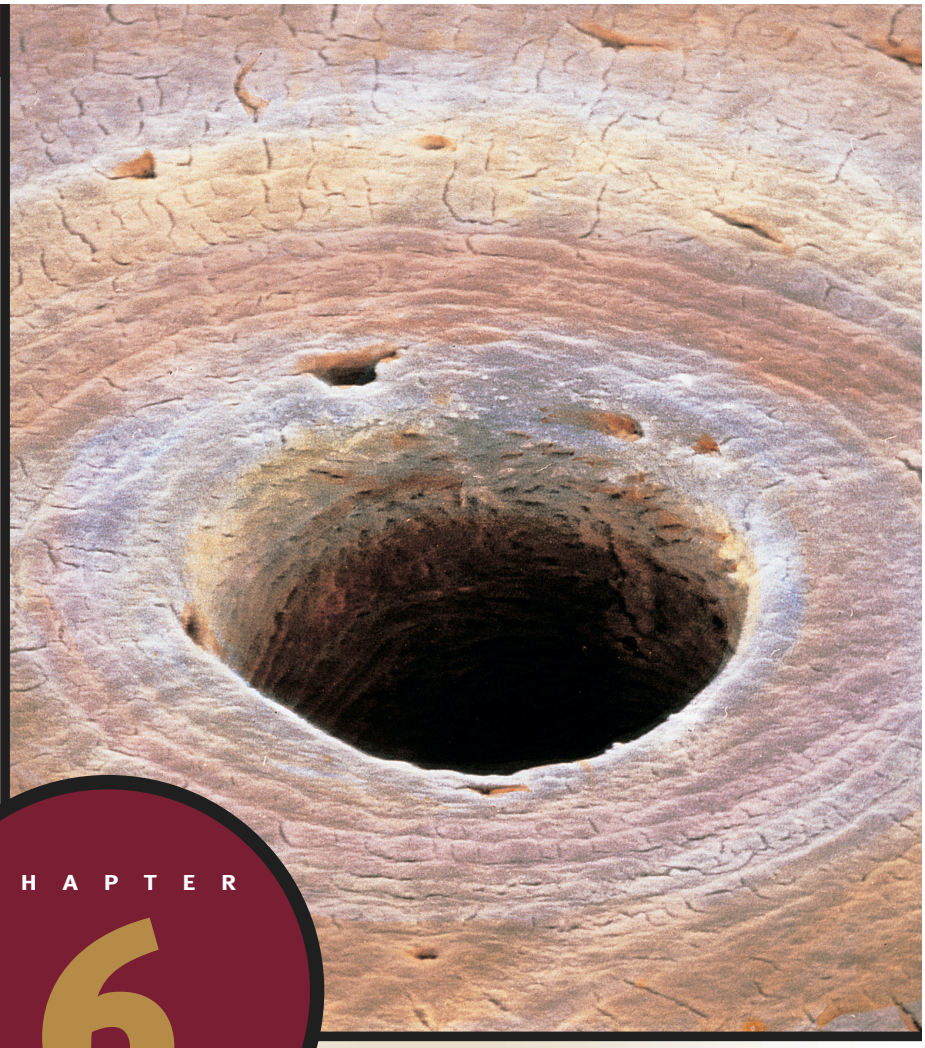
Skeletal System:

Bones and Bone Tissue

CHAPTER 6



Colorized scanning electron micrograph (SEM) of an osteon in compact bone. The large opening is the space through which blood vessels bring blood to the bone. The surrounding bone matrix is organized into circular layers.

Sitting, standing, walking, picking up a pencil, and taking a breath all involve the skeletal system. It is the structural framework that gives the body its shape and provides protection for internal organs and soft tissues. The skeletal system has four components: bones, cartilage, tendons, and ligaments. The term *skeleton* is derived from a Greek word meaning dried, indicating that the skeleton is the dried, hard parts left after the softer parts are removed. Even with the flesh and organs removed, the skeleton is easily recognized as human. Despite its association with death, however, the skeletal system actually consists of dynamic, living tissues that are capable of growth, adapt to stress, and undergo repair after injury.

This chapter describes the *functions of the skeletal system* (167), provides an explanation of *cartilage* (167), and examines *bone anatomy* (168), *bone histology* (171), *bone development* (175), *bone growth* (178), *bone remodeling* (183), *bone repair* (185), *calcium homeostasis* (187), and the *effects of aging on the skeletal system* (189).

Functions of the Skeletal System

Objective

- ***Name the major functions of the skeletal system.***

The skeletal system provides support and protection, allows body movements, stores minerals and fats, and is the site of blood cell production.

1. *Support.* Rigid, strong bone is well suited for bearing weight and is the major supporting tissue of the body. Cartilage provides a firm yet flexible support within certain structures, such as the nose, external ear, thoracic cage, and trachea. Ligaments are strong bands of fibrous connective tissue that attach to bones and hold them together.
2. *Protection.* Bone is hard and protects the organs it surrounds. For example, the skull encloses and protects the brain, and the vertebrae surround the spinal cord. The rib cage protects the heart, lungs, and other organs of the thorax.
3. *Movement.* Skeletal muscles attach to bones by tendons, which are strong bands of connective tissue. Contraction of the skeletal muscles moves the bones, producing body movements. Joints, which are formed where two or more bones come together, allow movement between bones. Smooth cartilage covers the ends of bones within some joints, allowing the bones to move freely. Ligaments allow some movement between bones but prevent excessive movements.
4. *Storage.* Some minerals in the blood are taken into bone and stored. Should blood levels of these minerals decrease, the minerals are released from bone into the blood. The principal minerals stored are calcium and phosphorus. Fat (adipose tissue) is also stored within bone cavities. If needed, the fats are released into the blood and used by other tissues as a source of energy.
5. *Blood cell production.* Many bones contain cavities filled with bone marrow that gives rise to blood cells and platelets (see chapter 19).

1. Name the four components of the skeletal system. List the five functions of the skeletal system.

Cartilage

Objective

- ***Describe the structure and growth of hyaline cartilage.***

Cartilage comes in three types: hyaline cartilage, fibrocartilage, and elastic cartilage (see chapter 4). Although each type of cartilage can provide support, hyaline cartilage is most intimately associated with bone. An understanding of hyaline cartilage is important because most of the bones in the body develop from it. In addition, the growth in length of bones and bone repair often involve the production of hyaline cartilage followed by its replacement with bone.

Hyaline cartilage consists of specialized cells that produce a matrix surrounding the cells (figure 6.1). The cells that produce new cartilage matrix are **chondroblasts** (kon′drō-blastz; *chondro* is from the Greek word *chondrion* and means cartilage). When matrix surrounds a chondroblast, it becomes a **chondrocyte** (kon′drō-sīt), which is a rounded cell that occupies a space within the matrix called a **lacuna** (lă-koo′nă). The matrix contains collagen, which provides strength, and proteoglycans, which make cartilage resilient by trapping water (see chapter 4).

The **perichondrium** (per-i-kon′drē-ŭm) is a double-layered connective tissue sheath covering most cartilage (see figure 6.1). The outer layer of the perichondrium is dense irregular connective tissue containing fibroblasts. The inner, more delicate layer has fewer fibers and contains chondroblasts. Blood vessels and nerves penetrate the

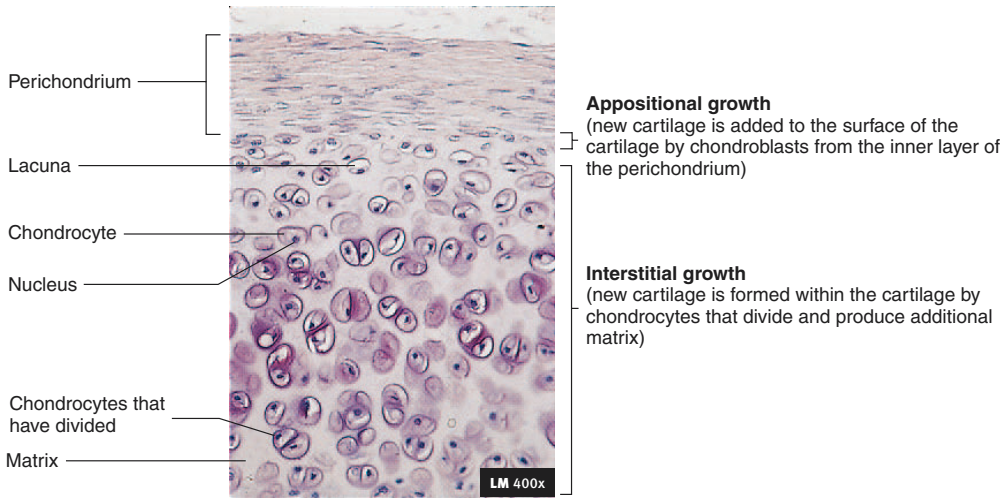


Figure 6.1 Hyaline Cartilage

Photomicrograph of hyaline cartilage covered by perichondrium. Chondrocytes within lacunae are surrounded by cartilage matrix.

outer layer of the perichondrium but do not enter the cartilage matrix, so that nutrients must diffuse through the cartilage matrix to reach the chondrocytes. **Articular** (ar-tik′ū-lăr) **cartilage,** which is the cartilage covering the ends of bones where they come together to form joints, has no perichondrium, blood vessels, or nerves.

PREDICT 1

Explain why damaged cartilage takes a long time to heal. What are the advantages of articular cartilage having no perichondrium, blood vessels, or nerves?

Cartilage grows in two different ways. Through **appositional growth,** chondroblasts in the perichondrium lay down new matrix and add new chondrocytes to the outside of the tissue, and through **interstitial growth,** chondrocytes within the tissue divide and add more matrix between the cells (see figure 6.1).

2. *Describe the structure of hyaline cartilage. Name two types of cartilage cells. What is a lacuna?*
3. *Describe the connective tissue and cells found in both layers of the perichondrium. How do nutrients from blood vessels in the perichondrium reach the chondrocytes?*
4. *Explain appositional and interstitial growth of cartilage.*

Bone Anatomy

Objective

- *Name the major bone shapes and describe their structures.*

Bone Shapes

Individual bones are classified according to their shape as long, short, flat, or irregular (figure 6.2). **Long bones** are longer than they are wide. Most of the bones of the upper and lower limbs are long bones. **Short bones** are about as broad as they are long. They are nearly cube-shaped or round and are exemplified by the bones of the wrist (carpals) and ankle (tarsals). **Flat bones** have a relatively thin, flattened shape and are usually curved. Examples of flat bones are certain skull bones, the ribs, the breastbone (sternum), and the shoulder blades (scapulae). **Irregular bones,** such as the vertebrae and facial bones, have shapes that don't fit readily into the other three categories.

Structure of a Long Bone

Each growing long bone has three major components: a diaphysis, an epiphysis, and an epiphyseal plate (figure 6.3*a* and table 6.1). The **diaphysis** (dī-af′i-sis), or shaft, is composed primarily of **compact bone,** which is mostly bone matrix with a few small spaces. The **epiphysis** (e-pif′i-sis), or end of the bone, consists primarily of **cancellous** (kan′sĕ-lŭs), or **spongy, bone,** which is mostly small spaces or cavities surrounded by bone matrix. The outer surface of the epiphysis is a layer of compact bone, and within joints the epiphyses are covered by articular cartilage. The **epiphyseal** (ep-i-fiz′ē-ăl), or **growth, plate** is hyaline cartilage located between the epiphysis and diaphysis. Growth in bone length occurs at the epiphyseal plate, but, when bone stops growing in length, the epiphyseal plate becomes ossified and is called the **epiphyseal line** (figure 6.3*b*).

In addition to the small spaces within cancellous bone and compact bone, the diaphysis of a long bone can have a large space called the **medullary cavity.** The cavities of cancellous bone and the medullary cavity are filled with marrow (mar′ō). **Red marrow** is the site of blood cell formation, and **yellow marrow** is mostly adipose tissue. In children, the spaces within bones are filled with red marrow. As children mature, yellow marrow replaces the red marrow in their skull and limbs. In adults, the bones of the skull and limbs, except for the proximal epiphyses, have yellow marrow (figure 6.4). The rest of the skeleton contains red marrow.

The **periosteum** (per-ē-os′tē-ŭm) is a connective tissue membrane that covers the outer surface of a bone (see figure 6.3*c*). The outer fibrous layer is dense, irregular collagenous connective tissue that contains blood vessels and nerves. The inner layer is a single layer of bone cells, which includes osteoblasts, osteoclasts, and osteochondral progenitor cells (see "Bone Cells" on p. 171). Where tendons and ligaments attach to bone, the collagen fibers of the tendon or ligament become continuous with those of the periosteum. In addition, some of the collagen fibers of the tendons or ligaments penetrate the periosteum into the outer part of the bone. These bundles of collagen fibers are called **perforating,** or **Sharpey's, fibers,** and they strengthen the attachment of the tendons or ligaments to the bone.

The **endosteum** (en-dos′tē-ŭm) is a connective tissue membrane that lines the internal surfaces of all cavities within bones, such as the medullary cavity of the diaphysis and the smaller cavities in cancellous and compact bone (see figure 6.3). The endosteum is a single layer of cells, which includes osteoblasts, osteoclasts, and osteochondral progenitor cells.

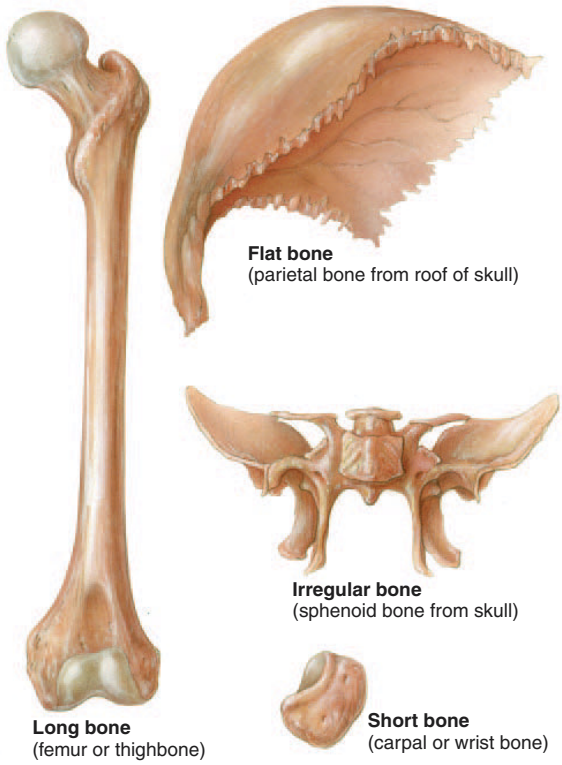


Figure 6.2 Bone Shapes

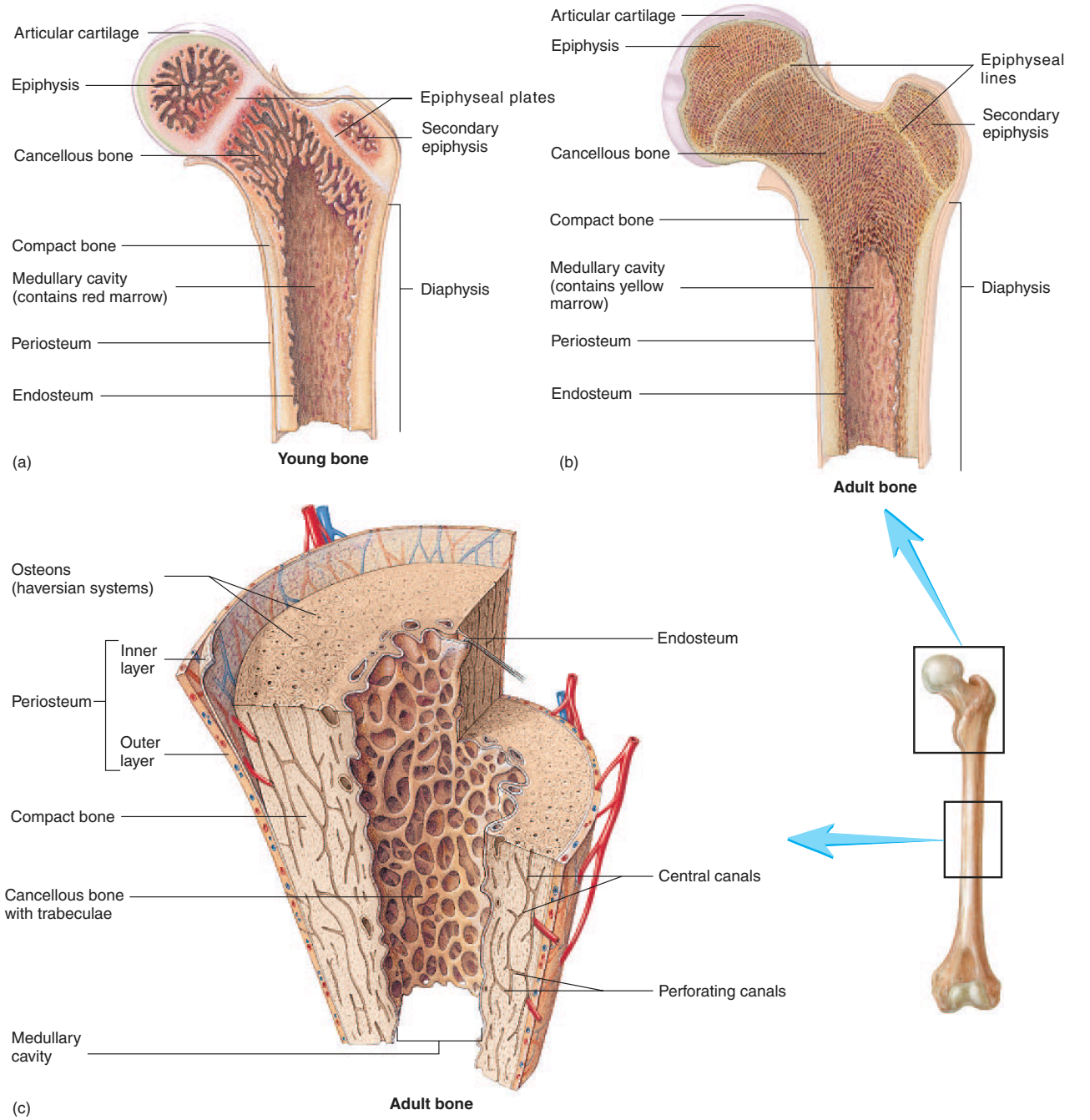


Figure 6.3 Long Bone

(*a*) Young long bone (the femur) showing epiphysis, epiphyseal plates, and diaphysis. (*b*) Adult long bone with epiphyseal lines. (*c*) Internal features of a portion of the diaphysis in (*a*).

Table 6.1 Gross Anatomy of a Long Bone

Part	Description	Part	Description
Diaphysis	Shaft of the bone	Epiphyseal plate	Area of hyaline cartilage between the diaphysis and epiphysis; cartilage growth followed by endochondral ossification results in bone growth in length
Epiphyses	Ends of the bone	Cancellous (spongy) bone	Bone having many small spaces; found mainly in the epiphysis; arranged into trabeculae
Periosteum	Double-layered connective tissue membrane covering the outer surface of bone except where articular cartilage exists; ligaments and tendons attach to bone through the periosteum; blood vessels and nerves from the periosteum supply the bone; the periosteum is the site of bone growth in diameter	Compact bone	Dense bone with few internal spaces organized into osteons; forms the diaphysis and covers the cancellous bone of the epiphyses
Endosteum	Thin connective tissue membrane lining the inner cavities of bone	Medullary cavity	Large cavity within the diaphysis
Articular cartilage	Thin layer of hyaline cartilage covering a bone where it forms a joint (articulation) with another bone	Red marrow	Connective tissue in the spaces of cancellous bone or in the medullary cavity; the site of blood cell production
		Yellow marrow	Fat stored within the medullary cavity or in the spaces of cancellous bone

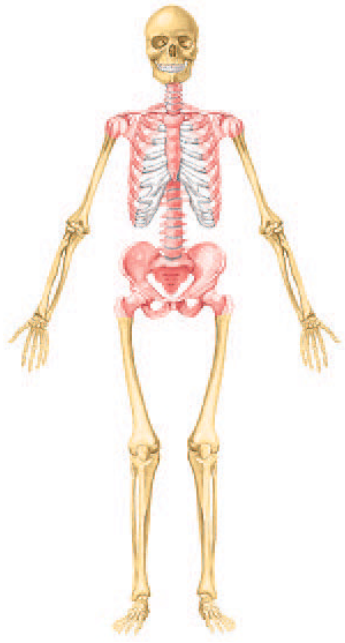


Figure 6.4 Bone Marrow
Distribution of red and yellow marrow in an adult.

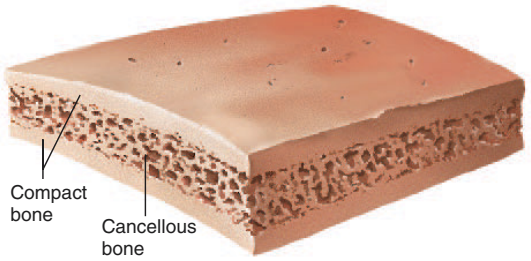


Figure 6.5 Structure of a Flat Bone
Outer layers of compact bone surround cancellous bone.

Structure of Flat, Short, and Irregular Bones

Flat bones usually have no diaphyses or epiphyses, and they contain an interior framework of cancellous bone sandwiched between two layers of compact bone (figure 6.5). Short and irregular bones have a composition similar to the epiphyses of long bones. They have compact bone surfaces that surround a cancellous bone center with small spaces that usually are filled with marrow. Short and irregular bones are not elongated and have no diaphyses. Certain regions of these bones, however, such as the processes (projections) of irregular bones, possess epiphyseal growth plates and therefore have small epiphyses.

Some of the flat and irregular bones of the skull have air-filled spaces called **sinuses** (sī′nŭs-ĕz) (see chapter 7), which are lined by mucous membranes.

5. *List the four basic shapes of individual bones, and give an example of each.*
6. *Define the diaphysis, epiphysis, epiphyseal plate, and epiphyseal line of a long bone.*
7. *What are red marrow and yellow marrow? Where are they located in a child and in an adult?*
8. *Where are the periosteum and endosteum located? What types of cells are found in the periosteum and endosteum? What is the function of perforating (Sharpey's) fibers?*
9. *Compare the structure of long bones to the structure of flat, short, and irregular bones. How are compact bone and cancellous bone arranged in each?*

Bone Histology

Objectives

- ***Describe bone matrix and the different types of bone cells.***
- ***List the features that characterize woven, lamellar, cancellous, and compact bone.***

Bone consists of extracellular bone matrix and bone cells. The composition of the bone matrix is responsible for the characteristics of bone. The bone cells produce the bone matrix, become entrapped within it, and break it down so that new matrix can replace the old matrix.

Bone Matrix

By weight, mature bone matrix normally is approximately 35% organic and 65% inorganic material. The organic material primarily consists of collagen and proteoglycans. The inorganic material primarily consists of a calcium phosphate crystal called **hydroxyapatite** (hī-drok′sē-ap-ă-tīt), which has the molecular formula $Ca_{10}(PO_4)_6(OH)_2$.

The collagen and mineral components are responsible for the major functional characteristics of bone. Bone matrix might be said to resemble reinforced concrete. Collagen, like reinforcing steel bars, lends flexible strength to the matrix, whereas the mineral components, like concrete, give the matrix compression (weight-bearing) strength.

If all the mineral is removed from a long bone, collagen becomes the primary constituent, and the bone becomes overly flexible. On the other hand, if the collagen is removed from the bone, the mineral component becomes the primary constituent, and the bone is very brittle (figure 6.6).

PREDICT 2

In general, the bones of elderly people break more easily than the bones of younger people. Give as many possible explanations as you can for this observation.

Bone Cells

Bone cells are categorized as osteoblasts, osteocytes, and osteoclasts, which have different functions and origins.

Osteoblasts

Osteoblasts (os′tē-ō-blastz) have an extensive endoplasmic reticulum and numerous ribosomes. They produce collagen and proteoglycans, which are packaged into vesicles by the Golgi apparatus and released from the cell by exocytosis. Osteoblasts also form vesicles that accumulate calcium ions (Ca^{2+}), phosphate ions (PO_4^{2-}), and various enzymes. The contents of these vesicles are released from the cell by exocytosis and are used to form hydroxyapatite crystals. As a result of these processes, mineralized bone matrix is formed.

Ossification (os′i-fi-kā′shŭn), or **osteogenesis** (os′tē-ō-jen′ĕ-sis), is the formation of bone by osteoblasts. Elongated cell processes from osteoblasts connect to cell processes of other osteoblasts through gap junctions (see chapter 4). The osteoblasts then form an extracellular bony matrix that surrounds the cells and their processes (figure 6.7).

Osteocytes

Once an osteoblast becomes surrounded by bone matrix, it is a mature bone cell called an **osteocyte** (os′tē-ō-sīt). Osteocytes become relatively inactive compared to most osteoblasts, but it's

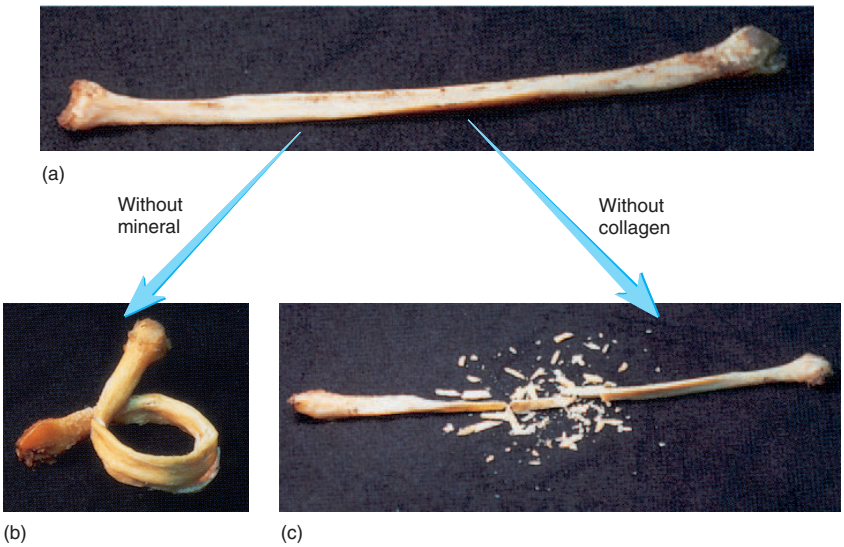


Figure 6.6 Effects of Changing the Bone Matrix

(*a*) Normal bone. (*b*) Demineralized bone, in which collagen is the primary remaining component, can be bent without breaking. (*c*) When collagen is removed, mineral is the primary remaining component, thus making the bone so brittle it's easily shattered.

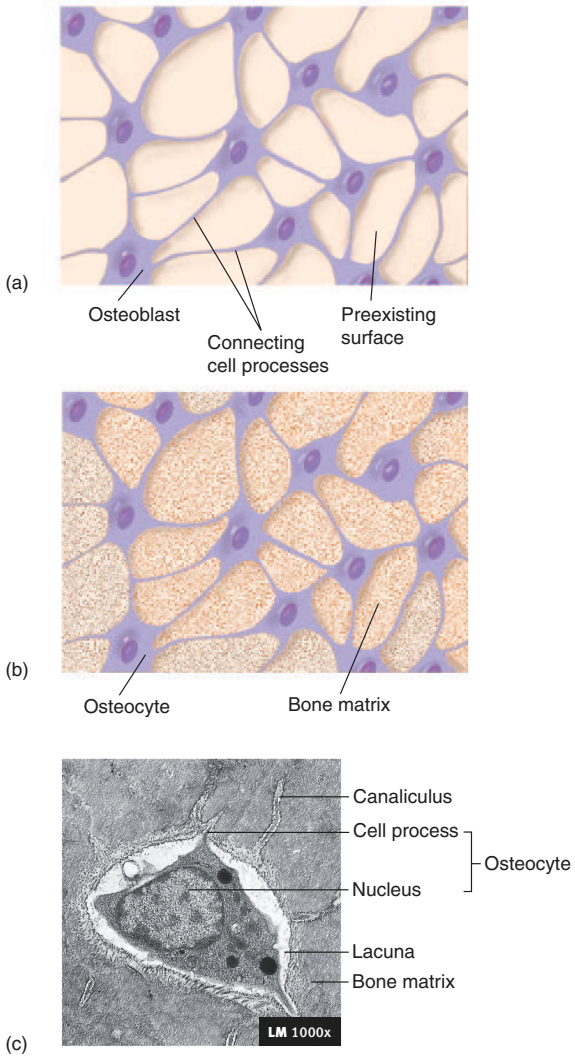


Figure 6.7 Ossification

(*a*) Osteoblasts on a preexisting surface, such as cartilage or bone. The cell processes of different osteoblasts join together. (*b*) Osteoblasts have produced bone matrix. The osteoblasts are now osteocytes. (*c*) Photomicrograph of an osteocyte in a lacuna with cell processes in the canaliculi.

possible for them to produce components needed to maintain the bone matrix.

The spaces occupied by the osteocyte cell bodies are called **lacunae** (lă-koo′nē), and the spaces occupied by the osteocyte cell processes are called **canaliculi** (kan-ă-lik′ū-lī; meaning little canals) (see figure 6.7). In a sense, the cells and their processes form a "mold" around which the matrix is formed. Bone differs from cartilage in that the processes of bone cells are in contact with one another through the canaliculi. Instead of diffusing through the mineralized matrix, nutrients and gases can pass through the small amount of fluid surrounding the cells in the canaliculi and lacunae or pass from cell to cell through the gap junctions connecting the cell processes.

Osteoclasts

Osteoclasts (os′tē-ō-klastz) are large cells with several nuclei and are responsible for the **resorption,** or breakdown, of bone. Where the plasma membrane of osteoclasts contacts bone matrix, it forms many projections called a **ruffled border.** Hydrogen ions are pumped across the ruffled border and produce an acid environment that causes decalcification of the bone matrix. The osteoclasts also release enzymes that digest the protein components of the matrix. Through the process of endocytosis, some of the breakdown products of bone resorption are taken into the osteoclast.

Osteoclasts break down bone best when they are in direct contact with mineralized bone matrix. Osteoblasts assist in the resorption of bone by osteoclasts by producing enzymes that break down the thin layer of unmineralized organic matrix normally covering bone. Removal of this layer by osteoblasts enables the osteoclasts to come into contact with the mineralized bone.

Origin of Bone Cells

Connective tissue develops embryologically from mesenchymal cells (see chapter 4). Some of the mesenchymal cells become **stem cells,** which have the ability to replicate and give rise to more specialized cell types. **Osteochondral progenitor cells** are stem cells that have the ability to become osteoblasts or chondroblasts. Osteochondral progenitor cells are located in the inner layer of the perichondrium, the inner layer of the periosteum, and in the endosteum. From these locations, they can be a potential source of new osteoblasts or chondroblasts.

Osteoblasts are derived from osteochondral progenitor cells, and osteocytes are derived from osteoblasts. Whether or not osteocytes freed from their surrounding bone matrix by resorption can revert to active osteoblasts is a debated issue. Osteoclasts are not derived from osteochondral progenitor cells but are derived instead from stem cells in red bone marrow (see chapter 19). The bone marrow stem cells that give rise to a type of white blood cell, called a monocyte, also are the source of osteoclasts. The multinucleated osteoclasts probably result from the fusion of many stem cell descendants.

10. *Name the components of bone matrix, and explain their contribution to the strength of bone.*
11. *What are the functions of osteoblasts, osteocytes, and osteoclasts? Name the spaces that are occupied by osteocyte cell bodies and cell processes.*
12. *What cells give rise to osteochondral progenitor cells? What kinds of cells are derived from osteochondral progenitor cells? What types of cells give rise to osteoclasts?*

Woven and Lamellar Bone

Bone tissue is classified as either woven or lamellar bone according to the organization of collagen fibers within the bone matrix. In **woven bone,** the collagen fibers are randomly oriented in many directions. Woven bone is first formed during fetal development or during the repair of a fracture. After its formation, osteoclasts break down the woven bone and osteoblasts build new matrix. This process of removing old bone and adding new bone is called

remodeling. It is an important process discussed later in this chapter (see p. 183). Woven bone is remodeled to form lamellar bone.

Lamellar bone is mature bone that is organized into thin sheets or layers approximately 3–7 micrometers (μm) thick called **lamellae** (lă-mel′ē). In general, the collagen fibers of one lamella lie parallel to one another but at an angle to the collagen fibers in the adjacent lamellae. Osteocytes, within their lacunae, are arranged in layers sandwiched between lamellae.

Cancellous and Compact Bone

Bone, whether woven or lamellar, can be classified according to the amount of bone matrix relative to the amount of space present within the bone. Cancellous bone has less bone matrix and more space than compact bone, which has more bone matrix and less space than cancellous bone.

Cancellous bone (figure 6.8*a*) consists of interconnecting rods or plates of bone called **trabeculae** (tră-bek′ū-lē; beam). Between the trabeculae are spaces that in life are filled with bone marrow and blood vessels. Cancellous bone is sometimes called spongy bone because of its porous appearance.

Most trabeculae are thin (50–400 μm) and consist of several lamellae with osteocytes located between the lamellae (figure 6.8*b*). Each osteocyte is associated with other osteocytes through canaliculi. Usually no blood vessels penetrate the trabeculae, so osteocytes must obtain nutrients through their canaliculi. The surfaces of trabeculae are covered with a single layer of cells consisting mostly of osteoblasts with a few osteoclasts.

Trabeculae are oriented along the lines of stress within a bone (figure 6.9). If the direction of weight-bearing stress is changed slightly (e.g., because of a fracture that heals improperly), the trabecular pattern realigns with the new lines of stress.

Compact bone (figure 6.10) is denser and has fewer spaces than cancellous bone. Blood vessels enter the substance of the bone itself, and the lamellae of compact bone are primarily oriented around those blood vessels. Vessels that run parallel to the long axis of the bone are contained within **central,** or **haversian** (ha-ver′shan), **canals.** Central canals are lined with endosteum and contain blood vessels, nerves, and loose connective tissue. **Concentric lamellae** are circular layers of bone matrix that surround a common center, the central canal. An **osteon** (os′tē-on), or **haversian system,** consists of a single central canal, its contents, and associated concentric lamellae and osteocytes. In cross section, an osteon resembles a circular target; the "bull's-eye" of the target is the central canal, and 4–20 concentric lamellae form the rings.

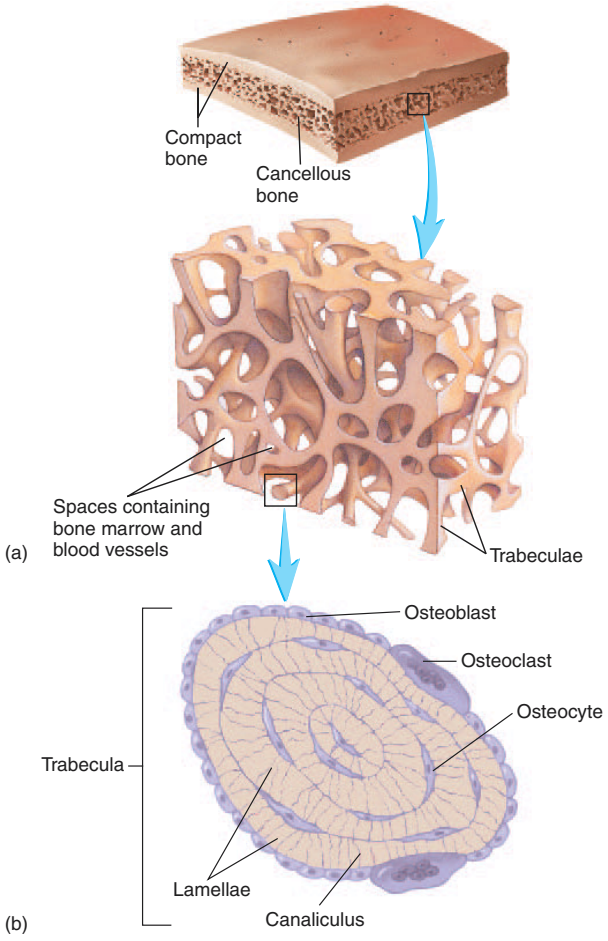


Figure 6.8 Cancellous Bone

(*a*) Beams of bone, the trabeculae, surround spaces in the bone. In life, the spaces are filled with red or yellow bone marrow and with blood vessels. (*b*) Transverse section of a trabecula.

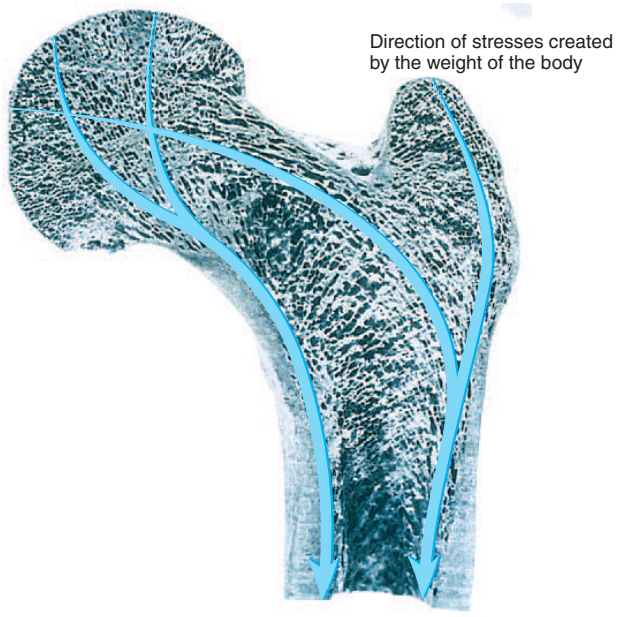


Figure 6.9 Lines of Stress

The proximal end of a long bone (femur) showing trabeculae oriented along lines of stress (*arrows*).

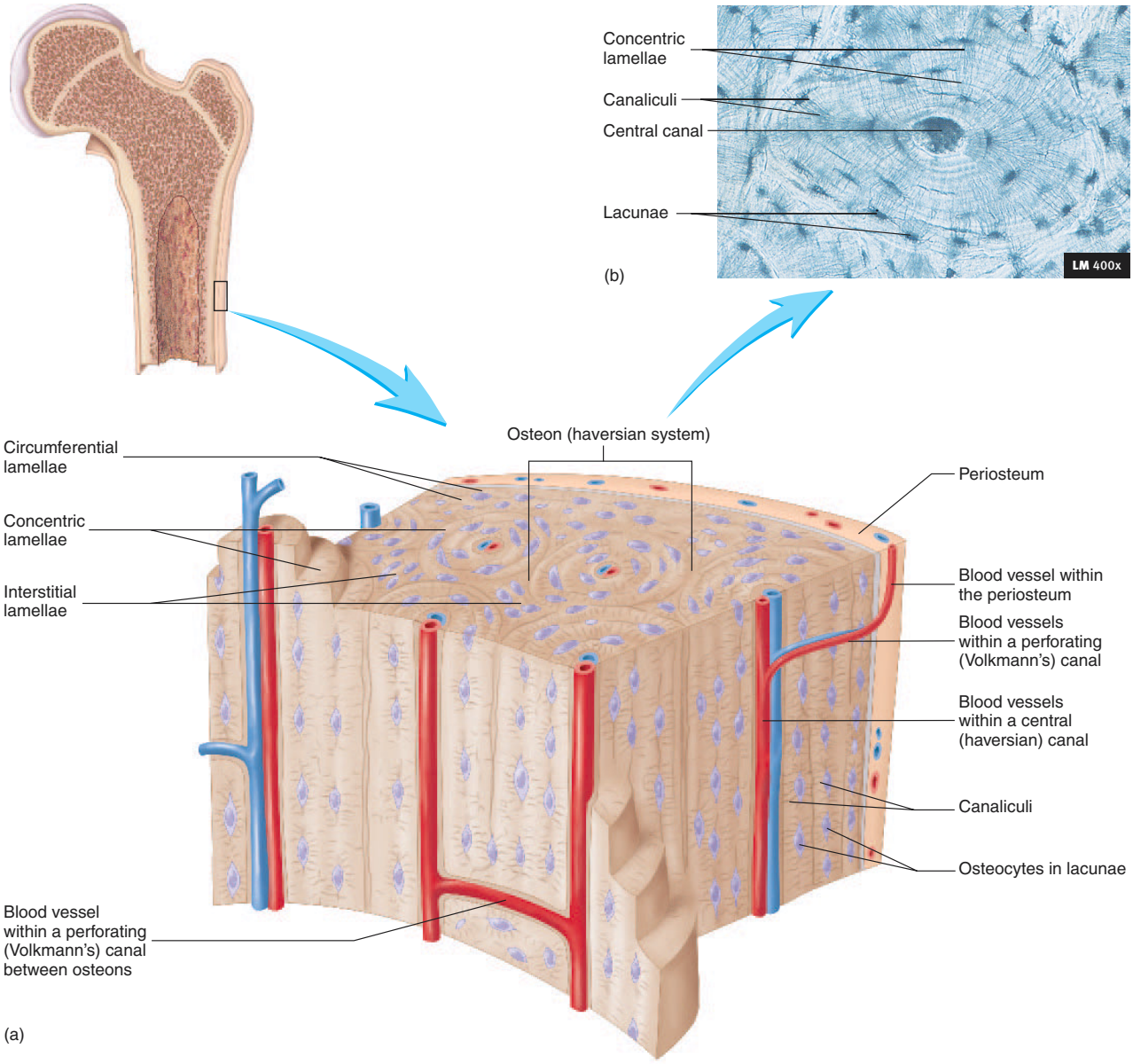


Figure 6.10 Compact Bone

(*a*) Compact bone consists mainly of osteons, which are concentric lamellae surrounding blood vessels within central canals. The outer surface of the bone is formed by circumferential lamellae, and bone between the osteons consists of interstitial lamellae. (*b*) Photomicrograph of an osteon.

Osteocytes are located in lacunae between the lamellar rings, and canaliculi radiate between lacunae across the lamellae, producing the appearance of minute cracks across the rings of the target.

The outer surfaces of compact bone are formed by **circumferential lamellae,** which are flat plates that extend around the bone (see figure 6.10). In some bones, such as certain bones of the face, the layer of compact bone can be so thin that no osteons exist, and the compact bone is composed of only circumferential lamellae. In between the osteons are **interstitial lamellae,** which are remnants of concentric or circumferential lamellae that were partially removed during bone remodeling.

Osteocytes receive nutrients and eliminate waste products through the canal system within compact bone. Blood vessels from the periosteum or medullary cavity enter the bone through **perforating,** or **Volkmann's, canals,** which run perpendicular to the long axis of the bone (see figure 6.10). Perforating canals are not surrounded by concentric lamellae but pass through the concentric lamellae of osteons. The central canals receive blood vessels from

perforating canals. Nutrients in the blood vessels enter the central canals, pass into the canaliculi, and move through the cytoplasm of the osteocytes that occupy the canaliculi and lacunae to the most peripheral cells within each osteon. Waste products are removed in the reverse direction.

13. *Distinguish between woven bone and lamellar bone. Where is woven bone found?*
14. *Describe the structure of cancellous bone. What are trabeculae, and what is their function? How do osteocytes within trabeculae obtain nutrients?*
15. *Describe the structure of compact bone. What is an osteon? Name three types of lamellae found in compact bone.*
16. *Trace the pathway nutrients must follow to go from blood vessels in the periosteum to osteocytes within osteons.*

PREDICT 3

Compact bone has perforating and central canals. Why isn't such a canal system necessary in cancellous bone?

Bone Development

Objective

- *Name the two patterns of bone formation, and describe the features of each.*

During fetal development, bone formation occurs in two patterns called **intramembranous** and **endochondral ossification.** The terms describe the tissues in which bone formation takes place: intramembranous ossification in connective tissue membranes and endochondral ossification in cartilage. Both methods of ossification initially produce woven bone that is then remodeled. After remodeling, bone formed by intramembranous ossification cannot be distinguished from bone formed by endochondral ossification. Table 6.2 compares intramembranous and endochondral ossification.

Intramembranous Ossification

At approximately the fifth week of development embryonic mesenchyme condenses around the developing brain to form a membrane of connective tissue with randomly oriented, delicate collagen fibers. Intramembranous ossification of the membrane begins at approximately the eighth week of development and is completed by approximately 2 years of age. Many skull bones, part of the mandible (lower jaw), and the diaphyses of the clavicles (collarbones) develop by intramembranous ossification (figure 6.11*a*).

Centers of ossification are the locations in the membrane where ossification begins. The centers of ossification expand to form a bone by gradually ossifying the membrane. Thus, the centers of ossification have the oldest bone and the expanding edges the youngest bone. The larger membrane-covered spaces between the developing skull bones that have not yet been ossified are called **fontanels,** or soft spots (figure 6.12) (see chapter 8). The bones eventually grow together, and all the fontanels have usually closed by the time an infant is 2 years of age.

1. Intramembranous ossification begins when some of the mesenchymal cells in the membrane become osteochondral progenitor cells, which specialize to become osteoblasts. The osteoblasts produce bone matrix that surrounds the collagen fibers of the connective tissue membrane, and the osteoblasts become osteocytes. As a result of this process, many tiny trabeculae of woven bone develop (figure 6.11*b*).
2. Additional osteoblasts gather on the surfaces of the trabeculae and produce more bone, thereby causing the trabeculae to become larger and longer (figure 6.11*c*).
3. Cancellous bone forms as the trabeculae join together, resulting in an interconnected network of trabeculae separated by spaces (figure 6.11*c*). Cells within the spaces of the cancellous bone specialize to form red bone marrow. As cancellous bone develops, cells surrounding the developing bone specialize and form the periosteum. Osteoblasts from the periosteum lay down bone matrix to form an outer surface of compact bone (figure 6.11*d*). Thus, the end products of intramembranous bone formation are bones with outer compact bone surfaces and cancellous centers (see figure 6.5). Remodeling converts woven bone to lamellar bone and contributes to the final shape of the bone.

Table 6.2 Comparison of Intramembranous and Endochondral Ossification

Intramembranous Ossification	Endochondral Ossification
Embryonic mesenchyme forms a collagen membrane containing osteochondral progenitor cells.	Embryonic mesenchymal cells become chondroblasts that produce a cartilage template surrounded by the perichondrium.
No stage is comparable.	Chondrocytes hypertrophy, the cartilage matrix becomes calcified, and the chondrocytes die.
Embryonic mesenchyme forms the periosteum, which contains osteoblasts.	The perichondrium becomes the periosteum when osteochondral progenitor cells within the periosteum become osteoblasts.
Osteochondral progenitor cells become osteoblasts at centers of ossification; internally the osteoblasts form cancellous bone; externally the periosteal osteoblasts form compact bone.	Blood vessels and osteoblasts from the periosteum invade the calcified cartilage template; internally these osteoblasts form cancellous bone at primary ossification centers (and later at secondary ossification centers); externally the periosteal osteoblasts form compact bone.
Intramembranous bone is remodeled and becomes indistinguishable from endochondral bone.	Endochondral bone is remodeled and becomes indistinguishable from intramembranous bone.

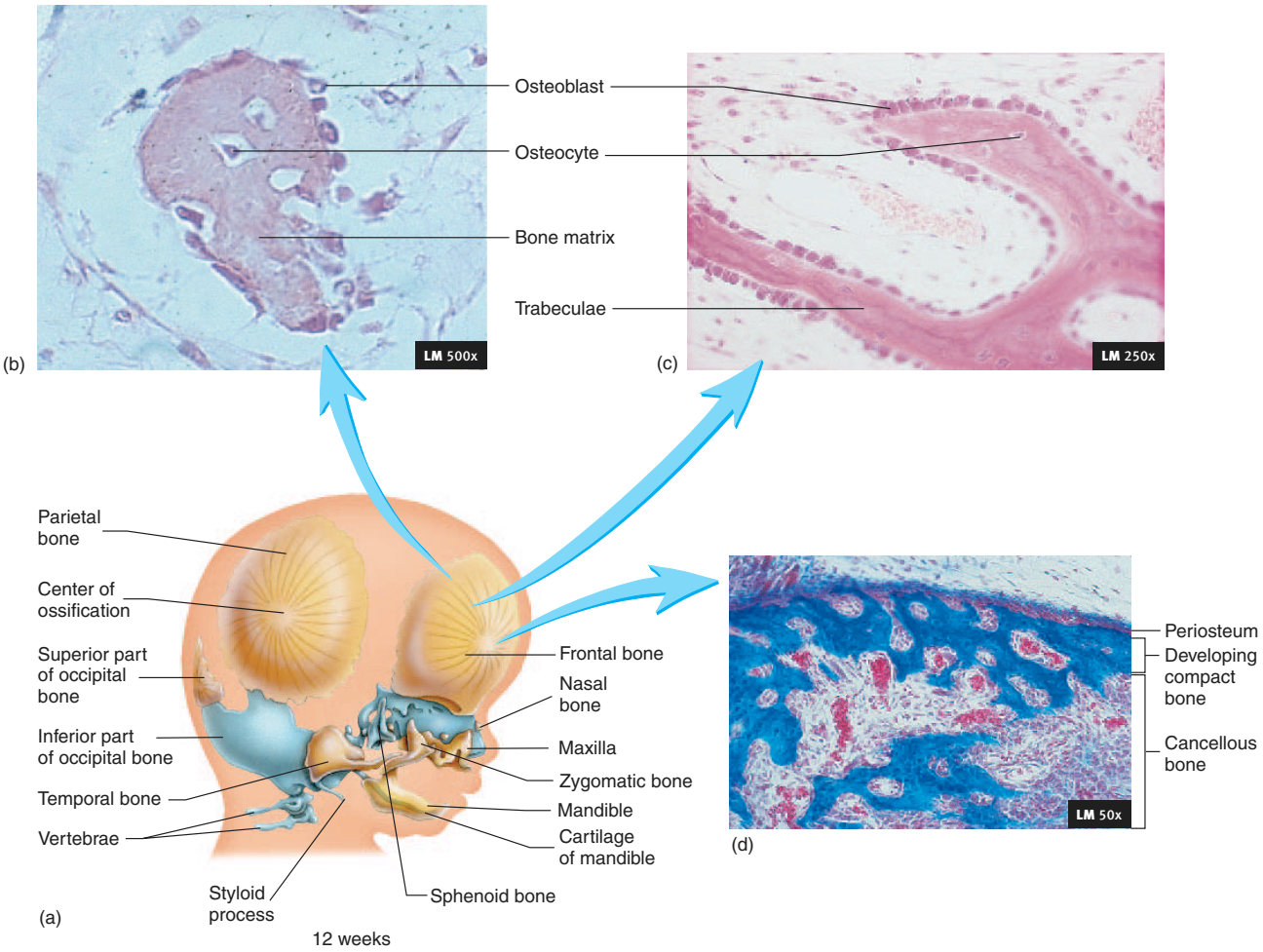


Figure 6.11 Intramembranous Ossification

(*a*) Twelve-week-old fetus showing skull bones that develop by intramembranous ossification (*yellow*). Bones formed by endochondral ossification (*blue*) are also shown. Intramembranous ossification starts at a center of ossification and expands outward. Therefore, the center of ossification has the oldest bone and the expanding edge the youngest bone. (*b*) Photomicrograph of a cross section of a newly formed trabecula. Osteocytes are surrounded by bone matrix and osteoblasts are forming a ring on the outer surface of the trabecula. As they lay down additional bone matrix, the trabecula increases in size. (*c*) Lower magnification photomicrograph than (*b*), showing cancellous bone, formed as a result of the enlargement and interconnections of many trabeculae. (*d*) Lower magnification photomicrograph than (*c*), with a different stain that makes bones appear blue. Beneath the periosteum is an outer layer of developing compact bone. Within the cancellous bone there is trabeculae (blue) and developing red bone marrow (pink).

Endochondral Ossification

The formation of cartilage begins at approximately the end of the fourth week of development. Endochondral ossification of some of this cartilage starts at approximately the eighth week of development. Endochondral ossification of some cartilage might not begin until as late as age 18–20 years. Bones of the base of the skull, part of the mandible, the epiphyses of the clavicles, and most of the remaining skeletal system develop through the process of endochondral ossification (see figures 6.11 and 6.12).

1. Endochondral ossification begins as mesenchymal cells aggregate in regions of future bone formation. The mesenchymal cells become chondroblasts, which produce a hyaline **cartilage model** having the approximate shape of the bone that will later be formed (figure 6.13 *1*). As the chondroblasts become surrounded by cartilage matrix, they become chondrocytes. The cartilage model is surrounded by perichondrium, except where a joint will form connecting one bone to another bone. Not shown in figure 6.13, the perichondrium is continuous with tissue

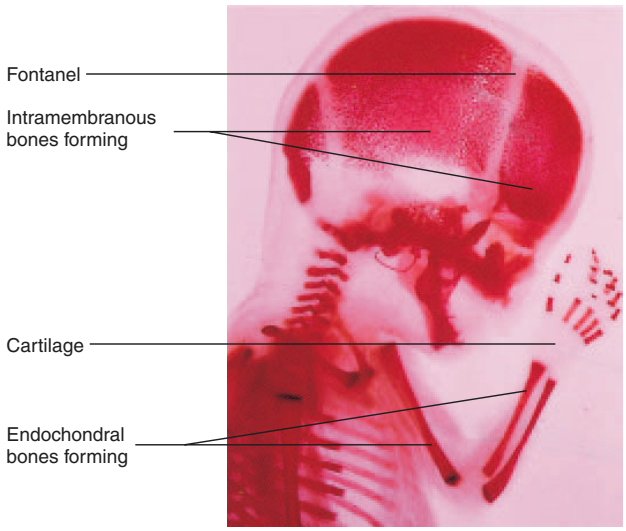


Figure 6.12 Bone Formation

Eighteen-week-old fetus showing intramembranous and endochondral ossification. Intramembranous ossification occurs at centers of ossification in the flat bones of the skull. Endochondral ossification has formed bones in the diaphyses of long bones. The epiphyses are still cartilage at this stage of development.

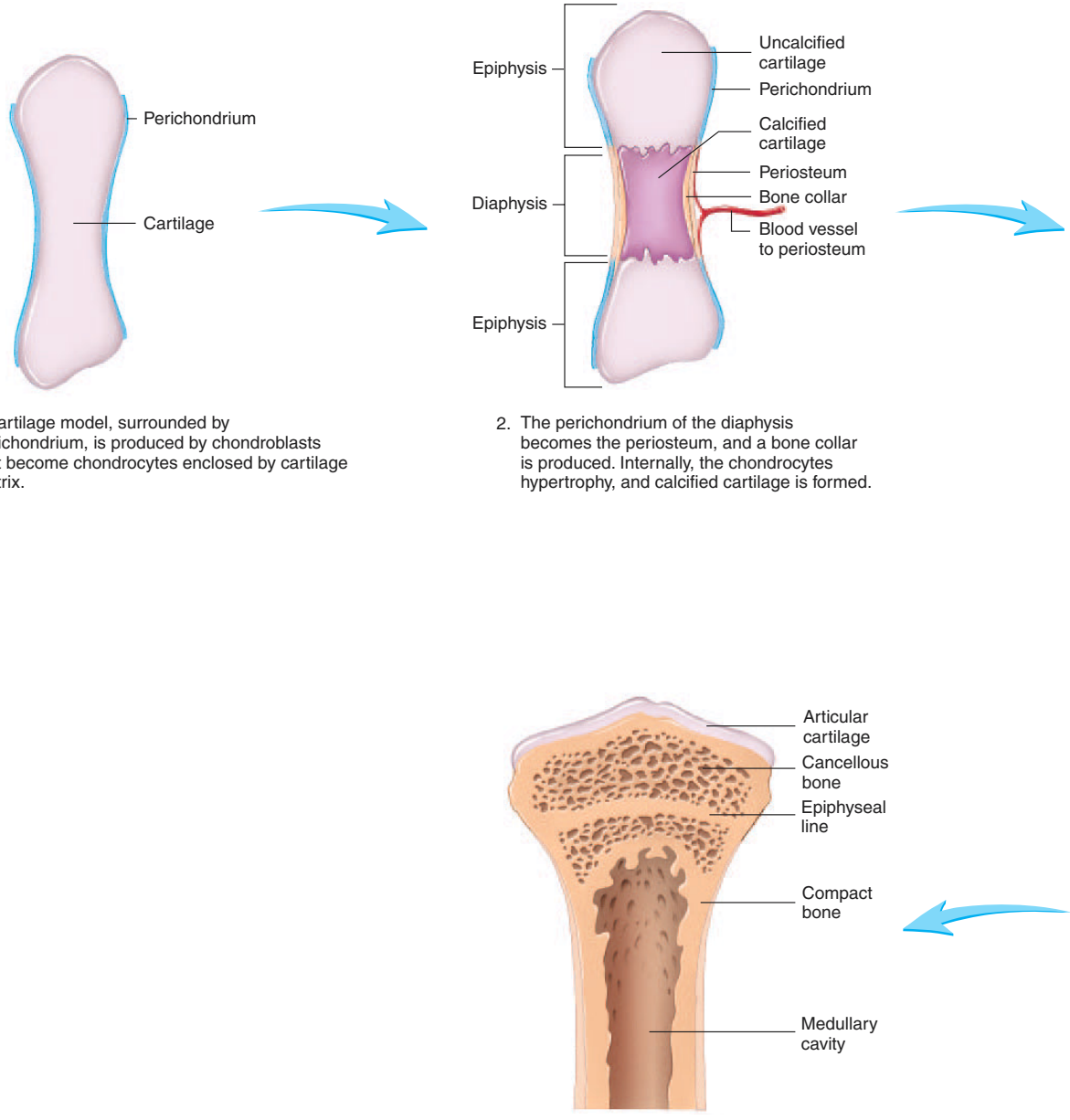
that will become the joint capsule (see chapter 8).

2. When blood vessels invade the perichondrium surrounding the cartilage model (figure 6.13 *2*), osteochondral progenitor cells within the perichondrium become osteoblasts. The perichondrium becomes the periosteum when the osteoblasts begin to produce bone. The osteoblasts produce compact bone on the surface of the cartilage model, forming a **bone collar.** Two other events are occurring at the same time that the bone collar is forming. First, the cartilage model increases in size as a result of interstitial and appositional cartilage growth. Second, the chondrocytes in the center of the cartilage model **hypertrophy** (hī-per′trō-fē), or enlarge, and the matrix between the enlarged cells becomes mineralized with calcium carbonate. At this point, the cartilage is referred to as **calcified cartilage**. The chondrocytes in this calcified area eventually die, leaving enlarged lacunae with thin walls of calcified matrix.
3. Blood vessels grow into the enlarged lacunae of the calcified cartilage (figure 6.13 *3*). The connective tissue surrounding the blood vessels brings in osteosblasts and osteoclasts from the periosteum. The osteoblasts produce bone on the surface of the calcified cartilage, forming bone trabeculae, which changes the calcified cartilage of the diaphysis into cancellous bone. This area of bone formation is called the **primary ossification center.**
4. As bone development proceeds, the cartilage model continues to grow, more perichondrium becomes periosteum, the bone collar thickens and extends further along the diaphysis, and additional cartilage within the diaphysis is calcified and transformed into cancellous bone (figure 6.13 *4*). Remodeling converts woven bone to lameller bone and contributes to the final shape of the bone. Osteoclasts remove bone from the center of the diaphysis to form the medullary cavity, and cells within the medullary cavity specialize to form red bone marrow.
5. In long bones the diaphysis is the primary ossification center, and additional sites of ossification, called **secondary ossification centers,** appear in the epiphyses (figure 6.13 *5*). The events occurring at the secondary ossification centers are the same as those occurring at the primary ossification centers, except that the spaces in the epiphyses don't enlarge to form a medullary cavity as in the diaphysis. Primary ossification centers appear during early fetal development, whereas secondary ossification centers appear in the proximal epiphysis of the femur, humerus, and tibia about 1 month before birth. A baby is considered full term if one of these three ossification centers can be seen on radiographs at the time of birth. At about 18–20 years of age the last secondary ossification center appears in the medial epiphysis of the clavicle.
6. Replacement of cartilage by bone continues in the cartilage model until all the cartilage, except that in the epiphyseal plate and on articular surfaces, has been replaced by bone (figure 6.13 *6*). The epiphyseal plate, which exists throughout an individual's growth, and the articular cartilage, which is a permanent structure, are derived from the original embryonic cartilage model.
7. In mature bone, cancellous and compact bone are fully developed and the epiphyseal plate has become the epiphyseal line. The only cartilage present is the articular cartilage at the ends of the bone (figure 6.13 *7*). All the original perichondrium that surrounded the cartilage model has become periosteum.

17. *Describe four major steps in the formation of cancellous and compact bone during intramembranous ossification. What are centers of ossification? What are fontanels?*
18. *For the process of endochondral ossification, describe the formation of these structures: cartilage model, bone collar, calcified cartilage, primary ossification center, medullary cavity, secondary ossification center, epiphyseal plate, epiphyseal line, and articular cartilage.*
19. *When do primary and secondary ossification centers appear during endochondral ossification?*

PREDICT 4

During endochondral ossification, calcification of cartilage results in the death of chondrocytes. However, ossification of the bone matrix does not result in the death of osteocytes. Explain.



1. A cartilage model, surrounded by perichondrium, is produced by chondroblasts that become chondrocytes enclosed by cartilage matrix.

2. The perichondrium of the diaphysis becomes the periosteum, and a bone collar is produced. Internally, the chondrocytes hypertrophy, and calcified cartilage is formed.

7. Mature bone in which the epiphyseal plate has become the epiphyseal line and all the cartilage in the epiphysis, except the articular cartilage, has become bone.

Process Figure 6.13 Endochondral Ossification

Endochondral ossification begins with the formation of a cartilage model in the upper left part of the figure. See successive steps as indicated by the *blue arrows*.

Bone Growth

Objective

- ***Explain how bone growth occurs, and describe the factors that affect bone growth.***

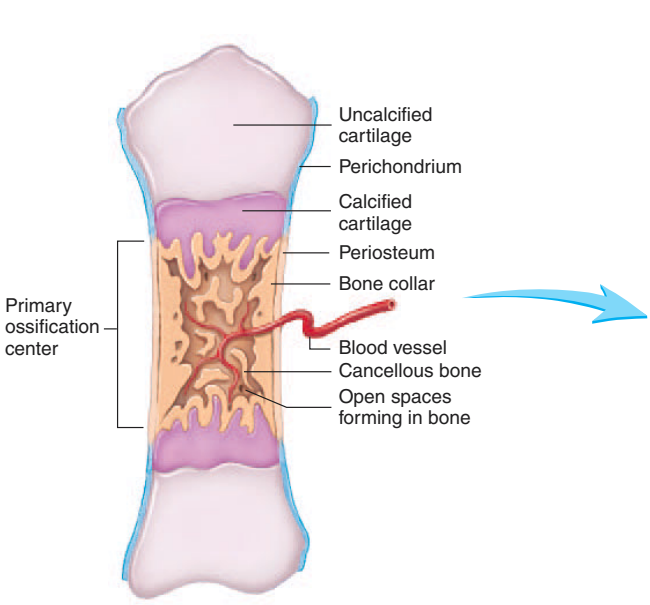
Unlike cartilage, bones cannot grow by interstitial growth. Bones increase in size only by **appositional growth,** the formation of new bone on the surface of older bone or cartilage. For example, trabeculae grow in size by the deposition of new bone matrix by osteoblasts onto the surface of the trabeculae (see figure 6.11).

PREDICT 5

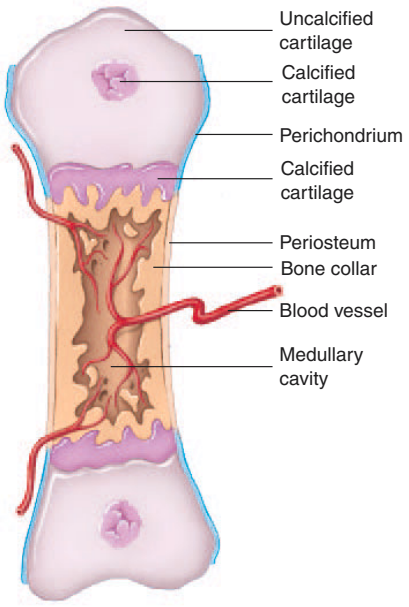
Explain why bones cannot undergo interstitial growth, as does cartilage.

Growth in Bone Length

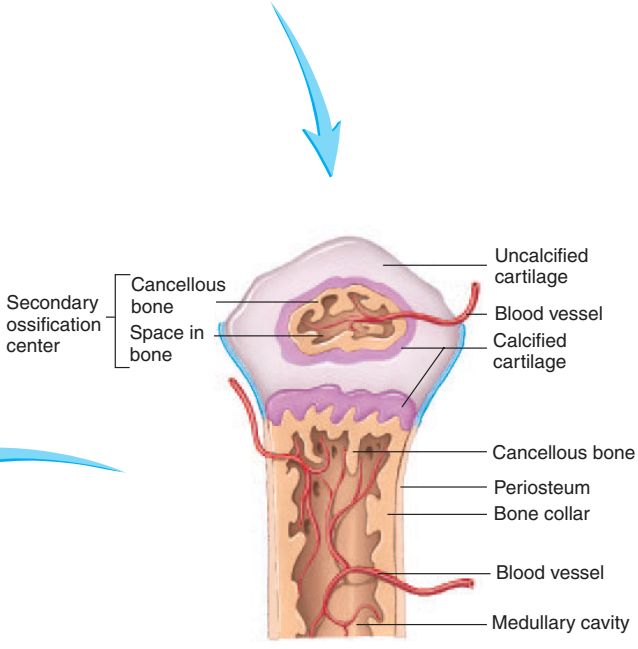
Long bones and bony projections increase in length because of growth at the epiphyseal plate. In a long bone, the epiphyseal plate



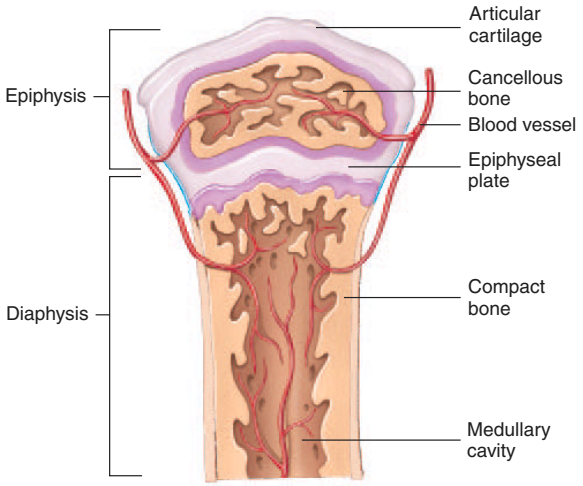
3. A primary ossification center forms as blood vessels and osteoblasts invade the calcified cartilage. The osteoblasts lay down bone matrix, forming cancellous bone.



4. The process of bone collar formation, cartilage calcification, and cancellous bone production continues. Calcified cartilage begins to form in the epiphyses. A medullary cavity begins to form in the center of the diaphysis.



5. Secondary ossification centers form in the epiphyses of long bones.



6. The original cartilage model is almost completely ossified. Unossified cartilage becomes the epiphyseal plate and the articular cartilage.

Process Figure 6.13 *(continued)*

separates the epiphysis from the diaphysis (figure 6.14*a*). Long projections of bones, such as the processes of vertebrae (see chapter 7), also have epiphyseal plates.

Growth at the epiphyseal plate involves the formation of new cartilage by interstitial cartilage growth followed by appositional bone growth on the surface of the cartilage. The epiphyseal plate is organized into four zones (figure 6.14*b*). The **zone of resting cartilage** is nearest the epiphysis and contains randomly arranged chondrocytes that do not divide rapidly. The chondrocytes in the **zone of proliferation** produce new cartilage through interstitial cartilage growth. The chondrocytes divide and form columns resembling stacks of plates or coins. In the **zone of hypertrophy,** the chondrocytes produced in the zone of proliferation mature and enlarge. Thus a maturation gradient exists in each column: cells nearer to the epiphysis are younger and are actively proliferating, whereas cells progressively nearer the diaphysis are older and are undergoing hypertrophy. The **zone of calcification** is very thin and consists of cartilage matrix mineralized with calcium carbonate. The hypertrophied chondrocytes die, and blood vessels from the diaphysis grow into the area. The connective tissue surrounding the blood vessels contains osteoblasts from the endosteum. The osteoblasts line up on the surface of the calcified cartilage and through appositional bone growth deposit new bone matrix, which is later remodeled.

As new cartilage cells form in the zone of proliferation, and as these cells enlarge in the zone of hypertrophy, the overall length of the diaphysis increases (figure 6.15). The thickness of the epiphyseal plate does not increase, however, because the rate of cartilage growth on the epiphyseal side of the plate is equal to the rate at which cartilage is replaced by bone on the diaphyseal side of the plate.

As the bones achieve normal adult size, growth in bone length ceases because the epiphyseal plate is ossified and becomes the epiphyseal line. This event, called closure of the epiphyseal plate, occurs between approximately 12 and 25 years of age, depending on the bone and the individual.

P R E D I C T 6

A 15-year-old football player is tackled during a game, and the epiphyseal plate of the left femur is damaged (figure 6.16). What are the results of such an injury, and why is recovery difficult?

Growth at Articular Cartilage

Epiphyses increase in size because of growth at the articular cartilage. In addition, growth at the articular cartilage increases the size of bones that do not have an epiphysis, such as short bones. The process of growth in articular cartilage is similar to that occurring in the epiphyseal plate, except that the chondrocyte columns are not as

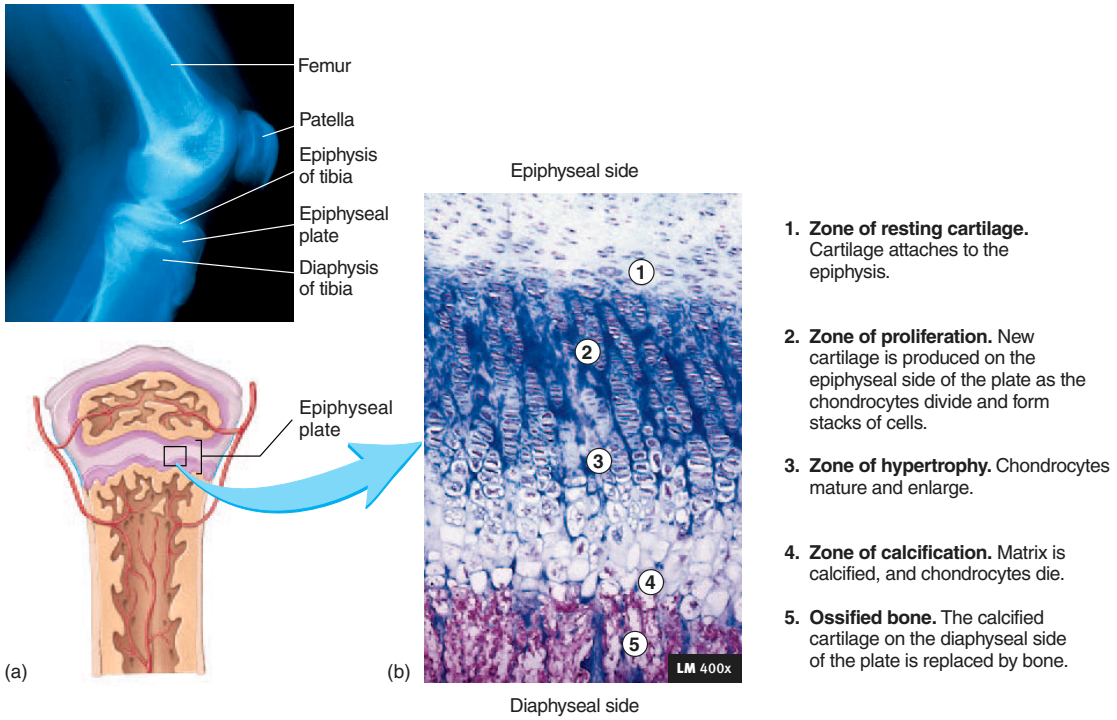


Figure 6.14 Epiphyseal Plate

(*a*) Radiograph of the knee, showing the epiphyseal plate of the tibia (shinbone). Because cartilage does not appear readily on x-ray film, the epiphyseal plate appears as a black area between the white diaphysis and the epiphyses. (*b*) Zones of the epiphyseal plate.

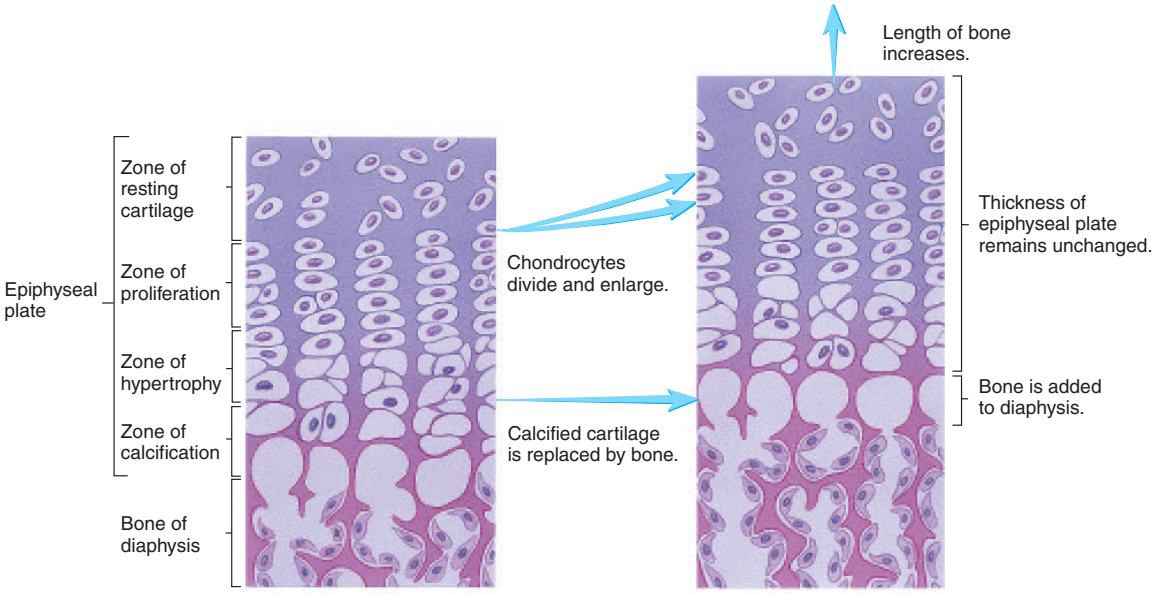


Figure 6.15 Bone Growth in Length at the Epiphyseal Plate

New cartilage is formed on the epiphyseal side of the plate at the same rate that new bone is formed on the diaphyseal side of the plate. Consequently, the epiphyseal plate remains the same thickness, but the length of the diaphysis increases.

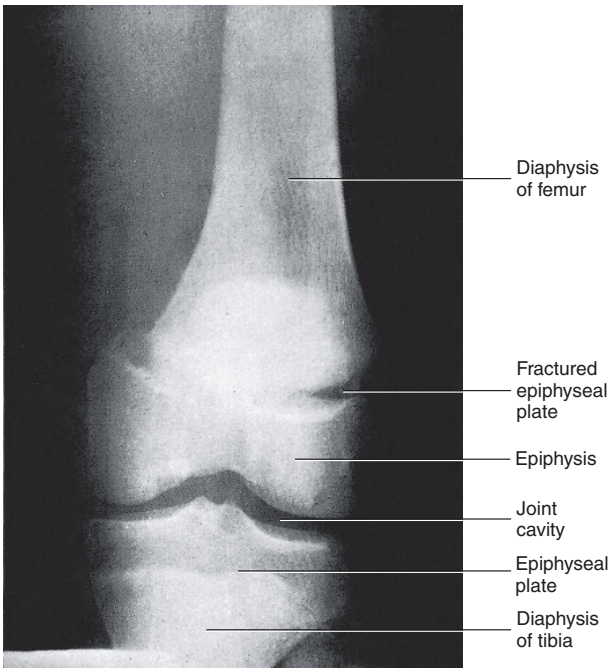


Figure 6.16 Fracture of the Epiphyseal Plate

Radiograph of an adolescent's knee. The femur (thighbone) is separated from the tibia (leg bone) by a joint cavity. The epiphyseal plate of the femur is fractured, thereby separating the diaphysis from the epiphysis.

obvious. The chondrocytes near the surface of the articular cartilage are similar to those in the zone of resting cartilage of the epiphyseal plate. In the deepest part of the articular cartilage, nearer bone tissue, the cartilage is calcified, dies, and is ossified to form new bone.

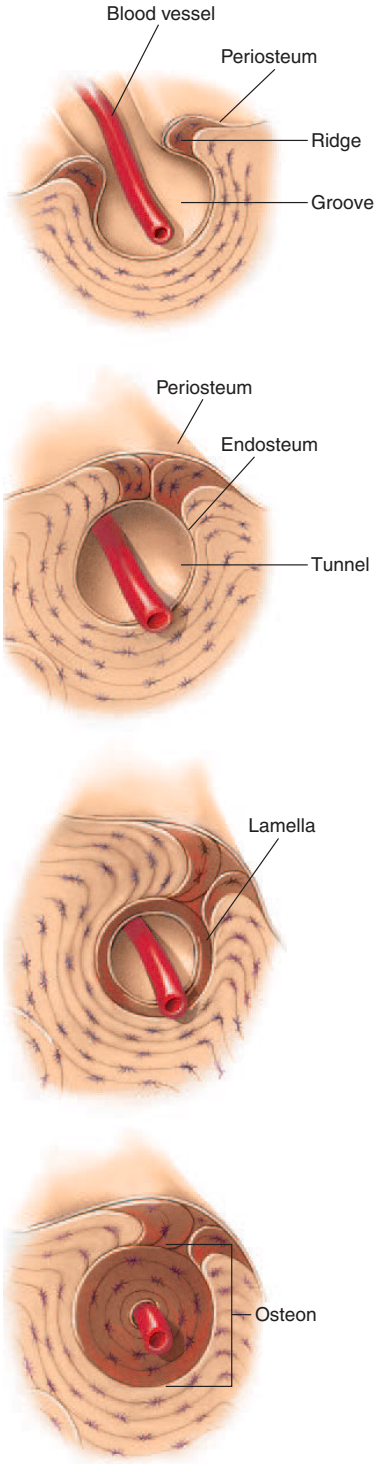
When the epiphyses reach their full size, the growth of cartilage and its replacement by bone ceases. The articular cartilage, however, persists throughout life and does not become ossified as does the epiphyseal plate.

P R E D I C T 7

Growth at the epiphyseal plate stops when the epiphyseal cartilage becomes ossified. The articular cartilage, however, does not become ossified when growth of the epiphysis ceases. Explain why it is advantageous for the articular cartilage not to be ossified.

Growth in Bone Width

Long bones increase in width (diameter) and other bones increase in size or thickness because of appositional bone growth beneath the periosteum. When bone growth in width is rapid, osteoblasts from the periosteum lay down bone to form a series of ridges with grooves between them (figure 6.17 *1*). The periosteum covers the bone ridges and extends down into the bottom of the grooves, and one or more blood vessels of the periosteum lies within each groove. As the osteoblasts continue to produce bone, the ridges increase in size, extend toward each other, and meet to change the groove into a tunnel (figure 6.17 *2*). The name of the periosteum in the tunnel changes to the endosteum because the membrane now lines an internal bone surface. Osteoblasts from the endosteum lay down bone to form a concentric lamella (figure 6.17 *3*). The



1. Osteoblasts beneath the periosteum lay down bone (*dark brown*) to form ridges separated by grooves. Blood vessels of the periosteum lie in the grooves.
2. The groove is transformed into a tunnel when the bone built on adjacent ridges meets. The periosteum of the groove becomes the endosteum of the tunnel.
3. Appositional growth by osteoblasts from the endosteum results in the formation of a new concentric lamella.
4. The production of additional concentric lamellae fills in the tunnel and completes the formation of the osteon.

Process Figure 6.17 Bone Growth in Width

Bones can increase in width by the formation of new osteons beneath the periosteum.

production of additional lamellae fills in the tunnel, encloses the blood vessel, and produces an osteon (figure 6.17 *4*).

When bone growth in width is slow, the surface of the bone becomes smooth as osteoblasts from the periosteum lay down even layers of bone to form circumferential lamellae. The circumferential lamellae are broken down during remodeling to form osteons (see Bone Remodeling on p. 183).

Factors Affecting Bone Growth

Bones of an individual's skeleton usually reach a certain length, thickness, and shape through the processes described in the previous sections. The potential shape and size of a bone and an individual's final adult height are determined genetically, but factors such as nutrition and hormones can greatly modify the expression of those genetic factors.

Nutrition

Because bone growth requires chondroblast and osteoblast proliferation, any metabolic disorder that affects the rate of cell proliferation or the production of collagen and other matrix components affects bone growth, as does the availability of calcium or other minerals needed in the mineralization process.

The long bones of a child sometimes exhibit lines of arrested growth, which are transverse regions of greater bone density crossing an otherwise normal bone. These lines are caused by greater calcification below the epiphyseal plate of a bone, where it has grown at a slower rate during an illness or severe nutritional deprivation. They demonstrate that illness or malnutrition during the time of bone growth can cause a person to be shorter than he or she would have been otherwise.

Certain vitamins are important in very specific ways to bone growth. **Vitamin D** is necessary for the normal absorption of calcium from the intestines (see chapters 5 and 24). The body can either synthesize or ingest vitamin D. Its rate of synthesis increases when the skin is exposed to sunlight.

Insufficient vitamin D in children causes **rickets,** a disease resulting from reduced mineralization of the bone matrix. Children with rickets can have bowed bones and inflamed joints. During the winter in northern climates if children are not exposed to sufficient sunlight, vitamin D can be taken as a dietary supplement to prevent rickets. The body's inability to absorb fats in which vitamin D is soluble can also result in vitamin D deficiency. This condition can occur in adults who suffer from digestive disorders and can be one cause of "adult rickets," or **osteomalacia** (os′tē-ō-mă-lā′shē-ă), which is a softening of the bones as a result of calcium depletion.

Vitamin C is necessary for collagen synthesis by osteoblasts. Normally, as old collagen breaks down, new collagen is synthesized to replace it. Vitamin C deficiency results in bones and cartilage that are deficient in collagen because collagen synthesis is impaired. In children, vitamin C deficiency can cause growth retardation. In children and adults, vitamin C deficiency can result in **scurvy,** which is marked by ulceration and hemorrhage in almost any area of the body because of the lack of normal collagen synthesis in connective tissues. Wound healing, which requires collagen synthesis, is hindered in patients with vitamin C deficiency. In extreme cases the teeth can fall out because the ligaments that hold them in place break down.

Hormones

Hormones are very important in bone growth. **Growth hormone** from the anterior pituitary increases general tissue growth (see chapters 17 and 18), including overall bone growth, by stimulating interstitial cartilage growth and appositional bone growth. **Thyroid hormone** is also required for normal growth of all tissues, including cartilage; therefore, a decrease in this hormone can result in decreased size of the individual. **Sex hormones** also influence bone growth. Estrogen (a class of female sex hormones) and testosterone (a male sex hormone) initially stimulate bone growth, which accounts for the burst of growth at the time of puberty, when production of these hormones increases. Both hormones also stimulate ossification of epiphyseal plates, however, and thus the cessation of growth. Females usually stop growing earlier than males because estrogens cause a quicker closure of the epiphyseal plate than does testosterone. Because their entire growth period is somewhat shorter, females usually don't reach the same height as males. Decreased levels of testosterone or estrogen can prolong the growth phase of the epiphyseal plates, even though the bones grow more slowly. Growth is very complex, however, and is influenced by many factors in addition to sex hormones, such as other hormones, genetics, and nutrition.

20. *Name and describe the events occurring in the four zones of the epiphyseal plate. Explain how the epiphyseal plate remains the same thickness while the bone increases in length.*
21. *Describe the process of growth at the articular cartilage. What happens to the epiphyseal plate and the articular cartilage when bone growth ceases?*
22. *Describe how new osteons are produced as a bone increases in width.*
23. *Explain how illness or malnutrition can affect bone growth. How do vitamins D and C affect bone growth?*
24. *What are the effects of growth hormone and thyroid hormone on bone growth?*
25. *What effects do estrogen and testosterone have on bone growth? How do these effects account for the average height difference observed in men and women?*

P R E D I C T 8

A 12-year-old female has an adrenal tumor that produces large amounts of estrogen. If untreated, what effect will this condition have on her growth for the next 6 months? On her height when she is 18?

Bone Remodeling

Objective

- *Explain how bone remodeling occurs, and describe how mechanical stress affects bone strength.*

Just as we renovate or remodel our homes when they become outdated, when bone becomes old, it's replaced with new bone in a process called **bone remodeling.** In this process, osteoclasts remove old bone and osteoblasts deposit new bone. Bone remodeling converts woven bone into lamellar bone, and it is involved in bone growth, changes in bone shape, the adjustment of the bone to stress, bone repair, and calcium ion regulation in the body. For example, as a long bone increases in length and diameter, the size of the medullary cavity also increases (figure 6.18). Otherwise, the

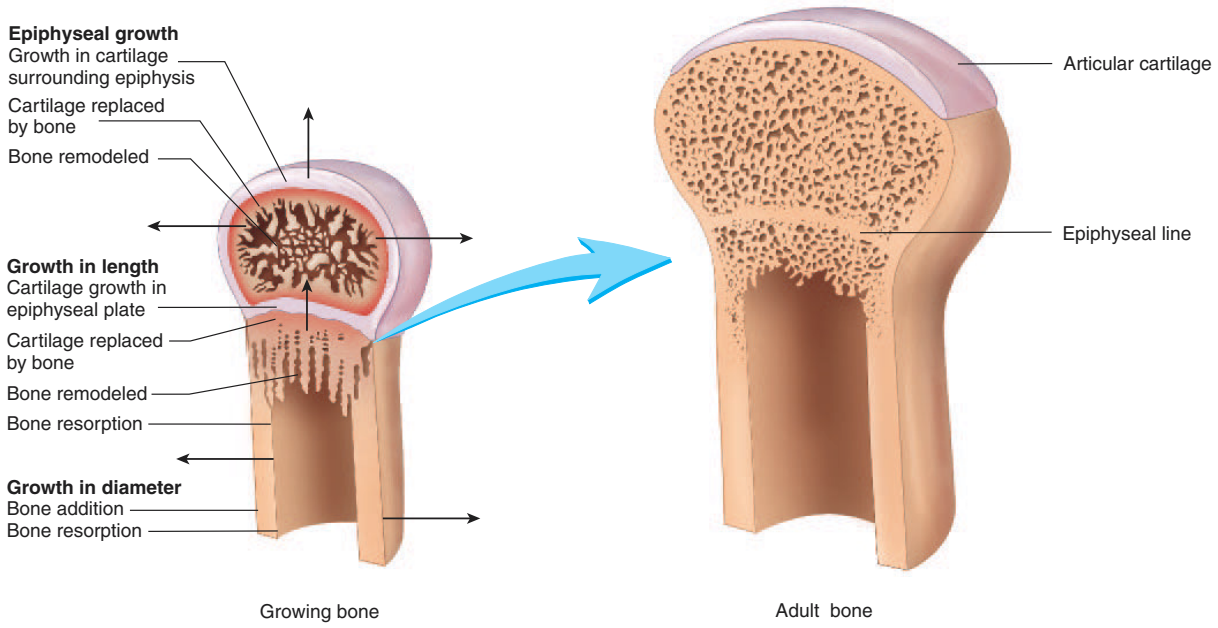


Figure 6.18 Remodeling of a Long Bone

The diameter of the bone increases as a result of bone growth on the outside of the bone, and the size of the medullary cavity increases because of bone resorption. The diaphysis increases in length and the epiphysis enlarges as new cartilage is formed and replaced by bone, which is remodeled.

Clinical Focus Bone Disorders

Growth and Development Disorders

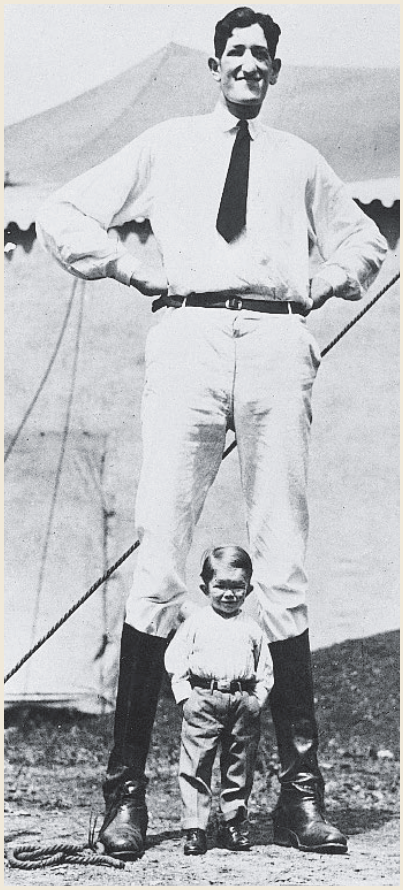
Giantism is a condition of abnormally increased height that usually results from excessive cartilage and bone formation at the epiphyseal plates of long bones (figure A*a*). The most common type of giantism, **pituitary giantism,** results from excess secretion of pituitary growth hormone. The large stature of some individuals, however, can result from genetic factors rather than from abnormal levels of growth hormone. **Acromegaly** (ak-rō-meg′ă-lē) is also caused by excess pituitary growth hormone secretion; however, acromegaly involves growth of connective tissue, including bones, after the epiphyseal plates have ossified. The effect mainly involves increased diameter of all bones and is most strikingly apparent in the face and hands. Many pituitary giants also develop acromegaly later in life.

Dwarfism, the condition in which a person is abnormally short, is the opposite of giantism (see figure A*a*). **Pituitary dwarfism** results when abnormally low levels of pituitary growth hormone affect the whole body, thus producing a small person who is normally proportioned. **Achondroplastic** (ā-kon-drō-plas′tik) **dwarfism** results in disproportionately short long bones. It's more common than proportionate dwarfing and produces a person with a nearly normal-sized trunk and head but shorter-than-normal limbs. Most cases of achondroplastic dwarfism are the result of genetic defects that cause deficient or improper growth of the cartilage model, especially the epiphyseal plate, and often involve deficient collagen synthesis. Often the cartilage matrix doesn't have its normal integrity, and the chondrocytes of the epiphysis cannot form their normal columns, even though rates of cell proliferation may be normal.

Osteogenesis imperfecta (os′tē-ō-jen′ĕ-sis im-per-fek′tă), a group of genetic disorders producing very brittle bones that are easily fractured, occurs because insufficient collagen develops to properly strengthen the bones. Intrauterine fractures of the extremities usually heal in poor alignment, thereby causing the limbs to appear bent and short (figure A*b*). Several other hereditary disorders of bone mineralization involve the enzymes responsible for normal phosphate or calcium metabolism. They closely resemble rickets and result in weak bones.

Bacterial Infections

Osteomyelitis (os′tē-ō-mī-ĕ-lī′tis) is bone inflammation that often results from bacterial infection. It can lead to complete destruction of the bone. *Staphylococcus aureus,* often introduced into the body through wounds, is a common cause of osteomyelitis (figure A*c*). Bone tuberculosis, a specific type of osteomyelitis, results from spread of the tubercular bacterium



(a)

Figure A Bone Disorders
(*a*) Giant and dwarf. (*b*) Osteogenesis imperfecta. (*c*) Osteomyelitis. (*d*) Bone tumor.

bone would consist of nearly solid bone matrix and would be very heavy. A cylinder with the same height, weight, and composition as a solid rod but with a greater diameter can support much more weight than the rod without bending. Bone therefore has a mechanical advantage as a cylinder rather than as a rod. The relative thickness of compact bone is maintained by the removal of bone on the inside by osteoclasts and the addition of bone to the outside by osteoblasts.

Remodeling is also responsible for the formation of new osteons in compact bone. This process occurs in two ways. First, within already existing osteons, osteoclasts enter a central canal through the blood vessels and begin to remove bone from the center of the osteon, resulting in an enlarged tunnel through the bone. New concentric lamellae are then formed around the vessels until the new osteon fills the area occupied by the old osteon. Second, a few osteoclasts in the periosteum remove bone, resulting in groove formation along the surface of the bone. Periosteal capillaries lie within these grooves and become surrounded to form a tunnel as the osteoblasts of the periosteum form new bone. Additional lamellae then are added to the inside of the tunnel until an osteon results.

Bone is constantly being removed by osteoclasts, and new bone is being formed by osteoblasts. This remodeling process, however, leaves behind portions of older bone called interstitial lamellae (see figure 6.10).

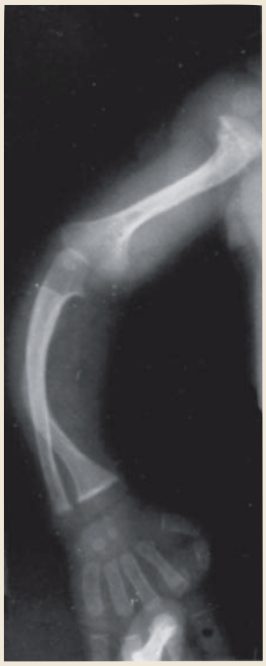
(Mycobacterium tuberculosis) from the initial site of infection such as the lungs to the bones through the circulatory system.

Tumors

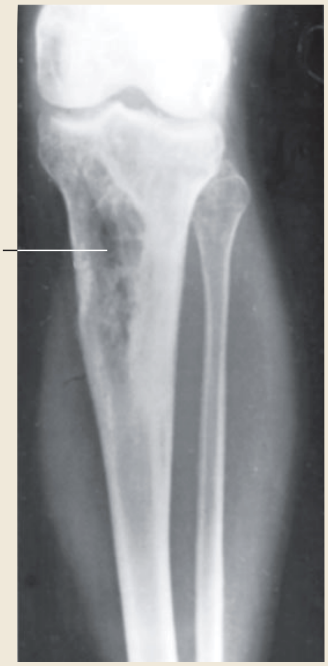
Many types of tumors occur that cause a wide range of resultant bone defects with varying prognoses (figure A*d*). Tumors can be benign or malignant. Malignant bone tumors can metastasize to other parts of the body, or they can spread to bone from metastasizing tumors elsewhere in the body.

Decalcification

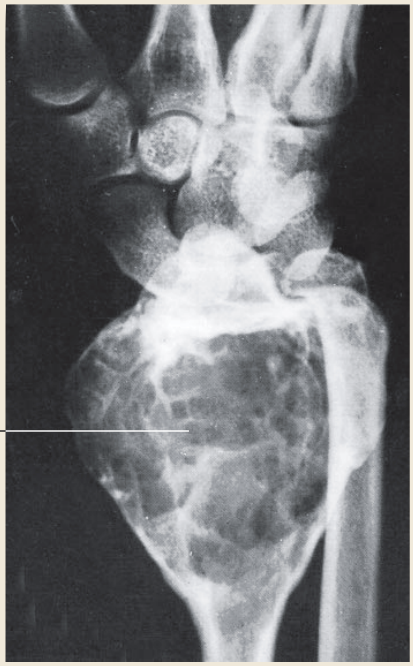
Osteomalacia (os′t-ē-ō-mă-lā′ shē-ă), or the softening of bones, results from calcium depletion from bones. If the body has an unusual need for calcium, such as during pregnancy, when growth of the fetus requires large amounts of calcium, it can be removed from the mother's bones, which consequently become soft and weakened. **Osteoporosis,** which is a major disorder of decalcification, is discussed in the Systems Pathology section on p. 190.



(b)



(c)



(d)

Mechanical Stress and Bone Strength

Remodeling, the formation of additional bone, alteration in trabecular alignment to reinforce the scaffolding, or other changes can modify the strength of the bone in response to the amount of stress applied to it. Mechanical stress applied to bone increases osteoblast activity in bone tissue, and removal of mechanical stress decreases osteoblast activity. Under conditions of reduced stress, such as when a person is bedridden or paralyzed, osteoclast activity continues at a nearly normal rate, but osteoblast activity is reduced, resulting in a decrease in bone density. In addition, pressure in bone causes an electrical change that increases the activity of osteoblasts. Applying weight (pressure) to a broken bone therefore speeds the healing process. Weak pulses of electric current applied to a broken bone sometimes are used clinically to speed the healing process.

26. *What cells are involved in bone remodeling? Describe how the medullary cavity of a long bone can increase in size as the width of the bone increases.*
27. *Explain two ways that remodeling is responsible for the formation of new osteons in compact bone.*
28. *How does bone adjust to stress? Describe the role of osteoblasts and osteoclasts in this process. What happens to bone that is not subjected to stress?*

Bone Repair

Objective

- ***Describe the process of bone repair.***

Bone is a living tissue that can undergo repair following damage to it. This process has four major steps.

1. *Hematoma formation* (figure 6.19 *1*). When bone is fractured, the blood vessels in the bone and surrounding periosteum are damaged, and a hematoma forms. A **hematoma** (hē-mă-tō′mă, hem-ă-tō′mă) is a localized mass of blood released from blood vessels but confined within an organ or space. Usually the blood in a hematoma forms a clot, which consists of fibrous proteins that stop the bleeding. Disruption of blood vessels in the central canals results in inadequate blood delivery to osteocytes, and bone tissue adjacent to the fracture site dies. Inflammation and swelling of tissues around the bone often occur following the injury.
2. *Callus formation* (figure 6.19 *2*). A **callus** (kal′ŭs) is a mass of tissue that forms at a fracture site and connects the broken ends of the bone. An **internal callus** forms *between* the ends of the broken bone, and in the marrow cavity if the fracture occurs in the diaphysis of a long bone. Several days after the fracture, blood vessels grow into the clot. As the clot dissolves (see chapter 19), macrophages clean up cell debris, osteoclasts break down dead bone tissue, and fibroblasts produce collagen and other extracellular materials to form granulation tissue (see chapter 4). As the fibroblasts continue to produce collagen fibers, a denser fibrous network, which helps to hold the bone together, is produced. Chondroblasts derived from osteochondral progenitor cells of the periosteum and endosteum begin to produce cartilage in the fibrous network. As these events are occurring, osteochondral progenitor cells in the endosteum become osteoblasts and produce new bone that contributes to the internal callus.

The **external callus** forms a collar *around* the opposing ends of the bone fragments. Osteochondral progenitor cells from the periosteum become osteoblasts, which produce bone, and chondroblasts, which produce cartilage. Cartilage production is more rapid than bone production, and cartilage from either side of the break eventually grows together. The external callus is a bone–cartilage collar that stabilizes the ends of the broken bone. In modern medical practice, stabilization of the bone is assisted by using a cast or surgical implantation of metal supports.

3. *Callus ossification* (figure 6.19 *3*). Like the cartilage models formed during fetal development, the cartilage in the external callus is replaced by woven, cancellous bone through endochondral ossification. The result is a stronger external callus. Even as the internal callus is forming and replacing the hematoma, osteoblasts from the periosteum and endosteum enter the internal callus and begin to produce bone. Eventually the fibers and cartilage of the internal callus are replaced by woven, cancellous bone, which further stabilizes the broken bone.
4. *Remodeling of bone* (figure 6.19 *4*). Filling the gap between bone fragments with an internal callus of woven bone is not the end of the repair process because woven bone is not as structurally strong as the original lamellar bone. Repair is not complete until the woven bone of the internal callus and the dead bone adjacent to the fracture site are replaced by compact bone. In this compact bone, osteons from both sides of the break extend across the fracture line to "peg" the bone fragments together. This

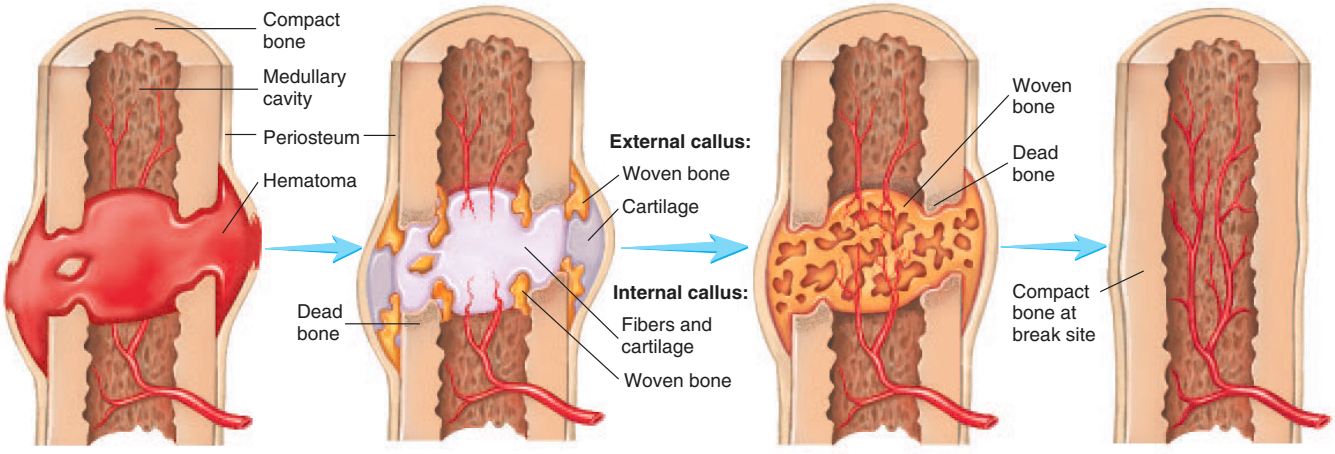


Figure 6.19 Bone Repair

(*1*) Hematoma formation following a fracture. (*2*) Callus formation. The internal callus replaces the hematoma. The external callus provides support. (*3*) Callus ossification. Woven, cancellous bone replaces the cartilage of the internal and external callus. (*4*) Remodeling of bone replaces the woven bone of the callus and the dead bone adjacent to the fracture site with compact bone. Healing is complete.

remodeling process takes time and may not be complete even after a year. As the internal callus is remodeled and becomes stronger, the external callus is reduced in size by osteoclast activity. Eventually, repair may be so complete that no evidence of the break remains, however, the repaired zone usually remains slightly thicker than the adjacent bone. If the fracture occurred in the diaphysis of a long bone, remodeling also restores the medullary cavity.

29. Describe the four major steps in the repair of a broken bone.

Uniting Broken Bones

Before formation of compact bone between the broken ends of a bone can take place, the appropriate substrate must be present. Normally this is the woven, cancellous bone of the internal callus. If formation of the internal callus is prevented by infections, bone movements, or the nature of the injury, then nonunion of the bone occurs. This condition can be treated by surgically implanting an appropriate substrate such as living bone taken from another site in the body or dead bone from cadavers. Other substrates have also been used. For example, a specific marine coral calcium phosphate is converted into a predominantly hydroxyapatite biomatrix that is very much like cancellous bone.

Calcium Homeostasis

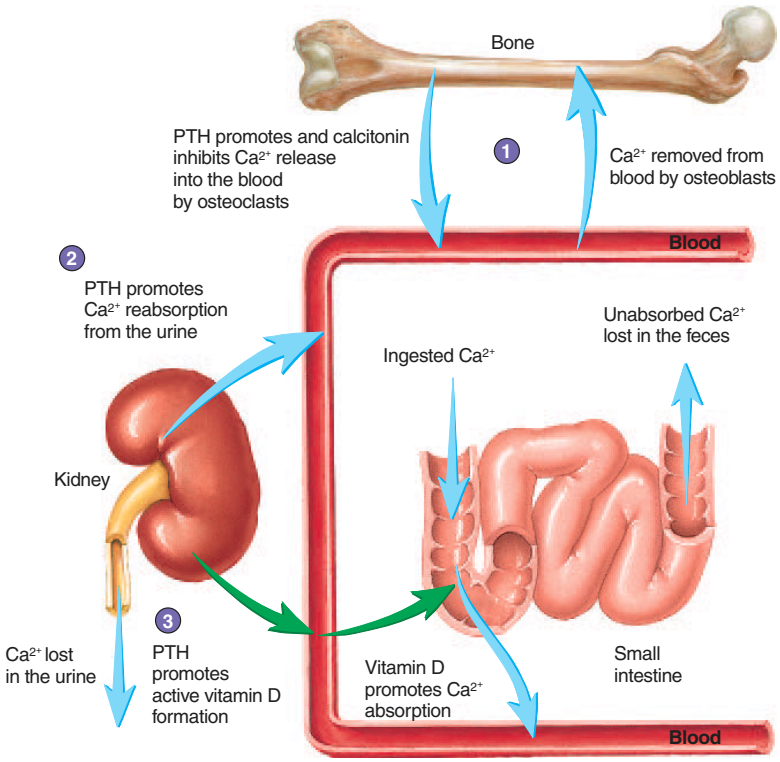
Objective

- *Explain the role of bone in calcium homeostasis.*

Bones play an important role in regulating blood calcium levels, which must be maintained within narrow limits for functions such as muscle contraction and membrane potentials to occur normally (see chapters 9 and 11). Bone is the major storage site for calcium in the body, and movement of calcium into and out of bone helps to determine blood calcium levels. Calcium moves into bone as osteoblasts build new bone and out of bone as osteoclasts break down bone (figure 6.20). When osteoblast and osteoclast activity is balanced, the movement of calcium into and out of a bone is equal.

When blood calcium levels are too low, osteoclast activity increases. More calcium is released by osteoclasts from bone into the blood than is removed by osteoblasts from the blood to make new bone. Consequently, a net movement of calcium occurs from bone into blood, and blood calcium levels increase. Conversely, if blood calcium levels are too high, osteoclast activity decreases. Less calcium is released by osteoclasts from bone into the blood than is taken from the blood by osteoblasts to produce new bone. As a

1. Osteoclasts break down bone and release calcium into the blood, and osteoblasts remove calcium from the blood to make bone. PTH regulates blood calcium levels by indirectly stimulating osteoclast activity, resulting in increased calcium release into the blood. Calcitonin plays a minor role in calcium maintenance by inhibiting osteoclast activity.
2. In the kidneys, PTH increases calcium reabsorption from the urine.
3. In the kidneys, PTH also promotes the formation of active vitamin D, which increases calcium absorption from the small intestine.



Process Figure 6.20 Calcium Homeostasis

Clinical Focus Classification of Bone Fractures

Bone fractures are classified in several ways. The most commonly used classification involves the severity of injury to the soft tissues surrounding the bone. An **open fracture** (formerly called compound) occurs when an open wound extends to the site of the fracture or when a fragment of bone protrudes through the skin. If the skin is not perforated, the fracture is called a **closed fracture** (formerly called simple). If the soft tissues around a closed fracture are damaged, the fracture is called a **complicated fracture.**

Two other terms to designate fractures are **incomplete,** in which the fracture does not extend completely across the bone, and **complete,** in which the bone is broken into at least two fragments (figure B*a*). An incomplete fracture that occurs on the convex side of the curve of the bone is a **greenstick fracture. Hairline fractures** are incomplete fractures in which the two sections of bone do not separate; they are common in skull fractures.

Comminuted (kom′i-noo-ted) **fractures** are complete fractures in which the bone breaks into more than two pieces—usually two major fragments and a smaller fragment (figure B*b*). **Impacted fractures** are those in which one fragment is driven into the cancellous portion of the other fragment (figure B*c*).

Fractures are also classified according to the direction of the fracture within a bone. **Linear fractures** run parallel to the long axis of the bone, and **transverse fractures** are at right angles to the long axis (figure B*b*). **Spiral fractures** have a helical course around the bone, and **oblique fractures** run obliquely in relation to the long axis (figure B*d*). **Dentate fractures** have rough, toothed, broken ends, and **stellate fractures** have breakage lines radiating from a central point.

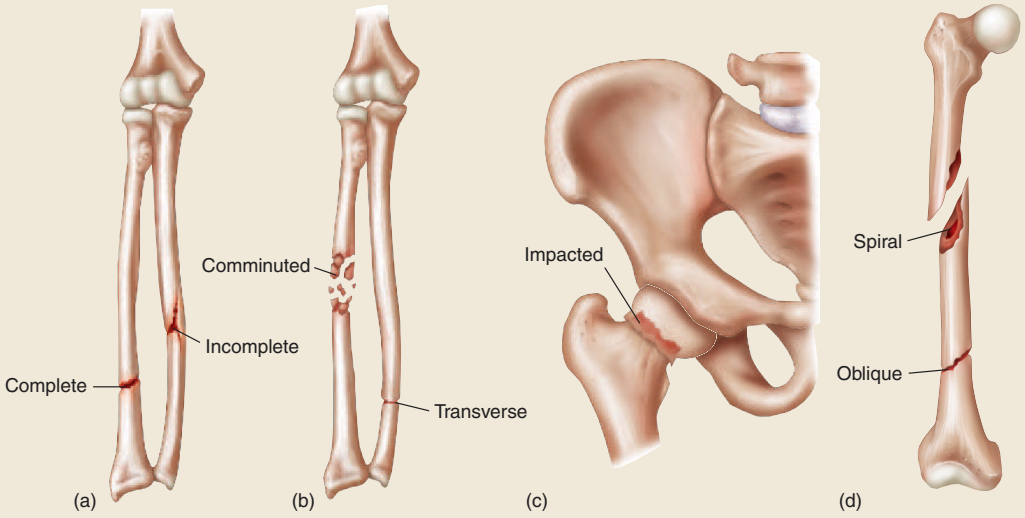


Figure B Bone Fractures

(*a*) Complete and incomplete. (*b*) Transverse and comminuted. (*c*) Impacted. (*d*) Spiral and oblique.

result, a net movement of calcium occurs from the blood to bone, and blood calcium levels decrease.

Parathyroid hormone (PTH) from the parathyroid glands (see figure 17.1) is the major regulator of blood calcium levels. If the blood calcium level decreases, the secretion of PTH increases, resulting in increased numbers of osteoclasts, which causes increased bone breakdown and increased blood calcium levels (see figure 6.20). In addition, osteoblasts respond to PTH by releasing enzymes that result in the breakdown of the layer of unmineralized organic bone matrix covering bone, thereby making the mineralized bone matrix available to osteocytes.

The regulation of osteoclast numbers is mediated through osteoblasts and red bone marrow stromal (stem) cells. When PTH levels increase, PTH binds to its receptors on osteoblasts/stromal cells. In response, these cells produce a surface molecule called **receptor for activation of nuclear factor kappa B ligand (RANKL).** When RANKL binds to its receptor on the surface of osteoclast precursor cells, the cells are stimulated to become osteoclasts. Increased PTH also inhibits the release from osteoblasts/stromal cells of a protein called **osteoprotegerin** (os′tē-ō-prō-teg′er-in) **(OPG).** OPG inhibits the formation of osteoclasts because it binds to RANKL and prevents it from stimulating osteoclast precursor cells. Thus,

increased PTH promotes an increase in osteoclast numbers by increasing RANKL, which stimulates osteoclast precursor cells, and by decreasing OPG, which decreases the inhibition of osteoclast precursor cells. Conversely, decreased PTH results in fewer osteoclasts by decreasing RANKL and increasing OPG.

PTH also regulates blood calcium levels by increasing calcium uptake in the small intestine (see figure 6.20). Increased PTH promotes the formation of vitamin D in the kidneys, and vitamin D increases the absorption of calcium from the small intestine. PTH also increases the reabsorption of calcium from urine in the kidneys, which reduces calcium lost in the urine.

Tumors that secrete large amounts of PTH can cause so much bone breakdown that bones become weakened and fracture easily. On the other hand, an increase in blood calcium levels results in less PTH secretion, decreased osteoclast activity, reduced calcium release from bone, and decreased blood calcium levels.

Calcitonin (kal-si-tō′nin), secreted from the thyroid gland (see figure 17.1), decreases osteoclast activity (see figure 6.20) by binding to receptors on the osteoclasts. An increase in blood calcium levels stimulates the thyroid gland to secrete calcitonin, which inhibits osteoclast activity. PTH and calcitonin are described more fully in chapters 18 and 27.

30. *Name the hormone that is the major regulator of calcium levels in the body. What stimulates the secretion of this hormone?*
31. *Describe how PTH controls the number of osteoclasts. What are the effects of PTH on the formation of vitamin D, calcium uptake in the small intestine, and reabsorption of calcium from urine?*
32. *What stimulates calcitonin secretion? How does calcitonin affect osteoclast activity?*

Effects of Aging on the Skeletal System

Objective

- *Describe the effects of aging on bones.*

The most significant age-related changes in the skeletal system affect the quality and quantity of bone matrix. Recall that a mineral (hydroxapatite) in the bone matrix gives bone compression (weight-bearing) strength, but collagen fibers make the bone flexible. The bone matrix in an older bone is more brittle than in a younger bone because decreased collagen production results in a matrix that has relatively more mineral and less collagen fibers. With aging, the amount of matrix also decreases because the rate of matrix formation by osteoblasts becomes slower than the rate of matrix breakdown by osteoclasts.

Bone mass is at its highest around age 30, and men generally have denser bones than women because of the effects of testosterone and greater body weight. Race also affects bone mass. African-Americans and Hispanics have higher bone masses than Caucasians and Asians. After age 35, both men and women have an age-related loss of bone of 0.3%–0.5% a year. This loss can increase 10-fold in women after menopause, and they can have a bone loss of 3%–5% a year for approximately 5–7 years (see "Systems Pathology: Osteoporosis" next).

Cancellous bone is lost at first as the trabeculae become thinner and weaker. The ability of the trabeculae to provide support also decreases as they become disconnected from each other. Eventually, some of the trabeculae completely disappear. Trabecular bone loss is greatest in the trabeculae that are under the least stress.

A slow loss of compact bone begins about age 40 and increases after age 45. The rate of compact bone loss, however, is approximately half the rate of trabecular bone loss. Bones become thinner, but their outer dimensions change little, because most loss of compact bone occurs under the endosteum on the inner surfaces of bones. In addition, the remaining compact bone becomes weaker as a result of incomplete bone remodeling. In a young bone, when osteons are removed, the resulting spaces are filled with new osteons. With aging, the new osteons fail to completely fill in the spaces produced when the older osteons are removed.

Significant loss of bone increases the likelihood of having bone fractures. For example, loss of trabeculae greatly increases the risk of compression fractures of the vertebrae (backbones) because the weight-bearing body of the vertebrae consists mostly of cancellous bone. In addition, loss of bone can cause deformity, loss of height, pain, and stiffness. For example, compression fractures of the vertebrae can cause an exaggerated curvature of the spine resulting in a bent-forward, stooped posture. Loss of bone from the jaws can also lead to tooth loss.

33. *What effect does aging have on the quality and quantity of bone matrix?*
34. *Describe how cancellous and compact bone change with age. How do these changes affect a person's health?*

Systems Pathology

Osteoporosis

Mrs. B is a 70-year-old grandmother. Since she was a teenager, she has been a heavy smoker. She is typically sedentary, seldom goes outside, has not had the best dietary habits, and is underweight. One of her favorite yearly events is the family picnic on the Fourth of July. During one picnic, misfortune struck when Mrs. B tripped on a lawn sprinkler and fell. She was unable to stand because of severe hip pain, so she was rushed to the hospital, where a radiograph revealed that her femur was broken (figure C*a*) and that she had osteoporosis (figure C*b*).

It was decided that hip replacement surgery was indicated. Before the surgery could be performed, however, a fat embolism from the fracture site lodged in her lungs, making it difficult for her to breathe. The surgery was postponed and the fracture immobilized until she recovered from the fat embolism. Three weeks after the accident, Mrs. B had a successful hip transplant and began physical therapy. She appeared to be on the road to recovery, but 6 weeks after the surgery she developed persistent pain and edema in her hip. A bone biopsy confirmed a postoperative infection that was successfully treated with antibiotics.

Background Information

Osteoporosis (os′tē-ō-pō-rō′ sis), or porous bone, results from reduction in the overall quantity of bone tissue. It occurs when the rate of bone resorption exceeds the rate of bone formation. The loss of bone mass makes bones so porous and weakened that they become deformed and prone to fracture. The occurrence of osteoporosis increases with age. In both men and women, bone mass starts to decrease at about age 35 and continually decreases thereafter. Women can eventually lose approximately half, and men a quarter, of their cancellous bone. Osteoporosis is two and a half times more common in women than in men.

In postmenopausal women, the decreased production of the female sex hormone, estrogen, can cause osteoporosis. Estrogen is secreted by the ovaries, and it normally contributes to the maintenance of normal bone mass by inhibiting the stimulatory effects of PTH on osteoclast activity. Following menopause, estrogen production decreases, resulting in degeneration of cancellous bone, especially in the vertebrae of the spine and the bones of the forearm. Collapse of the vertebrae can cause a decrease in height or, in more severe cases, can produce kyphosis, or a "dowager's hump," in the upper back.

Conditions that result in decreased estrogen levels, other than menopause, can also cause osteoporosis. Examples include removal of the ovaries before menopause, extreme exercise to the point of amenorrhea (lack of menstrual flow), anorexia nervosa (self-starvation), and cigarette smoking.

In males, reduction in testosterone levels can cause loss of bone tissue. Decreasing testosterone levels are usually less of a problem for men than decreasing estrogen levels are for women for two reasons. First, because males have denser bones than females, loss of some bone tissue has less of an effect. Second, testosterone levels generally don't decrease significantly until after age 65, and even then the rate of decrease is often slow.

Overproduction of PTH, which results in overstimulation of osteoclast activity, can also cause osteoporosis.

Inadequate dietary intake or absorption of calcium can contribute to osteoporosis. Absorption of calcium from the small intestine decreases with age, and individuals with osteoporosis often have insufficient intake of calcium or vitamin D. Drugs that interfere with calcium uptake or use can also increase the risk of osteoporosis.

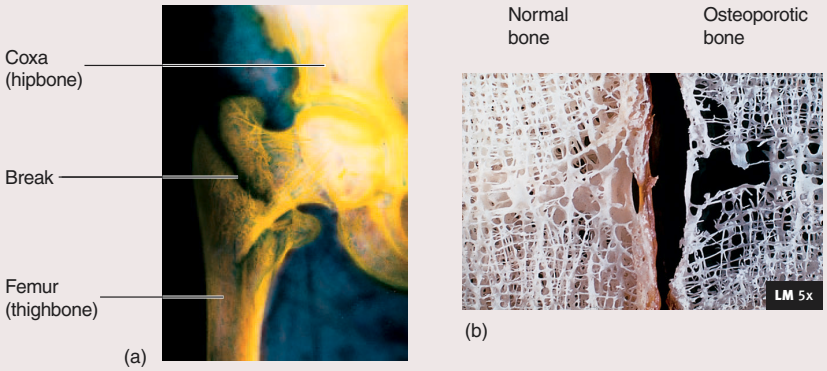


Figure C Osteoporosis

(*a*) Radiograph of a broken hip. A "broken hip" is actually a break of the femur (thighbone) in the hip region. (*b*) Photomicrograph of normal bone and osteoporotic bone.

Finally, osteoporosis can result from inadequate exercise or disuse caused by fractures or paralysis. Significant amounts of bone are lost after 8 weeks of immobilization.

Treatments for osteoporosis are designed to reduce bone loss or increase bone formation, or both. Increased dietary calcium and vitamin D can increase calcium uptake and promote bone formation. Daily doses of 1000–1500 mg of calcium and 800 IU (20 μg) of vitamin D are recommended. Exercise, such as walking or using light weights, also appears to be effective not only in reducing bone loss but in increasing bone mass.

In postmenopausal women, **hormone replacement therapy (HRT)** with estrogen decreases osteoclast numbers by inhibiting the production of RANKL (see p. 188). This reduces bone loss but does not result in an increase in bone mass because osteoclast activity still exceeds osteoblast activity. Clinical trials are underway to determine if estrogen therapy reduces the risk of fractures. Although potentially beneficial for bone, estrogen does increase the risk of developing breast cancer. **Selective estrogen receptor modulators (SERMs)** are a class of drugs that bind to estrogen receptors. They may be able to protect against bone loss without increasing the risk of breast cancer. For example, raloxifene (ral-ox′ĭ-fēn) stimulates estrogen receptors in bone but inhibits them in the breast and uterus. Osteoprotegerin, which prevents RANKL from binding to its receptors, is under consideration as a treatment for osteoporosis. Calcitonin (Miacalcin), which inhibits osteoclast activity, is now available as a nasal spray. Calcitonin can be used to treat osteoporosis in men and women and has been shown to produce a slight increase in bone mass. **Statins** (stat′ins) are drugs that inhibit cholesterol synthesis. It has been discovered that statins also stimulate osteoblast activity, and there is some evidence that statins can reduce the risk of fractures. Alendronate (Fosamax) belongs to a class of drugs called **bisphosphonates** (bis-fos′fō-nāts). Bisphosphonates concentrate in bone, and when osteoclasts break down bone, the bisphosphonates are taken up by the osteoclasts. The bisphosphonates interfere with certain enzymes, leading to inactivation and lysis of the osteoclasts. Alendronate increases bone mass and reduces fracture rates even more effectively than calcitonin. Slow-releasing sodium fluoride (Slow Fluoride) in combination with calcium citrate (Citracal) also appears to increase bone mass.

Leptin is a protein hormone produce by adipocytes (fat cells). When released from fat cells into the blood, leptin travels to the brain, where it is a signal involved in the regulation of feeding and energy balance (see chapter 25). There's also evidence that decreased leptin causes the release from the brain of a yet to be identified substance that can increase osteoblast activity. Understanding the leptin pathway may lead to treatments for diseases such as osteoporosis.

Early diagnosis of osteoporosis may lead to the use of more preventative treatments. Instruments that measure the absorption of photons (particles of light) by bone are currently used, of which dual-energy x-ray absorptiometry (DEXA) is considered the best.

P R E D I C T 9

What advice should Mrs. B give to her granddaughter so that the granddaughter will be less likely to develop osteoporosis when she is Mrs. B's age?

System Interactions

System	Interactions
Integumentary	Decreased exposure to sunlight because of an indoor lifestyle reduces vitamin D production and decreases calcium absorption. Surgical wounds through the skin can allow the entry of bacteria, resulting in postoperative infections.
Muscular	A sedentary lifestyle and decreased body weight reduces stress on bone and contributes to osteoporosis. Muscle atrophy and weakness make it difficult to maintain balance, which increases the likelihood of falling and injury. Following hip replacement surgery, physical therapy places stress on the bones and improves muscular strength.
Nervous	Pain sensations following the injury and during rehabilitation help to prevent further injury.
Endocrine	Although not a factor in this case of osteoporosis, elevated PTH (usually from a benign parathyroid tumor) or elevated thyroid hormone (Graves' disease) can result in excessive osteoclast activity. Calcitonin is being used to treat osteoporosis.
Cardiovascular	Blood clotting following the injury starts the process of tissue repair. Blood cells are carried to the injury site to fight infections and remove cell debris. Blood vessels grow into the recovering tissue, providing nutrients and removing waste products.
Lymphatic and Immune	Immune cells resist infections and release chemicals that promote tissue repair. New immune cells are produced in bone marrow.
Respiratory	Excessive smoking lowers estrogen levels, which increases bone loss. A fat embolism from a fractured bone can impair respiration.
Digestive	Inadequate calcium and vitamin D in the diet or inadequate calcium absorption by the digestive system can contribute to osteoporosis.
Urinary	Calcium released from the bones is excreted through the urinary system.
Reproductive	Decreased estrogen levels following menopause contribute to osteoporosis.

S U M M A R Y

Functions of the Skeletal System (p. 167)

1. The skeletal system consists of bones, cartilage, tendons, and ligaments.
2. The skeletal system supports the body, protects organs it surrounds, allows body movements, stores minerals and fats, and is the site of blood cell production.

Cartilage (p. 167)

1. Chondroblasts produce cartilage and become chondrocytes. Chondrocytes are located in lacunae surrounded by matrix.
2. The matrix of cartilage contains collagen fibers (for strength) and proteoglycans (trap water).
3. The perichondrium surrounds cartilage.
   - The outer layer contains fibroblasts.
   - The inner layer contains chondroblasts.
4. Cartilage grows by appositional and interstitial growth.

Bone Anatomy (p. 168)

Bone Shapes

Individual bones can be classified as long, short, flat, or irregular.

Structure of a Long Bone

1. The diaphysis is the shaft of a long bone, and the epiphyses are the ends.
2. The epiphyseal plate is the site of bone growth in length.
3. The medullary cavity is a space within the diaphysis.
4. Red marrow is the site of blood cell production, and yellow marrow consists of fat.
5. The periosteum covers the outer surface of bone.
   - The outer layer contains blood vessels and nerves.
   - The inner layer contains osteoblasts, osteoclasts, and osteochondral progenitor cells.
   - Perforating fibers hold the periosteum, ligaments, and tendons in place.
6. The endosteum lines cavities inside bone and contains osteoblasts, osteoclasts, and osteochondral progenitor cells.

Structure of Flat, Short, and Irregular Bones

Flat, short, and irregular bones have an outer covering of compact bone surrounding cancellous bone.

Bone Histology (p. 171)

Bone Matrix

1. Collagen provides flexible strength.
2. Hydroxyapatite provides compressional strength.

Bone Cells

1. Osteoblasts produce bone matrix and become osteocytes.
   - Osteoblasts connect to one another through cell processes and surround themselves with bone matrix to become osteocytes.
   - Osteocytes are located in lacunae and are connected to one another through canaliculi.
2. Osteoclasts (with assistance from osteoblasts) break down bone.
3. Osteoblasts originate from osteochondral progenitor cells, whereas osteoclasts originate from stem cells in red bone marrow.

Woven and Lamellar Bone

1. Woven bone has collagen fibers oriented in many different directions. It's remodeled to form lamellar bone.
2. Lamellar bone is arranged in thin layers, called lamellae, which have collagen fibers oriented parallel to one another.

Cancellous and Compact Bone

1. Cancellous bone has many spaces.
   - Lamellae combine to form trabeculae, beams of bone that interconnect to form a latticelike structure with spaces filled with bone marrow and blood vessels.
   - The trabeculae are oriented along lines of stress and provide structural strength.
2. Compact bone is dense with few spaces.
   - Compact bone consists of organized lamellae: circumferential lamellae form the outer surface of compact bones; concentric lamellae surround central canals, forming osteons; interstitial lamellae are remnants of lamellae left after bone remodeling.
   - Canals within compact bone provide a means for the exchange of gases, nutrients, and waste products. From the periosteum or endosteum perforating canals carry blood vessels to central canals, and canaliculi connect central canals to osteocytes.

Bone Development (p. 175)

Intramembranous Ossification

1. Some skull bones, part of the mandible, and the diaphyses of the clavicles develop from membranes.
2. Within the membrane at centers of ossification, osteoblasts produce bone along the membrane fibers to form cancellous bone.
3. Beneath the periosteum, osteoblasts lay down compact bone to form the outer surface of the bone.
4. Fontanels are areas of membrane that are not ossified at birth.

Endochondral Ossification

1. Most bones develop from a cartilage model.
2. The cartilage matrix is calcified, and chondrocytes die. Osteoblasts form bone on the calcified cartilage matrix, producing cancellous bone.
3. Osteoblasts build an outer surface of compact bone beneath the periosteum.
4. Primary ossification centers form in the diaphysis during fetal development. Secondary ossification centers form in the epiphyses.
5. Articular cartilage on the ends of bones and the epiphyseal plate is cartilage that does not ossify.

Bone Growth (p. 178)

1. Bones increase in size only by appositional growth, the adding of new bone on the surface of older bone or cartilage.
2. Trabeculae grow by appositional growth.

Growth in Bone Length

1. Epiphyseal plate growth involves the interstitial growth of cartilage followed by appositional bone growth on the cartilage.
2. Epiphyseal plate growth results in an increase in the length of the diaphysis and bony processes. Bone growth in length ceases when the epiphyseal plate becomes ossified and forms the epiphyseal line.

Growth at Articular Cartilage

1. Articular cartilage growth involves the interstitial growth of cartilage followed by appositional bone growth on the cartilage.
2. Articular cartilage growth results in larger epiphyses and an increase in the size of bones that don't have epiphyseal plates.

Growth in Bone Width

1. Appositional bone growth beneath the periosteum increases the diameter of long bones and the size of other bones.
2. Osteoblasts from the periosteum form ridges with grooves between them. The ridges grow together, converting the grooves into tunnels that are filled with concentric lamellae to form osteons.
3. Osteoblasts from the periosteum lay down circumferential lamellae, which can be remodeled.

Factors Affecting Bone Growth

1. Genetic factors determine bone shape and size. The expression of genetic factors can be modified.
2. Factors that alter the mineralization process or production of organic matrix, such as deficiencies in vitamins D and C, can affect bone growth.
3. Growth hormone, thyroid hormone, estrogen, and testosterone stimulate bone growth.
4. Estrogen and testosterone cause increased bone growth and closure of the epiphyseal plate.

Bone Remodeling (p. 183)

1. Remodeling converts woven bone to lamellar bone and allows bone to change shape, adjust to stress, repair itself, and regulate body calcium levels.
2. Bone adjusts to stress by adding new bone and by realignment of bone through remodeling.

Bone Repair (p. 185)

1. Fracture repair begins with the formation of a hematoma.
2. The hematoma is replaced by the internal callus consisting of fibers and cartilage.
3. The external callus is a bone–cartilage collar that stabilizes the ends of the broken bone.
4. The internal and external calluses are ossified to become woven bone.
5. Woven bone is remodeled.

Calcium Homeostasis (p. 187)

PTH increases blood calcium levels by increasing bone breakdown, calcium absorption from the small intestine, and reabsorption of calcium from the urine. Calcitonin decreases blood calcium by decreasing bone breakdown.

Effects of Aging on the Skeletal System (p. 189)

1. With aging, bone matrix is lost and the matrix becomes more brittle.
2. Cancellous bone loss results from a thinning and a loss of trabeculae. Compact bone loss mainly occurs from the inner surface of bones and involves less osteon formation.
3. Loss of bone increases the risk of fractures and causes deformity, loss of height, pain, stiffness, and loss of teeth.

REVIEW AND COMPREHENSION

1. Which of these is *not* a function of bone?
   a. internal support and protection
   b. provides attachment for the muscles
   c. calcium and phosphate storage
   d. blood cell production
   e. vitamin D storage
2. The extracellular matrix for hyaline cartilage
   a. is produced by chondroblasts.
   b. contains collagen.
   c. contains proteoglycans.
   d. is usually covered by the perichondrium.
   e. all of the above.
3. Chondrocytes are mature cartilage cells found within the _____, and they are derived from _____.
   a. perichondrium, fibroblasts
   b. perichondrium, chondroblasts
   c. lacunae, fibroblasts
   d. lacunae, chondroblasts
4. Which of these statements concerning cartilage is correct?
   a. Cartilage often occurs in thin plates or sheets.
   b. Chondrocytes receive nutrients and oxygen from blood vessels in the matrix.
   c. Articular cartilage has a thick perichondrium layer.
   d. The perichondrium has both chondrocytes and osteocytes.
   e. Appositional growth of cartilage occurs when chondrocytes within the tissue add more matrix from the inside.
5. A fracture in the shaft of a bone is a break in the
   a. epiphysis.
   b. perichondrium.
   c. diaphysis.
   d. articular cartilage.
6. Yellow marrow is
   a. found mostly in children's bones.
   b. associated mostly with flat bones.
   c. found in the epiphyseal plate.
   d. important for blood cell production.
   e. mostly adipose tissue.
7. The periosteum
   a. is an epithelial tissue membrane.
   b. covers the outer and internal surfaces of bone.
   c. contains only osteoblasts.
   d. becomes continuous with collagen fibers of tendons or ligaments.
   e. has a single fibrous layer.
8. Which of these substances makes up the major portion of bone?
   a. collagen
   b. hydroxyapatite
   c. proteoglycan aggregates
   d. osteocytes
   e. osteoblasts

9. The flexible strength of bone occurs because of
   a. osteoclasts.
   b. ligaments.
   c. hydroxyapatite.
   d. collagen fibers.
   e. periosteum.
10. The prime function of osteoclasts is to
   a. prevent osteoblasts from forming.
   b. become osteocytes.
   c. break down bone.
   d. secrete calcium salts and collagen fibers.
   e. form the periosteum.
11. Osteochondral progenitor cells
   a. can become osteoblasts or chondroblasts.
   b. are derived from mesenchymal stem cells.
   c. are located in the perichondrium, periosteum, and endosteum.
   d. do not produce osteoclasts.
   e. all of the above.
12. Lamellar bone
   a. is mature bone.
   b. is remodeled to form woven bone.
   c. is the first type of bone formed during early fetal development.
   d. has collagen fibers randomly oriented in many directions.
   e. all of the above.
13. Central canals
   a. connect perforating canals to canaliculi.
   b. connect cancellous bone to compact bone.
   c. are where blood cells are produced.
   d. are found only in cancellous bone.
   e. are lined with periosteum.
14. The type of lamellae found in osteons is _____ lamellae.
   a. circumferential
   b. concentric
   c. interstitial
15. Cancellous bone consists of interconnecting rods or plates of bone called
   a. osteons.
   b. canaliculi.
   c. circumferential lamellae.
   d. a haversian system.
   e. trabeculae.
16. Given these events:
   1. Osteochondral progenitor cells become osteoblasts.
   2. Connective tissue membrane is formed.
   3. Osteoblasts produce woven bone.

   Which sequence best describes intramembranous bone formation?
   a. 1,2,3
   b. 1,3,2
   c. 2,1,3
   d. 2,3,1
   e. 3,2,1
17. Given these processes:
   1. Chondrocytes die.
   2. Cartilage matrix calcifies.
   3. Chondrocytes hypertrophy.
   4. Osteoblasts deposit bone.
   5. Blood vessels grow into lacunae.

   Which sequence best represents the order in which they occur during endochondral bone formation?
   a. 3,2,1,4,5
   b. 3,2,1,5,4
   c. 5,2,3,4,1
   d. 3,2,5,1,4
   e. 3,5,2,4,1
18. Intramembranous bone formation
   a. occurs at the epiphyseal plate.
   b. is responsible for growth in diameter of a bone.
   c. gives rise to the flat bones of the skull.
   d. occurs within a hyaline cartilage model.
   e. produces articular cartilage in the long bones.
19. The ossification regions formed during early fetal development
   a. are secondary ossification centers.
   b. become articular cartilage.
   c. become medullary cavities.
   d. become the epiphyses.
   e. are primary ossification centers.
20. Growth in the length of a long bone occurs
   a. at the primary ossification center.
   b. beneath the periosteum.
   c. at the center of the diaphysis.
   d. at the epiphyseal plate.
   e. at the epiphyseal line.
21. During growth in length of a long bone, cartilage is formed and then ossified. The location of the ossification is the zone of
   a. calcification.
   b. hypertrophy.
   c. proliferation.
   d. resting cartilage.
22. Given these processes:
   1. An osteon is produced.
   2. Osteoblasts from the periosteum form a series of ridges.
   3. The periosteum becomes the endosteum.
   4. Osteoblasts lay down bone to produce a concentric lamella.
   5. Grooves are changed into tunnels.

   Which sequence best represents the order in which these processes occur during growth in width of a long bone?
   a. 1,4,2,3,5
   b. 2,5,3,4,1
   c. 3,4,2,1,5
   d. 4,2,1,5,3
   e. 5,4,2,1,3
23. Chronic vitamin D deficiency results in which of these consequences?
   a. Bones become brittle.
   b. The percentage of bone composed of hydroxyapatite increases.
   c. Bones become soft and pliable.
   d. Scurvy occurs.
   e. Both a and b.
24. Osteomalacia occurs as a result of a deficiency of
   a. growth hormone.
   b. sex hormones.
   c. thyroid hormone.
   d. vitamin C.
   e. vitamin D.
25. Estrogen
   a. stimulates a burst of growth at puberty.
   b. causes a later closure of the epiphyseal plate than does testosterone.
   c. causes a longer growth period in females than testosterone causes in males.
   d. tends to prolong the growth phase of the epiphyseal plates.
   e. all of the above.
26. Bone remodeling can occur
   a. when woven bone is converted into lamellar bone.
   b. as bones are subjected to varying patterns of stress.
   c. as a long bone increases in diameter.
   d. when new osteons are formed in compact bone.
   e. all of the above.

27. Given these processes:
    1. cartilage ossification
    2. external callus formation
    3. hematoma formation
    4. internal callus formation
    5. remodeling of woven bone into compact bone

    Which sequence best represents the order in which the processes occur during repair of a fracture?
    a. 1,2,3,4,5
    b. 2,4,3,1,5
    c. 3,4,2,1,5
    d. 4,1,5,2,3
    e. 5,3,4,2,1
28. Which of these processes during bone repair requires the longest period of time?
    a. cartilage ossification
    b. external callus formation
    c. hematoma formation
    d. internal callus formation
    e. remodeling of woven bone into compact bone
29. If the secretion of parathyroid hormone (PTH) increases, osteoclast activity _____, and blood calcium levels _____.
    a. decreases, decrease
    b. decreases, increase
    c. increases, decrease
    d. increases, increase
30. Osteoclast activity is inhibited by
    a. calcitonin.
    b. growth hormone.
    c. parathyroid hormone.
    d. sex hormones.
    e. thyroid hormone.

Answers in Appendix F

CRITICAL THINKING

1. When a person develops Paget's disease, for unknown reasons the collagen fibers in the bone matrix run randomly in all directions. In addition, the amount of trabecular bone decreases. What symptoms would you expect to observe?
2. When closure of the epiphyseal plate occurs, the cartilage of the plate is replaced by bone. Does this occur from the epiphyseal side of the plate or the diaphyseal side?
3. Assume that two patients have identical breaks in the femur (thighbone). If one is bedridden and the other has a walking cast, which patient's fracture heals faster? Explain.
4. Explain why running helps prevent osteoporosis in the elderly. Does the benefit include all bones or mainly those of the legs and spine?
5. Astronauts can experience a dramatic decrease in bone density while in a weightless environment. Explain how this happens, and suggest a way to slow the loss of bone tissue.
6. Would a patient suffering from kidney failure be more likely to develop osteomalacia or osteoporosis? Explain.
7. In some cultures eunuchs were responsible for guarding harems, which are the collective wives of one male. Eunuchs are males who, as boys, were castrated. Castration removes the testes, the major site of testosterone production in males. Because testosterone is responsible for the sex drive in males, the reason for castration is obvious. As a side effect of this procedure, the eunuchs grew to above-normal heights. Can you explain why?
8. When a long bone is broken, blood vessels at the fracture line are severed. The formation of blood clots stops the bleeding. Within a few days bone tissue on both sides of the fracture site dies. The bone only dies back a certain distance from the fracture line, however. Explain.
9. A patient has hyperparathyroidism because of a tumor in the parathyroid gland that produces excessive amounts of PTH. What effect does this hormone have on bone? Would administration of large doses of vitamin D help the situation? Explain.

Answers in Appendix G

ANSWERS TO PREDICT QUESTIONS

1. In the absence of a good blood supply, nutrients, chemicals, and cells involved in tissue repair enter cartilage tissue very slowly. As a result, the ability of cartilage to undergo repair is poor. Within a joint, the articular cartilage of one bone presses against and moves against the articular cartilage of another bone. If the articular cartilages were covered by perichondrium, or contained blood vessels and nerves, the resulting pressure and friction could damage these structures.
2. In the elderly, the bone matrix contains proportionately less collagen than hydroxyapatite compared to the bones of younger people. Collagen provides bone with flexible strength, and a reduction in collagen results in brittle bones. In addition, the elderly have less dense bones with less matrix. The combination of reduced matrix that is more brittle results in a greater likelihood of bones breaking.
3. Cancellous bone consists of trabeculae with spaces between them. Blood vessels can pass through these spaces. In compact bone, the blood vessels pass through the perforating and central canals. The trabeculae in cancellous bone are thin enough that nutrients and gases can diffuse from blood vessels around the trabeculae to the osteocytes through the canaliculi.
4. Chondroblasts are surrounded by cartilage matrix and receive oxygen and nutrients by diffusion through the matrix. When the matrix becomes calcified, diffusion is reduced to the point the cells die. When osteoblasts form bone matrix, they connect to one another by their cell processes. Thus, when the matrix is laid down, canaliculi are formed. Even though the ossified bone matrix is dense and prevents significant diffusion, it's possible for the osteocytes to receive gases and nutrients through the canaliculi or by movement from one osteocyte to another.

5. Interstitial growth of cartilage results from the division of chondrocytes within the cartilage followed by the addition of new cartilage matrix between the chondrocytes. The resulting expansion of the cartilage matrix is possible because cartilage matrix is not too rigid. Bones cannot undergo interstitial growth because bone matrix is rigid and cannot expand from within. New bone must therefore be added to the surface by apposition.
6. Damage to the epiphyseal plate interferes with bone elongation, and as a result the bone, and therefore the thigh, will be shorter than normal. Recovery is difficult because cartilage repairs very slowly.
7. Growth of articular cartilage results in an increase in the size of epiphyses. This is only one of the functions of articular cartilage; it also forms a smooth, resilient covering over the ends of the epiphyses within joints. Ossified articular cartilage could not perform that function.
8. Her growth for the next few months increases, and she may be taller than a typical 12-year-old female. Because the epiphyseal plates ossify earlier than normal, however, her height at age 18 will be less than otherwise expected.
9. Taking in adequate calcium and vitamin D through the digestive system during adulthood increases calcium absorption from the small intestine. The increased calcium is used to increase bone mass. The greater the bone mass before the onset of osteoporosis, the greater the tolerance for bone loss later in life. For this reason it's important for adults, especially women in their twenties and thirties, to ingest adequate amounts of calcium. Exercising the muscular system places stress on bone, which also increases bone density. The granddaughter shouldn't smoke because this reduces estrogen levels. Following menopause, estrogen replacement therapy can reduce bone loss.