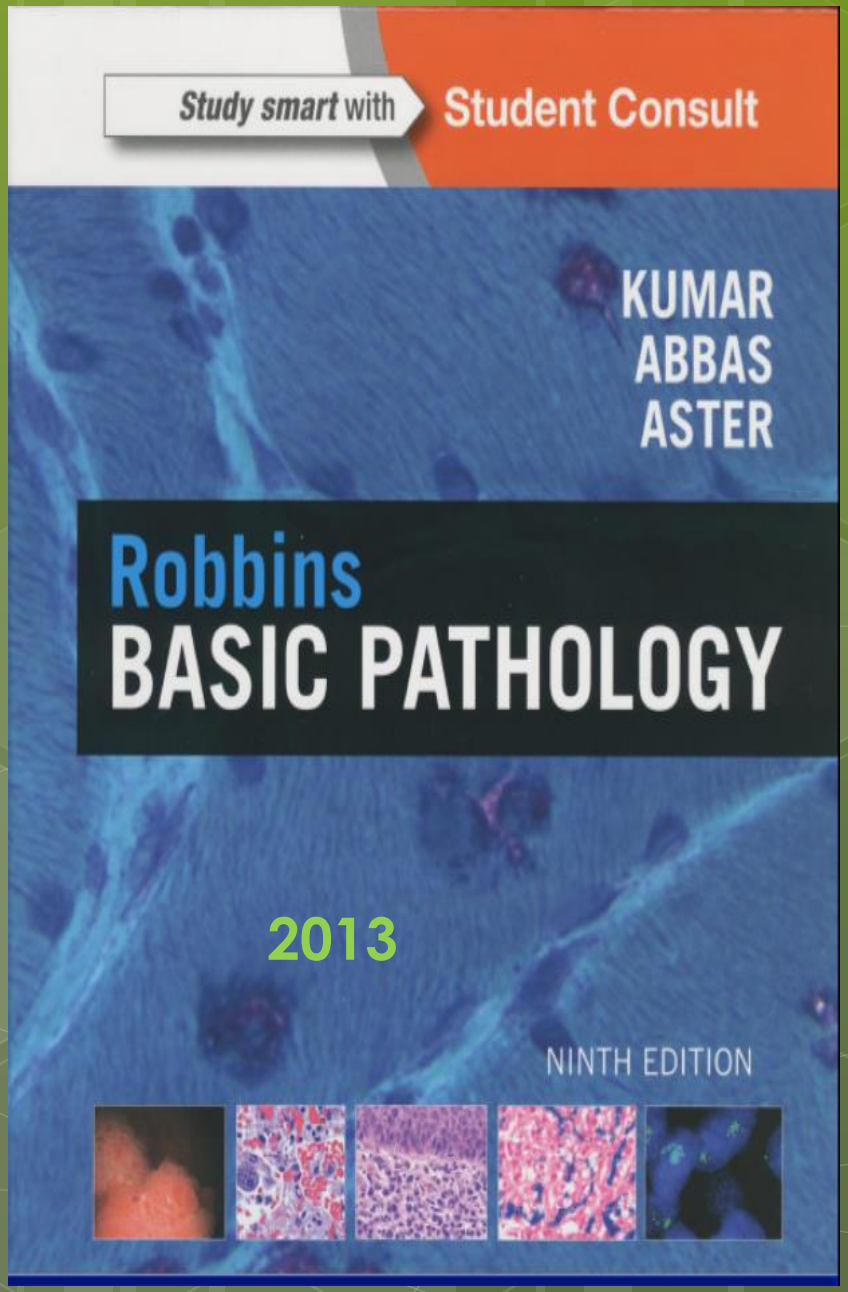
IN THE NAME OF GOD



chapter 20, pp 765-781

BONE PATHOLOGY

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BONES

- Congenital Disorders of Bone and Cartilage
  - Osteogenesis Imperfecta
  - Achondroplasia and Thanatophoric Dwarfism
  - Osteopetrosis
- Acquired Diseases of Bone
  - Osteoporosis
  - Paget Disease (Osteitis Deformans)
  - Rickets and Osteomalacia
  - Hyperparathyroidism
- Fractures
- Osteonecrosis (Avascular Necrosis)
- Osteomyelitis
  - Pyogenic Osteomyelitis
  - Tuberculous Osteomyelitis
- Bone Tumors
  - Bone-Forming Tumors
  - Cartilage-Forming Tumors
  - Fibrous and Fibroosseous Tumors
  - Miscellaneous Bone Tumors

BONES

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- The skeletal system is composed of 206 bones that vary in size and shape and are interconnected by a variety of joints that allow for a wide range of movement and promote structural stability.

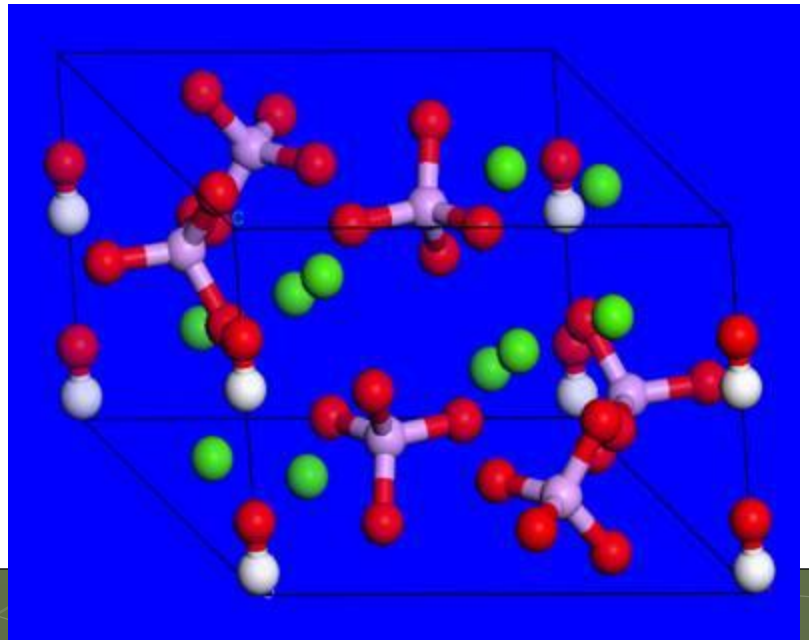
- Bones are composed of a unique type of mineralized connective tissue that undergoes mineralization with a distinctive admixture of organic matrix (35%) and inorganic elements (65%).
- The inorganic mineral component consists mainly of calcium hydroxyapatite [Ca10 (P04)6,(OH)2].

Minerals (IN-organic) of BONE

HYDROXY-APATITE

$Ca_5(PO_4)_3(OH)$

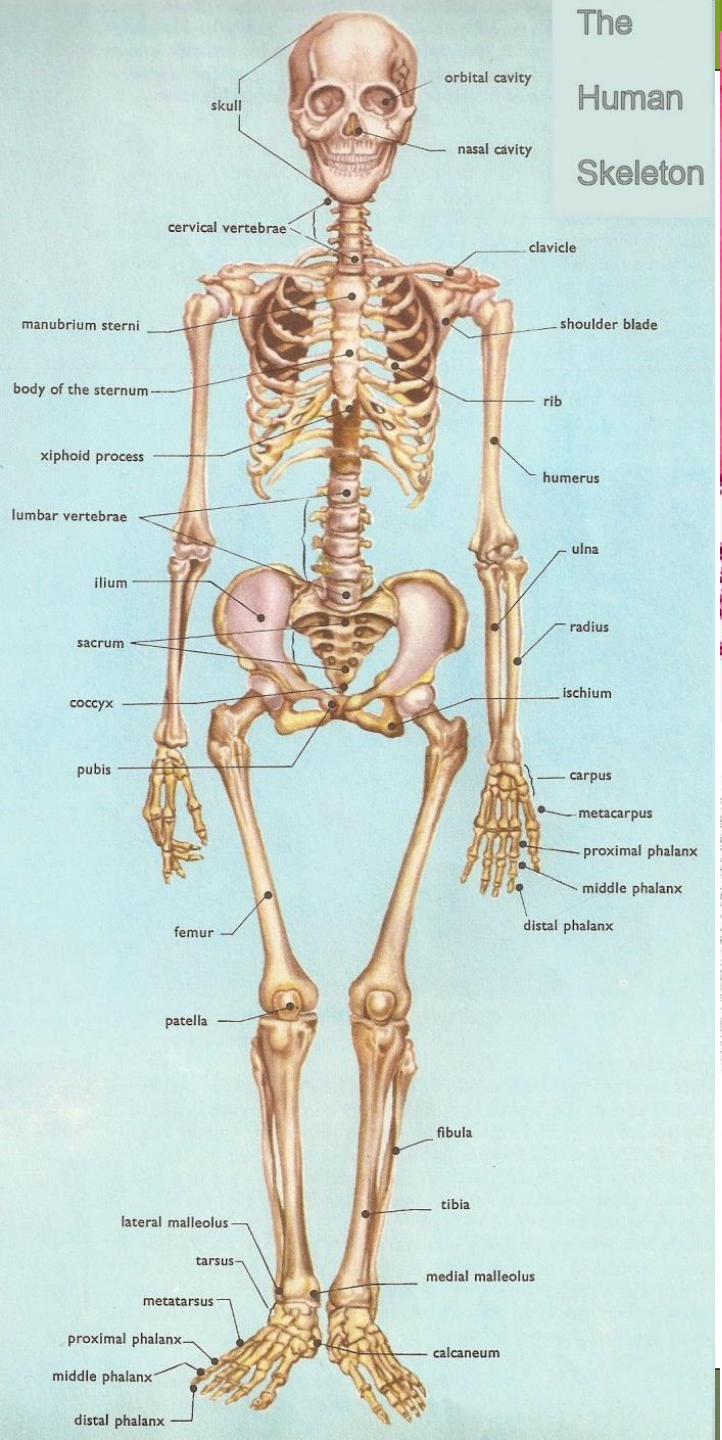
$Ca_{10}(PO_4)_6(OH)_2$

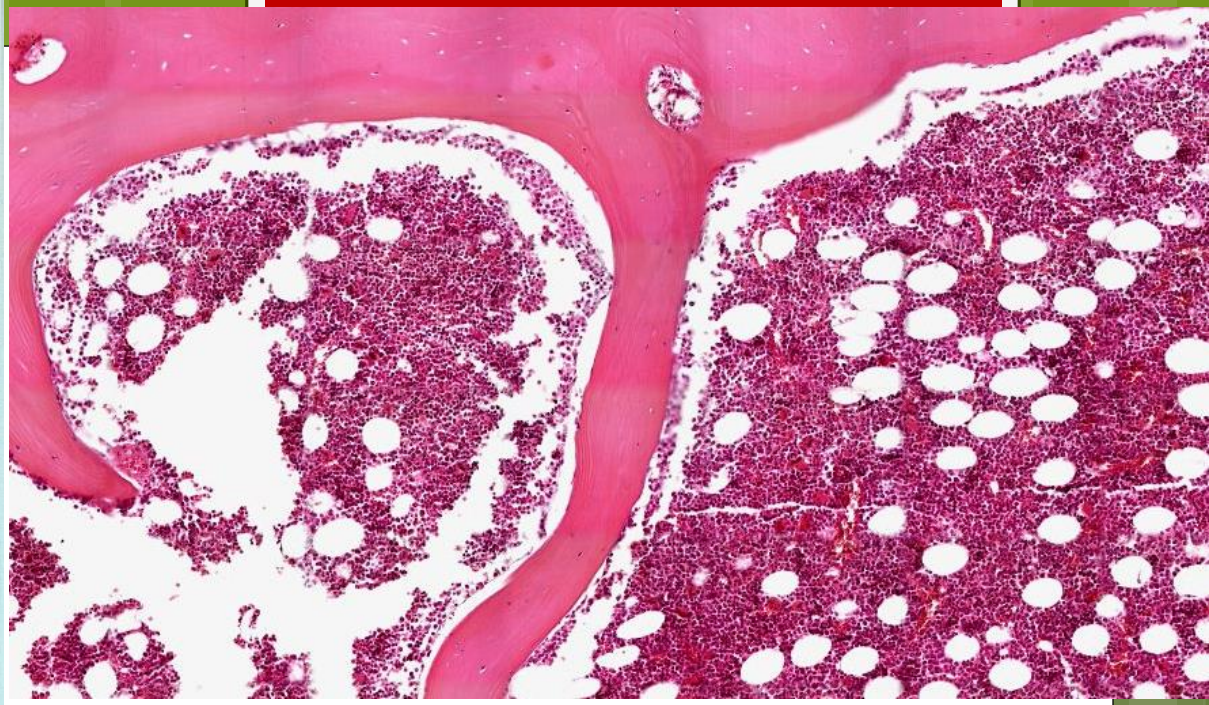


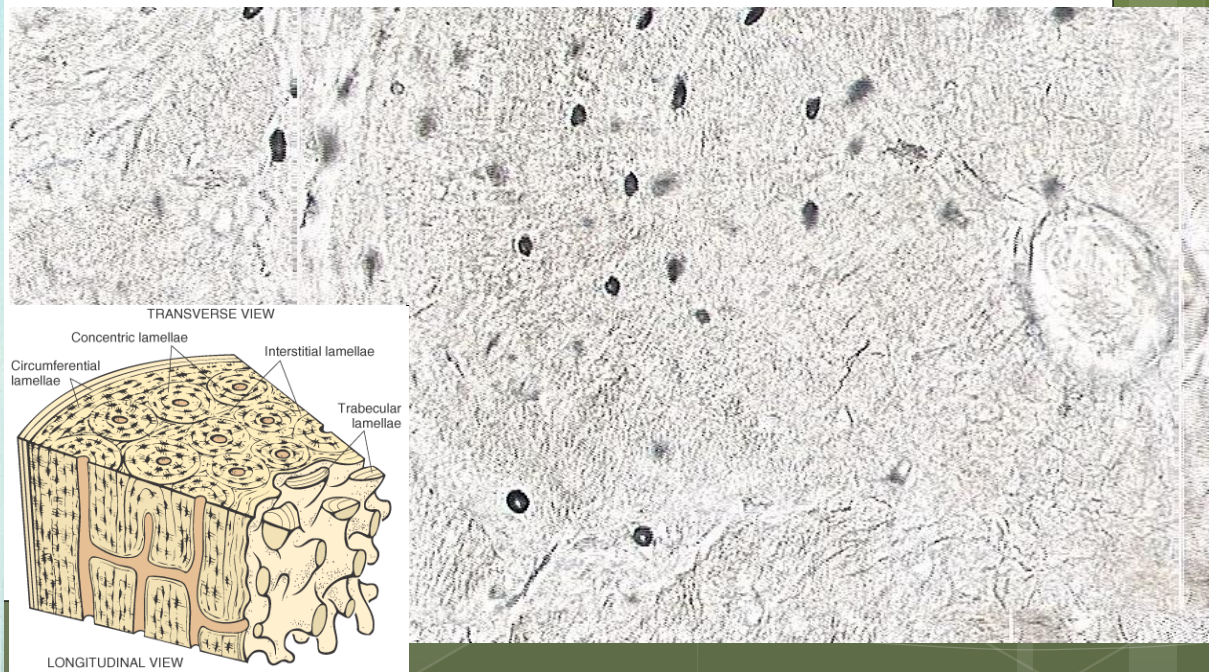
- This mineral gives bone strength and hardness and serves as the storehouse for 99% of the body's calcium, 85% of the body's phosphorus, and 65% of the body's sodium and magnesium.

- The organic component includes the cells of bone and the proteinaceous osteoid.
- The bone-forming cells include osteoblasts and osteocytes, while cells of the bone-digesting lineage include osteoclast precursor cells and mature functional osteoclasts (Fig.20-1).

The Human Skeleton







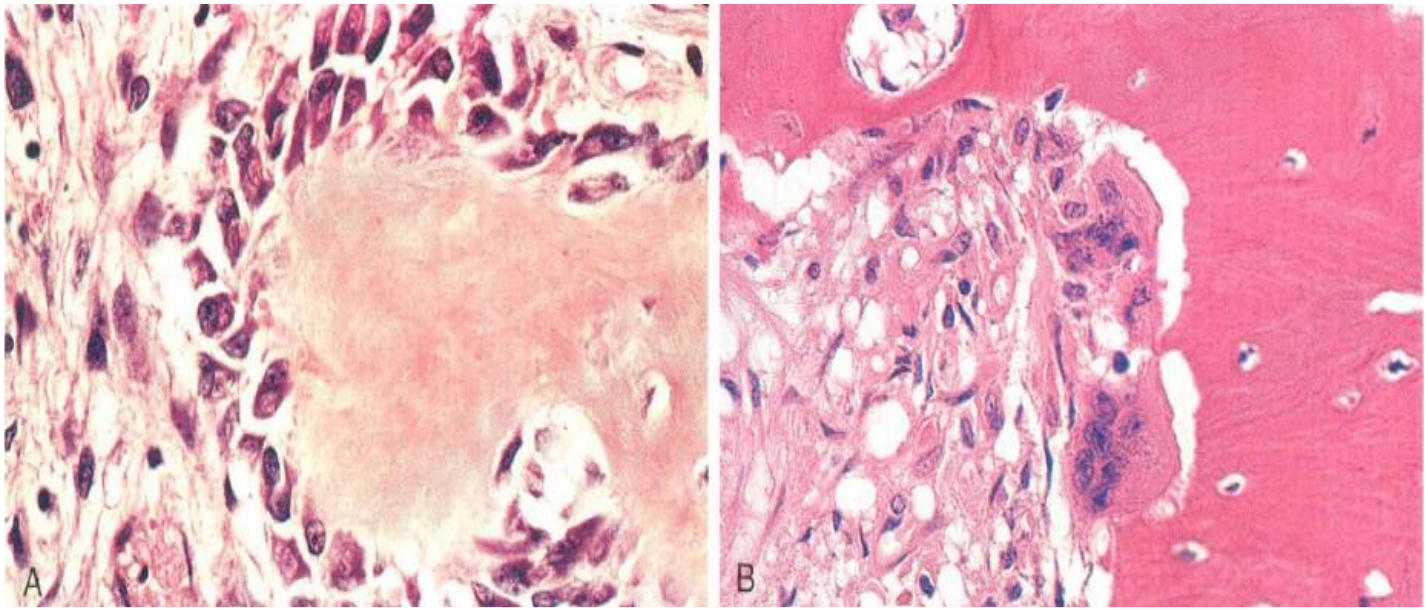
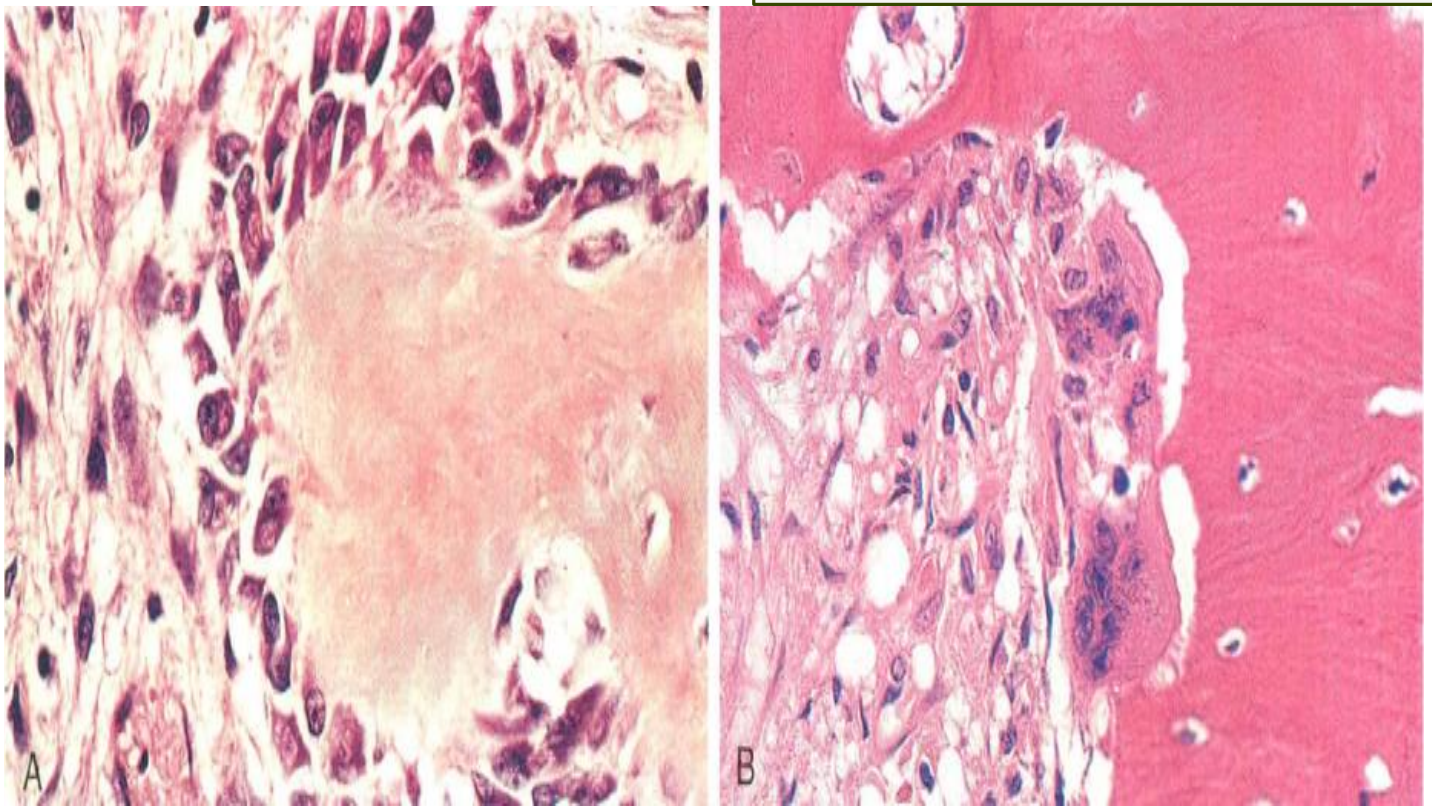


Figure 20-1 Cells of bone. A, Active osteoblasts synthesizing bone matrix proteins. The surrounding spindle cells are osteoprogenitor cells. B, Two osteoclasts resorbing bone. The smaller blue nuclei surrounded by a halo of clearing in the dense pink lamellar bone are osteocytes in their individual lacunae.

- To the uninitiated, bone appears to be an inert, stable tissue, but in fact it is very dynamic and subject to constant breakdown and renewal, a process referred to as remodeling.

- The net effects of remodeling may be bone maintenance , bone loss, or bone deposition, with the balance being determined by the relative activities of osteoblasts , which deposit bone, and osteoclasts, which resorb bone(Fig. 20-1, A and B).



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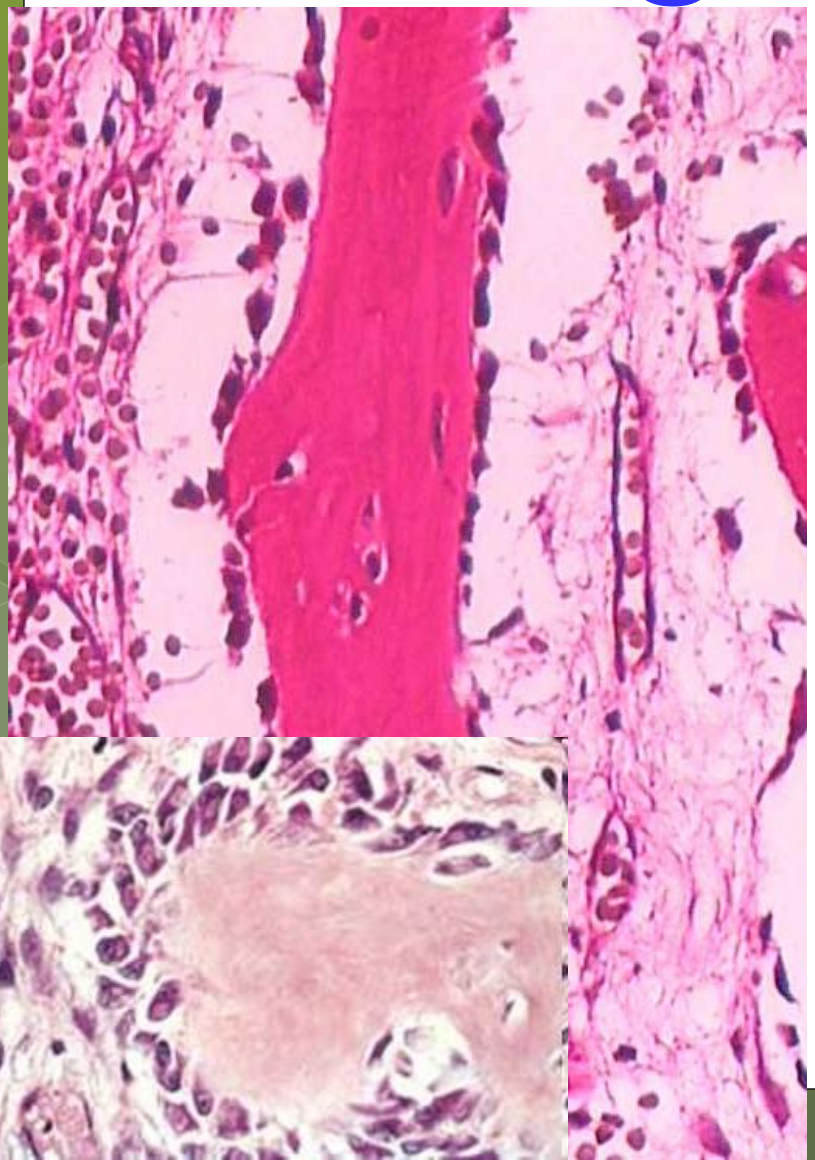
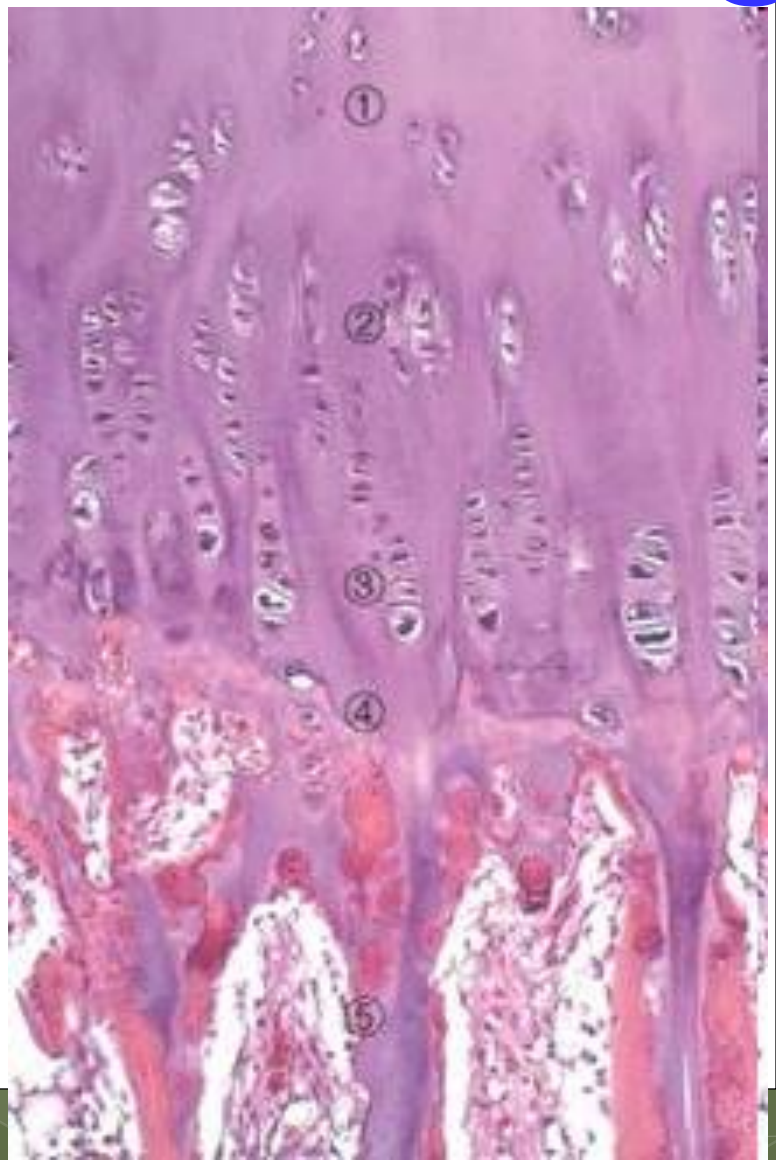
Modeling/RE-modeling

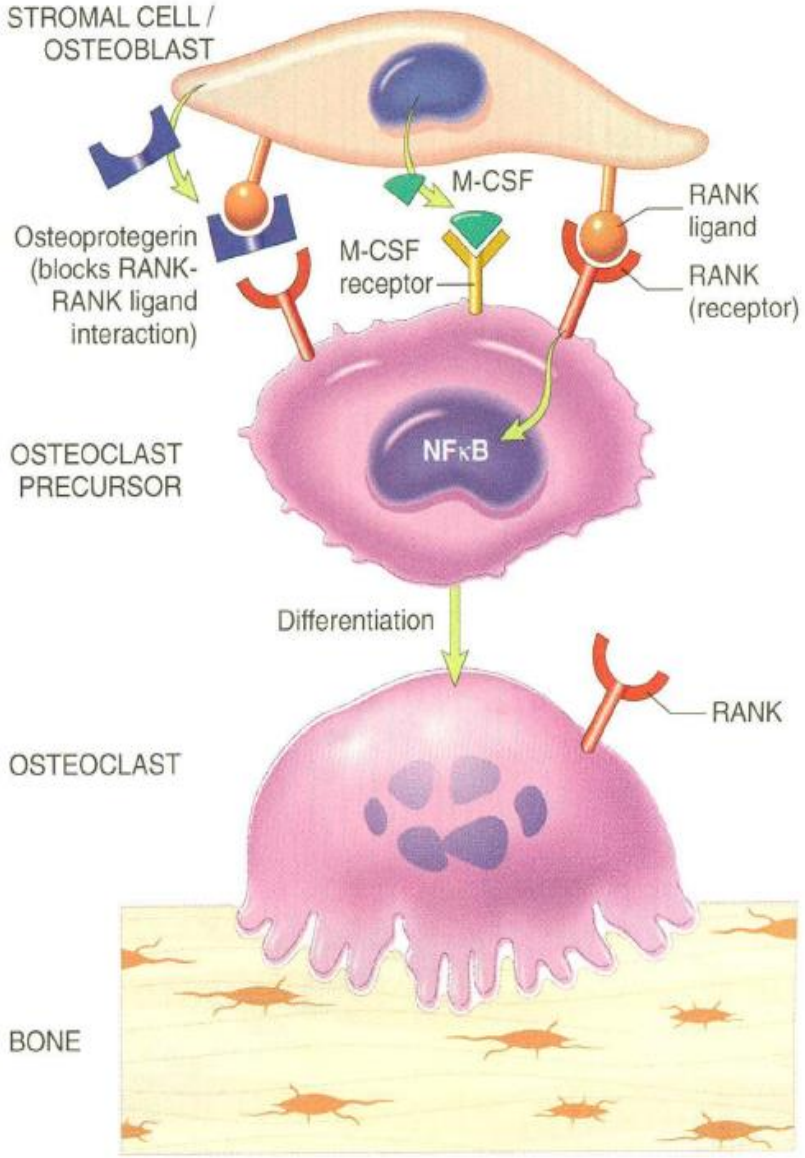




- As might be imagined, osteoblast and osteoclast activity is highly regulated and tightly integrated under normal circumstances, both by local crosstalk between these two cell types and by circulating factors that impact their activity, such as vitamin D and parathyroid hormone.

- The most important remodeling local factors
  - RANK (receptor activator for nuclear factor-KB),
  - RANK ligand (RANKL),
  - osteoprotegerin (OPG) (Fig 20-2).
- RANK, a member of the tumor necrosis factor (TNF) receptor family, is expressed on the cell membranes of preosteoclasts and mature osteoclasts.

Figure 20-2 Paracrine mechanisms regulating osteoclast formation and function. Osteoclasts are derived from the same stem cells that produce macrophages. RANK(receptor activator for nuclear factor- KB) receptors on osteoclast precursors bind RANK ligand (RANKL) expressed by osteoblasts and marrow stromal cells. Along with macrophage colony stimulating factor (M-CSF). the RANK-RANKL interaction drives the differentiation of functional osteoclasts. Stromal cells also secrete osteoprotegerin (OPG). which acts as a decoy receptor for RANKL. Preventing it from binding the RANK receptor on osteoclast precursors. Consequently.OPG prevents bone resorption by inhibiting osteoclast differentiation.



- Its ligand, RANKL, is expressed by osteoblasts and marrow stromal cells.
- RANK stimulation by RANKL leads to activation of the transcription factor NF-KB, which drives the expression of genes that stimulate osteoclast formation ,fusion, differentiation, function, and survival.
- RANKL production is upregulated by factors that stimulate osteoclastic activity.

- The actions of RANKL can be blocked by another member of the TNF receptor family, OPG, which is a "decoy" eceptor produced by a number of tissues including bone, hematopoietic marrow, and immune cells.
- OPG competitively binds to RANKL, preventing RANK from interacting with RANKL.

- OPG production is regulated by signals similar to those that stimulate RANKL.
- Therefore , these molecules enable osteoblasts and stromal cells to control osteoclast development and activity and provide a mechanism for a wide variety of biologic mediators hormones , cytokines, growth factors) to influence the homeostasis of bone tissue and bone mass.

CONGENITAL DISORDERS OF BONE AND CARTILAGE

- Congenital disorders of the skeleton are various and , depending on the resulting defect, become manifest at different ages.
- The most severe produce developmental abnormalities that are evident from the earliest stages of skeletogenesis.

CONGENITAL DISORDERS OF BONE AND CARTILAGE

- Developmental anomalies resulting from localized problems in the migration of mesenchymal cells and the formation of condensations are called dysostoses and may affect individual or a group of bones and can result from mutations in specific homeobox genes.

CONGENITAL DISORDERS OF BONE AND CARTILAGE

- The more common lesions include
  - Aplasia (congenital absence of a digit or rib),
  - Formation of extra bones (supernumerary digits or ribs),
  - Abnormal fusion of bones (e.g., premature closure of the cranial sutures or congenital fusion of the ribs).
- Such malformations may occur as isolated, sporadic lesions or as components of a more complex syndrome.

CONGENITAL DISORDERS OF BONE AND CARTILAGE

- Mutations that interfere with bone or cartilage formation,growth, and/or maintenance of normal matrix components have more diffuse effects; such disorders are called dysplasias - more specifically, osteodysplasias and chondrodyslasias.
- Dysplasia in this context refers to abnormal growth and does not imply precancerous lesions, as it does in other tissues .
- They number well over 350.

CONGENITAL DISORDERS OF BONE AND CARTILAGE

- Other genetic metabolic disorders not usually thought of as primary skeletal diseases (e.g., mucopolysaccharidoses such as Hurler syndrome) also affect the bone matrix;

Osteogenesis Imperfecta

- Ostcogcnesis Imperfecta (0I), also known as "brittle bone disease," is actually a group of genetic disorders caused by defcctive synthesis of type I collagen.

Osteogenesis Imperfecta

- Because type I collagen is a major component of extracellular matrix in other parts of the body, there are also numerous extraskeletal manifestations (affecting skin, joints, teeth, and eyes,).

Osteogenesis Imperfecta

- The mutations underlying 0I characteristically involve the coding sequences for α1 or < α2 chains of type 1 collagen.
- Because collagen synthesis and extracellular export require formation of a complete and intact triple helix, any primary defect in a collagen chain tends to disrupt the entire structure and results in its premature degradation (an example of a dominant negative mutation)

Osteogenesis Imperfecta

- As a consequence, most defects manifest as autosomal dominant disorders and may be associated with severe malformations.
- There is, however, a broad spectrum of severity, and mutations that result in qualitatively normal collagen but at only reduced levels generally have milder manifestations.

Osteogenesis Imperfecta

- Tile fundmnental abnormality in all forms of 0I is too little bone, resulting in extreme skeletal fragility.
- Four major subtypes are recognized.
- The type II variant is uniformly fatal in utero or immediately postpartum as a consequence of multiple fractures that occur before birth.

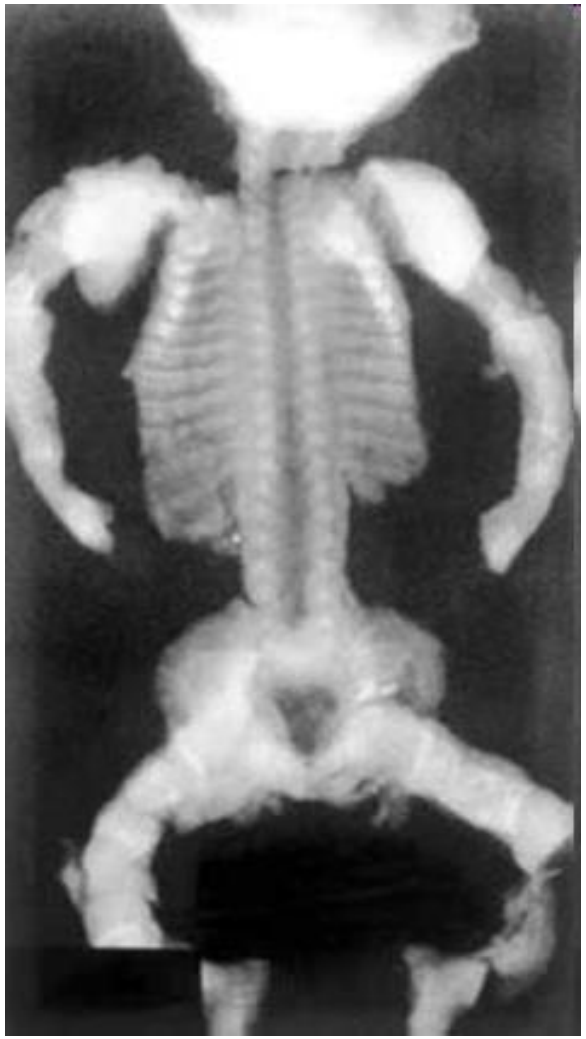
Osteogenesis Imperfecta

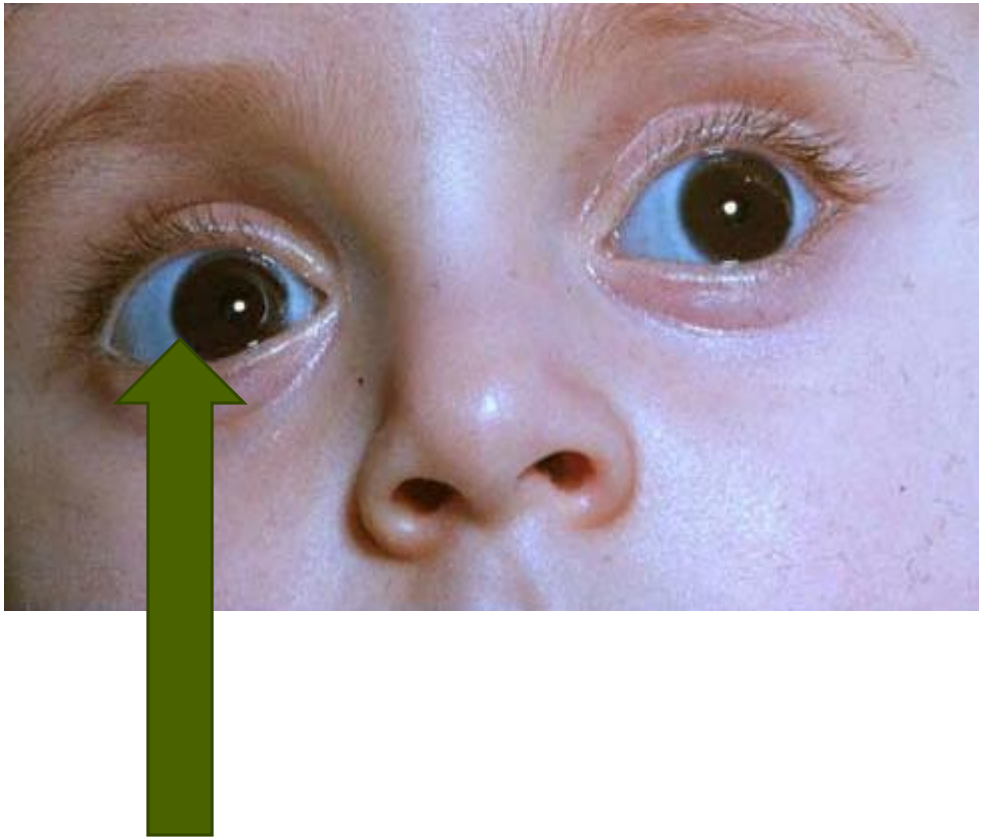
- By contrast , patients with type 1 0l have a normal lifespan, with only a modestly increased proclivity for fractures during childhood (decreasing in frequency after puberty).

Osteogenesis Imperfecta

- The classic finding of blue sclerae in type I or is attributable to decreased scleral collagen content; this deficit causes a relative transparency that allows the underlying choroid to be seen.
- Hearing loss can be related to conduction defects in the middle and inner ear bones, and small misshapen teeth are a result of dentin deficiency.

Osteogenesis Imperfecta





BLUE SCLERA

Achondroplasia and Thanatophoric Dwarfism

- Achondroplasia is thc most common form of dwmfism.
- It is caused by activating point mutations in fibroblast growth factor receptor 3 (FGFR3), a receptor with tyrosine kinase activity that transmits intracellular signals.

Achondroplasia and Thanatophoric Dwarfism

- Signals transmitted by FGFR3 inhibit the proliferation and function of growth plate chondrocytes; consequently, the growth of normal epiphyseal plates is suppressed, and the length of long bones is severely stunted.
- The disorder can be inherited in autosomal dominant fashion, but many cases arise from new spontaneous mutations.

Achondroplasia and Thanatophoric Dwarfism

- Achondroplasia affects all bones that develop by enchondral ossification.
- The most conspicuous changes include short stature, disproportionate shortening of the proximal extremities, bowing of the legs, and frontal bossing with mid face hypoplasia.
- The cartilage of the growth plates is disorganized and hypoplastic.

Achondroplasia and Thanatophoric Dwarfism

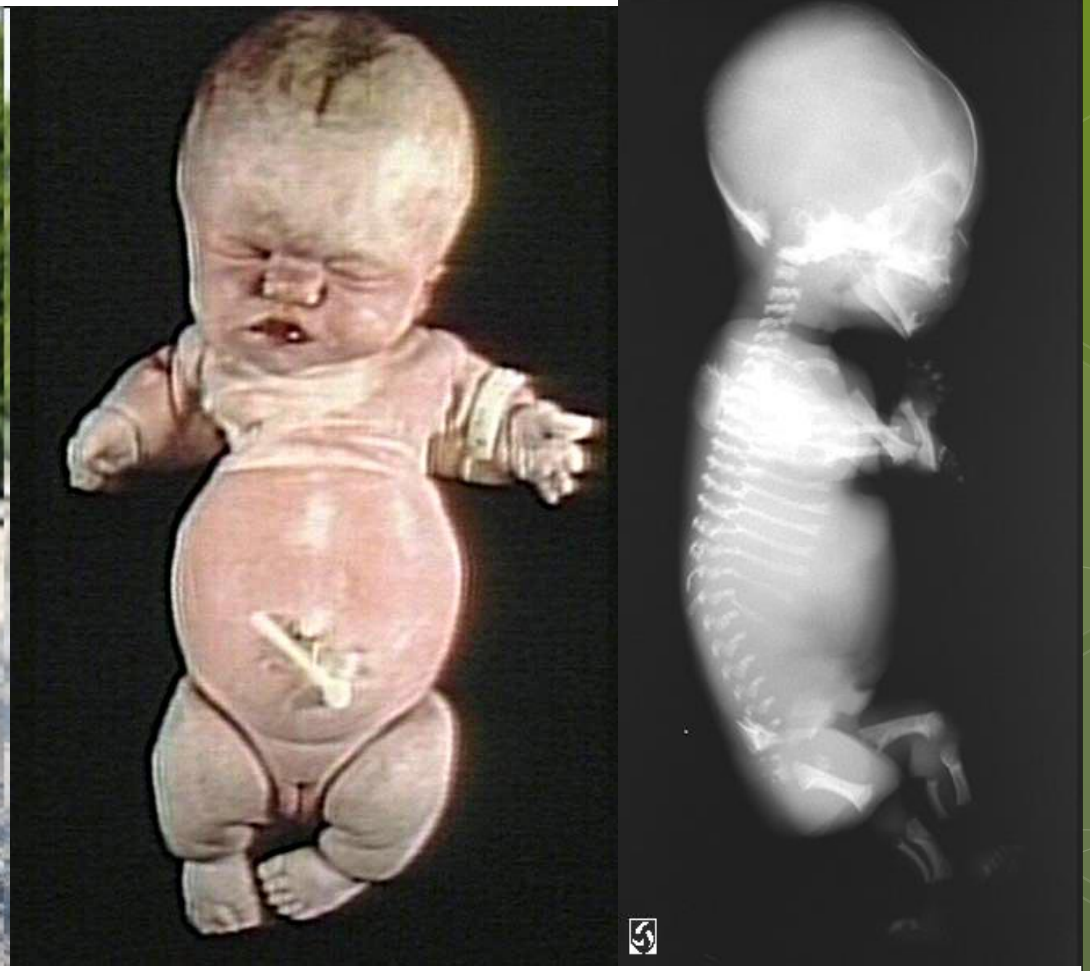
- Thanatophoric Dwarfismis a lethal variant of dwarfism,
- affecting 1 in every 20,000 live births (Thanatophoric means"death-loving").
- This disease is caused by missense or point mutations most commonly located in the extracellular domains of FGFR3.

Achondroplasia and Thanatophoric Dwarfism

- Affected heterozygotes exhibit
  - extreme shortening of the limbs,
  - frontal bossing of the skull,
  - an extremely small thorax,
    - which is the cause of fatal respiratory failure in the perinatal period.

Achondroplastic "dwarf"

Thanatophoric "dwarf", often lethal



Short arms and extra folds of skin

Osteopetrosis

- defective osteoclast-mediated bone resorption.
- Osteopetrosis (literally, "bone-that-is-like-stone disorder") is an appropriate name, since the bones are dense, solid, and stonelike.
- Paradoxically, because turnover is decreased, the persisting bone tissue becomes weak over time and predisposed to fractures like a piece of chalk.

Osteopetrosis

- Several variants are known, the two most common being an autosomal dominant adult form with mild clinical manifestations , and autosomal recessive infantile, with a severe/lethal phenotype .

- The defects that cause osteopetrosis are categorized into those that disturb osteoclast function and those that interfere with osteoclast formation and differentiation.

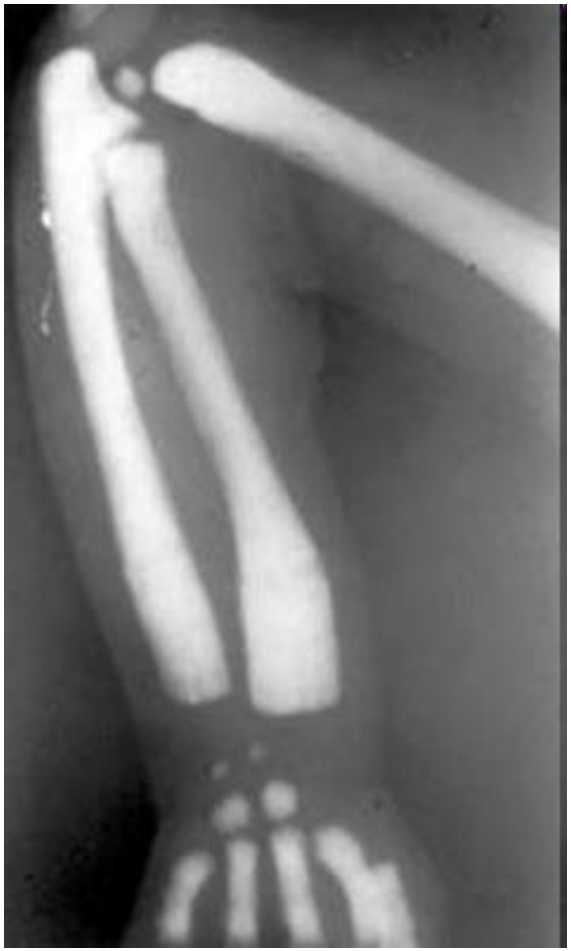
- The precise nature of the osteoclast dysfunction is unknown in many cases.
- Nevertheless, in some cases the abnormalities have been identified.
- These include carbonic anhydrase II deficiency, proton pump deficiency and chloride channel defect, all of which interfere with the ability of osteoclasts to resorb bone.
- A mouse model of osteopetrosis is caused by mutations in the monocyte-colony stimulating factor (M-CSF), which is required for osteoclast differentiation.
- No comparable defect has been identified in humans.

- Besides fractures, patients with osteopetrosis frequently have cranial nerve palsies (due to compression of nerves within shrunken cranial foramina), recurrent infections because of reduced marrow size and activity, and hepatosplenomegaly caused by extramedullary hematopoiesis resulting from reduced marrow space.

- Morphologically,the primary spongiosa, which normally is removed during growth, persists, filling the medullary cavity, and bone is deposited in increased amounts woven into the architecture.

- Because osteoclasts are derived from marrow monocyte precursors, hematopoietic stem cell transplantation holds the promise of repopulating recipients with progenitor cells capable of differentiating into fully functional osteoclasts.
- Indeed, many of the skeletal abnormalities appear to be reversible once normal precursor cells are provided.

OSTEOPETROSIS



Diffusely DENSE bone with “Erlenmeyer Flask deformity” of distal humerus

- **CHONG: Mnemonic for Etiologies of Erlenmeyer Flask Deformity**
- CHONG
- **Craniometaphyseal deformities**
- **Hemoglobinopathies**
  - **Thalassemia**
  - **Sickle cell disease**
- **Osteopetrosis**
- **Nieman Pick Disease**
- **Gaucher's Disease**
- **Other**
  - **Lead poisoning**
  - **Fibrous dysplasia**
  - **Hereditary multiple exostoses**

ACQUIRED DISEASESOF BONE

- Many nutritional, endocrine, and systemic disorders affect the development of the skeletal system.
- Nutritional deficiencies causing bone disease include deficiencies
  - vitamin C (involved in collagen cross-linking; deficiency causes scurvy)
  - vitamin D (involved in calcium uptake;deficiency causes rickets and osteomalacia).
- Primary and secondary forms of hyperparathyroidism
- also cause significant skeletal changes, which are briefly reviewed in this section.
- Many of these disorders are characterized by inadequate osteoid, also called osteopenia;
- The most important clinically significant osteopenia is osteoporosis.

Osteoporosis

- Osteoporosis is an acquired condition characterized by reduced bone mass, leading to bone fragility and susceptibility to fractures.
- The bone loss may be confined
  - certain bones or regions,
    - disuse osteoporosis of a limb,
  - generalized, involving the entire skeleton.
- Generalized osteoporosis may
  - primary
  - secondary
    - metabolic diseases,
    - vitamin deficiencies,
    - drug exposures (Table 20-1).

Table 20–1 Categories of Generalized Osteoporosis

Primary
Postmenopausal
Senile
Secondary
Endocrine Disorders
Hyperparathyroidism
Hypo or hyperthyroidism
Hypogonadism
Pituitary tumors
Diabetes, type I
Addison disease
Neoplasia
Multiple myeloma
Carcinomatosis
Gastrointestinal Disorders
Malnutrition
Malabsorption
Hepatic insufficiency
Vitamin C, D deficiencies
Idiopathic disease
Drugs
Anticoagulants
Chemotherapy
Corticosteroids
Anticonvulsants
Alcohol
Miscellaneous
Osteogenesis imperfecta
Immobilization
Pulmonary disease
Homocystinuria
Anemia

Categories of Generalized Osteoporosis

Primary

Postmenopausal

Senile

Idiopathic

Secondary

Endocrine disorders

Hyperparathyroidism

Hypo-hyperthyroidism

Hypogonadism

Pituitary tumors

Diabetes, type 1

Addison disease

Neoplasia

Multiple myeloma

Carcinomatosis

Gastrointestinal

Malnutrition, Malbs., Hepatic Insuf., Vit C,D

Rheumatologic disease

Drugs

Anticoagulants

Chemotherapy

Corticosteroids

Anticonvulsants

Alcohol

Miscellaneous

Osteogenesis imperfecta

Immobilization

Pulmonary disease

Homocystinuria

Anemia

Osteoporosis

- Primary forms of osteoporosis are most common and may be associated with aging (senile osteoporosis) or the postmenopausal state in women.
- The drop in estrogen following menopause tends to exacerbate the loss of bone that occurs with aging,
- placing older women at high risk of osteoporosis relative to men.

Osteoporosis

- The risk of osteoporosis with aging is related to the peak bone mass earlier in life, which is influenced by genetic, nutritional, and environmental factors.
- Bone mass peaks during young adulthood;
- The greater the peak bone mass,
- The greater the delay in onset of osteoporosis.
- In both men and women, beginning in the
- third or fourth decade of life,
- bone resorption begins to outpace bone formation

Osteoporosis

- The bone loss, averaging 0.5% per year, is a seemingly inevitable consequence of aging and is most prominent in areas containing abundant trabecular bone-namely the spine and femoral neck.

Osteoporosis

- The amount of bone loss with each cycle of remodeling is accelerated after menopause; hence, the vulnerability of women to osteoporosis and its complications.

Osteoporosis

- Regardless of the underlying cause, the progressive loss of bone mass is clinically significant because of the resultant increase in the risk of fractures.
- Roughly 1.5 million Americans each year experience an osteoporosis-related fracture, with those of greatest clinical significance involving the vertebrae and the hips.
- All told, the annual health care costs associated with osteoporosis-related fractures in the United States exceeds $18 billion.

Osteoporosis MORPHOLOGY

- The hallmark of osteoporosis is a loss of bone.
- The cortices are thinned, with dilated haversian canals, and the trabeculae are reduced in thickness and lose their interconnections.
- Osteoclastic activity is present but is not dramatically increased, and the mineral content of the bone tissue is normal.
- Once enough bone is lost, susceptibility to fractures increases (Fig. 20-3).

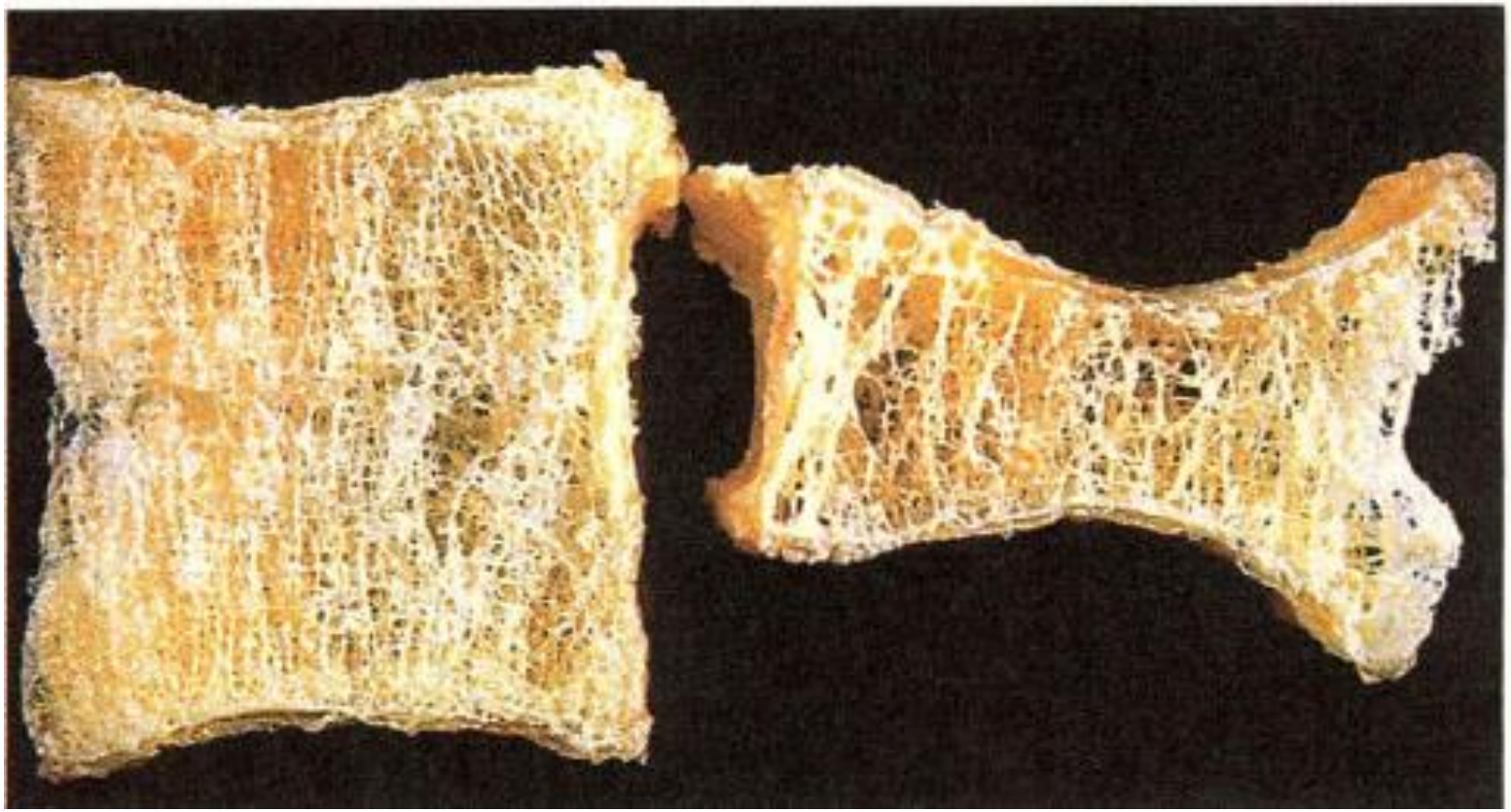
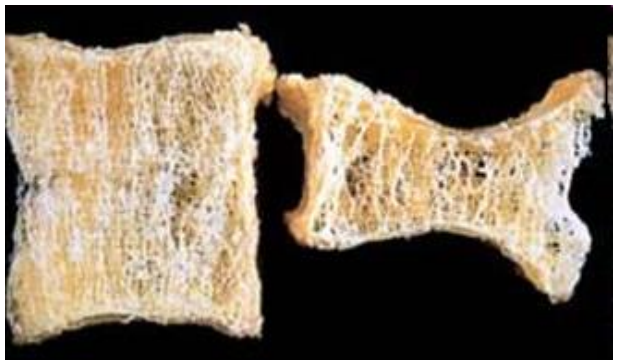
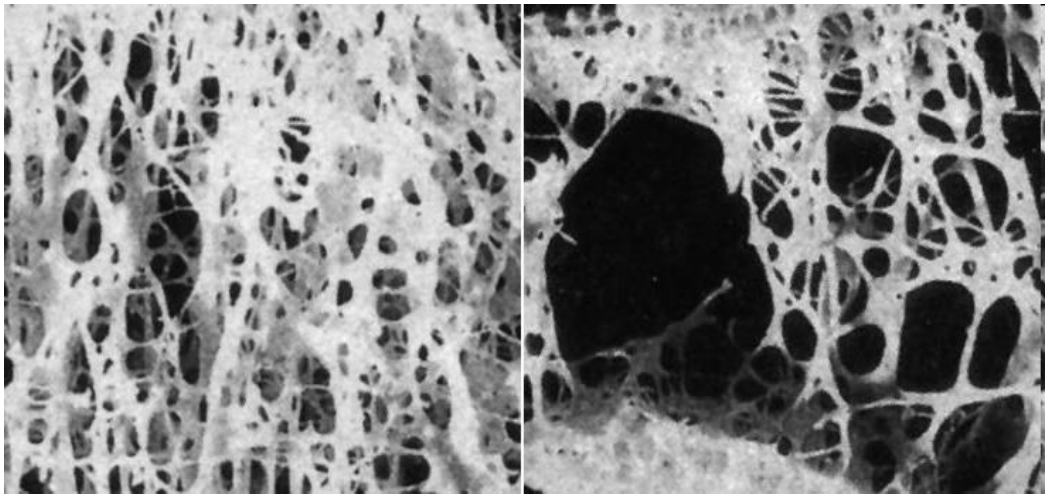


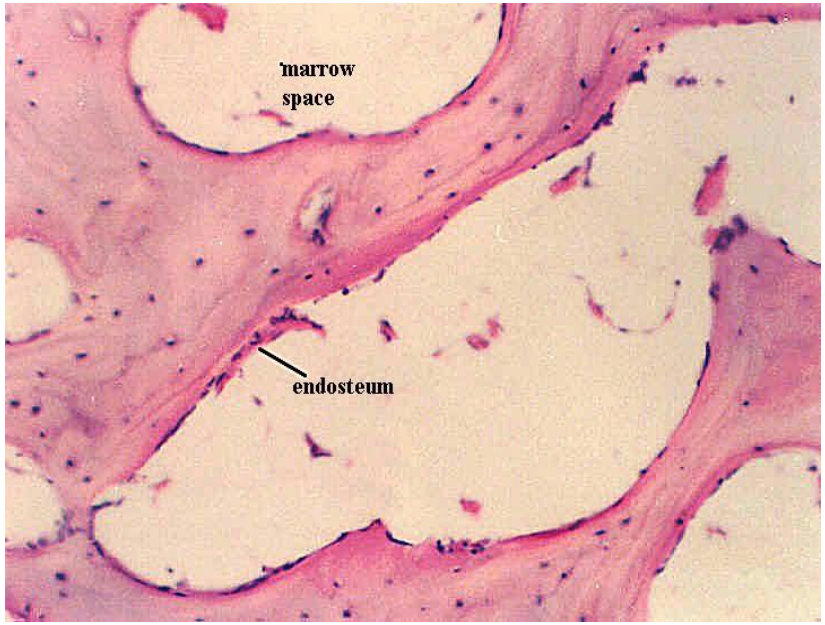
Figure 20-3 Osteoporotic vertebral body (right) shortened by compression fractures. compared with a normal vertebral body.

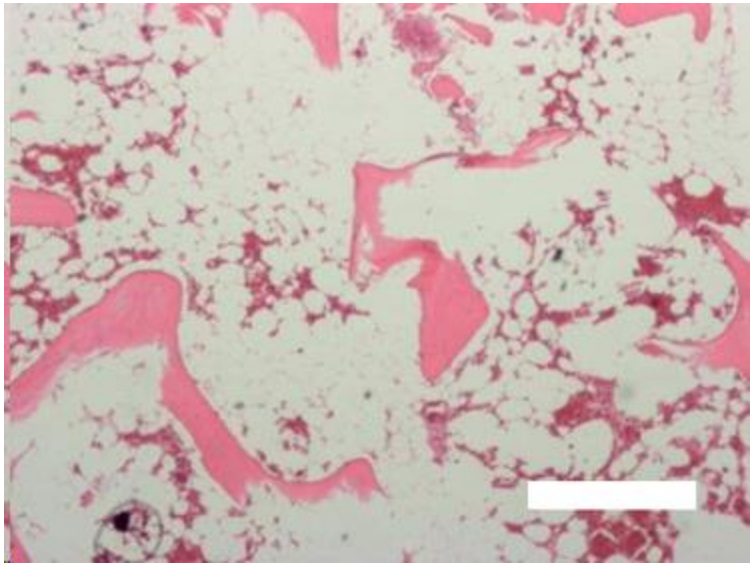
The osteoporotic vertebra exhibitsa characteristiclossof horizontal trabeculae and thickened vertical trabeculae.

OSTEOPOROSIS









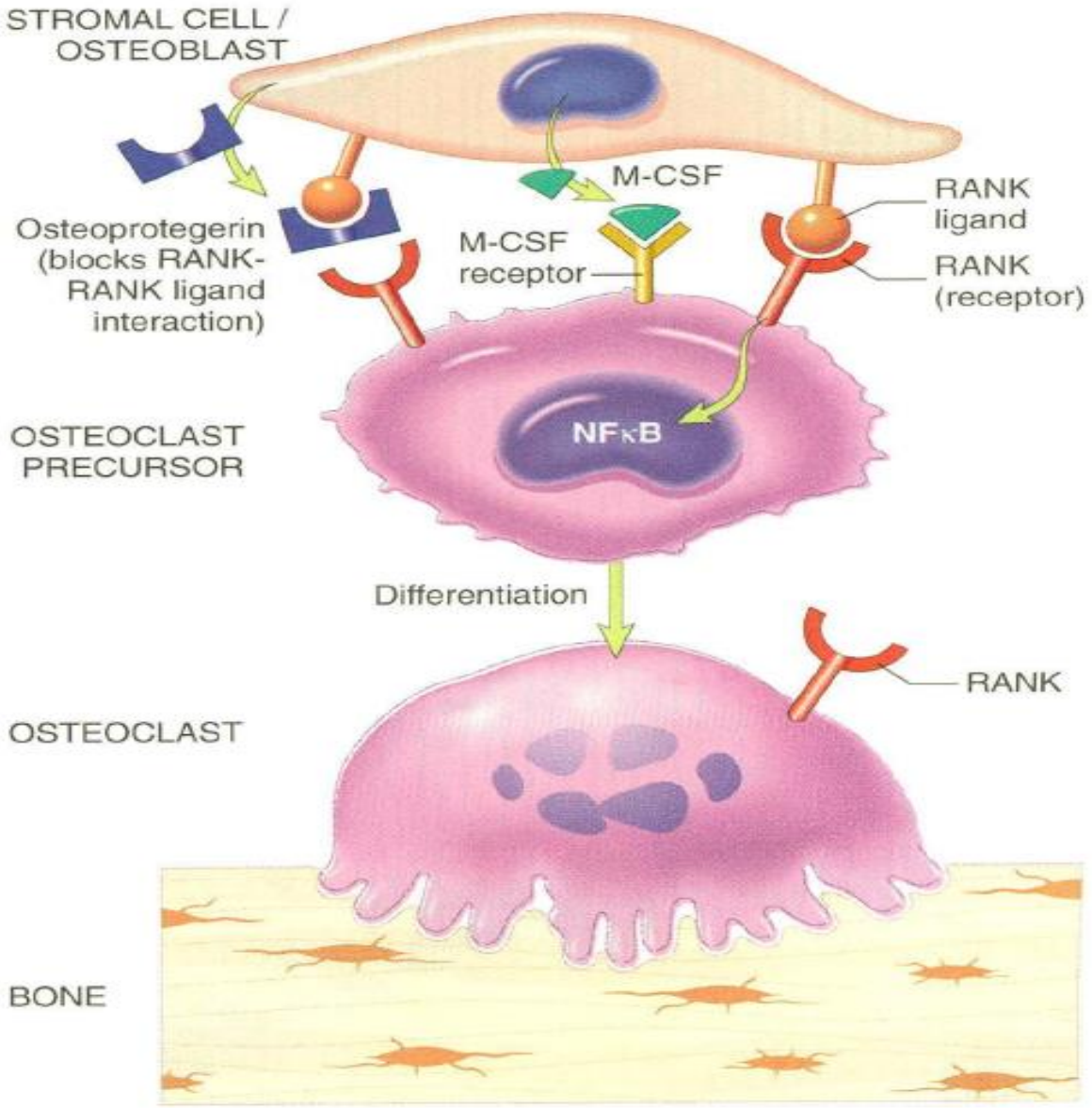
Osteoporosis MORPHOLOGY

- In postmenopausal osteoporosis, trabecular bone loss often is severe, resulting in compression fractures and collapse of vertebral bodies.
- In senile osteoporosis , cortical bone loss is prominent, predisposing to fractures in other weight-bearing bones, such as the femoral neck.

Osteoporosis PATHOGENESIS

- Osteoporosis occurs when the dynamic balance between bone formation by osteoblasts and bone resorption by osteoclasts (Fig. 20-2) tilts in favor of resorption.
- Several factors may tip the scales (Fig. 20-4):

Figure 20-2


STROMAL CELL / OSTEOBLAST
M-CSF
RANK ligand
RANK (receptor)
Osteoprotegerin (blocks RANK-RANK ligand interaction)
M-CSF receptor
OSTEOCLAST PRECURSOR
NFκB
Differentiation
RANK
OSTEOCLAST
BONE

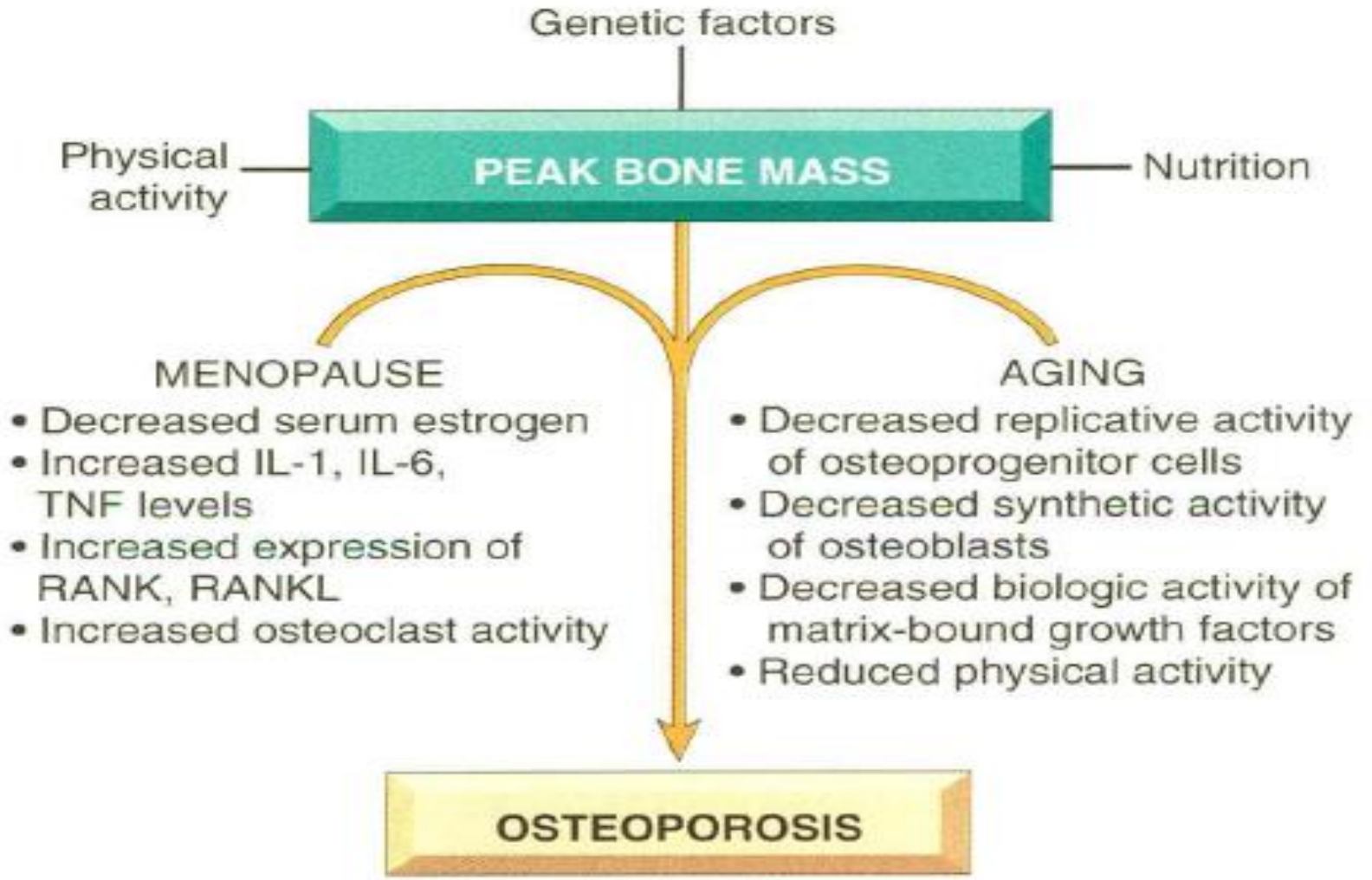


Figure 20-4 Pathophysiology of postmenopausaland senile osteoporosis

Age-related changes

- With increasing age, the replicative and matrix production activities of osteoblasts progressively diminish.
- The various growth factors deposited in the extracellular matrix also diminish with time.
- Unfortunately, while new bone synthesis wanes with advancing age, osteoclasts retain their youthful vigor.

Hormonal influences.

- The decline in estrogen levels associated with menopause correlates with an acceleration of cortical bone and trabecular (cancellous) bone loss.

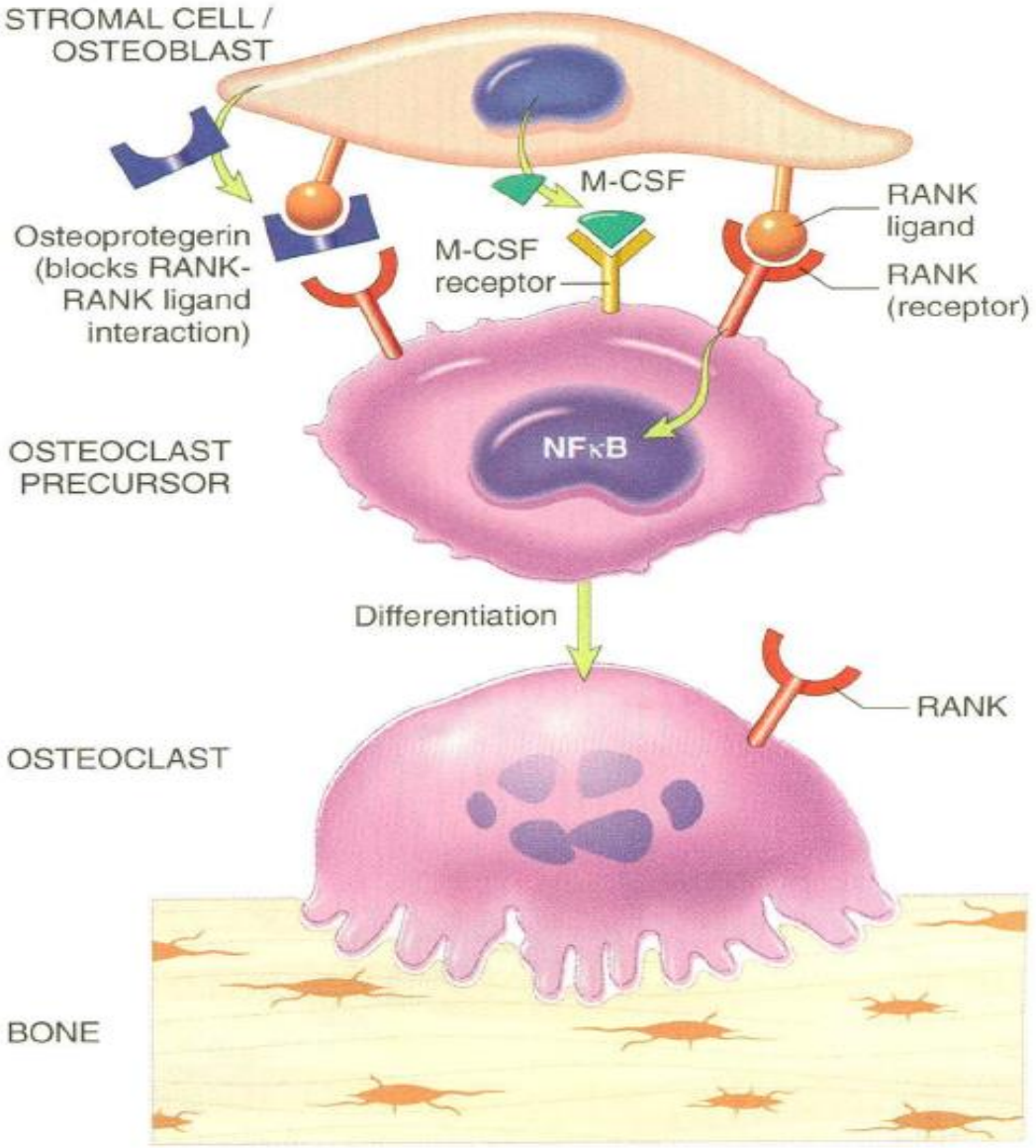
Hormonal influences.

- Over 30 to 40 years, this can result in the loss of up to 35% of cortical bone and 50% of trabecular bone!
- It is therefore not surprising that roughly half of postmenopausal women will suffer an osteoporotic fracture (compared with 2% to 3% of men of comparable age.

Hormonal influences.

- It appears that the postmenopausal drop in estrogen leads to increased cytokine production (especially IL-I, IL-6, and TNF), presumably from cells in the bone.
- These stimulate RANK-RANK ligand activity and suppress OPG production (Fig. 20-2).

Figure 20-2


STROMAL CELL / OSTEOBLAST
M-CSF
RANK ligand
RANK (receptor)
Osteoprotegerin (blocks RANK-RANK ligand interaction)
M-CSF receptor
NFκB
OSTEOCLAST PRECURSOR
Differentiation
RANK
OSTEOCLAST
BONE

- There is some compensatory osteoblastic activity, but it is inadequate to keep pace with osteoclastic bone resorption.
- While estrogen replacement can ameliorate some of the bone loss, such therapy is increasingly associated with cardiovascular risks

Physical activity

- Because mechanical forces stimulate bone remodeling, reduced physical activity increases bone loss.
- This effect is obvious in an immobilized limb and also occurs throughout the skeleton in astronauts working in a gravity-free environment.

- Decreased physical activity in older persons also contributes to senile osteoporosis.
- Because the magnitude of skeletal loading influences bone density more than does the number of load cycles. the type of physical activity is important.
- Thus, resistance exercises such as weight training increase bone mass more effectively than endurance activities such as jogging.

Genetic factors

- Vitamin D receptor polymorphisms appear to influence the peak bone mass early in life.
- Additional genetic variables can influence either calcium uptake or PTH synthesis and responses.

Calcium nutritional state.

- A majority of adolescent girls (but not boys) have insufficient dietary calcium.
- Unfortunately. this calcium deficiency occurs during a period of rapid bone growth.
- As a result. girls typically do not achieve the peak bone mass that could be otherwise expected and are accordingly more likely to develop clinically significant osteoporosis at an earlier age than their male counterparts.

Secondary causes of osteoporosis.

- These include prolonged glucocorticoid therapy. which increases bone resorption and reduces bone synthesis.
- Cigarette smoking and excess alcohol also can result in reduced bone mass.

Osteoporosis Clinical Course

- The clinical outcome with osteoporosis depends on which bones are involved.
- Thoracic and lumbar vertebral fractures are extremely common, leading to loss of height and various deformities, including kyphoscoliosis, which can compromise respiratory function.
- Pulmonary embolism and pneumonia are common complications of fractures of the femoral neck, pelvis, or spine and result in as many a 50,000 deaths annually

- Osteoporosis is difficult to diagnose because it is asymptomatic until skeletal fragility is announced with a fracture.

- Moreover, it cannot be reliably detected in plain radiographs until 30% to 40% of bone mass has already disappeared;serum levels of calcium, phosphorus, and alkaline phosphatase are notoriously insensitive.

- Current state-ofthe-art methods for bone loss estimation consist of specialized radiographic techniques to assess bone mineral density, such as dual-energy absorptiometry and quantitative computed tomography.

- Osteoporosis prevention and treatment begin with adequate dietary calcium intake, vitamin D supplementation , and a regular exercise regimen - starting before the age of 30 - to maximize the peak bone mass.
- Calcium and vitamin D supplements later in life can also modestly reduce bone loss.

- Pharmacologic treatments include use of antiresorptive and osteoanabolic agents.
- The antiresorptive agents,such as bisphosphonates, calcitonin, estrogen, and denosumab , decrease bone resorption by osteoclasts.
- The main anabolic agent is parathyroid hormone or an analogue ,given in amounts that stimulate osteoblastic activity

Paget Disease (Osteitis Deformans

- This unique skeletal disease is characterized by repetitive episodes of frenzied, regional osteoclastic activity and bone resorption (osteolytic stage), followed by exuberant bone formation (mixed osteoclastic-osteoblastic stage), and finally by an apparent exhaustion of cellular activity (osteosclerotic stage).
- The net effect of this process is a gain in bone IIIaSS;
- however, the newly formed bone is disordered and weak,
- so bones may become enlarged and misshapen.

- Paget disease usually presents in mid- to late adulthood.
- Marked variation in prevalence has been reported in different populations:
- The disorder is rare in Scandinavia,
- China, Japan, and Africa and relatively common in much of Europe, Australia, New Zealand, and the United States, affecting up to 2.5% of the adult populations.
- Of interest, it appears that the incidence of Paget disease is decreasing.

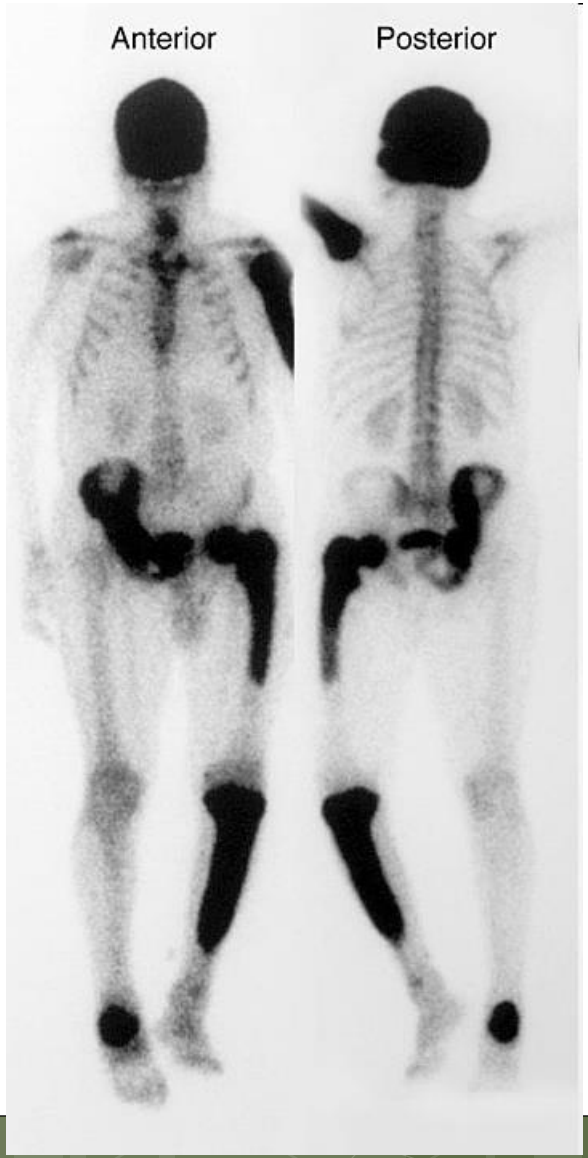
MORPHOLOGY

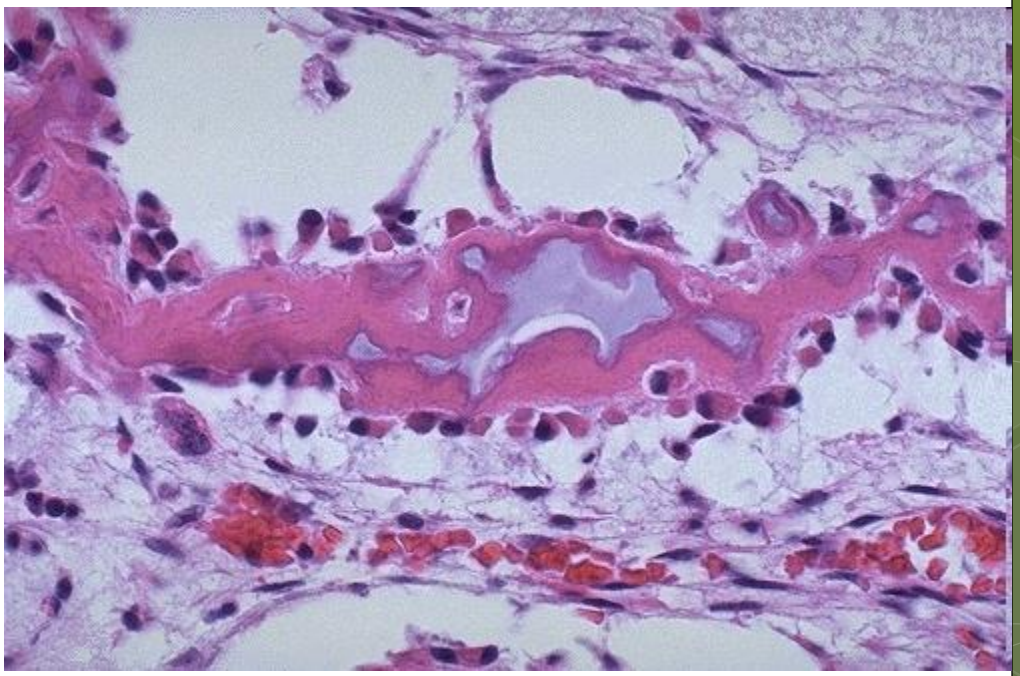
- Paget disease may manifest as a solitary lesion (monostotic) or may occur at multiple sites (polyostotic) usually asynchronously.
- In the initial lytic phase, osteoclasts (and their associated Howship lacunae) are numerous. abnormally large, and have increased numbers of nuclei.

- Osteoclasts persist in the mixed phase, but the bone surfaces become lined by prominent osteoblasts.
- The marrow is replaced by loose connective tissue containing osteoprogenitor cells, as well as numerous blood vessels needed to meet the increased metabolic demands of the tissue.

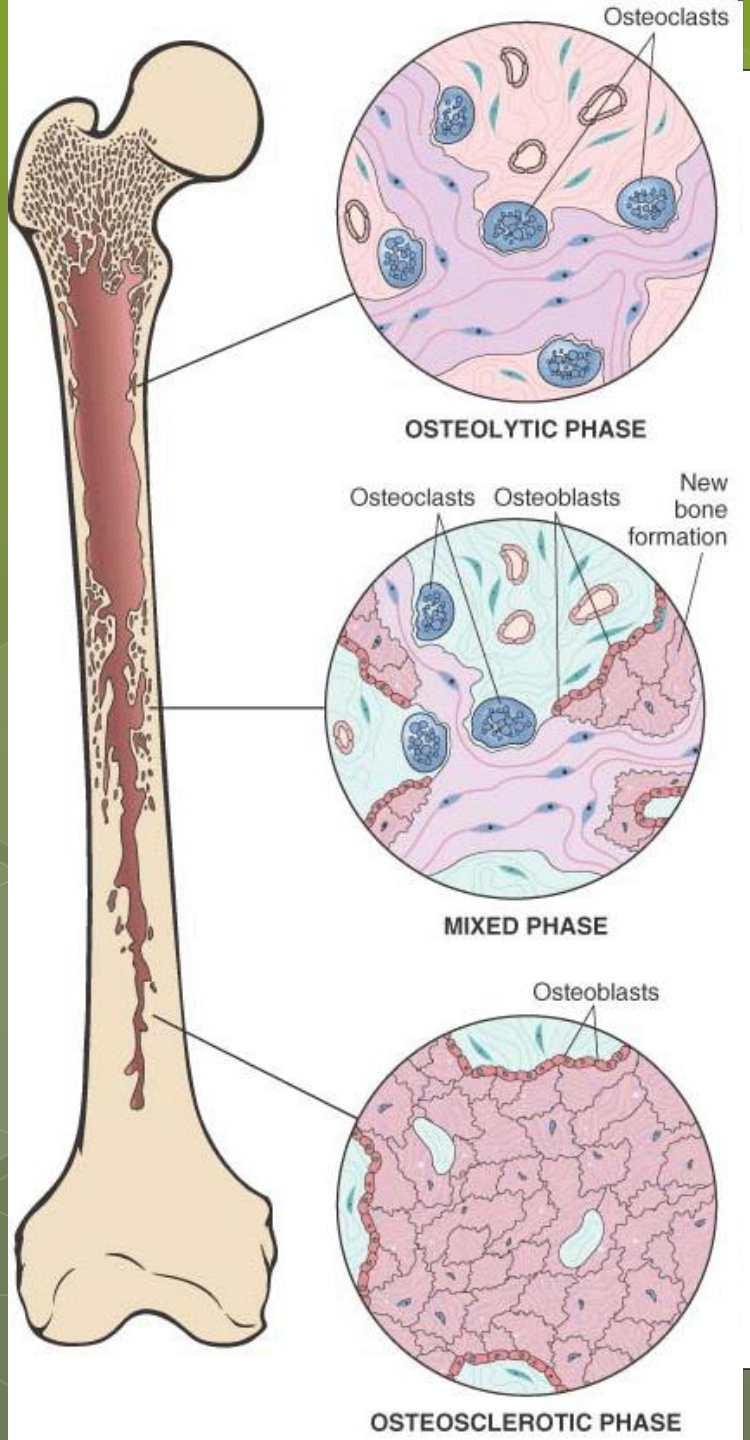
- The newly formed bone may be woven or lamellar, but eventually all of it is remodeled into abnormal lamellar bone with a pathognomonic mosaic pattern (likened to a jigsaw puzzle) due to prominent haphazardly arranged cement lines (Fig. 20-5

PAGET's DISEASE





NON-Lamellar bone

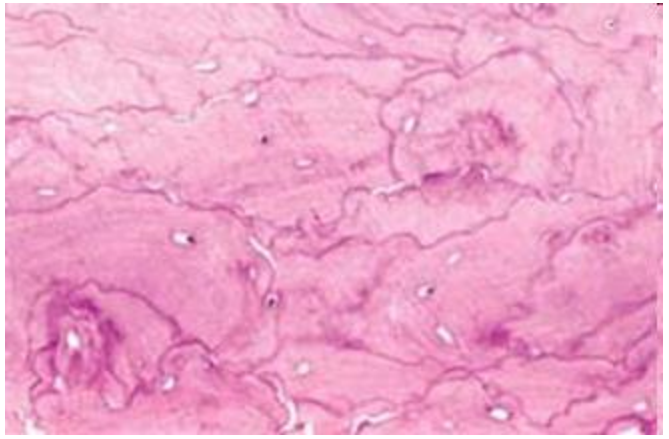


PAGET's DISEASE (of BONE)

85% MONOSTOTIC, WHOLE BONE

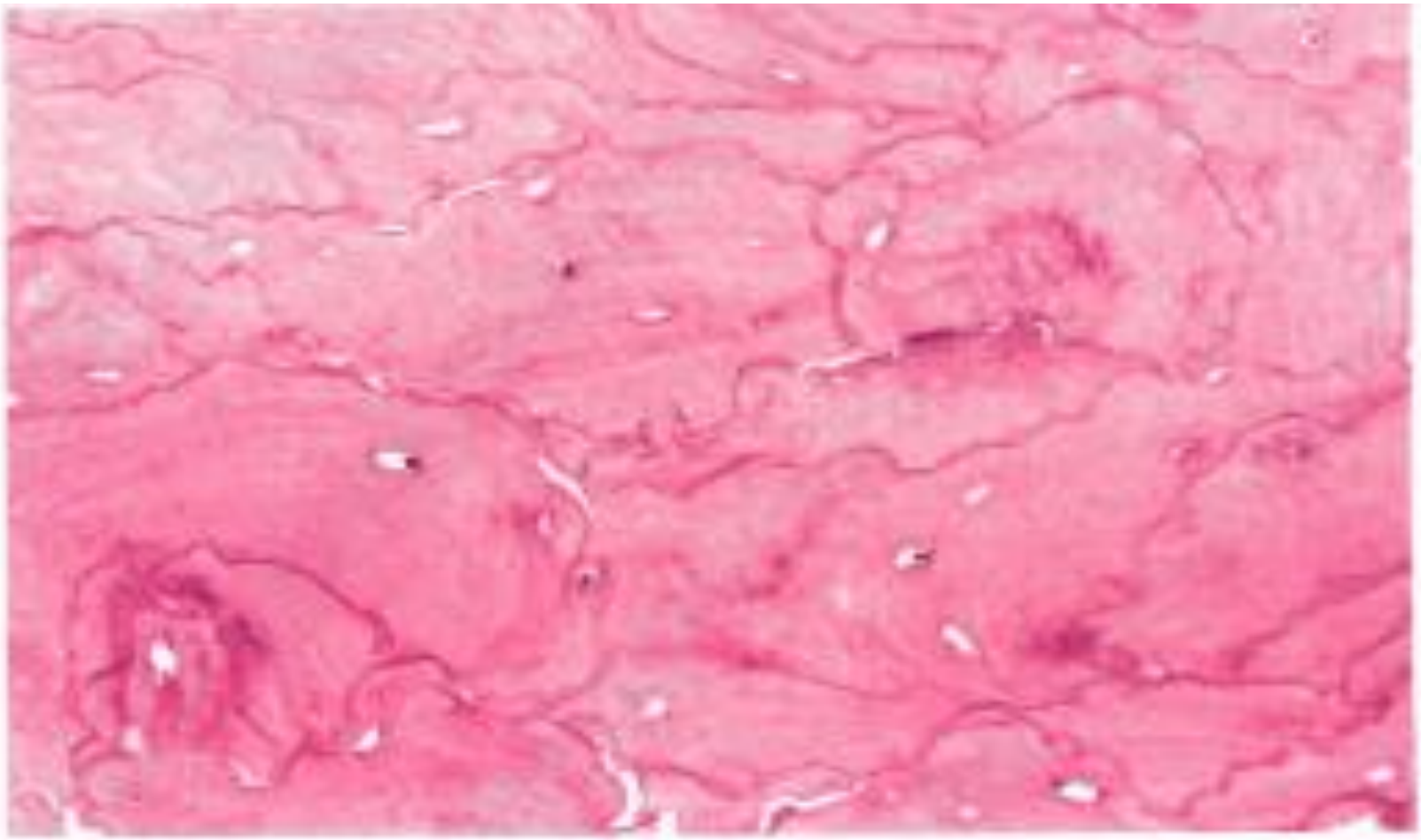
15% POLY-OSTOTIC (skull, pelvis)

"JIGSAW", NOT LAMINAR, BONE



CLINICAL: PAIN!!!

(MICROFRACTURES)



- Figure 20-5 Paget disease. showing a mosaic pattern of lamellar bone.

- As the osteoblastic activity ceases, the periosseous fibrovascular tissue recedes and is replaced by normal marrow.

- Although thickened. The resulting cortex is softer than normal and prone to deformation and fracture under stress.

PATHOGENESIS

- When he first described the disease, Sir James Paget attributed the skeletal changes to an inflammatory process, and assigned the moniker osteitis deformans.
- After many years and multiple alternative theories, Paget's original idea may prove to be correct. It has long been postulated that a paramyxovirus infection (a slow virus) underlies Page disease.

- Paramyxovirus antigens and particles resembling paramyxovirus can be demonstrated in osteoclasts.
- The causal connection is that paramyxoviruses can induce IL-I and IL-6 secretion from infected cells, and these cytokinesas well as macrophage colony-stimulating factor (M-CSF)-are produced in large amounts in pagetic bone

- As noted earlier, these potently activate osteoclasts.
- Nevertheless, as intriguing as these observations are, no infectious virus has been isolated from affected tissue.
- About 10% of affected patients have germline mutations in the gene SQSTM I, which encodes a protein that appears to increase osteoclastogenesis:
- these mutations are associated with earlier onset disease,
- a greater number of affected bones, and an increased incidence of fractures.

Clinical Course

- The clinical findings depend on the extent and site of the disease.
- Paget disease is monostotic (tibia, ilium, femur,skull, vertebrae, and humerus) in about 15% of cases and polyostotic in the remainder; the axial skeleton or the proximal femur is involved in as many as 80% of cases.

- Involvement of the ribs, fibulae, and small bones of the hands and feet is unusual.
- Although Paget dise<lse can produce a plethora of skeletal, neuromuscular, and cardiovascular complications, most cases are clinically mild, and the bone changes are discovered only incidentally in radiographs.
- .

- Elevations in serum alkaline phosphatase and increased urinary excretion of hydroxyproline reflect exuberant bone turnover

- In some patients, the early hypervascular bone lesions C<luse warmth of the overlying skin and subcutaneous tissue.
- With extensive polyostotic disease, hypervascularity can result in high-output congestive heart failure.

- In the proliferative phase of the disease involving the skull , common symptoms attributable to nerve impingement include headache and visual and auditory disturbances.
- Vertebral lesions cause back pain and may be associatedwith disabling fractures and nerve root compression.

- Affected long bones in the legs often are deformed, as a consequence of the inability of pagetoid bone to remodel appropriately in response to the stress of weight bearing.
- Brittle long bones in particular are subject to chalks tick fractures.
- The development of sarcoma is a dreaded but fortunately rare complication of Paget disease, occurring in only an estimalted 1% of patients.

- The sarcomas usually are osteogenic, although other histologic variants can occur.
- The distribution of osteosarcoma generally paralleis that of the Paget disease lesions, with the exception of vertebral bodies, which rarely harbor malignancy.

- The prognosis for patients who develop secondary sarcomas is exceedinglypoor, but otherwise Paget disease usually follows a relatively benign course.
- Most patients have mild symptoms that are readily controlled with bisphosphonates,drugs that interfere with bone resorption

ANY QUESTION