Pathology of bones and joints

Inflammation, bone tumors and metabolic disorders

Plan

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Bones

- The skeletal system has an essential role in mineral homeostasis, houses the hematopoietic elements, provides mechanical support for movement, protects viscera, and determines body size and shape.
- Despite bones stony hard structure, it is a dynamic tissue that is continuously resorbed, renewed, and remodeled.
- These processes are carried out by several different types of bone cells that are regulated by a number of transcription factors, cytokines, and growth factors

Bone Modeling, Remodeling, and Peak Bone Mass

- Local collections of osteocytes, osteoblasts, and osteoclasts work together to control bone **formation and resorption**, creating a functional unit referred to as the **basic multicellular unit** (BMU).
- Peak bone mass is achieved in early adulthood after the cessation of growth.
- Bone growth is determined by a variety of factors, including polymorphisms in the receptors for vitamin D and LRP5/6, nutrition, physical activity, age, and hormonal status.

Developmental Abnormalities in Bone Cells, Matrix, and Structure

- Developmental anomalies resulting from localized problems in the migration of the mesenchymal cells and the formation of the condensations are **dysostoses**.
- Mutations in the regulators of skeletal organogenesis affect cartilage and bone tissues globally are known as **dysplasias**.

MALFORMATIONS AND DISEASES CAUSED BY DEFECTS IN NUCLEAR PROTEINS AND TRANSCRIPTION FACTORS

- **failure of a bone to develop** (congenital absence of a phalanx, rib, or clavicle);
- **formation of extra bones** (supernumerary ribs or digits);
- **fusion of two adjacent digits** (syndactylism);
- **development of long, spider-like digits**.
- **extra digit between the third and fourth fingers** (mutation in the homeoboxHOXD13 gene)
- **cleidocranial dysplasia,** an autosomal dominant disorder characterized by patent fontanelles, delayed closure of cranial sutures, Wormian bones and short height (loss of function mutations in the RUNX2 gene)

DISEASES CAUSED BY DEFECTS IN HORMONES AND SIGNAL TRANSDUCTION MECHANISM

- Achondroplasia is an **autosomal dominant** disorder.
- Achondroplasia is **the most common disease** of the growth plate and is a major cause of dwarfism. It is caused by a mutation in the FGF receptor 3.
- Patients have shortened proximal extremities, a trunk of relative normal length, and an enlarged head with bulging forehead and conspicuous depression of the root of the nose.
- **Not associated** with changes in longevity, **intelligence,** or reproductive status.

DISEASES CAUSED BY DEFECTS IN HORMONES AND SIGNAL TRANSDUCTION MECHANISM

- Thanatophoric dwarfism is the **most common lethal** form of dwarfism.
- It is also caused by gain-of-function mutations in FGFR3.
- Affected individuals have **micromelic shortening of the limbs**, frontal bossing, relative macrocephaly, a small chest cavity, and a bell-shaped abdomen.
- The underdeveloped thoracic cavity leads to **respiratory insufficiency**, and patients frequently **die at birth or soon after**.

DISEASES CAUSED BY DEFECTS IN HORMONES AND SIGNAL TRANSDUCTION MECHANISM

- These diseases, namely endosteal **hyperostosis, Van Buchem disease, and autosomal dominant osteopetrosis type 1**, are characterized by **increased bone mass** including cortical thickening, enlarged and elongated mandible, and increased density and enlargement of the cranial vault; some affected individuals may develop torus palatinus.
- Caused by caused by gain-of-function mutations in the gene that encodes **LPR5.**

DISEASES ASSOCIATED WITH DEFECTS IN EXTRACELLULAR STRUCTURAL PROTEINS

- The importance of the structural bone proteins is exemplified by the diseases associated with deranged metabolism of the collagens important in bone and cartilage formation (types 1, 2, 9, 10, and 11).
- Their clinical manifestations are highly variable, ranging from **lethal disease to premature osteoarthritis**.

Type 1 Collagen Diseases (Osteogenesis Imperfecta)

- **Osteogenesis imperfecta, or brittle bone disease**, is a phenotypically diverse disorder caused by deficiencies in the synthesis of type 1 collagen. It is **the most common** inherited disorder of connective tissue.
- Osteogenesis imperfecta usually results from autosomal dominant mutations in the genes that encode the α1 and α2 chains of collagen and mutations in the genes for cartilage-associated protein (CRTAP) and leucine proline-enriched proteoglycan 1 (LEPRE1).
- Clinically, osteogenesis imperfecta is separated into **four major subtypes**.
- The **type II** variant is at one end of the spectrum and is **uniformly fatal** in utero or during the perinatal period. It is characterized by extraordinary bone fragility with multiple **intrauterine fractures**.
- Patients with the **type I** form have a normal life span but experience childhood fractures that decrease in frequency following puberty. Other findings include blue sclerae caused by decreased collagen content; hearing loss; and dental imperfections (small, misshapen, and blue-yellow teeth).

Diseases Associated with Mutations of Types 2, 9, 10, and 11 Collagen

- Types 2, 9, 10, and 11 collagens are important structural components of hyaline cartilage.
- Although uncommon, mutations in the genes encoding them produce an array of disorders ranging from the fatal to those compatible with life but associated with early destruction of joints.
- In the severe disorders, the type 2 collagen molecules are not secreted by the chondrocytes, and insufficient bone formation occurs.

DISEASES ASSOCIATED WITH DEFECTS IN FOLDING AND DEGRADATION OF MACROMOLECULES.

Mucopolysaccharidoses

- The mucopolysaccharidoses are a group of lysosomal storage diseases that are caused by deficiencies in the enzymes that degrade dermatan sulfate, heparan sulfate, and keratan sulfate.
- Mesenchymal cells, especially chondrocytes, normally metabolize extracellular matrix mucopolysaccharides.
- Many of the skeletal manifestations of the mucopolysaccharidoses result from abnormalities in hyaline cartilage: cartilage anlage, growth plates, costal cartilages, and articular surfaces.

DISEASES ASSOCIATED WITH DEFECTS IN METABOLIC PATHWAYS (ENZYMES, ION CHANNELS, AND TRANSPORTERS)

Osteopetrosis

Marble bone disease and Albers Schönberg disease, refers to a group of rare genetic diseases that are characterized by reduced bone resorption and diffuse symmetric skeletal sclerosis due to impaired formation or function of osteoclasts.

The two major groups include autosomal recessive and dominant forms.

Pathogenesis. Most of the mutations underlying osteopetrosis interfere with the process of acidification of the osteoclast resorption pit, which is required for the dissolution of the calcium hydroxyapatite within the matrix. Patients have fewer osteoclasts than normal.

Morphology. Deficient osteoclast activity. The bones lack a medullary canal, and the ends of long bones are bulbous and misshapen. The neural foramina are small and compress exiting nerves. Deposited bone is not remodeled and tends to be woven in architecture. In the end, these intrinsic abnormalities cause the bone to be brittle and predisposed to fracture. Histologically, the number of osteoclasts may be normal, increased, or decreased.

Clinical Features. Usually becomes evident in utero or soon after birth. Fracture, anemia, and hydrocephaly are often seen, resulting in postpartum mortality. Ones who survive into their infancy have cranial nerve defects (optic atrophy, deafness, and facial paralysis) and repeated—often fatal—infections.

Osteopetrosis was the first genetic disease treated with **bone marrow transplantation**

DISEASES ASSOCIATED WITH DECREASED BONE MASS. **Osteoporosis**

- Osteoporosis is a disease characterized by porous bones and a **reduced bone mass.**
- The associated structural changes predispose the bone to fracture.
- 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 may be primary or secondary.
- Effective treatment and prevention are imperative.

Osteoporosis. Pathogenesis.

- Both sexes are affected equally and whites more so than blacks.
- Decreased physical activity that is associated with aging contributes to senile osteoporosis.
- Genetic factors are also important - RANKL, OPG, and RANK, which encode key regulators of osteoclasts.
- Calcium deficiency, increased PTH concentrations, and reduced levels of vitamin D may also have a role in the development of senile osteoporosis.
- Women may lose as much as 35% of their cortical bone and 50% of their trabecular bone within the 30 to 40 years after menopause.

Osteoporosis. Morphology.

- The entire skeleton is affected in postmenopausal and senile osteoporosis.
- 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.

Osteoporosis. Clinical Course.

- The clinical manifestations of osteoporosis depend on which bones are involved. 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 and pneumonia.
- Osteoporosis cannot be reliably detected in plain radiograms.
- Osteoporosis is a difficult condition to diagnose accurately, since it remains asymptomatic until skeletal fragility is well advanced.
- The best procedures to accurately estimate the amount of bone loss are specialized radiographic imaging techniques, such as dual-energy X-ray absorptiometry and quantitative computed tomography, which measure bone density.

DISEASES CAUSED BY OSTEOCLAST DYSFUNCTION
Paget Disease (Osteitis Deformans)

- This unique skeletal disease can be divided into three phases;
- (1) an initial osteolytic stage,
- followed by (2) a mixed osteoclastic-osteoblastic stage, which ends with a predominance of osteoblastic activity and
- evolves ultimately into (3) a burnt-out quiescent osteosclerotic stage.

Paget disease usually begins in **late adulthood** (average age at diagnosis, 70 years).

Paget Disease (Osteitis Deformans) Pathogenesis.

- The cause of Paget disease remains uncertain, and current evidence suggests both environmental and genetic factors.
- The risk of developing the disorder is approximately seven times greater in first-degree relatives of affected individuals.
- Mutations in the SQSTM1 gene are present in 40% to 50% of cases of familial Paget disease, and in 5% to 10% of patients without a family history.
- Mutations in RANKL and RANK/OPG have also been found in genetic diseases that have some phenotypic overlap with Paget disease.
- When Sir James Paget first described this condition in 1876, he attributed the skeletal changes to an inflammatory process, hence the term osteitis deformans.

Paget Disease (Osteitis Deformans) Morphology.

- Paget disease is a focal process that shows remarkable histologic variation over time and from site to site. The hallmark is the mosaic pattern of lamellar bone.
- 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. The marrow adjacent to the bone-forming surface is replaced by loose connective tissue that contains osteoprogenitor cells and numerous blood vessels.
- The newly formed bone may be woven or lamellar, but eventually all of it is remodeled into lamellar bone. As the mosaic pattern unfolds and the cell activity decreases, the periosseous fibrovascular tissue recedes and is replaced by normal marrow.
- In the end, the bone becomes a caricature of itself: larger than normal and composed of coarsely thickened trabeculae and cortices that are soft and porous and lack structural stability.

Paget Disease (Osteitis Deformans) Clinical Course.

- Most cases are mild 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 compressesspinal and cranial nerve roots. Enlargement of the craniofacial skeleton may produce **leontiasis ossea** 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 structures. Weight bearing causes anterior bowing of the femurs and tibiae and distorts the femoral heads, resulting in the development of severe secondary osteoarthritis.
- **Chalkstick-type fractures** usually occur in the long bones of the **lower extremities**. **Compression fractures** of the spine result in spinal cord injury and the development of kyphoses.
- A variety of **tumor and tumor-like conditions develop in pagetic bone**. The benign lesions include giant-cell tumor, giant-cell reparative granuloma, and extra-osseous masses of hematopoiesis.
- Paget disease is **usually not a serious or life-threatening disease**.

DISEASES ASSOCIATED WITH ABNORMAL MINERAL HOMEOSTASIS. Rickets and Osteomalacia

- Rickets and osteomalacia are disorders characterized by a defect in matrix mineralization, most often related to a lack of vitamin D or some disturbance in its metabolism.
- The term **rickets** refers to the **disorder in children** in which deranged bone growth produces distinctive skeletal deformities.
- In the **adult** the disorder is called **osteomalacia**, because the bone that forms during the remodeling process is inadequately mineralized. This results in osteopenia and predisposition to insufficiency fractures

DISEASES ASSOCIATED WITH ABNORMAL MINERAL HOMEOSTASIS

Hyperparathyroidism

- Hyperparathyroidism is classified into primary and secondary types.
- Primary hyperparathyroidism results from autonomous hyperplasia or a tumor of the parathyroid gland, whereas secondary hyperparathyroidism is commonly caused by prolonged states of hypocalcemia resulting in compensatory hypersecretion of PTH.
- increased PTH concentrations are detected by receptors on osteoblasts, which then release factors that stimulate osteoclast activity.
- the skeletal manifestations of hyperparathyroidism are caused by unabated osteoclastic bone resorption.
- the entire skeleton is affected in hyperparathyroidism.
- Secondary hyperparathyroidism is usually not as severe or as prolonged as primary hyperparathyroidism, hence the skeletal abnormalities tend to be milder

Hyperparathyroidism. Morphology.

- For unknown reasons, the increased osteoclast activity in hyperparathyroidism affects cortical bone more severely than cancellous bone.
- Subperiosteal resorption produces thinned cortices and the loss of the lamina dura around the teeth.
- X-rays reveal a pattern of radiolucency that is virtually diagnostic of hyperparathyroidism.
- In cancellous bone, osteoclasts tunnel into and dissect centrally along the length of the trabeculae, creating the appearance of railroad tracks and producing what is known as dissecting osteitis .
- The correlative radiographic finding is a decrease in bone density or osteopenia
- The bone loss predisposes to microfractures and secondary hemorrhages that elicit an influx of macrophages and an ingrowth of reparative fibrous tissue, creating a mass of reactive tissue, known as a brown tumor. The brown color is the result of the vascularity, hemorrhage, and hemosiderin deposition, and it is not uncommon for the lesions to undergo cystic degeneration.
- The combined picture of increased bone cell activity, peritrabecular fibrosis, and cystic brown tumors is the hallmark of severe hyperparathyroidism and is known as generalized osteitis fibrosa cystica (**von Recklinghausen disease of bone**).

Renal Osteodystrophy

The term renal osteodystrophy is used to describe collectively all of the skeletal changes of chronic renal disease, including:

- (1) increased osteoclastic bone resorption mimicking osteitisfibrosa cystica,
- (2) delayed matrix mineralization (osteomalacia),
- (3) osteosclerosis,
- (4) growth retardation,
- (5) osteoporosis.

The various histologic bone changes in individuals with end-stage renal failure can be divided into three major types of disorders.

High-turnover osteodystrophy is characterized by increased bone resorption and bone formation, with the former predominating.

Low-turnover or aplastic disease is manifested by adynamic bone (little osteoclastic and osteoblastic activity) and, less commonly, osteomalacia.

Many affected individuals have the third type, which is a mixed pattern of disease

Renal Osteodystrophy. Pathogenesis.

Chronic renal failure results in phosphate retention and hyperphosphatemia.

Hyperphosphatemia induces secondary hyperparathyroidism, because phosphate seems to regulate PTH secretion directly.

Hypocalcemia ➡ vitamin D fall (decreased conversion from the vitamin D metabolite) ➡ inhibition of the renal hydroxylase ➡ high levels of phosphate ➡ reduced intestinal absorption of calcium.

There is decreased degradation and excretion of PTH because of compromised renal function.

The resultant secondary hyperparathyroidism produces increased osteoclast activity.

Fractures

- Traumatic and nontraumatic fractures are some of the most common pathologic conditions affecting bone.
- Fractures are classified as complete or incomplete; closed (simple) when the overlying tissue is intact; compound when the fracture site communicates with the skin surface; comminuted when the bone is splintered; or displaced when the ends of the bone at the fracture site are not aligned.
- If the break occurs in bone already altered by a disease process, it is described as a pathologic fracture.
- A stress fracture is a slowly developing fracture that follows a period of increased physical activity in which the bone is subjected to new repetitive loads.

Fractures

fracture

↓

hematoma, which fills the fracture gap

↓

fibrin mesh

↓

activation the osteoprogenitor cells

↓

stimulation osteoclastic and osteoblastic activity

↓

formation of uncalcified soft-tissue callus

↓

osteoprogenitor cells deposit subperiosteal trabeculae of woven bone

↓

fibrocartilage and hyaline cartilage

↓

newly formed cartilage along the fracture line undergoes enchondral ossification

↓

leftovers of bony callus resorbed

Osteonecrosis (Avascular Necrosis)

Infarction of bone and marrow is a relatively common event that can occur in the medullary cavity of the metaphysis or diaphysis and the subchondral region of the epiphysis.

Ischemia underlies all forms of bone necrosis, which can occur in the setting of diverse predisposing conditions or as an isolated, idiopathic event.

Aside from fracture, most cases of bone necrosis either are idiopathic or follow corticosteroid administration

Osteonecrosis. Morphology.

- Medullary infarcts are geographic and involve the cancellous bone and marrow.
- In subchondral infarcts, a triangular or wedgeshaped segment of tissue that has the subchondral bone plate as its base undergoes necrosis.
- The overlying articular cartilage remains viable because it receives nutrition from the synovial fluid. The dead bone, recognized by its empty lacunae, is surrounded by necrotic adipocytes that frequently rupture, releasing their fatty acids, which bind calcium and form insoluble calcium soaps that may persist for life.
- In subchondral infarcts the pace of this substitution is too slow to be effective, so there is eventual collapse of the necrotic cancellous bone and distortion, fracture, and even sloughing of the articular cartilage

Osteonecrosis. Clinical Course.

- The symptoms depend on the location and extent of infarction.
- Subchondral infarcts cause chronic pain that is initially associated only with activity but then becomes progressively more constant as secondary changes supervene.
- Medullary infarcts are clinically silent except for large ones occurring in Gaucher disease, dysbarism, and sickle cell anemia. Medullary infarcts usually remain stable over time.
- Subchondral infarcts often collapse and may predispose to severe, secondary osteoarthritis

Infections—Osteomyelitis

- Osteomyelitis denotes inflammation of bone and marrow, and the common use of the term virtually always implies 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 bacteria.
- Organisms may reach the bone by (1) hematogenous spread, (2) extension from a contiguous site, and (3) direct implantation.
- In otherwise healthy children, most cases of osteomyelitis are hematogenous in origin and develop in the long bones
- In adults, 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%.
- 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 open fractures.
- In the neonatal period, Haemophilus influenzae and group B streptococci are frequent pathogens.

PYOGENIC OSTEOMYELITIS Morphology.

- The morphologic changes of osteomyelitis depend on the stage (acute, subacute, or chronic) and location of the infection.
- Once in bone, the bacteria proliferate and induce an acute inflammatory reaction. The entrapped bone undergoes necrosis within the first 48 hours, and the bacteria and inflammation spread within the shaft of the bone and may percolate throughout the haversian systems to reach the periosteum.
- In children the periosteum is loosely attached to the cortex; sizable subperiosteal abscesses may form that can track for long distances along the bone surface; the dead piece of bone is known as a sequestrum.
- In **infants** 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**.
- After the first week chronic inflammatory cells become more numerous and their release of cytokines stimulates **osteoclastic bone resorption**, ingrowth of fibrous tissue, and the deposition of reactive bone in the periphery.
- When the newly deposited bone forms a sleeve of living tissue around the segment of devitalized infected bone, it is known as an **involucrum**.
- Several morphologic variants of osteomyelitis have eponyms: **Brodie abscess** is a small intraosseous abscess that frequently involves the cortex and is walled off by reactive bone; **sclerosing osteomyelitis of Garré** typically develops in the jaw and is associated with extensive new bone formation that obscures much of the underlying osseous structure

PYOGENIC OSTEOMYELITIS
Clinical Course.

- Clinically, hematogenous osteomyelitis may manifest as an acute systemic illness with malaise, fever, chills, leukocytosis, and marked-to-intense throbbing pain over the affected region.
- The diagnosis can be strongly suggested by the characteristic radiographic findings of a lytic focus of bone destruction surrounded by a zone of sclerosis.
- The combination of antibiotics and surgical drainage is usually curative.

TUBERCULOUS OSTEOMYELITIS

- Approximately 1% to 3% of individuals with pulmonary or extrapulmonary tuberculosis have osseous infection.
- The organisms are usually blood borne and originate from a focus of active visceral disease during the initial stages of primary infection.
- Direct extension (from a pulmonary focus into a rib or from tracheobronchial nodes into adjacent vertebrae) or spread via draining lymphatics may also occur. The bony infection is usually solitary and in some cases may be the only manifestation of the disease that may fester for years before being recognized.
- In the spine (Pott disease) the infection breaks through intervertebral discs to involve multiple vertebrae and extends into the soft tissues forming abscesses.
- The histologic findings are **typical of tuberculosis** elsewhere.
- Patients present with pain on motion, localized tenderness, low-grade fevers, chills, and weight loss.
- Severe destruction of vertebrae frequently results in permanent compression fractures that produce severe scoliotic or kyphotic deformities and neurologic defi cits secondary to spinal cord and nerve compression.

SKELETAL SYPHILIS

- In congenital syphilis the bone lesions begin to appear about the fifth month of gestation and are fully developed at birth. The spirochetes tend to localize in areas of active enchondral ossification (osteochondritis) and in the periosteum (periostitis).
- In acquired syphilis bone disease may begin early in the tertiary stage, which is usually 2 to 5 years after the initial infection. The bones most frequently involved are those of the nose, palate, skull, and extremities, especially the long tubular bones such as the tibia. The syphilitic saber shin is produced by massive reactive periosteal bone deposition on the medial and anterior surfaces of the tibia.
- Morphology. Syphilitic bone infection is characterized by edematous granulation tissue containing numerous plasma cells and necrotic bone. Typical gummas may also form.

Bone Tumors and Tumor-Like Lesions

- Can be innocuous to the rapidly fatal.
- Patients It is critical to diagnose these tumors correctly, stage them accurately, and treat them appropriately, so that affected patients not only survive, but also maintain optimal function of the affected body parts.
- classified according to the normal cell or tissue type they recapitulate.
- Matrix-producing and fibrous tumors are the most common, and among the benign tumors, osteochondroma and fibrous cortical defect are most frequent.
- Excluding malignant neoplasms of marrow origin, osteosarcoma is the most common primary cancer of bone, followed by chondrosarcoma and Ewing sarcoma.
- Benign tumors greatly outnumber their malignant counterparts and occur with greatest frequency within the first three decades of life, whereas in the elderly a bone tumor is likely to be malignant.
- The more common benign lesions are frequently asymptomatic and are detected as incidental findings. Many tumors, however, produce pain or are noticed as a slow-growing mass.
- In some circumstances the first hint of a tumor’s presence is a sudden pathologic fracture.
- Radiologic imaging studies have an important role in diagnosing these lesions.

BONE-FORMING TUMORS

- Osteoma
- Osteoid Osteoma and Osteoblastoma
- Osteosarcoma

Osteoma

- Osteomas are bosselated, round-to-oval sessile tumors that project from the subperiosteal surface of the cortex.
- arise on or inside the skull and facial bones.
- They are usually solitary and are detected in middle age.
- Multiple osteomas are seen in the setting of Gardner syndrome.
- They consist of a composite of woven and lamellar bone that is frequently deposited in a cortical pattern with haversian-like systems.
- Osteomas are generally slow-growing tumors of little clinical significance except when they cause obstruction of a sinus cavity, impinge on the brain or eye, interfere with function of the oral cavity, or produce cosmetic problems.

Osteoid Osteoma and Osteoblastoma

- Osteoid osteoma and osteoblastoma are terms used to describe benign bone tumors that have identical histologic features but differ in size, sites of origin, and symptoms.
- **Osteoid osteomas are less than 2 cm** in greatest dimension and usually occur in the teens and 20s, men outnumber women 2 : 1.
- They can arise in any bone but have a predilection for the appendicular skeleton and posterior elements of the spine.
- Osteoid osteomas produce severe nocturnal pain that is relieved by aspirin.
- **Osteoblastoma is larger than 2 cm** and involves the spine more frequently; the pain is dull, achy, and unresponsive to salicylates, and the tumor usually does not induce a marked bony reaction.
- **Morphology**. Osteoid osteoma and osteoblastoma are round-to-oval masses of hemorrhagic gritty tan tissue. They are well circumscribed and composed of randomly interconnecting trabeculae of woven bone that are prominently rimmed by osteoblasts. The actual tumor, known as the nidus, manifests radiographically as a small round lucency that may be centrally mineralized. Osteoid osteoma is frequently treated by radioablation. Osteoblastoma is usually curetted or excised en bloc in a conservative fashion.

Osteosarcoma

- Osteosarcoma is a malignant mesenchymal tumor in which the cancerous cells produce bone matrix.
- It is the most common primary malignant tumor of bone.
- Osteosarcoma occurs in all age groups but has a bimodal age distribution; 75% occur in persons younger than 20 years of age. The smaller second peak occurs in the elderly, who frequently suffer from conditions known to predispose to osteosarcoma—Paget disease, bone infarcts, and prior irradiation.
- men are more commonly affected than women (1.6 : 1).
- The tumors usually arise in the metaphyseal region of the long bones of the extremities, and almost 50% occur about the knee.

Osteosarcoma. Pathogenesis.

- Although the basic mechanisms that cause the development of osteosarcoma are still unknown, it is clear that defects in RB and p53 play important roles in the process.
- This association is emphasized by rare patients with germline mutations in RB, who have a roughly 1000-fold increased risk of osteosarcoma; and similarly by patients with Li-Fraumeni syndrome (germline p53 mutations), who also have a greatly elevated incidence of this tumor.
- Abnormalities in INK4a, which encodes p16 (a cell cycle regulator) and p14 (which aids and abets p53 function), also are seen in osteosarcoma.
- It is also noteworthy that osteosarcomas tend to occur at sites of bone growth, presumably because proliferation makes osteoblastic cells prone to acquire mutations that could lead to transformation.

Osteosarcoma. Morphology.

- Several subtypes of osteosarcoma are recognized and are grouped according to site of origin (intramedullary, intracortical, or surface)
- Degree of differentiation
- Multicentricity (synchronous, metachronous) Primary (underlying bone is unremarkable) or secondary to preexisting disorders such as benign tumors, Paget disease, bone infarcts, previous irradiation
- Histologic features (osteoblastic, chondroblastic, fibroblastic, telangiectatic, small cell, and giant cell).
- The most common subtype arises in the metaphysis of long bones and is primary, solitary, intramedullary, and poorly differentiated.
- Grossly, osteosarcomas are big bulky tumors that are gritty, gray-white, and often contain areas of hemorrhage and cystic degeneration. The tumors frequently destroy the surrounding cortices and produce soft-tissue masses.
- When joint invasion occurs, the tumor grows into it along tendoligamentous structures or through the attachment site of the joint capsule.
- Bizarre tumor giant cells are common, as are mitoses. The formation of bone by the tumor cells is characteristic.

Osteosarcoma. Clinical Course.

- Osteosarcomas typically present as painful, progressively enlarging masses.
- Sometimes a sudden fracture of the bone is the first symptom.
- Radiograms of the primary tumor usually show a large destructive, mixed lytic and blastic mass with infiltrative margins.
- The tumor frequently breaks through the cortex and lifts the periosteum, resulting in reactive periosteal bone formation.
- The triangular shadow between the cortex and raised ends of periosteum is known radiographically as Codman triangle. These aggressive neoplasms spread hematogenously, and at the time of diagnosis approximately 10% to 20% of affected individuals have demonstrable pulmonary metastases, and it is likely that many more have occult metastases.
- Osteosarcoma is treated with a multimodality approach.

CARTILAGE-FORMING TUMOR

- Osteochondroma
- Chondromas
- Chondroblastoma
- Chondromyxoid Fibroma
- Chondrosarcoma

Osteochondroma

- Osteochondroma, also known as an exostosis, is a benign cartilage-capped tumor that is attached to the underlying skeleton by a bony stalk.
- It is the most common benign bone tumor; about 85% are solitary. The remainder are seen as part of the multiple hereditary exostosis syndrome, which is an autosomal dominant hereditary disease. Hereditary exostoses are caused by germline loss-of-function mutations in either the EXT1 or EXT2 genes. Men are affected three times more often than women.
- Osteochondromas develop only in bones of endochondral origin and arise from the metaphysis near the growth plate of long tubular bones, especially about the knee. Occasionally, they develop from bones of the pelvis, scapula, and ribs, and in these sites they are frequently sessile and have short stalks.
- Morphology. Osteochondromas are sessile or mushroom shaped, and range in size from 1 to 20 cm. The cap is composed of benign hyaline cartilage varying in thickness and is covered peripherally by perichondrium. The cartilage has the appearance of dis organized growth plate and undergoes enchondral ossifi cation, with the newly made bone forming the inner portion of the head and stalk. The cortex of the stalk merges with the cortex of the host bone, so that the medullary cavity of the osteochondroma and bone are in continuity. Clinically, osteochondromas present as slow-growing masses, which can be painful if they impinge on a nerve or if the stalk is fractured. In many cases they are detected as an incidental finding. In multiple hereditary exostosis the underlying bones may be bowed and shortened, refl ecting an associated disturbance in epiphyseal growth.
- Osteochondromas usually stop growing at the time of growth plate closure.

Chondromas

- Chondromas are benign tumors of hyaline cartilage that usually occur in bones of enchondral origin. They can arise within the medullary cavity, where they are known as enchondromas, or on the surface of bone, where they are called subperiosteal or juxtacortical chondromas.
- Enchondromas are the most common at 20s to 40s.
- They are usually solitary metaphyseal lesions of tubular bones; the favored sites are the short tubular bones of the hands and feet. A syndrome of multiple enchondromas or enchondromatosis is known as Ollier disease. If the enchondromatosis is associated with soft-tissue hemangiomas, the disorder is called Maffucci syndrome.
- Morphology. Enchondromas are usually smaller than 3 cm and grossly are gray-blue and translucent. They are composed of well-circumscribed nodules of cytologically benign hyaline cartilage. The peripheral portion of the nodules may undergo enchondral ossifi cation, and the center can calcify and die.
- Clinical Features. Most enchondromas are asymptomatic and are detected incidentally. Occasionally they are painful and cause pathologic fracture. The tumors in enchondromatosis may be numerous and large, producing severe deformities. The radiographic features are characteristic; the unmineralized nodules of cartilage produce well-circumscribed oval lucencies that are surrounded by a thin rim of radiodense bone (C or O ring sign).
- Treatment depends on the clinical situation and is usually observation or curettage.

Chondroblastoma

- Chondroblastoma is a rare benign tumor that accounts for less than 1% of primary bone tumors. It usually occurs in young patients in their teens and has a male-to-female ratio of 2 : 1.
- Most arise about the knee. Chondroblastoma has a striking predilection for epiphyses and apophyses.
- Morphology. The tumor is composed of sheets of compact polyhedral chondroblasts that have welldefi ned cytoplasmic borders, moderate amounts of pink cytoplasm, and nuclei that are hyperlobulated with longitudinal grooves. Mitotic activity and necrosis are frequently present. The tumor cells are surrounded by scant amounts of hyaline matrix that is deposited in a lace-like configuration; nodules of well-formed hyaline cartilage are distinctly uncommon. When the matrix calcifies it produces a characteristic chicken-wire pattern of mineralization. Scattered through the lesion are nonneoplastic osteoclast-type giant cells.
- Chondroblastomas are usually painful, and because of their location near a joint they also cause effusions and restrict joint mobility. Radiographically, they produce a well-defined geographic lucency that commonly has spotty calcifications

Chondromyxoid Fibroma

- Chondromyxoid fibroma is the rarest of cartilage tumors and because of its varied morphology can be mistaken for sarcoma.
- It affects individuals in their teens and 20s and has a male preponderance.
- The tumors most frequently arise in the metaphysis of long tubular bones, but can involve virtually any bone of the body.
- Morphology. The tumors range from 3 to 8 cm in greatest dimension and are well-circumscribed, solid, and glistening tan-gray. Microscopically, there are nodules of poorly formed hyaline cartilage and myxoid tissue delineated by fibrous septae. The cellularity varies; the areas of greatest cellularity are at the periphery of the nodules. In the cartilaginous regions the tumor cells are situated in lacunae; however, in the myxoid areas, the cells are stellate, and their delicate cell processes extend through the mucinous ground substance and approach or contact neighboring cells. In contrast to other benign cartilage tumors, the neoplastic cells in chondromyxoid fi broma show varying degrees of cytologic atypia, including the presence of large hyperchromatic nuclei.
- Individuals with chondromyxoid fi broma usually complain of localized dull, achy pain. In most instances, radiograms demonstrate an eccentric geographic lucency that is well delineated from the adjacent bone by a rim of sclerosis.

Chondrosarcoma

- Chondrosarcomas are a group of tumors that span a broad spectrum of clinical and pathologic findings. The feature common to all of them is the production of neoplastic cartilage. Chondrosarcoma is subclassified according to site as central (intramedullary) and peripheral (juxtacortical and surface).
- Histologically, they include conventional (hyaline and/or myxoid), clear cell, dedifferentiated, and mesenchymal variants. Conventional central tumors constitute about 90% of chondrosarcomas.
- Individuals with chondrosarcoma are usually in their 40s or older. The tumor affects men twice as frequently as women.
- Morphology. Conventional chondrosarcoma is composed of malignant hyaline and myxoid cartilage. The large bulky tumors are made up of nodules of graywhite, somewhat translucent glistening tissue. In predominantly myxoid variants, the tumors are viscous and gelatinous and the matrix oozes from the cut surface. Spotty calcifications are typically present, and central necrosis may create cystic spaces. The adjacent cortex is thickened or eroded, and the tumor grows with broad pushing fronts into the surrounding soft tissue. The malignant cartilage infi ltrates the marrow space and surrounds pre-existing bony trabeculae. The tumors vary in degree ofcellularity, cytologic atypia, and mitotic activity. Low-grade or grade 1 lesions demonstrate mild hypercellularity, and the chondrocytes have plump vesicular nuclei with small nucleoli. Binucleate cells are sparse, and mitotic fi gures are diffi cult to fi nd. Portions of the matrix frequently mineralize, and the cartilage may undergo endochondral ossifi cation. By contrast, grade 3 chondrosarcomas are characterized by marked hypercellularity, extreme pleomorphism with bizarre tumor giant cells, and mitoses. Pure grade 3 chondrosarcomas are uncommon. Such malignant cartilage is more frequently a component of chondroblastic osteosarcoma. The hallmark of clear cell chondrosarcoma is sheets of large malignant chondrocytes that have abundant clear cytoplasm, numerous osteoclast-type giant cells, and intralesional reactive bone formation, which often causes confusion with osteosarcoma. Mesenchymal chondrosarcoma is composed of islands of well-differentiated hyaline cartilage surrounded by sheets of small round cells, which can mimic Ewing sarcoma. Chondrosarcomas commonly arise in the central portions of the skeleton, including the pelvis, shoulder, and ribs. The clear cell variant is unique in that it originates in the epiphyses of long tubular bones.
- There is a direct correlation between thegrade and the biologic behavior of the tumor.
- When chondrosarcomas metastasize, they spread preferentially to the lungs and skeleton.
- The treatment of conventional chondrosarcoma is wide surgical excision. The mesenchymal and dedifferentiated tumors are also treated with chemotherapy, because of their aggressive clinical course.

FIBROUS AND FIBRO-OSSEOUS TUMORS

- Fibrous Cortical Defect and Non-Ossifying Fibroma
- Fibrous Dysplasia
- Fibrosarcoma Variants

Fibrous Cortical Defect and Non-Ossifying Fibroma

- Fibrous cortical defects are extremely common, being found in 30% to 50% of children older than 2 years. They are believed to be developmental defects rather than neoplasms.
- The vast majority arise eccentrically in the metaphysis of the distal femur and proximal tibia, and almost half are bilateral or multiple. Often they are small, about 0.5 cm in diameter.
- **Morphology.** Both fibrous cortical defects and nonossifying fibromas produce elongated, sharply demarcated radiolucencies that are surrounded by a thin rim of sclerosis. They consist of gray to yellow-brown cellular lesions containing fibroblasts and macrophages. The cytologically bland fibroblasts are frequently arranged in a storiform (pinwheel) pattern, and the histiocytes are either multinucleated giant cells or clusters of foamy macrophages.
- Fibrous cortical defects are asymptomatic and are usually detected on radiography as an incidental finding.
- Most have limited growth potential and undergo spontaneous resolution within several years, being replaced by normal cortical bone.

Fibrous Dysplasia

- Fibrous dysplasia is a benign tumor that has been likened to a localized developmental arrest; all of the components of normal bone are present, but they do not differentiate into their mature structures. The lesions arise during skeletal growth and development, and appear in three distinctive but sometimes overlapping clinical patterns: (1) involvement of a single bone (monostotic); (2) involvement of multiple bones (polyostotic); and (3) polyostotic disease, associated with caféau-lait skin pigmentations and endocrine abnormalities. The skeletal, skin, and endocrine lesions result from a somatic gain-of-function mutation occurring during embryogenesis in the GNAS gene.
- Monostotic fibrous dysplasia accounts for 70% of all cases. It occurs equally in boys and girls, usually in early adolescence, and often stops enlarging at the time of growth plate closure. The femur, tibia, ribs, jawbones, calvaria, and humerus are most commonly affected. The lesion is frequently asymptomatic and usually discovered incidentally but it may cause pain, fracture, and discrepancies in limb length. Fibrous dysplasia can cause marked enlargement and distortion of bone, so that if the craniofacial skeleton is involved, disfigurement, sometimes severe, can occur. Monostotic disease does not evolve into the polyostotic form.
- Polyostotic fibrous dysplasia manifests at a slightly earlier age than the monostotic type and may continue to cause problems into adulthood. The bones affected, in descending order of frequency, are the femur, skull, tibia, humerus, ribs, fibula, radius, ulna, mandible, and vertebrae. Craniofacial involvement is present in 50% of those who have a moderate number of bones affected and in 100% of those with extensive skeletal disease. Polyostotic disease has a propensity to involve the shoulder and pelvic girdles, resulting in severe, sometimes crippling deformities (e.g., shepherd-crook deformity of the proximal femur) and spontaneous and often recurrent fractures. The endocrinopathies include sexual precocity, hyperthyroidism, pituitary adenomas that secrete growth hormone, and primary adrenal hyperplasia.

Fibrous Dysplasia

- Morphology. The lesions of fibrous dysplasia are well circumscribed, intramedullary, and vary greatly in size. Larger lesions expand and distort the bone. The lesional tissue is tan-white and gritty and is composed of curvilinear trabeculae of woven bone surrounded by a moderately cellular fi broblastic proliferation. The shapes of the trabeculae mimic Chinese letters, and the bone lacks prominent osteoblastic rimming. Nodules of hyaline cartilage with the appearance of disorganized growth plate are also present in approximately 20% of cases. Cystic degeneration, hemorrhage, and foamy macrophages are other common.
- Clinical Course. The natural history of fibrous dysplasia is variable and depends on the extent of skeletal involvement. Individuals with monostotic disease usually have minimal symptoms, except if the tumor is strategically located, such as in the femoral neck. The lesion is readily diagnosed by radiology because of its typical ground-glass appearance and well-defined margination.

Fibrosarcoma

- Affect the middle-aged and elderly.
- nearly equal sex distribution and usually arise de novo;
- **Morphology.** Grossly these tumors are large, hemorrhagic, tan-white masses that destroy the underlying bone and frequently extend into the soft tissues. They are composed of cytologically malignant fibroblasts arranged in a **herringbone storiform** pattern.
- Fibrosarcoma presents as an enlarging painful mass that usually arises in the metaphysis of long bones and pelvic flat bones. Pathologic fracture is a frequent complication.
- Radiographically it is permeative and lytic and often extends into the adjacent soft tissue.
- The prognosis depends on the size, location, stage, and grade of the tumor; large, high-grade tumors that are difficult to resect have a **very poor prognosis**.

Miscellaneous Tumors

- EWING SARCOMA/PRIMITIVE NEUROECTODERMAL TUMOR
- GIANT-CELL TUMOR
- ANEURYSMAL BONE CYST

The Ewing sarcoma

- The Ewing sarcoma family of tumors encompasses **Ewing sarcoma and primitive neuroectodermal tumor** (PNET). Tumors that demonstrate **neural differentiation are labeled PNETs**, and those that are **undifferentiated are diagnosed as Ewing sarcoma**.
- Of all bone sarcomas, Ewing sarcoma/PNET has the youngest average age at presentation, patints are 10 to 15 years old.
- Most Ewing sarcoma/PNET have the most commonly involved ETS gene is FLI1, as part of a (11;22) (q24;q12) translocation.
- **Morphology.** Arising in the medullary cavity, Ewing sarcoma and PNET usually invade the cortex, periosteum, and soft tissue. The tumor is soft, tan-white, and frequently contains areas of hemorrhage and necrosis. It is composed of sheets of uniform small, round cells that are slightly larger than lymphocytes. The presence of **Homer-Wright rosettes** (tumor cells arranged in a circle about a central fibrillary space) is indicative of neural differentiation. Necrosis may be prominent.
- **Clinical Features.** Tumors usually arise in the diaphysis of long **tubular bones**, especially the **femur** and the **flat bones of the pelvis**. They present as painful enlarging masses, and the affected site is frequently tender, warm, and swollen.
- Plain radiograms show a **destructive lytic tumor** that has permeative margins andextension into the surrounding soft tissues. The characteristic periosteal reaction produces layers of reactive bone deposited in an **onion-skin fashion**.
- Treatment includes chemotherapy and surgical excision with or without irradiation.
- The amount of chemotherapy induced necrosis is an important prognostic finding.

GIANT-CELL TUMOR

- the synonym is **osteoclastoma**.
- Relatively uncommon benign but **locally aggressive neoplasm**.
- Arises in individuals in their **20s to 40s**.
- The mononuclear cells in giant-cell tumors express RANKL.
- **Morphology.** These are large, red-brown tumors. They are mostly composed of uniform oval mononuclear cells that constitute the proliferating component of the tumor. Scattered within this background are numerous osteoclast-type giant cells **having 100 or more nuclei** that resemble those of the mononuclear cells. **Necrosis, hemorrhage, hemosiderin deposition**, and reactive bone formation are common secondary features.
- In adults involve both the **epiphyses and the metaphyses**, but in **adolescents** they are confined **proximally by the growth plate and are limited to the metaphysis**.
- The majority arise around the knee. The typical location of these tumors near joints frequently causes **arthritis-like symptoms**. Occasionally, they present with **pathologic fractures**.
- The **biologic unpredictability** of these neoplasms complicates their management.

ANEURYSMAL BONE CYST

- Aneurysmal bone cyst is a benign tumor of bone characterized by multiloculated blood-filled cystic spaces.
- **Benign** tumor.
- Associated with distinctive 17p13 translocations
- **Morphology.** Grossly, aneurysmal bone cyst consists of multiple blood-filled cystic spaces separated by thin, tan-white septa. The walls are composed of plump uniform fibroblasts, multinucleated osteoclast-like giant cells, and reactive woven bone. Approximately one third of cases contain an unusual cartilage-like matrix, called "**blue bone**."
- Occurs during the **first 2 decades** of life and has no sex predilection.
- It most frequently develops in the **metaphyses of long bones** and the posterior elements of vertebral bodies.
- The most common signs and symptoms are **pain and swelling**.
- Most lesions are **completely lytic** and often contain a thin shell of reactive bone at the periphery.
- The treatment of aneurysmal bone cyst is **surgical**.
- The **recurrence rate is low**, and spontaneous regression may occur following incomplete removal.

METASTATIC DISEASE

Metastatic tumors are **the most common** form of skeletal malignancy.

The pathways of spread include

- (1) direct extension,
- (2) lymphatic or hematogenous dissemination,
- (3) intraspinal seeding (via the Batson plexus of veins).

Any cancer can spread to bone, but in **adults** more than 75% of skeletal metastases originate from cancers of the **prostate, breast, kidney, and lung**.

In **children**, metastases to bone originate from **neuroblastoma, Wilms tumor, osteosarcoma, Ewing sarcoma, and rhabdomyosarcoma**.

Skeletal metastases are typically **multifocal**.

The radiographic manifestations of metastases may be purely lytic, purely blastic, or mixed lytic and blastic.