS

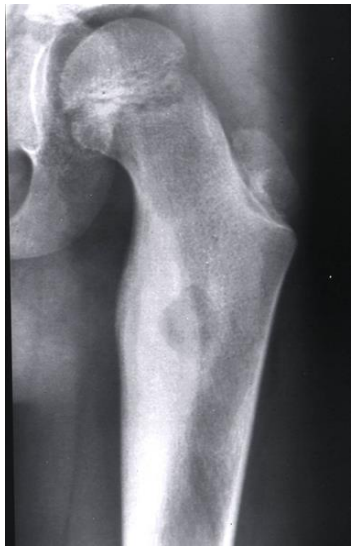


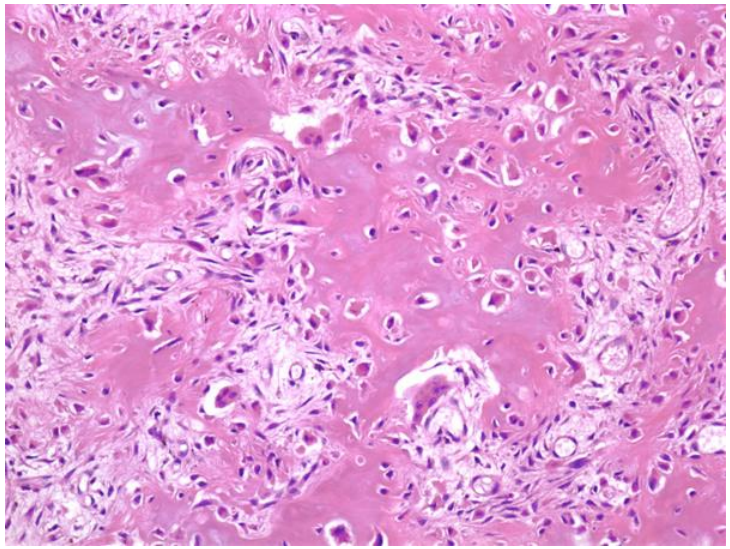




OSTEOBLASTOMA

- AXIAL SKELETON, i.e., SPINE
- NO nidus
- NO bony reaction
- NOT relieved by aspirin





ANY QUESTION