Osteogenesis

- **Intramembranous ossification**

Mesenchymal osteoblast

Secrets osteoid

- **Endochondral ossification**

Hyaline cartilage eroded

Osteoblast invade

Osteogenesis imperfecta:

- ↓Collagen I
- Defecte collagen I
- fracture

>> MEDICAL APPLICATION

Osteogenesis imperfecta, or "brittle bone disease," refers to a group of related congenital disorders in which the osteoblasts produce deficient amounts of type I collagen or defective type I collagen due to genetic mutations. Such defects lead to a spectrum of disorders, all characterized by significant fragility of the bones. The fragility reflects the deficit in normal collagen, which normally reinforces and adds a degree of resiliency to the mineralized bone matrix.

Intramembranous ossification

In flat bone

- condensed layer of Embryonic mesenchym
- Ossification centers
- Progenitor cell differentiation
- Osteoblast around vessels
- Osteoid secretion
- Calcification
- Woven trabecula formation
- Lacuna formation
- Ossification centers fusion
- Compact bone surrounded spongy bone

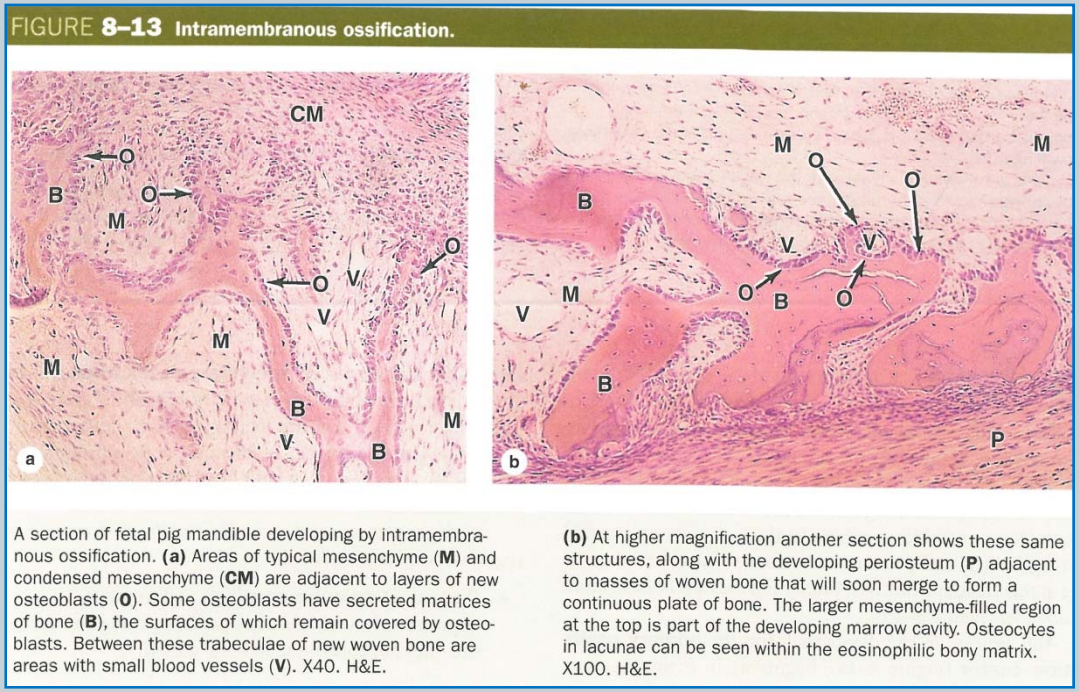


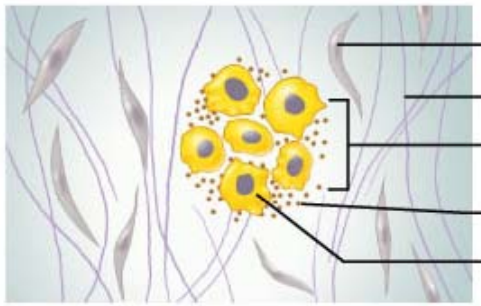
FIGURE **8–13** **Intramembranous ossification.**

A section of fetal pig mandible developing by intramembranous ossification. **(a)** Areas of typical mesenchyme (**M**) and condensed mesenchyme (**CM**) are adjacent to layers of new osteoblasts (**O**). Some osteoblasts have secreted matrices of bone (**B**), the surfaces of which remain covered by osteoblasts. Between these trabeculae of new woven bone are areas with small blood vessels (**V**). X40. H&E.

(b) At higher magnification another section shows these same structures, along with the developing periosteum (**P**) adjacent to masses of woven bone that will soon merge to form a continuous plate of bone. The larger mesenchyme-filled region at the top is part of the developing marrow cavity. Osteocytes in lacunae can be seen within the eosinophilic bony matrix. X100. H&E.

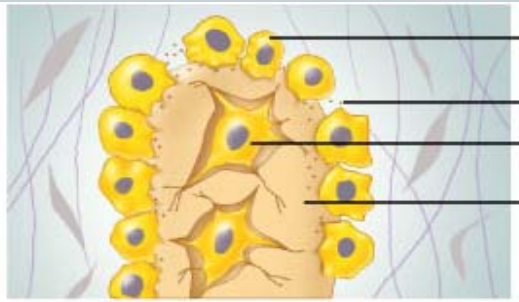
- Remaining connctive tissue forms:
- Endosteum
- periosteum

Stages of Intramembranous Ossification



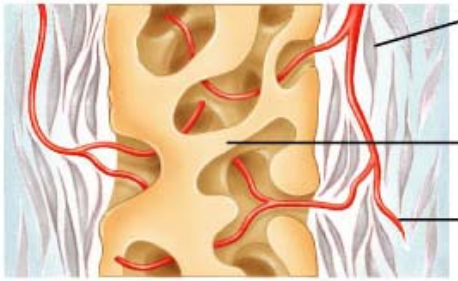
① **An ossification center appears in the fibrous connective tissue membrane.**

- Selected centrally located mesenchymal cells cluster and differentiate into osteoblasts, forming an ossification center.



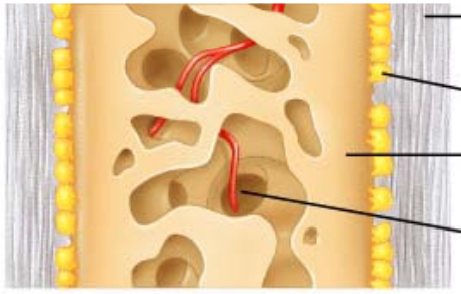
② **Bone matrix (osteoid) is secreted within the fibrous membrane.**

- Osteoblasts begin to secrete osteoid, which is mineralized within a few days.
- Trapped osteoblasts become osteocytes.



③ **Woven bone and periosteum form.**

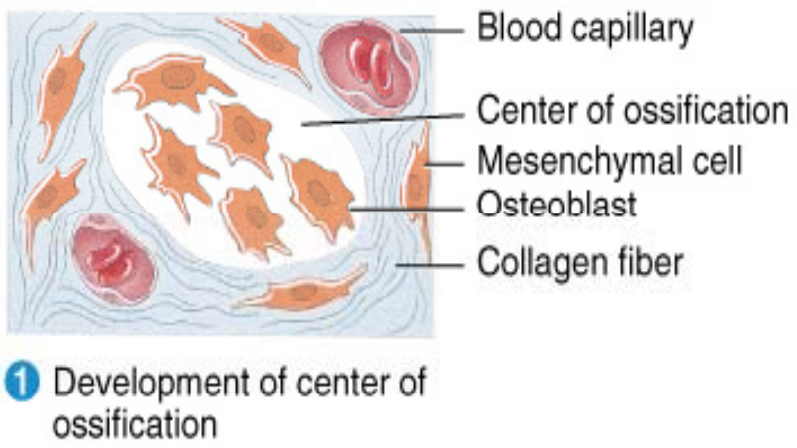
- Accumulating osteoid is laid down between embryonic blood vessels, which form a random network. The result is a network (instead of lamellae) of trabeculae.
- Vascularized mesenchyme condenses on the external face of the woven bone and becomes the periosteum.



④ **Bone collar of compact bone forms and red marrow appears.**

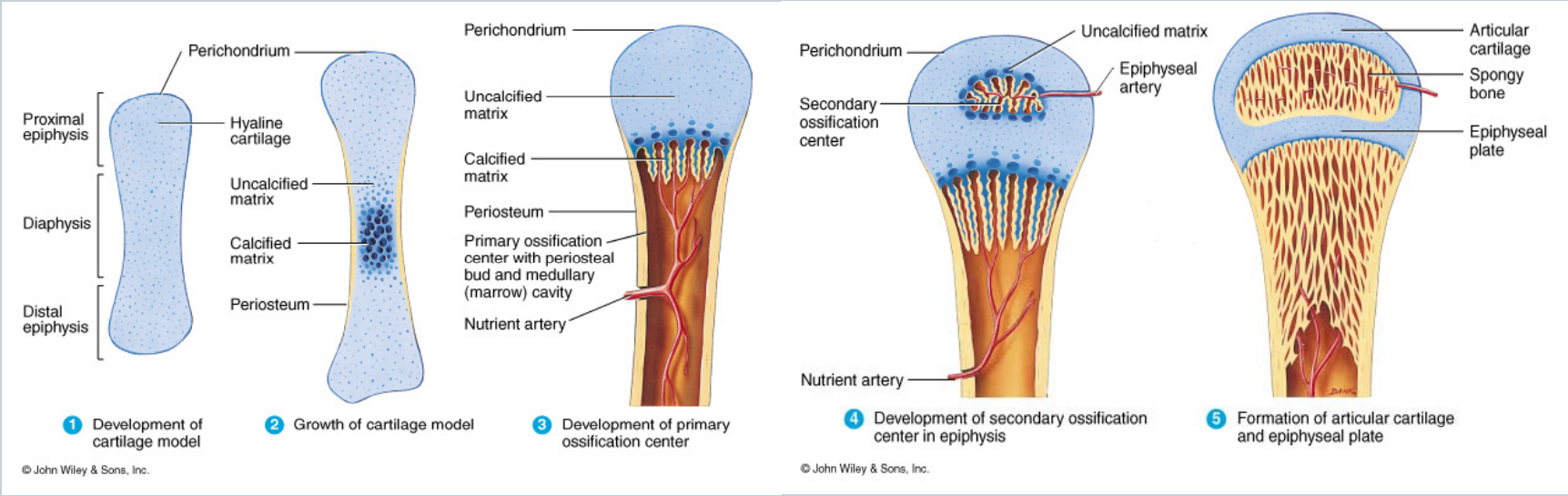
- Trabeculae just deep to the periosteum thicken, forming a woven bone collar that is later replaced with mature lamellar bone.
- Spongy bone (diploë), consisting of distinct trabeculae, persists internally and its vascular tissue becomes red marrow.

Stages of Intramembranous Ossification



Endochondral ossification

- Most bones (long bones)
- Bone Collar



Stages of Endochondral Ossification

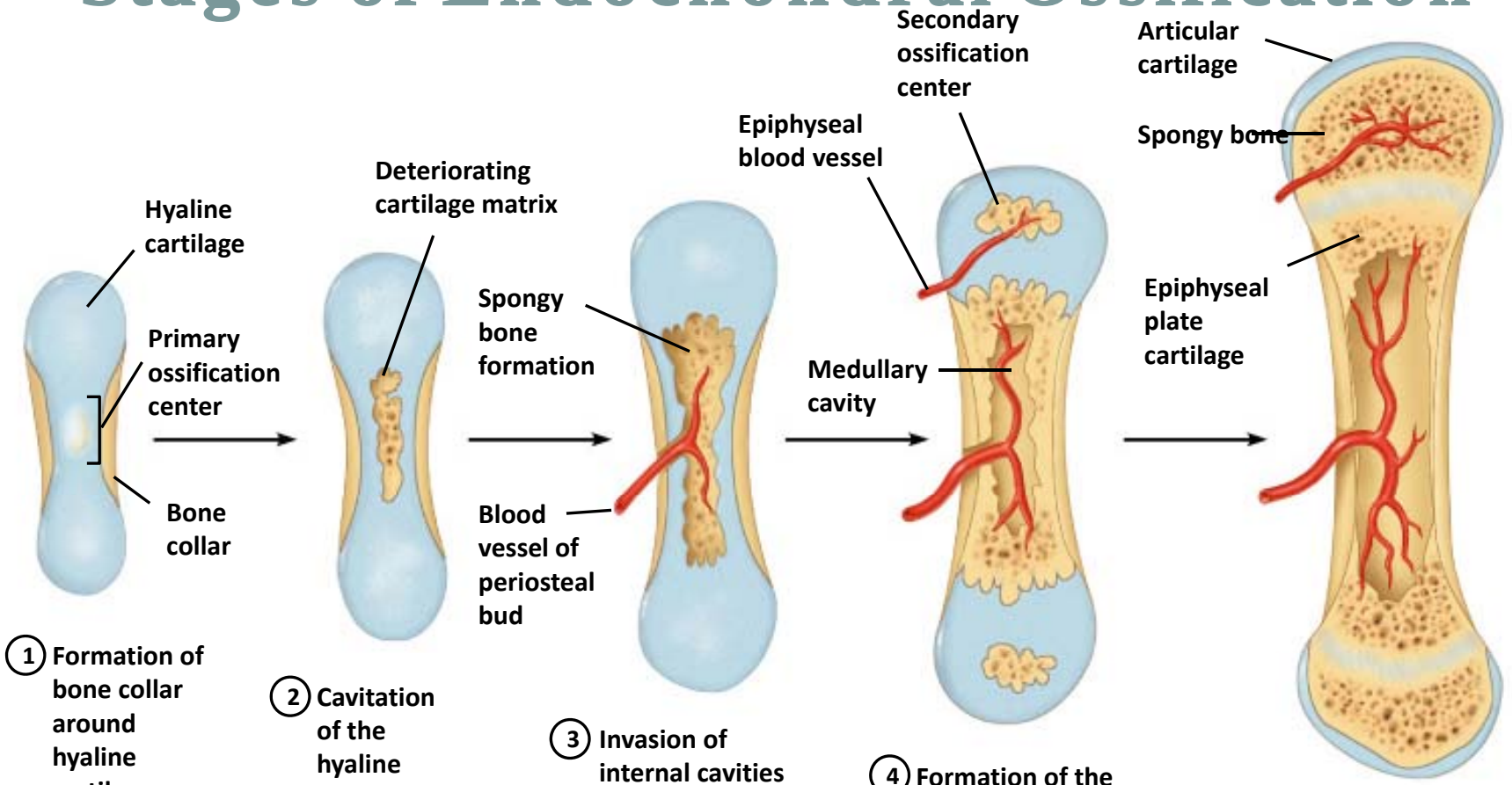
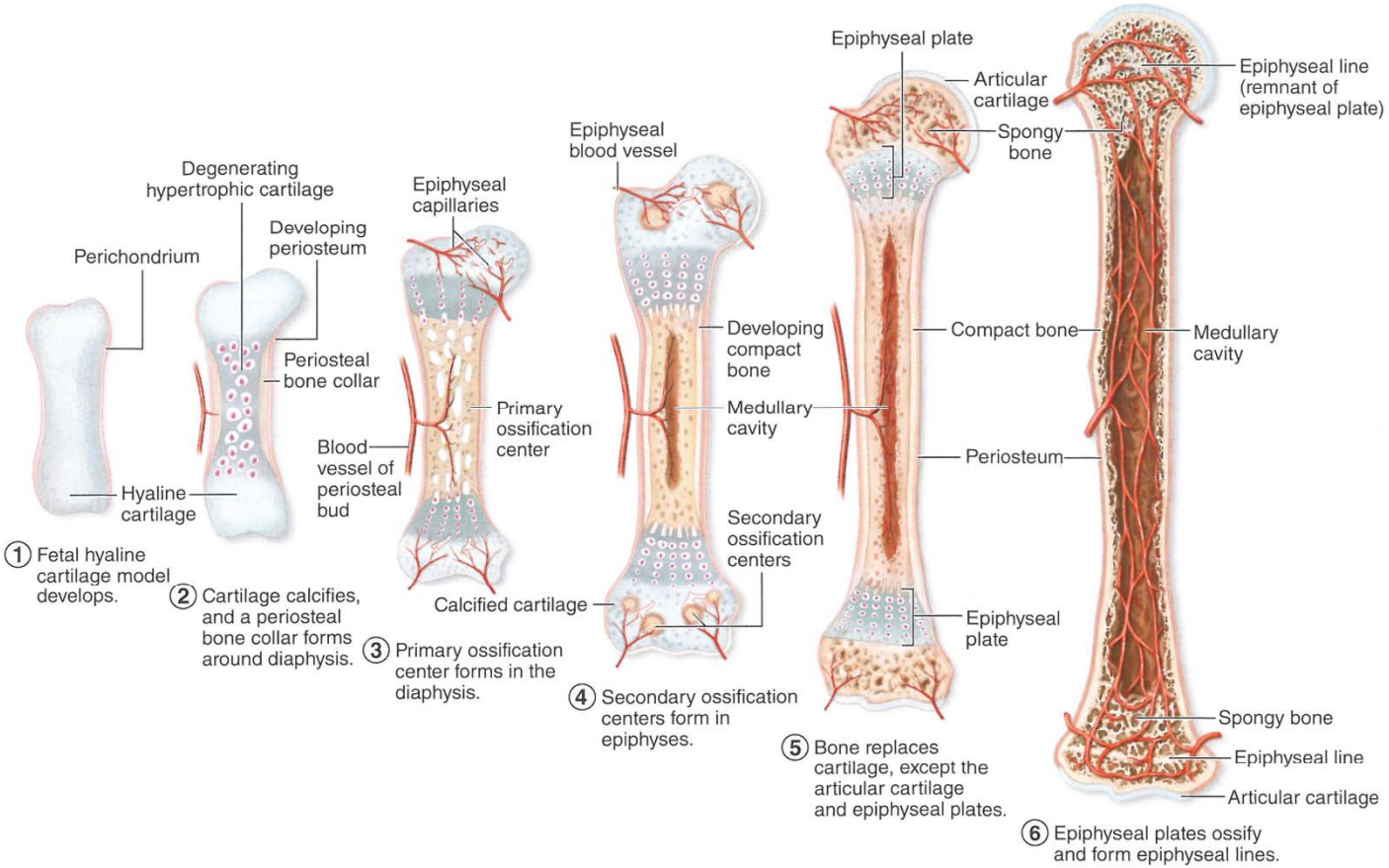


Figure 6.8

FIGURE 8–14 Osteogenesis of long bones by endochondral ossification.



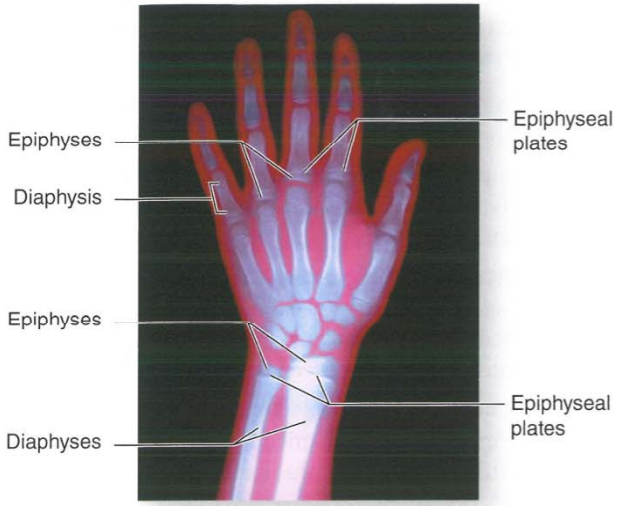
This process, by which most bones form initially, begins with embryonic models of the skeletal elements made of hyaline cartilage (**1**). Late in the first trimester, a bone collar develops beneath the perichondrium around the middle of the long bones' cartilage models, causing degeneration of the underlying cartilage (**2**).

This is followed by invasion of the degenerating cartilage by capillaries and osteoprogenitor cells from what is now the periosteum to produce a **primary ossification center** in the diaphysis (**3**). Here osteoid is deposited by the new osteoblasts, undergoes calcification into woven bone, and is remodeled as compact bone.

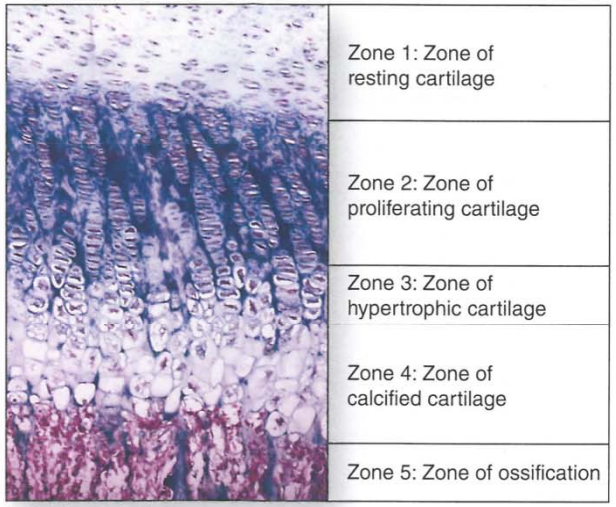
(**4**) Around the time of birth **secondary ossification centers** begin to develop by a similar process in the epiphyses. During childhood the primary and secondary ossification centers gradually come to be separated only by the **epiphyseal plate** (**5**) that provides for continued bone elongation. The two ossification centers do not merge until the epiphyseal plate disappears (**6**) when full stature is achieved. Osteoblasts of the periosteum provide for growth in the bone's diameter.

Bone growth in epiphyses

FIGURE **8–16** **Epiphyseal growth plate: Locations and zones of activity.**



a X-ray of a hand



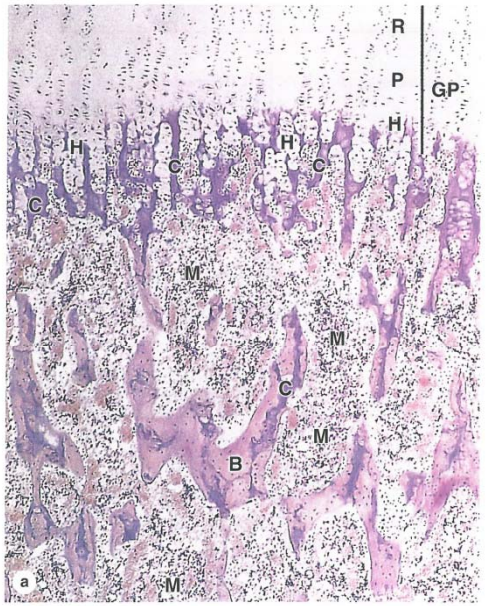
b Epiphyseal plate

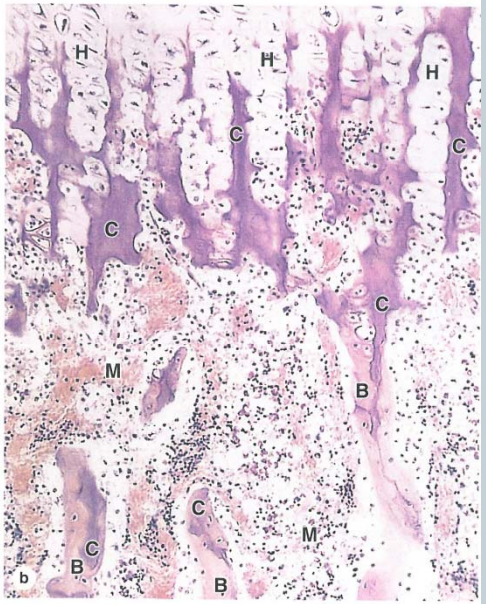
The large and growing primary ossification center in long bone diaphyses and the secondary ossification centers in epiphyses are separated in each developing bone by a plate of cartilage called the **epiphyseal plate**.

(a) Epiphyseal plates can be identified in an x-ray of a child's hand as marrow regions of lower density between the denser ossification centers. Cells in epiphyseal growth plates are responsible for continued elongation of bones until the body's full size is reached. Developmental activities in the epiphyseal growth plate occur in overlapping zones with distinct histological appearances.

(b) From the epiphysis to the diaphysis, five general zones have cells specialized for the following: (**1**) a reserve of normal hyaline cartilage, (**2**) cartilage with proliferating chondroblasts aligned as axial aggregates in lacunae, (**3**) degenerating cartilage in which the aligned cells are hypertrophic and the matrix condensed, (**4**) an area in which the chondrocytes have disappeared and the matrix is undergoing calcification, and (**5**) a zone in which blood vessels and osteoblasts invade the lacunae of the old cartilage, producing marrow cavities and osteoid for new bone. X100. H&E.

FIGURE **8–17** **Cells and matrices of the epiphyseal growth plate.**

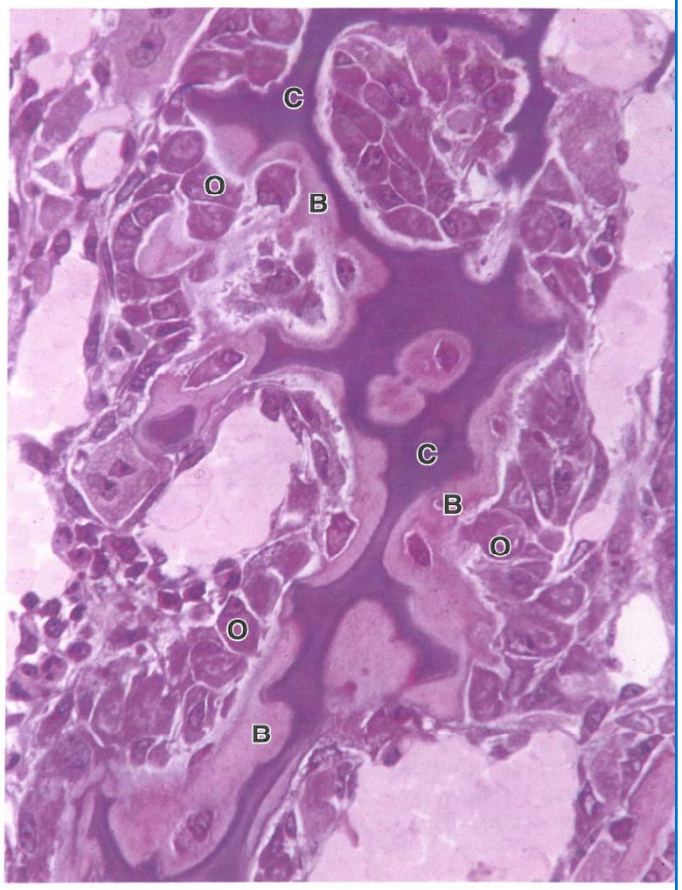




(a) At the top of the micrograph the growth plate (**GP**) shows its zones of hyaline cartilage with chondrocytes at rest (**R**), proliferating (**P**), and hypertrophying (**H**). As the chondrocytes swell and degenerate, they release phosphatase, activities that compress the matrix and cause an initial deposition of calcium phosphate. This produces calcified spicules (**C**) in the former cartilage matrix. The tunnel-like lacunae in which the chondrocytes have undergone apoptosis are invaded from the diaphysis by capillaries that begin to convert these spaces into marrow (**M**) cavities. Endosteum with osteoblasts also moves in from the diaphyseal primary ossification center, covering the spicules of calcified cartilage and laying down layers of osteoid to form a matrix of woven bone (**B**). X40. H&E.

(b) Higher magnification shows more detail of the cells and matrix spicules in the zones undergoing hypertrophy (**H**) and ossification. Staining properties of the matrix clearly change as it is compressed and begins to calcify (**C**), and when osteoid and bone (**B**) are laid down. The large spaces between the ossifying matrix spicules become the marrow cavity (**M**), in which pooled masses of eosinophilic red blood cells and aggregates of basophilic white blood cell precursors can be distinguished. Difficult to see at this magnification is the thin endosteum between the calcifying matrices and the marrow. X100. H&E.

FIGURE **8–15** **Cells and matrices of a primary ossification center.**



A small region of a primary ossification center showing key features of endochondral ossification. Compressed remnants of calcified cartilage matrix (**C**) are basophilic and devoid of chondrocytes. This material becomes enclosed by more lightly stained osteoid and woven bone (**B**) which contains osteocytes in lacunae. The new bone is produced by active osteoblasts (**O**) arranged as a layer on the remnants of old cartilage. X200. Pararosaniline–toluidine blue.

Rickets:

- In children
- Calcium deficiency
- Epiphys deformation
- Impaired growth
- malntririon
- Vit. D deficiency

Osteomalacia

- In adult
- Impaired calcification
- Much decalcification

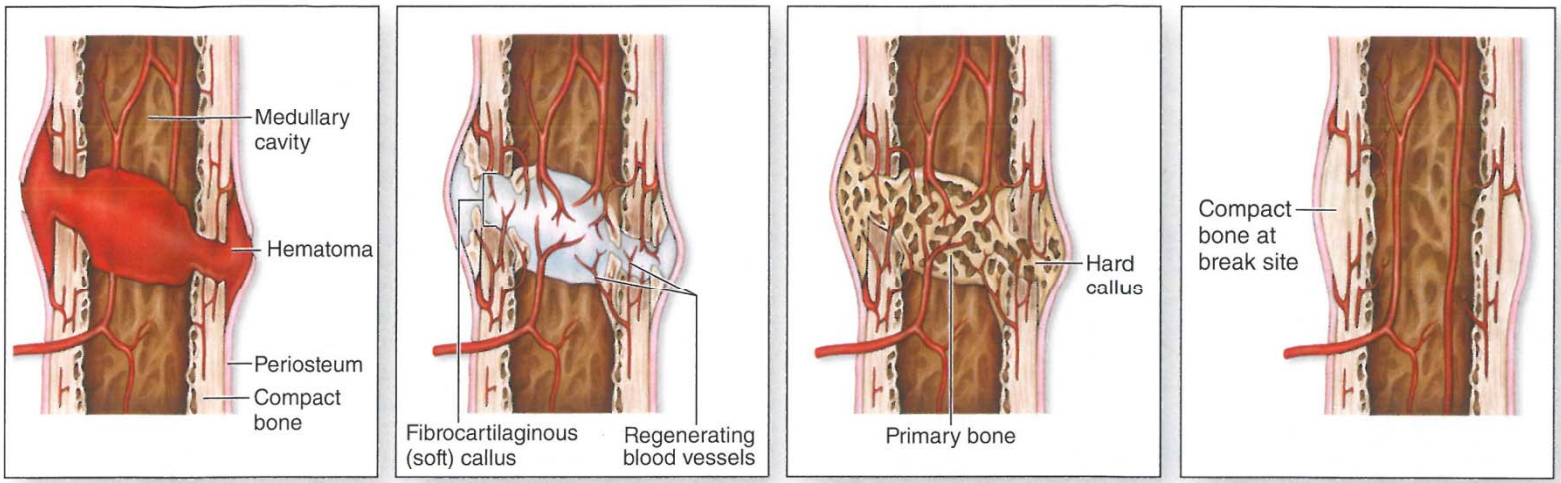
» MEDICAL APPLICATION

Calcium deficiency in children can lead to **rickets**, a disease in which the bone matrix does not calcify normally and the epiphyseal plate can become distorted by the normal strains of body weight and muscular activity. Ossification processes are consequently impeded, which causes bones to grow more slowly and often become deformed. The deficiency can be due either to insufficient calcium in the diet or a failure to produce the steroid prohormone vitamin D, which is important for the absorption of Ca^{2+} by cells of the small intestine.

In adults calcium deficiency can give rise to **osteomalacia** (osteon + Gr. *malakia*, softness), characterized by deficient calcification of recently formed bone and partial decalcification of already calcified matrix.

Bone growth, remodeling & repair

FIGURE **8–18** **Main features of bone fracture repair.**



(a) A fracture hematoma forms. **(b)** A fibrocartilaginous (soft) callus forms. **(c)** A hard (bony) callus forms. **(d)** The bone is remodeled.

Repair of a fractured bone occurs through several stages but utilizes mechanisms already in place for bone remodeling. **(a)** Blood vessels torn within the fracture release blood that clots to produce a large fracture hematoma. **(b)** This is gradually removed by macrophages and replaced by a soft fibrocartilage-like mass of procallus tissue rich in collagen and fibroblasts. If broken, the periosteum reestablishes continuity over this tissue. **(c)** This soft procallus is invaded by regrowing blood vessels and osteoblasts. In the next few weeks the fibrocartilage is gradually replaced by trabeculae of woven bone, forming a hard callus throughout the original area of fracture. **(d)** The woven bone is then remodeled as compact and cancellous bone in continuity with the adjacent uninjured areas and fully functional vasculature is reestablished.

›› MEDICAL APPLICATION

Bone fractures are repaired by a developmental process involving fibrocartilage formation and osteogenic activity of the major bone cells (Figure 8–18). Bone fractures disrupt blood vessels, causing bone cells near the break to die. The damaged blood vessels produce a localized hemorrhage or hematoma. Clotted blood is removed along with tissue debris by macrophages and the matrix of damaged, cell-free bone is resorbed by osteoclasts.

The periosteum and the endosteum at the fracture site respond with intense proliferation and produce a soft callus of fibrocartilage-like tissue that surrounds the fracture and covers the extremities of the fractured bone.

The fibrocartilaginous callus is gradually replaced in a process that resembles a combination of endochondral and intramembranous ossification. This produces a hard callus of woven bone around the fractured ends of bone.

Stresses imposed on the bone during repair and during the patient's gradual return to activity serve to remodel the bone callus. The immature, woven bone of the callus is gradually resorbed and replaced by lamellar bone, remodeling and restoring the original bone structure.

Metabolic role of bone

- PTH
- Calcitonin

- Growth hormone

Liver

Somatomedian (IGF)

Epiphysial growth

Pituitary dwarfism

Gigantism

Acromegaly

Rheumatoid Arthritis

Synovial membrane inflammation & thickening

Collagenase & hydrolitic enz.

Cartilage defect

›› MEDICAL APPLICATION

In addition to PTH and calcitonin, several other hormones act on bone. The anterior lobe of the pituitary synthesizes growth hormone (GH or somatotropin), which stimulates the liver to produce insulin-like growth factor-1 (IGF-1 or somatomedin). IGF has an overall growth-promoting effect, especially on the epiphyseal cartilage. Consequently, lack of growth hormone during the growing years causes **pituitary dwarfism**; an excess of growth hormone causes excessive growth of the long bones, resulting in **gigantism**. Adult bones cannot increase in length even with excess IGF because they lack epiphyseal cartilage, but they do increase in width by periosteal growth. In adults, an increase in GH causes **acromegaly**, a disease in which the bones—mainly the long ones—become very thick.

›› MEDICAL APPLICATION

In **rheumatoid arthritis** chronic inflammation of the synovial membrane causes thickening of this connective tissue and stimulates the macrophages to release collagenases and other hydrolytic enzymes. Such enzymes eventually cause destruction of the articular cartilage, allowing direct contact of the bones projecting into the joint.

Joints

- **Synarthrosis**
- **Diarthrosis**

- **Synarthrosis**

1. Synostosis (sutures)
2. Syndesmosis (distsl tibiofibular & sacroiliac j)
3. Symphysis (pubis symphysis)

Joints

- **Diarthrosis**

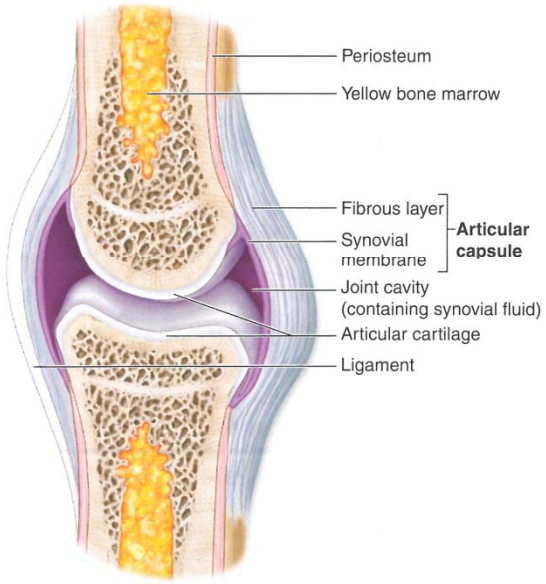
Joint cavity

Synovial fluid

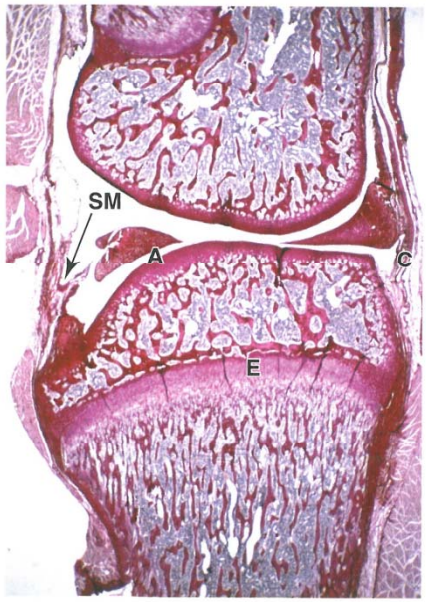
Synovial membrane

1. Macrophage like synovial cell (A type)
2. Fibroblastic synovial cell (B type)

FIGURE **8–19** **Diarthroses or synovial joints.**



a Typical synovial joint

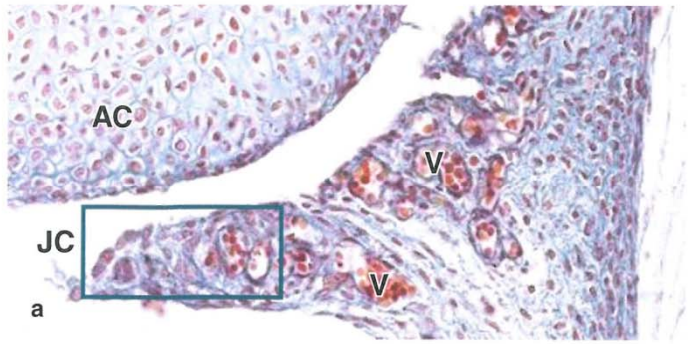


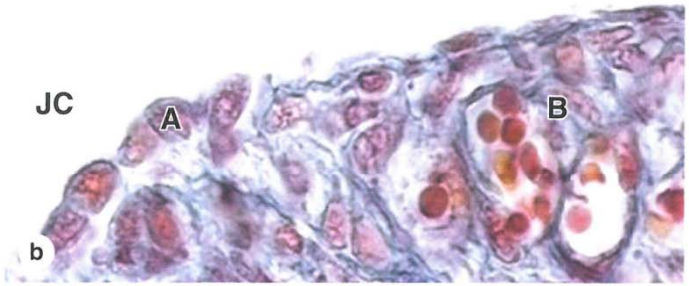
b

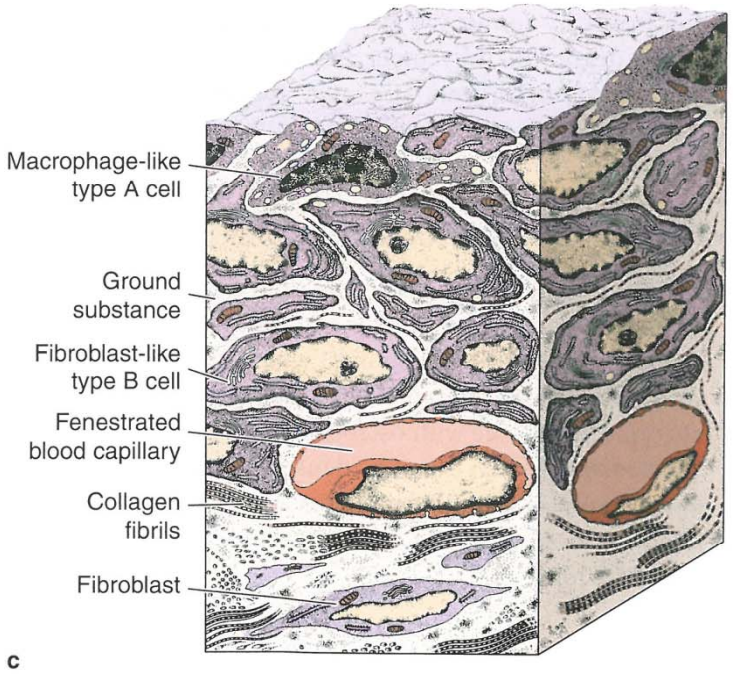
Diarthroses are joints that allow free movement of the attached bones, such as knuckles, knees, and elbows. **(a)** Diagram showing major components of a diarthrosis, including the **articular capsule** continuous with a ligament inserting into the periosteum of both bones; the **joint cavity** containing synovial fluid as a lubricant; and the ends of epiphyses covered by **articular cartilage**. The **synovial membrane** lines the capsule and produces the synovial fluid.

(b) Longitudinal section through a diarthrosis with growing bones of a rodent knee, showing the position near the boundaries of the capsule (**C**) of the epiphyseal growth plate (**E**) where endochondral ossification occurs. Also shown are the articular cartilage (**A**) and the folds of synovial membrane (**SM**), which extend prominently into the joint cavity from connective tissue of the capsule for production of synovial fluid. X10. PSH stain.

FIGURE 8–20 Synovial membrane.





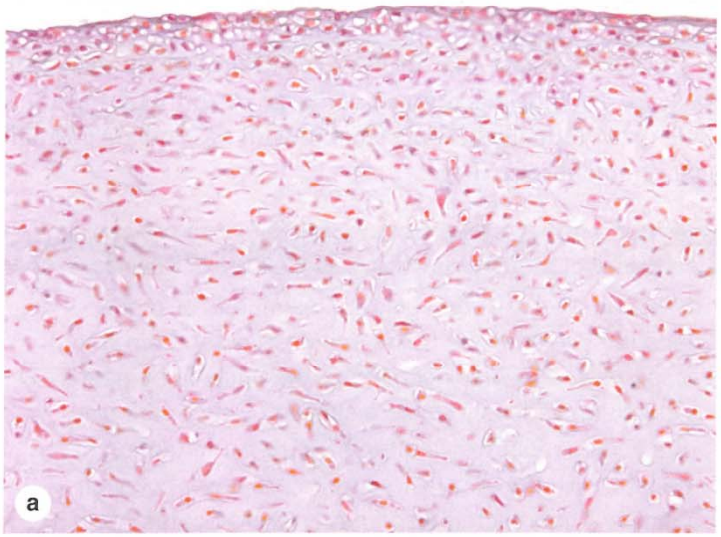


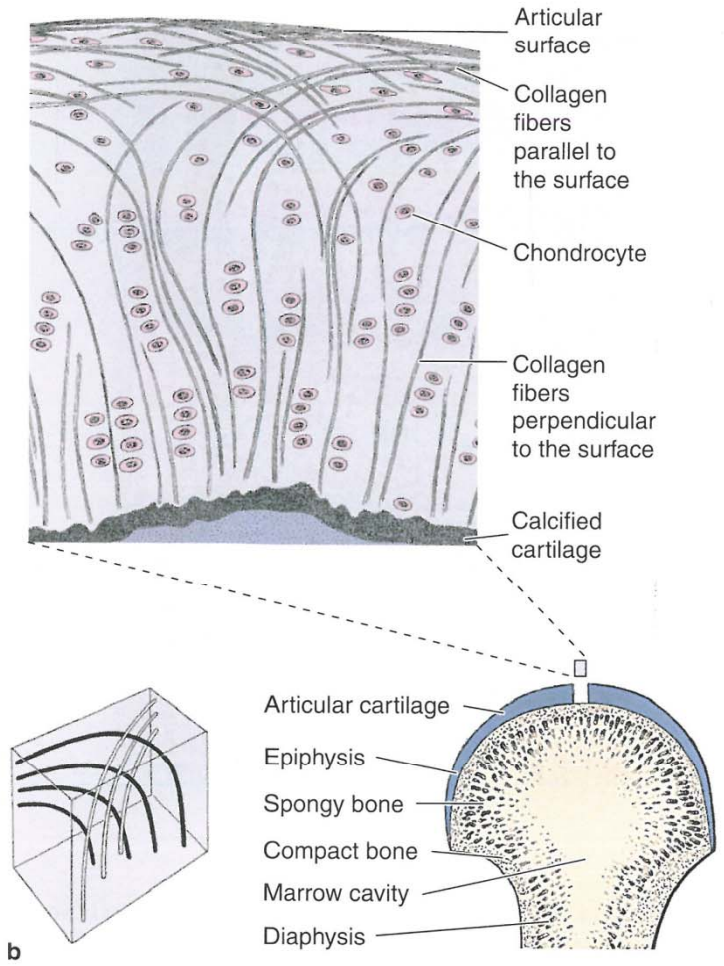
The synovial membrane is a specialized connective tissue that lines capsules of synovial joints and contacts the synovial fluid lubricant, which it is primarily responsible for maintaining. **(a)** The synovial membrane projects folds into the joint cavity (**JC**) and these contain many small blood vessels (**V**). The joint cavity surrounds the articular cartilage (**AC**). X100. Mallory trichrome.

(b) Higher magnification of the fold showing a high density of capillaries and two specialized types of cells called **synoviocytes**. Contacting the synovial fluid at the tissue surface are many rounded **macrophage-like synovial cells (type A)** derived from blood monocytes. These cells bind, engulf, and remove tissue debris from synovial fluid. These cells often form a layer at the tissue surface (**A**) and can superficially resemble an epithelium, but there is no basal lamina and the cells are not joined together by cell junctions. **Fibroblast-like (type B) synovial cells** (**B**) are mesenchymally derived and specialized for synthesis of hyaluronan that enters the synovial fluid, replenishing it. X400.

(c) Schematic representation of synovial membrane histology. Among the macrophage-like and fibroblast-like synovial cells are collagen fibers and other typical components of connective tissue. Surface cells have no basement membrane or junctional complexes denoting an epithelium, despite the superficial resemblance. Blood capillaries are fenestrated, which facilitates exchange of substances between blood and synovial fluid.

FIGURE 8–21 Articular cartilage.



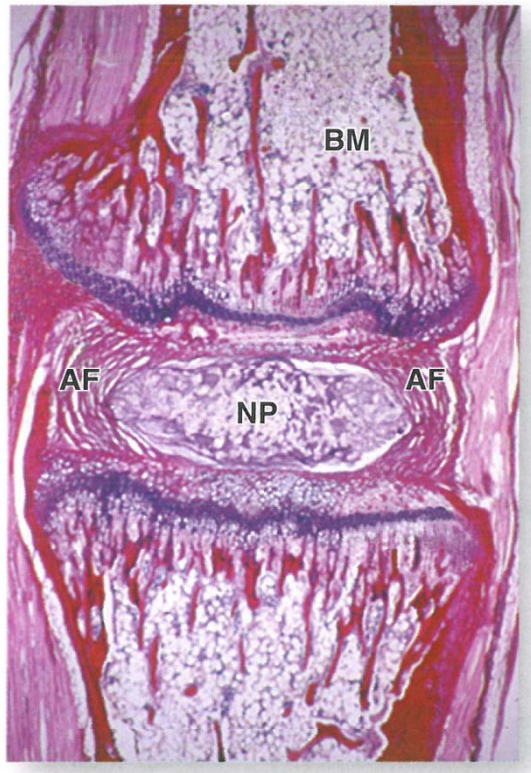


(a) Articular surfaces of a diarthrosis are made of hyaline cartilage that lacks the usual perichondrium covering. X40. H&E. **(b)** The large diagram shows a small region of articular cartilage in which collagen fibers run perpendicular to the tissue surface and then bend gradually, forming a broad arch parallel to that surface. The lower left diagram shows a 3D view of collagen fibers in articular cartilage. Proteoglycan aggregates bound to hyaluronic acid and collagen fill the space among the collagen fibers and bind a large amount of water, functioning as a biomechanical spring in articular cartilage. When pressure is applied, some water is forced out of the cartilage matrix into the synovial fluid. When pressure is released, water is attracted back into the interstices of the matrix. These water movements are brought about constantly by using the joint and are essential for nutrition of the cartilage and for facilitating the interchange of O_2, CO_2, and other molecules between the synovial fluid and the articular cartilage.

TABLE 8–1 Summary of bone types and their organization.

Type of Bone	Histological Features	Major Locations	Synonyms
Woven bone, newly calcified	Irregular and random arrangement of cells and collagen; lightly calcified	Developing and growing bones; hard callus of bone fractures	Immature bone; primary bone; bundle bone
Lamellar bone, remodeled from woven bone	Parallel bundles of collagen in thin layers (lamellae), with regularly spaced cells between; heavily calcified	All normal regions of adult bone	Mature bone; secondary bone
Compact bone, ~80% of all lamellar bone	Parallel lamellae or densely packed osteons, with interstitial lamellae	Thick, outer region (beneath periosteum) of bones	Cortical bone
Cancellous bone, ~20% of all lamellar bone	Interconnected thin spicules or trabeculae covered by endosteum	Inner region of bones, adjacent to marrow cavities	Spongy bone; trabecular bone; medullary bone

FIGURE **8–22** Intervertebral disc.



Section of a rat tail showing an intervertebral disc and two adjacent vertebrae with bone marrow (**BM**) cavities. The disc consists of concentric layers of fibrocartilage, comprising the annulus fibrosus (**AF**), which surrounds the nucleus pulposus (**NP**). The nucleus pulposus contains scattered residual cells of the embryonic notochord embedded in abundant gel-like matrix. The intervertebral discs function primarily as shock absorbers within the spinal column and allow greater mobility within the spinal column. X40. PSH.

›› MEDICAL APPLICATION

Within an intervertebral disc, collagen loss or other degenerative changes in the annulus fibrosus are often accompanied by displacement of the nucleus pulposus, a condition variously called a **slipped or herniated disc**. This occurs most frequently on the posterior region of the intervertebral disc where there are fewer collagen bundles. The affected disc frequently dislocates or shifts slightly from its normal position. If it moves toward nerve plexuses, it can compress the nerves and result in severe pain and other neurologic disturbances. The pain accompanying a slipped disc may be perceived in areas innervated by the compressed nerve fibers—usually the lower lumbar region.