4

Tissue: The Living Fabric

Amoebas and other unicellular (one-cell) organisms are rugged individualists. Each cell alone obtains and digests its food, ejects its wastes, and carries out all the other activities necessary to keep itself alive and "buzzin' around on all cylinders." But in the multicellular human body, cells do not operate independently. Instead, they form tight cell communities that live and work together.

Individual body cells are specialized, with each type performing specific functions that help maintain homeostasis and benefit the body as a whole. Cell specialization is obvious: How muscle cells look and act
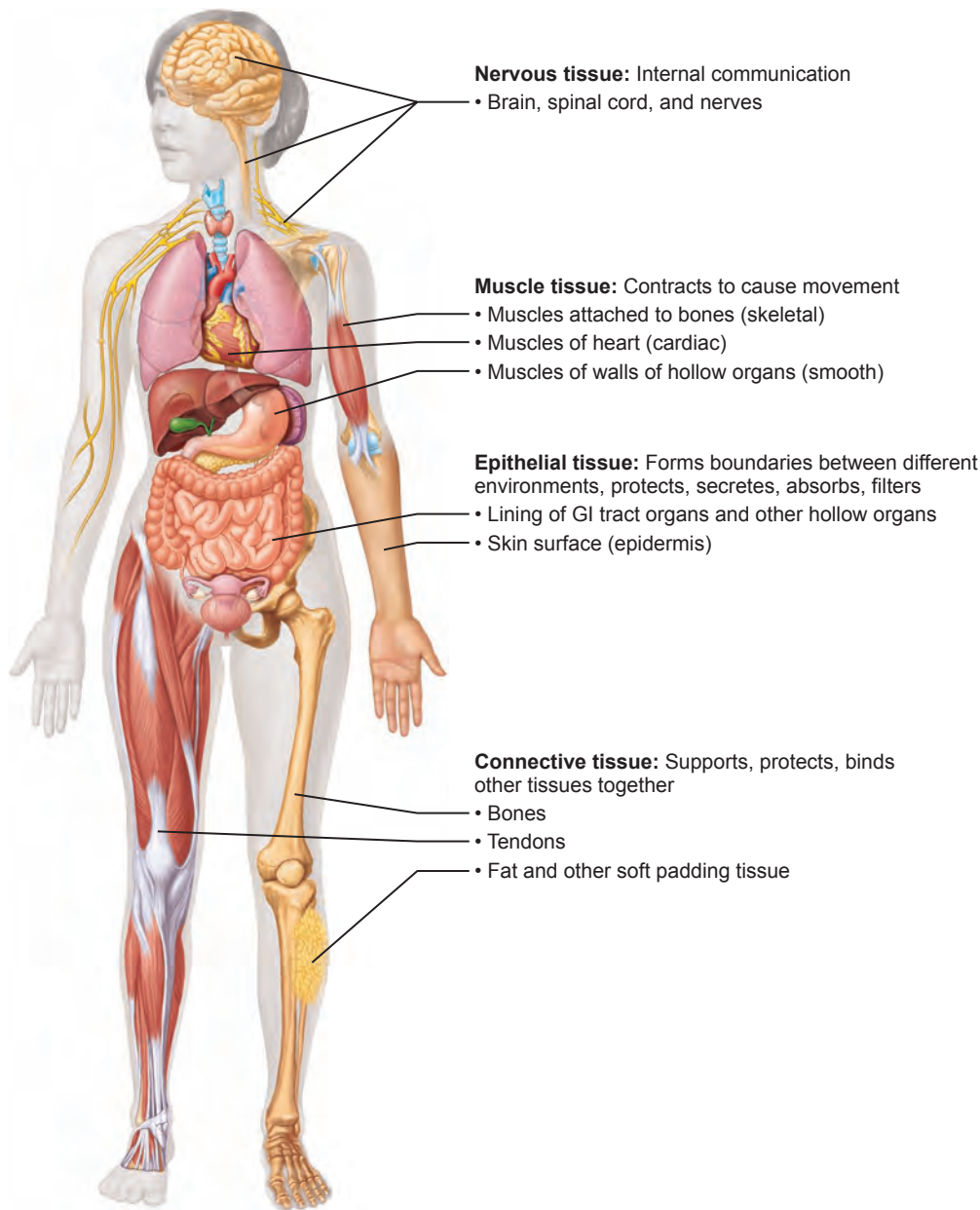
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Nervous tissue: Internal communication
• Brain, spinal cord, and nerves

Muscle tissue: Contracts to cause movement
• Muscles attached to bones (skeletal)
• Muscles of heart (cardiac)
• Muscles of walls of hollow organs (smooth)

Epithelial tissue: Forms boundaries between different environments, protects, secretes, absorbs, filters
• Lining of GI tract organs and other hollow organs
• Skin surface (epidermis)

Connective tissue: Supports, protects, binds other tissues together
• Bones
• Tendons
• Fat and other soft padding tissue

Figure 4.1 Overview of four tissue types: epithelial, connective, muscle, and nervous tissues.

differs greatly from skin cells, which in turn are easy to distinguish from brain cells. Cell specialization allows the body to function in sophisticated ways, but division of labor has certain hazards. When a particular group of cells is indispensable, its loss or injury can severely disable or even destroy the body.

Groups of cells that are similar in structure and perform a common or related function are called **tissues** (*tissu* = woven). Four primary tissue types interweave to form the "fabric" of the body. These basic tissues are epithelial (ep″i-the′le-ul), connective, muscle, and nervous tissue, and each has numerous subclasses or varieties. If we had to describe the general role of each primary tissue type in a single word, the words would most likely be *covering* (epithelial), *support* (connective), *movement* (muscle), and *control* (nervous). However, these words reveal only a fraction of the functions that each tissue performs **(Figure 4.1)**.

As we explained in Chapter 1, tissues are organized into organs such as the kidneys and the heart. Most organs contain all four tissue types, and their arrangement determines the organ's structure and capabilities. The study of tissues, or **histology**, complements the study of gross anatomy. Together they provide the structural basis for understanding organ physiology.

Preparing Human Tissue for Microscopy

▶ List the steps involved in preparing animal tissue for microscopic viewing.

Elaborate steps are taken to prepare human or animal tissue for microscopic viewing. The specimen must be **fixed** (preserved) and then cut into **sections** (slices) thin enough to transmit light or electrons. Finally the specimen must be **stained** to enhance contrast.

The stains used in light microscopy are beautifully colored organic dyes, most of which were originally developed by clothing manufacturers in the mid-1800s. Many dyes consist of negatively or positively charged molecules (acidic and basic stains, respectively) that bind within the tissue to macromolecules of the opposite charge. The stains distinguish different anatomical structures because different parts of cells and tissues take up different dyes.

For transmission electron microscopy (TEM), tissue sections are "stained" with heavy metal salts. These metals deflect electrons in the beam to different extents, providing contrast in the image. Electron-microscope images are in shades of gray because color is a property of light, not of electron waves, but the image may be artificially colored to enhance contrast. Another kind of electron microscopy, scanning electron microscopy (SEM), provides three-dimensional pictures of an unsectioned tissue surface. These striking images are scattered throughout this book.

Preserved tissue we see under the microscope has been exposed to many procedures that alter its original condition and introduce minor distortions called **artifacts**. For this reason, keep in mind that most microscopic structures we view are not exactly like those in living tissue.

CHECK YOUR UNDERSTANDING

1. What is the purpose of fixing tissue for microscopic viewing?
2. What types of stains are used to stain tissues to be viewed with an electron microscope?

For answers, see Appendix G.

Epithelial Tissue

▶ List several structural and functional characteristics of epithelial tissue.

▶ Name, classify, and describe the various types of epithelia, and indicate their chief function(s) and location(s).

Epithelial tissue, or an **epithelium** (plural: epithelia), is a sheet of cells that covers a body surface or lines a body cavity (*epithe* = laid on, covering). It occurs in the body as (1) *covering and lining epithelium* and (2) *glandular epithelium.* Covering and lining epithelium forms the outer layer of the skin, dips into and lines the open cavities of the cardiovascular, digestive, and respiratory systems, and covers the walls and organs of the closed ventral body cavity. Glandular epithelium fashions the glands of the body.

Epithelia form boundaries between different environments, and nearly all substances received or given off by the body must pass through an epithelium. For example, the epidermis of the skin lies between the inside and the outside of the body. Epithelium

lining the urinary bladder separates underlying cells of the bladder wall from urine.

In its role as an interface tissue, epithelium accomplishes many functions, including (1) protection, (2) absorption, (3) filtration, (4) excretion, (5) secretion, and (6) sensory reception. We describe each of these functions in detail later, but here we illustrate these functions briefly: The epithelium of the skin protects underlying tissues from mechanical and chemical injury and bacterial invasion and contains nerve endings that respond to various stimuli acting at the skin surface (pressure, heat, etc.). The epithelium lining the digestive tract is specialized to absorb substances. That found in the kidneys performs nearly the whole functional "menu"—excretion, absorption, secretion, and filtration. Secretion is the specialty of glands.

## Special Characteristics of Epithelium

Epithelial tissues have many characteristics that distinguish them from other tissue types.

1. **Polarity**. All epithelia have an **apical surface**, an upper free surface exposed to the body exterior or the cavity of an internal organ, and a lower attached **basal surface**. For this reason, all epithelia exhibit *apical-basal polarity*, meaning that cell regions near the apical surface differ from those near the basal surface in both structure and function. This situation is maintained, at least in part, by the highly ordered cytoskeleton of epithelial cells.

   Although some apical surfaces are smooth and slick, most have **microvilli**, fingerlike extensions of the plasma membrane. Microvilli tremendously increase the exposed surface area. In epithelia that absorb or secrete substances (those lining the intestine or kidney tubules, for instance), the microvilli are often so dense that the cell apices have a fuzzy appearance called a *brush border*. Some epithelia, such as that lining the trachea, have motile **cilia** (tiny hairlike projections) that propel substances along their free surface.

   Lying adjacent to the basal surface of an epithelium is a thin supporting sheet called the **basal lamina** (lam′ĭ-nah; "sheet"). This noncellular, adhesive sheet consists largely of glycoproteins secreted by the epithelial cells plus some fine collagen fibers. The basal lamina acts as a selective filter that determines which molecules diffusing from the underlying connective tissue are allowed to enter the epithelium. The basal lamina also acts as a scaffolding along which epithelial cells can migrate to repair a wound.

2. **Specialized contacts**. Except for glandular epithelia (discussed on pp. 121–124), epithelial cells fit close together to form continuous sheets. Adjacent cells are bound together at many points by lateral contacts, including *tight junctions* and *desmosomes* (see Chapter 3). The tight junctions help keep proteins in the apical region of the plasma membrane from diffusing into the basal region, and thus help to maintain epithelial polarity.

3. **Supported by connective tissue**. All epithelial sheets rest upon and are supported by connective tissue. Just deep to the basal lamina is the **reticular lamina**, a layer of

4

Basal surface
Simple

Stratified
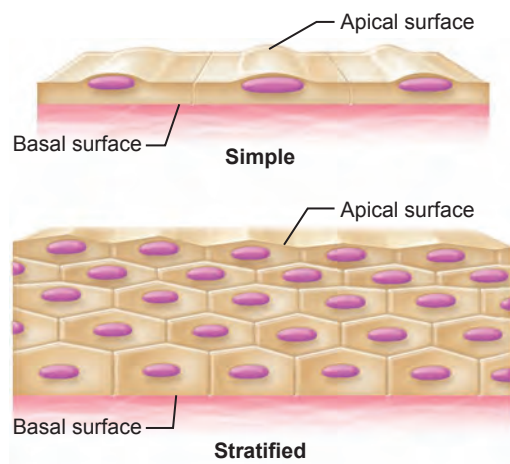
(a) Classification based on number of cell layers.

Squamous

Cuboidal

Columnar
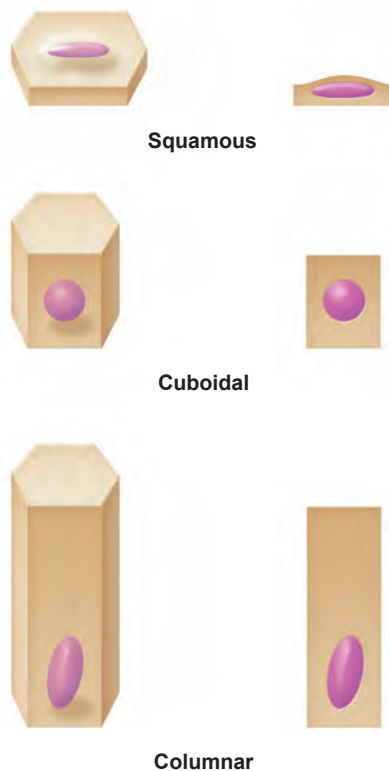
(b) Classification based on cell shape.

Figure 4.2 Classification of epithelia.

extracellular material containing a fine network of collagen protein fibers that "belongs to" the underlying connective tissue. Together the two laminae form the **basement membrane**. The basement membrane reinforces the epithelial sheet, helping it to resist stretching and tearing forces, and defines the epithelial boundary.

HOMEOSTATIC IMBALANCE

An important characteristic of cancerous epithelial cells is their failure to respect the basement membrane boundary, which they penetrate to invade the tissues beneath. ■

4. **Avascular but innervated.** Although epithelium is *innervated* (supplied by nerve fibers), it is *avascular* (contains no blood vessels). Epithelial cells are nourished by substances diffusing from blood vessels in the underlying connective tissue.

5. **Regeneration.** Epithelium has a high regenerative capacity. Some epithelia are exposed to friction and their surface cells rub off. Others are damaged by hostile substances in the external environment (bacteria, acids, smoke). If and when their apical-basal polarity and lateral contacts are destroyed, epithelial cells begin to reproduce themselves rapidly. As long as epithelial cells receive adequate nutrition, they can replace lost cells by cell division.

CHECK YOUR UNDERSTANDING

3. Epithelial tissue is the only tissue type that has polarity, that is, an apical and a basal surface. Why is this important?
4. Which of the following properties apply to epithelial tissue? Has blood vessels, can repair itself (regenerates), cells joined by lateral contacts.

For answers, see Appendix G.

Classification of Epithelia

Each epithelium is given two names. The first name indicates the number of cell layers present, and the second describes the shape of its cells. Based on the number of cell layers, there are simple and stratified epithelia **(Figure 4.2a)**. **Simple epithelia** consist of a single cell layer. They are typically found where absorption, secretion, and filtration occur and a thin epithelial barrier is desirable. **Stratified epithelia**, composed of two or more cell layers stacked one on top of the other, are common in high-abrasion areas where protection is important, such as the skin surface and the lining of the mouth.

In cross section, all epithelial cells have six (somewhat irregular) sides, and an apical surface view of an epithelial sheet looks like a honeycomb. This polyhedral shape allows the cells to be closely packed. However, epithelial cells vary in height, and on that basis, there are three common shapes of epithelial cells (Figure 4.2b). **Squamous cells** (skwa′mus) are flattened and scalelike (*squam* = scale). **Cuboidal cells** (ku-boi′dahl) are boxlike, approximately as tall as they are wide, and **columnar cells** (kŏ-lum′nar) are tall and column shaped.

In each case, the shape of the nucleus conforms to that of the cell. The nucleus of a squamous cell is a flattened disc; that of a cuboidal cell is spherical; and a columnar cell nucleus is elongated from top to bottom and usually located close to the cell base. Keep nuclear shape in mind when you attempt to identify epithelial types.

Simple epithelia are easy to classify by cell shape because all cells in the layer usually have the same shape. In stratified epithelia, however, the cell shapes usually differ among the different cell layers. To avoid ambiguity, stratified epithelia are named according to the shape of the cells in the *apical* layer. This naming system will become clearer as we explore the specific epithelial types.
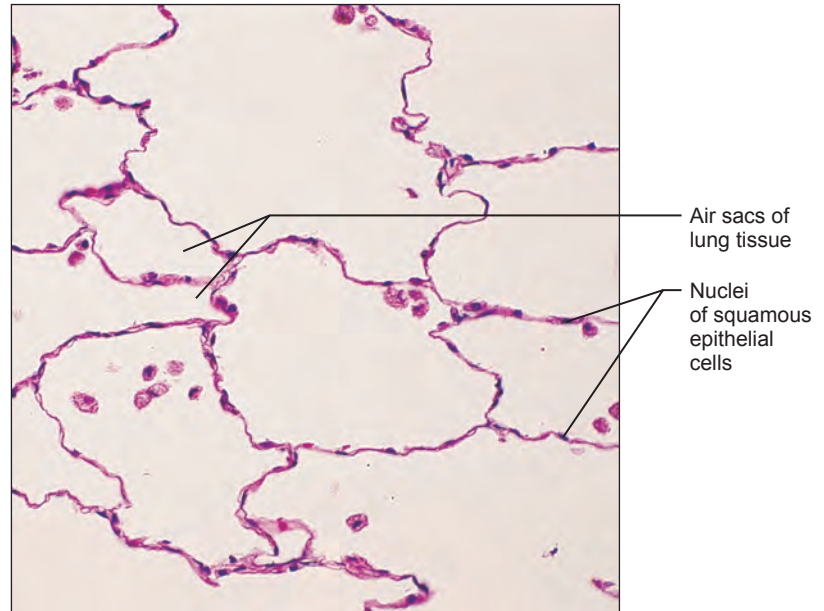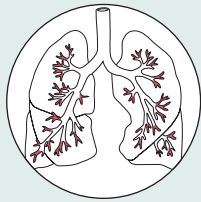
(a) Simple squamous epithelium

Description: Single layer of flattened cells with disc-shaped central nuclei and sparse cytoplasm; the simplest of the epithelia.

Function: Allows passage of materials by diffusion and filtration in sites where protection is not important; secretes lubricating substances in serosae.

Location: Kidney glomeruli; air sacs of lungs; lining of heart, blood vessels, and lymphatic vessels; lining of ventral body cavity (serosae).

Air sacs of lung tissue

Nuclei of squamous epithelial cells

Photomicrograph: Simple squamous epithelium forming part of the alveolar (air sac) walls (125×).

Figure 4.3 **Epithelial tissues. (a)** Simple epithelium. (See *A Brief Atlas of the Human Body,* Plates 1 and 2.)

As you read about the epithelial classes, study **Figure 4.3**. Using the photomicrographs, try to pick out the individual cells within each epithelium. This is not always easy, because the boundaries between epithelial cells often are indistinct. Furthermore, the nucleus of a particular cell may or may not be visible, depending on the precise plane of the cut made to prepare the tissue slides.

Simple Epithelia

The simple epithelia are most concerned with absorption, secretion, and filtration. Because they consist of a single cell layer and are usually very thin, protection is not one of their specialties.

Simple Squamous Epithelium   The cells of a **simple squamous epithelium** are flattened laterally, and their cytoplasm is sparse (Figure 4.3a). In a surface view, the close-fitting cells resemble a tiled floor. When the cells are cut perpendicular to their free surface, they resemble fried eggs seen from the side, with their cytoplasm wisping out from the slightly bulging nucleus. Thin and often permeable, this epithelium is found where filtration or the exchange of substances by rapid diffusion is a priority. In the kidneys, simple squamous epithelium forms part of the filtration membrane. In the lungs, it forms the walls of the air sacs across which gas exchange occurs.

Two simple squamous epithelia in the body have special names that reflect their location. **Endothelium** (en″do-the′le-um; "inner covering") provides a slick, friction-reducing lining in lymphatic vessels and in all hollow organs of the cardiovascular system—blood vessels and the heart. Capillaries consist exclusively of endothelium, and its exceptional thinness encourages the efficient exchange of nutrients and wastes between the bloodstream and surrounding tissue cells. **Mesothelium** (mez″o-the′le-um; "middlecovering") is the epithelium found in serous membranes lining the ventral body cavity and covering its organs.

Simple Cuboidal Epithelium   **Simple cuboidal epithelium** consists of a single layer of cells as tall as they are wide (Figure 4.3b). The spherical nuclei stain darkly, causing the cell layer to look like a string of beads when viewed microscopically. Important functions of simple cuboidal epithelium are secretion and absorption. This epithelium forms the walls of the smallest ducts of glands and of many kidney tubules.

Simple Columnar Epithelium   **Simple columnar epithelium** is seen as a single layer of tall, closely packed cells, aligned like soldiers in a row (Figure 4.3c). It lines the digestive tract from the stomach through the rectum. Columnar cells are mostly associated with absorption and secretion, and the digestive tract lining has two distinct modifications that make it ideal for that
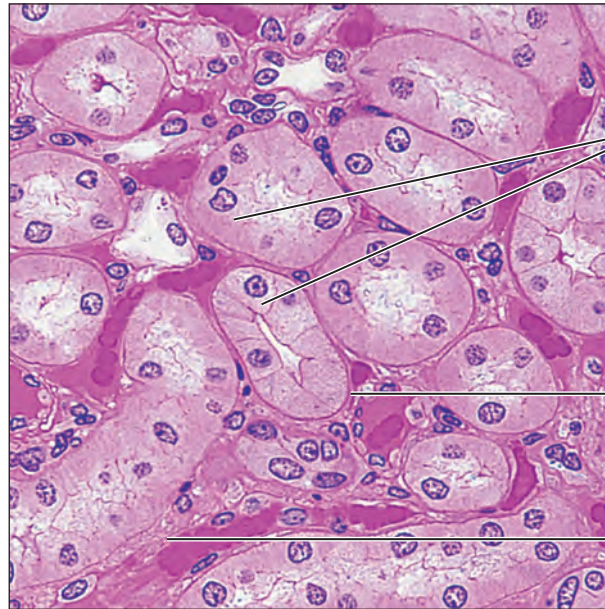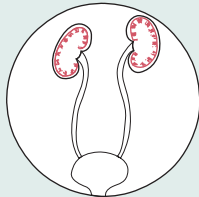
(b) Simple cuboidal epithelium

Description: Single layer of cubelike cells with large, spherical central nuclei.

Function: Secretion and absorption.

Location: Kidney tubules; ducts and secretory portions of small glands; ovary surface.
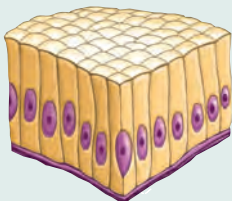

Simple cuboidal epithelial cells

Basement membrane

Connective tissue

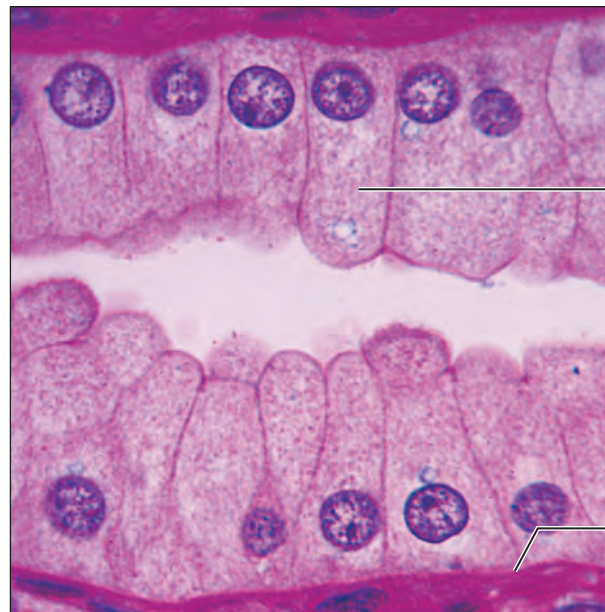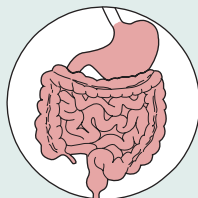**Photomicrograph:** Simple cuboidal epithelium in kidney tubules (430×).

(c) Simple columnar epithelium

Description: Single layer of tall cells with *round* to *oval* nuclei; some cells bear cilia; layer may contain mucus-secreting unicellular glands (goblet cells).

Function: Absorption; secretion of mucus, enzymes, and other substances; ciliated type propels mucus (or reproductive cells) by ciliary action.

Location: Nonciliated type lines most of the digestive tract (stomach to anal canal), gallbladder, and excretory ducts of some glands; ciliated variety lines small bronchi, uterine tubes, and some regions of the uterus.

Simple columnar epithelial cell

Basement membrane

Photomicrograph: Simple columnar epithelium of the stomach mucosa (860×).

Figure 4.3 *(continued)* **Epithelial tissues. (b)** and **(c)** Simple epithelium. (See *A Brief Atlas of the Human Body*, Plates 3, 4, and 5.)
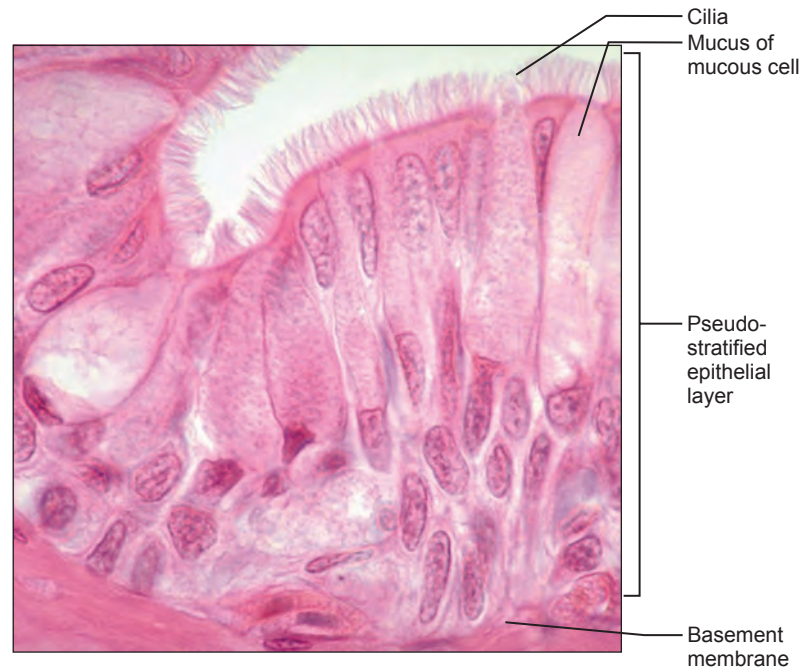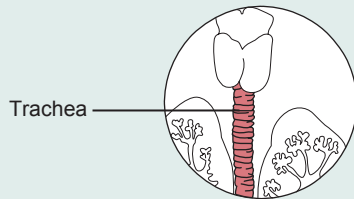
(d) Pseudostratified columnar epithelium

Description: Single layer of cells of differing heights, some not reaching the free surface; nuclei seen at different levels; may contain mucus-secreting cells and bear cilia.
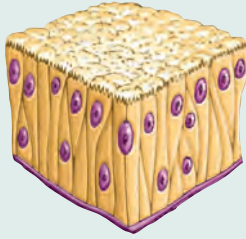
Function: Secretion, particularly of mucus; propulsion of mucus by ciliary action.

Location: Nonciliated type in male's sperm-carrying ducts and ducts of large glands; ciliated variety lines the trachea, most of the upper respiratory tract.

Trachea

Cilia

Mucus of mucous cell

Pseudo-stratified epithelial layer

Basement membrane

Photomicrograph: Pseudostratified ciliated columnar epithelium lining the human trachea (570×).

Figure 4.3 (continued) **(d)** Simple epithelium. (See *A Brief Altas of the Human Body,* Plate 6.)

dual function: (1) dense microvilli on the apical surface of absorptive cells and (2) cells that secrete a protective lubricating mucus. Some simple columnar epithelia display cilia on their free surfaces, which help to move substances or cells through an internal passageway.

Pseudostratified Columnar Epithelium The cells of **pseudostratified columnar epithelium** (soo″do-stră′tĭ-fīd) vary in height (Figure 4.3d). All of its cells rest on the basement membrane, but only the tallest reach the free surface of the epithelium. Because the cell nuclei lie at different levels above the basement membrane, the tissue gives the false (pseudo) impression that several cell layers are present; hence "pseudostratified." The short cells are relatively unspecialized and give rise to the taller cells. This epithelium, like the simple columnar variety, secretes or absorbs substances. A ciliated version containing mucus-secreting cells lines most of the respiratory tract. Here the motile cilia propel sheets of dust-trapping mucus superiorly away from the lungs.

Stratified Epithelia

Stratified epithelia contain two or more cell layers. They regenerate from below; that is, the basal cells divide and push apically to replace the older surface cells. Stratified epithelia are considerably more durable than the simple epithelia, and protection is their major role (but not their only role).

Stratified Squamous Epithelium **Stratified squamous epithelium** is the most widespread of the stratified epithelia (Figure 4.3e). Composed of several layers, it is thick and well suited for its protective role in the body. Its free surface cells are squamous, and cells of the deeper layers are cuboidal or columnar. This epithelium is found in areas subjected to wear and tear, and its surface cells are constantly being rubbed away and replaced by division of its basal cells. Because epithelium depends on diffusion of nutrients from a deeper connective tissue layer, the epithelial cells farther from the basement membrane are less viable and those at the apical surface are often flattened and atrophied.

To avoid memorizing all its locations, simply remember that this epithelium forms the external part of the skin and extends a short distance into every body opening that is directly continuous with the skin. The outer layer, or *epidermis*, of the skin is *keratinized* (ker′ah-tin″īzd), meaning its surface cells contain *keratin*, a tough protective protein. (We discuss the epidermis in Chapter 5.) The other stratified squamous epithelia of the body are *nonkeratinized*.

Stratified Cuboidal and Columnar Epithelia **Stratified cuboidal epithelium** is quite rare in the body, mostly found in the ducts of some of the larger glands (sweat glands, mammary glands). It typically has two layers of cuboidal cells.

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(e) Stratified squamous epithelium

Description: Thick membrane composed of several cell layers; basal cells are cuboidal or columnar and metabolically active; surface cells are flattened (squamous); in the keratinized type, the surface cells are full of keratin and dead; basal cells are active in mitosis and produce the cells of the more superficial layers.
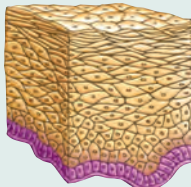
Function: Protects underlying tissues in areas subjected to abrasion.

Location: Nonkeratinized type forms the moist linings of the esophagus, mouth, and vagina; keratinized variety forms the epidermis of the skin, a dry membrane.
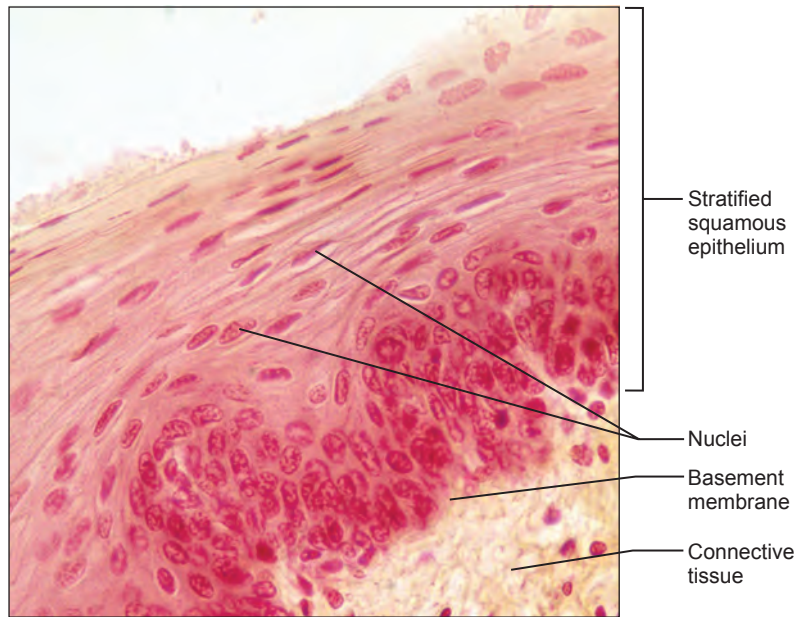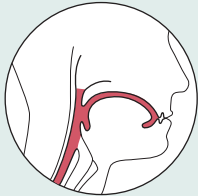
Photomicrograph: Stratified squamous epithelium lining the esophagus (285×).

(f) Transitional epithelium

Description: Resembles both stratified squamous and stratified cuboidal; basal cells cuboidal or columnar; surface cells dome shaped or squamouslike, depending on degree of organ stretch.
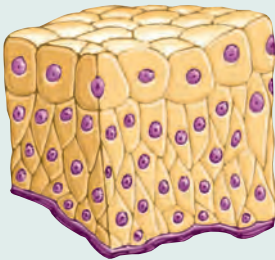
Function: Stretches readily and permits distension of urinary organ by contained urine.

Location: Lines the ureters, urinary bladder, and part of the urethra.
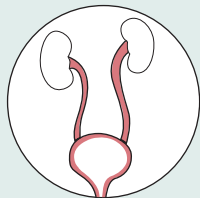
Photomicrograph: Transitional epithelium lining the urinary bladder, relaxed state (360×); note the bulbous, or rounded, appearance of the cells at the surface; these cells flatten and become elongated when the bladder is filled with urine.

Figure 4.3 *(continued)* **Epithelial tissues. (e)** and **(f)** Stratified epithelium. (See *A Brief Atlas of the Human Body*, Plates 7 and 10.)

Stratified columnar epithelium also has a limited distribution in the body. Small amounts are found in the pharynx, the male urethra, and lining some glandular ducts. This epithelium also occurs at transition areas or junctions between two other types of epithelia. Only its apical layer of cells is columnar. Because of their relative scarcity in the body, these two stratified epithelia are not illustrated in Figure 4.3, but are illustrated in *A Brief Atlas of the Human Body*, Plates 8 and 9, respectively.

Transitional Epithelium   Transitional epithelium forms the lining of hollow urinary organs, which stretch as they fill with urine (Figure 4.3f). Cells of its basal layer are cuboidal or columnar. The apical cells vary in appearance, depending on the degree of distension of the organ. When the organ is distended with urine, the transitional epithelium thins from about six cell layers to three, and its domelike apical cells flatten and become squamouslike. The ability of transitional cells to change their shape (undergo "transitions") allows a greater volume of urine to flow through a tubelike organ. In the bladder, it allows more urine to be stored.

CHECK YOUR UNDERSTANDING

5. Stratified epithelia are "built" for protection or to resist abrasion. What are the simple epithelia better at?

6. Some epithelia are pseudostratified. What does this mean?

7. Where is transitional epithelium found and what is its importance at those sites?

For answers, see Appendix G.

Glandular Epithelia

▶ Define gland.

▶ Differentiate between exocrine and endocrine glands, and between multicellular and unicellular glands.

▶ Describe how multicellular exocrine glands are classified structurally and functionally.

A **gland** consists of one or more cells that make and secrete (export) a particular product. This product, called a **secretion**, is an aqueous (water-based) fluid that usually contains proteins, but there is variation. For example, some glands release a lipid- or steroid-rich secretion.

Secretion is an active process. Glandular cells obtain needed substances from the blood and transform them chemically into a product that is then discharged from the cell. Notice that the term *secretion* can refer to both the gland's *product* and the *process* of making and releasing that product.

Glands are classified as *endocrine* ("internally secreting") or *exocrine* ("externally secreting") depending on where they release their product, and as *unicellular* ("one-celled") or *multicellular* ("many-celled") based on the relative cell number making up the gland. Unicellular glands are scattered

within epithelial sheets. By contrast, most multicellular epithelial glands form by invagination (inward growth) or evagination (outward growth) from an epithelial sheet and, at least initially, most have *ducts*, tubelike connections to the epithelial sheets.

Endocrine Glands

Because **endocrine glands** eventually lose their ducts, they are often called *ductless glands*. They produce **hormones**, regulatory chemicals that they secrete by exocytosis directly into the extracellular space. From there the hormones enter the blood or lymphatic fluid and travel to specific target organs. Each hormone prompts its target organ(s) to respond in some characteristic way. For example, hormones produced by certain intestinal cells cause the pancreas to release enzymes that help digest food in the digestive tract.

Endocrine glands are structurally diverse, so one description does not fit all. Most endocrine glands are compact multicellular organs, but some individual hormone-producing cells are scattered in the digestive tract mucosa and in the brain, giving rise to their collective description as the *diffuse endocrine system*. Their secretions are also varied, ranging from modified amino acids to peptides, glycoproteins, and steroids. Since not all endocrine glands are epithelial derivatives, we defer consideration of their structure and function to Chapter 16.

Exocrine Glands

Exocrine glands are numerous, and many of their products are familiar. All exocrine glands secrete their products onto body surfaces (skin) or into body cavities. The unicellular glands do so directly (by exocytosis), whereas the multicellular glands do so via an epithelium-walled duct that transports the secretion to the epithelial surface. Exocrine glands are a diverse lot. They include mucous, sweat, oil, and salivary glands, the liver (which secretes bile), the pancreas (which synthesizes digestive enzymes), and many others.

Unicellular Exocrine Glands   The only important examples of **unicellular** (or one-celled) **glands** are *mucous cells* and *goblet cells*. Unicellular glands are sprinkled in the epithelial linings of the intestinal and respiratory tracts amid columnar cells with other functions (see **Figure 4.4** and Figure 4.3d). In humans, all such glands produce **mucin** (mu′sin), a complex glycoprotein that dissolves in water when secreted. Once dissolved, mucin forms **mucus**, a slimy coating that both protects and lubricates surfaces. In **goblet cells** the cuplike accumulation of mucin distends the top of the cell, making the cells look like a glass with a stem (thus "goblet" cell). This distortion does not occur in **mucous cells**.

Multicellular Exocrine Glands   Compared to the unicellular glands, **multicellular exocrine glands** are structurally more complex. They have two basic parts: an epithelium-derived *duct* and a *secretory unit* (*acinus*) consisting of secretory cells. In all but the simplest glands, *supportive*
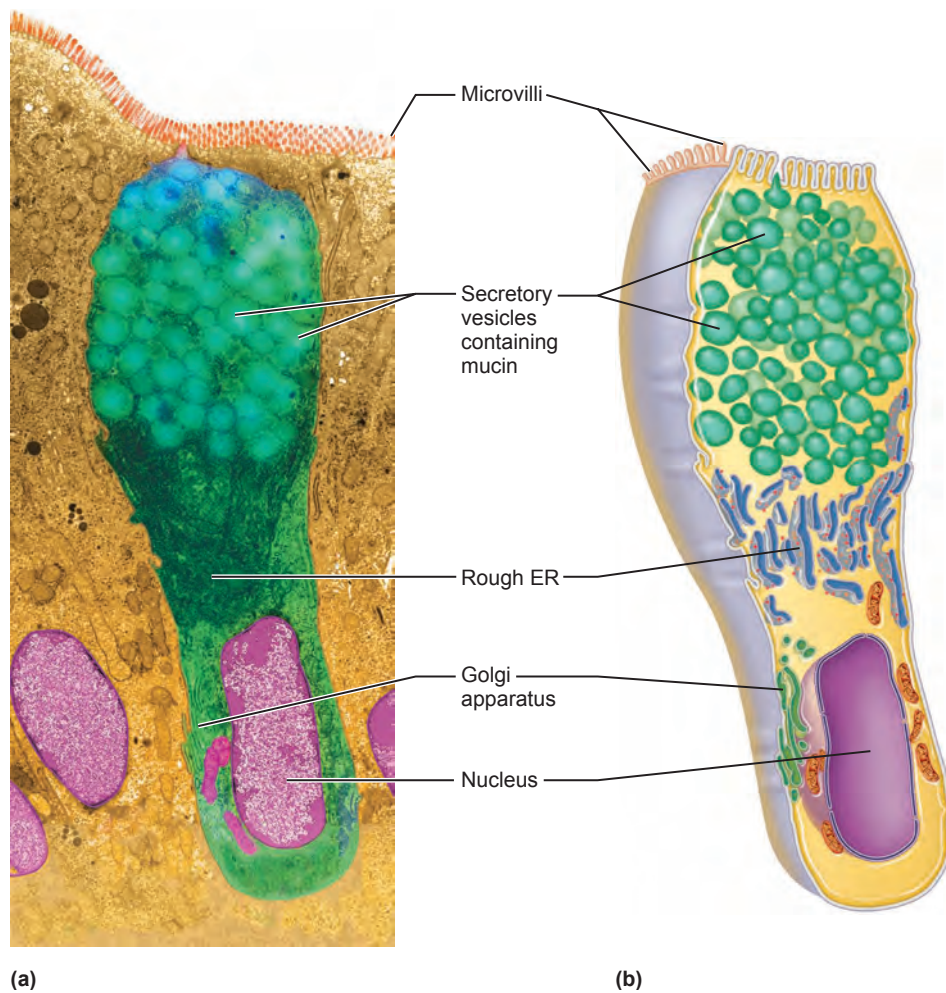
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Microvilli

Secretory vesicles containing mucin

Rough ER

Golgi apparatus

Nucleus

(a)   (b)

Figure 4.4 Goblet cell (unicellular exocrine gland). (a) Photomicrograph of a goblet cell in the simple columnar epithelium lining the small intestine (1640×). **(b)** Corresponding diagram. Notice the secretory vesicles and well-developed rough ER and Golgi apparatus.
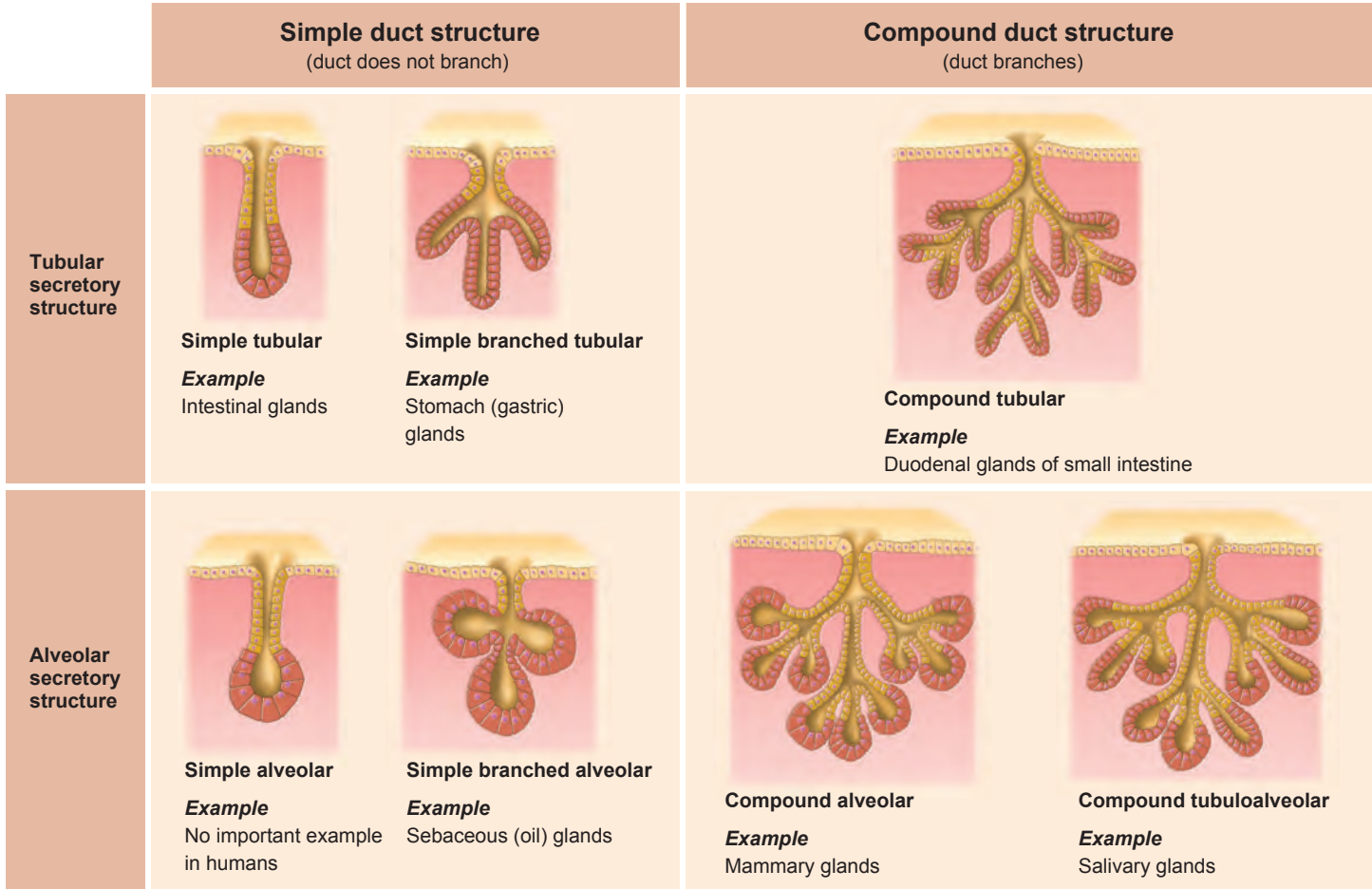
connective tissue surrounds the secretory unit and supplies it with blood vessels and nerve fibers, and forms a *fibrous capsule* that extends into the gland proper and divides the gland into *lobes*.

- **Structural classification**. On the basis of their duct structures, multicellular exocrine glands are either simple or compound **(Figure 4.5)**. **Simple glands** have an unbranched duct, whereas **compound glands** have a branched duct. The glands are further categorized by their secretory units as (1) **tubular** if the secretory cells form tubes; (2) **alveolar** (al-ve′o-lar) if the secretory cells form small, flasklike sacs (*alveolus* = "small hollow cavity"); and (3) **tubuloalveolar** if they have both types of secretory units. Note that the term **acinar** (as′ĭ-nar; "berrylike") is used interchangeably with alveolar.

- **Modes of secretion**. Multicellular exocrine glands secrete their products in different ways, so they can also be described functionally. Most are **merocrine glands** (mer′o-krin), which secrete their products by exocytosis as they are pro-

duced. The secretory cells are not altered in any way. The pancreas, most sweat glands, and salivary glands belong to this class **(Figure 4.6a)**.

Secretory cells of **holocrine glands** (hol′o-krin) accumulate their products within them until they rupture. (They are replaced by the division of underlying cells.) Because holocrine gland secretions include the synthesized product plus dead cell fragments (*holos* = all), you could say that their cells "die for their cause." Sebaceous (oil) glands of the skin are the only true example of holocrine glands (Figure 4.6b).

Although *apocrine glands* (ap′o-krin) are definitely present in other animals, there is some controversy over whether humans have this third gland type. Like holocrine glands, apocrine glands accumulate their products, but in this case only just beneath the free surface. Eventually, the apex of the cell pinches off (*apo* = from, off), releasing the secretory granules and a small amount of cytoplasm. The cell repairs its damage and the process repeats again and again. The best

Simple duct structure (duct does not branch)		**Compound duct structure** (duct branches)	
Tubular secretory structure	**Simple tubular** *Example* Intestinal glands	**Simple branched tubular** *Example* Stomach (gastric) glands	**Compound tubular** *Example* Duodenal glands of small intestine
Alveolar secretory structure	**Simple alveolar** *Example* No important example in humans	**Simple branched alveolar** *Example* Sebaceous (oil) glands	**Compound alveolar** *Example* Mammary glands **Compound tubuloalveolar** *Example* Salivary glands

☐ Surface epithelium ☐ Duct ☐ Secretory epithelium

Figure 4.5 Types of multicellular exocrine glands. Multicellular glands are classified according to duct type (simple or compound) and the structure of their secretory units (tubular, alveolar, or tubuloalveolar).
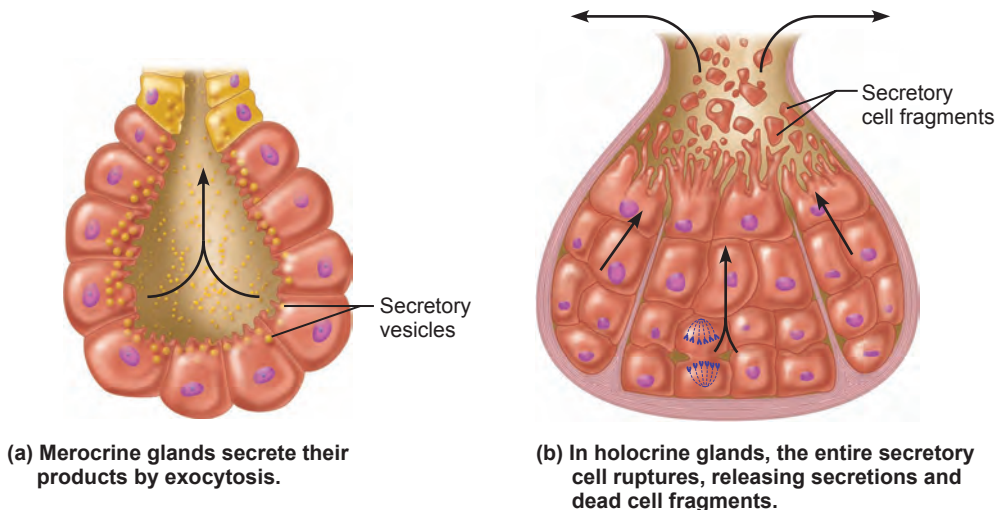

(a) Merocrine glands secrete their products by exocytosis.

— Secretory vesicles

— Secretory cell fragments

(b) In holocrine glands, the entire secretory cell ruptures, releasing secretions and dead cell fragments.

Figure 4.6 Chief modes of secretion in human exocrine glands.

possibility in humans is the release of lipid droplets by the mammary glands, but most histologists classify mammary glands as merocrine glands because this is the means by which milk proteins are secreted.

Connective Tissue

▶ Indicate common characteristics of connective tissue, and list and describe its structural elements.

Connective tissue is found everywhere in the body. It is the most abundant and widely distributed of the primary tissues, but its amount in particular organs varies. For example, skin consists primarily of connective tissue, while the brain contains very little.

There are four main classes of connective tissue and several subclasses (**Table 4.1** on p. 134). The main classes are (1) *connective tissue proper* (which includes fat and the fibrous tissue of ligaments), (2) *cartilage*, (3) *bone tissue*, and (4) *blood*.

Connective tissue does much more than just *connect* body parts. It has many forms and functions. Its major functions include (1) *binding and support*, (2) *protection*, (3) *insulation*, and as blood, (4) *transportation* of substances within the body. For example, bone and cartilage support and protect body organs by providing the hard underpinnings of the skeleton, and cushions of fat insulate and protect body organs and provide reserve energy fuel.

Common Characteristics of Connective Tissue

Despite their many and diverse functions in the body, connective tissues have some common characteristics that set them apart from other primary tissues:

1. **Common origin**. All connective tissues arise from *mesenchyme* (an embryonic tissue) and hence have a kinship.

2. **Degrees of vascularity**. Connective tissues run the entire gamut of vascularity. Cartilage is avascular. Dense connective tissue is poorly vascularized, and the other types of connective tissue have a rich supply of blood vessels.

3. **Extracellular matrix**. All other primary tissues are composed mainly of cells, but connective tissues are largely nonliving **extracellular matrix** (ma′triks; "womb"), which separates, often widely, the living cells of the

tissue. Because of its matrix, connective tissue is able to bear weight, withstand great tension, and endure abuses, such as physical trauma and abrasion that no other tissue would be able to tolerate.

Structural Elements of Connective Tissue

Connective tissues have three main elements: *ground substance*, *fibers*, and *cells* (Table 4.1). Together ground substance and fibers make up the extracellular matrix. (Note that some authors use the term *matrix* to indicate the ground substance only.)

The characteristics of the cells and the composition and arrangement of extracellular matrix elements vary tremendously. The result is an amazing diversity of connective tissues, each adapted to perform its specific function in the body. For example, the matrix can be delicate and fragile to form a soft "packing" around an organ, or it can form "ropes" (tendons and ligaments) of incredible strength. Nonetheless, connective tissues have a common structural plan, and we use *areolar connective tissue* (ah-re′o-lar) as our *prototype*, or model, for this group of tissues (**Figure 4.7** and Figure 4.8a). All other subclasses are simply variants of this common structural plan.

Ground Substance

Ground substance is the unstructured material that fills the space between the cells and contains the fibers. It is composed of *interstitial* (*tissue*) *fluid*, *cell adhesion proteins*, and *proteoglycans* (pro″te-o-gli′kanz). Cell adhesion proteins (*fibronectin*, *laminin*, and others) serve mainly as a connective tissue glue that allows connective tissue cells to attach themselves to matrix elements. The proteoglycans consist of a protein core to which *glycosaminoglycans* (GAGs) (gli″kos-ah-me″no-gli′kanz) are attached. The strandlike GAGs, most importantly *chondroitin sulfate* and *hyaluronic acid* (hi″ah-lu-ron′ik), are large, negatively charged polysaccharides that stick out from the core protein like the fibers of a bottle brush. The proteoglycans tend to form huge aggregates in which the GAGs intertwine and trap water, forming a substance that varies from a fluid to a viscous gel. In general, the higher the GAG content, the more viscous the ground substance.

The ground substance holds large amounts of fluid and functions as a molecular sieve, or medium, through which nutrients and other dissolved substances can diffuse between the blood capillaries and the cells. The fibers embedded in the ground substance make it less pliable and hinder diffusion somewhat.

Fibers

The fibers of connective tissue provide support. Three types of fibers are found in connective tissue matrix: collagen, elastic, and reticular fibers. Of these, collagen fibers are by far the strongest and most abundant.

Collagen fibers are constructed primarily of the fibrous protein *collagen*. Collagen molecules are secreted into the extracellular

Cell types

Extracellular matrix

Macrophage

Fibroblast

Lymphocyte

Fat cell

Mast cell

Neutrophil

Ground substance

Fibers
• Collagen fiber
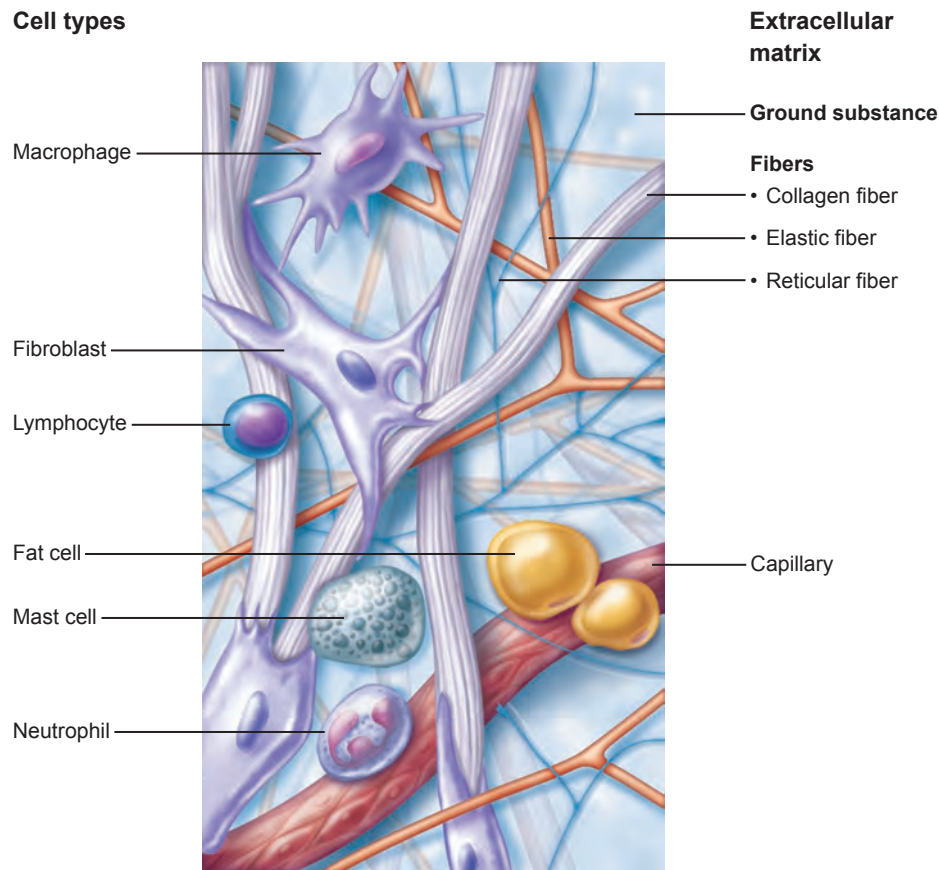• Elastic fiber
• Reticular fiber

Capillary

4

Figure 4.7 Areolar connective tissue: A prototype (model) connective tissue. This tissue underlies epithelia and surrounds capillaries. Notice the various cell types and three classes of fibers (collagen, reticular, elastic) embedded in the ground substance. (See Figure 4.8a for a less idealized version.)

space, where they assemble spontaneously into cross-linked fibrils, which in turn are bundled together into the thick collagen fibers seen with a microscope. Because of the cross-linking of their fibrils, collagen fibers are extremely tough and provide high tensile strength (that is, the ability to resist longitudinal stress) to the matrix. Indeed, stress tests show that collagen fibers are stronger than steel fibers of the same size! When fresh, they have a glistening white appearance, and for this reason, they are also called *white fibers*. (See the large lavender-white fibers in Figure 4.7.)

Elastic fibers are long, thin fibers that form branching networks in the extracellular matrix. These fibers contain a rubber-like protein, *elastin*, that allows them to stretch and recoil like rubber bands. Connective tissue can stretch only so much before its thick, ropelike collagen fibers become taut. Then, when the tension lets up, elastic fibers snap the connective tissue back to its normal length and shape. Elastic fibers are found where greater elasticity is needed, for example, in the skin, lungs, and blood vessel walls. Because fresh elastic fibers appear yellow, they are sometimes called *yellow fibers*. (See the thin orange fibers in Figure 4.7.)

Reticular fibers are short, fine, collagenous fibers with a slightly different chemistry and form. They are continuous with

collagen fibers, and they branch extensively, forming delicate networks (*reticul* = network) that surround small blood vessels and support the soft tissue of organs. They are particularly abundant where connective tissue abuts other tissue types, for example, in the basement membrane of epithelial tissues, and around capillaries, where they form fuzzy "nets" that allow more "give" than the larger collagen fibers. (See the thin, dark blue fibers in Figure 4.7.)

Cells

Each major class of connective tissue has a fundamental or resident cell type that exists in immature and mature forms (see Table 4.1). The undifferentiated cells, indicated by the suffix *blast* (literally, "bud" or "sprout," but the suffix means "forming"), are actively mitotic cells that secrete the ground substance and the fibers characteristic of their particular matrix. As listed in the third column of Table 4.1, the primary blast cell types by connective tissue class are (1) connective tissue proper: **fibroblast**; (2) cartilage: **chondroblast** (kon′dro-blast″); and (3) bone: **osteoblast** (os′te-o-blast″). The **hematopoietic stem cell** (hem″ah-to-poy-et′ik), which is the undifferentiated blast cell that produces blood cells, is not included in Table 4.1

because it is not located in "its" tissue (blood) and does not make the fluid matrix (plasma) of that tissue. Blood formation is considered in Chapter 17.

Once they synthesize the matrix, the blast cells assume their less active, mature mode, indicated by the suffix *cyte*, also shown in Table 4.1, third column. The mature cells maintain the health of the matrix. However, if the matrix is injured, they can easily revert to their more active state to repair and regenerate the matrix. (The blood-forming hematopoietic stem cells found in bone marrow are always actively mitotic.)

Additionally, connective tissue is home to an assortment of other cell types, such as nutrient-storing *fat cells* and mobile cells that migrate into the connective tissue matrix from the bloodstream. These mobile cells include defensive **white blood cells** (neutrophils, eosinophils, lymphocytes) and other cell types concerned with tissue response to injury, such as *mast cells* and *macrophages* (mak′ro-fāj-es). This wide variety of cells is particularly obvious in our prototype, areolar connective tissue (Figure 4.7).

We describe all of these accessory cell types in later chapters, but mast cells and macrophages are so important to overall body defense that they deserve a brief mention here. The oval **mast cells** typically cluster along blood vessels. These cells act as sensitive sentinels to detect foreign microorganisms (e.g., bacteria, fungi) and initiate local inflammatory responses against them.

In the mast cell cytoplasm are conspicuous secretory granules (*mast* = stuffed full of granules) containing several chemicals that mediate inflammation, especially in severe allergies. These chemicals include (1) *heparin* (hep′ah-rin), an anticoagulant chemical that prevents blood clotting when free in the bloodstream (but in human mast cells it appears to bind to and regulate the action of other mast cell chemicals); (2) *histamine* (his′tah-mēn), a substance that makes capillaries leaky; and (3) *proteases* (protein-degrading enzymes) and various other enzymes.

Macrophages (*macro* = large; *phago* = eat) are large, irregularly shaped cells that avidly phagocytize a broad variety of foreign materials, ranging from foreign molecules to entire bacteria to dust particles. These "big eaters" also dispose of dead tissue cells, and they are central actors in the immune system. In connective tissues, they may be attached to connective tissue fibers (fixed) or may migrate freely through the matrix.

Macrophages are peppered throughout loose connective tissue, bone marrow, and lymphatic tissue. Those in certain sites are given specific names. For example, those in the liver are called Kupffer cells. Some macrophages have selective appetites. For example, those of the spleen primarily dispose of aging red blood cells, but they will not turn down other "delicacies" that come their way.

CHECK YOUR UNDERSTANDING

11. What are four functions of connective tissue?
12. What are the three types of fibers found in connective tissues?

For answers, see Appendix G.

Types of Connective Tissue

▶ Describe the types of connective tissue found in the body, and indicate their characteristic functions.

As noted, all classes of connective tissue consist of living cells surrounded by a matrix. Their major differences reflect cell type, and fiber types and relative amounts, as summarized in Table 4.1.

As mentioned earlier, mature connective tissues arise from a common embryonic tissue, called **mesenchyme** (meh′zin-kīm), derived from embryonic mesoderm (see Figure 4.13, p. 141). Mesenchyme has a fluid ground substance containing fine sparse fibers and star-shaped *mesenchymal cells*. It arises during the early weeks of embryonic development and eventually differentiates (specializes) into all other connective tissue cells. However, some mesenchymal cells remain and provide a source of new cells in mature connective tissues.

The connective tissues that we describe in the next sections are illustrated in **Figure 4.8**. Study the parts of this figure as you read along.

Connective Tissue Proper—Loose Connective Tissues

Connective tissue proper has two subclasses: the **loose connective tissues** (areolar, adipose, and reticular) and **dense connective tissues** (dense regular, dense irregular, and elastic). Except for bone, cartilage, and blood, all mature connective tissues belong to this class. Let's look first at the loose variety.

Areolar Connective Tissue   The functions of **areolar connective tissue**, shared by some but not all connective tissues, include (1) supporting and binding other tissues (the job of the fibers); (2) holding body fluids (the ground substance's role); (3) defending against infection (via the activity of white blood cells and macrophages); and (4) storing nutrients as fat (in fat cells) (Figure 4.8a).

Fibroblasts, flat, branching cells that appear spindle shaped in profile, predominate, but numerous macrophages are also seen and present a formidable barrier to invading microorganisms. Fat cells appear singly or in clusters, and occasional mast cells are identified easily by the large, darkly stained cytoplasmic granules that often obscure their nuclei. Other cell types are scattered throughout.

The most obvious structural feature of this tissue is the loose arrangement of its fibers. For this reason, its classification as a *loose* connective tissue is fitting. The rest of the matrix, occupied by ground substance, appears to be empty space when viewed through the microscope, and in fact, the Latin term *areola* means "a small open space." Because of its loose nature, areolar connective tissue provides a reservoir of water and salts for surrounding body tissues, always holding approximately as much fluid as there is in the entire bloodstream. Essentially all body cells obtain their nutrients from and release their wastes into this "tissue fluid."

The high content of hyaluronic acid makes its ground substance quite viscous, like molasses, which may hinder the movement of cells through it. Some white blood cells, which protect the body from disease-causing microorganisms, secrete the enzyme hyaluronidase to liquefy the ground substance and ease their passage. (Unhappily, some potentially harmful bacteria have the same

(a) Connective tissue proper: loose connective tissue, areolar

Description: Gel-like matrix with all three fiber types; cells: fibroblasts, macrophages, mast cells, and some white blood cells.

Function: Wraps and cushions organs; its macrophages phagocytize bacteria; plays important role in inflammation; holds and conveys tissue fluid.

Location: Widely distributed under epithelia of body, e.g., forms lamina propria of mucous membranes; packages organs; surrounds capillaries.

Epithelium

Lamina propria

Elastic fibers

Collagen fibers

Fibroblast nuclei
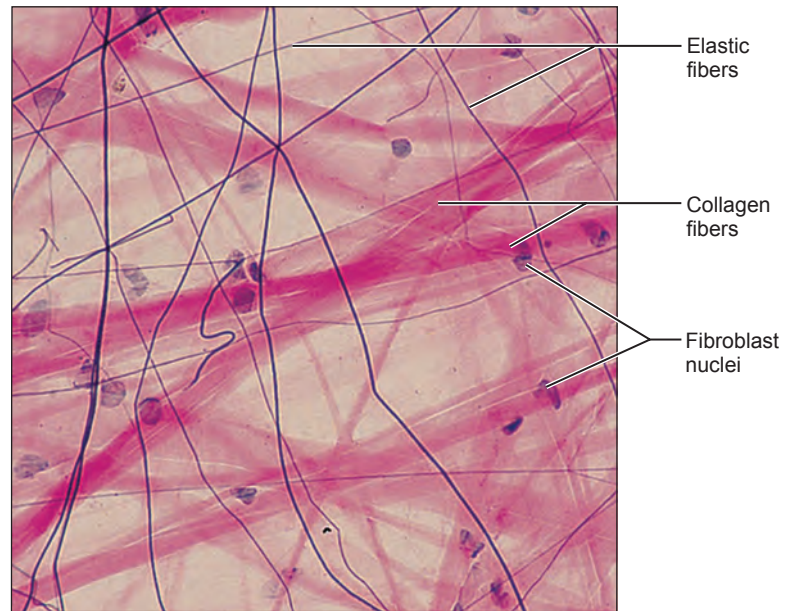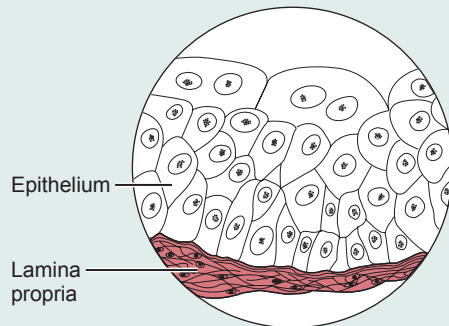
Photomicrograph: Areolar connective tissue, a soft packaging tissue of the body (300×).

Figure 4.8 Connective tissues. (a) Connective tissue proper. (See *A Brief Atlas of the Human Body*, Plate 11.)

ability.) When a body region is inflamed, the areolar tissue in the area soaks up excess fluids like a sponge, and the affected area swells and becomes puffy, a condition called **edema** (ĕ-de′mah).

Areolar connective tissue is the most widely distributed connective tissue in the body, and it serves as a kind of universal packing material between other tissues. It binds body parts together while allowing them to move freely over one another; wraps small blood vessels and nerves; surrounds glands; and forms the subcutaneous tissue, which cushions and attaches the skin to underlying structures. It is present in all mucous membranes as the *lamina propria*. (Mucous membranes line body cavities open to the exterior.)

Adipose (Fat) Tissue Adipose tissue (ad′ĭ-pōs) is similar to areolar tissue in structure and function, but its nutrient-storing ability is much greater. Consequently, **adipocytes** (ad′ĭ-po-sītz), commonly called *adipose* or *fat cells*, predominate and account for 90% of this tissue's mass. The matrix is scanty and the cells are packed closely together, giving a chicken-wire appearance to the tissue. A glistening oil droplet (almost pure triglyceride) occupies most of a fat cell's volume and displaces the nucleus to one side so that only a thin rim of surrounding cytoplasm is seen (Figure 4.8b). Mature adipocytes are among the largest cells in the body. As they take up or release fat, they become plumper or more wrinkled looking, respectively.

Adipose tissue is richly vascularized, indicating its high metabolic activity. Without the fat stores in our adipose tissue,

we could not live for more than a few days without eating. Adipose tissue is certainly abundant: It constitutes 18% of an average person's body weight, and a chubby person's body can be 50% fat without being considered morbidly obese.

Adipose tissue may develop almost anywhere areolar tissue is plentiful, but it usually accumulates in subcutaneous tissue, where it acts as a shock absorber, as insulation, and as an energy storage site. Because fat is a poor conductor of heat, it helps prevent heat loss from the body. Other sites where fat accumulates include surrounding the kidneys, behind the eyeballs, and at genetically determined fat depots such as the abdomen and hips.

The abundant fat beneath the skin serves the general nutrient needs of the entire body, and smaller depots of fat serve the local nutrient needs of highly active organs. Such depots occur around the hard-working heart and around lymph nodes (where cells of the immune system are furiously fighting infection), within some muscles, and as individual fat cells in the bone marrow, where new blood cells are produced at a rapid rate. Many of these local depots are highly enriched in special lipids.

The adipose tissue just described is sometimes called *white fat*, or *white adipose tissue*, to distinguish it from **brown fat**, or **brown adipose tissue**. White fat stores nutrients (mainly for other cells), but brown fat adipose cells contain abundant mitochondria, which use the lipid fuels to heat the bloodstream to warm the body (rather than to produce ATP molecules). The richly vascular brown fat occurs only in babies who (as yet) lack

4

(b) Connective tissue proper: loose connective tissue, adipose

Description: Matrix as in areolar, but very sparse; closely packed adipocytes, or fat cells, have nucleus pushed to the side by large fat droplet.

Function: Provides reserve food fuel; insulates against heat loss; supports and protects organs.

Location: Under skin in the hypodermis; around kidneys and eyeballs; within abdomen; in breasts.

Adipose tissue

Mammary glands
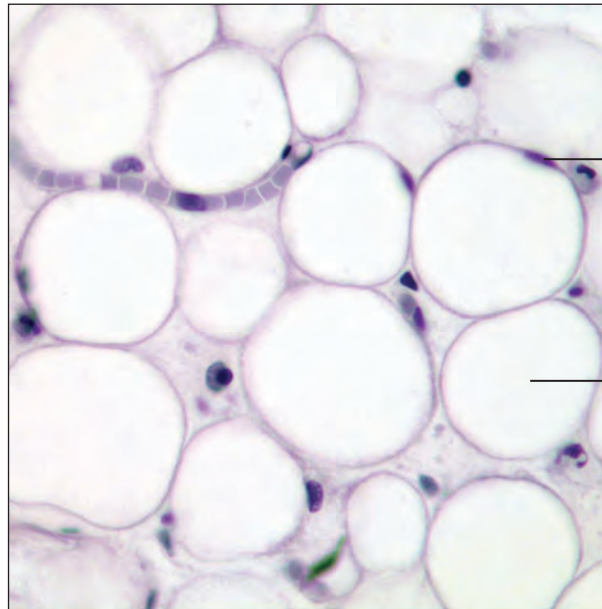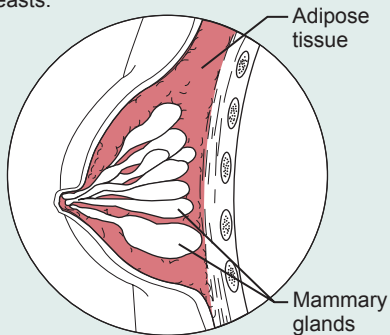
Nucleus of fat cell

Vacuole containing fat droplet

Photomicrograph: Adipose tissue from the subcutaneous layer under the skin (350×).

(c) Connective tissue proper: loose connective tissue, reticular

Description: Network of reticular fibers in a typical loose ground substance; reticular cells lie on the network.

Function: Fibers form a soft internal skeleton (stroma) that supports other cell types including white blood cells, mast cells, and macrophages.

Location: Lymphoid organs (lymph nodes, bone marrow, and spleen).
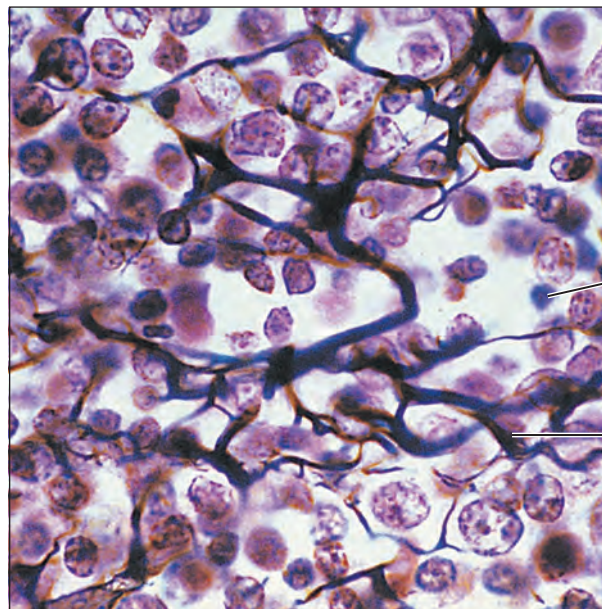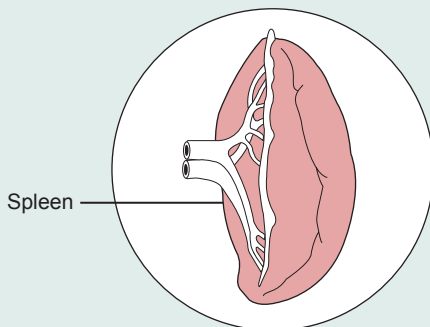
Spleen

White blood cell (lymphocyte)

Reticular fibers

Photomicrograph: Dark-staining network of reticular connective tissue fibers forming the internal skeleton of the spleen (350×).
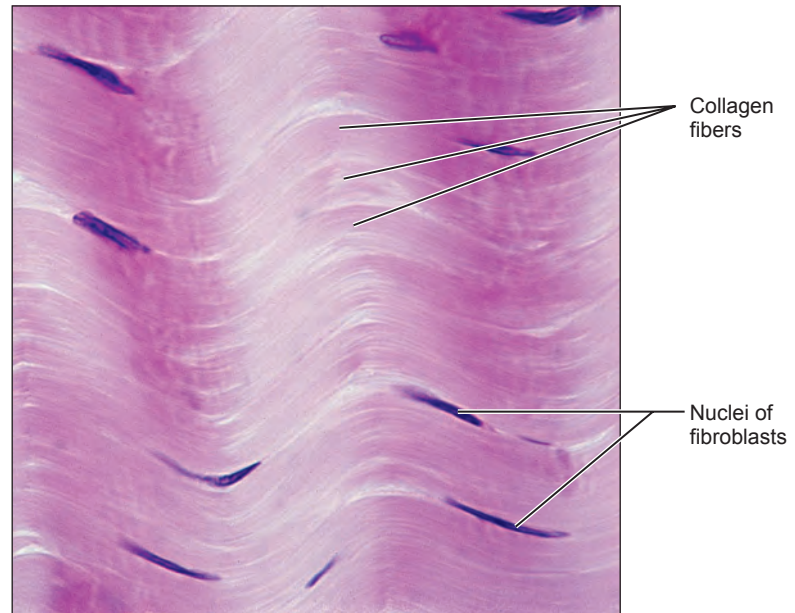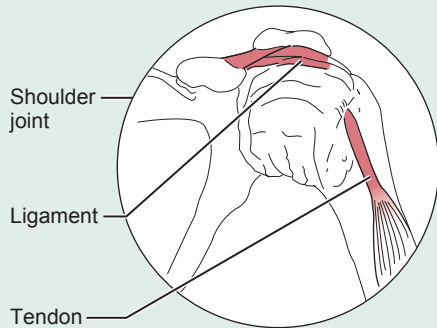
Figure 4.8 *(continued)* **Connective tissues. (b)** and **(c)** Connective tissue proper. (See *A Brief Atlas of the Human Body,* Plates 12 and 13.)

(d) Connective tissue proper: dense connective tissue, dense regular

Description: Primarily parallel collagen fibers; a few elastic fibers; major cell type is the fibroblast.

Function: Attaches muscles to bones or to muscles; attaches bones to bones; withstands great tensile stress when pulling force is applied in one direction.

Location: Tendons, most ligaments, aponeuroses.

Shoulder joint

Ligament

Tendon

Collagen fibers

Nuclei of fibroblasts

Photomicrograph: Dense regular connective tissue from a tendon (500×).

Figure 4.8 *(continued)* **(d)** Connective tissue proper. (See *A Brief Atlas of the Human Body*, Plate 15.)

the ability to produce body heat by shivering. Most such deposits are located between the shoulder blades, on the anterolateral neck, and on the anterior abdominal wall.

Reticular Connective Tissue **Reticular connective tissue** resembles areolar connective tissue, but the only fibers in its matrix are reticular fibers, which form a delicate network along which fibroblasts called **reticular cells** are scattered (Figure 4.8c). Although reticular *fibers* are widely distributed in the body, reticular *tissue* is limited to certain sites. It forms a labyrinth-like **stroma** (literally, "bed" or "mattress"), or internal framework, that can support many free blood cells (largely lymphocytes) in lymph nodes, the spleen, and bone marrow.

Connective Tissue Proper—Dense Connective Tissues

The three varieties of dense connective tissue have fibers as their prominent element. For this reason, the dense connective tissues are often referred to as **fibrous connective tissues**.

Dense Regular Connective Tissue **Dense regular connective tissue** contains closely packed bundles of collagen fibers running in the same direction, parallel to the direction of pull (Figure 4.8d). This arrangement results in white, flexible structures with great resistance to tension (pulling forces) where the tension is exerted in a single direction. Crowded between the

collagen fibers are rows of fibroblasts that continuously manufacture the fibers and scant ground substance.

As seen in Figure 4.8d, collagen fibers are slightly wavy. This allows the tissue to stretch a little, but once the fibers are straightened out by a pulling force, there is no further "give" to this tissue. Unlike our model (areolar) connective tissue, this tissue has few cells other than fibroblasts and is poorly vascularized.

With its enormous tensile strength, dense regular connective tissue forms the *tendons*, which are cords that attach muscles to bones, and flat, sheetlike tendons called *aponeuroses* (ap″o-nu-ro′sēz) that attach muscles to other muscles or to bones. It also forms fascia (fash′e-ah; "a bond"), a fibrous membrane that wraps around muscles, groups of muscles, blood vessels, and nerves, binding those structures together like plastic sandwich wrap; and the ligaments that bind bones together at joints. Ligaments contain more elastic fibers than tendons and are slightly more stretchy.
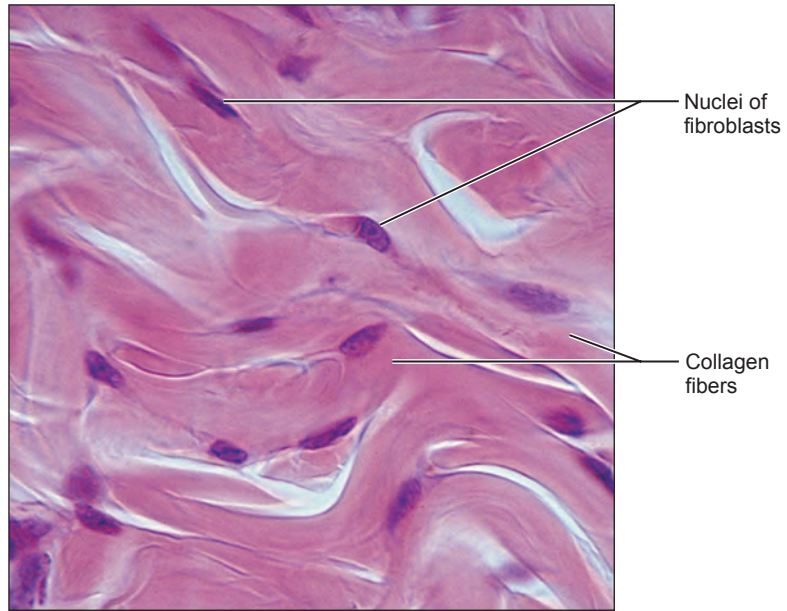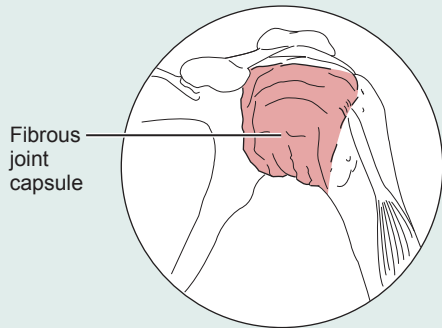
Dense Irregular Connective Tissue **Dense irregular connective tissue** has the same structural elements as the regular variety. However, the bundles of collagen fibers are much thicker and they are arranged irregularly; that is, they run in more than one plane (Figure 4.8e). This type of tissue forms sheets in body areas where tension is exerted from many different directions. It is found in the skin as the leathery *dermis*, and it forms fibrous joint capsules and the fibrous coverings that surround some organs (kidneys, bones, cartilages, muscles, and nerves).

(e) Connective tissue proper: dense connective tissue, dense irregular

Description: Primarily irregularly arranged collagen fibers; some elastic fibers; major cell type is the fibroblast.

Function: Able to withstand tension exerted in many directions; provides structural strength.

Location: Fibrous capsules of organs and of joints; dermis of the skin; submucosa of digestive tract.

Fibrous joint capsule

Nuclei of fibroblasts

Collagen fibers

Photomicrograph: Dense irregular connective tissue from the dermis of the skin (400×).

(f) Connective tissue proper: dense connective tissue, elastic

Description: Dense regular connective tissue containing a high proportion of elastic fibers.

Function: Allows recoil of tissue following stretching; maintains pulsatile flow of blood through arteries; aids passive recoil of lungs following inspiration.

Location: Walls of large arteries; within certain ligaments associated with the vertebral column; within the walls of the bronchial tubes.

Aorta

Heart

Elastic fibers
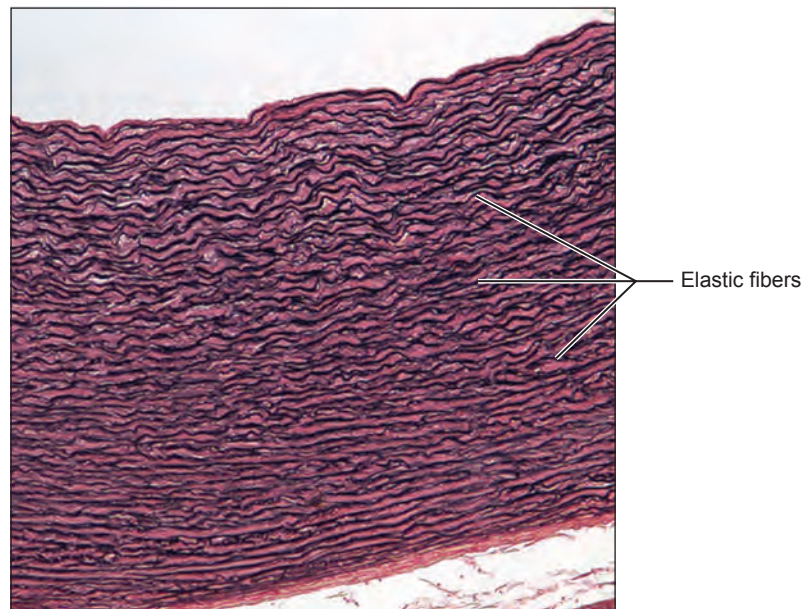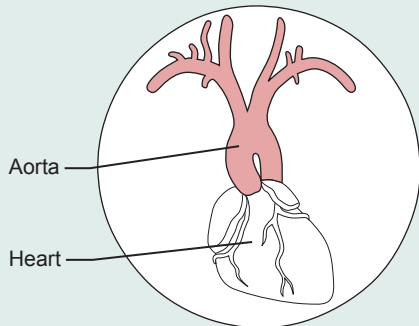
Photomicrograph: Elastic connective tissue in the wall of the aorta (250×).
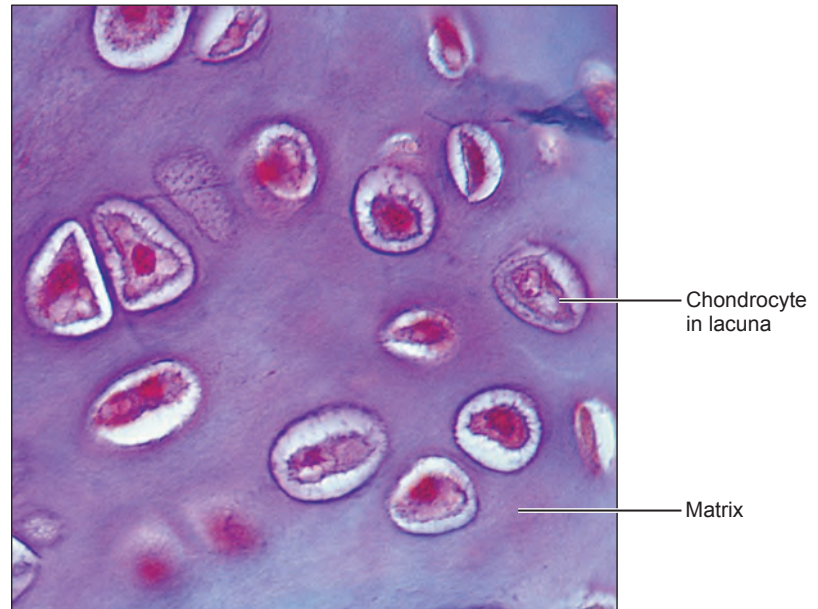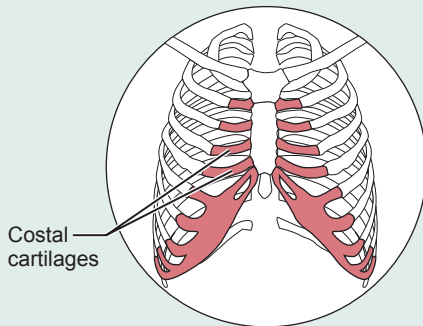
Figure 4.8 *(continued)* **Connective tissues. (e)** and **(f)** Connective tissue proper. (See *A Brief Atlas of the Human Body*, Plates 14 and 16.)

(g) Cartilage: hyaline

Description: Amorphous but firm matrix; collagen fibers form an imperceptible network; chondroblasts produce the matrix and when mature (chondrocytes) lie in lacunae.

Function: Supports and reinforces; has resilient cushioning properties; resists compressive stress.

Location: Forms most of the embryonic skeleton; covers the ends of long bones in joint cavities; forms costal cartilages of the ribs; cartilages of the nose, trachea, and larynx.

Costal cartilages

Chondrocyte in lacuna

Matrix

Photomicrograph: Hyaline cartilage from the trachea (750×).

Figure 4.8 *(continued)* **(g)** Cartilage. (See *A Brief Atlas of the Human Body*, Plate 17.)

Elastic Connective Tissue A few ligaments, such as the *ligamenta nuchae* and *flava* connecting adjacent vertebrae, are very elastic, so much so that the dense regular connective tissue in those structures is referred to more specifically as **elastic connective tissue** (Figure 4.8f).

Cartilage

Cartilage (kar′tĭ-lij), which stands up to both tension *and* compression, has qualities intermediate between dense connective tissue and bone. It is tough but flexible, providing a resilient rigidity to the structures it supports. Cartilage lacks nerve fibers and is avascular. It receives its nutrients by diffusion from blood vessels located in the connective tissue membrane (perichondrium) surrounding it. Its ground substance contains large amounts of the GAGs chrondroitin sulfate and hyaluronic acid, firmly bound collagen fibers (and in some cases elastic fibers), and is quite firm. Cartilage matrix also contains an exceptional amount of tissue fluid. In fact, cartilage is up to 80% water! The movement of tissue fluid in its matrix enables cartilage to rebound after being compressed and also helps to nourish the cartilage cells.

Chondroblasts, the predominant cell type in growing cartilage, produce new matrix until the skeleton stops growing at the end of adolescence. The firmness of the cartilage matrix prevents the cells from becoming widely separated, so **chondrocytes**, or mature cartilage cells, are typically found in small groups within cavities called *lacunae* (lah-ku′ne; "pits").

⚖ HOMEOSTATIC IMBALANCE

Because cartilage is avascular and aging cartilage cells lose their ability to divide, injured cartilages heal slowly. This phenomenon is excruciatingly familiar to those who have experienced sports injuries. During later life, cartilages tend to calcify or even ossify (become bony). In such cases, the chondrocytes are poorly nourished and die. ■

There are three varieties of cartilage: *hyaline cartilage*, *elastic cartilage*, and *fibrocartilage*, each dominated by a particular fiber type.

Hyaline Cartilage **Hyaline cartilage** (hi′ah-līn), or *gristle*, is the most abundant cartilage type in the body. Although it contains large numbers of collagen fibers, they are not apparent and the matrix appears amorphous and glassy (*hyalin* = glass) blue-white when viewed by the unaided eye (Figure 4.8g). Chondrocytes account for only 1–10% of the cartilage volume.

Hyaline cartilage provides firm support with some pliability. It covers the ends of long bones as *articular cartilage*, providing springy pads that absorb compression at joints. Hyaline cartilage also supports the tip of the nose, connects the ribs to the sternum, and supports most of the respiratory system passages. Most of the embryonic skeleton is formed of hyaline cartilage before bone is formed. Skeletal hyaline cartilage persists during childhood as the *epiphyseal plates* (e″pĭ-fis′e-ul), actively growing

(h) Cartilage: elastic

Description: Similar to hyaline cartilage, but more elastic fibers in matrix.

Function: Maintains the shape of a structure while allowing great flexibility.

Location: Supports the external ear (pinna); epiglottis.
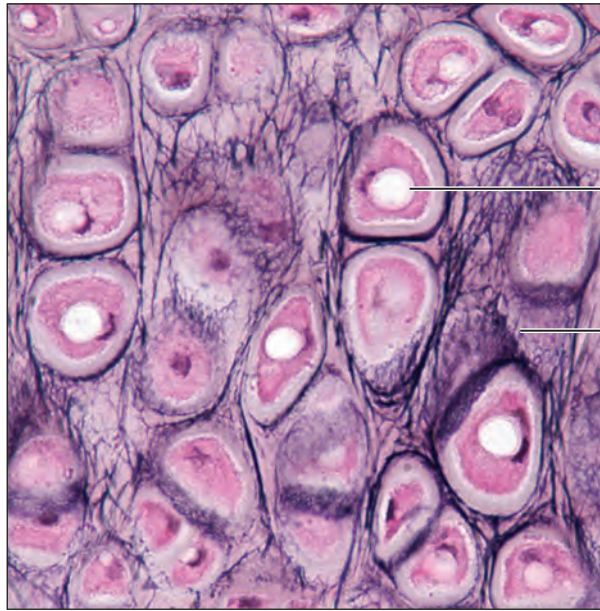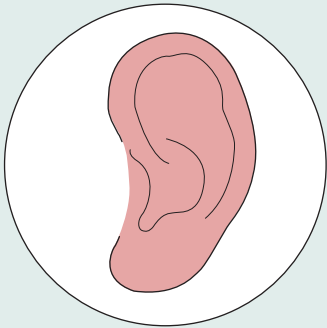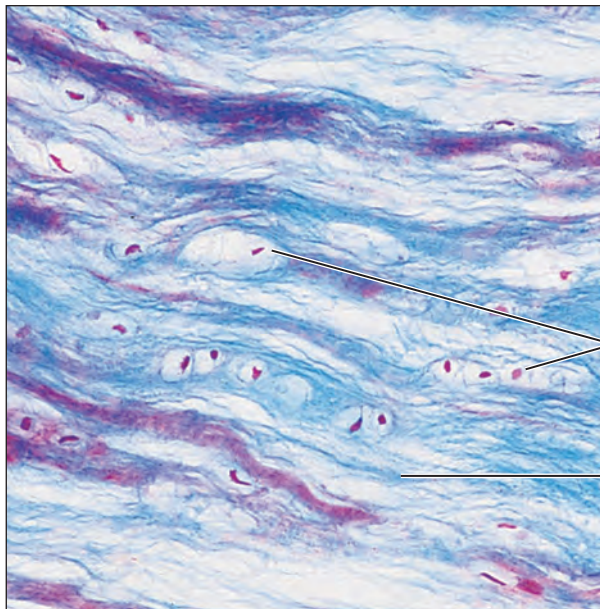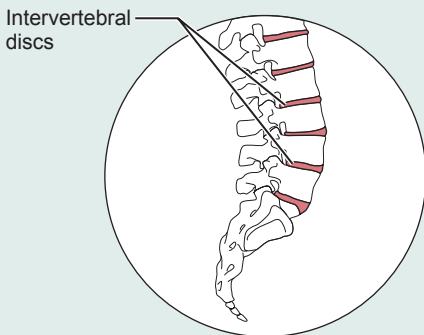

Chondrocyte in lacuna

Matrix

Photomicrograph: Elastic cartilage from the human ear pinna; forms the flexible skeleton of the ear (800×).

(i) Cartilage: fibrocartilage

Description: Matrix similar to but less firm than that in hyaline cartilage; thick collagen fibers predominate.

Function: Tensile strength with the ability to absorb compressive shock.

Location: Intervertebral discs; pubic symphysis; discs of knee joint.

Intervertebral discs

Chondrocytes in lacunae

Collagen fiber

**Photomicrograph:** Fibrocartilage of an intervertebral disc (125×). Special staining produced the blue color seen.

Figure 4.8 *(continued)* **Connective tissues. (h)** and **(i)** Cartilage. (See *A Brief Atlas of the Human Body*, Plates 18 and 19.)

(j) Others: bone (osseous tissue)

Description: Hard, calcified matrix containing many collagen fibers; osteocytes lie in lacunae. Very well vascularized.

Function: Bone supports and protects (by enclosing); provides levers for the muscles to act on; stores calcium and other minerals and fat; marrow inside bones is the site for blood cell formation (hematopoiesis).

Location: Bones

Central canal
Lacunae
Lamella
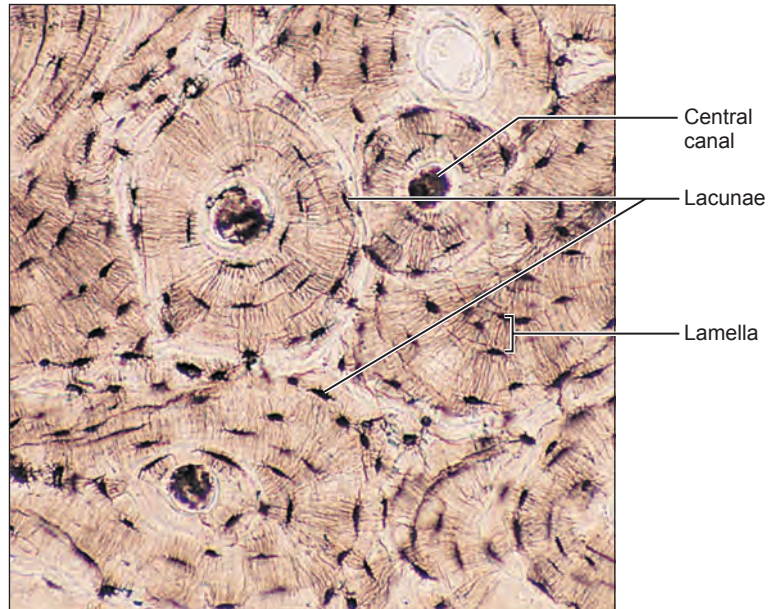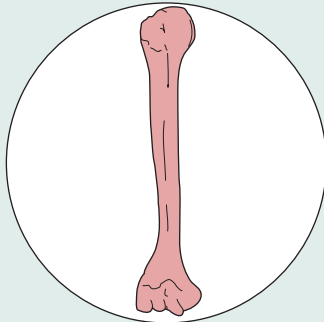
Photomicrograph: Cross-sectional view of bone (125×).

Figure 4.8 *(continued)* **(j)** Bone. (See *A Brief Atlas of the Human Body,* Plate 20.)

regions near the ends of long bones that provide for continued growth in length.

Elastic Cartilage   Histologically, **elastic cartilage** (Figure 4.8h) is nearly identical to hyaline cartilage. However, there are many more elastic fibers in elastic cartilage. Found where strength and exceptional stretchability are needed, elastic cartilage forms the "skeletons" of the external ear and the epiglottis. (The epiglottis is the flap that covers the opening to the respiratory passageway when we swallow, preventing food or fluids from entering the lungs.)

Fibrocartilage   **Fibrocartilage** is a perfect structural intermediate between hyaline cartilage and dense regular connective tissues. Its rows of chondrocytes (a cartilage feature) alternate with rows of thick collagen fibers (a feature of dense regular connective tissue) (Figure 4.8i). Because it is compressible and resists tension well, fibrocartilage is found where strong support and the ability to withstand heavy pressure are required. For example, the intervertebral discs (resilient cushions between the bony vertebrae) and the spongy cartilages of the knee (menisci) are fibrocartilage structures (see Figure 6.1, p. 174).

Bone (Osseous Tissue)

Because of its rocklike hardness, **bone**, or **osseous tissue** (os′e-us), has an exceptional ability to support and protect body structures. Bones of the skeleton also provide cavities for fat storage
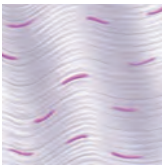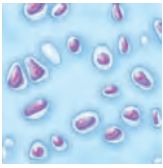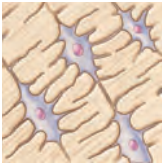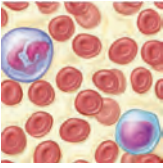
and synthesis of blood cells. Bone matrix is similar to that of cartilage but is harder and more rigid because, in addition to its more abundant collagen fibers, bone has an added matrix element—inorganic calcium salts (bone salts).

Osteoblasts produce the organic portion of the matrix, and then bone salts are deposited on and between the fibers. Mature bone cells, or **osteocytes**, reside in the lacunae within the matrix they have made (Figure 4.8j). In cross section, bone tissue is seen as closely packed structural units called *osteons* formed of concentric rings of bony matrix (lamellae) surrounding central canals containing the blood vessels and nerves serving the bone. Unlike cartilage, the next firmest connective tissue, bone is well supplied by invading blood vessels.

Blood

Blood, the fluid within blood vessels, is the most atypical connective tissue. It does *not* connect things or give mechanical support. It is classified as a connective tissue because it develops from mesenchyme and consists of *blood cells*, surrounded by a nonliving fluid matrix called *blood plasma* (Figure 4.8k). The vast majority of blood cells are red blood cells or erythrocytes, but scattered white blood cells (neutrophils, lymphocytes, monocytes, eosinophils, basophils) are also seen. The "fibers" of blood are soluble protein molecules that precipitate, forming visible fiberlike structures during blood clotting. Blood functions as the transport vehicle for the cardiovascular system, carrying nutrients, wastes, respiratory gases, and many other substances throughout the body.

TABLE 4.1	Comparison of Classes of Connective Tissues			

		COMPONENTS		
TISSUE CLASS AND EXAMPLE	**SUBCLASSES**	**CELLS**	**MATRIX**	**GENERAL FEATURES**
Connective Tissue Proper *Dense regular connective tissue*	1. Loose connective tissue ▪ Areolar ▪ Adipose ▪ Reticular 2. Dense connective tissue ▪ Regular ▪ Irregular ▪ Elastic	Fibroblasts Fibrocytes Defense cells Fat cells	Gel-like ground substance All three fiber types: collagen, reticular, elastic	Six different types; vary in density and types of fibers Functions as a binding tissue Resists mechanical stress, particulary tension
Cartilage *Hyaline cartilage*	1. Hyaline cartilage 2. Elastic cartilage 3. Fibrocartilage	Chondroblasts found in growing cartilage Chondrocytes	Gel-like ground substance Fibers: collagen, elastic fibers in some	Resists compression because of the large amounts of water held in the matrix Functions to cushion and support body structures
Bone Tissue *Compact bone*	1. Compact bone 2. Spongy bone	Osteoblasts Osteocytes	Gel-like ground substance calcified with inorganic salts Fibers: collagen	Hard tissue that resists both compression and tension Functions in support
Blood	Blood cell formation and differentiation are quite complex. Details are provided in Chapter 17.	Erythrocytes (RBC) Leukocytes (WBC) Platelets	Plasma No fibers	A fluid tissue Functions to carry O_2, CO_2, nutrients, wastes, and other substances (hormones, for example)

CHECK YOUR UNDERSTANDING

13. Which connective tissue has a soft weblike matrix capable of serving as a fluid reservoir?

14. What type of connective tissue is damaged when you lacerate your index finger tendon?

15. John wants to become a professional basketball player. Unfortunately he is short for his age and his epiphyseal plates have already fused. What type of connective tissue forms the epiphyseal plates?

For answers, see Appendix G.

Nervous Tissue

▶ Indicate the general characteristics of nervous tissue.

Nervous tissue is the main component of the nervous system—the brain, spinal cord, and nerves—which regulates and controls body functions. It contains two major cell types. **Neurons** are highly specialized nerve cells that generate and conduct nerve impulses **(Figure 4.9)**. Typically, they are branching cells with cytoplasmic extensions or processes. Their processes allow them to (1) respond to stimuli (a role of the processes called *dendrites*) and (2) to transmit electrical impulses over substantial distances within the body (the job of *axons*, which may be very long and myelinated, that is,

(k) Others: blood

Description: Red and white blood cells in a fluid matrix (plasma).

Function: Transport of respiratory gases, nutrients, wastes, and other substances.

Location: Contained within blood vessels.

Plasma

Neutrophil

Red blood cells
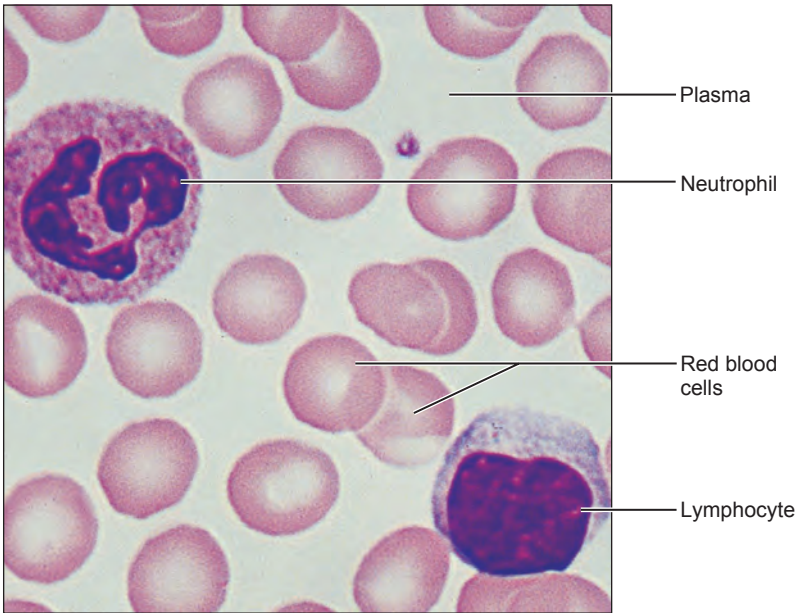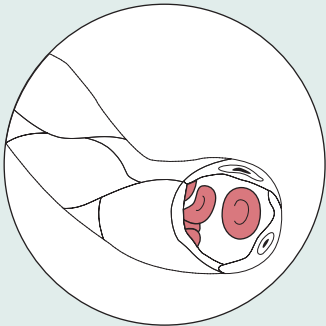
Lymphocyte

Photomicrograph: Smear of human blood (1860×); two white blood cells (neutrophil in upper left and lymphocyte in lower right) are seen surrounded by red blood cells.

Figure 4.8 *(continued)* **Connective tissues. (k)** Blood. (See *A Brief Atlas of the Human Body,* Plates 22–27.)
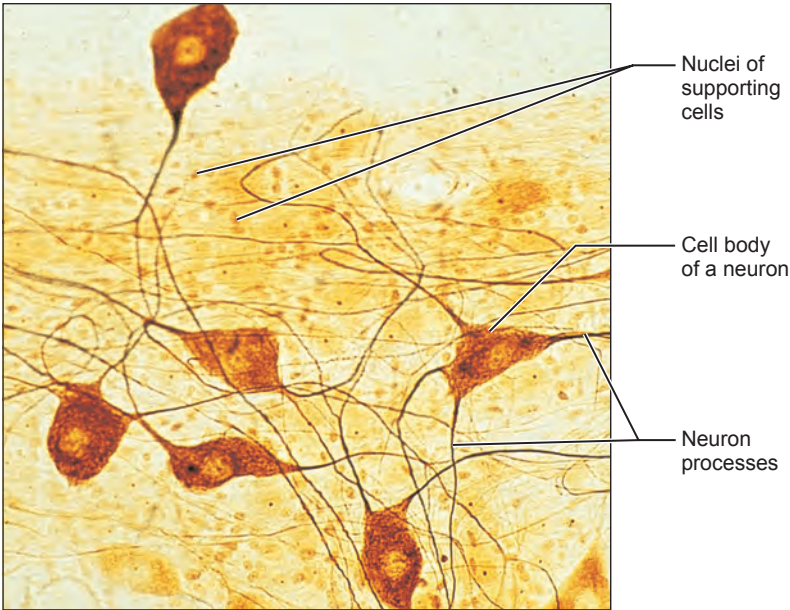
Nervous tissue

Description: Neurons are branching cells; cell processes that may be quite long extend from the nucleus-containing cell body; also contributing to nervous tissue are nonirritable supporting cells (not illustrated).

Neuron processes   Cell body

Axon   Dendrites
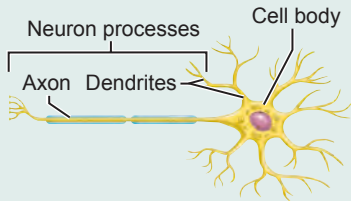
Function: Transmit electrical signals from sensory receptors and to effectors (muscles and glands) which control their activity.

Location: Brain, spinal cord, and nerves.

Nuclei of supporting cells

Cell body of a neuron

Neuron processes

Photomicrograph: Neurons (350×)

Figure 4.9 **Nervous tissue.** (See *A Brief Atlas of the Human Body,* Plate 33.)
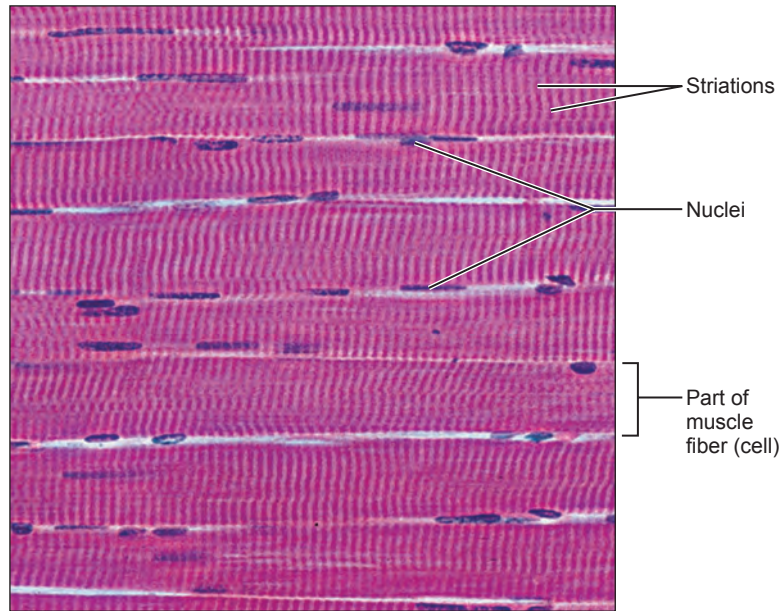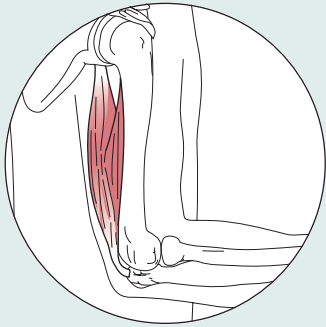
(a) Skeletal muscle

Description: Long, cylindrical, multinucleate cells; obvious striations.

Function: Voluntary movement; locomotion; manipulation of the environment; facial expression; voluntary control.

Location: In skeletal muscles attached to bones or occasionally to skin.

Striations

Nuclei

Part of muscle fiber (cell)

Photomicrograph: Skeletal muscle (approx. 460×). Notice the obvious banding pattern and the fact that these large cells are multinucleate.

Figure 4.10 Muscle tissues. (a) Skeletal muscle tissue. (See *A Brief Atlas of the Human Body,* Plate 28.)

covered with a fatty sheath that increases the speed of nerve transmission). The balance of nervous tissue consists of various types of supporting cells, nonconducting cells that support, insulate, and protect the delicate neurons. A more complete discussion of nervous tissue appears in Chapter 11.

Muscle Tissue

▶ Compare and contrast the structures and body locations of the three types of muscle tissue.

Muscle tissues are highly cellular, well-vascularized tissues that are responsible for most types of body movement. Muscle cells possess **myofilaments**, elaborate versions of the *actin* and *myosin* filaments that bring about movement or contraction in all cell types. There are three kinds of muscle tissue: skeletal, cardiac, and smooth.

 Skeletal muscle tissue is packaged by connective tissue sheets into organs called *skeletal muscles* that are attached to the bones of the skeleton. These muscles form the flesh of the body, and as they contract, they pull on bones or skin, causing body movements. Skeletal muscle cells, also called **muscle fibers**, are long, cylindrical cells that contain many nuclei. Their obvious banded, or *striated*, appearance reflects the precise alignment of their myofilaments **(Figure 4.10a)**.

 Cardiac muscle is found only in the walls of the heart. Its contractions help propel blood through the blood vessels to all parts of the body. Like skeletal muscle cells, cardiac muscle cells are striated. However, they differ structurally in that cardiac cells (1) are generally uninucleate and (2) are branching cells that fit together tightly at unique junctions called **intercalated discs** (in-ter′kah-la″ted) (Figure 4.10b).

 Smooth muscle is so named because its cells have no visible striations. Individual smooth muscle cells are spindle shaped and contain one centrally located nucleus (Figure 4.10c). Smooth muscle is found mainly in the walls of hollow organs other than the heart (digestive and urinary tract organs, uterus, and blood vessels). It acts to squeeze substances through these organs by alternately contracting and relaxing.

 Because skeletal muscle contraction is under our conscious control, skeletal muscle is often called **voluntary muscle**, and the other two types are called **involuntary muscle**. We describe skeletal muscle and smooth muscle in detail in Chapter 9, and cardiac muscle in Chapter 18.

CHECK YOUR UNDERSTANDING

16. How does the extended length of a neuron's processes aid its function in the body?
17. You are looking at muscle tissue through the microscope and you see striped branching cells that connect with one another. What type of muscle are you viewing?
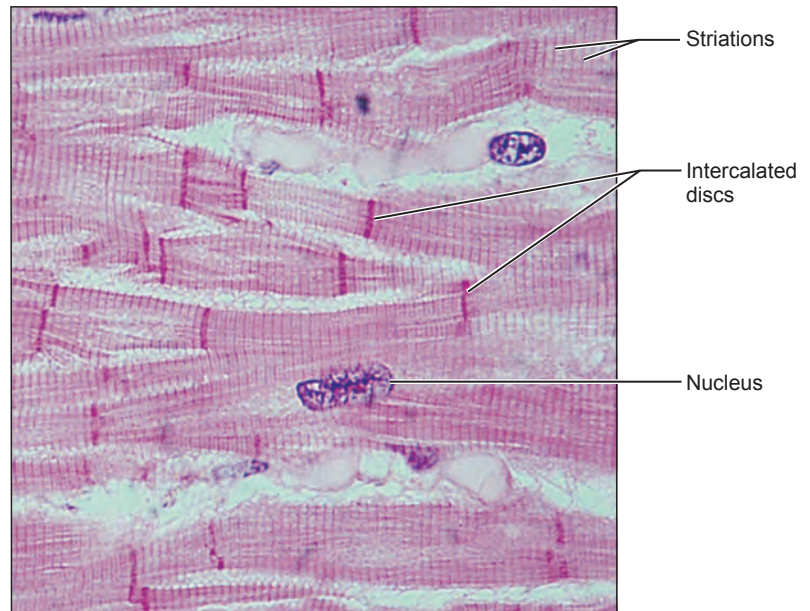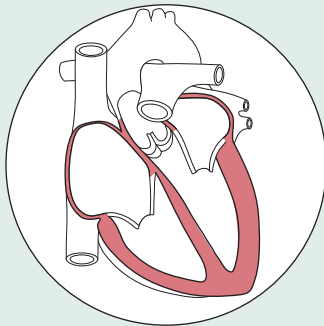
(b) Cardiac muscle

Description: Branching, striated, generally uninucleate cells that interdigitate at specialized junctions (intercalated discs).
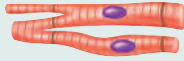
Function: As it contracts, it propels blood into the circulation; involuntary control.

Location: The walls of the heart.

Striations

Intercalated discs

Nucleus

Photomicrograph: Cardiac muscle (500×); notice the striations, branching of cells, and the intercalated discs.

(c) Smooth muscle

Description: Spindle-shaped cells with central nuclei; no striations; cells arranged closely to form sheets.
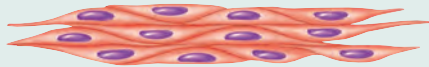
Function: Propels substances or objects (foodstuffs, urine, a baby) along internal passageways; involuntary control.

Location: Mostly in the walls of hollow organs.

Smooth muscle cell

Nuclei
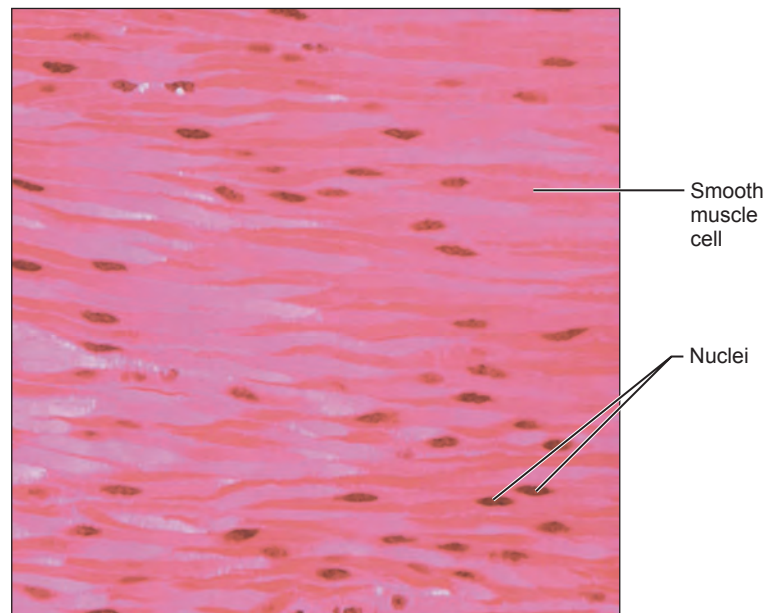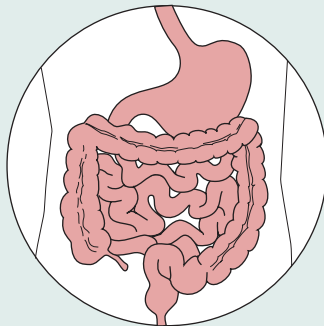
Photomicrograph: Sheet of smooth muscle (200×).

Figure 4.10 *(continued)* **(b)** Cardiac muscle tissue. (See *A Brief Atlas of the Human Body*, Plate 31.) **(c)** Smooth muscle tissue. (See *A Brief Atlas of the Human Body*, Plate 32.)

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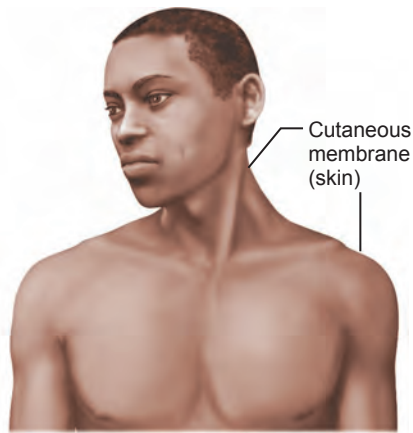
(a) **Cutaneous membrane (the skin) covers the body surface.**

Cutaneous membrane (skin)

Mucosa of nasal cavity

Mucosa of mouth

Esophagus lining

Mucosa of lung bronchi

(b) **Mucous membranes line body cavities open to the exterior.**

Parietal peritoneum

Visceral peritoneum
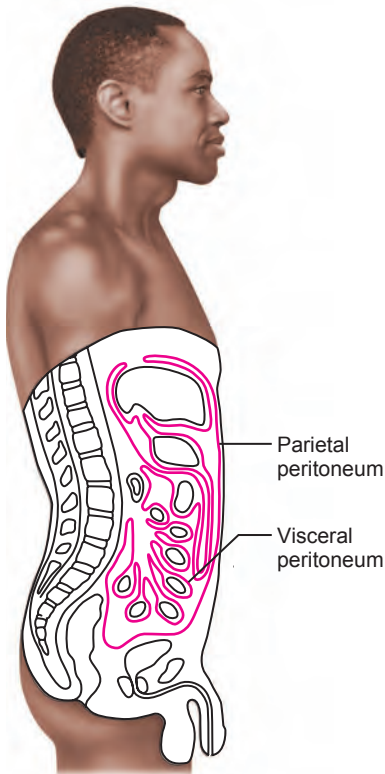
(c) **Serous membranes line body cavities closed to the exterior.**

Parietal pleura

Visceral pleura

Parietal pericardium   Visceral pericardium
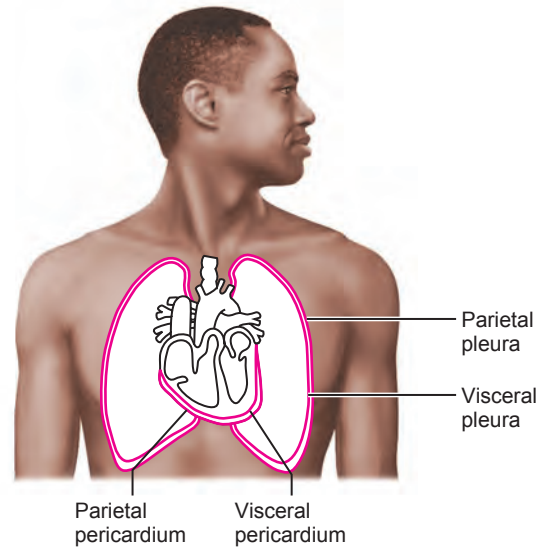
Figure 4.11 Classes of membranes.

18. Which muscle type(s) is voluntary? Injured when you pull a muscle while exercising?

For answers, see Appendix G.

Covering and Lining Membranes

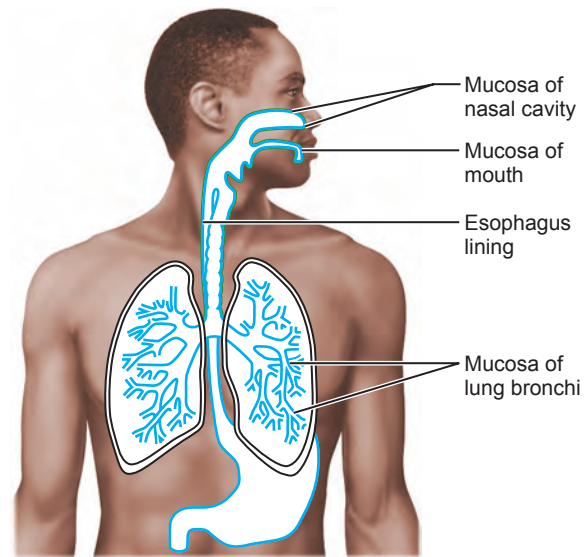▶ Describe the structure and function of cutaneous, mucous, and serous membranes.

Now that we have described all four primary tissues, we can consider the body's membranes that incorporate more than one type of tissue. The covering and lining membranes are of three types: *cutaneous*, *mucous*, or *serous*. Essentially they all are continuous multicellular sheets composed of at least two primary tissue types: an epithelium bound to an underlying layer of connective tissue proper. Hence, these membranes are simple organs. We describe the *synovial membranes*, which line joint cavities and consist of connective tissue only, in Chapter 8.

Cutaneous Membrane

The **cutaneous membrane** (ku-ta′ne-us; *cutis* = skin) is your skin **(Figure 4.11a)**. It is an organ system consisting of a keratinized stratified squamous epithelium (epidermis) firmly attached to a thick layer of dense irregular connective tissue (dermis). Unlike other epithelial membranes, the cutaneous membrane is exposed to the air and is a dry membrane. Chapter 5 is devoted to this unique organ system.

Mucous Membranes

Mucous membranes, or **mucosae** (mu-ko′se), line body cavities that open to the exterior, such as those of the hollow organs of the digestive, respiratory, and urogenital tracts (Figure 4.11b). In all cases, they are "wet," or moist, membranes bathed by secretions or, in the case of the urinary mucosa, urine. Notice that the term *mucosa* refers to the location of the membrane, *not* its cell composition, which varies. However, most mucosae contain either stratified squamous or simple columnar epithelia. The epithelial sheet is directly underlain by a layer of loose connective tissue called the **lamina propria** (lam′ĭ-nah pro′pre-ah; "one's own layer"). In some mucosae, the lamina propria rests on a third (deeper) layer of smooth muscle cells.

Mucous membranes are often adapted for absorption and secretion. Although many mucosae secrete mucus, this is not a requirement. The mucosae of both the digestive and respiratory tracts secrete copious amounts of lubricating mucus, but that of the urinary tract does not.

Serous Membranes

Serous membranes, or **serosae** (se-ro′se), introduced in Chapter 1, are the moist membranes found in closed ventral body cavities (Figure 4.11c). A serous membrane consists of simple squamous epithelium (a mesothelium) resting on a thin layer of loose connective (areolar) tissue. The mesothelial cells add hyaluronic acid to the fluid that filters from the capillaries in the associated connective tissue. The result is the thin, clear *serous fluid* that lubricates the facing surfaces of the parietal and visceral layers, so that they slide across each other easily.

The serosae are named according to their site and specific organ associations. For example, the serosa lining the thoracic wall and covering the lungs is the **pleura**; that enclosing the heart is the **pericardium**; and those of the abdominopelvic cavity and viscera are the **peritoneums**.

CHECK YOUR UNDERSTANDING

19. What type of membrane consists of epithelium and connective tissue, and lines body cavities open to the exterior?

20. What type of membrane lines the thoracic walls and covers the lungs, and what is it called?

For answers, see Appendix G.

Tissue Repair

▶ Outline the process of tissue repair involved in normal healing of a superficial wound.

The body has many techniques for protecting itself from uninvited "guests" or injury. Intact mechanical barriers such as the skin and mucosae, the cilia of epithelial cells lining the respiratory tract, and the strong acid (chemical barrier) produced by stomach glands represent three defenses exerted at the body's external boundaries.

When tissue injury occurs, these barriers are penetrated. This stimulates the body's inflammatory and immune responses, which wage their battles largely in the connective tissues of the body. The *inflammatory response* is a relatively nonspecific reaction that develops quickly wherever tissues are injured, while the *immune response* is extremely specific, but takes longer to swing into action. We consider the inflammatory and immune responses in detail in Chapter 21.

Steps of Tissue Repair

Tissue repair requires that cells divide and migrate, activities that are initiated by growth factors (wound hormones) released by injured cells. Repair occurs in two major ways: by regeneration and by fibrosis. Which of these occurs depends on (1) the type of tissue damaged and (2) the severity of the injury. **Regeneration** is replacement of destroyed tissue with the same kind of tissue, whereas **fibrosis** involves proliferation of fibrous connective tissue called **scar tissue**. In skin, the tissue we will use as our example, repair involves both activities. **Figure 4.12** illustrates the following steps in tissue repair.

① **Inflammation sets the stage**. Tissue injury sets inflammatory events into motion. First, the tissue trauma causes injured tissue cells, macrophages, mast cells, and others to release inflammatory chemicals, which cause the capillaries to dilate and become very permeable. This allows white blood cells (neutrophils, monocytes) and plasma fluid rich in clotting proteins, antibodies, and other substances to seep into the injured area. The leaked clotting proteins construct a clot, which stops the loss of blood, holds the edges of the wound together, and effectively walls in, or isolates, the injured area, preventing bacteria, toxins, or other harmful substances from spreading to surrounding tissues. The part of the clot exposed to air quickly dries and hardens, forming a *scab*. The inflammatory events leave behind excess fluid, bits of destroyed cells, and other debris, which are eventually removed via lymphatic vessels or phagocytized by macrophages.

② **Organization restores the blood supply**. Even while the inflammatory process is going on, the first phase of tissue repair, called **organization**, begins. During organization the blood clot is replaced by granulation tissue. **Granulation tissue** is a delicate pink tissue composed of several elements. It contains capillaries that grow in from nearby areas and lay down a new capillary bed. Granulation tissue is actually named for these capillaries, which protrude nublike from its surface, giving it a granular appearance. These capillaries are
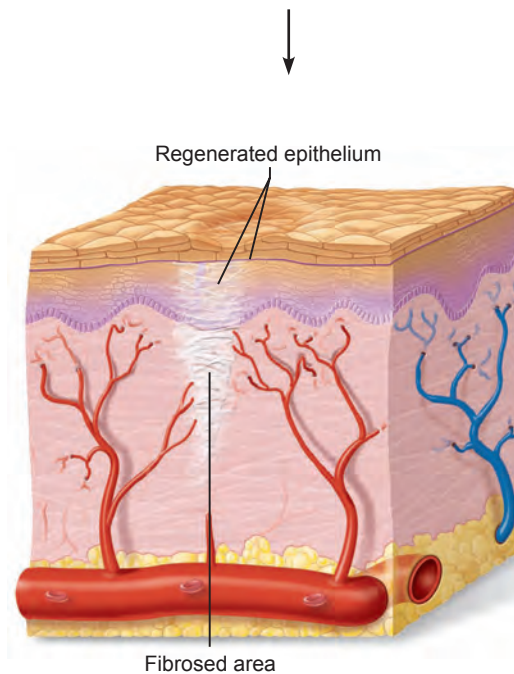
4
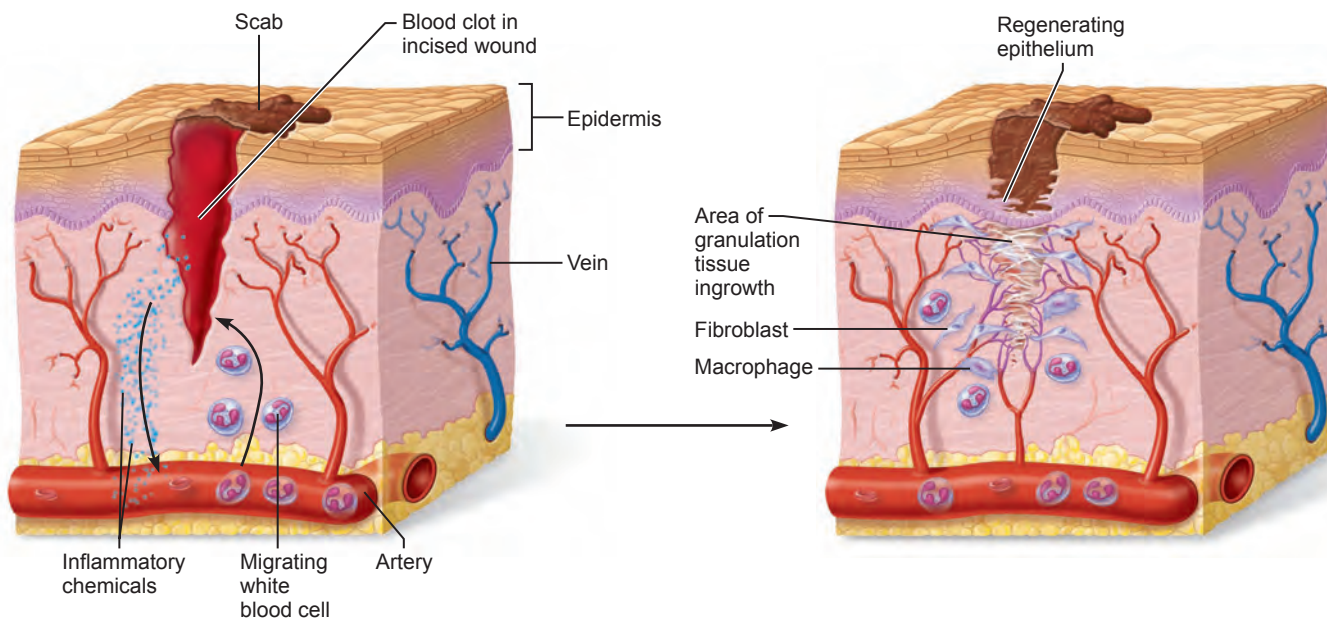
1 **Inflammation sets the stage:**
- Severed blood vessels bleed and inflammatory chemicals are released.
- Local blood vessels become more permeable, allowing white blood cells, fluid, clotting proteins and other plasma proteins to seep into the injured area.
- Clotting occurs; surface dries and forms a scab.

2 **Organization restores the blood supply:**
- The clot is replaced by granulation tissue, which restores the vascular supply.
- Fibroblasts produce collagen fibers that bridge the gap.
- Macrophages phagocytize cell debris.
- Surface epithelial cells multiply and migrate over the granulation tissue.

fragile and bleed freely, as we see when someone picks at a scab. Proliferating fibroblasts in granulation tissue produce growth factors as well as new collagen fibers to bridge the gap. Some of these fibroblasts have contractile properties that pull the margins of the wound together. As organization proceeds, macrophages digest the original blood clot and collagen fiber deposit continues. The granulation tissue, destined to become scar tissue (a permanent fibrous patch), is highly resistant to infection because it produces bacteria-inhibiting substances. As a rule, wound healing is a self-limited response. Once enough matrix has accumulated in the injured area, the fibroblasts either revert to the resting stage or undergo apoptosis.

3 **Regeneration and fibrosis effect permanent repair**. During organization, the surface epithelium begins to *regenerate,* growing under the scab, which soon detaches. As the fibrous tissue beneath matures and contracts, the regenerating epithelium thickens until it finally resembles that of the adjacent skin. The end result is a fully regenerated epithelium, and an underlying area of scar tissue. The scar may be invisible, or visible as a thin white line, depending on the severity of the wound.

The repair process that we have just described follows healing of a wound (cut, scrape, puncture) that breaches an epithelial barrier. In simple *infections* (a pimple or sore throat), healing is solely by regeneration. There is usually no clot formation or scarring. Only severe (destructive) infections lead to scarring.

3 **Regeneration and fibrosis effect permanent repair:**
- The fibrosed area matures and contracts; the epithelium thickens.
- A fully regenerated epithelium with an underlying area of scar tissue results.

Figure 4.12 **Tissue repair of a nonextensive skin wound: regeneration and fibrosis.**

Regenerative Capacity of Different Tissues

The different tissues vary widely in their capacity for regeneration. Epithelial tissues, bone, areolar connective tissue, dense irregular connective tissue, and blood-forming tissue regenerate extremely well. Smooth muscle and dense regular connective tissue have a moderate capacity for regeneration, but skeletal muscle and cartilage have a weak regenerative capacity. Cardiac muscle and the nervous tissue in the brain and spinal cord have virtually no *functional* regenerative capacity, and they are routinely replaced by scar tissue. However, recent studies have shown that some unexpected (and highly selective) cellular division occurs in both these tissues after damage, and efforts are under way to coax them to regenerate better.

In nonregenerating tissues and in exceptionally severe wounds, fibrosis totally replaces the lost tissue. Over a period of months, the fibrous mass shrinks and becomes more and more compact. The resulting scar appears as a pale, often shiny area composed mostly of collagen fibers. Scar tissue is strong, but it lacks the flexibility and elasticity of most normal tissues. Also, it cannot perform the normal functions of the tissue it has replaced.

HOMEOSTATIC IMBALANCE

Scar tissue that forms in the wall of the urinary bladder, heart, or other muscular organ may severely hamper the function of that organ. The normal shrinking of the scar reduces the internal volume of an organ and may hinder or even block movement of substances through a hollow organ. Scar tissue hampers muscle's ability to contract and may interfere with its normal excitation by the nervous system. In the heart, these problems may lead to progressive heart failure. In irritated visceral organs, particularly following abdominal surgery, *adhesions* may form as the newly forming scar tissue connects adjacent organs together. Such adhesions can prevent the normal shifting about (churning) of loops of the intestine, dangerously obstructing the flow of foodstuffs through it. Adhesions can also restrict heart movements and immobilize joints. ■

CHECK YOUR UNDERSTANDING

21. What are the three main steps of tissue repair?
22. Why does a deep injury to the skin result in abundant scar tissue formation?

For answers, see Appendix G.

Developmental Aspects of Tissues

▶ Indicate the embryonic origin of each tissue class.
▶ Briefly describe tissue changes that occur with age.

One of the first events of embryonic development is the formation of the three **primary germ layers**, which lie one atop the next like a three-layered cellular pancake. From superficial to deep, these layers are the **ectoderm**, **mesoderm** (mez′o-derm), and **endoderm**. As shown in **Figure 4.13**, these primary germ layers then specialize to form the four primary tissues—epithelium, nervous tissue, muscle, and connective tissues—that make up all body organs.

By the end of the second month of development, the primary tissues have appeared, and all major organs are in place. In general, tissue cells remain mitotic and produce the rapid growth that occurs before birth. The division of nerve cells, however, stops or nearly stops during the fetal period. After birth, the cells of most other tissues continue to divide until adult body size is achieved. Cellular division then slows greatly,
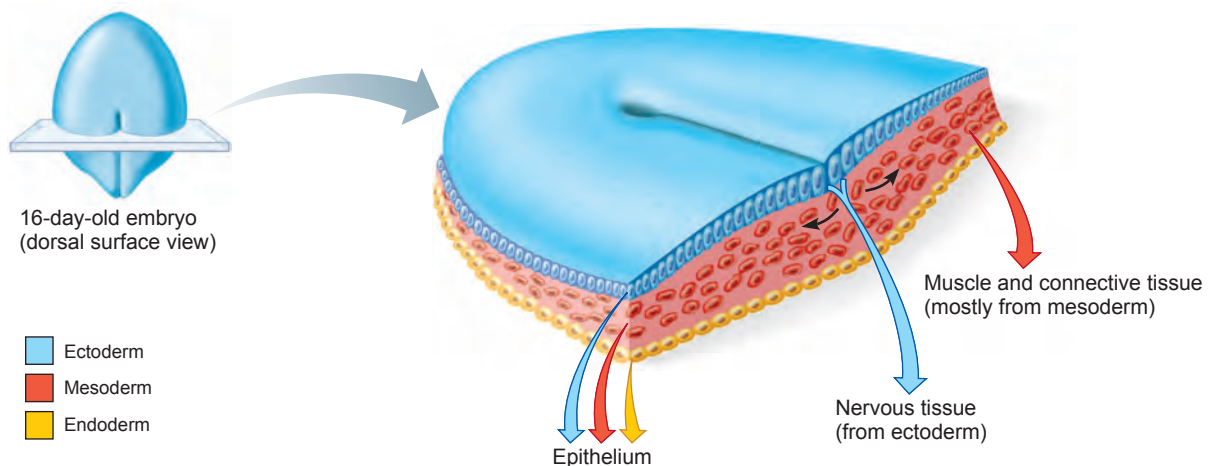
Figure 4.13 Embryonic germ layers and the primary tissue types they produce. The three embryonic layers collectively form the very early embryonic body.

A CLOSER LOOK
Cancer—The Intimate Enemy

The word *cancer* elicits dread in everyone. Why does cancer strike some and not others?

Although once perceived as disorganized cell growth, this disease is now known to be a logical, coordinated process in which a precise sequence of tiny alterations changes a normal cell into a killer. Let's take a closer look at what cancer really is.

When cells fail to follow normal controls of cell division and multiply excessively, an abnormal mass of proliferating cells called a **neoplasm** (ne′o-plazm, "new growth") results. Neoplasms are classified as **benign** ("kindly") or **malignant** ("bad"). A benign neoplasm is strictly a local affair. Its cells remain compacted, are often encapsulated, tend to grow slowly, and seldom kill their hosts if removed before they compress vital organs.

In contrast, cancers are malignant neoplasms, nonencapsulated masses that grow relentlessly and may become killers. Their cells resemble immature cells, and they invade their surroundings rather than pushing them aside, as reflected in the name *cancer*, from the Latin word for "crab." Whereas normal cells become fatally "homesick" and die when they lose contact with the surrounding matrix, malignant cells tend to break away from the parent mass, the primary tumor, and travel via blood or lymph to other body organs, where they form *secondary cancer masses.*

This capability for traveling to other parts of the body, called **metastasis** (mě-tas′tah-sis), probably has a lot to do with signaling molecules and the cell-surface glycoproteins the cancer cells bear. Metastasis and invasiveness distinguish cancer cells from the cells of benign neoplasms. Cancer cells consume an exceptional amount of the body's nutrients, leading to weight loss and tissue wasting that contribute to death.

Carcinogenesis
Autopsies on individuals aged 50–70 who died of another cause have revealed that most of us have microscopic (but dormant) in situ neoplasms. So what causes a normal cell to **transform** or change into a cancerous one? Some physical factors (radiation, mechanical trauma), certain viral infections, chronic inflammations, and many chemicals (tobacco tars, saccharine, some natural food chemicals) can act as

carcinogens (cancer-causers). What do these factors have in common? They all cause *mutations*—changes in DNA that alter the expression of certain genes. However, not all carcinogens do damage because most are eliminated by peroxisomal or lysosomal enzymes or by the immune system. Furthermore, one mutation usually isn't enough. It takes several genetic changes to transform a normal cell into a cancerous cell.

A clue to the role of genes in cancer was provided by the discovery of **oncogenes** (Greek *onco* = tumor), or cancer-causing genes, in rapidly spreading cancers. **Proto-oncogenes**, benign forms of oncogenes in normal cells, were discovered later. Proto-oncogenes code for proteins that are essential for cell division, growth, and cellular adhesion, among other things. Many have fragile sites that break when exposed to carcinogens, converting them to oncogenes. Failure to code for certain proteins may lead to loss of an enzyme that controls an important metabolic process. Oncogenes may also "switch on" dormant genes that allow cells to become invasive and metastasize. Known oncogenes now number over 100.

Oncogenes have been detected in only 15–20% of human cancers, so investigators were not too surprised by the discovery of **tumor suppressor genes**, or **anti-oncogenes**, which suppress cancer by inactivating carcinogens, aiding DNA repair, or enhancing the immune system's counterattack. In fact, over half of all cancers involve malfunction or loss of just 2 of the 15 identified tumor suppressor genes—*p53* and *p16*. This is not surprising when you learn that *p53* prompts most cells to make proteins that stop cell division in stressed cells by promoting apoptosis or cell cycle arrest. Its impairment invites uncontrolled division and cancer.

Furthermore, although each type of cancer is genetically distinct, human cancers appear to share a common master set of genes—an activated group of 67 genes—and almost all cancer cells have gained or lost entire chromosomes. Whatever genetic factors are at work, the "seeds" of cancer do appear to be in our own genes. Cancer is an intimate enemy indeed.

The illustration depicts some of the mutations involved in colorectal cancer, one of the best-understood human cancers.

As with most cancers, a metastasis develops gradually. One of the first signs is a polyp, a small benign growth consisting of apparently normal mucosa cells. As cell division continues, the growth enlarges, becoming an adenoma (a term for any neoplasm of glandular epithelium). As various tumor suppressor genes are inactivated and the *K-ras* oncogene is mobilized, the mutations pile up and the adenoma becomes increasingly abnormal. The final consequence is colon carcinoma, a form of cancer that metastasizes quickly.

Cancer Prevalence
Almost half of all Americans develop cancer in their lifetime and a fifth of us will die of it. Cancer can arise from almost any cell type, but the most common cancers originate in the skin, lung, colon, breast, and prostate gland. Although stomach and colon cancer incidence is down, skin and lymphoid cancer rates are up.

Many cancers are preceded by observable lumps or other structural changes in tissue—for instance, *leukoplakia*, white patches in the mouth caused by the chronic irritation of ill-fitting dentures or heavy smoking. Although these lesions sometimes progress to cancer, in many cases they remain stable or even revert to normal if the environmental stimulus is removed.

Diagnosis and Staging
Screening procedures are vital for early detection. Examples include *mammography* (X-ray examination of the breasts)*,* examining breasts or testicles for lumps, and checking fecal samples for blood. Unfortunately, most cancers are diagnosed only after symptoms have already appeared. In this case the diagnostic method is usually a **biopsy**: removing a tissue sample surgically and examining it microscopically for malignant cells. Increasingly, diagnosis is made by chemical or genetic analysis of the sample. Typing cancer cells by what genes are switched on or off tells clinicians which drugs to use. For example, taxol, quite successful with breast and ovarian cancer, works only against tumors with a specific genetic makeup.

Several techniques (physical and histological examinations, lab tests, and imaging techniques [MR, CT]) are used to determine the extent of the disease (size

of the neoplasm, degree of metastasis, etc.). Then, the cancer is assigned a **stage** from 1 to 4 according to the probability of cure (stage 1 has the best probability, stage 4 the worst).

Cancer Treatments

Most cancers are removed surgically if possible. To destroy metastasized cells, surgery is commonly followed by radiation therapy (X irradiation and/or treatment with radioisotopes) and chemotherapy (treatment with cytotoxic drugs). Recently, some oncologists have been using heat therapy (just a slight upward temperature change) to put the cancer cells on the "cliff's edge," so that they are sensitized and much more vulnerable to chemotherapy or radiation.

Chemotherapy is beset with the problem of resistance. Some cancer cells can eject the drugs in tiny bubbles or flattened vesicles dubbed exosomes, and these cells proliferate, forming new tumors that are invulnerable to chemotherapy. Furthermore, anticancer drugs have unpleasant side effects—nausea, vomiting, hair loss—because they kill all rapidly dividing cells, including normal tissue cells. The anticancer drugs also can severely damage the brain, producing a phenomenon called chemobrain—a mental fuzziness and memory loss reported by many cancer patients. X rays also have side effects because, in passing through the body, they destroy healthy tissue in their path as well as cancer cells.

Promising New Therapies

Traditional cancer treatments—"cut, burn, and poison"—are widely recognized as crude and painful. Promising new therapies focus on

- *Targeted drugs that interrupt the signaling pathways that fuel the cancer's growth*. Examples include imatinib (Gleevec), which incapacitates a mutated enzyme that triggers uncontrolled division of cells in two rare blood and digestive system cancers, and trastuzumab (Herceptin), used to treat breast cancer patients. These drugs have been strikingly successful in providing a few extra weeks of life, before their protective effects wear off and the disease progresses again.
- *Delivering drugs or radiation more precisely to the cancer while sparing normal tissue.* One approach is to inject the patient with tiny drug-coated metal

beads, which are guided to the tumor by a powerful magnet positioned over the body site. Or, a patient might take light-sensitive drugs that are drawn naturally into rapidly dividing cancer cells. Then, exposure to certain frequencies of laser light sets off reactions that kill the malignant cells. Another new procedure, proton therapy, delivers highly targeted killing doses of protons (radiation) that strike at cancer cells with incredible precision and with greater effectiveness than traditional X rays. Unlike X rays, which pass through the cancer and onward through the patient's body, protons can be slowed down and even directed to stop in the neoplasm.

- *Using genetically modified immune cells to target cancer cells*. One promising technique harvests a patient's most aggressive cancer-killing immune cells (T lymphocytes), inserts modified genes into them that make them even more efficient killers, multiplies the cells in the lab, and then infuses the immune cells back into the patient.
- *Using drugs that target cancer cell bioenergetics*. The fact that many cancers use glucose as their energy fuel almost exclusively has suggested a pharmaceutical approach that limits glucose use. In theory, this approach would kill cancer cells while sparing normal cells, which can also use amino acids and fats as energy fuels.

Other experimental treatments seek to starve cancer cells by cutting off their blood supply, fix defective tumor suppressor genes and oncogenes, destroy cancer cells with viruses, or signal cancer cells to commit suicide by apoptosis. Additionally, a cancer vaccine (TRICOM) contains genetically engineered viruses carrying genes for a cancer protein called carcinoembryonic antigen (CEA). When these proteins are delivered into the patient's body, they stimulate an immune response that orchestrates an attack on all CEA-bearing cancer cells.

At present, about half of all cancer cases are cured. Although average survival
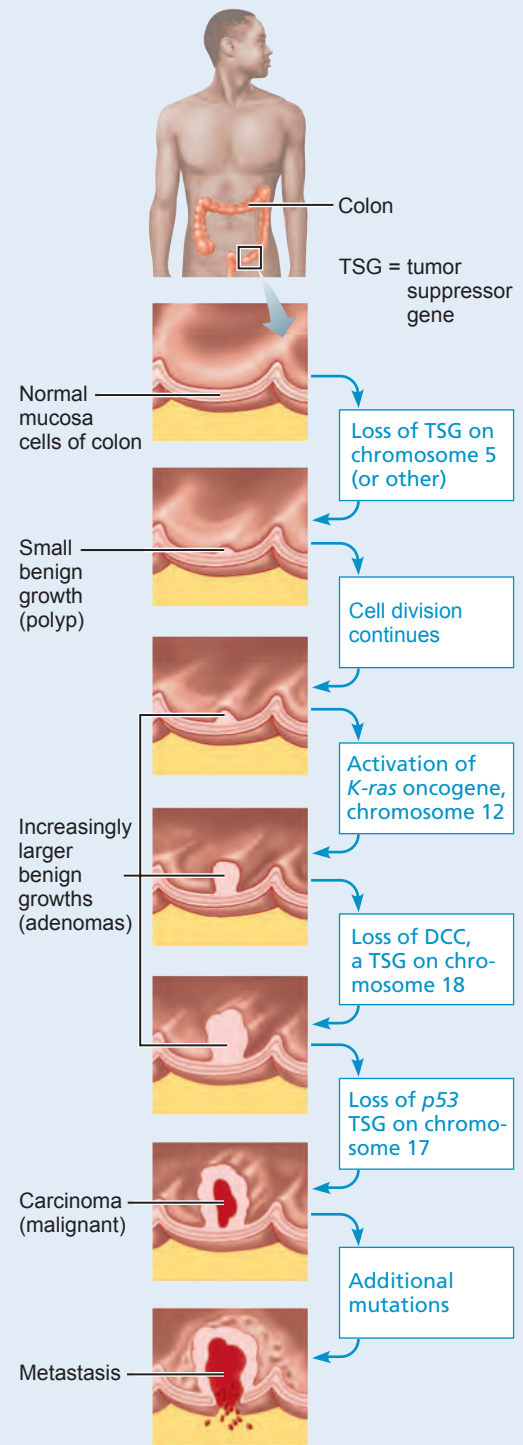
Some of the mutations involved in the development of colon cancer.

rates have not increased, the quality of life of cancer patients has improved in the last decade. We can offer better treatments for cancer-associated pain, and antinausea drugs and other helpful medicines can soothe the side effects of chemotherapy.

although many tissues retain the ability to regenerate. In adults, only epithelia and blood-forming tissues are highly mitotic. Some tissues that regenerate through life, such as the glandular cells of the liver, do so through division of their mature (specialized) cells. Others, like the epidermis of the skin and cells lining the intestine, have abundant *stem cells,* relatively undifferentiated cells that divide as necessary to produce new cells.

Given good nutrition, good circulation, and relatively infrequent wounds and infections, our tissues normally function efficiently through youth and middle age. But with increasing age, epithelia thin and are more easily breached. Tissue repair is less efficient, and bone, muscle, and nervous tissues begin to atrophy, particularly when a person is not physically active. These events are due partly to decreased circulatory efficiency, which reduces delivery of nutrients to the tissues, but in some cases, diet is a contributing factor. As income declines or as chewing becomes more difficult, older people tend to eat soft foods, which may be low in protein and vitamins. As a result, tissue health suffers.

Another problem of aging tissues is the likelihood of DNA mutations in the most actively mitotic cells, which increases the risk of cancer (as indicated in *A Closer Look* on p. 142).

CHECK YOUR UNDERSTANDING

23. What are the names of the three embryonic germ layers?
24. Which germ layer gives rise to the nervous system?
25. Which two tissue types remain highly mitotic throughout life?

For answers, see Appendix G.

As we have seen, body cells combine to form four discrete tissue types: epithelial, connective, muscle, and nervous tissues. The cells making up each of these tissues share certain features but are by no means identical. They "belong" together because they have basic functional similarities. The connective tissues assume many guises, but perhaps the most versatile cells are those of epithelium: They protect our outer and inner surfaces, permit us to obtain oxygen, absorb vital nutrients into the blood, and allow our kidneys to excrete wastes. The important concept to carry away with you is that tissues, despite their unique abilities, cooperate to keep the body safe, healthy, and whole.

RELATED CLINICAL TERMS

Adenoma (ad″ĕ-no′mah; *aden* = gland, *oma* = tumor) Any neoplasm of glandular epithelium, benign or malignant. The malignant type is more specifically called *adenocarcinoma.*

Autopsy (aw′top-se) Examination of the body, its organs, and its tissues after death to determine the actual cause of death; also called postmortem examination and necropsy.

Carcinoma (kar″sĭ-no′mah; *karkinos* = crab, cancer) Cancer arising in an epithelium; accounts for 90% of human cancers.

Healing by first intention The simplest type of healing; occurs when the edges of the wound are brought together by sutures, staples, or other means used to close surgical incisions. Only small amounts of granulation tissue need be formed.

Healing by second intention The wound edges remain separated, and the gap is bridged by relatively large amounts of granulation tissue; the manner in which unattended wounds heal. Healing is slower than in wounds in which the edges are brought together, and larger scars result.

Keloid (ke′loid) Abnormal proliferation of connective tissue during healing of skin wounds; results in large, unsightly mass of scar tissue at the skin surface.

Lesion (le′zhun; "wound") Any injury, wound, or infection that affects tissue over an area of a definite size (as opposed to being widely spread throughout the body).

Marfan's syndrome Genetic disease resulting in abnormalities of connective tissues due to a defect in fibrillin, a protein that is associated with elastin in elastic fibers. Clinical signs include loose-jointedness, long limbs and spiderlike fingers and toes, visual problems, and weakened blood vessels (especially the aorta) due to poor connective tissue reinforcement.

Pathology (pah-thol′o-je) Scientific study of changes in organs and tissues produced by disease.

Pus A collection of tissue fluid, bacteria, dead and dying tissue cells, white blood cells, and macrophages in an inflamed area.

Sarcoma (sar-ko′mah; *sarkos* = flesh; *oma* = tumor) Cancer arising in the mesenchyme-derived tissues, that is, in connective tissues and muscle.

Scurvy A nutritional deficiency caused by lack of adequate vitamin C needed to synthesize collagen; signs and symptoms include blood vessel disruption, delay in wound healing, weakness of scar tissue, and loosening of teeth.

VAC (vacuum-assisted closure) Innovative healing process for open-skin wounds and skin ulcers. Often induces healing when all other methods fail. Involves covering the wound with a special sponge, and then applying suction through the sponge. In response to the subsequent skin stretching, fibroblasts in the wound form more collagen tissue and new blood vessels proliferate, bringing more blood into the injured area, which also promotes healing.