Diseases of the bone

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• The constituents of bone include an extracellular matrix and specialized cells responsible for production and maintenance of the matrix.
• **Bone matrix** is the extracellular component of bone. It is composed of an organic component known as osteoid (35%) and a mineral component (65%).

• The **cellular component** of mature bone consists of bone synthesizing osteoblasts, osteocytes, and bone-resorbing osteoclasts.
Figure 26-2  A, Active osteoblasts synthesizing bone matrix. The surrounding spindle cells represent osteoprogenitor cells. B, Two osteoclasts resorbing bone.
Figure 26-4 Paracrine molecular mechanisms that regulate osteoclast formation and function. Osteoclasts are derived from the same mononuclear cells that differentiate into macrophages. Osteoclast/stromal cell membrane-associated RANKL binds to its receptor RANK located on the cell surface of osteoclast precursors. This interaction in the background of macrophage colony-stimulating factor (M-CSF) causes the precursor cells to produce 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.
Figure 26-5 Bone cells and their interrelated activities. Hormones, cytokines, growth factors, and signal-transducing molecules are instrumental in their formation and maturation, and allow communication between osteoblasts and osteoclasts. Bone resorption and formation in remodeling are coupled processes that are controlled by systemic factors and local cytokines, some of which are deposited in the bone matrix. BMP, bone morphogenetic protein; LRP5/6, LDL receptor related proteins 5 and 6.
• Lamellar bone
  mature bone » » in adult » » regular

• Woven bone
  immature bone » » in fetus » » irregular
Paget Disease (Osteitis Deformans)

• Paget disease is a disorder of increased, but disordered and structurally unsound, bone mass.

• This unique skeletal disease can be divided into three sequential phases:
  (1) An initial osteolytic stage
  (2) a mixed osteoclastic-osteoblastic stage, which ends with a predominance of osteoblastic activity
  (3) a final burned-out quiescent osteosclerotic stage
Figure 26-12 Diagrammatic representation of Paget disease of bone demonstrating the three phases in the evolution of the disease.
• Paget disease usually begins in late adulthood (average age at diagnosis, 70 years).

• Paget disease is relatively common in whites in England, France, Austria, regions of Germany, Australia, New Zealand, and the United States. In contrast, the disease is rare in the native populations of Scandinavia, China, Japan, and Africa.
- The cause of Paget disease remains uncertain, and current evidence suggests both genetic and environmental factors contribute.
  - Forty percent to 50% of cases of familial Paget disease, and 5% to 10% of sporadic cases, harbor mutations in the SQSTM1 gene. The net effect of these mutations is to increase the activity of NF-κB.
  - Activating mutations in RANK and inactivating mutations in OPG account for some cases of juvenile Paget disease.
  - Cell culture studies have show modulation of vitamin D sensitivity and IL-6 secretion by virally infected osteoclasts. These results suggest that chronic infection of osteoclast precursors by measles or other RNA viruses may play a role in the disease. The geographic distribution is also consistent with some environmental influence.
MORPHOLOGY:

Paget disease shows remarkable histologic variation over time and from site to site. The hallmark is a mosaic pattern of lamellar bone, seen in the sclerotic phase. This jigsaw puzzle-like appearance is produced by unusually prominent cement lines, which join haphazardly oriented units of lamellar bone.
Figure 26-13 Mosaic pattern of lamellar bone pathognomonic of Paget disease.
The findings during the other phases are less specific. In the initial lytic phase there are waves of osteoclastic activity and numerous resorption pits. The osteoclasts are abnormally large and have many more than the normal 10 to 12 nuclei; sometimes 100 nuclei are present. Osteoclasts persist in the mixed phase, but now many of the bone surfaces are lined by prominent osteoblasts.
- **Clinical Course:**
  - Clinical findings are extremely variable and depend on the extent and site of the disease.
  - Most cases are **asymptomatic** and are discovered as an incidental **radiographic finding**.
  - Paget disease is **monostotic in about 15% of cases** and **polyostotic** in the remainder.
  - **The axial skeleton or proximal femur** is involved in up to 80% of cases.
  - **Pain** localized to the affected bone is common. It is caused by microfractures or by bone overgrowth that compresses spinal and cranial nerve roots.
  - **Enlargement of the craniofacial skeleton** may produce leontiasis ossea (**lion face**) and a cranium so heavy that is difficult for the person to hold the head erect. The weakened Pagetic bone may lead to invagination of the skull base (**platybasia**) and compression of the posterior fossa. Weight bearing causes anterior bowing of the femurs and tibiae and distorts the femoral heads, resulting in the development of severe secondary osteoarthritis.
• **Chalk stick-type fractures** are another frequent complication and usually occur in the long bones of the lower extremities.

• Compression fractures of the spine result in **spinal cord injury** and the development of kyphosis.

• The hypervascularity of Pagetic bone warms the overlying skin, and in severe polyostotic disease the increased blood flow acts like an arteriovenous shunt, leading to **high-output heart failure** or exacerbation of underlying cardiac disease.

• A variety of **tumor and tumor-like conditions** develop in Pagetic bone (**osteosarcoma**).
In the absence of malignant transformation, Paget disease is usually not a serious or life-threatening disease. Most affected individuals have mild symptoms that are readily suppressed by treatment with calcitonin and bisphosphonates.
The term osteopenia refers to decreased bone mass, and osteoporosis is defined as osteopenia that is severe enough to significantly increase the risk of fracture.

Radiographically, osteoporosis is considered bone mass at least 2.5 standard deviations below mean peak bone mass in young adults and osteopenia as 1 to 2.5 standard deviations below the mean.

The disorder may be localized to a certain bone or region, as in disuse osteoporosis of a limb, or may involve the entire skeleton, as a manifestation of a metabolic bone disease. Generalized osteoporosis, in turn, may be primary or secondary to a large variety of conditions.
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<tr>
<th>Table 26-4 Categories of Generalized Osteoporosis</th>
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<tr>
<td><strong>Primary</strong></td>
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<td>Idiopathic</td>
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<td>Postmenopausal</td>
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<td>Senile</td>
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<td><strong>Secondary</strong></td>
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<td><strong>Endocrine Disorders</strong></td>
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<td>Addison disease</td>
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<td>Diabetes, type 1</td>
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<td>Neoplasia</td>
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<td>Carcinomatosis</td>
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<td>Multiple myeloma</td>
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<td><strong>Gastrointestinal</strong></td>
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<td>Hepatic insufficiency</td>
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<td>Malabsorption</td>
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<td>Malnutrition</td>
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<td>Vitamin C, D deficiencies</td>
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<td><strong>Drugs</strong></td>
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<td>Alcohol</td>
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<td>Anticoagulants</td>
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<td>Anticonvulsants</td>
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<td>Chemotherapy</td>
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<td>Corticosteroids</td>
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<td><strong>Miscellaneous</strong></td>
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<td>Anemia</td>
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<td>Homocystinuria</td>
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<td>Immobilization</td>
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<td>Osteogenesis imperfecta</td>
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<td>Pulmonary disease</td>
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• The most common forms of osteoporosis are the **senile and postmenopausal types**.
Pathogenesis:
- **Peak bone mass** is achieved during young adulthood.
- Its magnitude is determined largely by *hereditary* factors, especially polymorphisms in the genes that influence bone metabolism. **Physical activity, muscle strength, diet, and hormonal state** also make important contributions.
- Once maximal skeletal mass is attained, a **small deficit in bone formation** accrues with every resorption and formation cycle of each bone metabolic unit. Accordingly, *age-related bone loss*, which may average **0.7% per year**, is a normal and predictable biologic phenomenon. Both sexes are affected equally and whites more so than blacks. **Gender and racial differences** in peak bone mass may partially explain why certain populations are prone to develop this disorder.
• **senile osteoporosis/low-turnover variant osteoporosis:**

- **Age-related changes** in bone cells and matrix have a strong impact on bone metabolism.
- Osteoblasts from older individuals have reduced proliferative and biosynthetic potential when compared with osteoblasts from younger individuals.
- Also, the **cellular response to growth factors** bound to the extracellular matrix becomes **attenuated in older individuals**. **The net result is a diminished capacity to make bone.**
Postmenopausal osteoporosis/ high-turnover osteoporosis:
- characterized by an acceleration of bone loss.
- In the decade after menopause, yearly reductions in bone mass may reach up to 2% of cortical bone and 9% of cancellous bone.
- It is thus no surprise that post-menopausal women suffer osteoporotic fractures more commonly than men of the same age.
- Estrogen deficiency plays the major role in this phenomenon and close to 40% of postmenopausal women are affected by osteoporosis. Decreased estrogen levels after menopause actually increase both bone resorption and formation but the latter does not keep up with the former, leading to high-turnover osteoporosis.
- The decreased estrogen appears to increase secretion of inflammatory cytokines (IL-6, TNF-α, and IL-1) by blood monocytes and bone marrow cells. These cytokines stimulate osteoclast recruitment and activity by increasing the levels of RANKL, diminishing the expression of OPG, and preventing osteoclast apoptosis.
Figure 26-9 Pathophysiology of postmenopausal and senile osteoporosis (see text).
Reduced physical activity increases the rate of bone loss in experimental animals and humans, because mechanical forces stimulate normal bone remodeling. Bone loss in an immobilized or paralyzed extremity, the reduction of skeletal mass in astronauts in a zero gravity environment for prolonged periods, and the higher bone density in athletes exemplify the role of physical activity in preventing bone loss. The decreased physical activity that is associated with normal aging contributes to senile osteoporosis.
• **Genetic factors:** LRP5, RANKL, OPG, and RANK genes

• **Calcium nutritional state:** contributes to peak bone mass. **Adolescent girls** (more than boys) tend to have **insufficient calcium intake** in the diet. This calcium deficiency occurs during a period of rapid bone growth, restricting the peak bone mass ultimately achieved. Thus, these individuals are at greater risk of developing osteoporosis. Calcium deficiency, **increased PTH concentrations**, and **reduced levels of vitamin D** may also have a role in the development of **senile osteoporosis**.
• **MORPHOLOGY:**
  - The entire skeleton is affected in postmenopausal and senile osteoporosis, but certain bones tend to be more severely impacted.
  - The hallmark of osteoporosis is histologically normal bone that is decreased in quantity.
  - **In postmenopausal osteoporosis** the increase in osteoclast activity affects mainly bones or portions of bones that have increased surface area, such as the cancellous compartment of vertebral bodies. The trabecular plates become perforated, thinned, and lose their interconnections, leading to progressive microfractures and eventual vertebral collapse.
  - **In senile osteoporosis** the cortex is thinned by subperiosteal and endosteal resorption and the Haversian systems are widened. In severe cases the Haversian systems are so enlarged that the cortex mimics cancellous bone.
Clinical Course:
- **Vertebral fractures** that frequently occur in the thoracic and lumbar regions are painful, and, when multiple, can cause significant loss of height and various deformities, including lumbar lordosis and kyphoscoliosis.
- Complications of fractures of the femoral neck, pelvis, or spine, such as *pulmonary embolism*, are frequent and result in **40,000 to 50,000 deaths** per year.
• Osteoporosis cannot be reliably detected in plain radiographs until 30% to 40% of the bone mass is lost.
• dual-energy x-ray absorptiometry (DEXA) measures bone density.
• The prevention and treatment of senile and postmenopausal osteoporosis includes exercise, appropriate calcium and vitamin D intake, and pharmacologic agents, most commonly bisphosphonates, which reduce osteoclast activity and induce apoptosis. Although menopausal hormone therapy has been used to prevent fracture, complications, particularly deep venous thrombosis and stroke, have prompted search for more selective estrogen receptor modulators.
Rickets and Osteomalacia

- Both rickets and osteomalacia are manifestations of vitamin D deficiency (limited exposure to sunlight) or its abnormal metabolism.
- The fundamental defect is an impairment of mineralization and a resultant accumulation of unmineralized matrix. 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 whom it interferes with the deposition of bone in the growth plates. Craniotabes, squared appearance to the head, rachitic rosary, pigeon breast deformity, lumbar lordosis and bowing of the legs.
- **Osteomalacia** is the adult counterpart, in which bone formed during remodeling is undermineralized, resulting in predisposition to fractures.
Osteomyelitis

• Osteomyelitis denotes inflammation of bone and marrow, virtually always secondary to infection.
• Osteomyelitis may be a complication of any systemic infection but frequently manifests as a primary solitary focus of disease. All types of organisms, including viruses, parasites, fungi, and bacteria, can produce osteomyelitis, but infections caused by certain pyogenic bacteria and mycobacteria are the most common.
Pyogenic Osteomyelitis

• Pyogenic osteomyelitis is almost always caused by bacterial infections.
• **Organisms may reach the bone by:**
  (1) hematogenous spread (bacteremia)
  (2) extension from a contiguous site
  (3) direct implantation.

- In otherwise healthy children, most osteomyelitis is *hematogenous in origin* and develops in the long bones.
- In adults, however, osteomyelitis more often occurs as a complication of **open fractures**, surgical procedures, and diabetic infections of the feet.
Staphylococcus aureus is responsible for 80% to 90% of the cases of culture-positive pyogenic osteomyelitis.

Escherichia coli, Pseudomonas, and Klebsiella are more frequently isolated from individuals with genitourinary tract infections or who are intravenous drug abusers.

Mixed bacterial infections are seen in the setting of direct spread or inoculation of organisms during surgery or into open fractures.

In the neonatal period, Haemophilus influenzae and group B streptococci are frequent pathogens.

Individuals with sickle cell disease are predisposed to Salmonella infection.

In almost 50% of suspected cases, no organisms can be isolated.
The location of the bone infections is influenced by the osseous vascular circulation, which varies with age:

- **In the neonate** the metaphyseal vessels penetrate the growth plate, resulting in frequent infection of the metaphysis, epiphysis, or both.

- **In children**, localization of microorganisms in the metaphysis is typical.

- After growth plate closure, the metaphyseal vessels reunite with their epiphyseal counterparts and provide a route for the bacteria to seed the epiphyses and subchondral regions, which are common sites of infection in the **adult**.
In infants, but uncommonly in adults, **epiphyseal infection spreads** through the articular surface or along capsular and tendoligamentous insertions into a joint, producing septic or **suppurative arthritis**, which can cause destruction of the articular cartilage and permanent disability.
• **the acute phase**, bacteria proliferate and induce a neutrophilic inflammatory reaction. Necrosis of bone cells and marrow ensues within the first 48 hours. **The dead bone is known as a sequestrum.**

• Rupture of the periosteum leads to a soft tissue abscess which can channel to the skin as a draining sinus.

• After the first week, chronic inflammatory cells release cytokines that stimulates osteoclastic bone resorption, ingrowth of fibrous tissue, and the deposition of reactive bone at the periphery. **The newly deposited bone can form a shell of living tissue, known as an involucrum.**
Figure 26-20 Resected femur in a person with draining osteomyelitis. The drainage tract in the subperiosteal shell of viable new bone (involucrum) reveals the inner native necrotic cortex (sequestrum).
- Clinical Course:
  - Hematogenous osteomyelitis sometimes manifests as an **acute systemic illness** with malaise, fever, chills, leukocytosis, and marked-to-intense throbbing pain over the affected region.
  - In other instances, the presentation is subtle, with only **unexplained fever** (most often in infants) or localized pain (most often in adults).
  - The combination of **antibiotics and surgical drainage** is usually curative.
• In 5% to 25% of cases, **acute osteomyelitis fails to resolve and persists as chronic infection.**

• Chronic infections may develop when there is delay in diagnosis, extensive bone necrosis, inadequate antibiotic therapy or surgical debridement, or weakened host defenses.

• The course of chronic infections may be punctuated by acute flare-ups; these are usually spontaneous and may occur after years of dormancy.

• Other complications of chronic osteomyelitis include pathologic fracture, secondary amyloidosis, endocarditis, sepsis, and **development of squamous cell carcinoma in the draining sinus tracts** and sarcoma in the infected bone.