

23

Learn to Predict

Flashing lights at 2 a.m. alerted the neighbors that something was wrong at the Theron home. Mr. Theron, who has moderate emphysema, could not stop coughing, so his wife called 911. In the emergency room, a physician listened to Mr. Theron's respiratory sounds and concluded that his left lung had collapsed. **Explain how emphysema affected Mr. Theron's breathing, what caused his lung to collapse, and how the physician was able to detect the collapsed lung.**

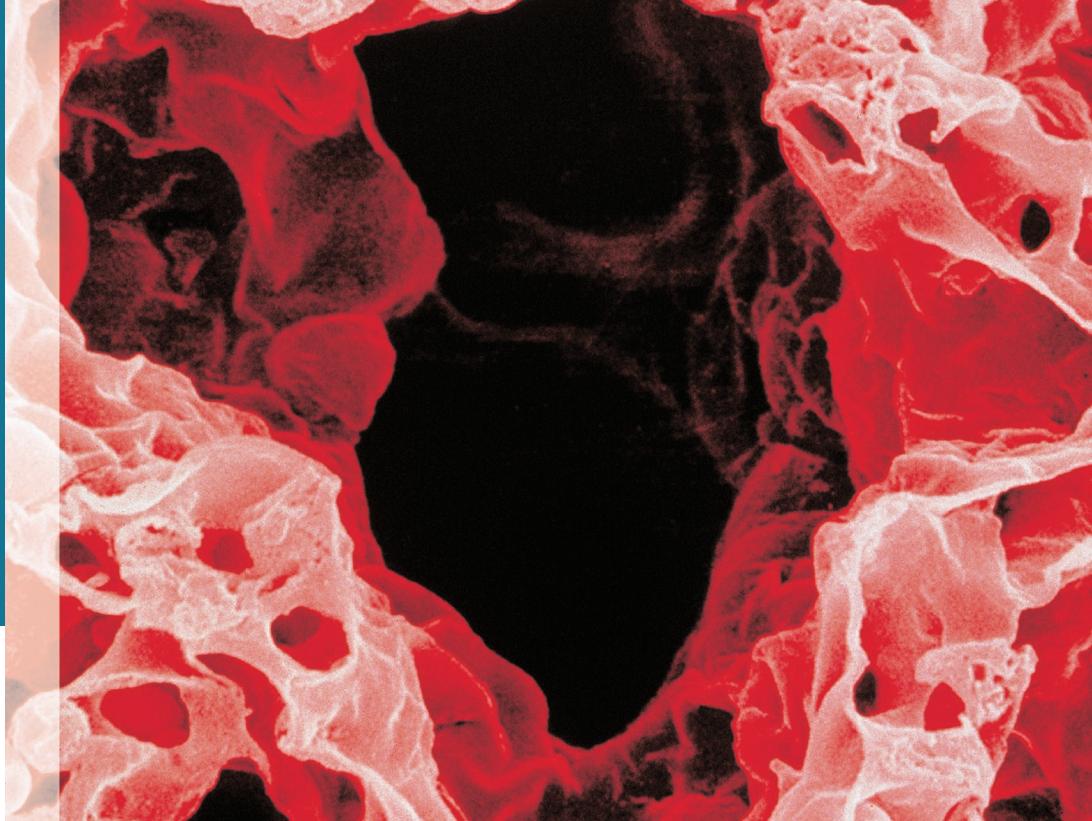


Photo: Colorized scanning electron micrograph of the lung, showing alveoli, which are small air chambers where gas exchange takes place between the air and the blood. ©David Phillips/Science Source

Respiratory System

If you've ever had a severe chest cold, bronchitis, or pneumonia, you might be able to relate to what Mr. Theron of this chapter's "Learn to Predict" experienced when his left lung collapsed. If we stop breathing, or breathing becomes difficult, within seconds we feel a strong need for air. From our first breath at birth, the rate and depth of our breathing are unconsciously matched to our activities, whether studying, sleeping, talking, eating, or exercising. Breathing is so characteristic of life that, along with the pulse, it is one of the first vital signs checked to determine whether an unconscious person is alive.

Breathing is necessary because all living cells of the body require oxygen and produce carbon dioxide. The respiratory system exchanges these gases between the air and the blood, and the cardiovascular system transports them between the lungs and the body cells. Without healthy respiratory and cardiovascular systems, the capacity to carry out normal activity is reduced.

23.1 Anatomy of the Respiratory System

LEARNING OUTCOMES

After reading this section, you should be able to

- List the structures that compose the respiratory system.
- Describe the structural and functional anatomy of the respiratory system.

The respiratory system consists of the structures used to acquire oxygen (O_2) and remove carbon dioxide (CO_2) from the blood. Oxygen is required for the body's cells to synthesize the chemical energy molecule, ATP. Carbon dioxide is a by-product of ATP production and must be removed from the blood. Otherwise, increased levels of CO_2 will lower the pH of the blood. The blood pH must be maintained within relatively narrow limits to maintain homeostasis.

There are seven structures that make up the respiratory system (figure 23.1). They include the following:

- External nose.* The external nose encloses the chamber for air inspiration. Although air can be inspired through the mouth, the mouth is part of the digestive system rather than the respiratory system.
- Nasal cavity.* The nasal cavity is a cleaning, warming, and humidifying chamber for inspired air.
- Pharynx.* The pharynx is commonly called the throat. It serves as a common passageway for food and air.

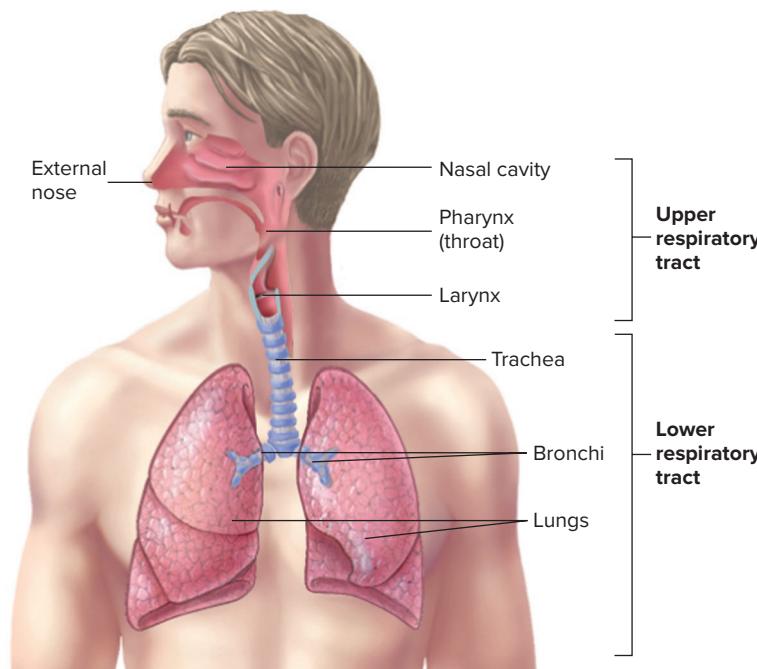


FIGURE 23.1 Respiratory System

The upper respiratory tract consists of the external nose, the nasal cavity, the pharynx (throat) and its associated structures, and the larynx. The lower respiratory tract consists of the trachea, the bronchi and smaller bronchioles, and the lungs.

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- Larynx.* The larynx is frequently called the voice box. Its rigid structure helps keep the airway constantly open, or patent.
- Trachea.* The trachea is commonly known as the windpipe. It serves as an air-cleaning tube to funnel inspired air to each lung.
- Bronchi.* The bronchi are tubes that direct air into the lungs.
- Lungs.* Each lung is a labyrinth of air tubes and a complex network of air sacs, called alveoli, and capillaries. The air sacs are separated by walls of connective tissue containing both collagenous and elastic fibers. Each air sac is the site of gas exchange between the air and the blood.

In this chapter, we will discuss the detailed anatomy of each component of the respiratory system and the mechanisms that control breathing and gas exchange.

ASSESS YOUR PROGRESS

Answers to these questions are found in the section you have just completed. Re-read the section if you need help in answering these questions.

- List the components of the respiratory system.

23.2 Functions of the Respiratory System

LEARNING OUTCOME

After reading this section, you should be able to

- Describe the functions of the respiratory system.

Respiration, or what we call breathing, is critical for homeostasis. There are two broad aspects of respiration: (1) **ventilation**, which is simply movement of air into and out of the lungs, and (2) **respiration**, which is the diffusion of gases across plasma membranes. There are two major types of respiration within the body: (1) **pulmonary respiration**, or *external respiration*, which is the movement of gases between atmospheric air in the lungs and the blood, and (2) **systemic respiration**, or *internal respiration*, which is the movement of gases between the blood and the body's cells.

Ventilation and respiration occur in different regions of the respiratory tract. Commonly the respiratory tract is separated into two regions: (1) the **upper respiratory tract**, which includes the structures from the nose to the larynx, and (2) the **lower respiratory tract**, which includes the structures from trachea through the alveoli in the lungs. Infections of the upper respiratory tract are among the top five reasons patients in the United States see their doctor. The upper and lower respiratory tract can be further subdivided between structures used strictly for ventilation and structures used for respiration. The **conducting zone** encompasses the structures from the nose to the smallest air tubes within the lungs and is strictly for ventilation. The **respiratory zone** is solely within the lungs and includes some specialized small air tubes and the alveoli. Gas exchange occurs within the respiratory zone.

For the respiratory system to accomplish gas exchange between the air and the blood, there are four simultaneous processes:

1. *Ventilation.* This is what we more commonly refer to as breathing. Air moves into and out of the respiratory passages.
2. *Pulmonary respiration.* At the terminal portion of the air tubes, are tiny air sacs called alveoli. O₂ moves out of the alveolar air and into the blood. At the same time, CO₂ diffuses out of the blood and joins the air in the alveoli.
3. *Gas transport.* Carbon dioxide and O₂ travel in the blood to and from cells.
4. *Systemic respiration.* Gas exchange with the tissues involves the exit of O₂ from the blood into cells, while CO₂ exits cells to enter the blood.

Sometimes, it could be confusing to hear the term *respiration* alone because it also refers to cellular metabolism, or **cellular respiration** (discussed in chapter 25); in fact, the two processes are related. Breathing provides the O₂ needed in cellular respiration to make ATP from glucose. Breathing also rids the body of potentially toxic CO₂, which is produced during cellular respiration.

In addition to respiration, the respiratory system performs the following functions:

1. *Regulation of blood pH.* The respiratory system can alter blood pH by changing blood CO₂ levels.
2. *Production of chemical mediators.* The lungs produce an enzyme called angiotensin-converting enzyme (ACE), which is an important component of blood pressure regulation (discussed in chapter 26).
3. *Voice production.* Air moving past the vocal folds makes sound and speech possible.
4. *Olfaction.* The sensation of smell occurs when airborne molecules are drawn into the nasal cavity (discussed in chapter 15).
5. *Protection.* The respiratory system provides protection against some microorganisms by preventing them from entering the body and removing them from respiratory surfaces.

ASSESS YOUR PROGRESS



2. What are the four steps of respiration?
3. Explain the functions of the respiratory system.

23.3 Structures and Histology of the Respiratory Tract

LEARNING OUTCOMES



After reading this section, you should be able to

- Describe the anatomy of the respiratory passages, beginning at the nose and ending with the alveoli.**
- State the parts of the respiratory membrane.**
- Explain the role of the thoracic wall in respiration.**
- Describe the structure of the lungs, including the blood and lymphatic supply.**
- Explain the role of the pleura in respiration.**

Structures of the upper and lower respiratory tract are well-adapted for the conduction of air through the respiratory tract.

These structures move, clean, warm, and humidify the air. In the upper respiratory tract, air is moved from the external environment toward the alveoli. Once air is in the alveoli, the respiratory function of the lower respiratory tract is readily carried out due to the close contact of the alveoli with blood capillaries.

The Upper Respiratory Tract

Nose and Nasal Cavity

The **nose**, or *nasus* (nā'süs), consists of the external nose and the nasal cavity. The **external nose** is the visible structure that forms a prominent feature of the face. The largest part of the external nose is composed of hyaline cartilage plates (see figure 7.10b). The nasal bones plus extensions of the frontal and maxillary bones constitute the *bridge* of the nose, which is where eyeglasses would rest.

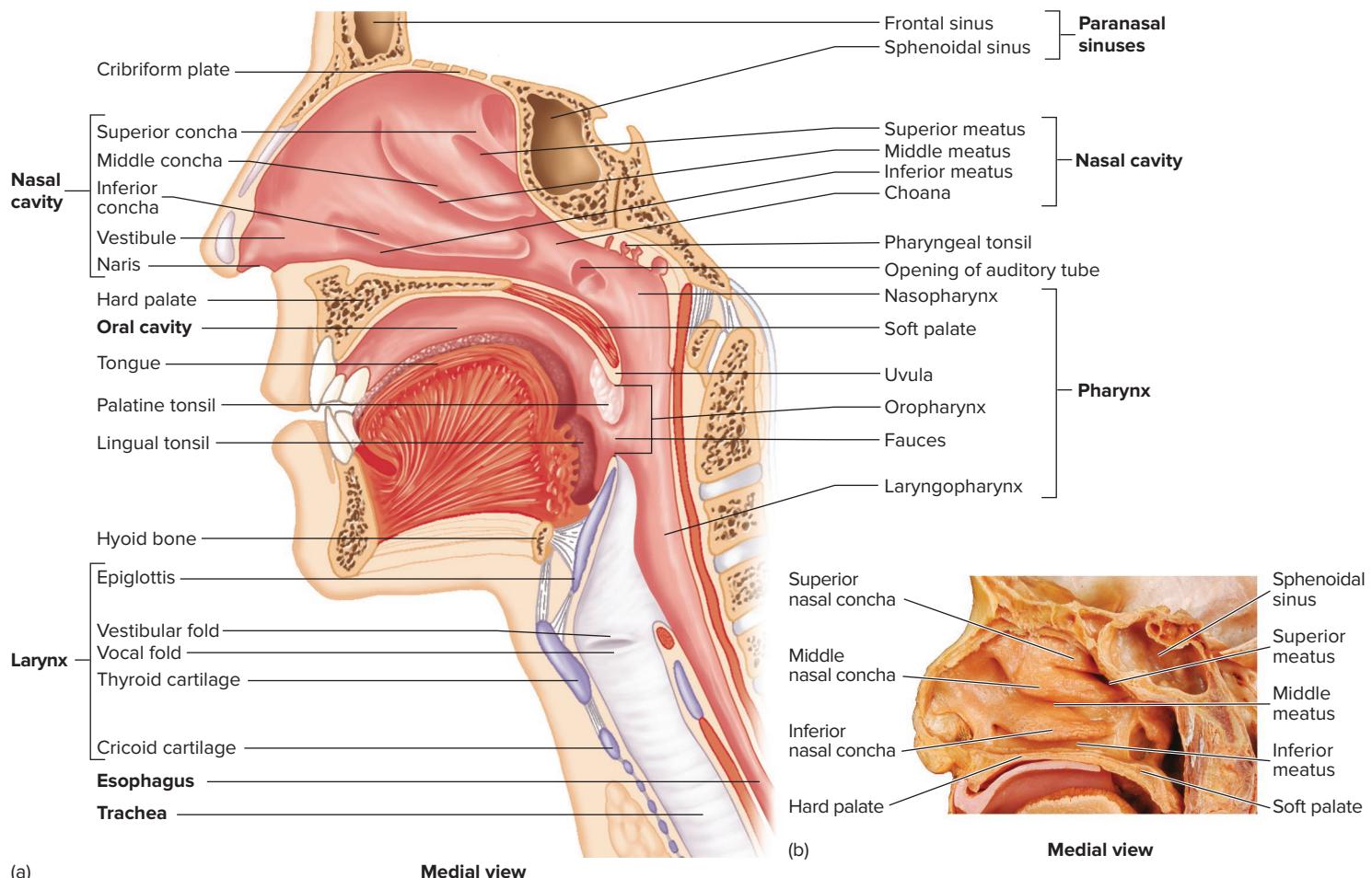
The **nasal cavity** is the open chamber inside the nose where air first enters the respiratory system. The nasal cavity begins at the anterior external openings called the **nares** (nā'res; sing. *naris*), or *nostrils*. It extends to posterior openings into the pharynx. These openings are called **choanae** (kō'an-ē; figure 23.2). Just inside each *naris*, in the anterior part of the nasal cavity, is a region called the **vestibule** (ves'ti-boot; entry room). The vestibule is lined with stratified squamous epithelium, which is continuous with the stratified squamous epithelium of the skin.

The floor of the nasal cavity, which separates it from the oral cavity in the mouth, is called the **hard palate** (pal'āt). The hard palate is formed by the palatine process of the maxillae and the palatine bone. Within the nasal cavity, the hard palate is covered by a highly vascular mucous membrane. It is this mucous membrane that helps warm and humidify inspired air. The nasal cavity is divided into right and left halves. The two halves are separated by a wall of tissue called the **nasal septum**. The anterior part of the nasal septum is composed of cartilage, while the posterior part consists of the vomer bone and the perpendicular plate of the ethmoid bone. A deviated nasal septum occurs when the septum bulges to one side and is a common cause of snoring (see figure 7.10a).

On each side of the nasal cavity, there are three lateral bony ridges called **conchae** (kon'kē; resembling a conch shell). The conchae used to be named the turbinata bones because they act as “wind turbines,” helping the air churn through the nasal cavity. In fact, people with chronic nasal congestion may have a turbinate reduction in which a surgeon performs a procedure to reduce the size of the nasal conchae. The air passes through tunnels beneath each concha. Each of these tunnels is called a **meatus** (mē-ā'tūs; tunnel or passageway). Within the superior and middle meatuses are openings from the various **paranasal sinuses** (see figure 7.11). Each inferior meatus also contains the opening of a **nasolacrimal** (nā-zō-lak'rī-māl) **duct** for tear drainage from the surface of the eye (see figure 15.10).

The nasal cavity is a critical component of the respiratory system. Its primary function is as the air intake portion of the respiratory system. It is here where the majority of the warming, cleaning, and humidifying of air occurs, which is critical for effective gas exchange within the lungs. In total, the nasal cavity has five functions:

1. *Serves as a passageway for air.* The nasal cavity remains open even when the mouth is full of food.

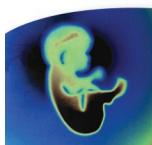
**FIGURE 23.2 Nasal Cavity and Pharynx**

(a) Sagittal section through the nasal cavity and pharynx. (b) Photograph of sagittal section of the head.

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2. *Cleans the air.* The vestibule is lined with hairs, which trap some of the large particles of dust in the air. The nasal septum and nasal conchae increase the surface area of the nasal cavity and make airflow within the cavity more turbulent, thereby increasing the likelihood that air will come into contact with the mucous membrane lining the nasal cavity. This mucous membrane consists of pseudostratified ciliated columnar epithelium with goblet cells. The goblet cells secrete mucus, which traps debris in the air. The cilia on the surface of the mucous membrane sweep the mucus posteriorly to the pharynx, where it is swallowed and eliminated by the acidic secretions of the stomach.
3. *Humidifies and warms the air.* Moisture is added to the air as it passes through the nasal cavity. There are two major sources for the moisture: (1) the mucous epithelium and (2) tears that drain into the nasal cavity through the nasolacrimal duct. Warm blood flowing through the mucous membrane warms the air within the nasal cavity before it passes into the pharynx, thus preventing damage to the rest of the respiratory passages due to cold air.
4. *Contains the olfactory epithelium.* The olfactory epithelium, the sensory organ for smell, is located in the most superior part of the nasal cavity (see figure 15.1).

5. *Helps determine voice sound.* The nasal cavity and paranasal sinuses are resonating chambers for speech. For example, most people know immediately when you have a cold because your voice sounds different.



Clinical IMPACT 23.1

Sinusitis

Sinusitis (sī-nū-sī'tis), commonly referred to as a sinus infection, is inflammation of sinus mucous membranes, especially those of the paranasal sinuses. Viral infections, such as the common cold, can cause mucous membranes to become inflamed and swollen and to produce excess mucus. As a result, the sinus opening into the nasal cavity is partially or completely blocked, allowing mucus to accumulate within the sinus, which can promote a bacterial infection. Treatments include taking antibiotics and using decongestants, hydration, and steam inhalation to promote sinus drainage. Sinusitis can also result from swelling caused by allergies or by polyps that obstruct the sinus opening into the nasal cavity.

Pharynx

The **pharynx** (far'ingks), or throat, is the common opening of both the digestive and the respiratory systems. The pharynx receives air from the nasal cavity and receives air, food, and drink from the oral cavity. Inferiorly, the pharynx is connected to the respiratory system at the larynx and to the digestive system at the esophagus. There are three regions of the pharynx: (1) the nasopharynx, (2) the oropharynx, and (3) the laryngopharynx (figure 23.2a).

The **nasopharynx** (nā'zō-far'ingks) is the most superior portion of the pharynx. It is immediately posterior to the nasal cavity. Specifically, it is a continuation of the nasal cavity from the choanae. The nasopharynx is superior to the **soft palate**. The soft palate is an incomplete partition composed of muscle and connective tissue. It separates the nasopharynx from the middle portion of the pharynx, the oropharynx. The extension of the soft palate is called the **uvula** (ū'vü-lä; grape). The soft palate prevents swallowed materials from entering the nasopharynx and nasal cavity. It pushes food and other materials toward the back of the pharynx. The nasopharynx is lined with a mucous membrane that traps debris such as dust, as well as microbes. This debris-laden mucus from the nasal cavity is moved through the nasopharynx and swallowed. Any swallowed pathogens are likely killed by the acid in the stomach. The nasopharynx is continuous with the middle ear through the auditory tubes, openings on each side of the nasopharynx (figure 23.2a; see figure 15.27). Air passes through the auditory tubes to equalize air pressure between the atmosphere and the tympanic membrane. The posterior wall of the nasopharynx houses the pharyngeal tonsil, or *adenoids* (ad' ē-noydz), which helps defend the body against infection (see chapter 22). An enlarged pharyngeal tonsil can interfere with normal breathing and airflow through the auditory tubes.

The **oropharynx** (ör'ō-far'ingks) is a continuation of the nasopharynx. The oropharynx is the middle portion of the pharynx. It is immediately posterior to the mouth and begins at the soft palate. From there, it descends to the superior portion of the larynx. A region called the **fauces** (faw'sēz) joins the mouth's oral cavity and the oropharynx. Thus, air, food, and drink all pass through the oropharynx. Moist stratified squamous epithelium lines the oropharynx and protects it against abrasion. Two groups of tonsils, called the palatine tonsils and the lingual tonsil, are located near the fauces.

The **laryngopharynx** (lä-ring'gō-far-ingks) is a continuation of the oropharynx. The laryngopharynx spans the posterior length of the larynx: from the most superior larynx structure, the epiglottis, to the esophagus. Food and drink pass through the laryngopharynx to the esophagus. Although most air passes from the laryngopharynx into the larynx, a small amount of air may be swallowed with food and drink. The laryngopharynx is lined with moist stratified squamous epithelium.

ASSESS YOUR PROGRESS



4. Name the parts of the upper and lower respiratory tracts.
5. Explain how the conducting zone differs from the respiratory zone.
6. Describe the structures of the nasal cavity.
7. What are the five functions of the nasal cavity?
8. Name the three regions of the pharynx. With what other structures does each part communicate?

Larynx

The **larynx** (lar'ingks) is commonly known as the voice box. It is located in the anterior part of the laryngopharynx and extends from the base of the tongue to the trachea. The larynx is held in place by membranes and muscles superior to the hyoid bone (figure 23.2a). The rigid walls of the larynx maintain an open passageway between the pharynx and the trachea. Its rigidity is due to an outer casing of nine cartilages connected to one another by muscles and ligaments (figure 23.3). Six of the nine cartilages are paired, and three are unpaired. The following is a list of the cartilages composing the larynx:

1. **Thyroid cartilage.** The **thyroid** (shield) **cartilage** is the largest of the cartilages. It is a single shield-shaped piece of cartilage, which is also known as the *Adam's apple*.
2. **Cricoid cartilage.** The **cricoid** (krī'koyd; ring-shaped) **cartilage** forms the base of the larynx. It is a single piece of cartilage upon which the other cartilages rest.
3. **Epiglottis.** The **epiglottis** (ep-i-glott'is; on the glottis) is a single piece of cartilage that is attached to the thyroid cartilage and projects superiorly. The epiglottis is unique among the larynx cartilages because it is a freely movable flap and is constructed of elastic cartilage rather than hyaline cartilage. It helps divert food away from the trachea opening during swallowing.
4. **Arytenoid cartilages.** The paired **arytenoid** (ar-i-tē'noyド; ladle-shaped) **cartilages** articulate with the superior border on the posterior of the cricoid cartilage.
5. **Corniculate cartilages.** The paired **corniculate** (kōr-nik'ü-lāt; horn-shaped) **cartilages** are attached to the superior tips of the arytenoid cartilages.
6. **Cuneiform cartilages.** The paired **cuneiform** (kū'nē-i-fōrm; wedge-shaped) **cartilages** are contained in a mucous membrane anterior to the corniculate cartilages.

The larynx is called the voice box because it houses the ligaments used for speech as well as for swallowing and other functions (figure 23.4). These ligaments include (1) the vestibular folds and (2) the vocal folds. Both pairs of ligaments are covered by a mucous membrane. The **vestibular folds**, or *false vocal cords*, are the superior pair of ligaments that extend from the anterior surface of the arytenoid cartilages to the posterior surface of the thyroid cartilage. The **vocal folds**, or *true vocal cords*, are the inferior ligaments. At the junction of the vocal folds is an opening; this opening, in combination with the vocal folds, is called the **glottis** (glot'is). The epithelium covering the vestibular and vocal folds is stratified squamous. The remainder of the larynx is lined with pseudostratified ciliated columnar epithelium. If the vocal folds become inflamed, **laryngitis** (lar-in-jī'tis) occurs and the person "loses" his or her voice.

The larynx, with its cartilages and the vestibular and vocal folds, perform four main functions:

1. Maintains an open passageway for air movements
2. Prevents swallowed materials from entering the larynx and lower respiratory tract
3. Produces sound for speech
4. Protects the lower respiratory tract from foreign materials.

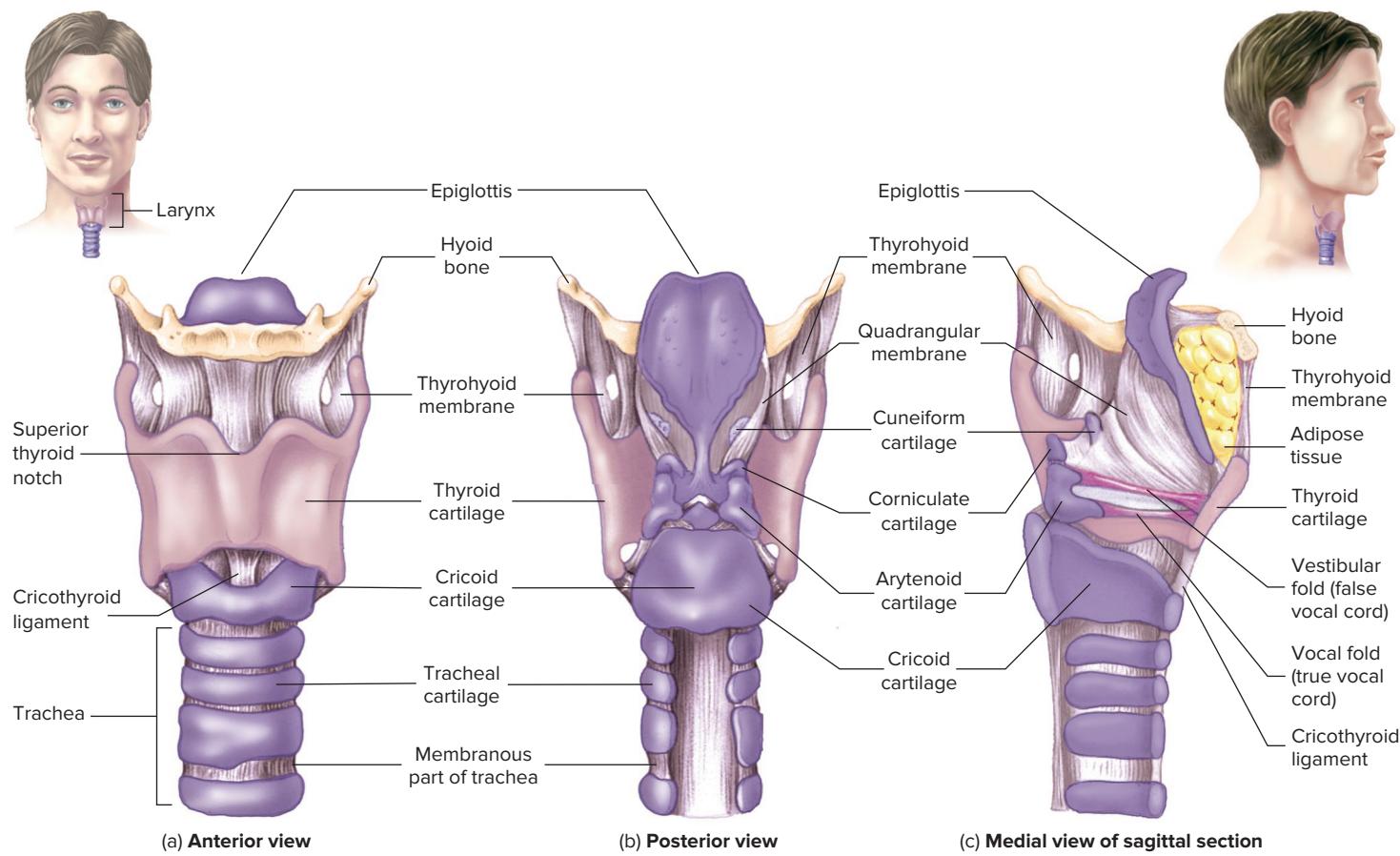


FIGURE 23.3 Anatomy of the Larynx

The larynx helps keep the airway open. (a) In the anterior view, the thyroid cartilage is visible. This is also known as the Adam's apple. (b) The posterior view shows the epiglottis, which moves inferiorly to prevent food and other swallowed materials from entering the trachea. (c) The medial view shows the vestibular and vocal folds, which are important in swallowing, speech, and other functions. AP|R

Functions of the Vestibular and Vocal Folds

The vocal folds are the primary source of sound production. Air moving past the vocal folds causes them to vibrate and produce sound. The force of air moving past the vocal folds determines the amplitude of the vibration and the loudness of the sound. The greater the amplitude of the vibration, the louder the sound. The frequency of vibrations determines pitch, with higher-frequency vibrations producing higher-pitched sounds and lower-frequency vibrations producing lower-pitched sounds. Variations in the length of the vibrating segments of the vocal folds affect the frequency of the vibrations. Higher-pitched tones are produced when only the anterior parts of the folds vibrate, and progressively lower tones result when longer sections of the folds vibrate. Because males usually have longer vocal folds than females, most males have lower-pitched voices. The sound produced by the vibrating vocal folds is modified by the tongue, lips, teeth, and other structures to form words. Interestingly, a person whose larynx has been removed due to carcinoma of the larynx can produce sound by swallowing air and causing the esophagus to vibrate.

Movement of the arytenoid and other cartilages is controlled by skeletal muscles, thereby changing the position and length of the vocal folds. When a person is simply breathing, lateral rotation of the arytenoid cartilages opens the vocal folds, which allows

greater movement of air (figure 23.4c). Medial rotation of the arytenoid cartilages closes the vocal folds, places them in position for producing sounds, and changes the tension on them (figure 23.4d). Anterior movement of the arytenoid cartilages decreases the length and tension of the vocal folds, lowering pitch. Posterior movement of the arytenoid cartilages increases the length and tension of the vocal folds, increasing pitch (figure 23.4e).

In addition to sound production, the vestibular and vocal folds provide the most important method for preventing swallowed materials from entering the larynx. During swallowing, food passes over the epiglottis toward the esophagus and the vestibular and vocal folds move together medially, closing the glottis. The closure of the vestibular and vocal folds can also prevent the passage of air, as when a person holds his or her breath or increases air pressure within the lungs prior to coughing or sneezing.

Predict 1

Jake told his girlfriend that the roller coaster did not bother him, but during the ride he let loose with a long, high-pitched scream. Explain how the muscles that control the vocal folds and the muscles that move the epiglottis helped produce Jake's scream.

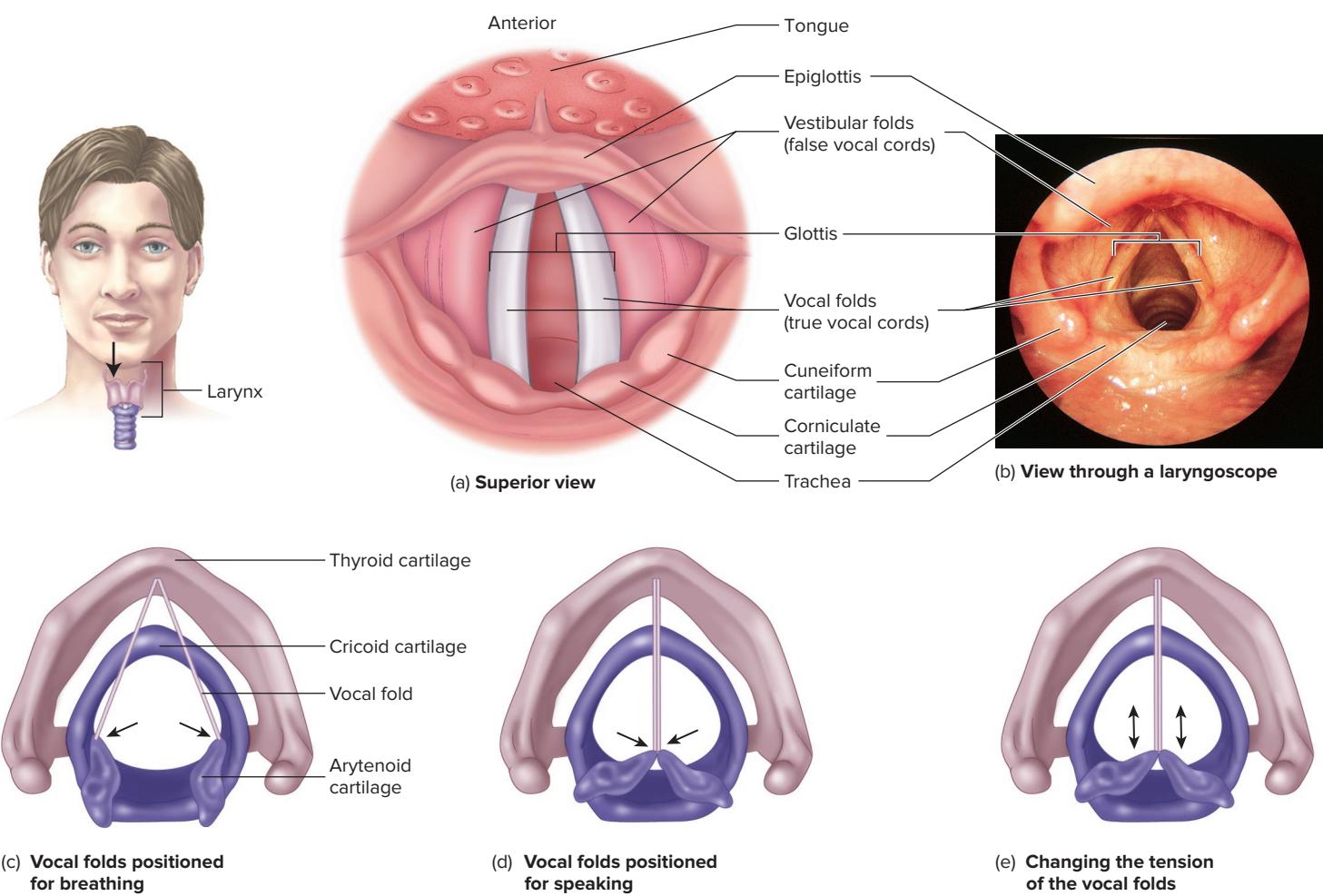


FIGURE 23.4 Vestibular Vocal Folds

(a) Relationship of the vestibular folds to the vocal folds and the laryngeal cartilages. (b) Laryngoscopic view of the vestibular and vocal folds. (c) Lateral rotation of the arytenoid cartilages moves the vocal folds laterally for breathing. (d) Medial rotation of the arytenoid cartilages moves the vocal folds medially for speaking. (e) Anterior/posterior movement of the arytenoid cartilages changes the length and tension of the vocal folds, altering the pitch of sounds. Arrows show the direction of viewing the vestibular and vocal folds. (b) ©CNRI/Phototake

The Lower Respiratory Tract

Trachea

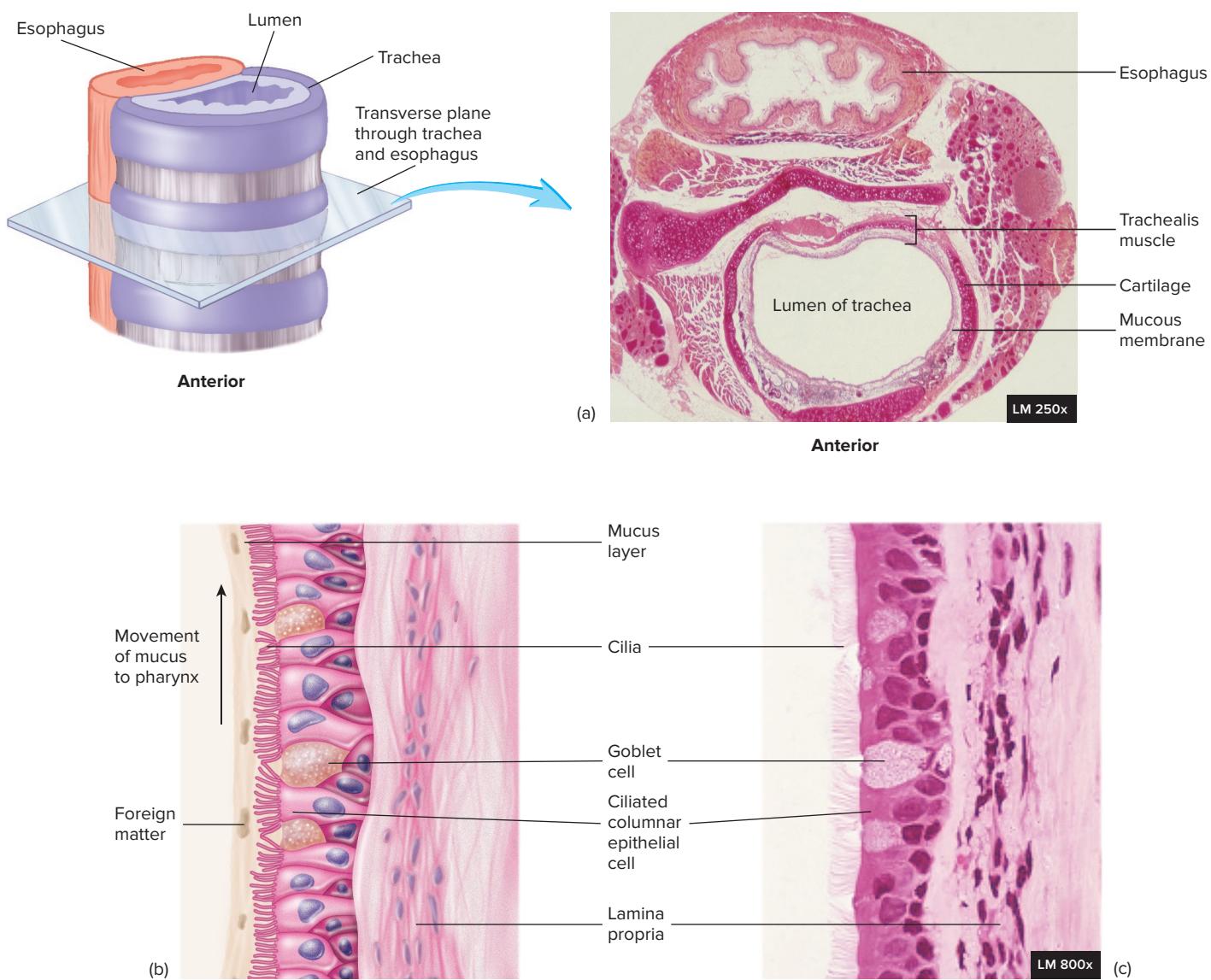
The **trachea** (trā'kē-ă) is commonly known as the windpipe. It allows air to flow into the lungs. The trachea is a membranous tube attached to the larynx and consists of dense regular connective tissue and smooth muscle (see figure 23.2). The trachea is reinforced with 15–20 C-shaped pieces of hyaline cartilage called **tracheal rings**. The tracheal rings support the trachea and prevent it from collapsing. The cartilages support the anterior and lateral sides of the trachea to protect it while maintaining a patent passageway for air (figure 23.5a). The trachea has an inside diameter of 12 mm and a length of 10–12 cm, descending from the larynx to the level of the fifth thoracic vertebra (figure 23.6). The tracheal rings are incomplete circles with the thickest portion of cartilage at the anterior wall of the trachea. The posterior wall of the trachea is devoid of cartilage and contains an elastic ligamentous membrane and bundles of smooth muscle. The smooth muscle, called the **trachealis** (trā'kē-ă-lis) **muscle**, can narrow the diameter of the trachea

by contracting, which aids in coughing. Narrowing the trachea's diameter causes air to move more forcefully through the trachea, helping to expel mucus and foreign objects during coughing. The esophagus lies immediately posterior to the cartilage-free posterior wall of the trachea.

Predict 2

Explain what happens to the shape of the trachea when a person swallows a large mouthful of food. Why is this change of shape advantageous?

A mucous membrane lines the trachea (figure 23.5b). The membrane's goblet cells produce mucus, which traps inspired dust, bacteria, and other foreign matter. The ciliated epithelium then moves the mucus and foreign matter into the larynx. From the larynx the foreign matter enters the pharynx and is swallowed (figure 23.5b,c). Constant, long-term irritation to the trachea, as occurs in smokers, can cause the tracheal epithelium to become

**FIGURE 23.5 Trachea**

(a) Light micrograph of a transverse section of the trachea. The esophagus is posterior to the trachea, next to the smooth muscle connecting the ends of the C-shaped cartilages of the trachea. (b) Mucus, produced by the goblet cells, traps foreign matter in the air. Movement of the cilia moves the mucus and foreign matter to the laryngopharynx. (c) Light micrograph of the surface of the mucous membrane lining the trachea. Goblet cells are interspersed between ciliated cells. (a) ©Biophoto Associates/Science Source; (c) ©Ed Reschke/Photolibrary/Getty Images AP|R

moist stratified squamous epithelium that lacks cilia and goblet cells. This transition prevents the normal function of the tracheal epithelium.

Bronchi

The trachea divides to form two smaller tubes called **main bronchi**, or *primary bronchi* (brong'kī; sing. *bronchus*, brong'küs; windpipe), each of which extends to a lung. At the location where the trachea divides into the two main bronchi is a ridge of cartilage called the **carina** (kă-rī'nă). The carina is an important landmark for reading x-rays. In addition, the mucous membrane of the carina is very sensitive to mechanical stimulation. If foreign matter is inspired to the level of the carina, it stimulates a powerful

cough reflex. Materials in the air passageways beyond the carina do not usually stimulate a cough reflex.

ASSESS YOUR PROGRESS

9. Name and describe the three single cartilages of the larynx. What are their functions?
10. Distinguish between the vestibular and vocal folds. How are sounds of different loudness and pitch produced by the vocal folds?
11. How does the position of the arytenoid cartilages change when a person is simply breathing versus making low-pitched and high-pitched sounds?
12. What are the four functions of the larynx?

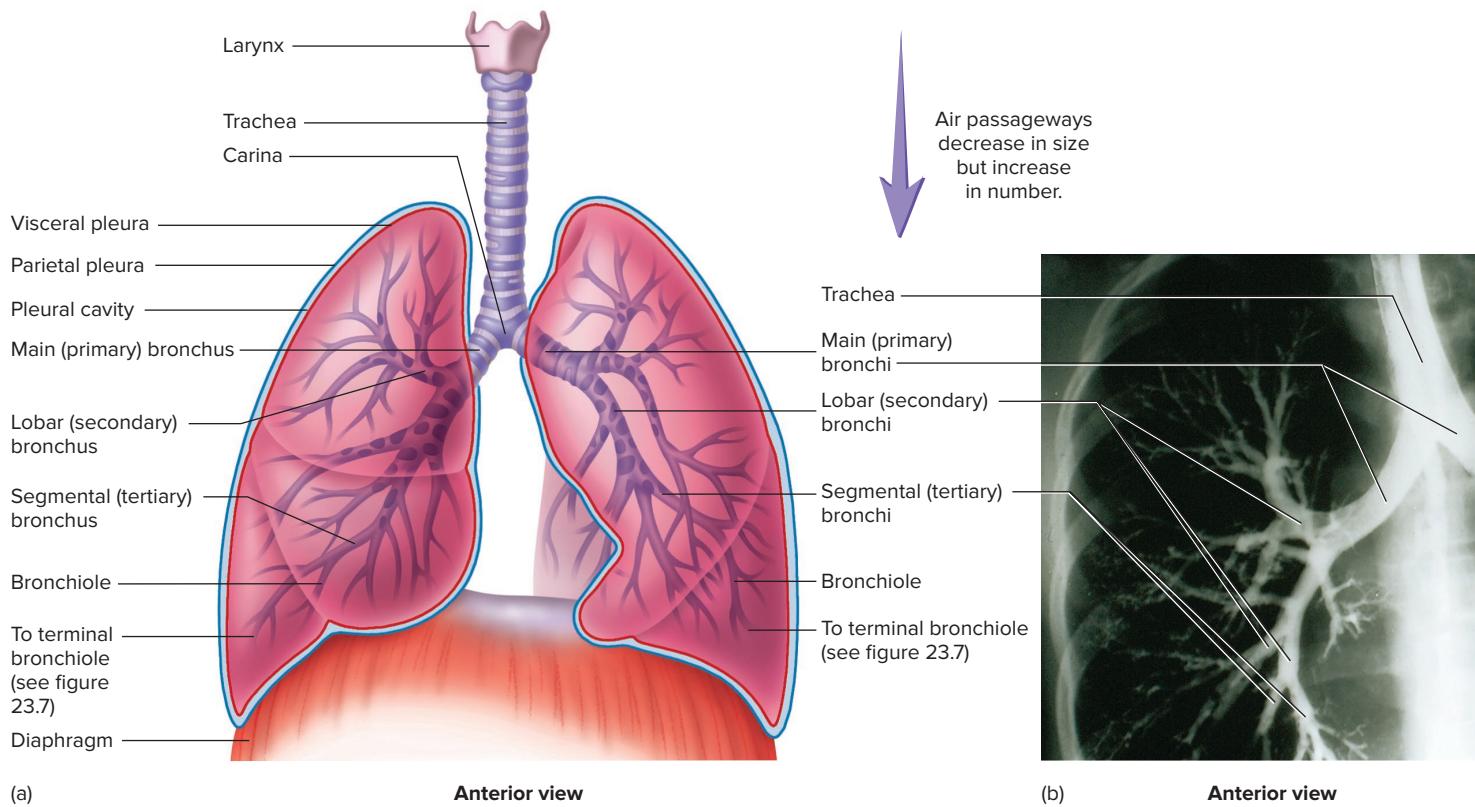


FIGURE 23.6 Tracheobronchial Tree

(a) The conducting zone of the tracheobronchial tree begins at the trachea and ends at the terminal bronchioles. (b) A bronchogram is a radiograph of the tracheobronchial tree. A contrast medium, which makes the passageways visible, is injected through a catheter after a topical anesthetic is applied to the mucous membranes of the nose, pharynx, larynx, and trachea. (b) ©Walter Reiter/Phototake AP|R

Tracheobronchial Tree

The **tracheobronchial** (trā'kē-ō-brong'kē-äl) **tree** consists of the trachea and the network of air tubes in the lungs (figure 23.6). The trachea divides to form a left and right main bronchus, each of which divides to form smaller and smaller bronchi. The smaller bronchi continue getting smaller until they terminate in microscopic tubes and sacs. The right main bronchus is larger in diameter and more directly in line with the trachea than the left main bronchus. Because the right main bronchus is more in line with the trachea, an inspired object is more likely to become lodged in it than in the left main bronchus. The main bronchi have cartilage rings like those in the trachea. Within each lung, there are four main classes of air passageways. Overall, approximately 16 generations of branching occur from the trachea to the smallest air tubes. The walls of each class of air passageway are supported by cartilage and smooth muscle, giving way to all smooth muscle in the smallest air passageways. In addition, each class of air passageway is lined with a type of ciliated epithelium, which functions as a mucus-cilia escalator, trapping debris from the air and moving it to the larynx. The four classes of air passageways, listed from largest to smallest, are the following:

1. **Lobar bronchi.** The **lobar bronchi**, or **secondary bronchi**, arise directly from the main bronchi. In the lobar bronchi, the C-shaped cartilage rings are replaced with cartilage

plates. Smooth muscle forms a layer between the cartilage and mucous membrane. The lobar bronchi are lined with pseudostratified ciliated columnar epithelium, which slowly changes as the tubes get smaller and smaller. In the left lung, there are two lobar bronchi. In the right lung, there are three lobar bronchi. Each lobar bronchus supplies its own section of each lung, which are called lobes.

2. **Segmental bronchi.** The **segmental bronchi**, or **tertiary bronchi**, supply subdivisions within each lung lobe, which are called bronchopulmonary segments. As the bronchi become smaller, the cartilage becomes sparse, and smooth muscle becomes more abundant.
3. **Bronchioles.** The **bronchioles** result from continued branching of the segmental bronchi. Bronchioles are less than 1 mm in diameter and have less cartilage and more smooth muscle. The larger bronchioles are lined with ciliated simple columnar epithelium.
4. **Terminal bronchioles.** The **terminal bronchioles** arise from several subdivisions of bronchioles. The terminal bronchioles have no cartilage in their walls, but the smooth muscle layer is prominent. The terminal bronchioles are lined with ciliated simple cuboidal epithelium.

Changes in Air Passageway Diameter

The bronchi and bronchioles are capable of changing their diameter. The smooth muscle layer in them can relax and contract. **Bronchodilation** occurs when the smooth muscle relaxes,



MICROBES In Your Body 23.1

Whooping Cough

Whooping cough, or pertussis, is a serious bacterial infection of the tracheobronchial tree, caused by the bacterium *Bordetella pertussis* (*B. pertussis*; -*tussis*, cough). Whooping cough is highly contagious and spreads through inhalation of airborne droplets or contact with droplet-covered surfaces. It is estimated that each newly infected person will pass the disease on to at least 10 other people. This is primarily because the incubation period is 7–10 days compared to only 1–3 days for the common cold. In addition, the first 2 weeks of symptoms are similar to those of a mild cold, and the patient may be less cautious around others, making it more likely that he or she will spread the infection. After the incubation phase, a severe cough develops that consists of bouts of intense coughing, which can cause vomiting, lack of sufficient gas exchange during the coughing episode, followed by a loud inspiratory high-pitched sound, or “whoop.” The coughing stage can last 10 weeks or more, but full recovery does not occur for another 2–3 months. The most severely affected patients are infants under 6 months of age, 50% of whom will require hospitalization. Infants and children under 6–7 years of age are also the most likely to develop serious side effects, which include development of pneumonia, apnea (interrupted breathing), seizures, brain hemorrhage, and even death by asphyxiation (suffocation).

B. pertussis affects both the respiratory and the immune systems simultaneously in two major ways: (1) by directly attacking the ciliated epithelium in the tracheobronchial tree and (2) by avoiding the effects of complement. In chapter 22, you learned that the tracheobronchial tree contributes to innate immunity by providing both a mechanical and a chemical barrier to invading pathogens. The mechanical barrier is formed by a mucus-producing, ciliated epithelium. The

cilia constantly sweep debris and bacteria-laden mucus toward the pharynx to be swallowed. The chemical barrier is provided by activation of the complement system by roaming macrophages in the mucosal lining of the tracheobronchial tree. The complement system consists of a group of proteins that, when activated, initiates a series of reactions, resulting in lysis of bacterial cells. Upon first entering the trachea, *B. pertussis* begins secreting chemicals called virulence factors. Some of these virulence factors are attachment proteins that allow the bacteria to bind to the plasma membrane of each cilium and the plasma membrane of the epithelial cells. This is similar to the way adjacent stratified squamous cells in the epidermis of the skin use attachment proteins to adhere to each other (see chapter 4). Once attached, the bacteria secrete another virulence factor, called tracheal cytotoxin, that causes stasis (nonmovement) of the cilia. This stasis is what induces the intense coughing fits, which benefit the bacteria by clearing mucus that could trap and kill the bacteria. Other virulence factors produced by *B. pertussis* include numerous polysaccharides and proteins that prevent binding of complement proteins to the bacterium. Without the actions of complement, the bacteria are able to survive. Unfortunately, antibiotic treatment does not prevent the clinical symptoms from developing, shorten the disease time, or prevent any serious side effects of whooping cough. The primary reason clinicians are encouraged to prescribe antibiotics is to kill the bacteria in the nasopharynx, which aids in reducing the rate of transmission to other people.

The most effective method to avoid whooping cough is vaccination. Prior to the 1940s and 1950s, whooping cough was a leading cause of infant death. Then in the 1940s, development of a universal vaccine caused a sharp drop in the number of U.S. whooping cough

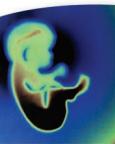
incidences and outbreaks. However, starting in the 1980s, the number of whooping cough cases began rising to levels not seen in over 60 years. Research has shown that the increase in whooping cough incidence is most likely due to several factors, all of which center around vaccination. These factors prompted the Centers for Disease Control and Prevention (CDC) to recommend a Tdap booster (a vaccine for tetanus, diphtheria, and acellular pertussis given to adolescents and adults) for all pregnant women past the 20th week of gestation. Even though the U.S. average vaccination rate is 95%, several states have rates that are lower, with the lowest rate at about 80%. High numbers of intentionally unvaccinated or undervaccinated people in a given region increase the likelihood of pertussis outbreaks. In addition, it seems that the efficacy of the early childhood DTaP vaccine (a five-dose vaccine for diphtheria, tetanus, and acellular pertussis for children younger than 7 years) may fade by the time a child is 11 or 12. This can be addressed by giving a Tdap booster at that time. Both the failure to vaccinate and the decreased vaccination rate (completion of all recommended doses) of infants and children have allowed *B. pertussis* to circulate freely throughout the population. Now *B. pertussis* has genetically adapted, so that it can avoid attack by our immune system even more effectively. In other words, the relatively recent increased number of cases has led to a decreased sensitivity of *B. pertussis* to the current vaccine. Development of a new, more effective vaccine to be given to all unvaccinated people may help eradicate this horrible disease.

► Predict 3

Predict how identifying and then purifying the complement system avoidance virulence factors that are produced by *B. pertussis* could help create a new, more effective pertussis vaccine.

making the bronchiole diameter larger. **Bronchoconstriction** occurs when the smooth muscle contracts, making the bronchiole diameter smaller. This works in the same way as vasoconstriction and vasodilation. The flow of air decreases when the resistance to airflow is increased by conditions that reduce the diameter of the respiratory passageways. According to Poiseuille's law (see

chapter 21), the resistance to airflow is proportional to the diameter (D) of a tube. Thus, a small change in diameter results in a large change in resistance, which greatly decreases airflow. For example, during exercise bronchodilation occurs, reducing the resistance to airflow, which increases air movement. However, during an **asthma attack**, the release of inflammatory chemicals,



Clinical IMPACT 23.2

Establishing Airflow

In cases of extreme emergency when the upper air passageway is blocked by a foreign object so that the person cannot breathe, quick reaction is required to save the person's life. **Abdominal thrusts**, or the *Heimlich maneuver*, are designed to force an object out of the air passage by the sudden application of pressure to the abdomen. The person who performs the technique stands behind the patient, with his or her arms under the patient's arms and hands over the patient's abdomen between the navel and the rib cage. With one hand formed into a fist and the other hand over it, the rescuer suddenly pulls both hands toward the abdomen with an upward motion. This

technique, if done properly, forces air up the trachea and dislodges most foreign objects.

There are other ways to establish airflow, but they should be performed only by trained medical personnel. In **intubation**, a tube is passed through the mouth or nose into the pharynx and then through the larynx to the trachea. Sometimes it is necessary to make an opening through which to pass the tube. The preferred point of entry in emergency cases is through the membrane between the cricoid and thyroid cartilages, a procedure called a **cricothyrotomy** (krī'kō-thi-rot'ō-mē).

A **tracheostomy** (trā-kē-os'tō-mē; *tracheo-* + *stoma*, mouth) is an operation per-

formed to make an opening into the trachea, commonly between the second and third cartilage rings. Usually, the opening is intended to be permanent, and a tube is inserted into the trachea to allow airflow and provide a way to remove secretions. The term **tracheotomy** (trā-kē-ot'ō-mē; *tracheo-* + *tome*, incision) refers to the actual cutting into the trachea, but sometimes the terms *tracheostomy* and *tracheotomy* are used interchangeably. In emergencies, opening the air passageway through the trachea is not advisable because it may damage the arteries, nerves, and thyroid gland overlying the anterior surface of the trachea.

such as leukotrienes, causes severe bronchoconstriction. The bronchoconstriction decreases the diameter of the airways, which increases resistance to airflow and greatly reduces air movement. In severe cases, air movement can be so restricted that the patient dies. Fortunately, medications, such as **albuterol** (al-bū'ter-ol), help counteract the effects of an asthma attack by promoting smooth muscle relaxation in the walls of terminal bronchioles, so that air can flow more freely. Emphysema produces increased airway resistance because the bronchioles are obstructed as a result of inflammation and because damaged bronchioles collapse during expiration, thus trapping air within the alveoli. Cancer can also occlude respiratory passages as the tumor replaces lung tissue. When there is increased resistance, increasing the pressure difference between alveoli and the atmosphere can help maintain airflow. Within limits, this can be accomplished by increased contraction of the muscles of respiration.

Alveoli

Thus far, all of the lower respiratory tract structures we've discussed have functioned only for ventilation, or within the conducting zone. Respiration can occur only where gas exchange between inspired air and the blood is possible. The sites of pulmonary respiration are the alveoli. **Alveoli** (al-vē'ō-lī; hollow cavities) are small, air-filled chambers where the air and the blood come into close contact with each other (figure 23.7). From the terminal bronchioles to the alveoli, there are approximately seven generations of branching. In order from largest to smallest these branches are:

1. **Respiratory bronchioles.** The **respiratory bronchioles** have a few attached alveoli. As the respiratory bronchioles divide to form smaller respiratory bronchioles, the number of attached alveoli increases.
2. **Alveolar ducts.** The **alveolar** (al-vē'ō-lär) **ducts** arise from the respiratory bronchioles. The alveolar ducts are like long, branching hallways with many open doorways. The

"doorways" open into alveoli. Eventually, the number of alveoli becomes so large that the wall of the alveolar duct becomes just a series of alveoli.

3. **Alveolar sacs.** **Alveolar sacs** are chambers connected to two or more alveoli at the end of an alveolar duct.

The tissue surrounding the alveoli contains elastic fibers, which allow the alveoli to expand during inspiration and recoil during expiration. The lungs are very elastic and, when inflated, are capable of expelling air and returning to their original, uninflated state. Even when not inflated, however, the lungs retain some air, which gives them a spongy quality. The walls of respiratory bronchioles consist of collagenous and elastic connective tissue with bundles of smooth muscle. The epithelium in the respiratory bronchioles is a simple cuboidal epithelium. The alveolar ducts and alveoli consist of simple squamous epithelium. Although the epithelium of the alveoli and respiratory bronchioles is not ciliated, debris from the air can be removed by macrophages that move over the surfaces of the cells. The macrophages do not accumulate in the respiratory zone because they either move into nearby lymphatic vessels or enter terminal bronchioles, thereby becoming entrapped in mucus that is swept to the pharynx.

Alveolar Structure

Approximately 300 million alveoli are in the two lungs. The average diameter of an alveolus is approximately 250 µm, and its wall is extremely thin. Two types of cells form the alveolar wall (figure 23.8a): (1) type I pneumocytes and (2) type II pneumocytes. **Type I pneumocytes** are thin squamous epithelial cells that form 90% of the alveolar surface. Most of the gas exchange between alveolar air and the blood takes place through these cells. **Type II pneumocytes** are round or cube-shaped secretory cells that produce surfactant, which makes it easier for the alveoli to expand during inspiration (see section 23.3).

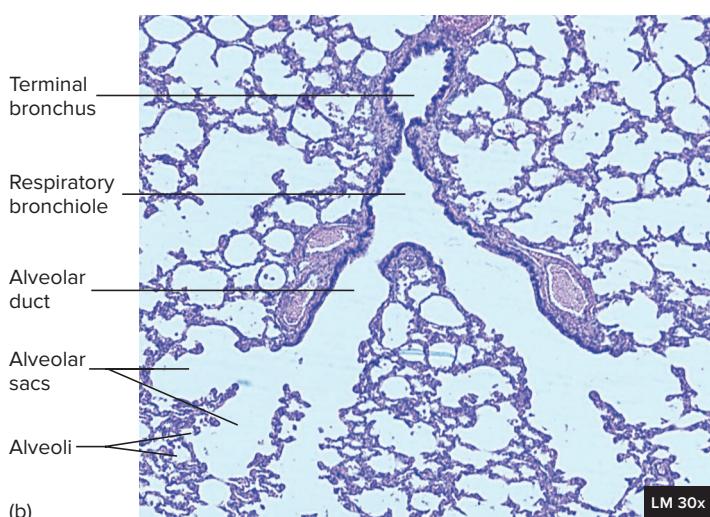
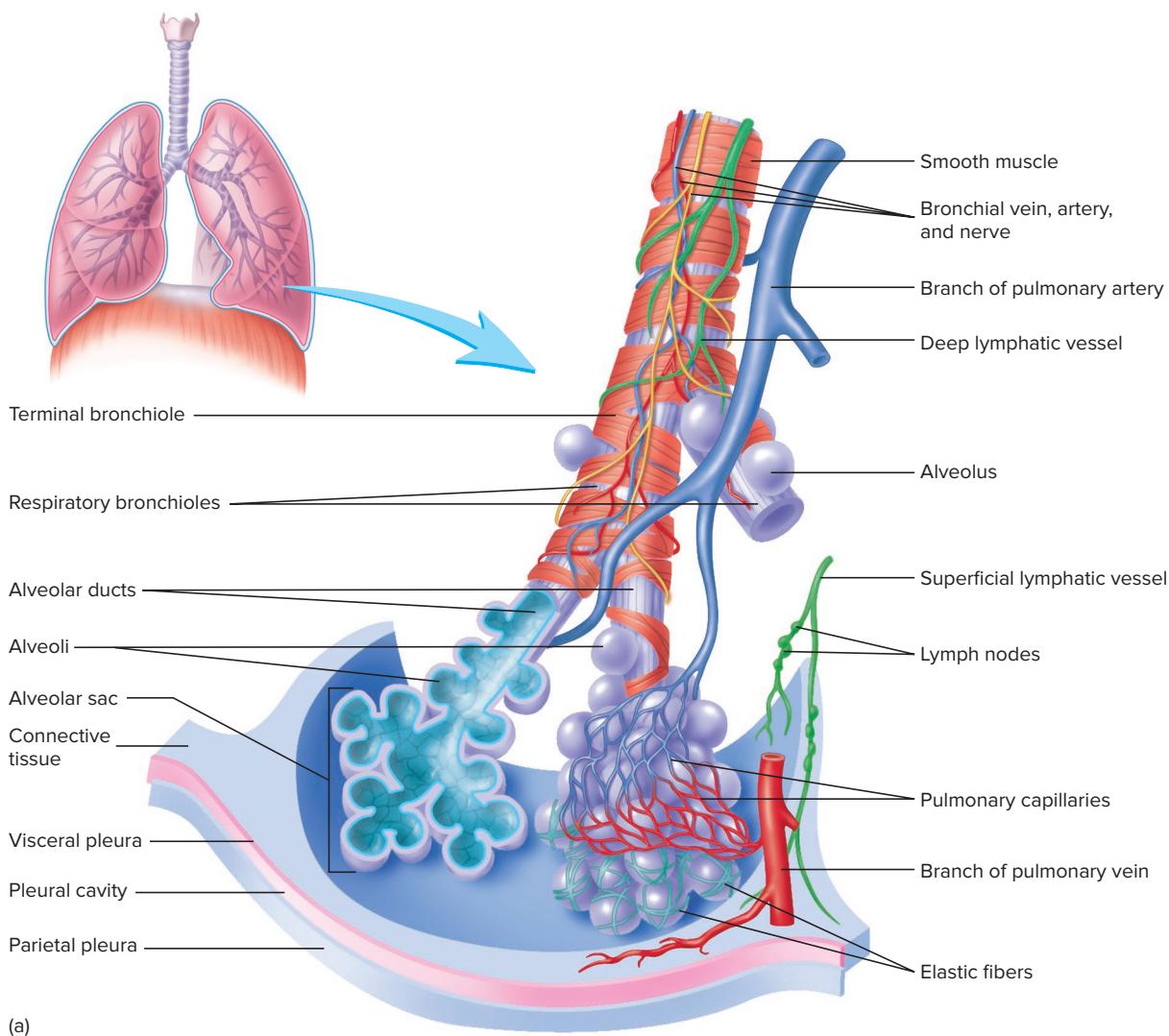


FIGURE 23.7 Bronchioles and Alveoli

(a) A terminal bronchiole branches to form respiratory bronchioles, which give rise to alveolar ducts. Alveoli connect to the alveolar ducts and respiratory bronchioles. The alveolar ducts end as two or three alveolar sacs. (b) Photomicrograph of lung tissue. (b) ©Carolina Biological/Phototake

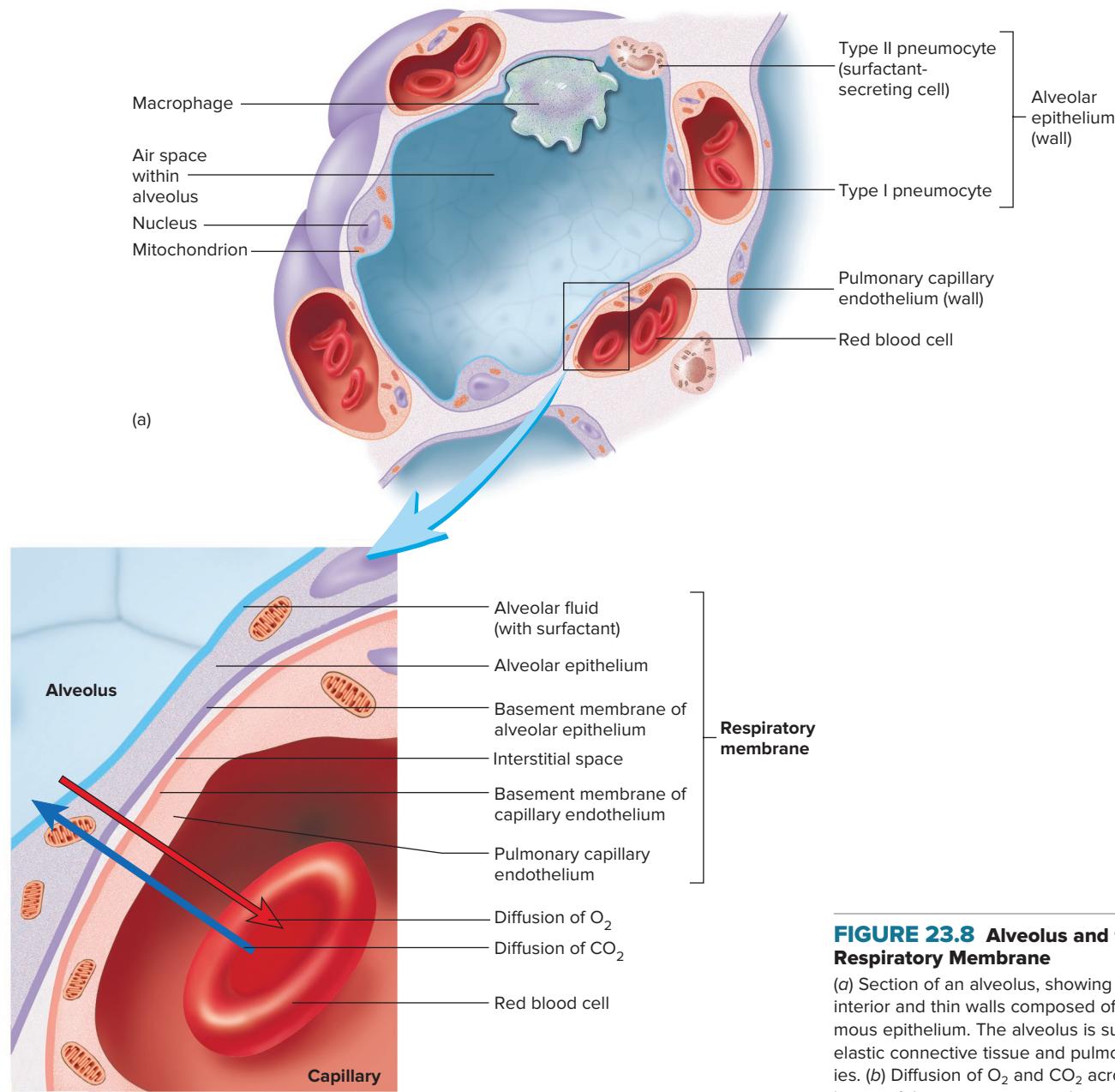


FIGURE 23.8 Alveolus and the Respiratory Membrane

(a) Section of an alveolus, showing the air-filled interior and thin walls composed of simple squamous epithelium. The alveolus is surrounded by elastic connective tissue and pulmonary capillaries. (b) Diffusion of O₂ and CO₂ across the six thin layers of the respiratory membrane. **AP|R**

The Respiratory Membrane

The alveolar walls and surrounding pulmonary capillaries form the **respiratory membrane** in the lungs (figure 23.8b). The respiratory membrane is the location of pulmonary respiration. In other words, it is where O₂ enters the blood and CO₂ exits the blood. To facilitate diffusion of gases, the respiratory membrane is extremely thin; it is thinner than a sheet of tissue paper. The general respiratory membrane components are the following:

1. The alveolar cell layer
2. The capillary endothelial layer
3. An interstitial space between the alveolar layer and the capillary layer

Associated with each of the three components are secreted fluids and basement membranes. If any of these components were to increase in thickness, the rate of gas diffusion could be appreciably changed. Thus, understanding the identity of all of the individual layers is helpful to understand respiration. The individual layers are:

1. A thin layer of alveolar fluid
2. The alveolar epithelium, which is a single layer of simple squamous epithelium
3. The basement membrane of the alveolar epithelium
4. A thin interstitial space
5. The basement membrane of the capillary endothelium
6. The capillary endothelium, which is a single layer of simple squamous cells



Clinical GENETICS 23.1

Emphysema

Emphysema (em-fí-zé'má) is a condition in which lung alveoli become progressively enlarged as the walls between them are destroyed. Individuals who have emphysema experience shortness of breath and coughing.

Cigarette smoking is the major risk factor for emphysema. Chemicals in cigarette smoke damage lung tissues and stimulate inflammation. As part of the inflammatory response, neutrophils and macrophages release **proteases**, which are enzymes that break down proteins. Proteases in the lungs protect against some bacteria and foreign substances, but too much protease activity can result in the breakdown of lung tissue proteins, especially elastin in elastic fibers. **Alpha-1 anti-trypsin (AAT)**, which is synthesized in the liver, is a

protease inhibitor. Normally, AAT inhibits protease activity, preventing the destruction of lung tissue. However, excess protease production stimulated by cigarette smoke can cause lung damage, leading to emphysema. Approximately 1–2% of emphysema cases are due to a deficiency of AAT caused by defects in the AAT gene. The mutated gene reduces the amount of secreted AAT. Multiple alleles for AAT have been identified. Individuals who are homozygous for the normal allele produce normal levels of AAT. Individuals with one copy of the normal allele and one copy of the most common abnormal allele have about 60% of normal levels of AAT. This is sufficient activity to prevent protease damage. However, individuals with

two copies of the *abnormal* allele produce only about 15–20% of normal AAT levels. If these individuals smoke, the development of emphysema is accelerated by 10–15 years. Other variant alleles cause different levels of AAT. The most severe form results in no AAT and the development of emphysema by age 30, even in nonsmokers. Treatment of AAT deficiency follows the normal course of treatment for emphysema. Stopping smoking reduces the destruction of lung tissue by removing the stimulus for excess protease activity. Drugs, such as danazol[®] and tamoxifen[®], can stimulate increased AAT production in the liver. In addition, patients may receive intravenous infusions of AAT, a process called alpha-1 antitrypsin augmentation.

ASSESS YOUR PROGRESS



13. Explain the branching of the tracheobronchial tree.
14. Describe the arrangement of cartilage, smooth muscle, and epithelium in the tracheobronchial tree. Explain why breathing becomes more difficult during an asthma attack.
15. How is debris removed from the tracheobronchial tree?
16. Name the two types of cells in the alveolar wall, and state their functions.
17. List the individual layers of the respiratory membrane.

Thoracic Wall and Muscles of Respiration

The thoracic wall consists of the (1) thoracic vertebrae, (2) ribs, (3) costal cartilages, (4) sternum, and (5) associated muscles (see chapters 7 and 10). The **thoracic cavity** is the space enclosed by the thoracic wall and the **diaphragm** (dī'ā-fram; partition). Recall from chapter 10 that the diaphragm is a sheet of skeletal muscle separating the thoracic cavity from the abdominal cavity. The diaphragm and other skeletal muscles associated with the thoracic wall change thoracic volume during ventilation (figure 23.9). We will discuss the specific roles of the muscles of respiration during ventilation in section 23.4.

Lungs

The **lungs** are the primary organs of respiration. Based on their volume, they are among the largest organs of the body. Each lung is conical in shape, and extends from the diaphragm to a point approximately 2.5 cm superior to the clavicle. The portion of the lungs in contact with the diaphragm is the **base**. The portion of the lungs that extends above the clavicle

is called the **apex**. The right lung is larger than the left and weighs an average of 620 g, whereas the left lung weighs an average of 560 g.

The **hilum** (hī'lūm) is an indentation on the medial surface of the lung. The hilum is where structures, such as the main bronchus, blood vessels, nerves, and lymphatic vessels, enter or exit the lung. All the structures passing through the hilum are referred to as the **root of the lung**.

The right lung has three large sections called **lobes**, while the left lung has two lobes. The lung lobes are separated by deep, prominent **fissures** on the surface of the lung. Each lung lobe is supplied by a lobar bronchus. The left lung also has a medial indentation called the **cardiac notch** (figure 23.10). This structural arrangement provides room for the heart to lie between the lungs. The lung lobes are further subdivided into **bronchopulmonary segments**. Each bronchopulmonary segment is supplied by the segmental bronchi. There are 9 bronchopulmonary segments in the left lung and 10 in the right lung. The bronchopulmonary segments are separated from each other by connective tissue partitions, which are not visible as surface fissures. Individual diseased bronchopulmonary segments can be surgically removed because major blood vessels and bronchi do not cross the connective tissue partitions. This leaves the rest of the lung relatively intact. The bronchopulmonary segments are even further subdivided into **lobules** by partial walls of connective tissue. Bronchioles supply each lobule.

Blood Supply to the Lungs

Blood that has passed through the lungs and picked up O₂ is called **oxygenated blood**, and blood that has passed through

FUNDAMENTAL Figure

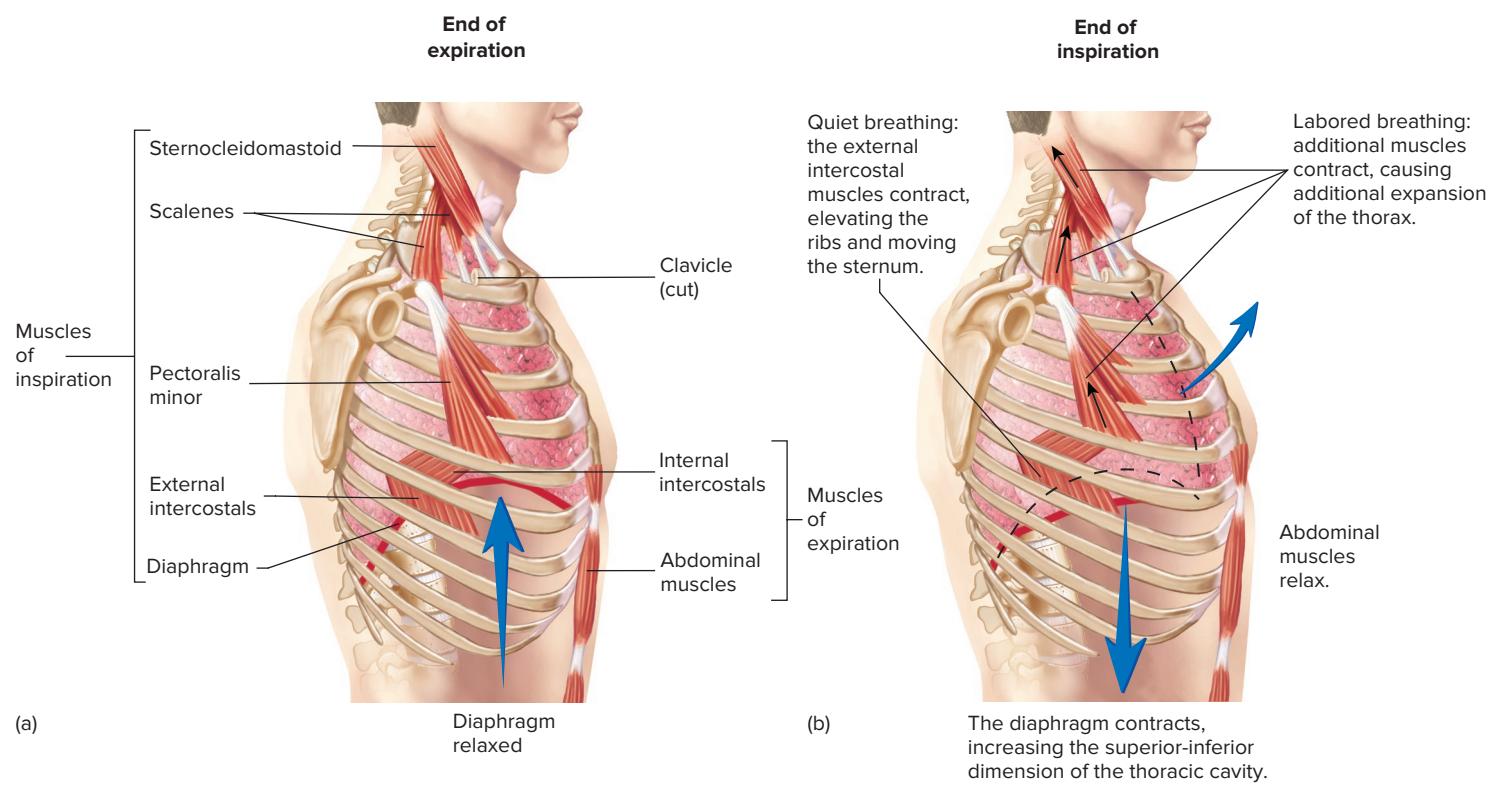


FIGURE 23.9 Effect of the Respiratory Muscles on Thoracic Volume

(a) Muscles of respiration at the end of expiration. (b) Muscles of respiration at the end of inspiration.

the tissues and released some of its O₂ is called **deoxygenated blood**. There are two blood flow routes to the lungs: (1) blood flow to the alveoli and (2) blood flow to the tissues of the bronchial tree. The major route takes deoxygenated blood to the alveoli in the lungs, where it is oxygenated (see chapter 21). To get to the alveoli, the deoxygenated blood flows through pulmonary arteries to pulmonary capillaries. In the capillaries, the blood becomes oxygenated and returns to the heart through pulmonary veins. The second route takes oxygenated blood to the tissues of the bronchi down to the respiratory bronchioles. The oxygenated blood flows from the thoracic aorta through bronchial arteries to capillaries, where O₂ is released. Deoxygenated blood from the proximal part of the bronchi returns to the heart through the bronchial veins and the azygos venous system (see chapter 21). More distally, the venous drainage from the bronchi enters the pulmonary veins. Thus, the oxygenated blood returning from the alveoli in the pulmonary veins is mixed with a small amount of deoxygenated blood returning from the bronchi. However, the available O₂ is not significantly reduced.

Lymphatic Supply to the Lungs

The lungs have two lymphatic supplies: (1) the superficial lymphatic vessels and (2) the deep lymphatic vessels. The **superficial lymphatic vessels** are deep to the connective tissue that surrounds each lung, called the **visceral pleura**. These vessels drain lymph

from the superficial lung tissue and the visceral pleura. The **deep lymphatic vessels** follow the bronchi. These vessels drain lymph from the bronchi and associated connective tissues. There are no lymphatic vessels located in the walls of the alveoli. Both the superficial and deep lymphatic vessels exit the lung at the hilum.

Phagocytic cells within the lungs phagocytize carbon particles and other debris from inspired air and move them to the lymphatic vessels. In an older person, especially one who smokes or has lived most of his or her life in a city with air pollution, these particles accumulate and cause the surface of the lungs to become gray or black. Though the lymphatic vessels primarily serve as a way to remove harmful substances from the lung tissue, cancer cells from the lungs can spread to other parts of the body through the lymphatic vessels.

Pleura

The lungs are contained within the thoracic cavity. There are two pleural cavities within the thoracic cavity. Each pleural cavity houses one lung. The **pleural** (ploor'äl; relating to the ribs) **cavities** are lined with a serous membrane (figure 23.11). Recall from chapter 20 that separating the two pleural cavities is a central region called the **mediastinum** (mē'dē-as-tī'nūm). The mediastinum houses the heart, trachea, esophagus, and other structures, such as blood vessels and the thymus. The serous membrane that covers the inner thoracic wall, the superior surface of the diaphragm, and the mediastinum is called the **parietal pleura**. At the

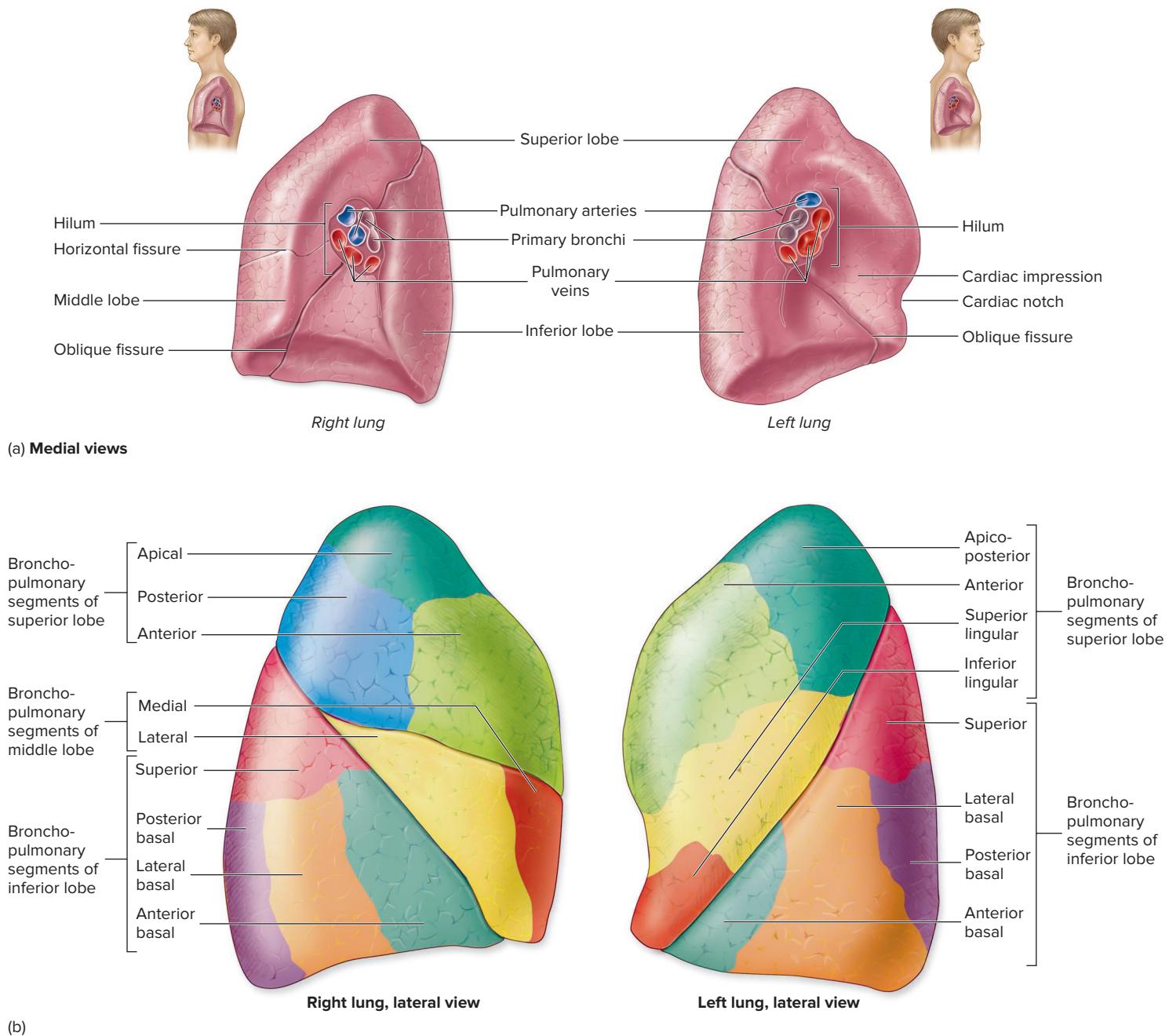


FIGURE 23.10 Lobes and Bronchopulmonary Segments of the Lungs

(a) Gross anatomy of the lungs, showing the lung lobes and bronchi. The right lung is divided into three lobes by the horizontal and oblique fissures. The left lung is divided into two lobes by the oblique fissure. A main bronchus supplies each lung. A lobar bronchus supplies each lung lobe, and segmental bronchi supply the bronchopulmonary segments (not visible). (b) Bronchopulmonary segments are supplied by segmental bronchi.

hilum, the parietal pleura is continuous with the visceral pleura, which covers the surface of the lung.

ASSESS YOUR PROGRESS

- 18.** Distinguish among a lung, a lung lobe, a bronchopulmonary segment, and a lobule. How are they related to the tracheobronchial tree?

- 19.** How many lobes are in the right lung and in the left lung? Why is there a difference in the number of lobes?
- 20.** What are the two major routes of blood flow to and from the lungs? What is the function of each route?
- 21.** Describe the lymphatic supply of the lungs.
- 22.** Name the pleurae of the lungs. What is their function?

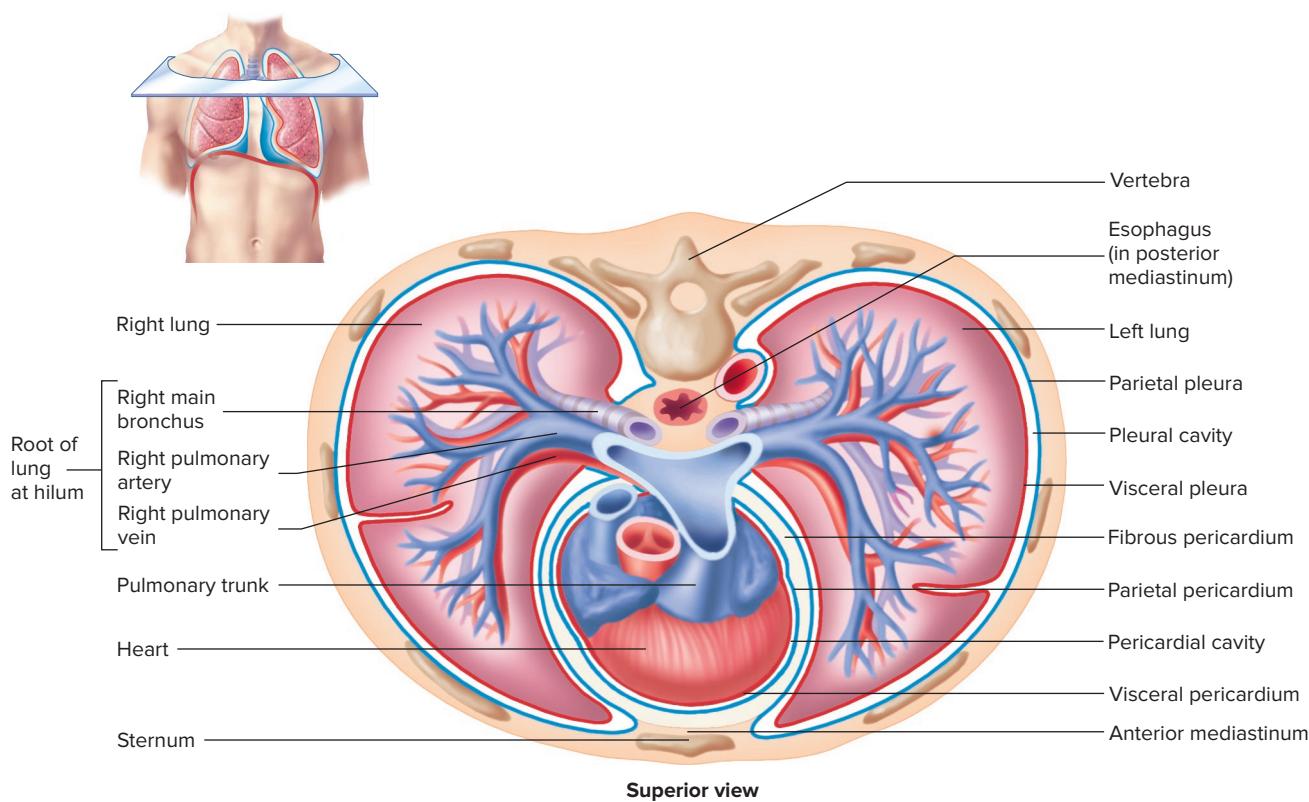


FIGURE 23.11 Pleural Cavities and Membranes

Transverse section of the thorax, showing the relationship of the pleural cavities to the thoracic organs. Each lung is surrounded by a pleural cavity. The parietal pleura lines the wall of each pleural cavity, and the visceral pleura covers the surface of the lungs. The space between the parietal and visceral pleurae is small and filled with pleural fluid.

23.4 Behavior of Gases

LEARNING OUTCOMES

- After reading this section, you should be able to
- Explain the role of the pleura in respiration.
 - Explain partial pressure and its relationship to the concentration of gases in the body.
 - List the pulmonary volumes and capacities, and define each of them.
 - Distinguish between anatomical dead space and physiological dead space.
 - Define compliance, minute volume, and alveolar ventilation.

As we've stated, the process of breathing is twofold: ventilation and respiration. To understand each of these mechanisms, we must examine the relationships governing the movement of gases.

Behavior of Gases and Ventilation

Ventilation, as we described earlier, is simply the movement of air into and out of the lungs. There are two primary aspects to ventilation: (1) actions of the muscles of respiration and (2) air pressure gradients.

Muscles of Respiration

The function of the muscles of respiration is to change the volume of the thoracic cavity, which allows for air to flow into and out of the lungs. There are several **muscles of inspiration** that act to increase the volume of the thoracic cavity. They include the (1) diaphragm, (2) external intercostals, (3) pectoralis minor, and (4) scalene muscles. The **muscles of expiration** are the muscles that decrease thoracic volume by depressing the ribs and sternum. These are the (1) internal intercostals and (2) transverse thoracis, with assistance from the abdominal muscles. Although the internal intercostals and the transverse thoracis are most active during expiration, and the external intercostals are most active during inspiration, the primary function of these muscles is to stiffen the thoracic wall by contracting at the same time. In this way, they prevent the thoracic cage from collapsing inward during inspiration.

Muscles of Inspiration

During inspiration, the thoracic cavity volume increases. Downward movement of the diaphragm upon contraction is responsible for approximately two-thirds of the thoracic volume increase. The diaphragm is dome-shaped, and the base of the dome attaches to the inner circumference of the inferior thoracic cage (see figure 10.16). The top of the dome is a flat

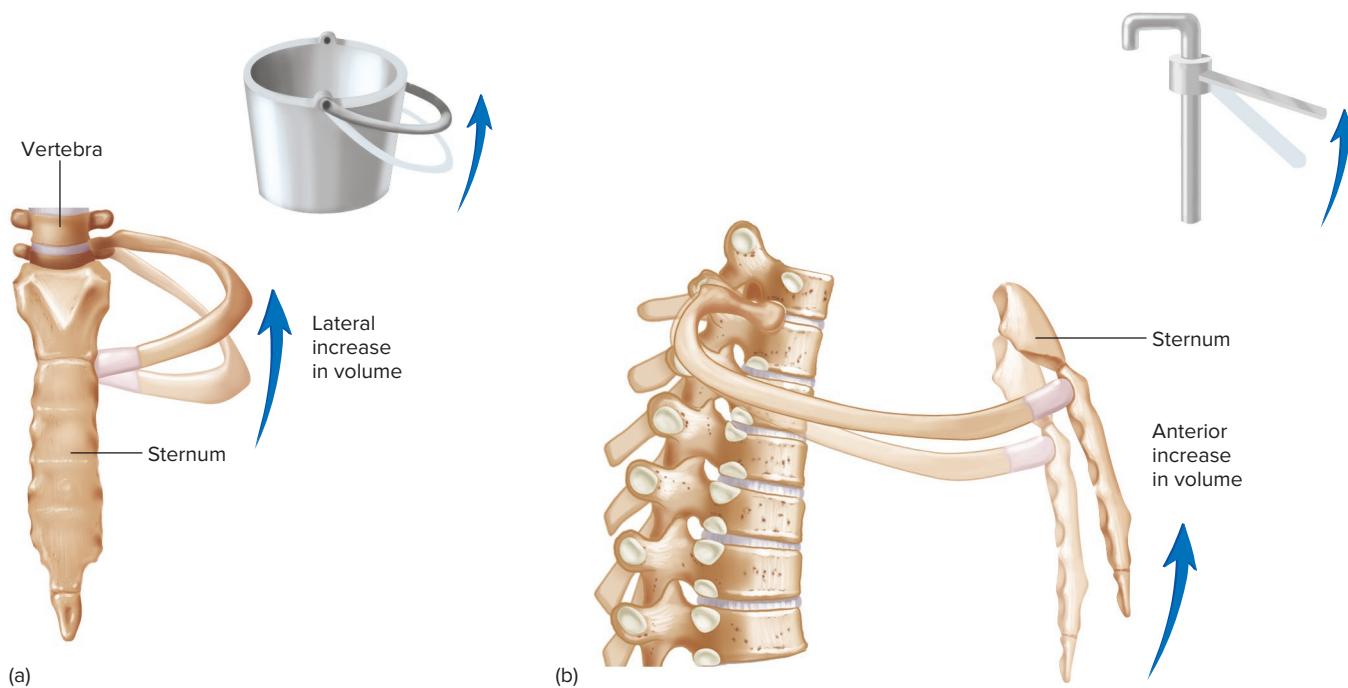


FIGURE 23.12 Effect of Rib and Sternum Movement on Thoracic Volume

(a) Elevation of the rib in the “bucket-handle” movement increases thoracic volume laterally. (b) As the rib is elevated, rotation of the rib in the “pump-handle” movement increases thoracic volume anteriorly. **AP|R**

sheet of connective tissue called the **central tendon**. In normal, quiet inspiration, contraction of the diaphragm causes the central tendon to move downward. There is very little change in the overall shape of the diaphragm. This downward movement is facilitated by relaxation of the abdominal muscles, which moves the abdominal organs out of the way. This is noticeable when your hands rest on your stomach. However, as the depth of inspiration increases, the abdominal organs prevent the central tendon from moving inferiorly. Continued contraction of the diaphragm causes it to flatten as the lower ribs are elevated.

The remaining muscles of inspiration, such as the external intercostals, increase thoracic volume by elevating the ribs. As the ribs are elevated, the costal cartilages allow lateral rib movement and lateral expansion of the thoracic cavity (figure 23.12). The ribs slope inferiorly from the vertebrae to the sternum, and elevation of the ribs also increases the anterior-posterior dimension of the thoracic cavity.

Muscles of Expiration

During expiration, the thoracic cavity volume decreases. During quiet breathing, expiration is a passive process due to significant amounts of elastic tissue in the thorax wall and the lungs. When tension is removed, the thorax wall and the lungs spring back into a smaller, relaxed state. In addition, the diaphragm relaxes, which causes it to move upward. Also, the external intercostals relax and the ribs move downward. Contractions of abdominal muscles also cause the thoracic cavity volume to decrease and

push the abdominal organs upward into the diaphragm, which moves it superiorly.

Muscles of Respiration in Quiet Breathing Compared with Labored Breathing

Several differences can be recognized between normal, quiet breathing and labored breathing. During labored inspiration, more air moves into the lungs because all of the inspiratory muscles are active. They contract more forcefully than during quiet breathing, which causes a greater increase in thoracic volume (see figure 23.9b). During labored expiration, more air moves out of the lungs due to the forceful contraction of the internal intercostals and the abdominal muscles. This produces a more rapid and greater decrease in thoracic volume than would be produced by the passive recoil of the thorax and lungs.

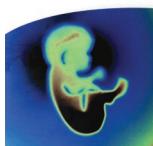
The Relationship Between Pressure Gradients and Ventilation

In order to fully understand why increasing thoracic cavity volume allows inspiration to occur, it is necessary to recognize the relationship between pressure and volume.

Pressure and Volume

The relationship between pressure and volume is an inverse one. That is to say that as the volume of a container increases, the pressure in that container decreases. The pressure of a gas in a container at a constant temperature follows **Boyle’s law**:

$$P = k/V \quad (23.1)$$



Clinical Impact 23.3

Effect of Spinal Cord Injury on Ventilation

The diaphragm is supplied by the phrenic nerves, which arise from spinal nerves C3–C5 (see figure 12.16), descend along each side of the neck to enter the thorax, and pass to the diaphragm. The intercostal muscles are supplied by the intercostal nerves (see figure 12.15), which arise from spinal nerves T1–T11 and extend along the spaces between the ribs. Spinal cord injury superior to the origin of the phrenic nerves causes paralysis of the diaphragm and intercostal muscles and results in death unless artificial respiration is provided. A spinal cord injury inferior to the origin of the phrenic nerves causes paralysis of the intercostal muscles. Even though the diaphragm can function maximally, ventilation is drastically reduced because the intercostal muscles no longer prevent the thoracic wall from collapsing inward. Vital capacity is reduced to about 300 mL. If the spinal cord is injured inferior to the origin of the intercostal nerves, both the diaphragm and the intercostal muscles function normally. The importance of the abdominal muscles in breathing can be observed in a person with a spinal cord injury that causes flaccid paralysis of the abdominal muscles. In the upright position, the abdominal wall muscles sag, which allows the abdominal organs to protrude anteriorly. Picture letting your stomach wall “pooch” outward. Without the force of the abdominal organs pushing upward on the diaphragm and lungs, the thoracic cavity volume does not decrease sufficiently. Passive recoil of the thorax and lungs is inadequate for normal expiration. An elastic binder around the abdomen can help such patients. However, when a person is lying down, the weight of the abdominal organs alone assists in expiration.

where P is gas pressure, k is a constant for a given temperature, and V is the volume of the container. Body temperature in humans can be considered a constant. Thus, Boyle’s law explains why, upon inspiration, the air pressure within the thoracic cavity decreases. Conversely, upon expiration, the air pressure within the thoracic cavity increases because the volume of the thoracic cavity decreases (table 23.1).

Pressure Gradients and Airflow

During inspiration, air flows into the lungs down its pressure gradient. During expiration, air flows out of the lungs down its pressure gradient. This pressure gradient is provided, in part, by atmospheric pressure—the combined force of all the gases that make up the air we breathe. The physics of airflow in tubes, such as the ones that make up the respiratory passages, is the same as that of the flow of blood in blood vessels (see chapter 21):

$$F = \frac{P_1 - P_2}{R} \quad (23.2)$$

where F is airflow (milliliters per minute) in a tube, P_1 is pressure at point 1, P_2 is pressure at point 2, and R is resistance to airflow.

TABLE 23.1 Gas Laws

Description	Importance
Boyle’s Law $P = k/V$ <p>The pressure of a gas is inversely proportional to its volume at a given temperature.</p>	Air flows from areas of higher to lower pressure. When alveolar volume increases, causing pleural pressure to decrease below atmospheric pressure, air moves into the lungs. When alveolar volume decreases, causing pleural pressure to increase above atmospheric pressure, air moves out of the lungs.
Dalton’s Law $\text{Partial Pressure} = \% \text{ of gas} \times \text{total gas pressure}$ <p>The partial pressure of a gas in a mixture of gases is the percentage of the gas in the mixture.</p>	Gases move from areas of higher to lower partial pressure. The greater the difference in partial pressure between two points, the greater the rate of gas movement. Maintaining partial pressure differences ensures gas movement.
Henry’s Law $\text{Concentration of dissolved gas} = \text{Pressure of gas} \times \text{Solubility coefficient}$ <p>The concentration of a gas dissolved in a liquid is equal to the partial pressure of the gas times the solubility coefficient of the gas.</p>	Only a small amount of the gases in air dissolves in the fluid lining the alveoli. Carbon dioxide, however, is 24 times more soluble than O_2 ; therefore, CO_2 exits through the respiratory membrane more readily than O_2 enters.

Air moves through tubes because of a pressure difference: Air moves from areas of higher pressure to areas of lower pressure. Thus, when P_1 is greater than P_2 , gas flows from P_1 to P_2 . For example, during inspiration, air pressure outside the body is greater than air pressure in the alveoli, and air flows into the body through the trachea and bronchi to the alveoli.

In addition, as we will discuss, the greater the pressure difference, the faster the flow rate. If the pressure difference decreases, the flow rate also decreases. For example, at higher altitudes, atmospheric pressure is lower than at sea level, making the pressure difference less. The decrease in the pressure gradient between the atmospheric air and our alveoli is why it seems harder to breathe at high altitudes.

ASSESS YOUR PROGRESS

23. List the muscles of inspiration, and describe their role in quiet inspiration. List the muscles of expiration, and describe their role in quiet expiration. How does this change during labored breathing?
24. What is ventilation?
25. How do pressure differences and resistance affect airflow through a tube?
26. What happens to the pressure within a container when the volume of the container increases? Whose law describes this relationship?
27. Describe the process of making intra-alveolar pressure changes that occurs during quiet resting breathing.

Measurement of Lung Function

Sometimes, a person's lungs do not move sufficient amounts of air to support normal activities. In that case, several types of medical tests can be performed to determine what might be causing the lung malfunction. The patient's measurements are then used to diagnose specific diseases and to track recovery.

Pulmonary Volumes and Capacities

Spirometry (spī-rom'ē-trē) is the process of measuring volumes of air that move into and out of the respiratory system, and a **spirometer** (spī-rom'ē-ter) is the device used to measure these pulmonary volumes. There are four different pulmonary volumes measured in spirometry (figure 23.13). The four pulmonary volumes for a young adult male are:

1. **Tidal volume.** The **tidal volume** is the normal volume of air inspired and expired with each breath. At rest, quiet breathing results in a tidal volume of approximately 500 mL.
2. **Inspiratory reserve volume.** The **inspiratory reserve volume** is the amount of air that can be inspired forcefully after a normal inspiration (approximately 3000 mL at rest).
3. **Expiratory reserve volume.** The **expiratory reserve volume** is the amount of air that can be forcefully expired after a normal expiration (approximately 1100 mL at rest).

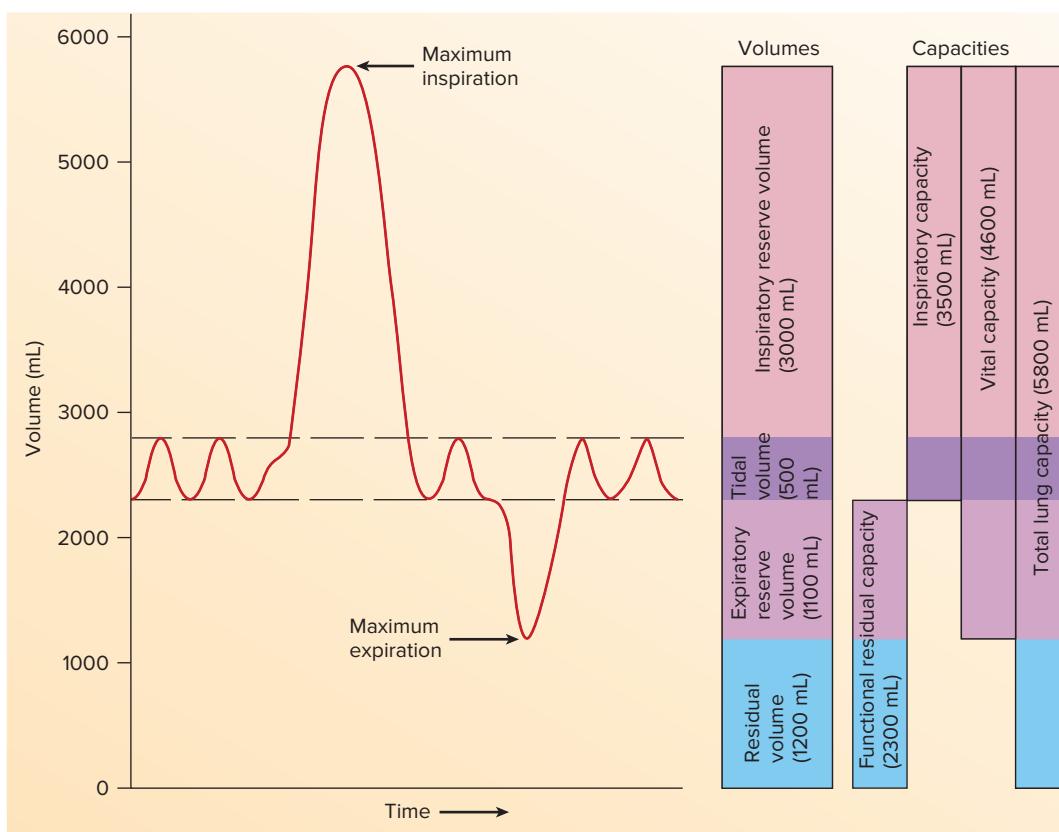


FIGURE 23.13 Lung Volumes and Lung Capacities

The tidal volume during resting conditions is represented.

4. **Residual volume.** The **residual volume** is the volume of air still remaining in the respiratory passages and lungs after the most forceful expiration (approximately 1200 mL).

The tidal volume increases when a person is more active. Because the maximum volume of the respiratory system does not change from moment to moment, an increase in tidal volume causes a decrease in the inspiratory and expiratory reserve volumes.

Pulmonary capacities are the sum of two or more pulmonary volumes (figure 23.13). Examples of pulmonary capacities are the following:

1. **Inspiratory capacity** is the tidal volume plus the inspiratory reserve volume. It is the amount of air a person can inspire maximally after a normal expiration (approximately 3500 mL at rest).
2. **Functional residual capacity** is the expiratory reserve volume plus the residual volume. It is the amount of air remaining in the lungs at the end of a normal expiration (approximately 2300 mL at rest).
3. **Vital capacity** is the sum of the inspiratory reserve volume, the tidal volume, and the expiratory reserve volume. It is the maximum volume of air a person can expel from the respiratory tract after a maximum inspiration (approximately 4600 mL).
4. **Total lung capacity** is the sum of the inspiratory and expiratory reserve volumes plus the tidal volume and the residual volume (approximately 5800 mL).

A functional measure of lung performance is the **forced vital capacity**. This is a simple and clinically important pulmonary test. In conditions such as chronic obstructive pulmonary disease (COPD), emphysema, and chronic bronchitis, the vital capacity may not be dramatically affected, but how rapidly air is expired can be greatly decreased. The **forced expiratory volume in 1 second (FEV₁)** is the amount of air expired within the first second of the test. A lower FEV₁ measure indicates that the severity of the disease has worsened. The patient inspires maximally and then expires maximally into a spirometer as rapidly as possible. The volume of air expired at the end of the test is the vital capacity. The spirometer also records the volume of air expired per second.

Minute Volume

The **respiratory rate** is the number of breaths per minute. This is one of the vital signs health professionals measure in

clinics and hospitals. The **minute volume** is a measure of the amount of air moved through the respiratory system per minute. The minute volume can be calculated by multiplying the tidal volume by the respiratory rate. For example, the average minute volume for a young adult male would be:

$$\text{Tidal Volume} \times \text{Respiratory Rate} = \text{Minute Volume} \quad (23.3)$$

$$500 \text{ mL} \times 12 \text{ breaths/minute} = 6000 \text{ mL/min}$$

(tidal volume) (respiratory rate) or 6 L/min

Although minute volume measures the amount of air moving into and out of the respiratory system per minute, it is not a measure of the amount of air available for gas exchange. However, minute volume is clinically important because it is an indication of CO₂ levels, an important physiological parameter (see section 23.5).

Alveolar Ventilation

Alveolar ventilation is the measure of the volume of air available for gas exchange per minute. Recall that part of the respiratory system functions solely to move air. Only a portion of each breath reaches the alveoli for gas exchange. The remaining areas where no gas exchange occurs is called the dead space. There are two types of dead space within the respiratory system: (1) anatomical dead space and (2) physiological dead space. The **anatomical dead space** areas include all the structures of the upper respiratory tract, and structures of the lower respiratory tract to the terminal bronchioles. These are all of the conducting zone areas. The volume of air in the anatomical dead space is approximately 1 mL per pound of an individual's ideal body weight. The **physiological dead space** is the combination of the anatomical dead space and the volume of any alveoli with lower than normal gas exchange. To calculate alveolar ventilation, the following formula is used:

$$\dot{V}_A = f(V_T - V_D) \quad (23.4)$$

where \dot{V}_A is alveolar ventilation (milliliters per minute), f is respiratory rate (frequency; breaths per minute), V_T is tidal volume (milliliters per respiration), and V_D is dead space (milliliters per respiration). The dot over the letter V means that this is a *per minute* measure. Thus, for each breath, physiologically relevant air is only that volume inside healthy alveoli. Predict question 4 provides an opportunity to calculate a representative alveolar ventilation rate.

Predict 4

What is the alveolar ventilation of a resting person with a tidal volume of 500 mL, a dead space of 150 mL, and a respiratory rate of 12 breaths per minute? Suppose the person exercises, so that tidal volume increases to 4000 mL, dead space increases to 300 mL due to dilation of the respiratory passageways, and respiratory rate increases to 24 breaths per minute. What is the alveolar ventilation then? How is the change in alveolar ventilation beneficial for doing exercise?

Factors Affecting Ventilation

Gender, Age, Body Size, and Physical Fitness

Factors such as gender, age, body size, and physical conditioning cause variations in respiratory volumes and capacities from one individual to another. For example, the vital capacity of adult

females is usually 20–25% less than that of adult males. The vital capacity reaches its maximum amount in young adults and gradually decreases in the elderly. Taller people usually have a greater vital capacity than people with a shorter stature, and slender people have a greater vital capacity than obese individuals. Well-trained athletes can have a vital capacity 30–40% above that of people with a sedentary lifestyle. In patients whose respiratory muscles are paralyzed by spinal cord injury or diseases such as poliomyelitis or muscular dystrophy, vital capacity can be reduced to values not consistent with survival (less than 500–1000 mL).

Disease States

In a healthy person, anatomical and physiological dead spaces are nearly the same, meaning that most alveoli are functional. However, in patients with emphysema, alveolar walls degenerate, and small alveoli combine to form larger alveoli. The result is not only fewer alveoli but also alveoli with an increased volume and decreased surface area. Although the enlarged alveoli are still ventilated, their surface area is inadequate for complete gas exchange, and the physiological dead space increases.

Compliance of the Lungs and Thorax

Compliance is a measure of the ease with which the lungs and thorax expand. The compliance of the lungs and thorax is the volume by which they increase for each unit of change in intra-alveolar pressure. It is usually expressed in liters (volume of air) per mm Hg (pressure), and for a normal person the compliance of the lungs and thorax is 0.18 L/mm Hg. That is, for every 1 mm Hg change in intra-alveolar pressure, the volume changes by 0.18 L. A lower-than-normal compliance means that it is harder to expand the lungs and thorax. There are many conditions that could decrease compliance. These include the deposition of inelastic fibers in lung tissue (pulmonary fibrosis), the collapse of the alveoli (infant respiratory distress syndrome and pulmonary edema), increased resistance to airflow caused by airway obstruction (asthma, bronchitis, and lung cancer), and deformities of the thoracic wall that reduce its ability to expand and allow the thoracic volume to increase (kyphosis and scoliosis). Pulmonary diseases that result in decreased compliance can markedly affect the total amount of energy required for ventilation and increase the total amount of energy expended by the body by up to 30%.

On the other hand, if the lungs and thorax have lost some of their elasticity, the compliance will be greater. If this becomes the case, it is easier to expand the lungs and thorax. For example, emphysema sometimes causes the destruction of elastic lung tissue. This reduces the elastic recoil force of the lungs, thereby making expansion of the lungs easier and resulting in a higher-than-normal compliance. However, because the elastic recoil of the lungs is reduced, expiration is not as efficient.

ASSESS YOUR PROGRESS

- 28. Distinguish among tidal volume, inspiratory reserve volume, expiratory reserve volume, and residual volume.
- 29. Differentiate among inspiratory capacity, functional residual capacity, vital capacity, and total lung capacity.



30. What is forced expiratory volume in 1 second, and why is it clinically important?
31. What is the difference between minute volume and alveolar ventilation?
32. What is compliance? What is the effect on lung expansion when compliance increases or decreases?
33. What is dead space? Contrast anatomical dead space with physiological dead space.

Behavior of Gases and Respiration

Ventilation supplies atmospheric air to the alveoli. Pulmonary respiration is the next step in the process of respiration. Pulmonary respiration is the diffusion of gases between the alveoli and the blood in the pulmonary capillaries. The molecules of gas move down their partial pressure gradient from the air into the blood for O₂ and from the blood into the air for CO₂.

Partial Pressure

To understand the mechanism behind the movement of O₂ into the blood and CO₂ out of the blood, we must first discuss how the amount of a gas in a mixture of gases is measured. Atmospheric pressure is due to a mixture of gases, each of which is present in a different amount. The term *pressure* is used to express the amount of each gas in a mixture. This is comparable to using the term *concentration* for solutes. According to **Dalton's law**, the total pressure of a gas is the sum of the individual pressures of each gas (see table 23.1). The individual pressure of each gas is called the **partial pressure**. At sea level, the pressure of all the gases in the air, or atmospheric pressure, is approximately 760 mm Hg (table 23.2).

To determine the partial pressure of each gas, its percentage is multiplied times the total pressure. The partial pressure of each gas in dry atmospheric air is as follows:

Nitrogen:

$$(79\%) \text{ PN}_2 = 0.79 \times 760 \text{ mm Hg} = 600 \text{ mm Hg}$$

Oxygen:

$$(21\%) \text{ Po}_2 = 0.21 \times 760 \text{ mm Hg} = 160 \text{ mm Hg}$$

Carbon Dioxide:

$$(0.04\%) \text{ Pco}_2 = 0.04 \times 760 \text{ mm Hg} = 0.3 \text{ mm Hg}$$

Water Vapor:

$$(0.0\%) \text{ PH}_2\text{O} = 0.0 \times 760 \text{ mm Hg} = 0.0 \text{ mm Hg}$$

Thus, atmospheric pressure of dry air at sea level is calculated using the following:

$$\begin{aligned} \text{Atmospheric air: } & \text{PN}_2 + \text{Po}_2 + \text{Pco}_2 + \text{PH}_2\text{O} = 760.3 \text{ mm Hg} \\ & \text{PN}_2 = 600 \text{ mm Hg} \\ & \text{Po}_2 = 160 \text{ mm Hg} \\ & \text{Pco}_2 = 0.3 \text{ mm Hg} \\ & \text{PH}_2\text{O} = 0.0 \text{ mm Hg} \\ & \hline & 760.3 \text{ mm Hg} \end{aligned} \quad (23.5)$$

A common misconception is that at higher altitudes there is "less" O₂ in the air. However, this is not the case. Rather, it is total atmospheric pressure that is lower at higher altitudes than at sea level. For example, the atmospheric pressure at an elevation of 14,000 ft above sea level, the elevation of Pike's Peak in Colorado, is about 430 mm Hg. The percentage of the air that is O₂ remains at 21%. Thus,

$$0.21 \times 430 \text{ mm Hg} = 90 \text{ mm Hg}$$

Therefore, at high altitudes your body does, in fact, react as if there were "less" O₂. However, it is the O₂ partial pressure gradient that has reduced, causing less O₂ to enter the lungs per breath. The normal initial adaptation to high altitudes is an increased breathing rate per minute, thereby allowing a sufficient amount of O₂ delivery to the lungs.

Three factors cause differences in the composition among alveolar air, expired air, and atmospheric air: (1) Air entering the respiratory system is humidified; (2) O₂ diffuses from the alveoli into the blood, while CO₂ diffuses from the blood into the alveoli; (3) the alveolar air is only partially replaced with atmospheric air during each inspiration.

Diffusion of Gases into and out of Liquids

Gas molecules move from the air into a liquid, or from a liquid into the air, down their partial pressure gradients. Gases move from a higher partial pressure to a lower partial pressure. When partial pressures of gases are equal between the air and a liquid, they are in equilibrium. However, to calculate the amount of a gas in a liquid, the partial pressure alone is not sufficient. The amount of the gas is also dependent on how readily a gas dissolves in the liquid, which is called the **solubility coefficient**. Thus, at a given temperature, **Henry's law** describes the concentration of a gas at equilibrium in a liquid (see table 23.1):

$$\begin{aligned} \text{Concentration of dissolved gas} &= \text{Pressure of gas} \\ &\times \text{Solubility coefficient} \end{aligned} \quad (23.6)$$

In water, the solubility coefficient for O₂ is 0.024; for CO₂ it is 0.57. Thus, CO₂ is approximately 24 times more soluble in water than O₂ is.

TABLE 23.2 Partial Pressures of Gases at Sea Level

	Dry Air		Humidified Air		Alveolar Air		Expired Air	
Gases	mm Hg	%	mm Hg	%	mm Hg	%	mm Hg	%
Nitrogen	600	79	562.4	74	569	74.9	566	74.5
Oxygen	160	21	152	20	104	13.6	120	15.7
Carbon dioxide	0.3	0.04	0.3	0.04	40	5.3	27	3.6
Water vapor	0.0	0.00	47	6.20	47	6.2	47	6.2

Predict 5

As a scuba diver descends, the pressure of the water on the body prevents normal expansion of the lungs. To compensate, the diver breathes pressurized air, which has a greater pressure than air at sea level. What effect does the increased pressure have on the amount of gas dissolved in the diver's body fluids? A scuba diver who suddenly ascends to the surface from a great depth can develop decompression sickness (the bends), in which bubbles of nitrogen gas form. The expanding bubbles damage tissues or block blood flow through small blood vessels. Explain why the bubbles develop.

Diffusion Coefficient

To determine the rate at which a gas diffuses into and out of a liquid or tissue, two factors must be considered: (1) the solubility coefficient of the gas and (2) the molecular weight of the gas. This rate is called the **diffusion coefficient**. For example, if the diffusion coefficient of O₂ is assigned a value of 1, the relative diffusion coefficient of CO₂ is 20, which means CO₂ diffuses through the respiratory membrane about 20 times more readily than O₂ does. The diffusion coefficient of CO₂ compared to O₂ is 20:1. The diffusion coefficient becomes very important when the respiratory membrane becomes progressively damaged as a result of disease. The capacity of the respiratory membrane for allowing O₂ to move into the blood is often so impaired that death from O₂ deprivation results. If life is being maintained by extensive O₂ therapy, which increases the concentration of O₂ in the lung alveoli, the reduced capacity for the diffusion of CO₂ across the respiratory membrane can result in substantial increases in CO₂ in the blood. Increased CO₂ levels in the blood can be very toxic (see section 23.6).

ASSESS YOUR PROGRESS

34. According to Dalton's law, what is the partial pressure of a mixture of gases? What is water vapor pressure?
35. Why are the compositions of inspired, alveolar, and expired air different?
36. According to Henry's law, how do partial pressure and solubility of a gas affect its concentration in a liquid?

23.5 Physiology of the Respiratory System

LEARNING OUTCOMES

After reading this section, you should be able to

- A. **Describe the changes in alveolar pressure that are responsible for the movement of air into and out of the lungs.**
- B. **Explain how surfactant and pleural pressure prevent the collapse of the lungs and how changes in pleural pressure cause changes in alveolar volume.**
- C. **Describe the partial pressure gradients for O₂ and CO₂.**
- D. **Explain the factors that affect gas movement through the respiratory membrane.**

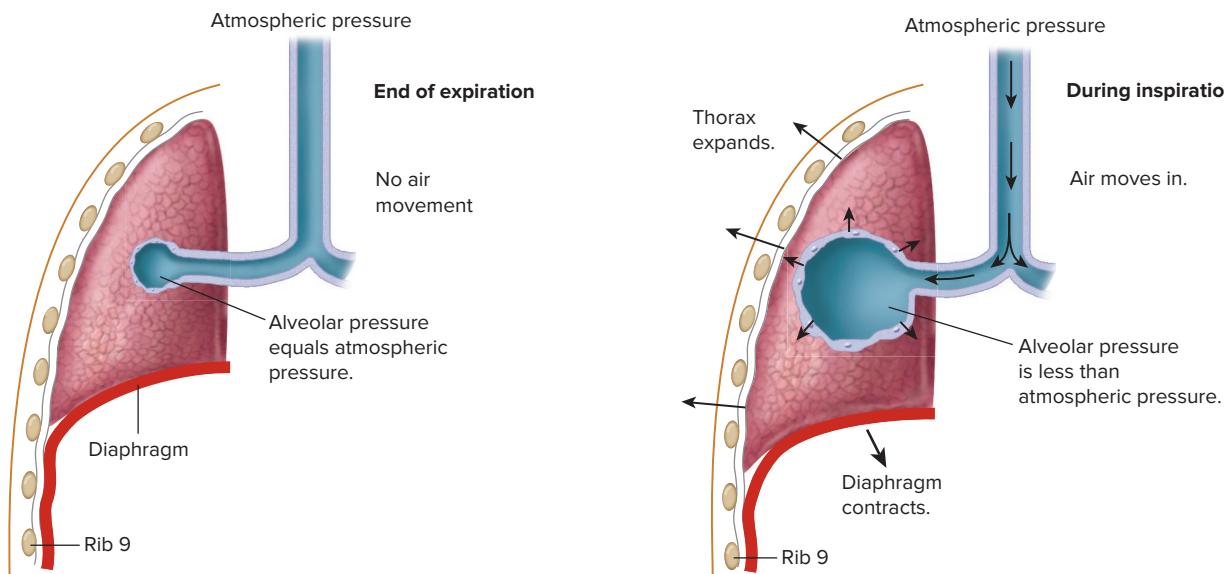
Now that we've established that the major driving force of ventilation is a pressure difference between atmospheric air and the thoracic cavity, let's look more closely at the step-by-step mechanisms of alveolar ventilation.

Mechanisms of Alveolar Ventilation

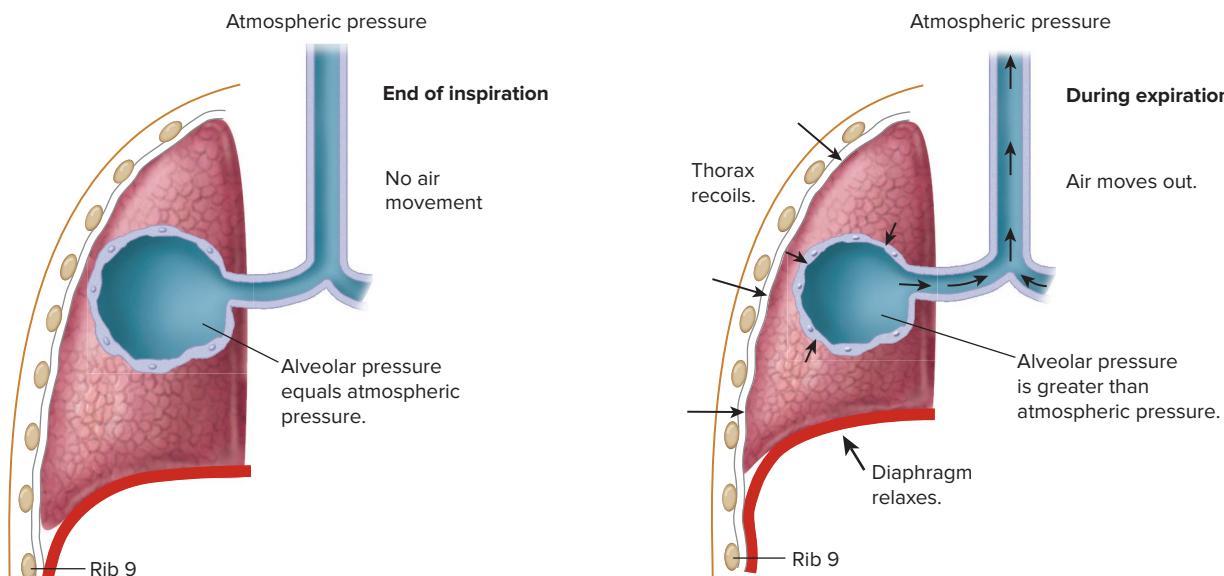
As we step through one respiratory cycle, or one breath, we will track the relative pressure difference between the atmosphere and the alveoli (figure 23.14). Atmospheric air pressure outside the body is referred to as **barometric air pressure (P_B)**. Respiratory physiologists assign P_B a value of zero for simplicity. Air pressure in the alveoli is called **intra-alveolar pressure (P_{alv})**. When a person inspires, the P_{alv} decreases because the alveolar volume has increased. Conversely, when a person expires, the P_{alv} increases because the alveolar volume has decreased. Because the difference upon inspiration and expiration between the alveolus and the atmosphere is usually around 1 mm Hg, pressure differences fluctuate 1 mm Hg above or below zero. For example, if pressure in the alveoli is higher than P_B, the alveolar pressure is expressed at +1 mm Hg. If pressure in the alveoli is lower than atmospheric pressure, the alveolar pressure is expressed at -1 mm Hg. It is the pressure difference between P_B and P_{alv} that results in air movement during one respiratory cycle. The details of this process during quiet resting breathing are as follows:

1. *Alveolar pressure equals atmospheric pressure (figure 23.14, step 1).* At the end of expiration, before the next respiratory cycle starts, P_B and P_{alv} are equal and no air moves into or out of the lungs.
2. *Alveolar pressure is less than atmospheric pressure (figure 23.14, step 2).* As inspiration begins, contraction of inspiratory muscles increases thoracic volume, which results in expansion of the lungs and an increase in alveolar volume. The increased alveolar volume causes a decrease in intra-alveolar pressure below barometric air pressure to approximately -1 mm Hg. Air flows into the lungs because barometric air pressure is greater than intra-alveolar pressure.
3. *Alveolar pressure again equals atmospheric pressure (figure 23.14, step 3).* At the end of inspiration, the thorax stops expanding, the alveoli stop expanding, and intra-alveolar pressure becomes equal to barometric air pressure because of airflow into the lungs. No movement of air occurs after intra-alveolar pressure becomes equal to barometric pressure, but the volume of the lungs is larger than it was at the end of expiration.
4. *Alveolar pressure is greater than atmospheric pressure (figure 23.14, step 4).* During expiration, the volume of the thorax decreases as the diaphragm relaxes, and the thorax and lungs recoil. Because thoracic volume determines alveolar volume, the smaller thoracic volume results in a corresponding decrease in alveolar volume. Thus, intra-alveolar pressure rises over barometric air pressure to approximately +1 mm Hg. Because intra-alveolar pressure is greater than barometric air pressure, air flows out of the lungs. As expiration ends, the decrease in thoracic volume stops, and the alveoli stop changing size. The process repeats, beginning at step 1.

FUNDAMENTAL Figure



- 1 At the end of expiration, alveolar pressure is equal to atmospheric pressure, and there is no air movement.
- 2 During inspiration, increased thoracic volume results in increased alveolar volume and decreased alveolar pressure. Atmospheric pressure is greater than alveolar pressure, and air moves into the lungs.



- 3 At the end of inspiration, alveolar pressure is equal to atmospheric pressure, and there is no air movement.
- 4 During expiration, decreased thoracic volume results in decreased alveolar volume and increased alveolar pressure. Alveolar pressure is greater than atmospheric pressure, and air moves out of the lungs.

PROCESS FIGURE 23.14 Intra-alveolar Pressure Changes During Inspiration and Expiration

The combined space of all the alveoli is represented by a large “bubble” (blue). The alveoli are actually microscopic and would not be visible at the scale of this illustration. **AP|R**

How would traveling to higher altitude, where atmospheric pressure is lower, affect step 2?

Factors Affecting Alveolar Ventilation

While changes in pressure differences are the principal factors in driving alveolar ventilation, there are two other factors that influence the ability of alveoli to increase and decrease in volume. These two factors are (1) lung recoil and (2) pleural pressure.

Lung Recoil

Lung recoil is the tendency for the lungs to decrease in size after they are stretched. Imagine a stretched rubber band snapping back to its original size when released. Similarly, upon expiration, the tension on the lungs is released and they return to their original, smaller size, which compresses the alveoli. Lung recoil occurs for two reasons: (1) elastic recoil and (2) surface tension. Elastic recoil occurs because elastic fibers within the lungs and thoracic wall return to their original shape and size once the tension on them is released, just like the rubber band.

Lung recoil due to surface tension is because of hydrogen bonding within the alveoli. Alveoli are lined with an aqueous alveolar fluid, which adheres to the wall of the alveoli. However, the water molecules in the alveolar fluid are also attracted to each other toward the center of each alveolus. As hydrogen bonds form, the walls of each alveolus are pulled inward, which causes it to collapse. Collapse of the alveoli due to surface tension is prevented by the molecule **surfactant** (ser-fak'tānt; surface acting agent). Surfactant is a mixture of lipoprotein molecules produced by the type II pneumocytes of the alveolar epithelium. It forms a one-molecule-thick

layer over the alveolar fluid, which reduces the surface tension in the alveoli. With surfactant, the force produced by surface tension is approximately 3 mm Hg; without surfactant, the force can be as high as 30 mm Hg. Thus, surfactant greatly reduces the tendency of the lungs to collapse. Premature infants do not produce enough surfactant. This is what is meant by the common statement that “their lungs are immature” (see Clinical Impact 23.4).

Pleural Pressure

Pleural pressure is the pressure within the pleural cavity between the parietal pleura and the visceral pleura. Recall that the parietal and visceral pleurae are adhered to each other by pleural fluid. The pleural fluid is analogous to a thin film of water between two sheets of glass (the visceral and parietal pleurae); the glass sheets can easily slide over each other, but it is difficult to separate them. When the thoracic wall expands during inspiration, the parietal pleura exerts an outward force on the visceral pleura covering the lungs and the lungs expand. Pleural pressure pulls the lungs outward and is lower than intra-alveolar pressure. This aids in alveolar expansion. After expiration, pleural pressure is -4 mm Hg and intra-alveolar pressure is 0 mm Hg.

If the visceral and parietal pleurae become separated, such as if the thoracic wall or lung is pierced, the lungs collapse. Because the two pleural cavities are independent, it is possible to have only one lung collapse. The separation of the visceral and parietal pleurae increases pleural pressure. This increase in pleural pressure is called a **pneumothorax**. A pneumothorax has two major possible causes: (1) penetrating trauma and (2) nonpenetrating trauma. Types of penetrating traumas include being stabbed, getting shot by a gun, and breaking a rib. Types of nonpenetrating traumas include a blow to the chest; a medical procedure, such as insertion of a catheter to withdraw pleural fluid; disease, such as an infection or emphysema; and severe, spastic coughing. A pneumothorax may be treated by inserting a chest tube that aspirates the pleural cavity and restores a negative pressure, which can cause reexpansion of the lung. Surgery may also be necessary to close the opening into the pleural cavity.

In a **tension pneumothorax**, the pressure within the pleural cavity is always higher than barometric air pressure. Any situation where a pneumothorax occurred can lead to a tension pneumothorax. If a tear in the pleural cavity forms a tissue flap that acts as a flutter valve, it will allow air to enter the pleural cavity during inspiration but will not allow it to exit during expiration. The result is an increase in air and pressure within the pleural cavity, which could lead to inadequate delivery of O_2 to tissues. The insertion of a large-bore needle into the pleural cavity allows air to escape and releases the pressure.

Summary of Pressure Changes During a Normal Breathing Cycle

At the end of a normal expiration, pleural pressure is -4 mm Hg, and intra-alveolar pressure is equal to barometric pressure (0 mm Hg). During normal, quiet inspiration, pleural pressure decreases to -7 mm Hg (figure 23.15, *step 1*). Consequently, the alveolar volume increases, intra-alveolar pressure decreases below barometric air pressure, and air flows into the lungs. As air flows into the lungs,

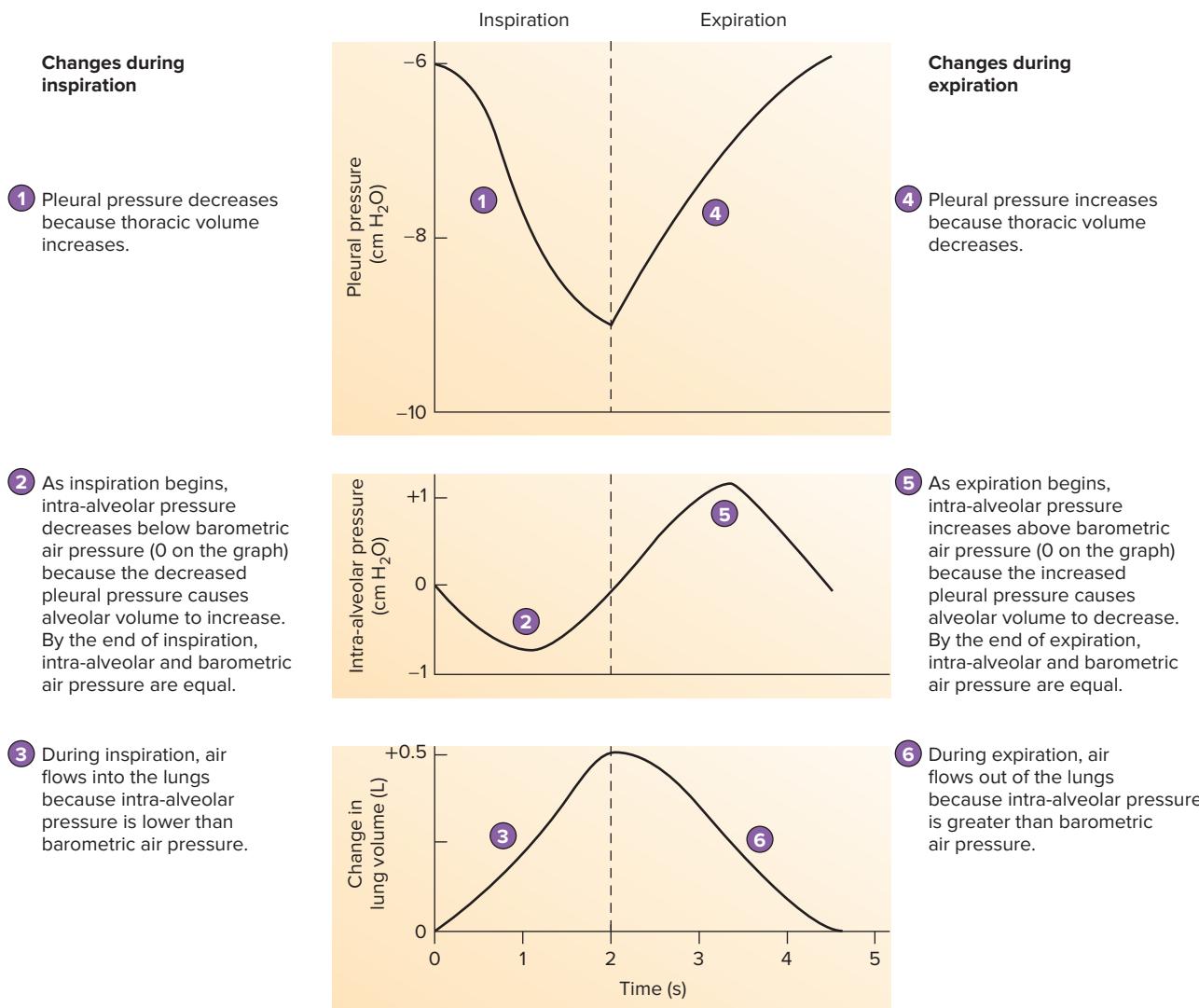


Clinical IMPACT 23.4

Infant Respiratory Distress Syndrome

Infant respiratory distress syndrome is common in premature infants, especially those with a gestation age of less than 28 weeks. This condition occurs because surfactant is not produced in adequate quantities until approximately 28 weeks of development. Thereafter, the amount produced increases as the fetus matures. Pregnant women who are likely to deliver prematurely can be given cortisol, which crosses the placenta into the fetus and stimulates surfactant synthesis.

If a newborn produces insufficient surfactant, the lungs tend to collapse. Thus, the muscles of respiration must exert a great deal of energy to keep the lungs inflated, and even then, ventilation is inadequate. Without specialized treatment, most babies with this disease die soon after birth as a result of inadequate ventilation of the lungs and fatigued respiratory muscles. Infants with infant respiratory distress syndrome are treated with pressurized air, which delivers oxygen-rich air to the lungs. The pressure helps keep the alveoli inflated. In addition, surfactant administered with the pressurized air can reduce surface tension in the alveoli. Surfactant can be obtained from cow, pig, and human lungs; from human amniotic fluid; or from genetically modified bacteria. Synthetic surfactant is also available.



PROCESS FIGURE 23.15 Dynamics of a Normal Breathing Cycle

During inspiration, air flows into the lungs because the pressure in the thoracic cavity decreases. During expiration, air flows out of the lungs because the pressure in the thoracic cavity increases.

? If a patient is inside a hyperbaric chamber, would the value of the barometric air pressure on these three graphs change?

intra-alveolar pressure increases and becomes equal to barometric pressure at the end of inspiration (figure 23.15, steps 2 and 3).

The decrease in pleural pressure during inspiration occurs for two reasons. First, because changing volume affects pressure (Boyle's law), the increased volume of the thoracic cavity causes decreased pleural pressure. Second, as the thoracic cavity expands, the lungs expand because they adhere to the inner thoracic wall through the pleurae. As the lungs expand, their tendency to recoil increases, resulting in an increased suction effect and a lowering of pleural pressure. The tendency for the lungs to recoil increases as the lungs are stretched, similar to the increased force generated in a stretched rubber band.

During expiration, pleural pressure increases because of decreased thoracic volume and decreased lung recoil (figure 23.15, step 4). As pleural pressure increases, alveolar volume decreases, intra-alveolar pressure increases above barometric air pressure, and air flows out of the lungs. As air flows out of the lungs, intra-alveolar pressure decreases and becomes equal to barometric pressure at the end of expiration (figure 23.15, steps 5 and 6).

ASSESS YOUR PROGRESS

- What are the assigned values for barometric air pressure and for intra-alveolar pressure?
- What is lung recoil, and what two factors cause it?
- How does surfactant reduce lung recoil? What happens if the alveoli have insufficient surfactant?
- What is pleural pressure? What happens to alveolar volume when pleural pressure decreases? What causes pleural pressure to be lower than intra-alveolar pressure?
- How does a pneumothorax cause a lung to collapse? How does a pneumothorax affect the chest cavity?
- During inspiration, what causes pleural pressure to decrease? What effect does this have on intra-alveolar pressure and air movement?
- During expiration, what causes pleural pressure to increase? What effect does this have on intra-alveolar pressure and air movement?

Factors Affecting Diffusion Through the Respiratory Membrane

In order for humans to utilize O₂ in the air we breathe, O₂ must be able to diffuse across the respiratory membrane into the blood. Three major factors influence the rate of gas diffusion through the respiratory membrane: (1) partial pressure gradients for O₂ and CO₂, (2) the thickness of the respiratory membrane, and (3) the surface area of the respiratory membrane.

Partial Pressure Gradients

The determining factor of gas movement direction is the partial pressure gradient for each gas. If the partial pressure gradient of a gas is higher in the alveolus, it will diffuse across the respiratory membrane into the blood. On the other hand, if the partial pressure of a gas is higher in the blood, it will diffuse across the respiratory membrane into the alveolus. When the partial pressure of a gas is greater on one side of the respiratory membrane than on the other side, net diffusion occurs from the higher to the lower partial pressure (see figure 23.8b). Normally, the partial pressure of oxygen (P_{O₂}) is greater in the alveoli than in the blood of the pulmonary capillaries, and the partial pressure of carbon dioxide (P_{CO₂}) is greater in the blood than in the alveolar air.

If faster gas exchange is needed, increasing alveolar ventilation will create a steeper partial pressure gradient for both O₂ and CO₂. The greater volume of atmospheric air exchanged with the residual volume raises alveolar P_{O₂} and lowers alveolar P_{CO₂}. This promotes gas exchange. Conversely, inadequate ventilation causes a lower than normal partial pressure gradient for both O₂ and CO₂, which causes inadequate gas exchange.

Oxygen Partial Pressure Gradients

The partial pressure gradient for O₂ is into the blood from the alveoli. Once in the blood, the partial pressure gradient for O₂ is into the body's cells from the blood. Figure 23.16 illustrates the partial pressures responsible for gas exchange. The following steps describe the specific partial pressures for O₂ as it moves toward the body's cells:

1. The P_{O₂} of alveolar air averages approximately 104 mm Hg (figure 23.16, step 1). The P_{O₂} in the pulmonary capillaries is approximately 40 mm Hg. Thus, because the P_{O₂} is higher in the alveolar air, O₂ diffuses into the pulmonary capillaries, down its partial pressure gradient.
2. Even if a person is exercising, by the time blood reaches the venous ends of the pulmonary capillaries, an equilibrium has been achieved and the P_{O₂} in the blood is 104 mm Hg (figure 23.16, step 2).
3. There is a slight decrease in the P_{O₂} of blood in the pulmonary veins to about 95 mm Hg (figure 23.16, step 3). This slight decrease is due to mixing of deoxygenated blood from the bronchial veins with blood leaving the pulmonary capillaries.
4. The P_{O₂} of arterial blood as it arrives in the tissues is still 95 mm Hg compared to the P_{O₂} of the interstitial fluid, which is 40 mm Hg (figure 23.16, step 4). The P_{O₂} in individual tissue cells is around 20 mm Hg. Thus, O₂ diffuses out of the capillaries into the interstitial fluid and across the plasma

membrane of individual cells. The individual cells then use the O₂ to produce ATP, which releases CO₂ as a by-product.

5. By the time blood has reached the venous end of a capillary network, it has achieved an equilibrium with the cells and interstitial fluid (figure 23.16, step 5).

Carbon Dioxide Partial Pressure Gradients

The partial pressure gradient for CO₂ is the opposite that for O₂. Carbon dioxide moves out of the body's cells and into the blood. Once in the blood, the partial pressure gradient for CO₂ is out of the blood into the alveoli.

We will now follow the steps in reverse order in figure 23.16 as it describes the specific partial pressures for CO₂ as it moves away from the body's cells toward the alveoli.

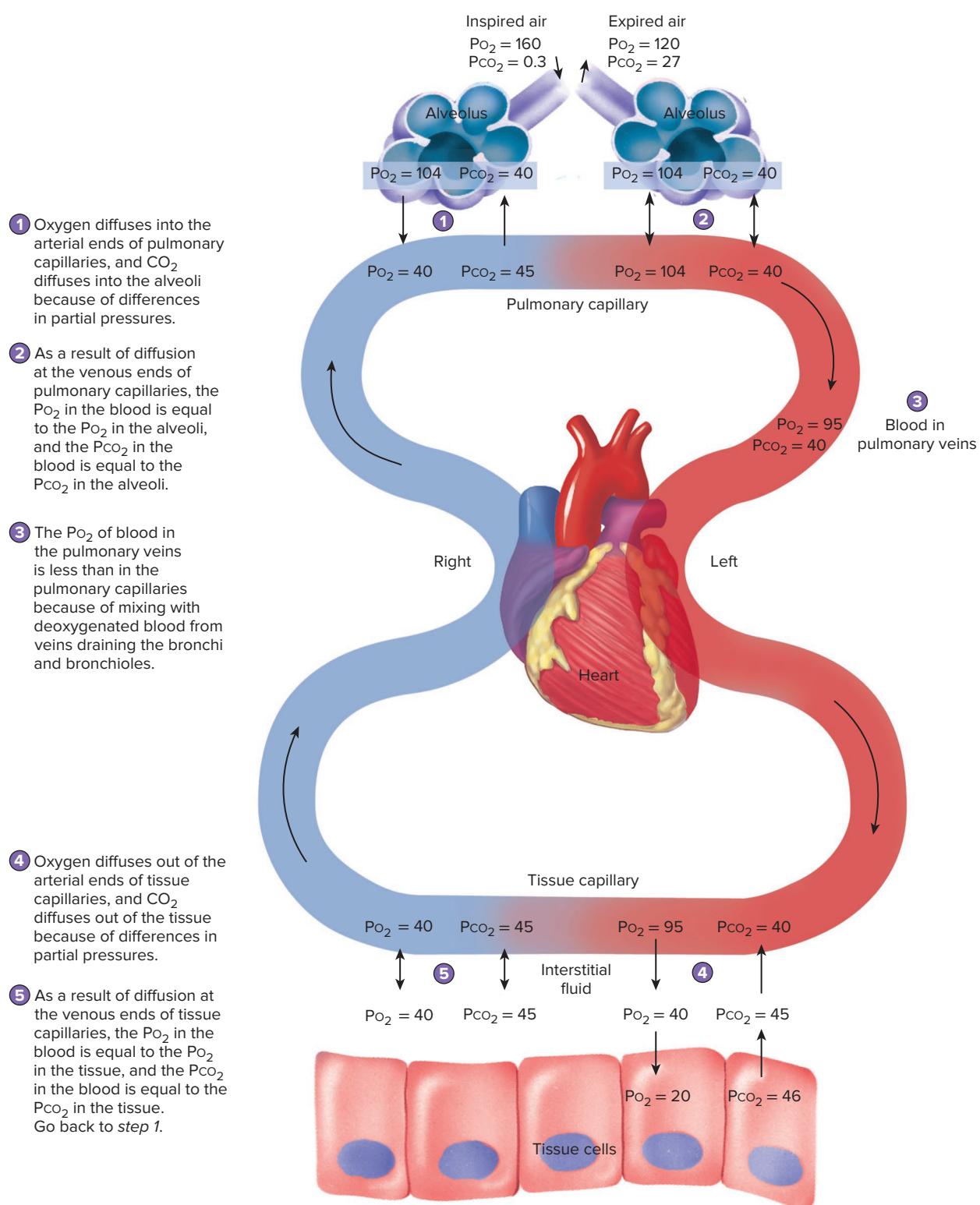
1. As cells produce CO₂, the intracellular P_{CO₂} increases to approximately 46 mm Hg and the interstitial fluid P_{CO₂} is approximately 45 mm Hg (figure 23.16, step 5). The P_{CO₂} of arterial blood as it arrives in the tissues is 40 mm Hg. Thus, CO₂ diffuses out of the cells, into the interstitial fluid and into the blood, down its partial pressure gradient. By the time blood has reached the venous end of the capillary network, it has achieved an equilibrium with the interstitial fluid and has a P_{CO₂} of 45 mm Hg.
2. The P_{CO₂} of the blood when it returns to the arterial end of the pulmonary capillaries is still 45 mm Hg compared to a P_{CO₂} of 40 mm Hg in the alveoli (figure 23.16, steps 1 and 2). Thus, at the alveoli, CO₂ diffuses out of the blood down its partial pressure gradient. At the venous end of the pulmonary capillaries, P_{CO₂} has achieved an equilibrium with the alveoli and has decreased to 40 mm Hg.

Respiratory Membrane Thickness

Increasing the thickness of the respiratory membrane decreases the rate of gas diffusion. The thickness of the respiratory membrane normally averages 0.6 μm, but diseases increase its thickness. A two- or three-fold thickness increase markedly decreases the rate of gas exchange. The most common cause of increased respiratory membrane thickness is an accumulation of fluid in the alveoli, known as *pulmonary edema*. Alveolar fluid accumulation is usually caused by failure of the left side of the heart. Left-side heart failure increases venous pressure in the pulmonary capillaries and causes fluid to accumulate in the alveoli. Conditions that result in inflammation of the lung tissues, such as with tuberculosis or pneumonia, can also cause fluid accumulation within the alveoli.

Respiratory Membrane Surface Area

In a healthy adult, the total surface area of the respiratory membrane is approximately 70 m² (approximately one-fourth of the size of a tennis court or the floor area of a 25- × 30-foot room). Several respiratory diseases, including emphysema and lung cancer, cause a decrease in the surface area of the respiratory membrane. Even small decreases in this surface area adversely affect the respiratory exchange of gases during strenuous exercise. When the total surface area of the respiratory membrane is decreased to one-third



PROCESS FIGURE 23.16 Gas Exchange

Partial pressure gradients of O_2 and CO_2 between the alveoli and the pulmonary capillaries and between the tissues and the tissue capillaries are responsible for gas exchange. All partial pressures shown are expressed in mm Hg. **AP|R**

What effect would breathing into and out of a paper bag have on CO_2 diffusion at the alveoli?

or one-fourth of normal, the exchange of gases is significantly restricted, even under resting conditions.

A decreased surface area for gas exchange can also result from the surgical removal of lung tissue, the destruction of lung tissue by cancer, the degeneration of the alveolar walls by emphysema, or the replacement of lung tissue by connective tissue due to tuberculosis. More acute conditions that cause the alveoli to fill with fluid also reduce the surface area for gas exchange because the increased thickness of the respiratory membrane caused by the fluid accumulation makes the alveoli nonfunctional. This may occur in pneumonia or in pulmonary edema resulting from failure of the left ventricle.

ASSESS YOUR PROGRESS



- 44.** Describe the four factors that affect the diffusion of gases through the respiratory membrane. Give examples of diseases that decrease diffusion by altering these factors.
- 45.** Does O₂ or CO₂ diffuse more easily through the respiratory membrane?
- 46.** What effect do alveolar ventilation and pulmonary capillary perfusion have on gas exchange?
- 47.** Describe the partial pressure of O₂ and CO₂ in the alveoli, lung capillaries, tissue capillaries, and tissues.
- 48.** How do these pressures account for the movement of O₂ and CO₂ between air and blood and between blood and tissues?

23.6 Oxygen and Carbon Dioxide Transport in the Blood

LEARNING OUTCOMES



After reading this section, you should be able to

- A. Contrast fetal hemoglobin with maternal hemoglobin.**
- B. Explain how O₂ and CO₂ are transported in the blood.**
- C. Explain the CO₂ exchange in the lungs and at the tissues.**
- D. Discuss the factors that affect O₂ and CO₂ transport in the blood.**

Once O₂ and CO₂ enter the blood, they each interact with components there that aid in their solubility and reduce the potentially dangerous impact CO₂ could have on blood pH. Both O₂ and CO₂ are transported by the protein, hemoglobin; however, CO₂ is also transported in other ways.

Hemoglobin

Hemoglobin is a complex protein synthesized by immature red blood cells. Recall from chapter 19 that hemoglobin remains within the cytoplasm of red blood cells and occupies about one-third of their total volume. There are four types of hemoglobin molecules: (1) embryonic, (2) fetal, (3) adult, and (4) an altered hemoglobin, hemoglobin-S.

Embryonic and fetal hemoglobin are unique forms of hemoglobin found in the red blood cells of embryos and fetuses only (see chapter 19). As fetal blood circulates through the placenta, O₂ is released from the mother's blood into the fetal blood, and CO₂ is released from fetal blood into the mother's blood. These forms of hemoglobin are particularly effective for O₂ transport because (1) the concentration of fetal hemoglobin is approximately 50% greater than the concentration of maternal hemoglobin and (2) for a given Po₂, fetal hemoglobin has a higher affinity for O₂ than maternal hemoglobin does.

Adult hemoglobin consists of four subunits, each containing one iron-based heme group. It is the heme group to which O₂ binds, so one hemoglobin can carry up to four O₂ molecules.

The fourth type of hemoglobin is the altered form found in individuals with sickle-cell disease. This hemoglobin is called hemoglobin-S. Recall from chapter 19 that under low O₂ conditions, the hemoglobin-S molecules aggregate together inside red blood cells causing them to become sickle-shaped. The sickle-shaped red blood cells become lodged inside small capillaries and block blood flow.

Transport of O₂

Once O₂ diffuses through the respiratory membrane into the blood, it is transported to all the cells of the body. Approximately 98.5% of O₂ is transported reversibly bound to hemoglobin within red blood cells, and the remaining 1.5% is dissolved in the plasma. Cells use O₂ in aerobic respiration to synthesize ATP (see chapter 25).

Transport of CO₂

Carbon dioxide is formed as a by-product of the breakdown of glucose when cells use O₂ to produce ATP. The CO₂ diffuses out of individual cells into the blood. The blood concentration of CO₂ needs to be very tightly regulated because too much CO₂ in the blood causes the blood to become acidic. There are three ways CO₂ is transported in the blood: (1) dissolved in the plasma, (2) bound to hemoglobin, and (3) converted to bicarbonate ion (HCO₃⁻) (figure 23.17).

Transport of CO₂ in the Plasma

About 7% of CO₂ dissolves directly in the plasma as it diffuses out of the cells and into the blood. The remaining CO₂ diffuses into the red blood cells where it either binds to hemoglobin or is converted to HCO₃⁻.

Transport of CO₂ by Hemoglobin

Approximately 23% of CO₂ is transported bound to hemoglobin (see figure 23.17). Many CO₂ molecules bind in a reversible fashion to the α- and β-globin chains of hemoglobin molecules. Carbon dioxide's ability to bind to hemoglobin is affected by the amount of O₂ bound to hemoglobin. The smaller the amount of O₂ bound to hemoglobin, the greater the amount of CO₂ able to bind to it, and vice versa. This relationship is called the **Haldane effect**. In tissues, as hemoglobin binds CO₂, the affinity of hemoglobin for O₂ is reduced. This is beneficial because

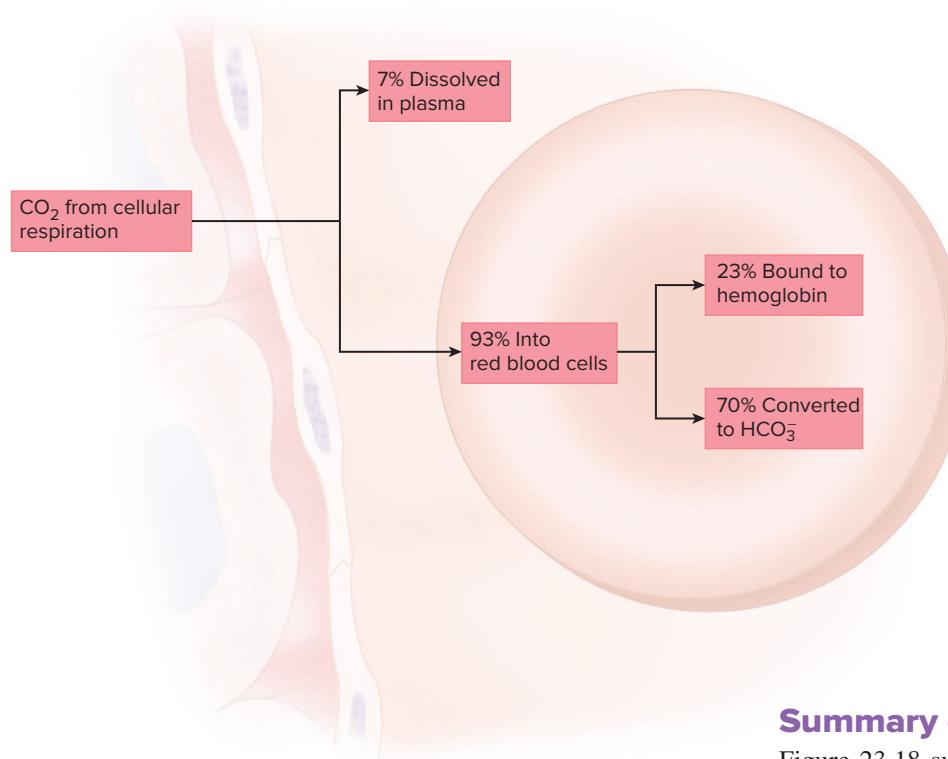


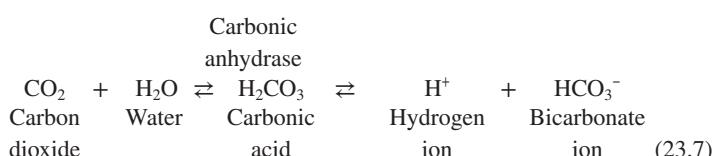
FIGURE 23.17 Transport of CO₂

Carbon dioxide is transported in three different ways in the blood: (1) a small portion dissolves directly in the plasma, (2) some binds to the globin portion of hemoglobin in the cytoplasm of red blood cells, and (3) the majority is converted by carbonic anhydrase to bicarbonate ion in the cytoplasm of red blood cells. The bicarbonate ions are transported out of the red blood cells and into the plasma.

tissues with higher levels of CO₂ demand more O₂ in order to continue aerobic respiration, our cells' most efficient means of producing ATP.

Transport of CO₂ as Bicarbonate Ions

About 70% of blood CO₂ is transported in the form of HCO₃⁻, dissolved in either the cytoplasm of red blood cells or the plasma of the blood. Within red blood cells, an enzyme called **carbonic anhydrase** catalyzes a reversible reaction (see chapter 2). Carbonic anhydrase catalyzes the production of carbonic acid (H₂CO₃) from CO₂ and H₂O. The H₂CO₃ then dissociates into H⁺ and HCO₃⁻ shown by the following equation:



As CO₂ levels increase, more H⁺ is produced. Recall from chapter 2 that higher concentrations of H⁺ cause the pH to decrease and the solution becomes acidic. However, because this is a reversible reaction, if CO₂ levels decrease, carbonic anhydrase creates H₂CO₃ upon the combining of H⁺ and HCO₃⁻. The H₂CO₃ then dissociates to form CO₂ and H₂O, which lowers H⁺ concentration and pH increases into a more basic (alkaline) range.

At the tissues, where CO₂ levels are higher, HCO₃⁻ is removed from the red blood cell by an HCO₃⁻/Cl⁻ antiporter. This process is called the **chloride shift**. In the chloride shift, HCO₃⁻ diffuses out of the red blood cell while Cl⁻ diffuses in through the antiporter. This exchange maintains electrical neutrality in the red blood cells and plasma. Removing HCO₃⁻ from inside the red blood cells also promotes greater CO₂ transport. As HCO₃⁻ concentrations decrease within the red blood cell, more CO₂ reacts with water to form additional HCO₃⁻ and H⁺.

Although elevated H⁺ levels usually create an acidic environment, there are mechanisms within the red blood cells that dampen the effect of increased H⁺. Hemoglobin serves as a buffer within the red blood cell cytoplasm. Hemoglobin binds to H⁺ preventing an increase in H⁺ concentration.

Summary of Gas Transport

Figure 23.18 summarizes the events in the transport of both O₂ from the lungs to the tissues and CO₂ from the tissues to the lungs. Figure 23.18a summarizes the events as O₂ is delivered to the tissues and CO₂ is transported away from the tissues. Figure 23.18b summarizes the events as O₂ enters the blood from the alveoli and CO₂ exits the blood. There are many physiological factors that modulate the affinity of hemoglobin for both O₂ and CO₂. For example, under conditions of increased O₂ demand, the affinity of hemoglobin for O₂ is reduced. A discussion of some of these conditions follows.

Physiological Factors Affecting Gas Transport

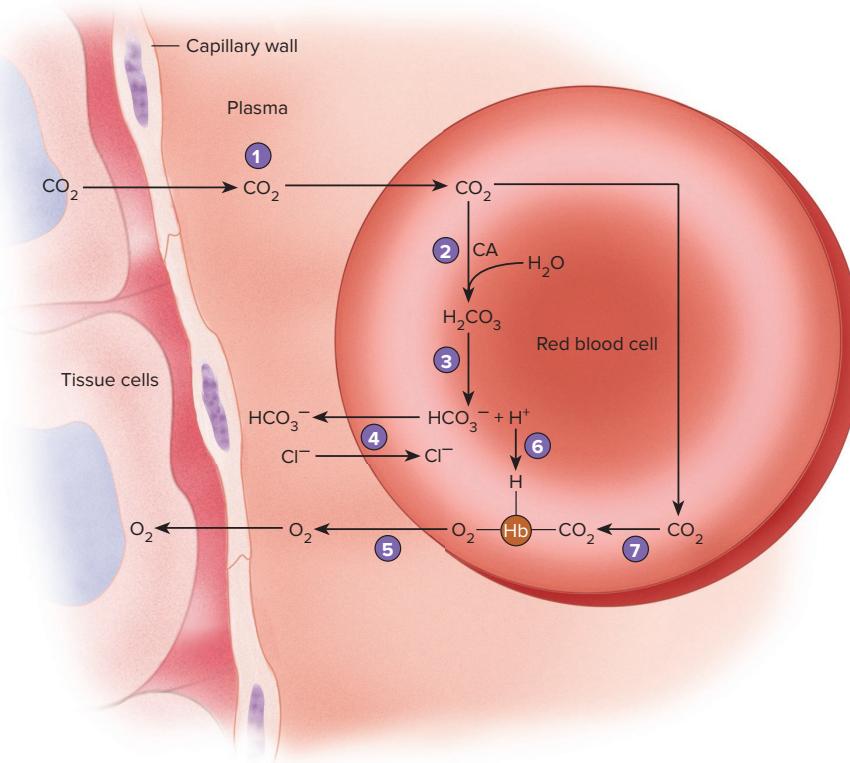
The respiratory system maintains blood O₂ and CO₂ concentrations and blood pH within normal values. Changes in these levels out of their normal range have a noticeable influence on the relationship between hemoglobin, O₂, and CO₂. **Chemoreceptors** are specialized neurons that detect changes in the concentration of specific chemicals. The chemoreceptors involved in regulating respiration respond to changes in pH, changes in Po₂, Pco₂, or all three. **Central chemoreceptors** are located bilaterally and ventrally in the **chemosensitive area** of the medulla oblongata, and they are connected to the respiratory center. **Peripheral chemoreceptors** are found in the carotid and aortic bodies. These structures are small, vascular sensory organs encapsulated in connective tissue and located near the carotid sinuses and the aortic arch (see chapter 21).

Effect of Po₂ on O₂ Transport

The relationship between O₂ and hemoglobin is similar to that of a ligand and its receptor in that hemoglobin has specific binding sites for O₂. These binding sites are the heme groups of the hemoglobin. Hemoglobin is 100% saturated with O₂

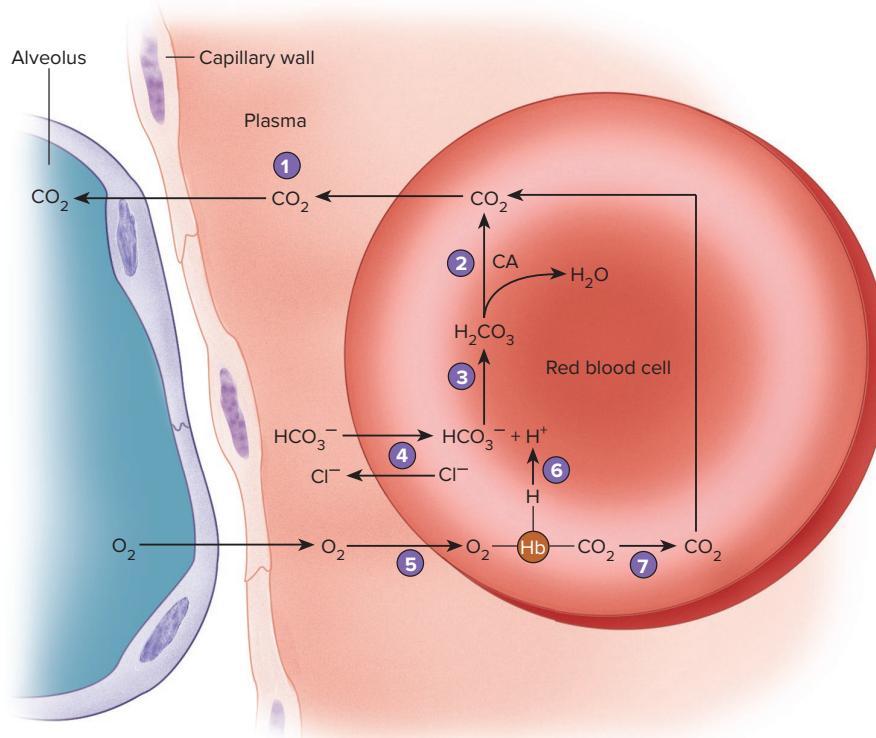
FUNDAMENTAL Figure

- ① In the tissues, CO_2 diffuses into the plasma and into red blood cells. Some of the CO_2 remains in the plasma.
- ② In red blood cells, CO_2 reacts with water (H_2O) to form carbonic acid (H_2CO_3) in a reaction catalyzed by the enzyme carbonic anhydrase (CA).
- ③ Carbonic acid dissociates to form bicarbonate ions (HCO_3^-) and hydrogen ions (H^+).
- ④ In the chloride shift, as HCO_3^- diffuse out of the red blood cells, electrical neutrality is maintained by the diffusion of chloride ions (Cl^-) into them.
- ⑤ Oxygen is released from hemoglobin (Hb). Oxygen diffuses out of red blood cells and plasma into the tissue.
- ⑥ Hydrogen ions combine with hemoglobin, which promotes the release of O_2 from hemoglobin (Bohr effect).
- ⑦ Carbon dioxide combines with hemoglobin. Hemoglobin that has released O_2 readily combines with CO_2 (Haldane effect).



(a) Gas exchange in the tissues

- ① In the lungs, CO_2 diffuses from red blood cells and plasma into the alveoli.
- ② Carbonic anhydrase catalyzes the formation of CO_2 and H_2O from H_2CO_3 .
- ③ Bicarbonate ions and H^+ combine to replace H_2CO_3 .
- ④ In the chloride shift, as HCO_3^- diffuse into red blood cells, electrical neutrality is maintained by the diffusion of chloride ions (Cl^-) out of them.
- ⑤ Oxygen diffuses into the plasma and into red blood cells. Some of the O_2 remains in the plasma. Oxygen binds to hemoglobin.
- ⑥ Hydrogen ions are released from hemoglobin, which promotes the uptake of O_2 by hemoglobin (Bohr effect).
- ⑦ Carbon dioxide is released from hemoglobin. Hemoglobin that is bound to O_2 readily releases CO_2 (Haldane effect).



(b) Gas exchange in the lungs

PROCESS FIGURE 23.18 Gas Exchange

(a) In the tissues, CO_2 diffuses into red blood cells, where the enzyme carbonic anhydrase (CA) is located. CA catalyzes the reaction of CO_2 with H_2O to form carbonic acid (H_2CO_3). H_2CO_3 dissociates to form bicarbonate ions (HCO_3^-) and hydrogen ions (H^+). Oxygen is released from hemoglobin (Hb) and diffuses into tissue cells. (b) In the lungs, CO_2 diffuses from red blood cells into the alveoli. CA catalyzes the formation of CO_2 and H_2O from H_2CO_3 . H^+ and HCO_3^- combine to replace H_2CO_3 . Oxygen diffuses into red blood cells and binds to hemoglobin.

?

How would the cytoplasmic pH of red blood cells be affected by anemia that is caused by reduced hemoglobin levels?

when four O₂ molecules are bound to each hemoglobin molecule in the red blood cells. When there is an average of two O₂ molecules bound to each hemoglobin molecule, hemoglobin is 50% saturated. The **oxygen-hemoglobin dissociation curve** describes the percent saturation of hemoglobin in the blood at different blood Po₂ values. The degree of hemoglobin saturation is determined by many factors that affect the “attraction” of hemoglobin for O₂. This attraction is called affinity. The first factor we will consider is the effect of Po₂ on hemoglobin’s affinity for O₂.

Normally, the Po₂ in the blood leaving the lungs is 104 mm Hg. At that partial pressure, hemoglobin is 98% saturated (figure 23.19a). Decreases in the Po₂ in the pulmonary capillaries have a relatively small effect on hemoglobin saturation, as shown by the fairly flat shape of the upper part of the oxygen-hemoglobin dissociation curve. Even if the blood Po₂ decreases from 104 mm Hg

to 60 mm Hg, hemoglobin is still 90% saturated. Because the affinity of hemoglobin for O₂ is stable over a wide range of Po₂ levels, hemoglobin is effective at picking up O₂ in the lungs even if the Po₂ drops significantly.

In a resting person, the normal blood Po₂ leaving the tissues is 40 mm Hg, which correlates to 75% hemoglobin saturation. Thus, 23% (98 – 75 = 23) of the O₂ picked up in the lungs is released from hemoglobin. Oxygen then diffuses into the cells of the tissues (figure 23.19b). The 75% of O₂ still bound to the hemoglobin is an O₂ reserve, which can be released if blood Po₂ decreases further. In the tissues, at lower Po₂ levels, a relatively small change in blood Po₂ results in a relatively large change in hemoglobin saturation. This is shown by the steep slope of the oxygen-hemoglobin dissociation curve (figure 23.19b). For example, during vigorous exercise, the Po₂ in skeletal muscle capillaries can decline to levels as low as

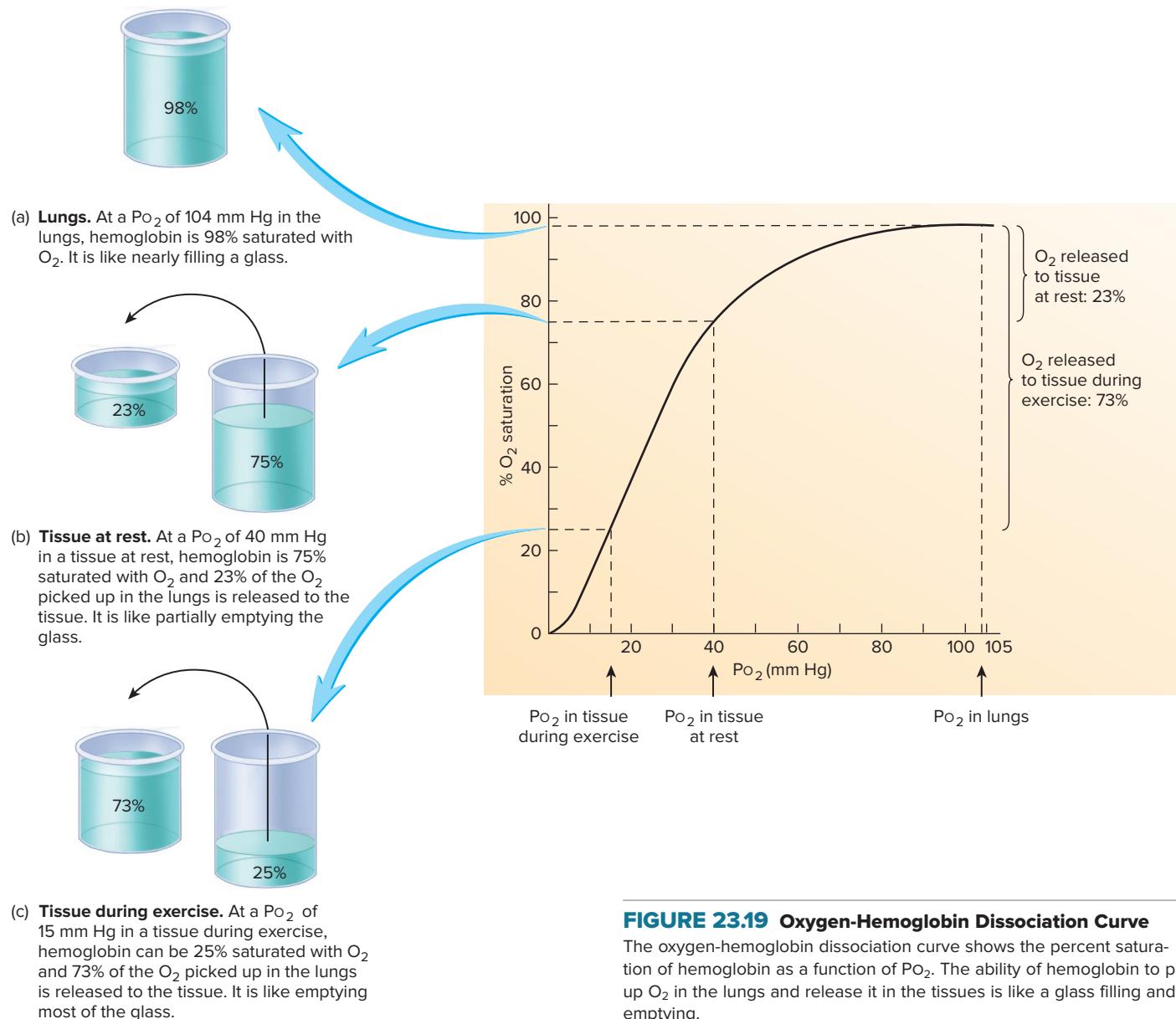
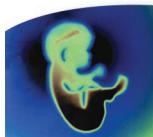


FIGURE 23.19 Oxygen-Hemoglobin Dissociation Curve

The oxygen-hemoglobin dissociation curve shows the percent saturation of hemoglobin as a function of Po₂. The ability of hemoglobin to pick up O₂ in the lungs and release it in the tissues is like a glass filling and emptying.



Clinical IMPACT 23.5

Importance of Reduced Po_2

Carbon dioxide is much more important than O_2 as a regulator of normal alveolar ventilation, but under certain circumstances a reduced Po_2 in the arterial blood plays an important stimulatory role. During conditions of shock when blood pressure is very low, the Po_2 in arterial blood can drop low enough to strongly stimulate carotid and aortic body sensory receptors. At high altitudes, where barometric air pressure is low, the Po_2 in arterial blood can also drop to levels low enough to stimulate the carotid and aortic bodies. Although Po_2 levels in the blood are reduced, the respiratory system's ability to eliminate CO_2 is not greatly affected by low barometric air pressure. Thus, blood CO_2 levels become lower than normal because of the increased alveolar ventilation initiated in response to low Po_2 .

In people with emphysema, the destruction of the respiratory membrane allows less O_2 to move into the blood. The resulting low arterial Po_2 levels stimulate an increased rate and depth of respiration. At first, arterial Pco_2 levels may be unaffected by the reduced surface area of the respiratory membrane because CO_2 diffuses across the respiratory membrane 20 times more readily than does O_2 . However, if alveolar ventilation increases to the point that CO_2 exchange increases above normal, arterial CO_2 becomes lower than normal. More severe emphysema, in which the surface area of the respiratory membrane is reduced to a minimum, can decrease CO_2 exchange to the point that arterial CO_2 becomes elevated.

15 mm Hg. Skeletal muscle cells use a significant amount of O_2 for aerobic respiration (see chapter 9). At a Po_2 of 15 mm Hg, hemoglobin is only 25% saturated, resulting in the release of 73% ($98 - 25 = 73$) of the O_2 picked up in the lungs (figure 23.19c). Thus, as tissues use more O_2 , hemoglobin releases more O_2 to those tissues.

► Predict 6

In carbon monoxide (CO) poisoning, CO binds to hemoglobin, thereby decreasing the uptake of O_2 by hemoglobin. In addition, when CO binds to hemoglobin, the oxygen-hemoglobin dissociation curve shifts to the left. How does this shift affect the ability of tissues to get O_2 ? Explain.

Effect of Po_2 on CO_2 Transport

The largest effect of Po_2 on CO_2 transport is at low Po_2 levels. Recall that when Po_2 levels are low, the Haldane effect allows hemoglobin to bind more CO_2 . In turn, as more CO_2 binds to hemoglobin, the affinity of hemoglobin for O_2 decreases.

Effect of pH and Pco_2 on O_2 Transport

In addition to Po_2 , other factors, such as blood pH and Pco_2 , influence the saturation of hemoglobin (figure 23.20). As the pH of the

blood drops (due to higher H^+ levels), the affinity of hemoglobin for O_2 at any given Po_2 is much lower. The higher H^+ levels bind to nonheme portions of hemoglobin, which changes its overall shape. Following the concept of form following function, changing the shape of hemoglobin would change its affinity for O_2 . Conversely, an increase in blood pH results in an increased affinity of hemoglobin for O_2 . This effect of pH on the oxygen-hemoglobin dissociation curve is called the **Bohr effect**, after its discoverer, Christian Bohr. An increase in Pco_2 also decreases hemoglobin's ability to bind O_2 due to the effect of CO_2 on pH. Changes in CO_2 levels indirectly produce a Bohr effect by altering pH. In addition, CO_2 can directly affect hemoglobin's ability to bind O_2 . When CO_2 binds to the α - and β -globin chains of hemoglobin (see chapter 19), hemoglobin's affinity for O_2 is reduced. The Bohr effect is beneficial to tissues when they are in high demand for O_2 .

► Predict 7

How does the movement of CO_2 from fetal blood into maternal blood increase the movement of O_2 from maternal blood into fetal blood?

(Hint: Consider the shift of the oxygen-hemoglobin dissociation curve.)

Effect of pH and Pco_2 on CO_2 Transport

The principal effect of pH and Pco_2 is on the affinity of hemoglobin for O_2 . However, a higher Pco_2 results in a larger decrease in pH. The decrease in pH triggers an increased respiratory rate as we will discuss in section 23.7. The sensitivity to CO_2 is valuable for maintaining appropriate blood pH levels.

► Predict 8

Explain the effect of (1) hyperventilation and (2) holding one's breath on blood pH.

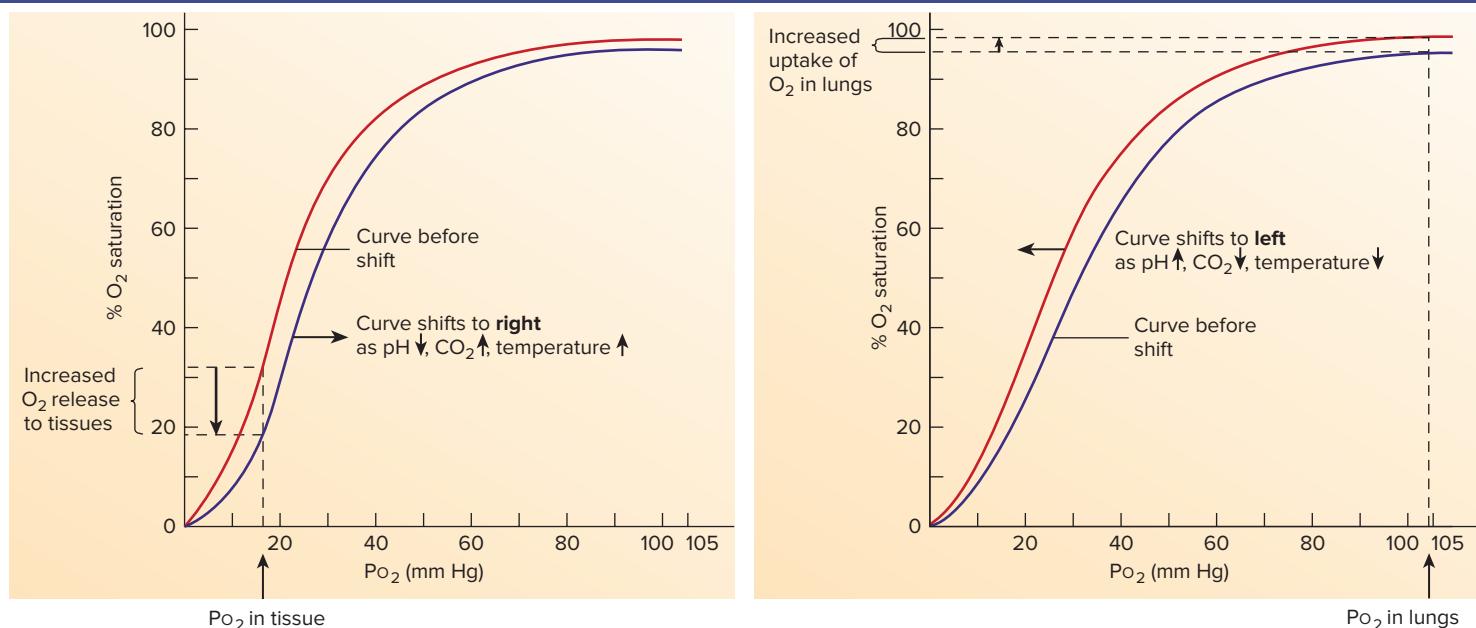
Effect of Temperature on O_2 Transport

An increase in temperature also decreases O_2 's tendency to remain bound to hemoglobin. Therefore, elevated temperatures resulting from increased metabolism increase the amount of O_2 released into the tissues by hemoglobin. In less metabolically active tissues in which the temperature is lower, less O_2 is released from hemoglobin.

When hemoglobin's affinity for O_2 decreases, the oxygen-hemoglobin dissociation curve is shifted to the right, and hemoglobin releases more O_2 (figure 23.20a). During exercise, when CO_2 and acidic substances accumulate and the temperature increases in the tissue spaces, the oxygen-hemoglobin curve shifts to the right. Under these conditions, as much as 75–85% of the O_2 is released from the hemoglobin. In the lungs, however, the curve shifts to the left because of the lower CO_2 levels, lower temperature, and lower acid levels. Therefore, hemoglobin's affinity for O_2 increases, and it becomes easily saturated (figure 23.20b).

During resting conditions, approximately 5 mL of O_2 are transported to the tissues in each 100 mL of blood, and cardiac output is approximately 5000 mL/min. Consequently, 250 mL of O_2 are delivered to the tissues each minute. During exercise, this value can increase up to 15 times. Oxygen transport can be

FUNDAMENTAL Figure



- (a) In the tissues, the oxygen-hemoglobin dissociation curve shifts to the right. As pH decreases, P_{CO₂} increases, or temperature increases, the curve (red) shifts to the right (blue), resulting in an increased release of O₂.

- (b) In the lungs, the oxygen-hemoglobin dissociation curve shifts to the left. As pH increases, P_{CO₂} decreases, or temperature decreases, the curve (blue) shifts to the left (red), resulting in an increased ability of hemoglobin to pick up O₂.

FIGURE 23.20 Effects of Shifting the Oxygen-Hemoglobin Dissociation Curve

(a) Tissues that are producing more ATP than when at rest release more CO₂, which lowers the pH. In addition, the increased activity raises the temperature in the tissues. The right shift under these conditions is advantageous to the tissues because more O₂ is needed to support the increased ATP production.

(b) A left shift in the lungs is advantageous because the hemoglobin will attract O₂ with a stronger affinity, which will encourage its diffusion into the blood.

increased threefold because of a greater degree of O₂ release from hemoglobin in the tissue capillaries, and the rate of O₂ transport is increased another five times because of the increase in cardiac output. Consequently, the volume of O₂ delivered to the tissues can be as high as 3750 mL/min (15 × 250 mL/min). Highly trained athletes can increase this volume to as high as 5000 mL/min.

Effect of Temperature on CO₂ Transport

Typically, when body temperature increases, the rate of ATP production is increased. Thus, more CO₂ enters the blood and eventually is converted into H⁺ and HCO₃⁻, lowering the pH. As we discussed, the response is often an increased respiratory rate, which removes excess CO₂ from the body.

Effect of BPG on O₂ Transport

As red blood cells metabolize glucose for energy, they produce a by-product called **2,3-bisphosphoglycerate (BPG)** (formerly called diphosphoglycerate). BPG binds to hemoglobin, which reduces its affinity for O₂. Thus, hemoglobin releases more O₂. A potent trigger for increased BPG production is low blood O₂. For example, barometric pressure is lower at high altitudes than at sea level, causing both the partial pressure of O₂ in the alveoli and the percent saturation of blood with O₂ in the pulmonary capillaries to be lower. Consequently, the blood holds less O₂ for delivery to tissues. BPG helps increase O₂ delivery to tissues because higher levels of BPG increase the release of O₂ in tissues (the oxygen-hemoglobin dissociation curve shifts to the right). On the other hand, when blood is

removed from the body and stored in a blood bank, the BPG levels in the stored blood decrease. As BPG levels decrease, the blood becomes unsuitable for transfusion after approximately 6 weeks because the hemoglobin releases less O₂ to the tissues. Banked blood is, therefore, discarded after 6 weeks of storage.

Effect of BPG on CO₂ Transport

BPG enhances the Haldane effect since hemoglobin with less O₂ bound can transport more CO₂.

Predict 9

If a person lacks the enzyme necessary for BPG synthesis, does he or she exhibit anemia (a lower-than-normal number of red blood cells) or erythrocytosis (a higher-than-normal number of red blood cells)? Explain.

ASSESS YOUR PROGRESS

49. Name the two ways O₂ is transported in the blood, and state the percentage of total O₂ transport for which each method is responsible.
50. How does the oxygen-hemoglobin dissociation curve explain the uptake of O₂ in the lungs and the release of O₂ in tissues?
51. What is the Bohr effect? How is it related to blood CO₂?
52. Why is it advantageous for the oxygen-hemoglobin dissociation curve to shift to the left in the lungs and to the right in tissues?

53. How does temperature affect O_2 's tendency to bind to hemoglobin?
54. How does BPG affect the release of O_2 from hemoglobin?
55. Why is fetal hemoglobin's affinity for O_2 greater than that of maternal hemoglobin?
56. How does the lowering HCO_3^- concentrations inside red blood cells affect CO_2 transport?
57. What is the chloride shift, and what does it accomplish?
58. Name three effects produced by H^+ binding to hemoglobin.
59. What is the Haldane effect?
60. What effect does blood CO_2 level have on blood pH?

23.7 Regulation of Ventilation

LEARNING OUTCOMES



After reading this section, you should be able to

- A. **Describe the relationship between alveolar ventilation and pulmonary capillary perfusion.**
- B. **Describe the respiratory areas of the brainstem and how they produce a rhythmic pattern of ventilation.**
- C. **Explain how blood pH, CO_2 , and O_2 levels affect ventilation.**
- D. **Discuss the Hering-Breuer reflex and its importance.**
- E. **Explain how the cerebral cortex and limbic system can affect ventilation.**
- F. **Describe the effect of exercise on ventilation.**

There are many factors that regulate respiratory rate. The body is particularly sensitive to changes in CO_2 levels and blood pH. We will first discuss blood flow regulation and neural structures that control ventilation. We will then consider regulation of this rate by different physiological factors.

Local Control

Normally, resting ventilation provides the body with all the O_2 it needs to maintain homeostasis. This is because there are many alveoli, each of which is supplied with ample blood. The flow of blood to the alveoli through pulmonary capillaries is called **pulmonary capillary perfusion**. The relationship between ventilation of the alveoli and blood flow to the alveoli is called **ventilation-perfusion coupling**. However, there are certain conditions that disrupt normal ventilation-perfusion coupling.

First, it is important to realize that even with normal ventilation-perfusion coupling, not 100% of cardiac output is fully saturated with O_2 . Blood that is not completely oxygenated is called shunted blood. There are two types of shunts in the lungs: (1) an anatomical shunt and (2) a physiological shunt. The **anatomical shunt** is due to deoxygenated blood from the bronchi and bronchioles mixing with blood in the pulmonary veins (see section 23.2). Blood that passes through pulmonary capillaries without becoming fully oxygenated is also shunted blood. The **physiological shunt** is the combination of the anatomical shunt

and incompletely oxygenated blood from the alveoli. Normally, the physiological shunt makes up 1–2% of cardiac output.

There are two main situations that can cause normal ventilation-perfusion coupling to be disrupted: (1) if there is insufficient blood flow to the alveoli and (2) if there is insufficient air flow to the alveoli. Sometimes alveolar ventilation is sufficient but blood flow to the alveoli has been reduced. For example, this can happen because of inadequate cardiac output after a heart attack. Another factor that influences differences in blood flow to different areas of the lung is body position. When a person is standing, greater blood flow and ventilation occur in the base of the lung than in the top of the lung because gravity tends to pull the blood down toward the base of the lungs. Thus, when standing, more gas exchange occurs at the base of the lungs.

In other instances, alveolar ventilation is severely reduced and the blood in the pulmonary capillaries does not become fully oxygenated. This happens during an asthma attack when bronchioles become constricted. In pneumonia or pulmonary edema, a buildup of fluid in the alveoli results in poor gas diffusion and less oxygenated blood.

Although gravity is the major factor affecting regional blood flow in the lung, under certain circumstances alveolar Po_2 can also have an effect. In most tissues, low Po_2 results in increased blood flow through the tissues (see chapter 21). However, in the lung, low Po_2 has the opposite effect. Low Po_2 causes arterioles to constrict, which reduces blood flow. This response helps keep gas exchange in the lungs efficient. Blood is routed away from areas of low O_2 toward parts of the lung that are better oxygenated. Because the function of the lungs is to acquire O_2 for the body, it is more efficient to avoid low O_2 areas in the lungs. For example, if a bronchus becomes partially blocked, ventilation of alveoli past the blockage site decreases, which in turn decreases gas exchange between the air and blood. The effect of this decreased gas exchange is diminished by rerouting the blood to better-ventilated alveoli.

► Predict 10

Even people in “good shape” may have trouble breathing at high altitudes. Explain how this can happen, even when ventilation of the lungs increases.

Neural Control

The medulla oblongata controls the respiratory rate. Neurons there control the basic rhythm of ventilation through stimulation of the muscles of respiration. The recruitment of muscle fibers and the more frequent stimulation of muscle fibers result in stronger muscle contractions and increased depth of respiration. The rate of respiration is determined by how frequently the respiratory muscles are stimulated.

Respiratory Areas in the Brainstem

Neurons involved with respiration are aggregated in certain parts of the brainstem. Scientists have learned that neurons that are active during inspiration are intermingled with those that are active during expiration.

The **medullary respiratory center** in the medulla oblongata consists of two sets of neurons: (1) the dorsal respiratory group and

(2) the ventral respiratory group. The **dorsal respiratory group** forms a longitudinal column of cells in the dorsal part of each half of the medulla oblongata. The **ventral respiratory group** forms a longitudinal column of cells located in the ventral part of each half of the medulla oblongata (figure 23.21). Communication occurs

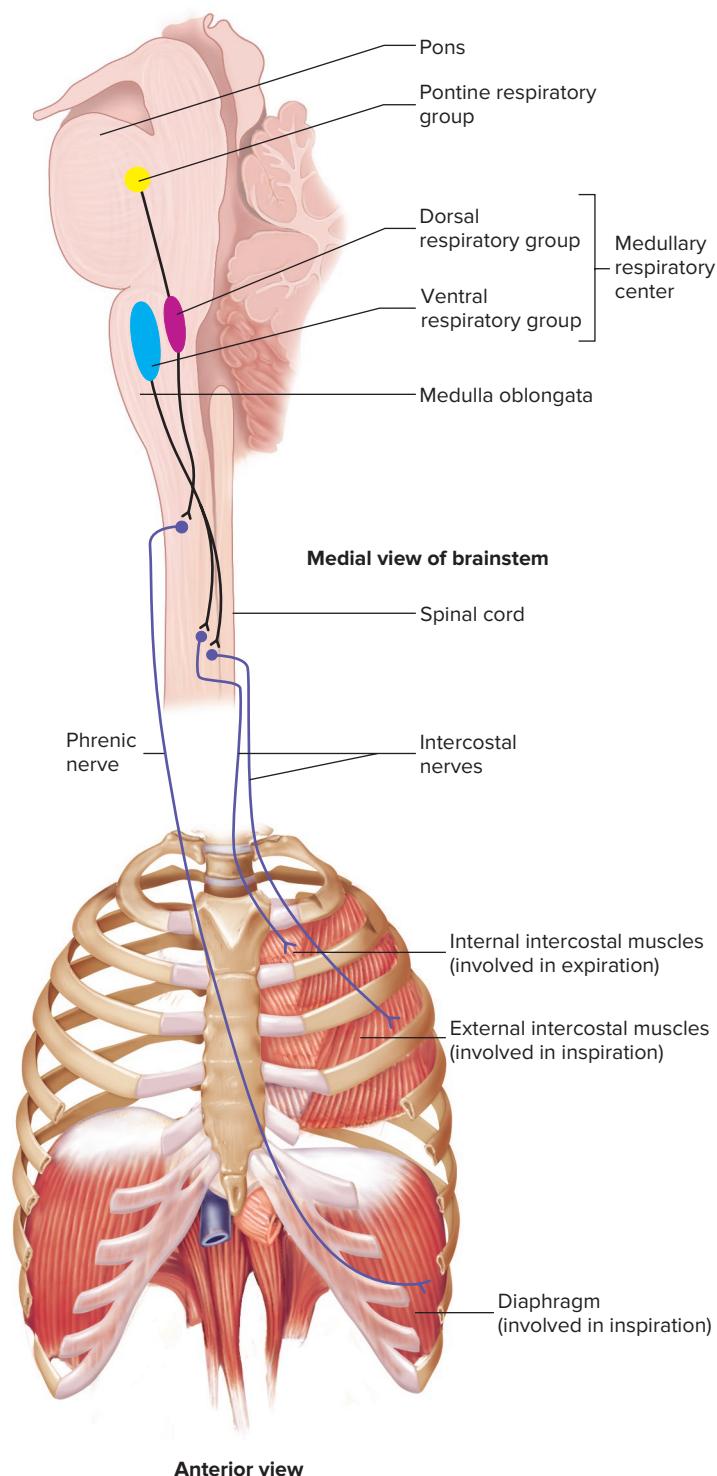


FIGURE 23.21 Respiratory Structures in the Brainstem

This figure shows the relationship of respiratory structures to each other and to the nerves innervating the muscles of respiration on the left side of the body.

between the two halves of the medulla within a respiratory group, so that respiratory movements are symmetrical. Communication also occurs between the dorsal and ventral respiratory groups.

The dorsal respiratory group is a collection of neurons that are most active during inspiration, but some are active during expiration. The dorsal respiratory groups stimulate contraction of the diaphragm. They receive input from other parts of the brain and peripheral receptors, which allows the modification of respiration.

The ventral respiratory group is a collection of neurons that are active during both inspiration and expiration. These neurons primarily stimulate the external intercostal, internal intercostal, and abdominal muscles. A part of the ventral respiratory group, the **pre-Bötzinger complex**, is believed to establish the basic rhythm of respiration.

The **pontine respiratory group**, formerly called the pneumotoxic center, is a collection of neurons in the pons that helps regulate respiration rate (figure 23.21). Some of the neurons are active only during inspiration, some only during expiration, and others during both inspiration and expiration. The precise function of the pontine respiratory group is unknown, but it has connections with the medullary respiratory center and appears to play a role in switching between inspiration and expiration, thus fine-tuning the breathing pattern. It is not considered essential for the generation of the respiratory rhythm.

Generation of Rhythmic Ventilation

One explanation for the generation of rhythmic ventilation involves the integration of a series of stimuli that start and stop inspiration:

1. *Starting inspiration.* Neurons in the medullary respiratory center spontaneously establish the basic rhythm of ventilation. The medullary respiratory center constantly receives stimulation from receptors that monitor blood gas levels, blood temperature, and the movements of muscles and joints. In addition, stimulation from the parts of the brain concerned with voluntary respiratory movements and emotions can occur. Inspiration starts when the combined input from all these sources causes the production of action potentials in the neurons that stimulate respiratory muscles.
2. *Increasing inspiration.* Once inspiration begins, more and more neurons are gradually activated. The result is progressively stronger stimulation of the respiratory muscles, which lasts for approximately 2 seconds.
3. *Stopping inspiration.* The neurons stimulating the muscles of respiration also stimulate the neurons in the medullary respiratory center that are responsible for stopping inspiration. The neurons responsible for stopping inspiration also receive input from the pontine respiratory group, stretch receptors in the lungs, and probably other sources. When these inhibitory neurons are activated, they inhibit the neurons that stimulate respiratory muscles. Relaxation of respiratory muscles results in expiration, which lasts approximately 3 seconds. The next inspiration begins again at step 1, *Starting inspiration*.

Although the medullary neurons establish the basic rate and depth of ventilation, their activities can be influenced by input

from other parts of the brain and by input from peripherally located receptors.

Effect of Po₂ on Respiratory Rate

Carbon dioxide is the principal regulator of respiratory rate. However, changes in Po₂ can also affect respiration (figure 23.22). A decrease in O₂ below its normal values is called **hypoxia** (hī-pok'sē-ă). If Po₂ levels in the arterial blood are markedly reduced while the pH and Pco₂ are held constant, an increase in ventilation rate occurs. However, within a normal range of Po₂ levels, the effect of O₂ on the regulation of respiration is small. Only after arterial Po₂ decreases to approximately 50% of its normal value does it begin to have a large stimulatory effect on respiratory movements.

At first, it is somewhat surprising that small changes in Po₂ do not cause changes in respiratory rate. But the reason becomes clear if we consider the oxygen-hemoglobin dissociation curve (see figure 23.19). At any Po₂ above 80 mm Hg, nearly all of the hemoglobin is saturated with O₂. If Po₂ levels decrease below 80 mm Hg, the oxygen-carrying capacity of the blood is significantly reduced.

When Po₂ levels are low, the carotid and aortic body chemoreceptors stimulate the respiratory center. This keeps it active despite decreasing O₂ levels. However, if Po₂ decreases sufficiently, the respiratory center can fail, resulting in death.

Effect of Pco₂ on Respiratory Rate

Blood CO₂ levels are a major regulator of respiration during both resting conditions and intense exercise. Even a small increase in CO₂ in the bloodstream triggers a large increase in the rate and depth of ventilation. For example, an increase in Pco₂ of only 5 mm Hg causes an increase in ventilation of 100%. A greater-than-normal amount of CO₂ in the blood is called **hypercapnia** (hī-per-kap'nē-ă) and a lower than normal CO₂ level is called **hypocapnia** (hī-pō-kap'nē-ă). Hypocapnia results in periods when the breathing rate is reduced or does not occur at all.

The chemoreceptors in the chemosensitive area of the medulla oblongata and in the carotid and aortic bodies respond to changes in CO₂ primarily because of the effects of CO₂ on blood pH (figure 23.22). The chemosensitive area in the medulla oblongata is far more important in regulating Pco₂ and pH than either the carotid or the aortic bodies. The carotid and aortic bodies are responsible for, at most, 15–20% of the total response to changes in Pco₂ or pH. During intense exercise, however, the carotid bodies respond more rapidly to changes in blood pH than does the chemosensitive area of the medulla.

Effect of pH on Respiratory Rate

The central chemoreceptors in the medulla oblongata detect changes in blood pH due to changes in CO₂. The carotid and aortic bodies detect changes in pH due to changes in H⁺ concentrations. Because H⁺ does not easily cross the blood-brain barrier or the blood-cerebrospinal fluid barrier (see chapter 11), the central chemoreceptors detect changes in blood pH through changes in blood CO₂. Carbon dioxide easily diffuses across the blood-brain barrier

and the blood-cerebrospinal fluid barrier. The lower pH then stimulates the respiratory center, resulting in a greater rate and depth of breathing reducing CO₂ levels, and blood pH increases to normal levels.

Maintaining body pH levels within normal limits is necessary for the proper functioning of cells. Because changes in CO₂ levels can change pH, the respiratory system plays an important role in acid-base balance. The respiratory system's role in maintaining pH is considered in greater detail in chapter 27.

The Hering-Breuer Reflex and Respiratory Rate

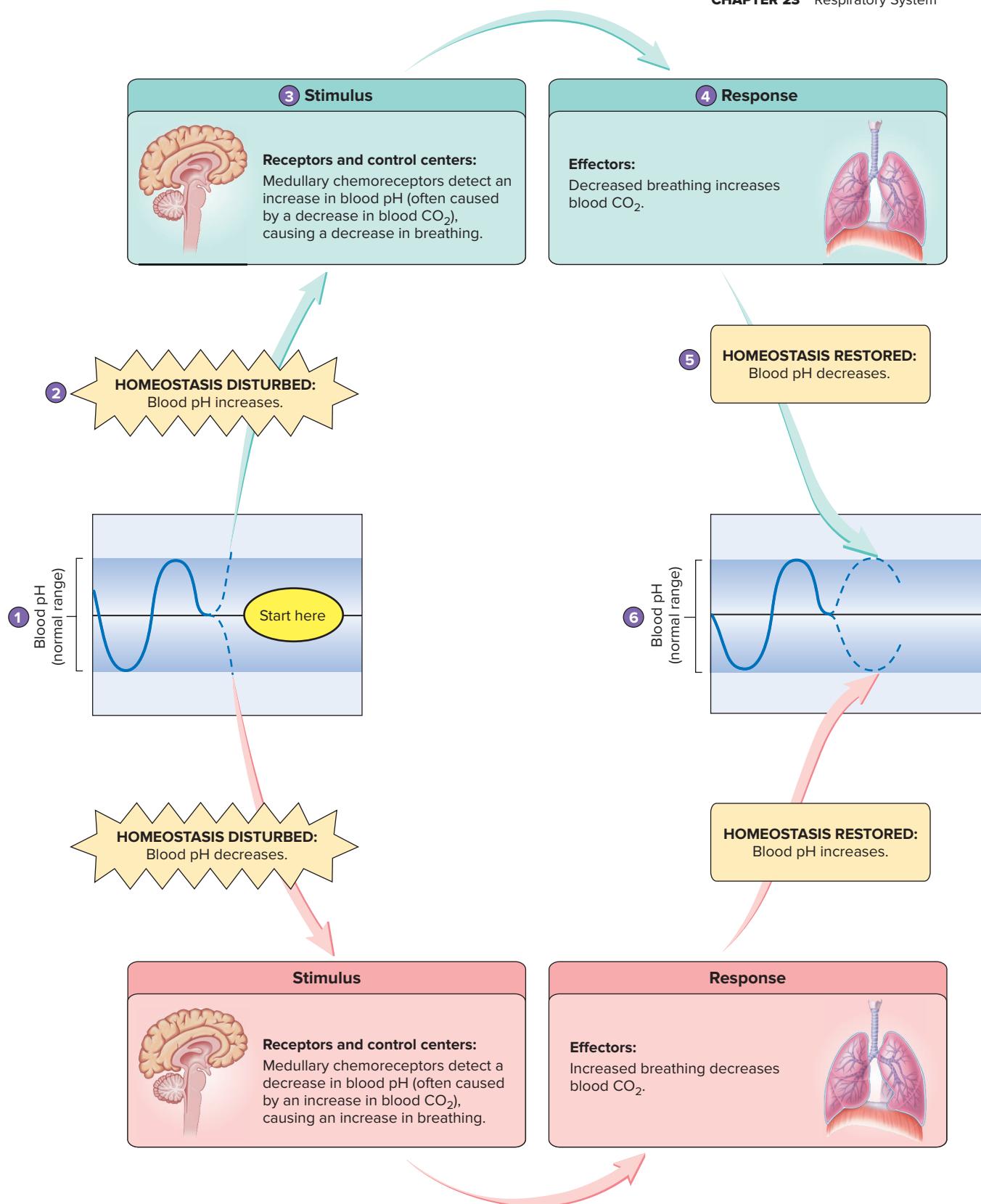
The Hering-Breuer (her'ing-broy'er) reflex limits the depth of inspiration and prevents overinflation of the lungs (see figure 23.23d). This reflex depends on stretch receptors in the walls of the bronchi and bronchioles of the lungs. Action potentials are initiated in these stretch receptors when the lungs are inflated and are passed along sensory neurons within the vagus nerves to the medulla oblongata. The action potentials have an inhibitory influence on the respiratory center and result in expiration. As expiration proceeds, the stretch receptors are no longer stimulated, and the decreased inhibitory effect on the respiratory center allows inspiration to begin again.

In infants, the Hering-Breuer reflex plays a role in regulating the basic rhythm of breathing and in preventing overinflation of the lungs. In adults, however, the reflex is important only when the tidal volume is large, such as during exercise.

Cerebral and Limbic System Control of Respiratory Rate

The rate and depth of breathing is controlled both voluntarily and involuntarily by the cerebral cortex (see figure 23.23). For example, during talking or singing, air movement is controlled to produce sounds, as well as to facilitate gas exchange.

During exercise, respiratory rate changes are controlled through various inputs to the respiratory center. Initially, there is a very rapid increase that occurs too quickly to be accounted for by changes in metabolism. For example, movement of the limbs has a strong stimulatory influence on the respiratory center (figure 23.23e). After the initial immediate increase in respiratory rate, there is a gradual increase that levels off within 4–6 minutes. The highest level of exercise that can be performed without causing a significant change in blood pH is called the **anaerobic threshold**. If the exercise intensity is high enough to exceed the anaerobic threshold, blood pH drops. The drop in pH stimulates the carotid bodies, which increases ventilation. In fact, ventilation can increase so much that arterial Pco₂ decreases below resting levels and arterial Po₂ increases above resting levels. In response to training, athletic performance increases because the cardiovascular and respiratory systems become more efficient at delivering O₂ and picking up CO₂. Ventilation does not limit performance in most individuals because ventilation can increase to a greater extent than does cardiovascular function. In conditioned athletes, the respiratory rate at rest or during submaximal exercise is slightly lower than in a non-athlete. However, athletes have higher respiratory rates at maximal exercise.



HOMEOSTASIS FIGURE 23.22 Regulation of Blood pH

(1) Blood pH is in its normal range. (2) Blood pH increases outside its normal range, which disturbs homeostasis. (3) The control centers for blood pH, the medullary chemoreceptors, detect an increase in blood pH (blood becomes more basic) and respond to the increased pH by signaling a decreased breathing rate. (4) The effectors, the diaphragm and other respiratory muscles, respond by slowing their contraction rate, which lowers the rate of breathing. (5) As a result, more CO₂ is retained, which causes pH to drop (blood becomes more acidic). (6) Blood pH returns to its normal range and homeostasis is maintained. Observe the responses to a decrease in blood pH by following the red arrows.

- (a) Higher centers of the brain (speech, emotions, voluntary control of breathing, and action potentials in motor pathways)

- (b) Medullary (chemosensitive area) chemoreceptors
 $\downarrow \text{pH}$, $\uparrow \text{CO}_2$

- (c) Carotid and aortic body chemoreceptors
 $\downarrow \text{pH}$, $\uparrow \text{CO}_2$, $\downarrow \text{O}_2$

- (d) Hering-Breuer reflex (stretch receptors in lungs)

- (e) Proprioceptors in muscles and joints

- (f) Receptors for touch, temperature, and pain stimuli

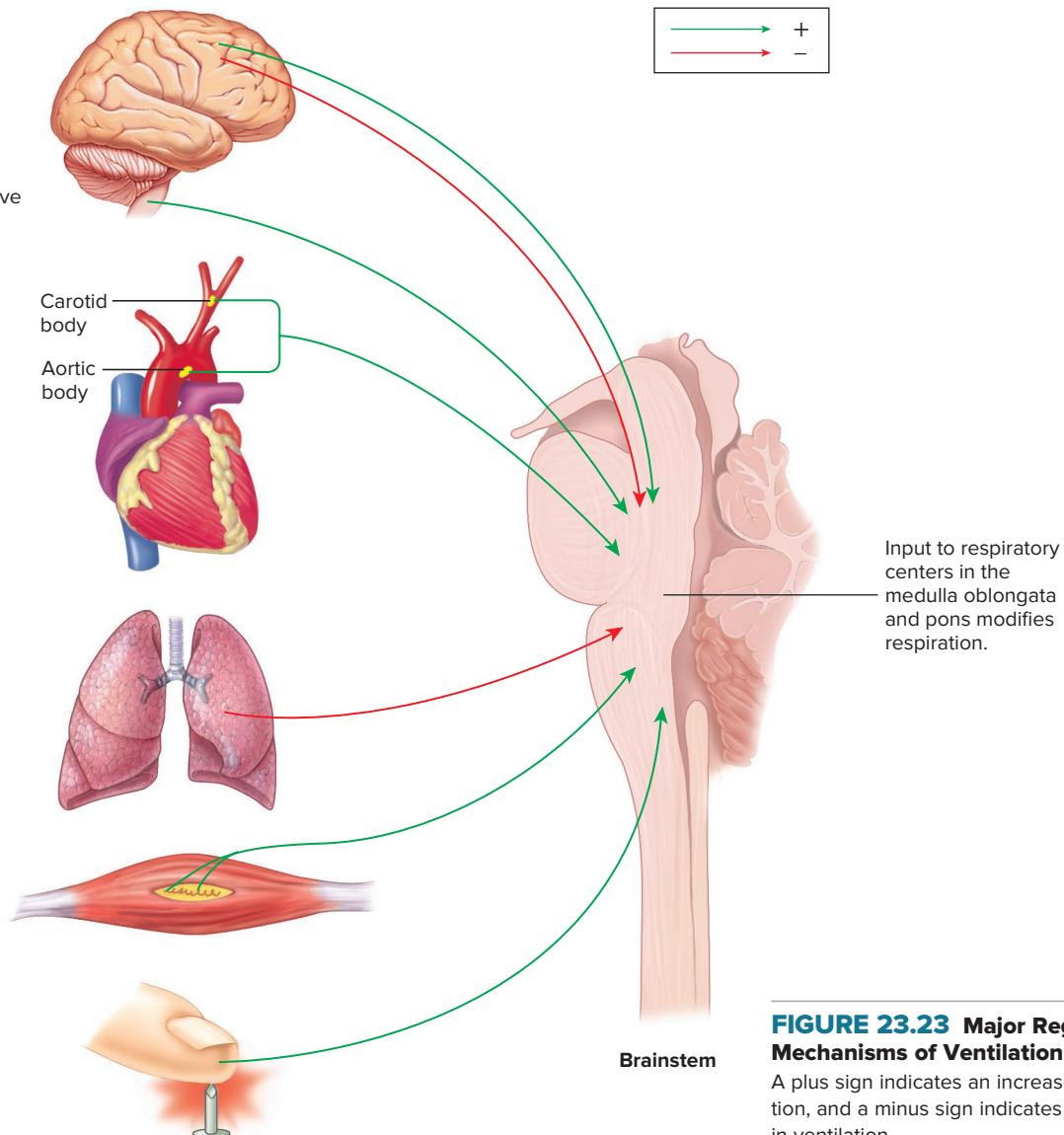


FIGURE 23.23 Major Regulatory Mechanisms of Ventilation

A plus sign indicates an increase in ventilation, and a minus sign indicates a decrease in ventilation.

Apnea (ap'nē-ă) is the absence of breathing. A person may stop breathing voluntarily. As the period of voluntary apnea increases, a greater and greater urge to breathe develops. That urge is primarily due to higher PCO_2 levels in the arterial blood. Finally, the PCO_2 reaches levels that cause the respiratory center to override the conscious influence from the cerebrum. Occasionally, people are able to hold their breath until the blood PO_2 declines to a level low enough that they lose consciousness. After consciousness is lost, the respiratory center resumes its normal automatic control of respiration.

On the other hand, voluntary hyperventilation decreases blood PCO_2 levels far enough, which causes vasodilation of the peripheral blood vessels and a corresponding drop in blood pressure (see chapter 21). Dizziness or a giddy feeling can result because the decreased blood pressure results in a decreased rate of blood flow to the brain, and therefore less O_2 is delivered to the brain.

Emotions acting through the limbic system of the brain can also affect the respiratory center (figure 23.23a). For example, strong emotions can cause hyperventilation or produce the sobs and gasps of crying.

Other Modifications of Ventilation

Higher brain centers control the respiratory system when touch, thermal, or pain receptors are activated (see figure 23.23f). For example, irritants in the nasal cavity can initiate a sneeze reflex, and irritants in the lungs can stimulate a cough reflex. An increase in body temperature can stimulate increased ventilation because metabolism is elevated and more CO_2 is produced, which then needs to be expelled from the body.

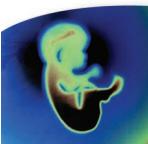
Predict 11

Suppose that cold water is suddenly splashed on you. Describe your respiratory response. In the past, newborn babies were sometimes swatted on the buttocks. Explain the rationale for this procedure.

ASSESS YOUR PROGRESS

61. Define the anatomical shunt and the physiological shunt of the respiratory system.

62. What are the effects of gravity and alveolar PO_2 on blood flow in the lung?



Clinical IMPACT 23.6

Cough and Sneeze Reflexes

Both the cough reflex and the sneeze reflex dislodge foreign matter or irritating material from the respiratory passages. The bronchi and trachea contain sensory receptors that detect such substances and initiate action potentials that pass along the vagus nerves to the medulla oblongata, where the cough reflex is triggered.

The movements resulting in a cough occur as follows: Approximately 2.5 L of air are inspired; the vestibular and vocal folds close tightly to trap the inspired air in the lungs; the abdominal muscles contract to force the abdominal organs up against the diaphragm; and the muscles of expiration contract forcefully. As a consequence, the pressure in the lungs increases to 100 mm Hg or more. Then the vestibular and vocal folds

open suddenly, the soft palate is elevated, and air rushes from the lungs and out the oral cavity at a high velocity, carrying foreign matter with it.

The sneeze reflex is similar to the cough reflex in that air is forcefully expelled from the lungs, but it differs in several ways. The irritation that initiates the sneeze reflex occurs in the nasal passages instead of in the trachea and bronchi, and the action potentials travel along the trigeminal nerves to the medulla oblongata, where the reflex is triggered. During the sneeze reflex, the soft palate is depressed, so that air is directed primarily through the nasal passages, although a considerable amount passes through the oral cavity. The rapidly flowing air dislodges particulate matter from the nasal passages and can propel it a considerable distance from the nose.

About 25% of people have a photic sneeze reflex, which is stimulated by exposure to bright light, such as the sun. The sneeze reflex may be connected to the pupillary reflex, which causes the pupils to constrict in response to bright light. Researchers speculate that the complicated “wiring” of the pupillary and sneeze reflexes are intermixed in some people, so that, when bright light activates a pupillary reflex, it also activates a sneeze reflex. Sometimes the photic sneeze reflex is fancifully called ACHOO, which stands for *autosomal dominant compelling helio-ophthalmic outburst*. As the name suggests, the reflex is inherited as an autosomal dominant trait. A person needs to inherit only one copy of the gene to have a photic sneeze reflex.

63. Name the three respiratory groups, and describe their main functions.
64. How is rhythmic ventilation generated?
65. Explain how the cerebral cortex and limbic system can exert control over ventilation. What is apnea?
66. Where are central chemoreceptors and peripheral chemoreceptors? Which are most important for regulating blood pH and CO₂ level? How does this change during intense exercise?
67. Define hypercapnia and hypocapnia.
68. How does a decrease in blood pH affect respiratory rate? How does a decrease in CO₂ affect respiratory rate?
69. What is hypoxia? Why must arterial Po₂ change significantly before it affects respiratory rate?
70. What mechanisms regulate ventilation at the onset of exercise and then during exercise? What is the anaerobic threshold?
71. Describe the Hering-Breuer reflex and its function.

23.8 Effects of Aging on the Respiratory System

LEARNING OUTCOME



After reading this section, you should be able to

A. Describe the effects of aging on the respiratory system.

Most aspects of the respiratory system are affected by aging. However, even though vital capacity, maximum ventilation rates, and gas exchange decrease with age, the elderly can engage in light to moderate exercise because the respiratory system has a large reserve capacity.

Vital capacity decreases with age because of a decreased ability to fill the lungs (decreased inspiratory reserve volume) and a decreased ability to empty the lungs (decreased expiratory reserve volume). As a result, maximum minute volume rates decrease, which in turn decreases the ability to perform intense exercise. These changes are related to weakening of respiratory muscles and to decreased compliance of the thoracic cage caused by the stiffening of cartilage and ribs. Lung compliance actually increases with age, but this effect is offset by the decreased thoracic cage compliance. Lung compliance increases because parts of the alveolar walls are lost, which reduces lung recoil. No significant age-related changes take place in lung elastic fibers or surfactant.

Alveolar ducts and many of the larger bronchioles expand in diameter with age, which increases residual volume. Larger bronchioles and alveolar ducts create more dead space, lowering the amount of air available for gas exchange (alveolar ventilation). In addition, gas exchange across the respiratory membrane is reduced because parts of the alveolar walls are lost, which decreases the surface area available for gas exchange, and the remaining walls thicken, which decreases the diffusion of gases. A gradual rise in resting tidal volume with age compensates for these changes.

With age, mucus accumulates within the respiratory passageways because it becomes more viscous and because the number of cilia and their rate of movement decrease. As a consequence, the elderly are more susceptible to respiratory infections and bronchitis. Table 23.3 describes several other diseases and disorders of the respiratory system that can occur during any stage of life.

ASSESS YOUR PROGRESS

72. Why do vital capacity, alveolar ventilation, and the diffusion of gases across the respiratory membrane decrease with age?
73. Why are the elderly more likely to develop respiratory infections and bronchitis?



Systems PATHOLOGY

Asthma

Background Information

Will is an 18-year-old track athlete in seemingly good health. Despite suffering from a slight cold, Will went jogging one morning with his running buddy, Al. After a few minutes of exercise, Will felt that he could hardly get enough air. Even though he stopped jogging, he continued to breathe rapidly and wheeze forcefully. Because his condition was not improving, Al took him to the emergency room of a nearby hospital.

The emergency room doctor used a stethoscope to listen to Will's lungs and noted that air movement was poor. Will inhaled a bronchodilator drug, which rapidly improved his condition.

Asthma (az'mă; difficult breathing) is characterized by abnormally increased constriction of the trachea and bronchi in response to various stimuli, which results in narrowed air passageways and decreased ventilation efficiency. Symptoms include rapid and shallow breathing, wheezing, coughing, and shortness of breath (figure 23.24a). In contrast to many other respiratory disorders, the symptoms of asthma typically reverse either spontaneously or with therapy.

There is no definitive pathological feature or diagnostic test for asthma, but three important characteristics of the disease are chronic airway inflammation, airway hyperreactivity, and airflow obstruction. The inflammation results in tissue damage, edema, and mucous buildup, which can block airflow through the bronchi. Airway hyperreactivity means that the smooth muscle in the trachea and bronchi contracts greatly in response to a stimulus, thus decreasing the diameter of the airway and increasing resistance to airflow. The effects of inflammation and airway hyperreactivity combine to cause airflow obstruction (figure 23.24b and c).

Many cases of asthma appear to be associated with a chronic inflammatory response by the immune system. The number of immune cells in the bronchi, including mast cells, eosinophils, neutrophils, macrophages, and lymphocytes, increases. Inflammation appears to be linked to airway hyperreactivity by some chemical mediators released by immune cells (e.g., leukotrienes, prostaglandins, and interleukins), which increase the airway's sensitivity to stimulation and cause smooth muscle contraction.

The stimuli that prompt airflow obstruction in asthma vary from one individual to another. Some asthmatics react to particular allergens, which are foreign substances that evoke an inappropriate immune system response (see chapter 22). Examples include inhaled pollen, animal dander, and dust mites. Many cases of asthma are caused by an allergic reaction to substances in the droppings and carcasses of cockroaches, which may explain the higher rate of asthma in poor, urban areas. However, other inhaled substances, such as chemicals in the workplace or cigarette smoke, can provoke an asthma attack without stimulating an allergic reaction. Over 200 substances have been associated with occupational asthma. An asthma attack can also be stimulated by ingested substances, such as aspirin; nonsteroidal anti-inflammatory compounds, such as ibuprofen (ɪ'bū-prō'fēn); sulfites in food preservatives; and tartrazine (tar'trā-zēn) in food colorings. Asthmatics can substitute acetaminophen (as-ət-ă-mē'nō-fēn, a-set-ă-min'ō-fēn; e.g., Tylenol) for aspirin.

Other stimuli, such as strenuous exercise (especially in cold weather) can precipitate an asthma attack. Such episodes can often be avoided by using a bronchodilator prior to exercise. Viral infections, emotional upset, stress, air pollution, and even reflux of stomach acid into the esophagus are known to elicit an asthma attack.

Treatment of asthma involves avoiding the causative stimulus and taking medications. Steroids and mast cell-stabilizing agents, which prevent the release of chemical mediators from mast cells, can reduce airway inflammation. Bronchodilators are used to increase airflow. Figure 23.25 illustrates the widespread effects of asthma on the body's other organ systems.

► Predict 12

It is not usually necessary to assess arterial blood gases when diagnosing and treating asthma. However, this information can sometimes be useful in severe asthma attacks. Suppose that Will had a Po₂ of 60 mm Hg and a Pco₂ of 30 mm Hg when he first went to the emergency room. Explain how that could happen.



(a)

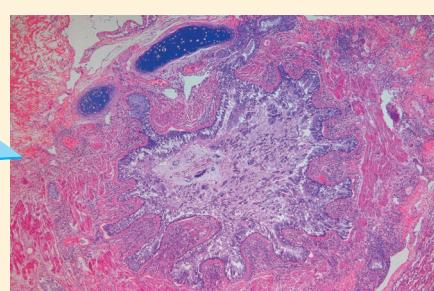
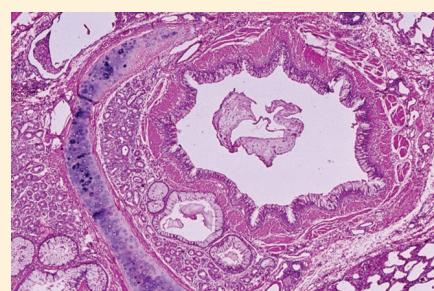
(b) **Asthmatic bronchiole:**
Note how constricted it is.(c) **Normal bronchiole:**
Note how clear it is.

FIGURE 23.24

(a) Strenuous exercise is one of the many factors that can bring on an asthma attack. (b) Changes in bronchiole diameter during an asthma attack. The diameter of the bronchioles is dramatically reduced during an asthma attack, slowing airflow. (c) The diameter of the bronchioles is normally sufficient to allow air to flow into and out of the lungs freely. (a) ©Ammentorp Photography/Alamy; (b) ©McGraw-Hill Education; (c) ©Carolina Biological/Phototake

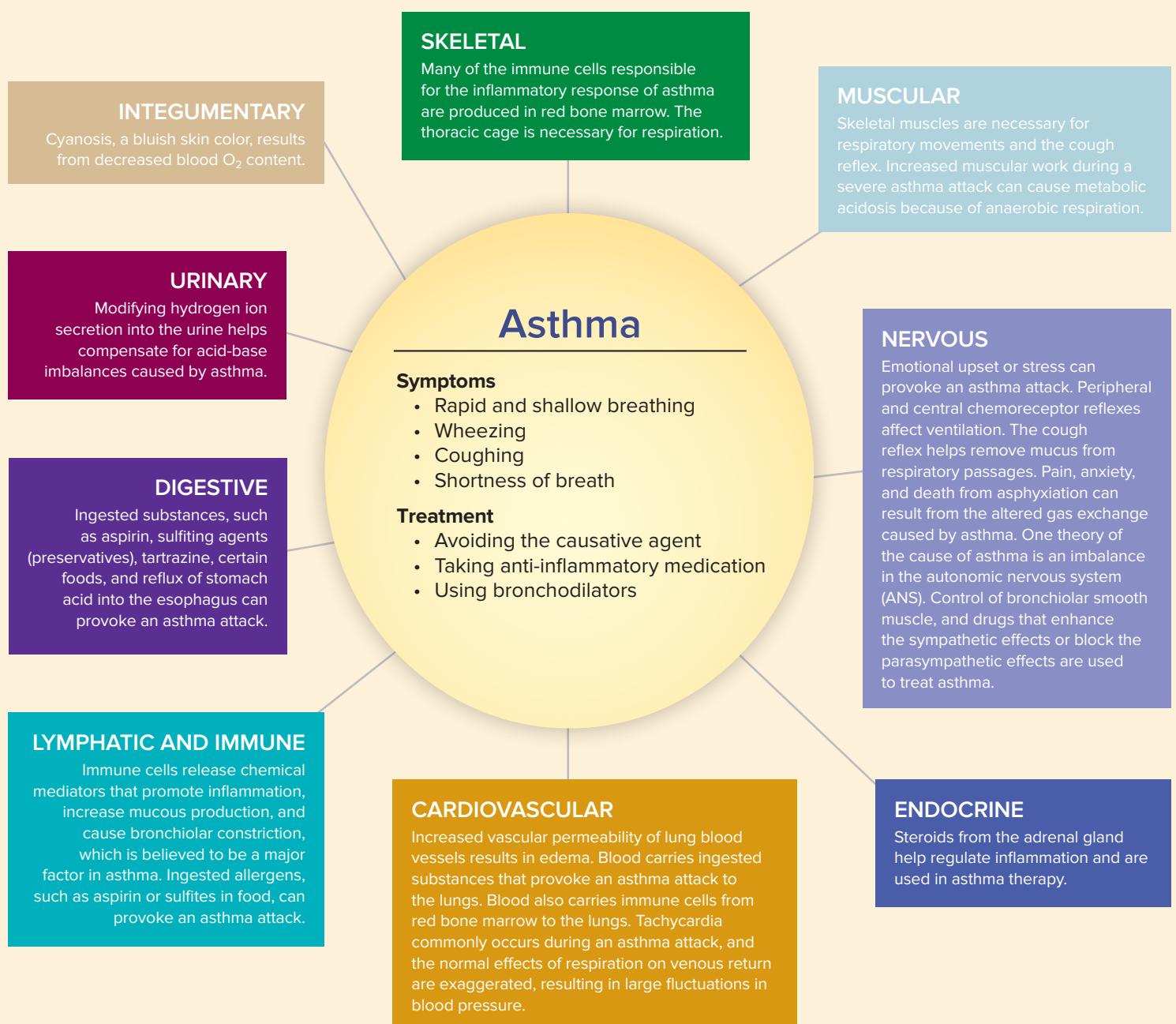


FIGURE 23.25 Interactions of Asthma with Other Body Systems

During an asthma attack, the body cannot get sufficient O₂ nor can it eliminate adequate amounts of CO₂. The lack of O₂ causes many complications, for example, blood vessel permeability to increase, which can result in edema throughout the body. The inability to eliminate adequate CO₂ causes the body fluid pH to become more acidic and many processes cannot proceed normally.

TABLE 23.3

Representative Diseases and Disorders of the Respiratory System

RESPIRATORY DISORDERS

Condition	Description
Bronchi and Lungs	
Bronchitis (brong-kī'tis)	Inflammation of the bronchi caused by irritants, such as cigarette smoke or infection; swelling impairs breathing; bronchitis can progress to emphysema
Emphysema (em-fē-sē'mā)	Destruction of alveolar walls; increased coughing increases pressure on the alveoli, causing rupture and destruction; loss of alveoli decreases surface area for gas exchange and decreases the lungs' ability to expel air; progression can be slowed, but there is no cure; in combination with bronchitis, the condition is known as chronic obstructive pulmonary disease (COPD)
Adult respiratory distress syndrome (ARDS)	Caused by damage to the respiratory membrane, which promotes inflammation; amount of surfactant is reduced, and fluid fills the alveoli, lessening gas exchange; ARDS usually develops after an injurious event, such as inhaling smoke from a fire or breathing toxic fumes
Cystic fibrosis (fi-brō'sis)	Genetic disorder that affects mucous secretions throughout the body due to an abnormal transport protein; mucus is much more viscous and accumulates in ducts and tubes, such as the bronchioles; airflow is restricted, and infections are more likely
Pulmonary fibrosis	Replacement of lung tissue with fibrous connective tissue, making the lungs less elastic; exposure to asbestos or coal dust is a common cause
Lung cancer	Occurs in the epithelium of the respiratory tract; can easily spread to other parts of the body because of the rich blood and lymphatic supply to the lungs
Asthma	See Systems Pathology, later in this chapter
Circulatory System	
Thrombosis of the pulmonary arteries	Blood clot in lung blood vessels, causing inadequate blood flow through the pulmonary capillaries, which affects respiratory function
Anemia	Reduced hemoglobin lowers oxygen-carrying capacity of blood
Carbon monoxide poisoning	Carbon monoxide binds more strongly to hemoglobin than O ₂ does and prevents already-bound O ₂ from entering tissues
Nervous System	
Sudden infant death syndrome (SIDS)	Most frequent cause of death of infants between 2 weeks and 1 year of age; cause is still unknown, but at-risk babies can be placed on monitors that warn if breathing stops
Paralysis of the respiratory muscles	Damage to the spinal cord in the cervical or thoracic region interrupts nervous signals to the muscles of respiration
Thoracic Wall	
	Decreased elasticity of the thoracic wall prevents it from expanding to full capacity and reduces air movement; two spinal curvature conditions that reduce elasticity of the thoracic wall are scoliosis (skō-lē-ō'sis) and kyphosis (kī-fō'sis)
INFECTIOUS DISEASES OF THE RESPIRATORY SYSTEM	
Upper Respiratory Tract	
Strep throat	Caused by streptococcal bacteria (<i>Streptococcus pyogenes</i>); characterized by inflammation of the pharynx and fever
Diphtheria (dif-thē'rē-ă)	Caused by the bacterium <i>Corynebacterium diphtheriae</i> ; a grayish membrane forms in the throat and can completely block respiratory passages; DTaP immunization for children partially targets diphtheria
Common cold	Results from a viral infection
Lower Respiratory Tract	
Whooping cough (pertussis; per-tū'sis)	Caused by the bacterium <i>Bordetella pertussis</i> , which destroys cilia lining the respiratory epithelium, allowing mucus to accumulate; leads to a very severe cough; DTaP immunization for children targets pertussis
Tuberculosis (tū-ber'kyū-lō'sis)	Caused by the bacterium <i>Clostridium tuberculosis</i> , which forms small, lumpy lesions called tubercles; immune system targets tubercles and causes larger lesions; certain strains of tuberculosis are resistant to antibiotics
Pneumonia (noo-mō'nē-ă)	Can be caused by a number of bacterial or viral infections of the lungs that cause fever, difficulty in breathing, and chest pain; edema in the lungs decreases their inflation ability and reduces gas exchange
Flu (influenza; in-flū-en'ză)	Viral infection of the respiratory system; does not affect the digestive system, as is commonly misunderstood; causes chills, fever, headache, and muscle aches
Fungal diseases	Fungal spores enter the respiratory tract attached to dust particles, usually resulting in minor respiratory infections that in some cases can spread to other parts of the body; examples are histoplasmosis and coccidioidomycosis

Answer

Learn to Predict

Mr. Theron suffers from emphysema, a respiratory disorder that results in the destruction of alveoli. This chapter explained that the alveoli form the respiratory membrane, the site of gas exchange between the atmosphere and the blood. Alveolar destruction would directly reduce the respiratory membrane surface and therefore gas exchange. As a consequence, Mr. Theron has exaggerated respiratory movements to compensate for the reduction in surface area. Blood Po_2 is an important stimulus for the respiratory center, and the increased respiratory movements keep the ventilation just adequate to maintain blood Po_2 in the low normal range. Because CO_2 diffuses across the respiratory membrane at a faster rate than O_2 , the elevated respiration required to maintain blood Po_2 causes too much CO_2 to be expired, resulting in his blood Pco_2 level dropping below normal.

This chapter explained that a pneumothorax, or the introduction of air into the pleural cavity through an opening in the thoracic

wall or lung, can cause a lung to collapse. Due to his emphysema, Mr. Theron's lung collapsed when alveoli near the surface of the lung ruptured, allowing air to enter the pleural space. The physician was able to diagnose Mr. Theron's collapsed lung by listening for respiratory sounds with a stethoscope. He detected respiratory sounds in the right lung but not in the left lung. We would expect Mr. Theron's respiratory movements to be even more exaggerated, since the respiratory membrane was reduced by half when his left lung collapsed. The reduction in the respiratory membrane would cause a drop in Po_2 and an increase in Pco_2 , both of which would stimulate respiratory centers to increase ventilation.

Answers to the odd-numbered Predict questions from this chapter appear in appendix E.

Summary

23.1 Anatomy of the Respiratory System

The respiratory system structures start with the nose and end with the alveoli in the lungs.

23.2 Functions of the Respiratory System

- Respiration includes the movement of air into and out of the lungs, the exchange of gases between the air and the blood, the transport of gases in the blood, and the exchange of gases between the blood and tissues.
- Other functions of the respiratory system are regulation of blood pH, production of chemical mediators, voice production, olfaction, and protection against some microorganisms.

23.3 Structures and Histology of the Respiratory Tract

The Upper Respiratory Tract

Nose and Nasal Cavity

- The nose consists of the external nose and the nasal cavity.
- The bridge of the nose is bone, and most of the external nose is cartilage.
- Openings of the nasal cavity
 - The nares open to the outside, and the choanae lead to the pharynx.
 - The paranasal sinuses and the nasolacrimal duct open into the nasal cavity.
- Parts of the nasal cavity
 - The nasal cavity is divided by the nasal septum.
 - The anterior vestibule contains hairs that trap debris.

- The nasal cavity is lined with pseudostratified ciliated columnar epithelium that traps debris and moves it to the pharynx.
 - The superior part of the nasal cavity contains the olfactory epithelium.
- The nasal cavity serves as a passageway for air; cleans and humidifies air; is the location for the sense of smell; and, with the paranasal sinuses, functions as a resonating chamber for speech.

Pharynx

- The nasopharynx joins the nasal cavity through the internal choanae and contains the openings to the auditory tube and the pharyngeal tonsils.
- The oropharynx joins the oral cavity and contains the palatine and lingual tonsils.
- The laryngopharynx opens into the larynx and the esophagus.

Larynx

- Cartilage

Three of the nine cartilages are single cartilages. The thyroid cartilage and cricoid cartilage form most of the larynx. The epiglottis covers the opening of the larynx during swallowing. Six of the cartilages are paired. The vocal folds attach to the arytenoid cartilages.
- The larynx maintains an open air passageway, regulates the passage of swallowed materials and air, produces sounds, and removes debris from the air.
- Sounds are produced as the vocal folds vibrate when air passes through the larynx.

Tightening the folds produces sounds of different pitches by controlling the length of the fold, which is allowed to vibrate.

The Lower Respiratory Tract

Trachea

1. The trachea connects the larynx to the main bronchi.
2. The trachealis muscle regulates the diameter of the trachea.

Bronchi

1. The trachea divides to form two main bronchi, which extend to the lungs.

Tracheobronchial Tree

1. The main bronchi divide to form lobar bronchi, which divide to form segmental bronchi, which divide to form bronchioles, which divide to form terminal bronchioles.
2. The trachea to the terminal bronchioles is a passageway for air movement.
 - The area from the trachea to the terminal bronchioles is ciliated to facilitate the removal of inspired debris.
 - Cartilage helps hold the tube system open (from the trachea to the bronchioles).
 - Smooth muscle controls the diameter of the tubes (terminal bronchioles).

Alveoli

1. Terminal bronchioles divide to form respiratory bronchioles, which give rise to alveolar ducts. Air-filled chambers called alveoli open into the respiratory bronchioles and alveolar ducts. The alveolar ducts end as alveolar sacs, which are chambers that connect to two or more alveoli.
2. Gas exchange occurs between the respiratory bronchioles and the alveoli.
3. The components of the respiratory membrane are a film of water, the walls of the alveolus and the capillary, and an interstitial space.

Thoracic Wall and Muscles of Respiration

The thoracic wall consists of vertebrae, ribs, the sternum, and muscles that allow expansion of the thoracic cavity.

Lungs

1. The thoracic cavity contains two lungs.
2. The lungs are divided into lobes, bronchopulmonary segments, and lobules.
3. There are three lung lobes on the right and two lung lobes on the left.
4. Each lung lobe is further subdivided into bronchopulmonary segments.

Blood Supply to the Lungs

1. Deoxygenated blood is transported to the lungs through the pulmonary arteries, and oxygenated blood leaves through the pulmonary veins.
2. Oxygenated blood is mixed with a small amount of deoxygenated blood from the bronchi.

Lymphatic Supply to the Lungs

The superficial and deep lymphatic vessels drain lymph from the lungs.

Pleura

The pleural membranes surround the lungs and protect against friction.

23.4 Behavior of Gases

Behavior of Gases and Ventilation

Ventilation is the movement of air into and out of the lungs.

Muscles of Respiration

1. Contraction of the diaphragm increases thoracic volume.
2. Muscles can elevate the ribs and increase thoracic volume or depress the ribs and decrease thoracic volume.

The Relationship Between Pressure Gradients and Ventilation

1. Air moves from an area of higher pressure to an area of lower pressure.
2. Pressure is inversely related to volume.

Measurement of Lung Function

Pulmonary Volumes and Capacities

1. Four pulmonary volumes exist: tidal volume, inspiratory reserve volume, expiratory reserve volume, and residual volume.
2. Pulmonary capacities are the sum of two or more pulmonary volumes and include inspiratory capacity, functional residual capacity, vital capacity, and total lung capacity.
3. The forced expiratory vital capacity measures vital capacity while the individual expires as rapidly as possible.

Minute Volume

1. Minute volume is the total amount of air moved into and out of the respiratory system per minute.
2. Dead space is the part of the respiratory system where gas exchange does not take place.

Alveolar Ventilation

Alveolar ventilation is how much air per minute enters the parts of the respiratory system where gas exchange takes place.

Factors Affecting Ventilation

1. Gender, age, body size, and physical fitness all affect the degree of ventilation.
2. Ventilation is typically reduced in certain disease states.
3. Compliance is a measure of lung expansion caused by intra-alveolar pressure.
4. Reduced compliance means that it is more difficult than normal to expand the lungs.

Behavior of Gases and Respiration

Partial Pressure

1. Partial pressure is the contribution of a gas to the total pressure of a mixture of gases (Dalton's law).
2. Water vapor pressure is the partial pressure produced by water.
3. Atmospheric air, alveolar air, and expired air have different compositions.

Diffusion of Gases into and out of Liquids

The concentration of a dissolved gas in a liquid is determined by its pressure and by its solubility coefficient (Henry's law).

23.5 Physiology of the Respiratory System

Mechanisms of Alveolar Ventilation

Changes in thoracic volume cause changes in pleural pressure, resulting in changes in alveolar volume, intra-alveolar pressure, and airflow.

Factors Affecting Alveolar Ventilation

Lung Recoil

- Lung recoil results from elastic fibers and water surface tension.
- Surfactant reduces water surface tension.

Pleural Pressure

- A negative pleural pressure can cause the alveoli to expand.
- Pneumothorax is an opening between the pleural cavity and the air that causes a loss of pleural pressure.

Summary of Pressure Changes During a Normal Breathing Cycle

1. Pleural pressure is -4 mm Hg at the end of a normal expiration; air stops flowing out of the lungs.
2. Pleural pressure decreases to -7 mm Hg during inspiration; air flows into the lungs.

Factors Affecting Diffusion Through the Respiratory Membrane

The respiratory membrane is thin and has a large surface area that facilitates gas exchange.

Partial Pressure Gradients

1. Oxygen moves from the alveoli ($P_{O_2} = 104$ mm Hg) into the blood ($P_{O_2} = 40$ mm Hg). Blood is almost completely saturated with O_2 when it leaves the capillary.
2. The P_{O_2} in the blood decreases ($P_{O_2} = 95$ mm Hg) when it mixes with deoxygenated blood.
3. Oxygen moves from the tissue capillaries ($P_{O_2} = 95$ mm Hg) into the tissues ($P_{O_2} = 40$ mm Hg).
4. Carbon dioxide moves from the tissues ($P_{CO_2} = 45$ mm Hg) into tissue capillaries ($P_{CO_2} = 40$ mm Hg).
5. Carbon dioxide moves from the pulmonary capillaries ($P_{CO_2} = 45$ mm Hg) into the alveoli ($P_{CO_2} = 40$ mm Hg).

Respiratory Membrane Thickness

The rate of diffusion of gases through the respiratory membrane depends on its thickness, the diffusion coefficient of the gas.

Respiratory Membrane Surface Area

The surface area of the membrane and the partial pressure of the gases in the alveoli and the blood affect the rate of gas diffusion.

23.6 Oxygen and Carbon Dioxide Transport in the Blood

Hemoglobin

1. There are four types of hemoglobin—embryonic, fetal, adult, hemoglobin-S.
2. Fetal hemoglobin has a higher affinity for O_2 than maternal hemoglobin does.
3. Adult hemoglobin is fully saturated when four O_2 are bound to it.
4. Hemoglobin-S is found in individuals with sickle-cell disease.

Transport of O_2

Oxygen is transported by hemoglobin (98.5%) and is dissolved in plasma (1.5%).

Transport of CO_2

Transport of CO_2 in the Plasma

Carbon dioxide is transported dissolved in plasma (7%).

Transport of CO_2 by Hemoglobin

In the Haldane effect, the smaller the amount of O_2 bound to hemoglobin, the greater the amount of CO_2 bound to it, and vice versa.

Transport of CO_2 as Bicarbonate Ions

In tissue capillaries, the following events occur:

- Carbon dioxide combines with water inside red blood cells to form carbonic acid, which dissociates to form HCO_3^- . Decreasing HCO_3^- concentrations promote CO_2 transport.
- Exchange of Cl^- for HCO_3^- occurs between plasma and red blood cells; this is called the chloride shift.
- Hydrogen ions binding to hemoglobin promote CO_2 transport, prevent a pH change in red blood cells, and produce a Bohr effect.

Summary of Gas Transport

Affinity of hemoglobin for O_2 decreases as O_2 demand increases.

Physiological Factors Affecting Gas Transport

The affinity of hemoglobin for O_2 is altered by several parameters including pH, temperature, and CO_2 levels.

Effect of P_{O_2} on O_2 Transport

The oxygen-hemoglobin dissociation curve shows that hemoglobin is almost completely saturated when P_{O_2} is 80 mm Hg or above. At lower partial pressures, the hemoglobin releases O_2 .

Effect of P_{CO_2} on CO_2 Transport

At low P_{CO_2} levels, hemoglobin binds more CO_2 .

Effect of pH and P_{CO_2} on O_2 Transport

1. Hemoglobin's ability to hold O_2 decreases because of a shift of the oxygen-hemoglobin dissociation curve to the right due to decreased pH (Bohr effect) or increased CO_2 .
2. Hemoglobin's ability to hold O_2 increases because of a shift of the oxygen-hemoglobin dissociation curve to the left due to increased pH (Bohr effect), decreased CO_2 , or decreased temperature.

Effect of pH and P_{CO_2} on CO_2 Transport

There is little effect of pH on CO_2 transport.

Effect of Temperature on O_2 Transport

An increase in temperature decreases the affinity of hemoglobin for O_2 . This is seen as a right shift of the oxygen-hemoglobin dissociation curve.

Effect of Temperature on CO_2 Transport

At higher body temperatures, more CO_2 is produced, which results in an increased respiratory rate.

Effect of BPG on O_2 Transport

The substance 2,3-bisphosphoglycerate increases hemoglobin's ability to release O_2 .

Effect of BPG on CO_2 Transport

BPG enhances the Haldane effect.

23.7 Regulation of Ventilation

Local Control

1. Increased alveolar ventilation or increased pulmonary capillary perfusion increases gas exchange.
2. The physiological shunt is the deoxygenated blood returning from the lungs.

Neural Control

Respiratory Areas in the Brainstem

1. The medullary respiratory center consists of the dorsal and ventral respiratory groups.
 - The dorsal respiratory groups stimulate the diaphragm.
 - The ventral respiratory groups stimulate the intercostal and abdominal muscles.
2. The pontine respiratory group is involved with switching between inspiration and expiration.

Generation of Rhythmic Ventilation

1. Neurons in the medullary respiratory center establish the basic rhythm of ventilation.
2. When stimuli from receptors or other parts of the brain exceed a threshold level, inspiration begins.
3. As respiratory muscles are stimulated, neurons that stop inspiration are stimulated. When the stimulation of these neurons exceeds a threshold level, inspiration is inhibited.

Effect of Po_2 on Respiratory Rate

Oxygen levels in the blood affect ventilation when a 50% or greater decrease from normal exists. Decreased O_2 is detected by receptors in the carotid and aortic bodies, which then stimulate the respiratory center.

Effect of Pco_2 on Respiratory Rate

Carbon dioxide is the major regulator of ventilation. An increase in CO_2 or a decrease in pH can stimulate the chemosensitive area, causing a greater rate and depth of ventilation.

Effect of pH on Respiratory Rate

A low pH stimulates an increased respiratory rate, which expels excess CO_2 . A lower level of CO_2 returns pH to normal levels.

The Hering-Breuer Reflex and Respiratory Rate

Stretch of the lungs during inspiration can inhibit the respiratory center and contribute to a cessation of inspiration.

Cerebral and Limbic System Control of Respiratory Rate

1. Ventilation can be voluntarily controlled and can be modified by emotions.
2. Collateral fibers from motor neurons and from proprioceptors stimulate the respiratory centers during exercise.
3. Chemosensitive mechanisms and learning fine-tune the effects produced through the motor neurons and proprioceptors during exercise.

Other Modifications of Ventilation

Touch, thermal, and pain sensations can modify ventilation.

23.8 Effects of Aging on the Respiratory System

1. Vital capacity and maximum minute volume decrease with age because of weakened respiratory muscles and decreased thoracic cage compliance.
2. Residual volume and dead space increase because of the enlarged diameter of respiratory passageways. As a result, alveolar ventilation decreases.
3. An increase in resting tidal volume compensates for decreased alveolar ventilation, loss of alveolar walls (surface area), and thickening of alveolar walls.
4. The ability to remove mucus from the respiratory passageways decreases with age.

REVIEW AND COMPREHENSION



1. The nasal cavity
 - a. has openings for the paranasal sinuses.
 - b. has a vestibule, which contains the olfactory epithelium.
 - c. is connected to the pharynx by the nares.
 - d. has passageways called conchae.
 - e. is lined with squamous epithelium, except for the vestibule.
2. The larynx
 - a. connects the oropharynx to the trachea.
 - b. has three single and six paired cartilages.
 - c. contains the vocal folds.
 - d. contains the vestibular folds.
 - e. All of these are correct.
3. Terminal bronchioles branch to form

a. the alveolar duct.	c. bronchioles.
b. alveoli.	d. respiratory bronchioles.
4. During an asthma attack, a person has difficulty breathing because of constriction of the

a. trachea.	d. alveoli.
b. bronchi.	e. respiratory membrane.
c. terminal bronchioles.	
5. During quiet expiration, the

a. abdominal muscles relax.	c. lower than the barometric pressure.
b. diaphragm moves inferiorly.	d. unchanged.
6. The parietal pleura

a. covers the surface of the lung.	c. is the connective tissue partition that divides the thoracic cavity into right and left pleural cavities.
b. covers the inner surface of the thoracic cavity.	d. covers the inner surface of the alveoli.
c. is the membrane across which gas exchange occurs.	e. is the membrane across which gas exchange occurs.
7. Contraction of the bronchiolar smooth muscle has which of these effects?

a. A smaller pressure gradient is required to get the same rate of airflow, compared with normal bronchioles.	c. It increases resistance to airflow.
b. It increases airflow through the bronchioles.	d. It increases alveolar ventilation.
8. During expiration, the intra-alveolar pressure is

a. lower than the pleural pressure.	c. lower than the barometric pressure.
b. greater than the barometric pressure.	d. unchanged.

9. Normally, which of the following keeps the lungs from collapsing?
 - a. surfactant
 - b. pleural pressure
 - c. elastic recoil
 - d. Both a and b are correct.
10. Immediately after the creation of an opening through the thorax into the pleural cavity
 - a. air flows through the hole and into the pleural cavity.
 - b. air flows through the hole and out of the pleural cavity.
 - c. air flows neither out nor in.
 - d. the lung protrudes through the hole.
11. Compliance of the lungs and thorax
 - a. is the volume by which the lungs and thorax change for each unit change of intra-alveolar pressure.
 - b. increases in emphysema.
 - c. decreases because of lack of surfactant.
 - d. All of these are correct.
12. Given these lung volumes:
 - (1) tidal volume = 500 mL
 - (2) residual volume = 1000 mL
 - (3) inspiratory reserve volume = 2500 mL
 - (4) expiratory reserve volume = 1000 mL
 - (5) dead space = 1000 mL

The vital capacity is

 - a. 3000 mL.
 - b. 3500 mL.
 - c. 4000 mL.
 - d. 5000 mL.
 - e. 6000 mL.
13. Alveolar ventilation is the
 - a. tidal volume times the respiratory rate.
 - b. minute volume plus the dead space.
 - c. amount of air available for gas exchange in the lungs.
 - d. vital capacity divided by the respiratory rate.
 - e. inspiratory reserve volume times minute volume.
14. The rate of diffusion of a gas across the respiratory membrane increases as the
 - a. respiratory membrane becomes thicker.
 - b. surface area of the respiratory membrane decreases.
 - c. partial pressure gradient of the gas across the respiratory membrane increases.
 - d. diffusion coefficient of the gas decreases.
 - e. All of these are correct.
15. Oxygen is mostly transported in the blood
 - a. dissolved in plasma.
 - b. bound to blood proteins.
 - c. within HCO_3^- .
 - d. bound to the heme portion of hemoglobin.
16. The oxygen-hemoglobin dissociation curve is adaptive because it
 - a. shifts to the right in the pulmonary capillaries and to the left in the tissue capillaries.
 - b. shifts to the left in the pulmonary capillaries and to the right in the tissue capillaries.
 - c. does not shift.
17. Carbon dioxide is mostly transported in the blood
 - a. dissolved in plasma.
 - b. bound to blood proteins.
 - c. within HCO_3^- .
 - d. bound to the heme portion of hemoglobin.
 - e. bound to the globin portion of hemoglobin.
18. The chloride shift
 - a. promotes the transport of CO_2 in the blood.
 - b. occurs when Cl^- replaces HCO_3^- within red blood cells.
 - c. maintains electrical neutrality in red blood cells and the plasma.
 - d. All of these are correct.
19. Which of these parts of the brainstem is correctly matched with its main function?
 - a. ventral respiratory groups—stimulate the diaphragm
 - b. dorsal respiratory groups—limit inflation of the lungs
 - c. pontine respiratory group—is involved in the switch between inspiration and expiration
 - d. All of these are correct.
20. The chemosensitive area
 - a. stimulates the respiratory center when blood CO_2 levels increase.
 - b. stimulates the respiratory center when blood pH increases.
 - c. is located in the pons.
 - d. stimulates the respiratory center when blood O_2 levels increase.
 - e. All of these are correct.
21. Blood O_2 levels
 - a. are more important than CO_2 levels in the regulation of respiration.
 - b. need to change only slightly to cause a change in respiration.
 - c. are detected by sensory receptors in the carotid and aortic bodies.
 - d. All of these are correct.

Answers appear in appendix F.

CRITICAL THINKING

1. A person's vital capacity is measured while standing and while lying down. What difference, if any, in the measurement do you predict and why?
2. Jenny wanted to do some underwater exploration. Instead of buying expensive SCUBA equipment, she obtained a long hose and an innertube. She attached one end of the hose to the innertube so that the end was always out of the water, and she inserted the other end of the hose in her mouth and went diving. What happened to her alveolar ventilation and why? How can she compensate for this change? How does diving affect lung compliance and the work of ventilation?
3. The bacteria that cause gangrene (*Clostridium perfringens*) are anaerobic microorganisms that do not thrive in the presence of O_2 . Hyperbaric oxygenation (HBO) treatment places a person in a chamber containing O_2 at three to four times normal atmospheric pressure. Explain how HBO helps treat gangrene.
4. One technique for artificial respiration is mouth-to-mouth resuscitation. The rescuer takes a deep breath, blows air into the patient's mouth, and then lets air flow out. The process is repeated. Explain the following: (1) Why do the patient's lungs expand? (2) Why does air move out of the patient's lungs? (3) What effect do the PO_2 and the PCO_2 of the rescuer's air have on the victim?



5. The left phrenic nerve supplies the left side of the diaphragm, and the right phrenic nerve supplies the right side. Damage to the left phrenic nerve results in paralysis of the left side of the diaphragm. During inspiration, does the left side of the diaphragm move superiorly, move inferiorly, or stay in place?
6. Suppose that the thoracic wall is punctured at the end of a normal expiration, producing a pneumothorax. Does the thoracic wall move inward, move outward, or not move at all?
7. During normal, quiet respiration, when does the maximum rate of diffusion of O₂ in the pulmonary capillaries occur? When does the maximum rate of diffusion of CO₂ occur?
8. Experimental evidence suggests that the overuse of erythropoietin (EPO; see chapter 19) reduces athletic performance. What side effects of EPO abuse reduce exercise stamina?
9. Predict what would happen to tidal volume if (a) the vagus nerves were cut, (b) the phrenic nerves were cut, or (c) the intercostal nerves were cut.
10. You and your physiology instructor are trapped in an overturned ship. To escape, you must swim under water a long distance. You

tell your instructor it would be a good idea to hyperventilate before making the escape attempt. Your instructor calmly replies, “What good would that do, since your pulmonary capillaries are already 100% saturated with oxygen?” What should you do and why?

11. Stephanie was hysterical and hyperventilating, so a doctor made her breathe into a paper bag. An especially astute student said to the doctor, “When Stephanie was hyperventilating, she was reducing blood CO₂ levels; when she breathed into the paper bag, CO₂ was trapped in the bag, and she was rebreathing it, thus causing blood CO₂ levels to increase. As Stephanie’s blood CO₂ levels increased, her urge to breathe should have increased. Instead, she began to breathe more slowly. Please explain.” How do you think the doctor responded? (*Hint:* Recall that the effect of decreased blood CO₂ on the vasomotor center results in vasodilation and a sudden decrease in blood pressure.)

Answers to odd-numbered questions appear in appendix G.

26

Learn to Predict

Fifty-seven-year-old Bobbie is living proof that a person can live with type 2 diabetes. Since being diagnosed with the condition 15 years ago, she has taken good care of herself, watching her diet and regularly monitoring her blood glucose and blood pressure at home. Therefore, she was immediately aware when her blood pressure began to rise. She also felt tired much of the time, and her face appeared puffy. Her physician confirmed the hypertension and detected generalized edema. After ordering several laboratory tests, he concluded that Bobbie was suffering from chronic renal failure. **Explain the cause of chronic renal failure and predict the results of Bobbie's blood test and urinalysis that led to this diagnosis. What is the probable prognosis for Bobbie in the future?**



Photo: Removal of a healthy kidney, as shown in this photo, is performed when the patient donates his or her kidney to a recipient who may otherwise die. The donor can expect to live a normal life with just one kidney.
©Hank Morgan/Science Source

Urinary System

It must have been fate. Sam met Dave when they played on the same softball team, and the two became great friends. A few years later, Dave was diagnosed with a fatal, progressive kidney disease. Like Bobbie in this chapter's "Learn to Predict," Dave began feeling tired and suffering from generalized edema. Without a kidney transplant, Dave could expect to live only a few more years. Immediately, Sam volunteered to be tested as a possible kidney donor and, amazingly, he was a nearly perfect match. After months of testing and planning, one of Sam's kidneys was removed and placed into Dave's body. Within a week, Dave's new kidney was functioning at almost normal capacity. Meanwhile, Sam recovered quickly, and his spirits were high because his donation had saved his friend's life. Doctors assured him that his remaining kidney, containing more than a million nephrons, would be sufficient for his future needs. The kidneys are remarkable organs that perform life-sustaining functions as part of the urinary system.

26.1 Functions of the Urinary System

LEARNING OUTCOMES

After reading this section, you should be able to

- List the organs of the urinary system.
- Describe the main functions of the kidneys.

The **urinary system** is the major excretory system of the body. Some organs in other systems also eliminate wastes, but are not able to fully compensate in case of kidney failure. The urinary system consists of two kidneys, the primary excretory organs. Each kidney's excretory products are carried by a ureter to a single urinary bladder. The urinary bladder is emptied of the waste liquid by the urethra (figure 26.1).

The kidneys each filter a large volume of blood. Wastes from the blood are collected and form urine. Urine consists of (1) excess water; (2) excess ions; (3) metabolic wastes, including the protein by-product, urea; and (4) toxic substances. In addition to their role as excretory organs, the kidneys are important for many other important metabolic activities. The functions of the kidneys include:

- Excretion.* The kidneys filter waste products from the blood. Nearly 21% of cardiac output is filtered by the kidneys each

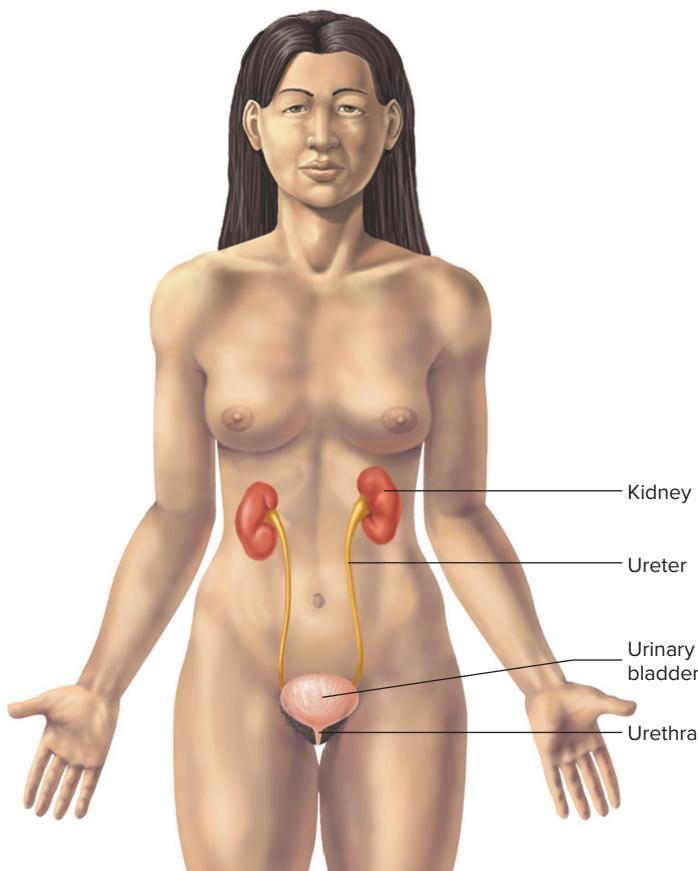


FIGURE 26.1 Urinary System

The urinary system consists of two kidneys, two ureters, the urinary bladder, and the urethra. **AP|R**

minute. Fluid and waste are captured by an extensive network of tubes found throughout the kidney. Large molecules, such as proteins, remain in the blood, whereas smaller molecules and ions enter the filtered fluid. As the fluid flows through the kidneys, it is slowly modified until it is converted into urine.

- Regulation of blood volume and pressure.* The kidneys play a major role in controlling the extracellular fluid volume in the body. The kidneys can produce either a large volume of dilute urine or a small volume of concentrated urine, depending on the hydration level of the body. Through urine production, the kidneys regulate blood volume and hence blood pressure.
- Regulation of blood solute concentrations.* The kidneys help regulate the concentration of the major ions, such as Na^+ , Cl^- , K^+ , Ca^{2+} , HCO_3^- , and HPO_4^{2-} . The kidneys also regulate other solute concentrations, such as urea.
- Regulation of extracellular fluid pH.* The kidneys secrete variable amounts of H^+ to help regulate the extracellular fluid pH.
- Regulation of red blood cell synthesis.* The kidneys secrete a hormone, erythropoietin, which stimulates the synthesis of red blood cells in red bone marrow (see chapter 19).
- Regulation of vitamin D synthesis.* The kidneys play an important role in controlling blood levels of Ca^{2+} by regulating the synthesis of vitamin D (see chapter 6).

ASSESS YOUR PROGRESS

Answers to these questions are found in the section you have just completed. Re-read the section if you need help in answering these questions.

- Name the organs that make up the urinary system.
- List the functions performed by the kidneys, and briefly describe each.

26.2 Kidney Anatomy and Histology

LEARNING OUTCOMES

After reading this section, you should be able to

- Describe the location and external anatomy of the kidneys.
- Describe the inner regions of the kidney.
- Give the details of the nephron's structure and histology.
- Explain the blood supply of the kidney.

Location and External Anatomy of the Kidneys

The **kidneys** are bean-shaped organs. They are **retroperitoneal** (re'trō-per'i-tō-nē'äl), which means they lie behind the peritoneum (see chapter 1) and are located on each side of the vertebral column near the psoas major muscles (figure 26.2). They are each about the size of a tightly clenched fist. The kidneys extend from the lower portion of the rib cage at the level of the last thoracic (T12) vertebra to the third lumbar (L3) vertebra (see figure 7.23). The liver is superior to the right kidney, causing the right kidney to be slightly lower than the left. Each kidney measures about 11 cm long, 5 cm wide,

and 3 cm thick, and each weighs about 130 g, which is approximately the weight of 1 cup of flour. The kidneys are each surrounded by an outer layer of connective tissue, called the **renal** (derived from *renes*, the Latin word for kidney) **capsule**. Surrounding the outside of the capsule is a thick layer of adipose tissue, which cushions

and protects the kidneys. A thin layer of connective tissue, the **renal fascia**, surrounds the adipose tissue and helps anchor the kidneys to the abdominal wall. More adipose tissue surrounds the renal fascia.

The **hilum** (hī'lūm) is a small area on the concave, medial side of the kidney that is continuous with an adipose and connective tissue-filled cavity of the kidney, called the **renal sinus**. The renal artery and nerves enter the kidney at the hilum then pass through the renal sinus. The renal vein, ureter, and lymphatic vessels also pass through the renal sinus before they exit the kidney at the hilum (figure 26.3).

ASSESS YOUR PROGRESS

3. Describe the location, size, and shape of the kidneys.
4. Describe the renal capsule and the structures that surround the kidney.
5. List the structures found at the hilum and in the renal sinus of a kidney.

Internal Anatomy and Histology of the Kidneys

To fully appreciate the function of the kidneys, we must first understand their ultrastructure. The kidneys are organized into two major regions: (1) an outer **cortex** and (2) an inner **medulla** that surrounds the renal sinus (figure 26.3). The cortex is the location for the blood-filtering structures of the kidney. These are discussed in more detail in the next section.

The medulla is composed of many cone-shaped structures called **renal pyramids**, whose bases project into the cortex. These projections are called **medullary rays**. Between the renal pyramids and their medullary rays, there are extensions of cortical tissue toward the medulla, called **renal columns**. The renal pyramids are a collection of tubes and ducts that transport fluid throughout the kidney and modify it into urine. Once urine is formed, ducts in the renal pyramids transport it toward the renal sinus. The tips of the pyramids, the **renal papillae**, point toward the renal sinus. In the renal sinus, another set of tubes collects the urine for movement to the urinary bladder. When urine leaves a renal papilla, it empties into a small, funnel-shaped chamber surrounding the tip of the papilla called a **minor calyx** (kal'ix; pl. calyces). Urine from several minor calyces are emptied into a larger, funnel-shaped chamber called a **major calyx**. In each kidney, there are between 8 and 20 minor calyces converging to form about 2 or 3 major calyces. From the

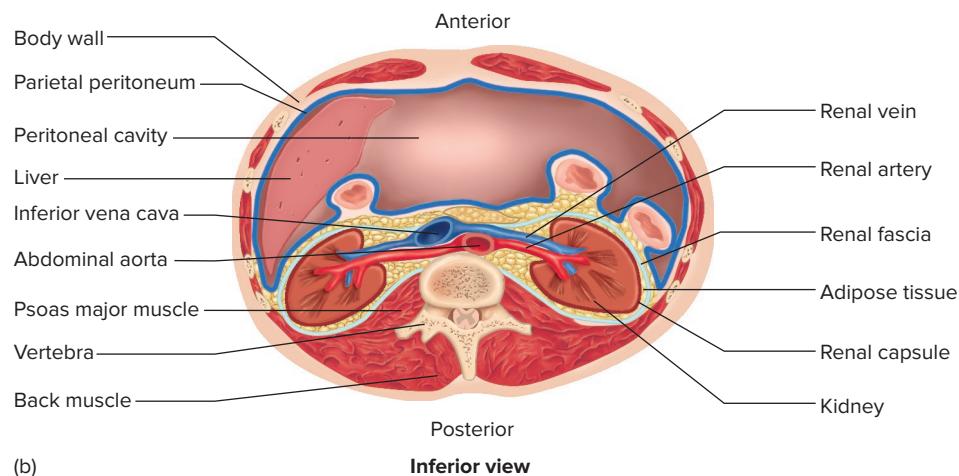
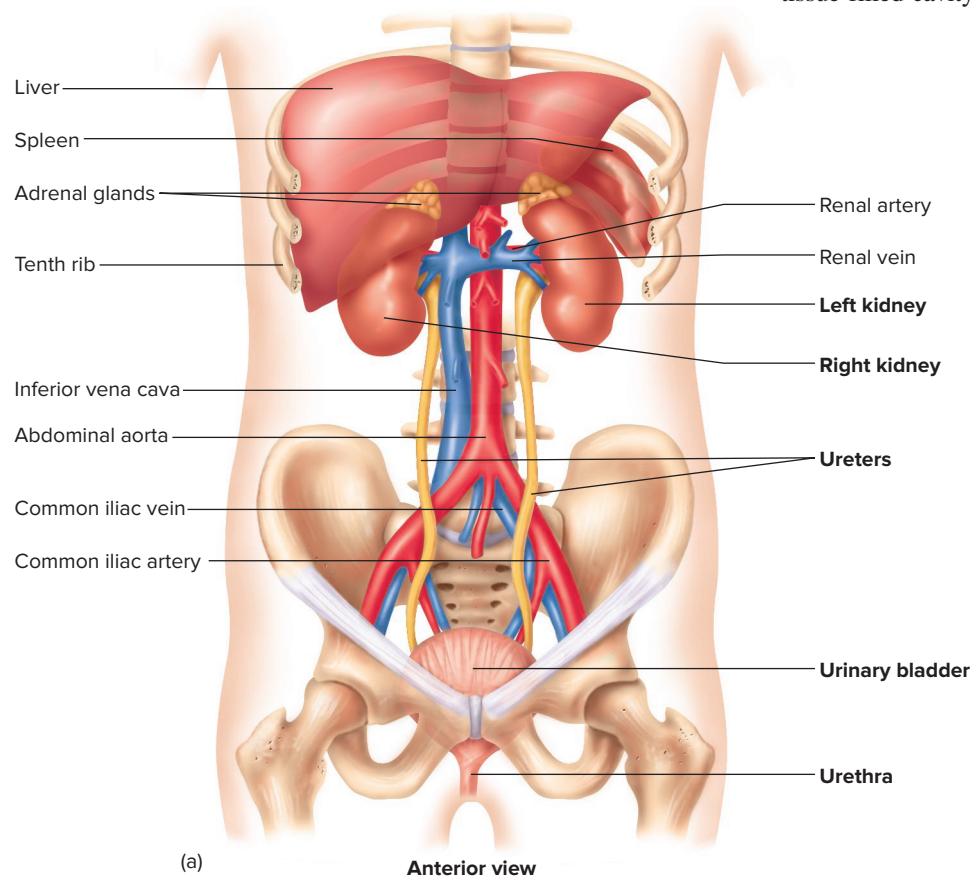
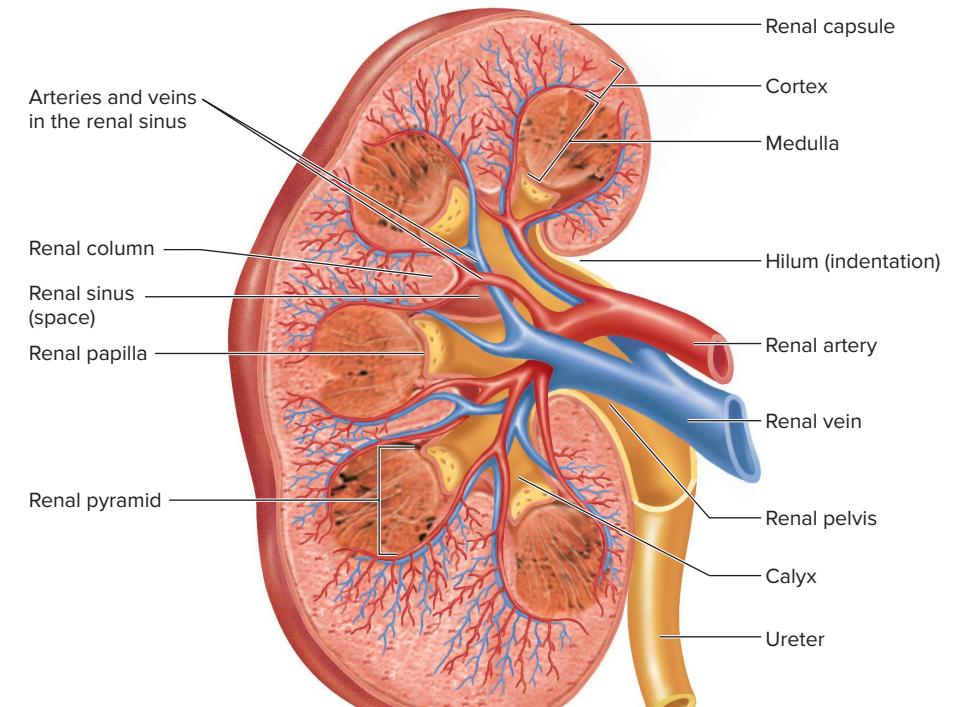
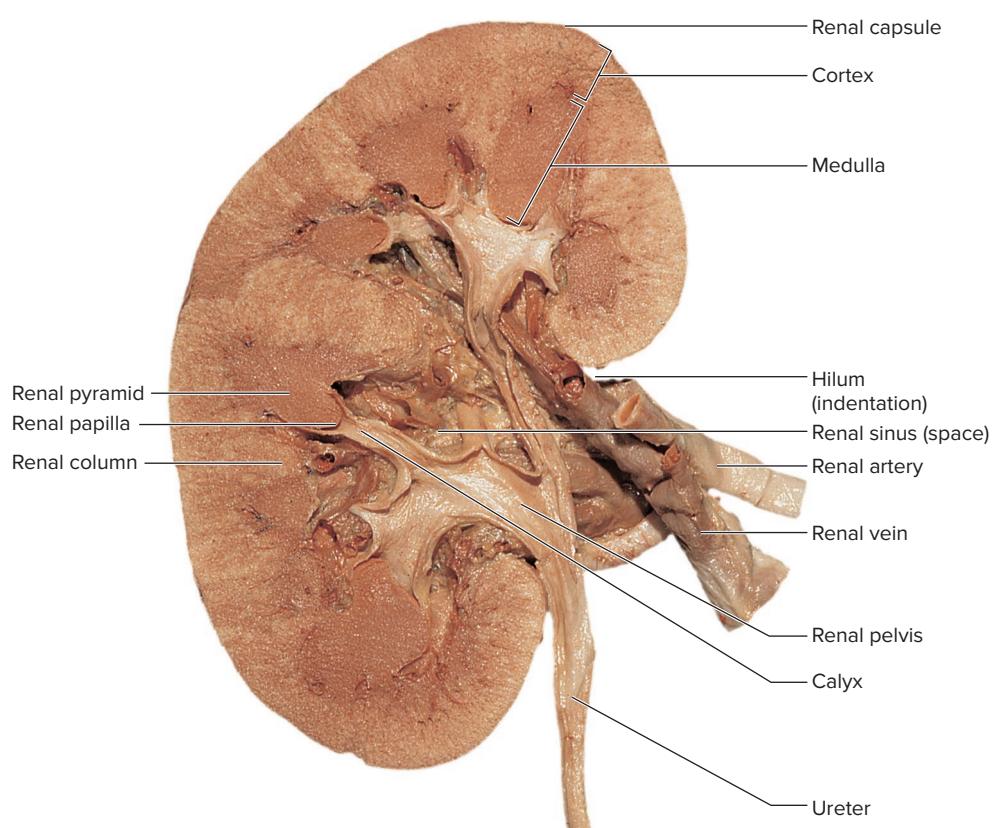


FIGURE 26.2 Anatomy of the Urinary System

(a) The kidneys are located in the abdominal cavity, with the right kidney just below the liver and the left kidney below the spleen. A ureter extends from each kidney to the urinary bladder within the pelvic cavity. An adrenal gland is located at the superior pole of each kidney. (b) The kidneys are located behind the parietal peritoneum, surrounded by adipose tissue. A connective tissue layer, the renal fascia, anchors the kidney to the abdominal wall. The renal arteries extend from the abdominal aorta to each kidney, and the renal veins extend from the kidneys to the inferior vena cava. **AP|R**



(a)



(b)

FIGURE 26.3 Frontal Section of the Kidney and Ureter

(a) A frontal kidney section shows that the cortex forms the outer part of the kidney, and the medulla forms the inner part. A central cavity called the renal sinus contains the renal pelvis. The renal columns of the kidney project from the cortex into the medulla and separate the pyramids. (b) Photograph of a longitudinal section of a human kidney and ureter. (b) ©McGraw-Hill Education/Rebecca Gray, photographer AP|R

major calyces, urine empties into a single, enlarged, funnel-shaped chamber called the **renal pelvis**. The renal pelvis is embedded in and surrounded by the renal sinus. At the hilum, it narrows significantly, forming the small-diameter tube called the **ureter**. Urine moves from the renal pelvis into the ureter for transport to the urinary bladder.

Structure of a Nephron

The **nephron** (nef'ron) is the histological and functional unit of the kidney (figure 26.4). There are approximately 1.3 million nephrons distributed throughout the cortex and medulla of each kidney. Nephrons usually measure about 50–55 mm in length. There are four separate regions of a nephron. These four regions include: (1) a **renal corpuscle**, (2) a **proximal convoluted tubule**, (3) a **loop of Henle**, and (4) a **distal convoluted tubule**. Each portion of a nephron plays a different role in urine production. Generally speaking, the renal corpuscle filters the blood, the proximal convoluted tubule returns filtered substances to the blood, the loop of Henle helps conserve water and solutes, and the distal convoluted tubule rids the blood of additional wastes. The fluid in the distal convoluted tubule then empties into a collecting duct, which carries the newly formed urine from the cortex of the kidney toward the renal papilla deep in the medulla. Near the tip of the renal papilla, several collecting ducts merge into a larger-diameter tubule called a **papillary duct**, which empties into a minor calyx.

Types of Nephrons

There are two types of nephrons in the kidney: (1) juxtamedullary nephrons and (2) cortical nephrons. **Juxtamedullary** (juks'ta-med'ü-lär-ë; next to medulla) **nephrons** have renal corpuscles that are found deep in the cortex near the medulla. They have long loops of Henle, which extend deep into the medulla. Longer loops of Henle are well adapted for water conservation (see section 26.3). Only about 15% of nephrons are juxtamedullary nephrons.

Cortical nephrons have renal corpuscles that are distributed throughout the cortex. Their loops of Henle are shorter than those of juxtamedullary nephrons and are closer to the outer edge of the cortex (figure 26.4).

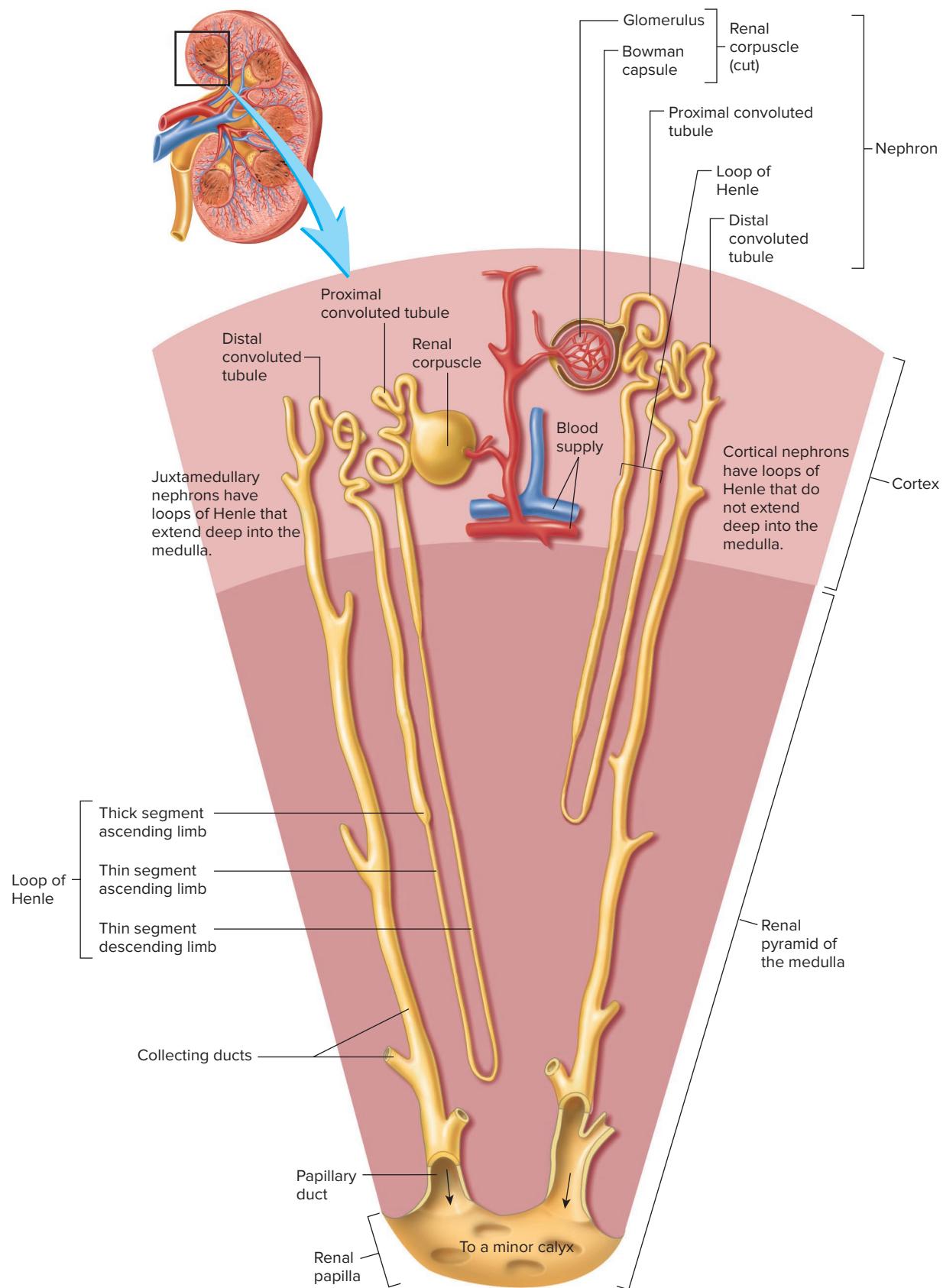


FIGURE 26.4 Functional Unit of the Kidney—the Nephron

A nephron consists of a renal corpuscle, proximal convoluted tubule, loop of Henle, and distal convoluted tubule. The distal convoluted tubule empties into a collecting duct. Juxamedullary nephrons (those near the medulla of the kidney) have loops of Henle that extend deep into the medulla, whereas other nephrons do not. Collecting ducts undergo a transition to larger-diameter papillary ducts near the tip of the renal papilla. The papillary ducts empty into a minor calyx. **AP|R**

The Renal Corpuscle

The filtration portion of the nephron is housed in the renal corpuscle. The renal corpuscle consists of (1) the glomerulus and (2) the Bowman capsule. The **glomerulus** (glō-mär'ū-lüs; ball of yarn) is a network of capillaries twisted around each other like a ball of yarn (figure 26.5a,b). Fluid filtered from the glomerular capillaries is called the filtrate. The **Bowman capsule** is an indented, double-walled chamber surrounding the glomerulus. From the Bowman capsule, the filtered fluid flows into the proximal convoluted tubule of the renal tubule.

A Bowman capsule consists of two layers: (1) the parietal layer and (2) the visceral layer (figure 26.5b). The outer layer is the **parietal layer**. It is constructed of simple squamous epithelial cells. The epithelial cells become cube-shaped at the beginning of the proximal convoluted tubule. The inner layer is the **visceral layer**. It is constructed of specialized cells called **podocytes**, which wrap around the glomerular capillaries.

The renal corpuscle has several unique characteristics that make it particularly efficient at filtration—the main function of the kidneys.

1. *Fenestrae.* The glomerular capillaries are highly permeable due to the presence of **fenestrae** (fe-nes'trē; windows). Recall from chapter 21 that capillaries have different levels of permeability, depending on the size of their pores. In the case of fenestrae, neither large proteins nor blood cells can fit through them.
2. *Filtration slits.* Gaps, called **filtration slits**, are between the cell processes of the podocytes of the visceral layer (figure 26.5c). A basement membrane lies sandwiched between the endothelial cells of the glomerular capillaries and the podocytes of the Bowman capsule.
3. *High pressure.* An **afferent** (af'er-ent) **arteriole** supplies blood to the glomerulus for filtration. An **efferent** (ef'er-ent) **arteriole** transports the filtered blood away from the glomerulus (figure 26.5a). The glomerular capillaries have much higher pressure than other capillaries due to the smaller diameter of the efferent arteriole compared to the afferent arteriole.

Together, the structures in the corpuscle make up the **filtration membrane**. The filtration membrane consists of capillary endothelium, the basement membrane, and the podocytes of the Bowman

capsule (figure 26.5d). We will discuss the filtration membrane in greater detail in section 26.3. The filtration membrane performs the first major step in urine production. Urine production begins when the filtration membrane filters the blood. The filtered fluid then enters the lumen, or space, inside the Bowman capsule.

An important regulatory structure, called the **juxtaglomerular apparatus**, is located next to the glomerulus (figure 26.5b).

The juxtaglomerular apparatus consists of a unique set of afferent arteriole cells and specialized cells in the distal convoluted tubule that are in close contact with each other. These specialized cells include the following:

1. At the point where the afferent arteriole enters the renal corpuscle, it has a cuff of specialized smooth muscle cells around it. These cells are called **juxtaglomerular cells**.
2. A part of the distal convoluted tubule of the nephron lies between the afferent and efferent arterioles next to the renal corpuscle. In this section of the distal convoluted tubule, there is a group of specialized cells called the **macula** (mak'ū-lă) **densa**.

Secretion of the enzyme renin by the juxtaglomerular apparatus plays an important role in the regulation of filtrate formation and blood pressure (see section 26.4).

The Renal Tubule

Once the blood is filtered, the resulting fluid is modified to form urine as it passes through each section of the renal tubule. The first section is the **proximal convoluted tubule**. It is approximately 14 mm long and 60 μm in diameter. The wall of the proximal convoluted tubule is composed of simple cuboidal epithelium. The proximal convoluted tubule cells rest on a basement membrane, which forms the outer surface of the tubule. These cells have many microvilli projecting from the luminal (next to the filtrate) surface of the cells (figure 26.6a,b).

As the proximal convoluted tubule continues descending toward the medulla, the cell type begins to change. At this point the renal tubule is called the **loop of Henle**. Every loop of Henle has two limbs: (1) the **descending limb** and (2) the **ascending limb**. The first part of the descending limb is similar in structure to the proximal convoluted tubule. The portion of the loop of Henle that extends into the medulla becomes very thin near the



Clinical GENETICS 26.1

Polycystic Kidney Disease

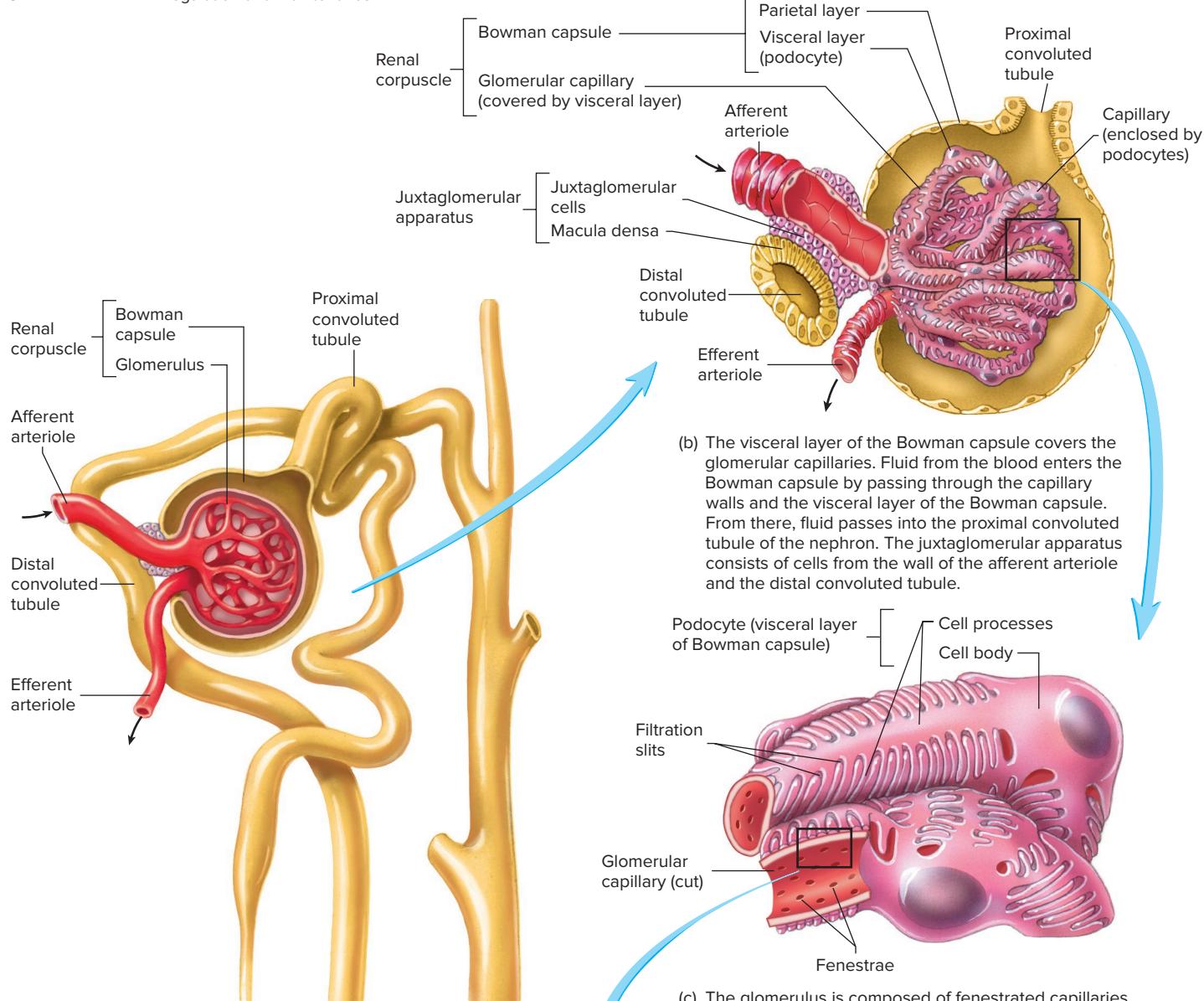
Polycystic kidney disease is the third-leading cause of renal failure (after diabetes mellitus and high blood pressure). Approximately 90% of patients inherit the condition as an autosomal dominant trait. Consequently, if one parent carries an allele for this disorder, each child has a 50% chance of also having the disorder (see chapter 29). The gene for this condition codes

for a protein that may regulate cell-to-cell interactions.

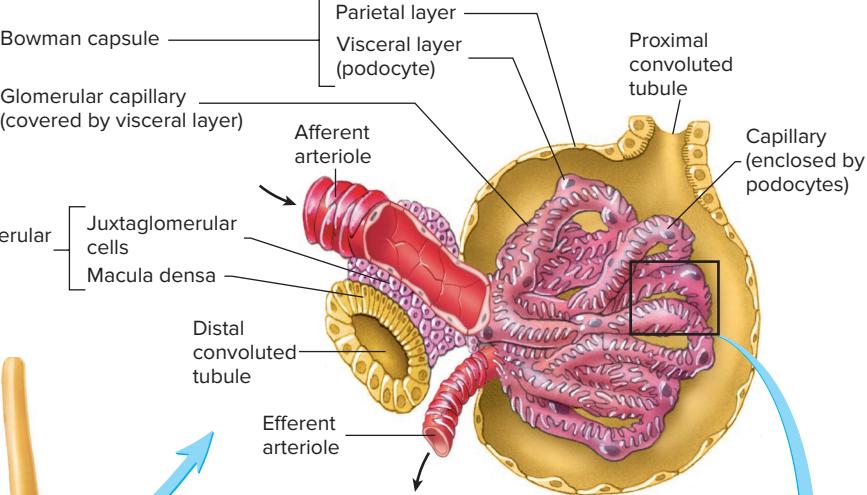
In people affected by polycystic kidney disease, the kidneys are enlarged and often contain large, fluid-filled cysts varying in size from a few millimeters to centimeters. The cysts increase in number and enlarge as the person ages. Development of the cysts results from abnormal cell-to-cell interactions and causes

excess proliferation of the epithelial cells that make up the kidney nephrons and collecting ducts.

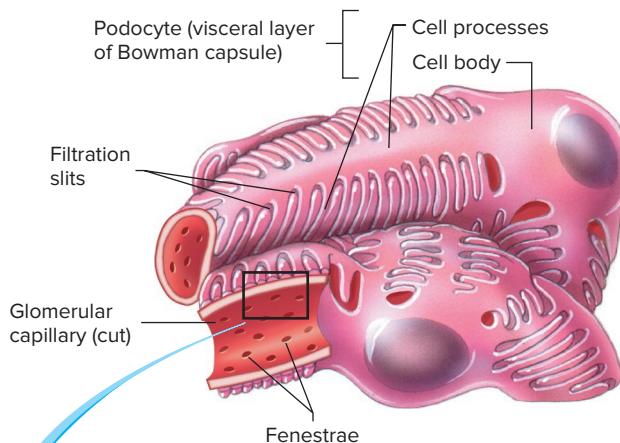
Polycystic kidney disease is often detected using ultrasound techniques. The condition is usually diagnosed when patients are between 30 and 50 years of age. Approximately 50% of patients require hemodialysis (see this chapter's Systems Pathology) by 70 years of age.



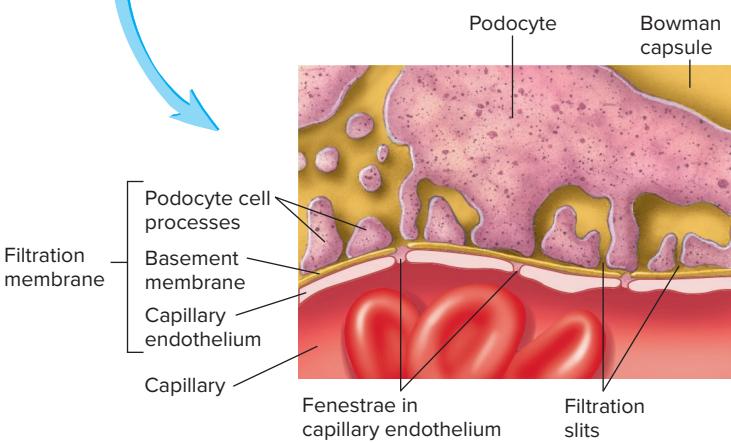
(a) The renal corpuscle consists of the Bowman capsule and the glomerulus. The Bowman capsule is the enlarged end of the renal tubule, which is indented to form a double-walled chamber. The Bowman capsule surrounds the glomerulus, which is a network of capillaries. Blood flows from the afferent arteriole into the glomerulus and leaves the glomerulus through the efferent arteriole.



(b) The visceral layer of the Bowman capsule covers the glomerular capillaries. Fluid from the blood enters the Bowman capsule by passing through the capillary walls and the visceral layer of the Bowman capsule. From there, fluid passes into the proximal convoluted tubule of the nephron. The juxtaglomerular apparatus consists of cells from the wall of the afferent arteriole and the distal convoluted tubule.



(c) The glomerulus is composed of fenestrated capillaries. The visceral layer of the Bowman capsule consists of specialized cells called podocytes. Spaces between the podocyte cell processes are called filtration slits.



(d) The filtration membrane consists of the fenestrated glomerular capillary endothelium, a basement membrane, and the podocyte cell processes. Fluid passes from the capillary through the filtration membrane into the Bowman capsule.

FIGURE 26.5 Renal Corpuscle

Filtration of the blood occurs in the renal corpuscle.

FUNDAMENTAL Figure

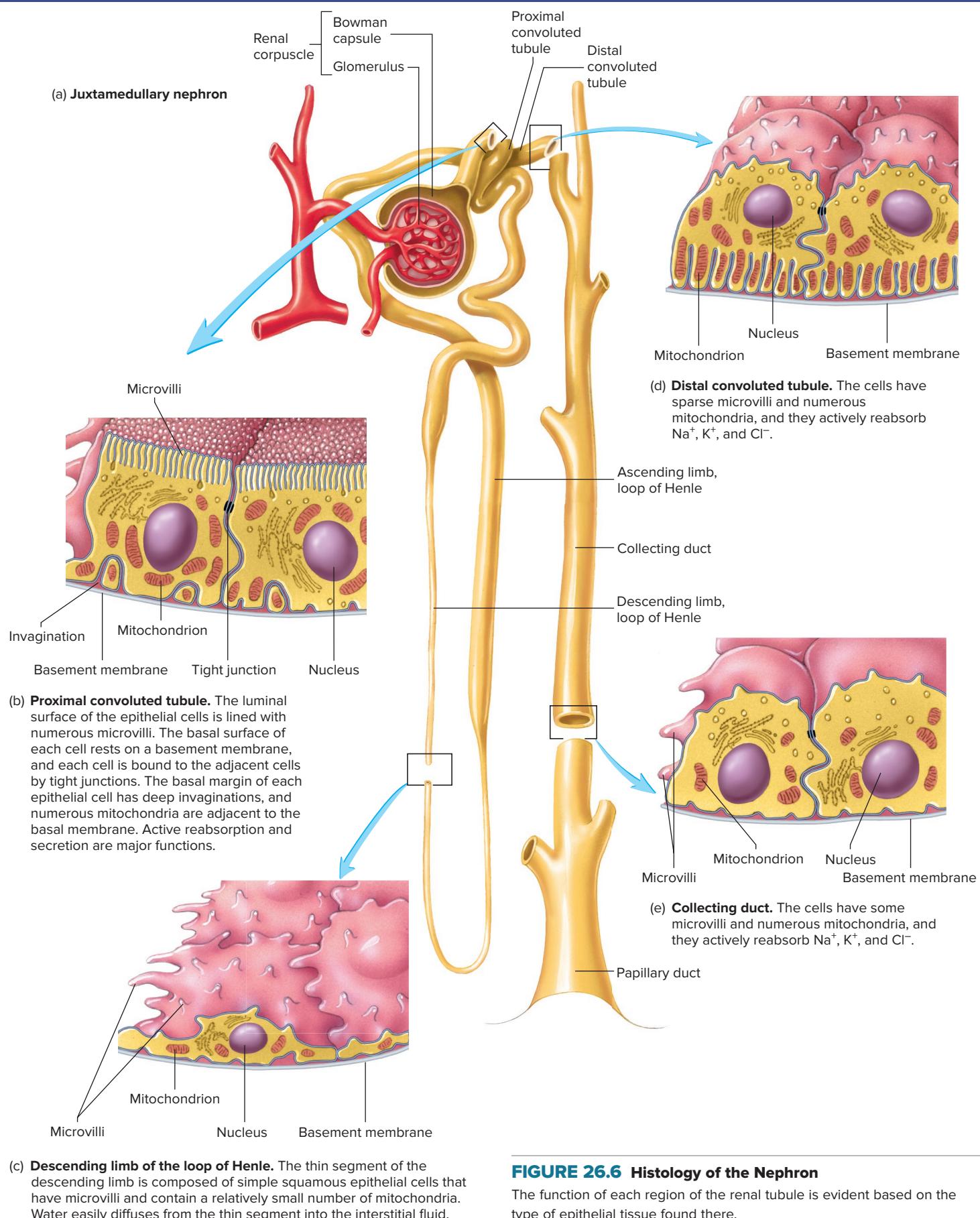


FIGURE 26.6 Histology of the Nephron

The function of each region of the renal tubule is evident based on the type of epithelial tissue found there.

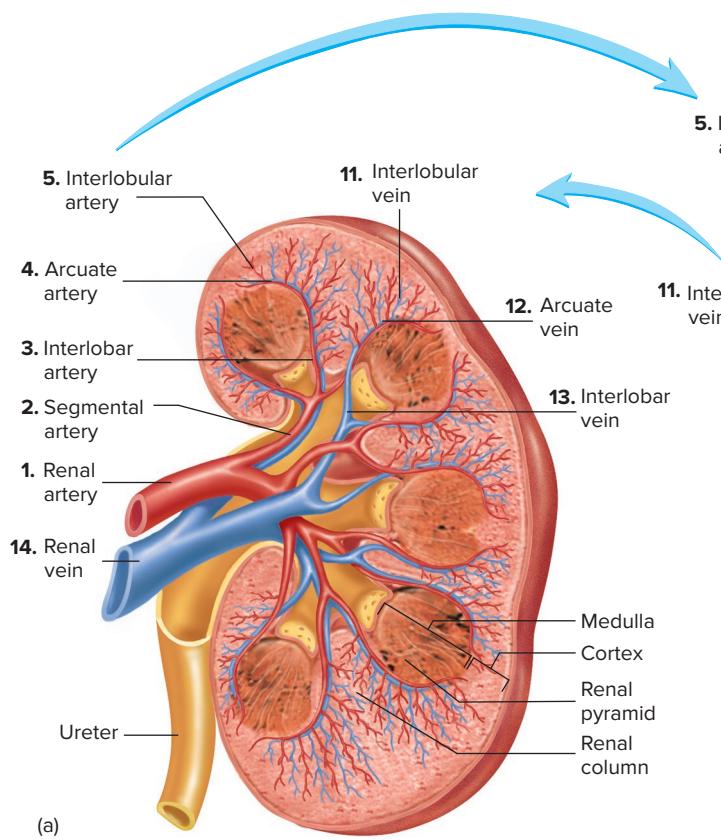
bend of the loop (figure 26.6a,c). The lumen in the thin part narrows, and an abrupt transition occurs from simple cuboidal epithelium to simple squamous epithelium. Like the descending limb, the first part of the ascending limb is thin and made of simple squamous epithelium. Soon, however, it becomes thicker, and simple cuboidal epithelium replaces the simple squamous epithelium. The thick part of the ascending limb returns toward the renal corpuscle and ends by transitioning to the distal convoluted tubule near the macula densa.

The **distal convoluted tubule** is shorter than the proximal convoluted tubule. Its epithelium is simple cuboidal. However, these cells are smaller and have fewer microvilli (figure 26.6d). Several distal convoluted tubules connect to a single **collecting duct**, which is composed of simple cuboidal epithelium (figure 26.6c). The collecting duct, which is larger in diameter than the segments of the nephron, form much of the medullary rays and extend through the medulla toward the tips of the renal pyramids.

Arteries and Veins of the Kidneys

A system of blood vessels allows the exchange of materials that occurs in the kidneys. The renal arteries branch off the abdominal aorta and enter the kidneys (figure 26.7). The vessels in order of branching, starting with the renal artery, are the following:

1. The **renal artery** delivers approximately 21% of cardiac output per minute.
2. The **segmental arteries** branch from the renal artery to each portion of the kidney.



3. The **interlobar** (in-ter-lō'bar; between the lobes) **arteries** pass between the renal pyramids.
4. The **arcuate** (ar'kū-āt; arched) **arteries** branch from the interlobar arteries. They arch between the cortex and the medulla.
5. **Interlobular arteries** branch off the arcuate arteries and project into the cortex.
6. The **afferent arterioles** arise from branches of the interlobular arteries. The afferent arterioles lead into the glomerular capillaries.
7. The **glomerular capillaries** are the locations of filtration.
8. **Efferent arterioles** extend from the glomerular capillaries.
9. The **peritubular** (around the tubes) **capillaries** branch from the efferent arterioles. They surround the proximal convoluted tubules, the distal convoluted tubules, and the loops of Henle. The **vasa recta** (vā'sā rek'tā; straight vessels) are specialized portions of the peritubular capillaries that extend deep into the medulla of the kidney and surround the loops of Henle and collecting ducts.

Blood from the peritubular capillaries, including the vasa recta, will return to the general circulation through the veins of the kidneys (see figure 26.7a,b).

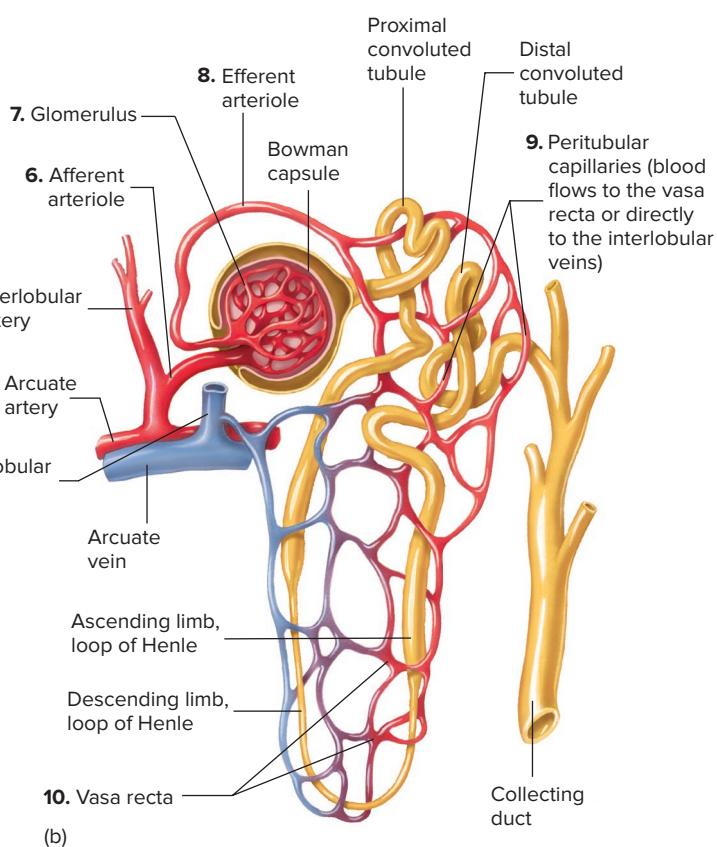


FIGURE 26.7 Blood Flow Through the Kidney

Numbers 1–14 show the sequence of blood flow through the kidney.

(a) Blood flow through the larger arteries and veins of the kidney.

(b) Blood flow through the arteries, capillaries, and veins that provide circulation to the nephrons.

AP|R

ASSESS YOUR PROGRESS

- 6.** What is the functional unit of the kidney? Name its parts.
- 7.** Distinguish between cortical and juxtamedullary nephrons.
- 8.** List the components of a renal corpuscle.
- 9.** Describe the structure of the Bowman capsule, the glomerulus, and the filtration membrane.
- 10.** Describe the structure of the afferent and efferent arterioles and the juxtaglomerular apparatus. What is the function of the juxtaglomerular apparatus?
- 11.** Describe the structure and location of the proximal convoluted tubule, loop of Henle, distal convoluted tubule, collecting duct, and papillary duct.
- 12.** Explain the blood supply for the kidney.

26.3 Urine Production**LEARNING OUTCOMES**

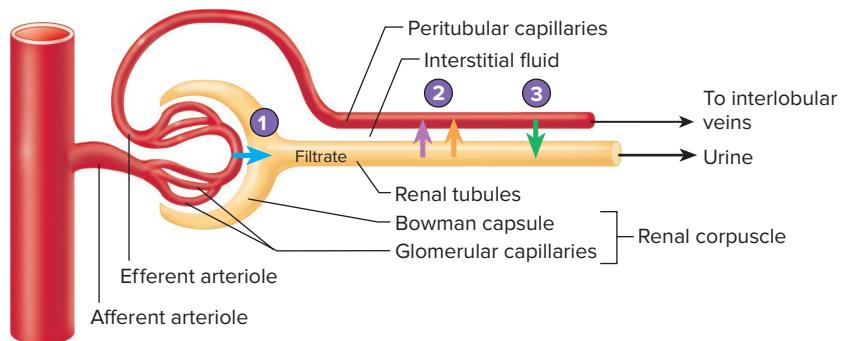
After reading this section, you should be able to

- A.** Briefly describe the three processes necessary for urine production.
- B.** Identify the principal factors that influence filtration and explain how they affect the rate of filtrate formation.
- C.** Explain how filtration is regulated.
- D.** Describe the role of the various regions of the kidney tubule in the process of reabsorption.
- E.** Explain how substances are able to move across the wall of the tubule.

FUNDAMENTAL Figure

Urine production results from the following three processes:

- 1 Filtration** Filtration (blue arrow) is the movement of materials across the filtration membrane into the Bowman capsule to form filtrate.
- 2 Tubular reabsorption** Solutes are reabsorbed (purple arrow) across the wall of the renal tubule into the interstitial fluid by transport processes, such as active transport and cotransport. Water is reabsorbed (orange arrow) across the wall of the renal tubule by osmosis. Water and solutes pass from the interstitial fluid into the peritubular capillaries.
- 3 Tubular secretion** Solutes are secreted (green arrow) across the wall of the renal tubule into the filtrate.

**PROCESS FIGURE 26.8 Urine Production**

Urine formation involves three processes: filtration, reabsorption, and secretion.

- F.** Relate the types of substances that are moved during tubular secretion and explain how those substances are moved.
- G.** Describe the three mechanisms that explain the kidney's ability to concentrate urine.

The primary function of the kidney is regulation of body fluid composition. The kidney is the organ that sorts the substances from the blood for either removal in the urine or return to the blood. Substances that are waste products, toxins, and excess materials are permanently removed from the body, whereas other substances need to be preserved to maintain homeostasis. The structural components that perform this sorting are the nephrons, the functional units of the kidney. If you have ever decided to organize your “junk” drawer in your desk or kitchen, you may realize just how difficult it is to quickly sort through all its contents. In fact, you may have found yourself simply emptying the drawer onto a table and then sorting the contents one by one as you place objects into a “save group” or a “throw away group.” In a sense, the kidney uses the same approach when regulating blood composition. The “throw away” items end up in the urine, and the “save” items go back into the blood.

There are three major steps in urine production: (1) filtration, (2) tubular reabsorption, and (3) tubular secretion (figure 26.8).

- 1. Filtration.** Blood pressure in the glomerular capillaries forces fluid and small molecules out of the blood. The filtered fluid is now called filtrate. Filtration is nonselective and separates based only on size or charge of molecules. Filtration is comparable to emptying your “junk” drawer of everything except large, permanent items. Filtration does not

- AP|R **?** What would happen to water reabsorption if the osmotic pressure of the blood were to increase above normal?

TABLE 26.1

Concentrations of Major Solutes in Urine

Substance	Plasma	Filtrate	Net Movement of Solute*	Urine	Urine Concentration/ Plasma Concentration†
Water (L)	180	180	178.6	1.4	—
Organic molecules (mg/100 mL)					
Protein	3900–5000	6–11	−100.0	0‡	0
Glucose	100	100	−100.0	0	0
Urea	26	26	−11.4	1820	70
Uric acid	3	3	−2.7	42	14
Creatinine	1.1	1.1	0.5	196	180
Ions (mEq/L)					
Na ⁺	142	142	−141.0	128	0.9
K ⁺	5	5	−4.5	60	12.0
Cl [−]	103	103	−101.9	134	1.3
HCO ₃ [−]	28	28	−27.9	14	0.5

*In many cases, solute moves into and out of the nephron. Numbers indicate net movement. Negative numbers are net movement out of the filtrate, and positive numbers are net movement into the filtrate.

†Trace amounts of protein can be found in the urine. A value of zero is assumed here.

‡Represents solute added to urine via secretion from the interstitial fluid.

remove everything in the blood. Filtration removes only those substances small enough to fit through the filtration membrane.

2. **Tubular reabsorption.** Cells in the renal tubules contain many transport proteins. These transport proteins move water and some filtered molecules from the filtrate back into the blood in the peritubular capillaries. This prevents them from being lost from the body as components of urine (these are the “saved” items from your junk drawer). Most of the filtered water and useful solutes have been returned to the blood by the time the filtrate has been modified to urine, whereas the remaining waste or excess substances, and a small amount of water form urine (table 26.1).
3. **Tubular secretion.** Certain tubule cells transport additional solutes from the blood into the filtrate. Some of these solutes may not have been filtered by the filtration membrane (these are some “throw away” items that had been left behind in your junk drawer).

Urine consists of substances filtered directly from the blood and those that are secreted into the renal tubule, minus any reabsorbed substances.

Filtration

Filtration is a nonspecific process whereby materials are separated based on size or charge. A simple example of size filtration is demonstrated by a coffee maker. In this case, the driving force of filtration is gravity. The kidneys also demonstrate size filtration by filtering the blood, but here, the driving force of filtration is blood pressure. Filtration is the first step in urine production. All blood components except blood cells and most proteins can leave the glomerular capillaries and enter the Bowman capsule as filtrate. It is the filtrate that will be modified into urine.

The importance of filtration is indicated by the large percentage of cardiac output, or blood, sent through the kidneys each minute. This percentage of cardiac output that flows through the kidneys is called the **renal fraction**. It varies from 12% to 30% of the cardiac output in healthy, resting adults, but it averages 21% (table 26.2).

There are several measurements of filtration that can be calculated as an indication of proper kidney function. These calculations can measure either (1) rate of whole blood flow or (2) rate of plasma flow.

To calculate the rate of whole blood flow through the kidneys, called **renal blood flow rate**, two pieces of information are necessary: (1) the renal fraction, or 21% and (2) the cardiac output, or 5600 mL/min. The following equation (26.1) is used:

$$\text{Renal blood flow rate} = \text{Cardiac output} \times \text{Renal fraction}$$

$$1176 \text{ mL/min} = 5600 \text{ mL/min} \times 0.21 \quad (26.1)$$

To calculate the rate of plasma flow through the kidneys, called the **renal plasma flow rate**, we must account for the percentage of whole blood made up by plasma, which is approximately 55%. The equation is the following:

$$\text{Renal plasma flow rate} = \text{Renal blood flow rate} \times \% \text{ of whole blood that is plasma}$$

$$650 \text{ mL/min} = 1176 \text{ mL/min} \times 0.55 \quad (26.2)$$

To calculate the rate of filtrate formed per minute, called the **glomerular filtration rate (GFR)**, you first need to know what percentage of plasma is filtered from the blood. This is called the **filtration fraction**. The filtration fraction is approximately 19%. Thus, to calculate the GFR, the following equation is used.

$$\text{GFR} = \text{Renal plasma flow rate} \times \text{Filtration fraction}$$

$$123.5 \text{ mL plasma/min} = 650 \text{ mL/min} \times 0.19 \quad (26.3)$$

TABLE 26.2

Calculation of Renal Flow Rates

	Amount per Minute (mL)	Calculation
Renal Blood Flow	1176	Amount of blood flowing through the kidneys per minute = cardiac output \times the percentage of cardiac output that enters the kidneys $5600 \text{ mL blood/min} \times 0.21 = 1176 \text{ mL blood/min}$
Renal Plasma Flow	650	Amount of plasma flowing through the kidneys per minute = renal blood flow \times % of the blood that is plasma $1176 \text{ mL blood/min} \times 0.55 \approx 650 \text{ mL plasma/min}$
Glomerular Filtration Rate (GFR)	125	Amount of plasma (filtrate) that enters the Bowman capsule per minute = renal plasma flow \times % of the plasma that enters the renal capsule $650 \text{ mL plasma/min} \times 0.19 \approx 125 \text{ mL filtrate/min}$
Urine	1	Nonreabsorbed filtrate that leaves the kidneys per minute = glomerular filtration rate \times % of the filtrate that is not reabsorbed into the blood $125 \text{ mL filtrate/min} \times 0.008 = 1 \text{ mL urine/min}$ Milliliters of urine per minute can be converted to liters of urine per day by multiplying by 1.44. $1 \text{ mL urine/min} \times 1.44 = 1.4 \text{ L/day}$

In other words, the GFR indicates that the kidneys form approximately 125 mL/min of filtrate. When calculated over the entire day, there are about 180,000 mL, or 180 L, of filtrate produced daily.

This enormous volume is equal to about ninety 2-liter soft drink bottles per day. Because a healthy person produces only 1000–2000 milliliters (1–2 liters) of *urine* each day, the equivalent of one 2-liter soft drink bottle, it is readily apparent that not all of the filtrate becomes urine. In fact, about 99% of the filtrate volume is reabsorbed into the blood as it travels through the renal tubule, and less than 1% becomes urine. Although it may seem pointless to remove so much material from the blood only to return it right away, it is important that filtration remains continuous, so that waste products can be removed from the blood as quickly as possible.

Filtration Membrane

Recall that the renal corpuscles in the renal cortex house the filtration structures, each of which is called a **filtration membrane**. It separates materials on the basis of size and charge of the blood components. Thus the filtration membrane allows water and small molecules to leave the blood while preventing blood cells and most proteins from leaving the blood. Several structures make up the filtration membrane:

1. The fenestrated glomerular capillaries
2. The basement membrane between the capillary wall and the visceral layer of the Bowman capsule
3. Podocytes of the visceral layer of the Bowman capsule (see figure 26.5d)

Together, these components prevent molecules larger than 7 nm in diameter or those having a molecular mass equal to or greater than 40,000 daltons from passing through. For comparison, an antibody molecule is 12 nm, glucose is 0.9 nm, and the amino

acid methionine is 0.7 nm in diameter. The exclusion of molecules larger than 7 nm is partially due to the fact that the fenestrae are about 7 nm in size. Most plasma proteins are slightly larger than 7 nm in diameter and are retained in the glomerular capillaries. However, albumin, which has a diameter just slightly less than 7 nm, enters the filtrate only in small amounts. Therefore, the filtrate is not protein-free but, rather, contains about 0.03% protein. In addition, some protein hormones, such as thyrotropin-releasing hormone, oxytocin, and antidiuretic hormone, are small enough to pass through the filtration membrane. Any protein that is filtered is actively reabsorbed by endocytosis and metabolized by the cells in the proximal convoluted tubule. The basement membrane and the podocytes further contribute to filtration through charge exclusions. They contain negatively charged glycoproteins, which repel negatively charged plasma proteins and prevent them from exiting the blood. In summary, the combined effect of the filtration membrane components prevents most proteins from exiting the blood on the basis of size and charge, and only a small amount of protein is found in the urine of healthy people.

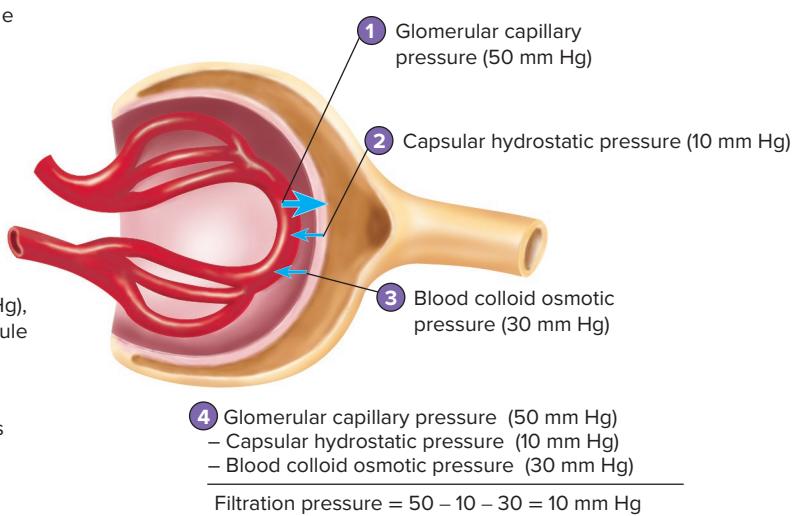
Predict 1

A hemoglobin molecule has a smaller diameter than an albumin molecule, but very little hemoglobin passes from the blood into the filtrate. Explain why. Under what circumstances do large amounts of hemoglobin enter the filtrate?

Filtration Pressure

No matter the type of size-based filter, there is one commonality: They all require a force to cause movement through it. For example, for a coffee maker, as noted earlier, the force is gravity. For the filtration membrane, three forces, or pressures, determine the amount of filtrate formed. The combination of these three

- 1 Glomerular capillary pressure (GCP), the blood pressure (50 mm Hg) within the glomerulus, moves fluid from the blood into the Bowman capsule.
- 2 Capsular hydrostatic pressure (CHP), the fluid pressure inside the Bowman capsule (10 mm Hg), moves fluid from the Bowman capsule into the blood.
- 3 Blood colloid osmotic pressure (BCOP), produced by the concentration of blood proteins in the glomerular capillaries (30 mm Hg), moves fluid from the Bowman capsule into the blood by osmosis.
- 4 Filtration pressure is equal to the glomerular capillary pressure minus the capsular hydrostatic and blood colloid osmotic pressures.



PROCESS FIGURE 26.9 Filtration Pressure

Filtration pressure across the filtration membrane is equal to the glomerular capillary pressure (GCP) minus the blood colloid osmotic pressure (BCOP) in the glomerular capillary minus the capsular hydrostatic pressure (CHP) in the Bowman capsule.

? Suppose a person consumed a high-protein diet. What effect might this have on filtrate pressure and volume?

pressures is called **filtration pressure** (figure 26.9). The three pressures contributing to filtration pressure are:

1. **Glomerular capillary pressure (GCP).** The GCP is essentially the blood pressure inside the glomerular capillaries. It is an *outward pressure* from blood pressing on the fenestrated capillary walls. The GCP forces fluid and solutes out of the blood into the Bowman capsule. This GCP is higher than that in other capillaries of the body. The higher GCP is due to the smaller diameter of the efferent arteriole compared to that of the afferent arteriole and glomerular capillaries. As you learned in chapter 21, when the diameter of a vessel decreases, the resistance to blood flow through the vessel is greater. Thus, as the blood flows from the larger-diameter afferent arteriole through the glomerular capillaries to the smaller-diameter efferent arteriole, the blood pressure increases in the glomerular capillaries. Consequently, filtrate is forced across the filtration membrane into the lumen of the Bowman capsule. The GCP is approximately 50 mm Hg compared with approximately 30 mm Hg at the arterial end of other capillary networks.
2. **Capsular hydrostatic pressure (CHP).** The CHP is an *inward pressure* that opposes filtration. CHP is due to pressure from the filtrate fluid in the capsular space. The CHP is about 10 mm Hg.
3. **Blood colloid osmotic pressure (BCOP).** The BCOP is also an *inward pressure* that opposes filtration. It is due to the osmotic pressure of plasma proteins in the glomerular capillaries. Through osmosis, these proteins draw fluid back into the glomerular capillary from the Bowman capsule. The BCOP is greater at the end of the glomerular capillary than at its beginning because there is a higher protein concentration at the end of the glomerulus. The average BCOP is approximately 30 mm Hg.

To calculate filtration pressure, all three filtration pressures are summed. In a normal kidney GCP is greater than the combination of CHP and BCOP. The filtration pressure is a net *outward* pressure of approximately 10 mm Hg:

$$\begin{array}{rcl} \text{Filtration} & \text{Glomerular} & \text{Capsular} \\ \text{pressure} & \text{hydrostatic} & \text{Blood colloid} \\ & \text{pressure} & \text{pressure} \\ 10 \text{ mm Hg} & = 50 \text{ mm Hg} & - 10 \text{ mm Hg} - 30 \text{ mm Hg} \end{array} \quad (26.4)$$

Normally, the filtrate does not exert an osmotic force on fluid movement out of the glomerular capillaries because the solute concentration of the filtrate is very low. This is because few proteins cross the filtration membrane. However, in a disease such as **glomerular nephritis**, the filtration membrane becomes more permeable, allowing more protein than normal to enter the filtrate. The elevated protein in the filtrate increases the colloid osmotic pressure of the filtrate. This results in elevated filtration pressure, thereby increasing the filtrate volume.

Prolonged elevated blood pressure, or **hypertension**, can be very damaging to the glomerular capillaries. The persistent outward force on these delicate vessels can cause microtears, weakening their walls, which eventually leads to scarring of the glomerular capillaries. Over time, the available surface area for filtration and removal of excess fluid and wastes is dramatically reduced, leading to even higher blood pressure and further damage to remaining healthy vessels. An extended period of untreated hypertension could result in such severe damage to kidneys that the only treatment option is a kidney transplant. To prevent such damage, patients with hypertension can employ lifestyle habits to keep blood pressure from becoming excessively elevated.

Regulation of Glomerular Filtration Rate

The GFR is very stable. It does not significantly change even if systemic blood pressure drops as low as 90 mm Hg or rises as high as 180 mm Hg. There are two ways through which the GFR is regulated: (1) intrinsic mechanisms and (2) extrinsic mechanisms. The intrinsic mechanisms are collectively referred to as **autoregulation** and are due to properties inherent to structures of the renal corpuscle. The extrinsic mechanisms are governed by the autonomic nervous system and particular hormones.

Intrinsic Mechanisms: Autoregulation

Autoregulation is achieved through two processes: (1) the myogenic mechanism and (2) tubuloglomerular feedback. The **myogenic mechanism** is associated with intrinsic properties of smooth muscle cells. In the afferent and efferent arterioles, smooth muscle cells act as stretch receptors. These stretch receptors detect changes in blood pressure. Elevated blood pressure causes increased stretch of the smooth muscle cells in the wall of the afferent arteriole. The smooth muscle cells contract in direct response to stretch. This causes vasoconstriction of the afferent arteriole. On the other hand, smooth muscle cells in the wall of the afferent arteriole relax when blood pressure decreases. Relaxation of the smooth muscle cells causes vasodilation of the afferent arteriole. In this way, blood supply to the glomerulus, and thus GFR, fluctuates very little, even when the mean arterial pressure changes.

Tubuloglomerular feedback matches filtrate flow past the macula densa cells of the juxtaglomerular apparatus to GFR. When the macula densa cells detect an increased flow rate, they send a signal to the juxtaglomerular cells of the afferent arteriole to constrict. Thus, glomerular filtration rate decreases due to a decreased glomerular capillary pressure.

Extrinsic Mechanisms: Sympathetic Nervous System and Hormones

Autoregulation maintains renal blood flow and filtrate formation at a relatively constant rate unless sympathetic stimulation is intense. In severe conditions such as hemorrhage or dehydration, the mean arterial pressure can drop below 90 mm Hg, and the sympathetic nervous system causes a dramatic decrease in renal blood flow and GFR to maintain homeostatic blood pressure. Because norepinephrine-secreting sympathetic neurons innervate the blood vessels of the kidneys, sympathetic stimulation constricts the small arteries and afferent arterioles, thereby decreasing renal blood flow and filtrate formation. Intense sympathetic stimulation, as may occur during shock or intense exercise, decreases the rate of filtrate formation to only a few milliliters per minute; however, small changes in sympathetic stimulation have a minimal effect on renal blood flow and filtrate formation.

Severe stress or circulatory shock causes dramatic vasoconstriction of the afferent arterioles. This lowers renal blood flow so severely that the blood supply to the kidney is inadequate to maintain normal kidney metabolism. As a consequence, kidney tissues can be damaged and thus unable to perform their normal functions if blood flow is not reestablished. Therefore, shock should be treated quickly. On the other hand, reduced blood flow to the

kidneys during stress or shock is consistent with homeostasis. Intense vasoconstriction maintains blood pressure at levels adequate to sustain blood flow to organs such as the heart and brain. A reduction in blood flow to organs such as the kidneys is only harmful if the lack of blood flow is prolonged.

Under low blood pressure conditions, the juxtaglomerular cells in the juxtaglomerular apparatus secrete the enzyme renin. Recall from chapter 21 that secretion of this enzyme results in the activation of the potent vasoconstrictor angiotensin II. By stimulating vasoconstriction, angiotensin II helps maintain GFR at normal levels. This mechanism is discussed in greater detail in section 26.4.

ASSESS YOUR PROGRESS

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13. Name the three general processes involved in producing urine.
 14. Contrast the rates of renal blood flow, renal plasma flow, and glomerular filtration. How do they affect urine production?
 15. Describe the filtration membrane. What substances do not pass through it?
 16. What is filtration pressure? How does glomerular capillary pressure affect filtration pressure and the amount of urine produced?
 17. How do systemic blood pressure and afferent arteriole diameter affect glomerular capillary pressure?
 18. Describe autoregulation.
 19. Explain the effect of sympathetic stimulation on the kidney and the GFR during rest, exercise, and shock.

Tubular Reabsorption

The process of tubular reabsorption entails nearly every type of cell transport mechanism you learned in chapter 3. **Tubular reabsorption** is the transport of water and solutes from the filtrate into the blood. Principally, water movement in the kidney is governed by osmosis. Recall that osmosis is the movement of water toward solutions with higher solute concentrations, or high osmotic pressure. Solute movement is quite often through diffusion across the renal tubule cells. Diffusion is the net movement of solutes down their concentration gradient. However, some molecules are too large to pass through the plasma membrane, or the cell may need to move a molecule against its concentration gradient. In these instances, cells use transport proteins. There are several types of transport proteins used by renal tubule cells. For example, symporters move two molecules or ions in the same direction. Occasionally, the energy from Na^+ diffusion drives the movement of a second ion or molecules. This process is secondary active transport.

Proper tubular reabsorption is critical in preventing the body from becoming overly dehydrated and deficient in important materials. Nearly all (99%) of the water and solutes are rapidly returned to the blood via the renal tubules, and because of this, toxins are quickly removed from the blood. The filtrate leaves the lumen of the Bowman capsule and flows first through the proximal convoluted tubule, onto the loop of Henle, and the distal convoluted tubule and then finally into the collecting ducts. As the filtrate passes through

these structures, many of the substances in the filtrate are removed. Inorganic salts, organic molecules, and about 99% of the filtrate volume leave the renal tubule and enter the interstitial fluid. Because the pressure is low in the peritubular capillaries, these substances enter the peritubular capillaries and flow through the renal veins to enter the general circulation (see figure 26.8).

Solutes reabsorbed from the lumen of the renal tubule to the interstitial fluid include amino acids, glucose, and fructose, as well as Na^+ , K^+ , Ca^{2+} , HCO_3^- , and Cl^- . A more complete list is provided in table 26.3 for each part of the nephron.

TABLE 26.3 Reabsorption of Major Solutes from the Nephron	
Apical Membrane	Basal Membrane
Proximal Convoluted Tubule	
Substances Symported with Na^+	Active Transport Na^+ (exchanged for K^+)
K^+	Facilitated Diffusion
Cl^-	K^+
Ca^{2+}	Cl^-
Mg^{2+}	Ca^{2+}
HCO_3^-	HCO_3^-
PO_4^{3-}	PO_4^{3-}
Amino acids	Amino acids
Glucose	Glucose
Fructose	Fructose
Galactose	Galactose
Lactate	Lactate
Succinate	Succinate
Citrate	Citrate
Diffusion Between Tubule Cells	
K^+	
Ca^{2+}	
Mg^{2+}	
Thick Ascending Limb of the Loop of Henle	
Substances Symported with Na^+	Active Transport Na^+ (exchanged for K^+)
K^+	Facilitated Diffusion
Cl^-	K^+
Ca^{2+}	Cl^-
Diffusion Between Tubule Cells	
K^+	
Ca^{2+}	
Mg^{2+}	
Distal Convoluted Tubule and Collecting Duct	
Substances Symported with Na^+	Active Transport Na^+ (exchanged for K^+)
Cl^-	Facilitated Diffusion
K^+	K^+
Ca^{2+}	Cl^-

The small volume of the filtrate (approximately 1%) that forms urine contains urea, uric acid, creatinine, K^+ , and other substances. The regulation of solute reabsorption and the permeability characteristics of portions of the nephron allow for the production of a small volume of very concentrated urine or a large volume of very dilute urine.

Reabsorption in the Proximal Convolute Tubule

The proximal convoluted tubule is the site of the majority of reabsorption. The mechanisms underlying reabsorption can be better understood by considering the cells found there. The cells of the proximal convoluted tubule have numerous microvilli, which dramatically increase the surface area available for reabsorption. To establish the portion of each proximal convoluted tubule cell where a particular process for reabsorption occurs, these portions are named. The portions of each cell are the following:

1. **Basal membrane.** The basal membranes form the outer wall of the renal tubules.
2. **Apical membrane.** The apical membranes make up the inside surface of the renal tubule wall. It is the apical membrane of the proximal convoluted tubule that houses the microvilli.
3. **Lateral surface.** The lateral surfaces bind the renal tubules cells to adjacent cells in the renal tubule.

Reabsorption of most solutes is linked to the diffusion of Na^+ into the cells of the proximal convoluted tubule. There is a steep concentration gradient for Na^+ from the filtrate into the cytoplasm of the cells of the proximal convoluted tubule. This concentration gradient is established by active transport of Na^+ across the basal membrane of the cells of the proximal convoluted tubule. The Na^+-K^+ pump actively transports Na^+ out of these cells and into the interstitial fluid, which keeps the concentration of Na^+ low in their cytoplasm (figure 26.10). Thus, Na^+ moves by facilitated diffusion through a symporter from the filtrate into the cytoplasm of the cells of the proximal convoluted tubule. This movement of Na^+ into these cells is responsible for the secondary active transport of many other solutes from the lumen of the proximal convoluted tubule into the cytoplasm of the tubule cells.

Carrier proteins that transport amino acids, glucose, and other solutes are located within the **apical membrane**, which separates the lumen of the proximal convoluted tubule from the cytoplasm of the cells of the proximal convoluted tubule. Each of these carrier proteins binds specifically to one of those substances to be transported and to Na^+ . The concentration gradient for Na^+ provides the energy that moves both the Na^+ and the other molecules or ions from the lumen into the tubule cell. Once the symported molecules are inside the cell, they cross the basal membrane of the cell by facilitated diffusion or symport. The number of carrier proteins limits the rate at which a substance can be transported. For example, the high blood glucose in someone with untreated diabetes mellitus can lead to such high glucose levels in the filtrate that not all of it can be removed by the glucose transport proteins. The excess glucose remains in the filtrate and becomes part of the urine (see section 26.5).

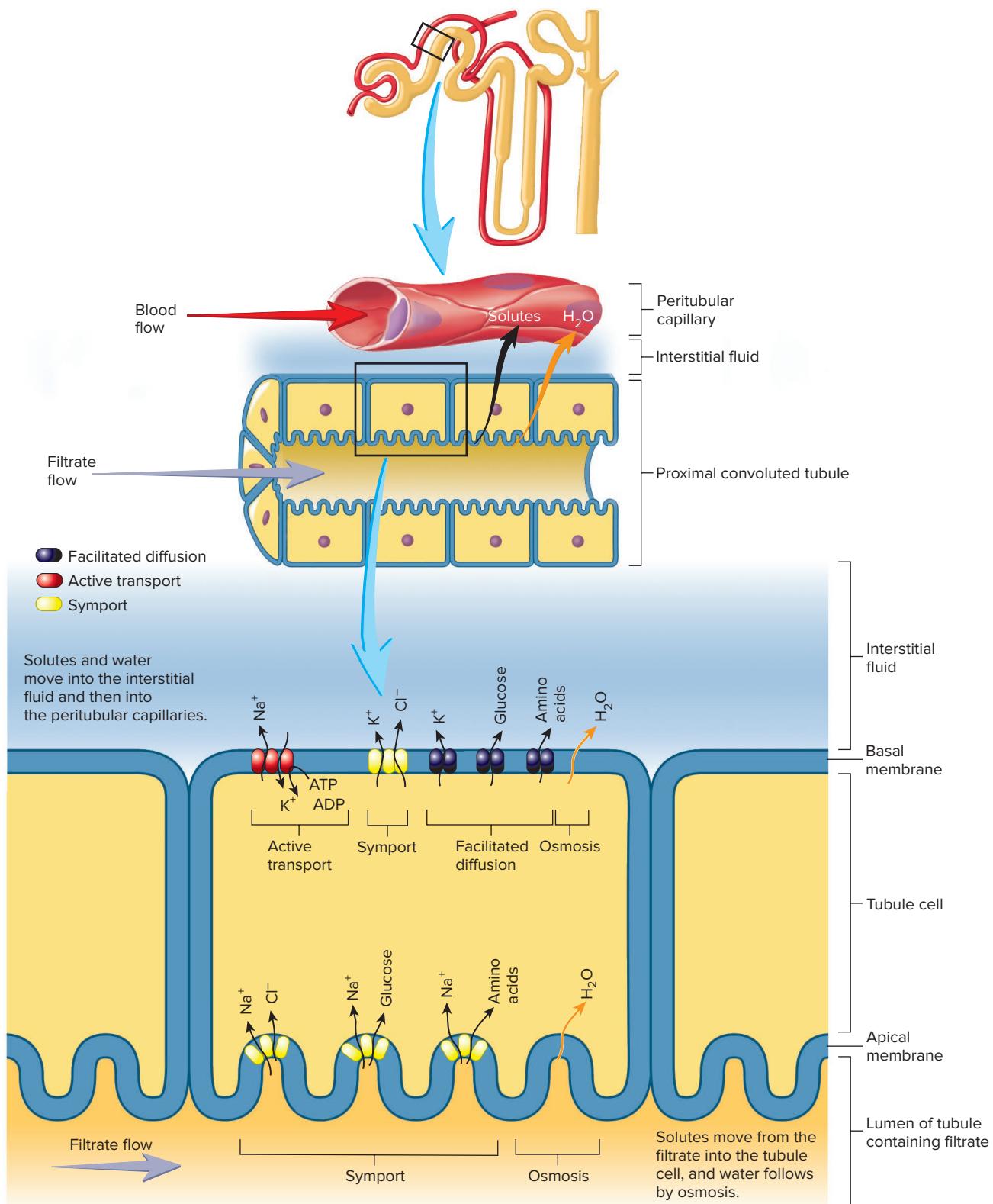


FIGURE 26.10 Reabsorption of Solutes in the Proximal Convoluted Tubule

The symport of molecules and ions across the epithelial lining of the proximal convoluted tubule depends on the active transport of Na⁺, in exchange for K⁺, across the basal membrane. Symport is the process by which carrier proteins move molecules or ions with Na⁺ across the apical membrane. The Na⁺ concentration gradient provides the energy for symport. Amino acids, glucose, K⁺, Cl⁻, and most other solutes are transported into the tubule cells with Na⁺. Water enters and leaves the cell by osmosis. Glucose, amino acids, Na⁺, Cl⁻, and many other solutes leave the cells across the basal membrane by facilitated diffusion.

Some solutes also diffuse from the lumen of the proximal convoluted tubule into the interstitial fluid by moving *between* the cells across their lateral surfaces. As other solutes are transported out of the lumen, through the proximal convoluted tubule cells, and into the interstitial fluid, water follows by osmosis. The reabsorption of water causes the concentration of solutes that remain in the lumen to increase. When the concentration of these solutes in the lumen becomes higher than in the interstitial fluid, these solutes will diffuse between the tubule cells into the interstitial fluid. Examples of solutes that diffuse between tubule cells of the proximal convoluted tubule include K^+ , Ca^{2+} , and Mg^{2+} . These solutes are reabsorbed by diffusion, even though the same ions are also sometimes reabsorbed by symport processes.

Reabsorption of both solutes and water in the proximal convoluted tubule is extensive. As solute molecules are transported out of the filtrate, water also moves by osmosis out of the filtrate. By the time the filtrate has reached the end of the proximal convoluted tubule, its volume has been reduced by approximately 65%. However, because the proximal convoluted tubule is permeable to water, the concentration of the filtrate there remains about the same as that of the interstitial fluid (300 mOsm/kg).

Reabsorption in the Loop of Henle

Earlier, we described the loop of Henle and its two limbs. The two limbs differ in the type of epithelial tissue present in each. This difference in cell type is linked to the permeability of each limb to water and solutes.

1. *Reabsorption in the descending limb of the loop of Henle.* The epithelial tissue in the majority of the descending limb, in particular the thin segment, is simple squamous epithelial tissue (figure 26.11a). Remember from chapter 4 that simple squamous cells are highly permeable to water, which means the descending limb is highly permeable to water. In addition, the descending limb is moderately permeable to ions such as Na^+ and Cl^- , as well as molecules such as urea. Water moves by osmosis out of the descending limb, while some solutes move by diffusion into the descending limb. The particular factors determining the direction of water and solute movement in the descending limb will be discussed later in this section. Ultimately, by the time the filtrate has reached the end of the thin segment, the volume of the filtrate has been reduced by another 15% and its concentration has significantly increased to 1200 mOsm/L.
2. *Reabsorption in the ascending limb of the loop of Henle.* As the loop of Henle makes its hairpin turn into the ascending limb, the simple squamous epithelium persists, but it has become impermeable to water (figure 26.11b). However, it is still permeable to solutes, which exit the ascending limb, thereby again reducing the concentration of the filtrate.

As the ascending limb continues, the epithelial tissue transitions to become simple cuboidal. This portion of the ascending limb is now called the thick segment. The thick segment of the ascending limb is impermeable to both water and solutes. Instead, the cells of the thick segment house multiple types of transport proteins including ATP-powered pumps and symporters. These transport proteins remove a

significant portion of the solutes from the filtrate, which then enters the interstitial fluid. It is this active transport of solutes that contributes to the kidneys' ability to conserve water.

Symport is responsible for moving K^+ and Cl^- with Na^+ across the apical membrane of the ascending limb of the loop of Henle (figure 26.12). Once inside the cells of the ascending limb, Cl^- and K^+ exit the cells of the ascending limb via facilitated diffusion. The concentration of Na^+ in the lumen of the ascending limb is high, and the concentration inside the cells of the ascending limb is low. This concentration gradient is created by the active transport of the Na^+ out of the cell in exchange for K^+ across the basal membrane (figure 26.12).

As we follow the filtrate through the loop of Henle, we see that it becomes very concentrated toward the bend of the loop of Henle, but the concentration of the filtrate is reduced to about 100 mOsm/kg by the time the fluid reaches the distal convoluted tubule. In contrast, the concentration of the interstitial fluid in the cortex is about 300 mOsm/kg. Thus, the filtrate entering the distal convoluted tubule is much more dilute (hypotonic) than the interstitial fluid surrounding it.

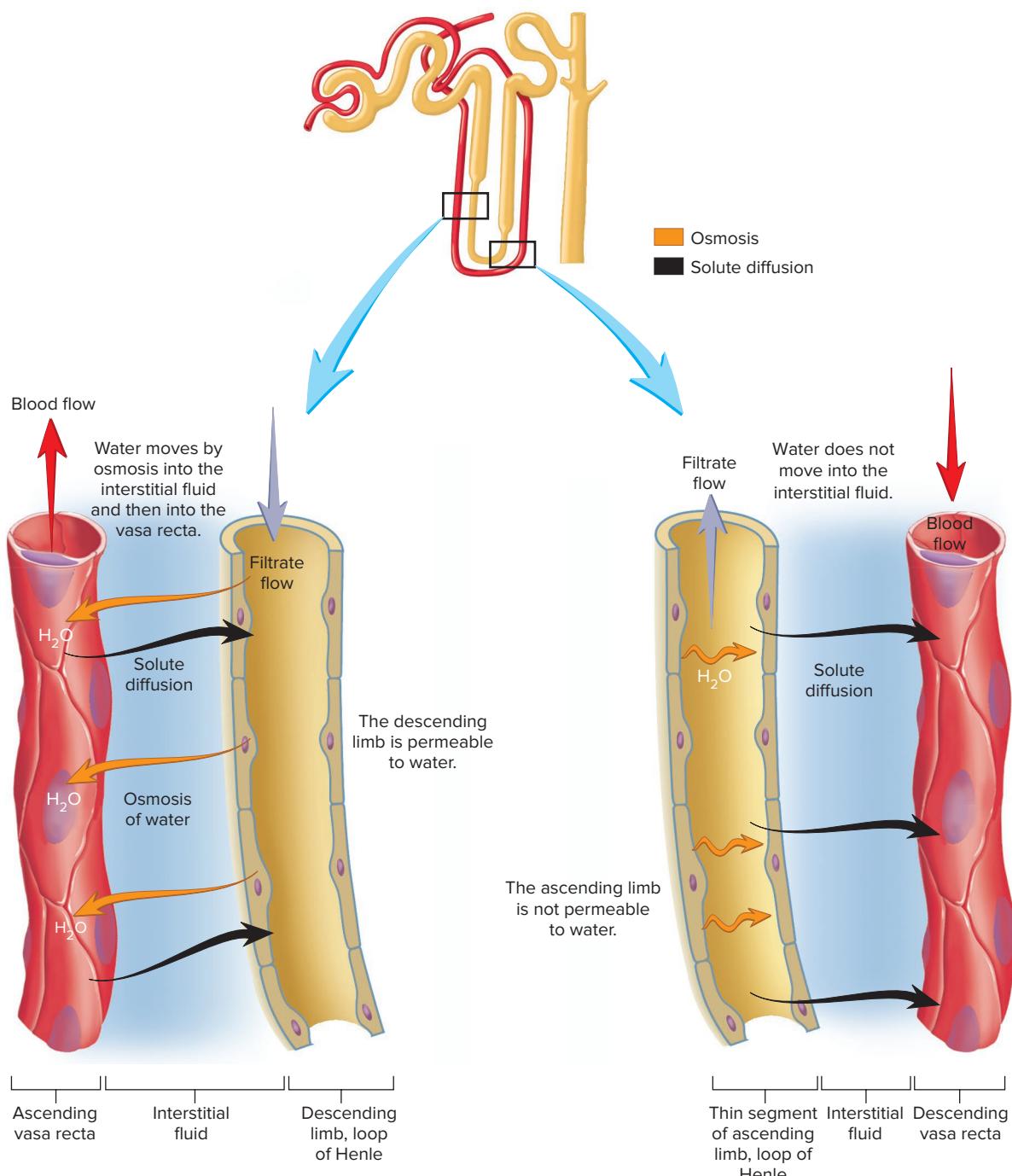
Reabsorption in the Distal Convolved Tubule and Collecting Duct

Some solutes (K^+ and H^+) are not reabsorbed until farther along the renal tubule in the distal convoluted tubule or collecting duct. The reabsorption of these solutes is generally under hormonal control and depends on the current conditions of the body. The distal convoluted tubule and the collecting duct are not always permeable to water; however, hormone regulation can change their permeability to water (see section 26.4). Reabsorption of water occurs through osmosis across the wall of the distal convoluted tubule and the collecting duct when the hormone ADH is present (see chapter 18). The interstitial fluid surrounding the distal convoluted tubule and collecting duct is more concentrated than the filtrate, so the water moves toward the high solute concentration area. In these conditions, a small volume of concentrated urine is produced. ADH causes the tubule wall to become more permeable to water, a mechanism discussed in more detail later in this chapter. When ADH is absent, the distal convoluted tubule and collecting duct are not permeable to water and water stays in the filtrate. In this case, a large volume of dilute urine is produced.

The distal convoluted tubule also plays a major role in secretion, which is discussed later in this section.

Changes in the Concentration of Urea and Other Solutes in the Nephron

One of the nephron's major functions is to remove wastes from the body. For example, **urea** ($\ddot{u}\text{-r}\acute{e}'\ddot{a}$), a protein breakdown product, enters the glomerular filtrate at the same concentration as in the plasma. Renal tubules are only moderately permeable to urea, which slows the reabsorption of urea. As the volume of filtrate decreases in the renal tubule, the concentration of urea increases. Only 40–60% of the urea is passively reabsorbed by the renal tubule, although about 99% of the water is reabsorbed. In addition to urea, urate ions, creatinine, sulfates, phosphates,



(a) The wall of the thin segment of the descending limb of the loop of Henle is permeable to water and, to a lesser extent, to solutes. The interstitial fluid in the medulla of the kidney and the blood in the vasa recta have a high solute concentration (high osmolality). Water therefore moves by osmosis from the tubule into the interstitial fluid and into the vasa recta. An additional 15% of the filtrate volume is reabsorbed. To a lesser extent, solutes diffuse from the vasa recta and interstitial fluid into the tubule.

(b) The thin segment of the ascending limb of the loop of Henle is not permeable to water but is permeable to solutes. The solutes diffuse out of the tubule and into the more dilute interstitial fluid as the ascending limb projects toward the cortex. Then the solutes diffuse into the descending vasa recta.

FIGURE 26.11 Reabsorption in the Loop of Henle: The Descending Limb and the Thin Segment of the Ascending Limb

(a) Thin segment of the descending limb of the loop of Henle. (b) Thin segment of the ascending limb of the loop of Henle.

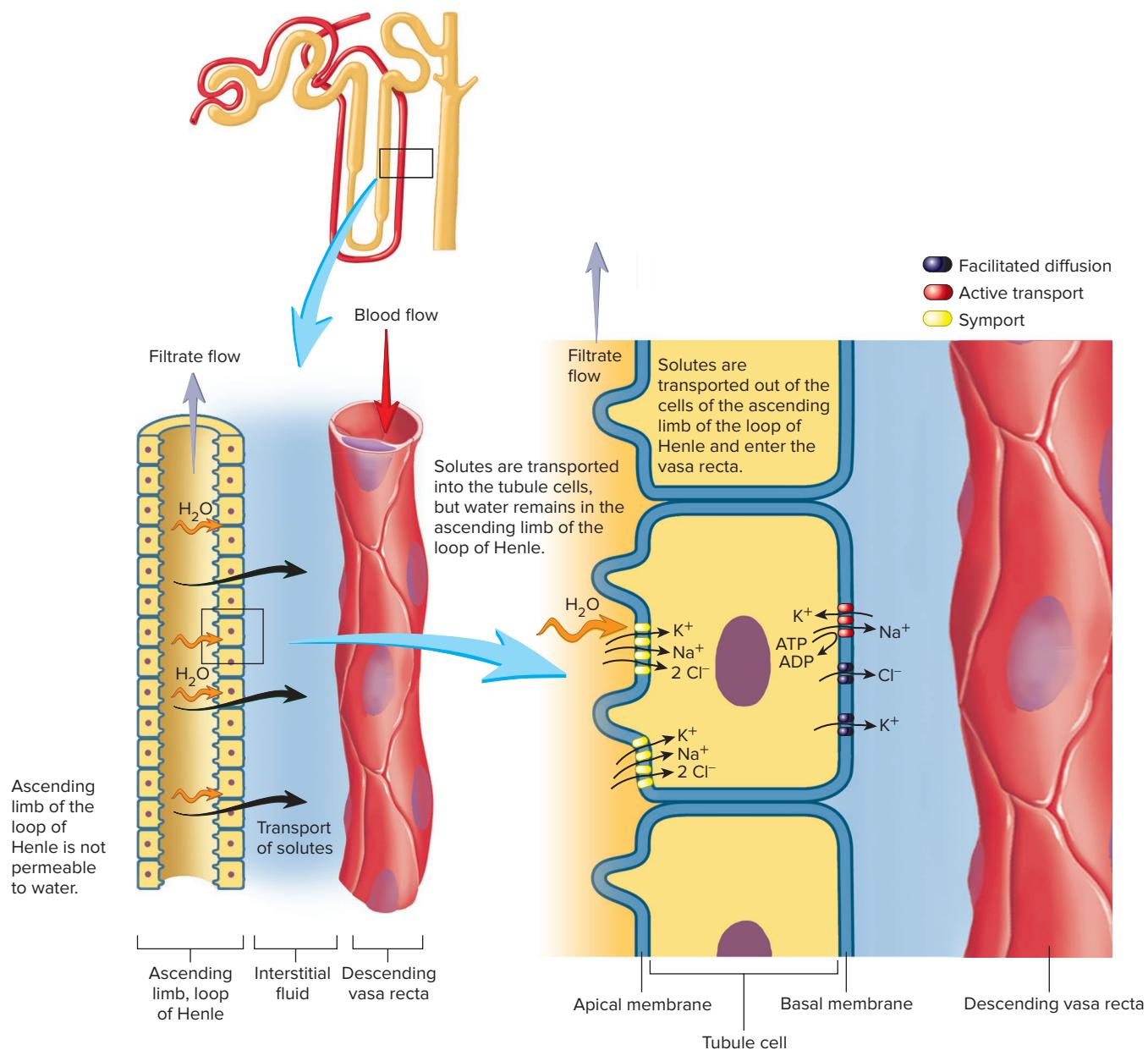


FIGURE 26.12 Reabsorption in the Thick Segment of the Ascending Limb of the Loop of Henle

The wall of the ascending limb of the loop of Henle is not permeable to water. Sodium ions move across the wall of the basal membrane by active transport, establishing a concentration gradient for Na⁺. Potassium ions and Cl⁻ are symported with Na⁺ across the apical membrane, and ions pass by facilitated diffusion across the basal membrane of the tubule cells.

and nitrates are reabsorbed, but not to the same extent as water. Therefore, they also become more concentrated in the filtrate as the volume of the filtrate becomes smaller. These substances are toxic if they build up in the body, so their accumulation in the filtrate and elimination in urine help maintain homeostasis (see table 26.1).

Tubular Secretion

Tubular secretion is the movement of nonfiltered substances from the blood into the filtrate. These substances include toxic by-products of metabolism and drugs or molecules not normally produced by the body (table 26.4). As with tubular reabsorption,

tubular secretion can be either active or passive. For example, ammonia is a toxic by-product of protein metabolism. It is produced when the epithelial cells of the renal tubule remove amino groups from amino acids, which diffuse into the lumen of the renal tubule. On the other hand, H⁺, K⁺, penicillin, and **para-aminohippuric acid** (par'ă-a-mī'nō-hi-pür'ik; p-aminohippuric acid; PAH; a medical diagnostic chemical) are actively secreted by either active transport or antiport processes into the renal tubule. An example of an antiport process in the kidney is the secretion of H⁺, which plays a major role in regulating body fluid pH and is discussed in more detail in chapter 27. If blood pH is too acidic, the kidney secretes H⁺. The secreted H⁺ is produced when CO₂ and water react to form

TABLE 26.4 Secretion of Substances into the Renal Tubule	
Transport Process	Substance Transported
Proximal Convoluted Tubule	
Antiport	H ⁺
Active transport	Hydroxybenzoates Para-aminohippuric acid Neurotransmitters Dopamine Acetylcholine Epinephrine Bile pigments Uric acid Drugs and toxins Penicillin Atropine Morphine Ammonia
Diffusion	
Distal Convoluted Tubule	
Antiport	K ⁺
	H ⁺
Active transport	K ⁺

H⁺ and HCO₃⁻. A Na⁺/H⁺ antiporter in the tubule cells will move Na⁺ into the proximal and distal convoluted tubule cells and move H⁺ out of the proximal and distal convoluted tubule cells (figure 26.13). More specifically, Na⁺ and HCO₃⁻ are symported across the basal membrane of the tubule cells and enter the peritubular capillaries. Hydrogen ions are secreted into the lumens of the proximal and distal convoluted tubules. By secreting H⁺, the blood pH stays in its normal range and does not become too acidic.

ASSESS YOUR PROGRESS

20. What is the direction of movement of substances in tubular reabsorption?
21. Describe what happens to most of the filtrate that enters the renal tubule.
22. On what side of the renal tubule cell does active transport take place during reabsorption of materials?
23. Describe how symport works in the renal tubule.
24. Name the substances that are moved by active and passive transport. In what part of the renal tubule does this movement take place?
25. Explain the differences between the descending limb and the ascending limb of the loop of Henle.
26. Where does tubular secretion take place? What is the direction of movement?
27. What substances are secreted? List the mechanisms by which these substances are transported.

Urine Concentration Mechanism

As you have just read, the kidneys are remarkable at regulating blood composition. The kidneys are able to produce urine with concentrations ranging from a minimum of 65 mOsm/kg to a maximum of 1200 mOsm/kg while maintaining the extracellular fluid concentration very close to 300 mOsm/kg. But how does the kidney move such a large volume of fluid from the blood into the filtrate and then back into the blood? The kidneys' ability to control the volume and concentration of the urine depends on several factors: (1) countercurrent mechanisms, (2) a medullary concentration gradient, and (3) hormonal mechanisms.

Countercurrent Mechanisms

The kidneys utilize a **countercurrent mechanism**. A countercurrent mechanism is one where fluid in separate structures flows in opposite directions relative to each other. As the fluids pass by each other, materials can be exchanged between the fluids. There are two types of countercurrent mechanisms in the kidney that are critical for either conserving or eliminating water in the body (figure 26.14). These two mechanisms are (1) a countercurrent multiplier and (2) a countercurrent exchanger.

The **countercurrent multiplier** in the loop of Henle is responsible for a large percentage of a very high concentration of solutes that is found in the interstitial fluid within the medulla of the kidney. The permeability changes in the loop of Henle are responsible for its role as the countercurrent multiplier.

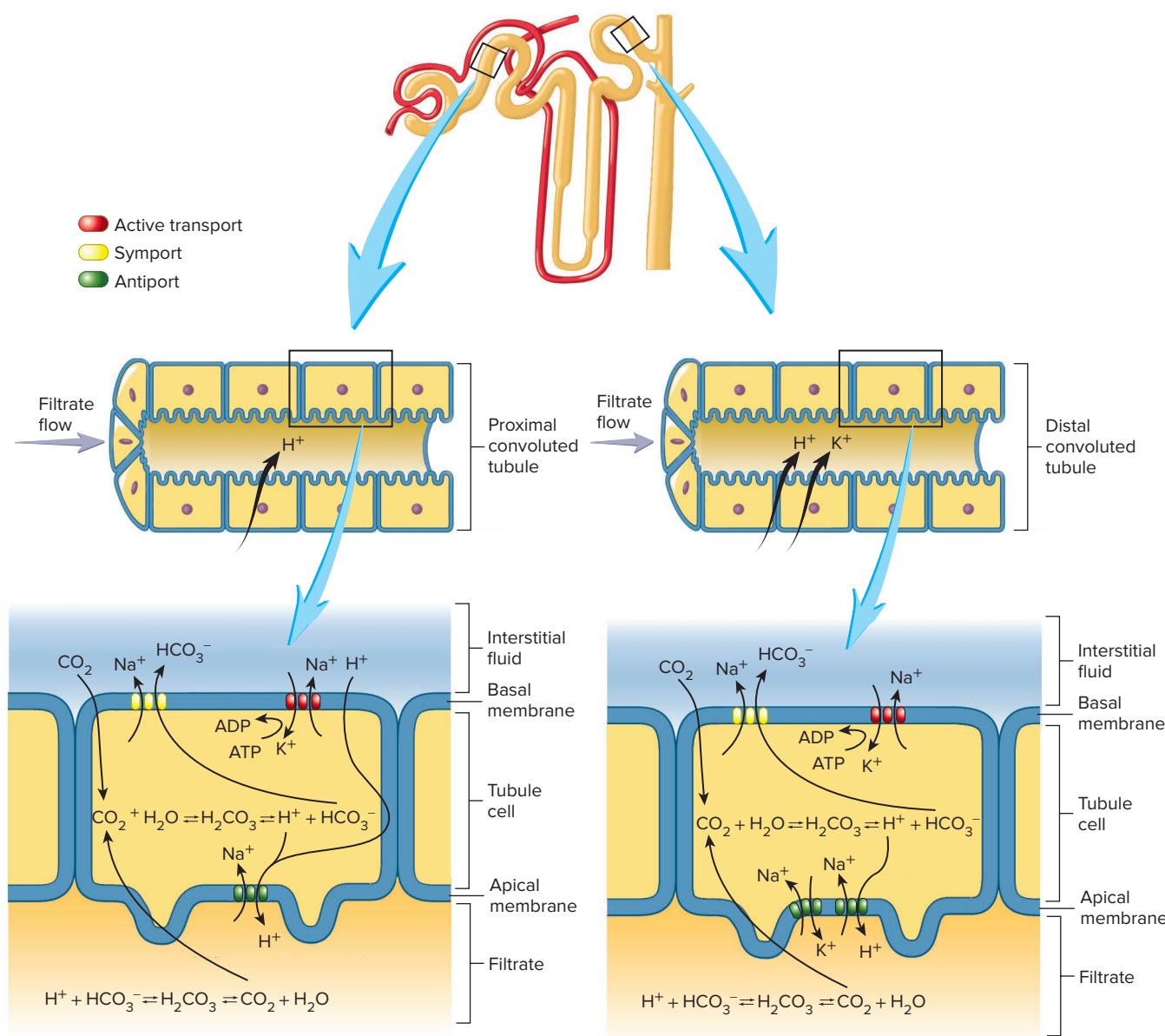
The **countercurrent exchanger** in the vasa recta maintains the high solute concentration in the interstitial fluid. Because the flow rate and blood pressure in the vasa recta are so slow and very low, the blood and the interstitial fluid are always in equilibrium and solutes are not carried away from the interstitial fluid by the blood in the vasa recta.

Countercurrent Mechanisms: Medullary Concentration Gradient

The interstitial fluid in the medulla of the kidney has a very high solute concentration compared with that of the cortex. This is called the **medullary concentration gradient**. The high solute concentration of the interstitial fluid develops from (1) the actions of the two countercurrent mechanisms and (2) the recycling of the protein breakdown product, urea. The concentration of solutes in the medulla increases from 300 mOsm/kg to 1200 mOsm/kg deep in the medulla at the tip of the renal pyramid (see figure 26.14).

To create and maintain the medullary concentration gradient, the following processes occur:

- 1a. *Countercurrent multiplier.* As filtrate travels through the descending limb of the loop of Henle, water moves across its simple squamous epithelium by osmosis toward the higher solute concentration in the interstitial fluid. As we discussed, this osmosis of water out of the filtrate causes the filtrate to become highly concentrated. Then, as the filtrate begins to move through the ascending limb, the permeability of the epithelium shifts such that solutes diffuse out of the filtrate. This increases the concentration of the interstitial fluid even



(a) Hydrogen ions are secreted into the filtrate by an antiport mechanism in the proximal convoluted tubule, in which H^+ are exchanged for Na^+ . The H^+ are derived from two sources. They diffuse from the peritubular capillaries into the interstitial fluid and then into epithelial cells of the tubule, or they are derived from the reaction between CO_2 and water in the cells of the tubule. Sodium ions and HCO_3^- are symported across the basal membrane into the interstitial fluid and then diffuse into the peritubular capillaries.

(b) Hydrogen ions and K^+ are secreted into the filtrate by antiport mechanisms in the distal convoluted tubule. Sodium ions and K^+ are moved by active transport across the basal membrane of the tubule cell. Sodium ions and HCO_3^- are symported across the basal membrane into the interstitial fluid and then diffuse into the peritubular capillaries.

FIGURE 26.13 Secretion of H^+ and K^+ into the Renal Tubule

(a) Secretion of H^+ and K^+ in the proximal convoluted tubule. (b) Secretion of H^+ and K^+ in the distal convoluted tubule.

more. In addition, the cells of the thick segment of the ascending limb actively pump solutes into the interstitial fluid, causing a very concentrated solution to form. Hence, the movement of solutes out of the loop of Henle dramatically increases the solute concentration of the interstitial fluid.

Only the juxtaglomerular nephrons have loops of Henle that descend deep into the medulla, but enough of them exist to maintain the high concentration of solutes in the interstitial

fluid of the medulla. Not all of the nephrons need to have loops of Henle that descend into the medulla to concentrate urine effectively. The cortical nephrons have the same function as the juxtaglomerular nephrons, but their loops of Henle are not as efficient at concentrating urine. However, because the filtrate from the cortical nephrons passes through the collecting ducts, water can diffuse out of the collecting ducts into the interstitial fluid, thus concentrating the filtrate. Animals

- (a)
- Water diffuses out of the thin segment of the loop of Henle.
 - The filtrate concentration is 1200 mOsm.
 - Sodium and other solutes are actively transported out of the loop of Henle into the medulla.

(b)

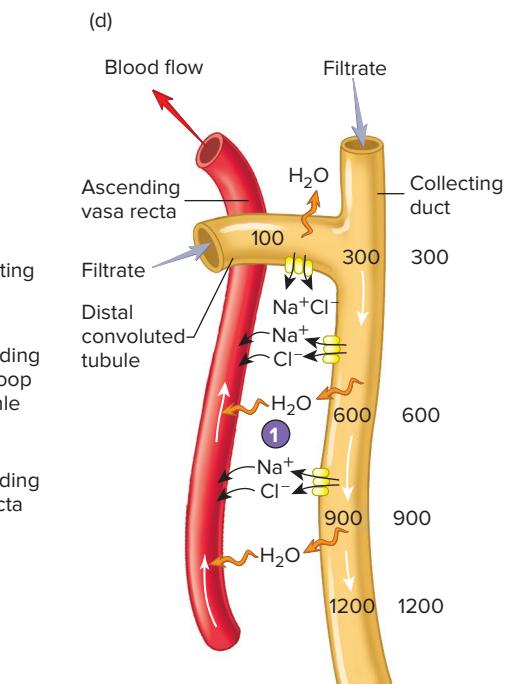
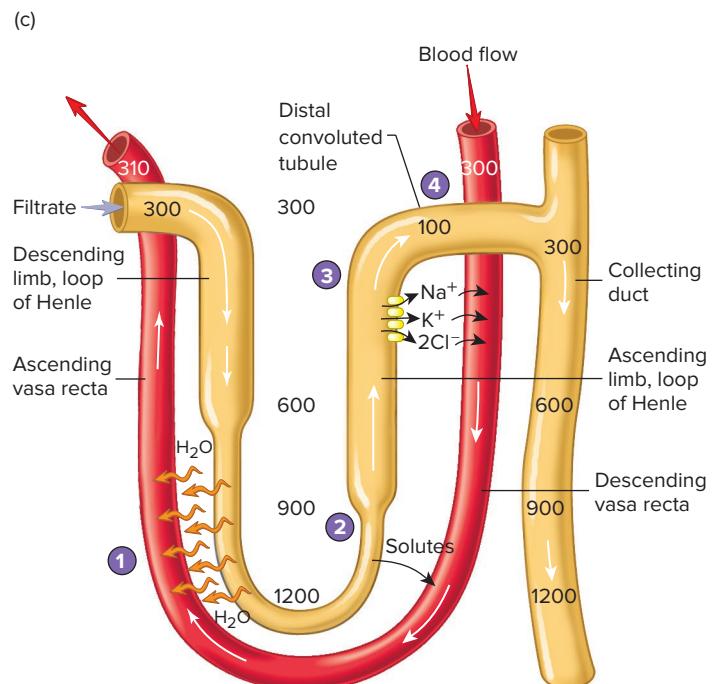
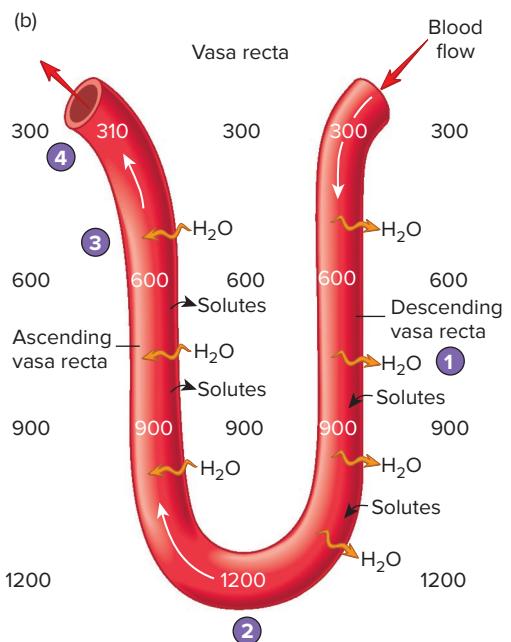
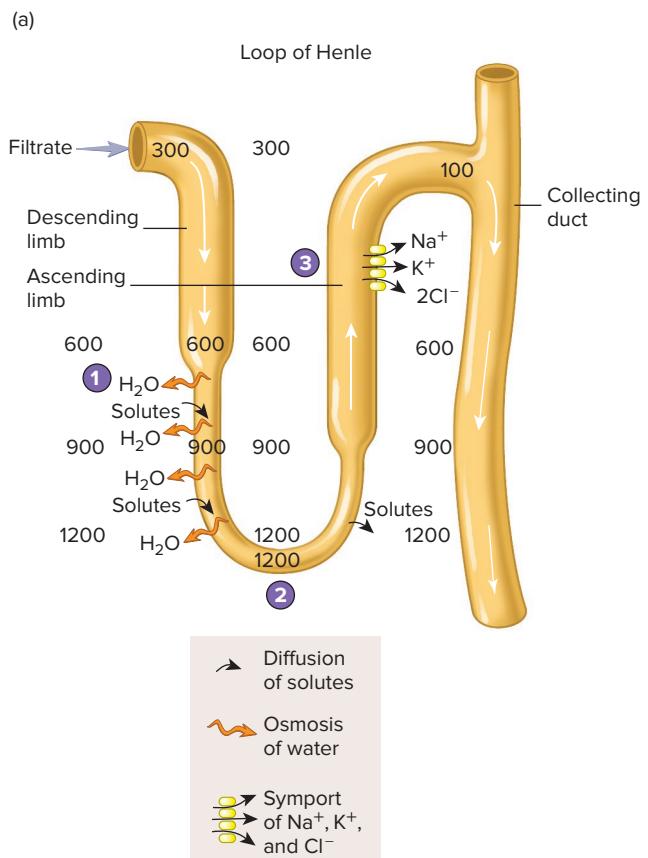
- Water diffuses out and solutes diffuse into the descending portion of the vasa recta.
- The blood concentration is 1200 mOsm.
- Water diffuses into and solutes diffuse out of the ascending portion of the vasa recta.
- At the end of the vasa recta, the blood osmolarity is only slightly greater than the osmolarity of the blood at the beginning of the vasa recta.

(c)

- Water moves out of the descending limb of the loop of Henle and enters the ascending vasa recta.
- Solutes diffuse out of the ascending thin segment of the loop of Henle and enter the vasa recta.
- Solutes transported out of the thick segment of the ascending limb of the loop of Henle enter the descending vasa recta. The vasa recta do not dilute the high medullary concentration.
- The concentration of the filtrate is reduced to 100 mOsm/kg by the time it reaches the distal convoluted tubule.

(d)

- Water and solutes, such as Na^+ and Cl^- leave the distal convoluted tubule and the collecting duct and enter the ascending vasa recta.



PROCESS FIGURE 26.14 Filtrate Concentration and the Medullary Concentration Gradient

The loop of Henle and the vasa recta function together to maintain a high concentration of solutes in the medulla of the kidney. (a) In the loop of Henle, the filtrate is concentrated in the descending limb and then diluted in the ascending limb. (b) In the vasa recta, the osmolarity of the blood does not change appreciably due to its low pressure and slow flow. (c) The water that diffuses out of the loop of Henle is returned to the general circulation by way of the vasa recta. (d) Reabsorbed materials from the distal convoluted tubule and the collecting duct enter the vasa recta.

? The desert kangaroo rat does not produce dilute, liquid urine, but instead produces thick, highly concentrated urine. Explain how having loops of Henle that are proportionally longer than other terrestrial animals allows for this. How is production of thick, concentrated urine advantageous to a desert animal?

that concentrate urine more effectively than humans have a greater percentage of nephrons descending into the kidney medulla. For example, in desert mammals, many nephrons descend into the medulla, and the renal pyramids are longer than those in humans and most other mammals.

1b. *Countercurrent exchanger*. The vasa recta supply blood to the kidney medulla, and they remove excess water and solutes from the medulla without changing the high concentration of solutes in the medullary interstitial fluid. The vasa recta have a countercurrent mechanism because blood flows through them to the kidney medulla, and after the vessels turn near the tip of the renal pyramid, the blood flows the opposite direction, back toward the cortex. The walls of the vasa recta are permeable to both water and solutes. As blood flows toward the medulla, water moves out of the vasa recta, and some solutes diffuse into them. As blood flows back toward the cortex, water moves into the vasa recta, and some solutes diffuse out of them (figure 26.14b). The directions of diffusion are such that the vasa recta carry slightly more water and solute from the medulla than to it. Thus, the composition of the blood at both ends of the vasa recta is nearly the same, with the volume and osmolality slightly greater as the blood once again reaches the cortex. In addition, blood pressure in the vasa recta is very low and blood flow rate is extremely slow, even sluggish. This encourages ready diffusion of solutes into and back out of the vasa recta, ensuring the maintenance of the high medullary concentration gradient. Figure 26.14c,d further illustrates this mechanism by showing the close anatomical relationship of the loops of Henle, the collecting ducts, and the vasa recta.

2. *Urea cycling*. Urea is responsible for a substantial part of the high osmolality in the kidney medulla (figure 26.15). Due to their histology, the walls of the descending limbs of the loops of Henle are permeable to urea; thus, urea diffuses into the descending limbs from the interstitial fluid. However, due to their histology, the ascending limbs of the loops of Henle and the distal convoluted tubules are impermeable to urea, so the urea remains in the loop of Henle until it reaches the collecting ducts, which are permeable to urea. Some urea then diffuses out of the collecting ducts into the interstitial fluid of the medulla. Therefore, urea is recycled from the interstitial fluid into the descending limbs of the loops of Henle, through the ascending limbs, through the distal convoluted tubules, and into the collecting ducts. Most urea then diffuses from the collecting ducts back into the interstitial fluid of the medulla. Consequently, a high urea concentration is maintained in the medulla of the kidney.

To summarize, several key events occur in the renal tubule to establish and maintain a high medullary solute concentration:

- Sodium ions and other solutes are actively transported into the interstitial fluid of the medulla, maintaining a high medullary osmolarity.
- Because blood flows sluggishly and there is low blood pressure in the vasa recta, solutes are not washed away from the medulla.
- Much urea returns to the medulla from the collecting duct, rather than exiting with the urine.

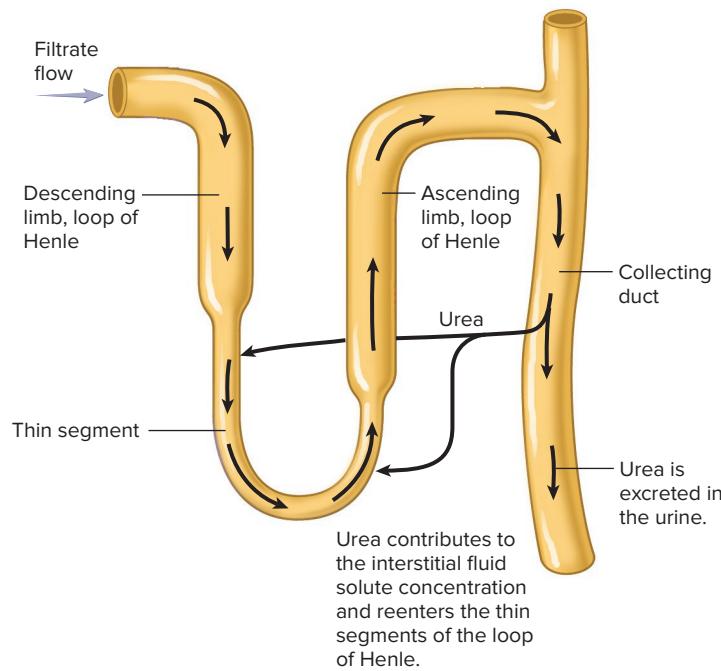


FIGURE 26.15 Medullary Concentration Gradient and Urea Cycling

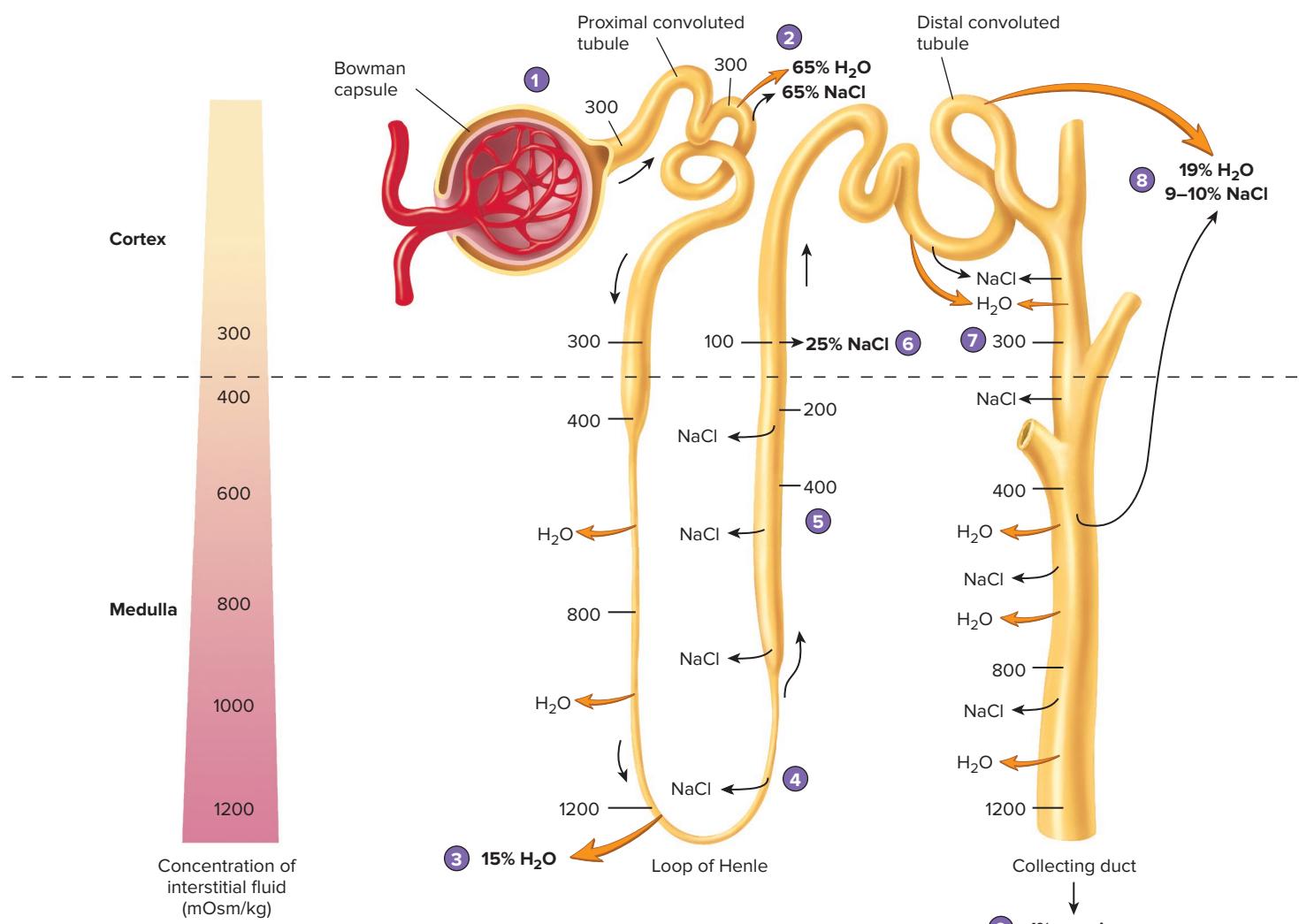
The concentration of urea in the medulla of the kidney is high and contributes to the overall high concentration of solutes there. The wall of the collecting duct is permeable to urea. Urea diffuses out of the collecting duct into the interstitial fluid of the medulla. The wall of the descending limb of the loop of Henle is also permeable to urea. Urea diffuses from the interstitial fluid into the descending limb. Thus, a cycle is produced: Urea flows into the descending limb, through the ascending limb, through the distal convoluted tubule, through the collecting duct, out of the collecting duct, and back into the descending limb.

Summary of Urine Formation

Following are the steps in urine production from the proximal convoluted tubule to the collecting duct. In the average person, about 180 L of filtrate enter the proximal convoluted tubules daily. Glucose, amino acids, Na^+ , Ca^{2+} , K^+ , Cl^- , water, and other substances (see table 26.3) move from the lumens of the proximal convoluted tubules into the interstitial fluid. The excess solutes and water then enter the peritubular capillaries. Consequently, cells of the proximal convoluted tubule reabsorb approximately 65% of the filtrate, which moves solutes and water into the interstitial fluid. The osmolality of both the interstitial fluid and the filtrate is maintained at about 300 mOsm/kg.

As the filtrate continues to flow through the renal tubule, it enters the descending limbs of the loops of Henle. This portion of the loops of Henle is highly permeable to water and solutes. As the descending limbs penetrate deep into the kidney medulla, the surrounding interstitial fluid has a progressively greater osmolality. Water diffuses out of the loops of Henle as solutes slowly diffuse into them. By the time the filtrate reaches the deepest part of the loops of Henle, its volume has been reduced by an additional 15% of the original volume, at least 80% of the filtrate volume has been reabsorbed, and its osmolality has increased to about 1200 mOsm/kg (figure 26.16).

FUNDAMENTAL Figure



- Approximately 180 L of filtrate enters the nephrons each day. The filtrate concentration is 300 mOsm/kg.
- Approximately 65% of the water and NaCl in the original filtrate is reabsorbed in the proximal convoluted tubule. The filtrate concentration is 300 mOsm/kg.
- Approximately 15% of the water is reabsorbed in the thin segment of the descending limb of the loop of Henle. At the tip of the renal pyramid, filtrate concentration is 1200 mOsm/kg, which is equal to the interstitial fluid concentration.

- The thin segment of the ascending limb of the loop of Henle is not permeable to water. Sodium chloride diffuses out of the thin segment.
- The thick segment of the ascending limb of the loop of Henle is not permeable to water. Sodium ions are actively transported into the interstitial fluid and Cl⁻ follow by diffusion.
- The volume of the filtrate does not change as it passes through the ascending limb, but the concentration is greatly reduced. By the time the filtrate reaches the cortex, the concentration is 100 mOsm/kg, and an additional 25% of NaCl has been reabsorbed.

- The distal convoluted tubules and collecting ducts reabsorb water and NaCl.
- If ADH is present, water moves by osmosis from the less concentrated filtrate into the more concentrated interstitial fluid. By the time the filtrate reaches the tip of the renal pyramid, an additional 19% of water and 9–10% of NaCl has been reabsorbed.
- One percent or less of the filtrate remains as urine when ADH is present (see section 26.4).

PROCESS FIGURE 26.16 Urine-Concentrating Mechanism

The concentration gradient from the cortex to the inner medulla is shown on the left. Interstitial fluid increases in concentration from 300 mOsm/kg in the cortex to 1200 mOsm/kg in the medulla. The concentrations of the filtrate in different parts of the nephron are also shown.

- What is the advantage of producing 180 L of filtrate each day only to reabsorb 178 L (99%) of the filtered material?

After passing through the descending limbs of the loops of Henle, the filtrate enters the ascending limbs. Both the thin and thick segments are impermeable to water, but solutes diffuse out of the thin segment, and Na⁺, Cl⁻, and K⁺ are symported from the

filtrate into the interstitial fluid in the thick segments (figure 26.16). The movement of solutes, but not water, across the wall of the ascending limbs causes the osmolality of the filtrate to decrease from 1200 to about 100 mOsm/kg by the time the filtrate again

reaches the kidney cortex. The volume of the filtrate does not change as it passes through the ascending limbs. As a result, the filtrate entering the distal convoluted tubules is dilute, compared with the concentration of the surrounding interstitial fluid, which has an osmolality of about 300 mOsm/kg.

The changes just described are *obligatory*; that is, they occur regardless of the concentration and volume of urine that the kidney finally produces. The mechanisms by which the kidney forms concentrated and dilute urine are described in section 26.4.

ASSESS YOUR PROGRESS



- 28.** List the major mechanisms that create and maintain the high solute concentration in the renal medulla.
- 29.** Describe the roles of the loop of Henle, the vasa recta, and urea cycling in maintaining a high interstitial solute concentration in the kidney medulla.
- 30.** Describe how the filtrate volume and concentration change as filtrate flows through the renal tubules and collecting ducts.

26.4 Regulation of Urine Concentration and Volume

LEARNING OUTCOME



After reading this section, you should be able to

- A. Explain how antidiuretic hormone, the renin-angiotensin-aldosterone hormone mechanism, and atrial natriuretic hormone influence the concentration and volume of urine.**

Urine can be dilute or very concentrated, and it can be produced in large or small amounts. Mechanisms that maintain the kidneys' extracellular fluid and volume keep the urine concentration and volume within narrow limits.

Filtrate reabsorption in the proximal convoluted tubules and the descending limbs of the loops of Henle is obligatory and therefore remains relatively constant. However, filtrate reabsorption in the distal convoluted tubules and collecting ducts is tightly regulated and can change dramatically, depending on the conditions to which the body is exposed. If homeostasis requires the elimination of a large volume of dilute urine, the dilute filtrate can pass through the distal convoluted tubules and collecting ducts with little change in concentration. On the other hand, if water must be conserved to maintain homeostasis, water is reabsorbed from the filtrate as it passes through the distal convoluted tubules and collecting ducts. This results in a small volume of very concentrated urine. The regulation of urine concentration and volume involves hormonal mechanisms, described next, as well as autoregulation and the sympathetic nervous system, described earlier.

Hormonal Mechanisms

Two major hormonal mechanisms are involved in regulating urine concentration and volume: (1) the renin-angiotensin-aldosterone

hormone mechanism and (2) the antidiuretic hormone (ADH) mechanism. Each mechanism is activated by different stimuli, but they work together to achieve homeostasis. The renin-angiotensin-aldosterone hormone mechanism is more sensitive to changes in blood pressure, and the ADH mechanism is more sensitive to changes in blood osmolality.

Renin-Angiotensin-Aldosterone Hormone Mechanism

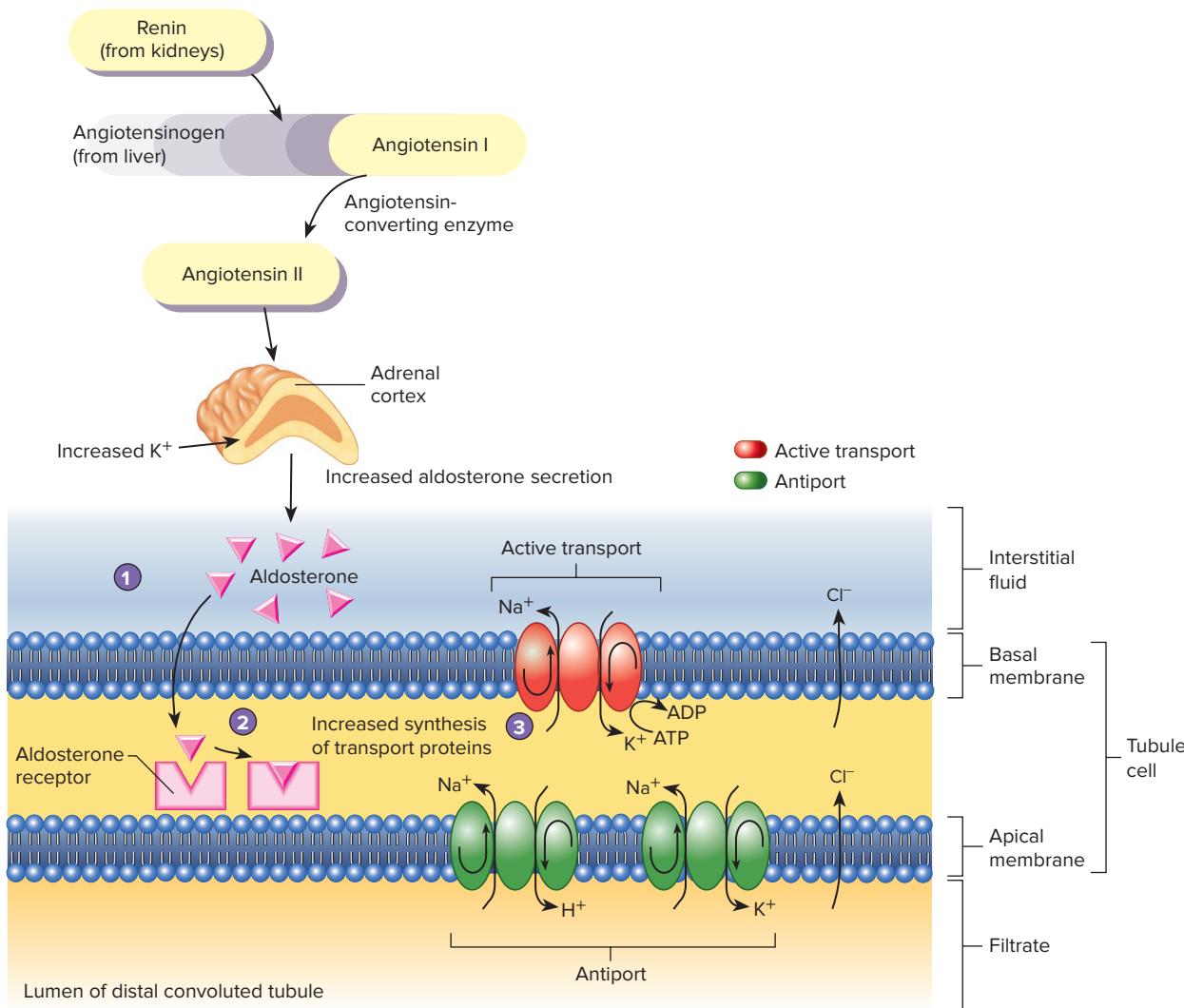
The renin-angiotensin-aldosterone mechanism is initiated under low blood pressure conditions. When blood pressure decreases, cells of the juxtaglomerular apparatuses in the kidneys secrete the enzyme **renin** (rē'nin, ren'in). The kidneys detect the low blood pressure when juxtaglomerular cells detect reduced stretch of the afferent arteriole. In addition, the macula densa cells signal the juxtaglomerular cells to secrete renin when the Na^+ concentration of the filtrate drops. Upon secretion, renin enters the blood and converts **angiotensinogen**, a plasma protein produced by the liver, to **angiotensin I**. **Angiotensin-converting enzyme (ACE)** is a proteolytic enzyme produced by capillaries of organs such as the lungs. ACE converts angiotensin I to **angiotensin II** (figure 26.17). Angiotensin II is a potent vasoconstricting hormone that increases peripheral resistance, causing blood pressure to increase. However, angiotensin II is rapidly broken down, so its effect lasts for only a short time. Angiotensin II also increases the rate of aldosterone secretion, the sensation of thirst, salt appetite, and ADH secretion.

The rate of renin secretion decreases if blood pressure in the afferent arteriole increases, or if the Na^+ concentration of the filtrate increases as it passes by the macula densa of the juxtaglomerular apparatuses.

A large decrease in the concentration of Na^+ in the interstitial fluid acts directly on the aldosterone-secreting cells of the adrenal cortex to increase the rate of aldosterone secretion. However, angiotensin II is much more important than the blood level of Na^+ for regulating aldosterone secretion. In addition, angiotensin II is critical for returning GFR to normal levels.

Aldosterone is a steroid hormone secreted by the cortex of the adrenal glands (see chapter 18). Aldosterone binds to its receptor in both the distal convoluted tubules and the collecting ducts. Aldosterone molecules diffuse through the plasma membranes and bind to their nuclear receptors. Binding of aldosterone to its receptor increases synthesis of the Na^+-K^+ pump and other Na^+ transport proteins. The Na^+-K^+ pump increases the reabsorption of Na^+ and the secretion of K^+ across the basal membrane of tubule cells. While the other Na^+ transport proteins increase the transport of Na^+ across the apical membrane of tubule cells. As a result, the rate of Na^+ reabsorption increases. Simultaneously, because of the action of the Na^+-K^+ pump, K^+ secretion increases, rather than its reabsorption (figure 26.17).

Reduced secretion of aldosterone decreases the rate of Na^+ reabsorption. Reduced Na^+ reabsorption keeps the concentration of Na^+ in the distal convoluted tubules and the collecting ducts elevated. Because the concentration of filtrate passing through the distal convoluted tubules and the collecting ducts has a greater-than-normal concentration of solutes, water's capacity to move by osmosis from the distal convoluted tubules and the collecting



- ① Aldosterone secreted from the adrenal cortex enters cells of the distal convoluted tubule.
- ② Aldosterone binds to nuclear receptors and increases the synthesis of transport proteins of the apical and basal membranes.
- ③ Newly synthesized transport proteins increase the rate at which Na^+ is absorbed and K^+ and H^+ are secreted. Chloride ions move with the Na^+ because they are attracted to the positive charge of Na^+ .

PROCESS FIGURE 26.17 Effect of Aldosterone on the Distal Convoluted Tubule

Aldosterone, which is secreted under low blood pressure conditions, stimulates Na^+ reabsorption in the distal convoluted tubule.

? How would blood pressure be affected if a person suffered from hypoaldosteronism (insufficient aldosterone secretion)? Would blood K^+ levels also be affected? If so, how?

ducts is diminished, urine volume increases, and the urine has a greater concentration of Na^+ .

Because increases in the number of Na^+-K^+ pumps increases the rate of K^+ secretion, increases in blood K^+ levels stimulate aldosterone secretion. Conversely, decreases in blood K^+ levels decrease aldosterone secretion (see chapter 27).

Predict 2

Drugs that increase urine volume are called diuretics. Some diuretics inhibit the active transport of Na^+ in the renal tubule. Explain how these diuretic drugs cause increased urine volume.

ASSESS YOUR PROGRESS

31. What factors stimulate the release of renin? What will decrease the rate of renin secretion?
32. How is angiotensin II activated? What effects does it produce?
33. Where is aldosterone produced? What factors stimulate its secretion?
34. What are the effects of aldosterone on Na^+ and Cl^- transport? How does aldosterone affect urine concentration, urine volume, and blood pressure?

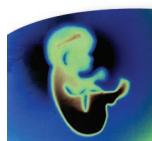
Antidiuretic Hormone Mechanism

Neurons of the supraoptic nucleus of the hypothalamus produce **antidiuretic hormone (ADH)**, also known as *vasopressin*, which is stored in the posterior pituitary gland (see chapter 18). ADH is released into the blood from the posterior pituitary. Cells called osmoreceptor cells in the supraoptic nucleus are very sensitive to even slight changes in the osmolality of the interstitial fluid. If the osmolality of the blood and interstitial fluid increases, these cells stimulate the ADH-secreting neurons. Action potentials are then propagated along the axons of the ADH-secreting neurons to the posterior pituitary gland, where the axons release ADH from their ends. Reduced osmolality of the interstitial fluid within the supraoptic nucleus inhibits ADH secretion from the posterior pituitary gland (see figure 18.5). Baroreceptors that monitor blood pressure in the atria of the heart, large veins, carotid sinuses, and aortic arch also influence ADH secretion when the blood pressure changes by more than 5–10%. Decreases in blood pressure are detected by baroreceptors when there is reduced stretch of the blood vessel wall. This reduced stretch of the baroreceptors causes them to send a lower frequency of action potentials to the hypothalamus along afferent pathways. These pathways terminate in the supraoptic nucleus of the hypothalamus (see chapter 13). As a result, the hypothalamus triggers secretion of more ADH. The distal convoluted tubules and collecting ducts remain

relatively impermeable to water in the absence of ADH (figure 26.18). More urine is produced when little ADH is secreted. A large part of the 19% of the filtrate that is normally reabsorbed in the distal convoluted tubules and the collecting ducts becomes part of the urine.

Insufficient ADH secretion results in a condition called **diabetes insipidus** (dī-ä-be'tēz in-sip'i-dūs); the word *diabetes* refers to the production of a large volume of urine, and the word *insipidus* means the urine is clear, tasteless, and dilute. People who secrete insufficient ADH often produce 10–20 L of urine per day and develop major problems, such as dehydration and ion imbalances. In contrast to diabetes insipidus, **diabetes mellitus** (me-lī'tūs) refers to the production of a large volume of urine that contains a high concentration of glucose (*mellitus*, honeyed, sweet).

ADH secretion promotes increased water reabsorption by the distal convoluted tubule when blood osmolality increases or when blood pressure declines significantly. Water reabsorption lowers blood osmolality. It also increases blood volume, which elevates blood pressure. Conversely, when blood osmolality decreases or when blood pressure goes up, ADH secretion declines. The reduced ADH levels cause the kidneys to reabsorb less water and to produce a larger volume of dilute urine. The greater loss of water in the urine raises blood osmolality and lowers blood pressure. ADH secretion occurs in response to small changes in osmolality,



Clinical Impact 26.1

Diabetic Nephropathy and Renal Failure

Diabetic nephropathy (ne-frop'ă-thē) is a disease of the kidneys associated with diabetes mellitus, and it is the principal cause of chronic renal failure. This condition damages renal glomeruli and ultimately destroys functional nephrons through progressive scar tissue formation, mediated in part by an inflammatory response. The damaged glomeruli no longer filter the blood effectively, allowing proteins to pass through the filtration membrane and be excreted in the urine. The presence of protein in the urine of people who have type 2 diabetes strongly suggests significant diabetic nephropathy, which can lead to end-stage renal failure. About 1 in 14 Americans over age 30 have some degree of type 2 diabetes mellitus, and most hemodialysis patients have type 2 diabetes mellitus.

The development of diabetic nephropathy is complex. Although the mechanism is not completely understood, the level of angiotensin II is elevated in diabetes mellitus. This causes exaggerated efferent arteriole vasoconstriction and consequently increased glomerular

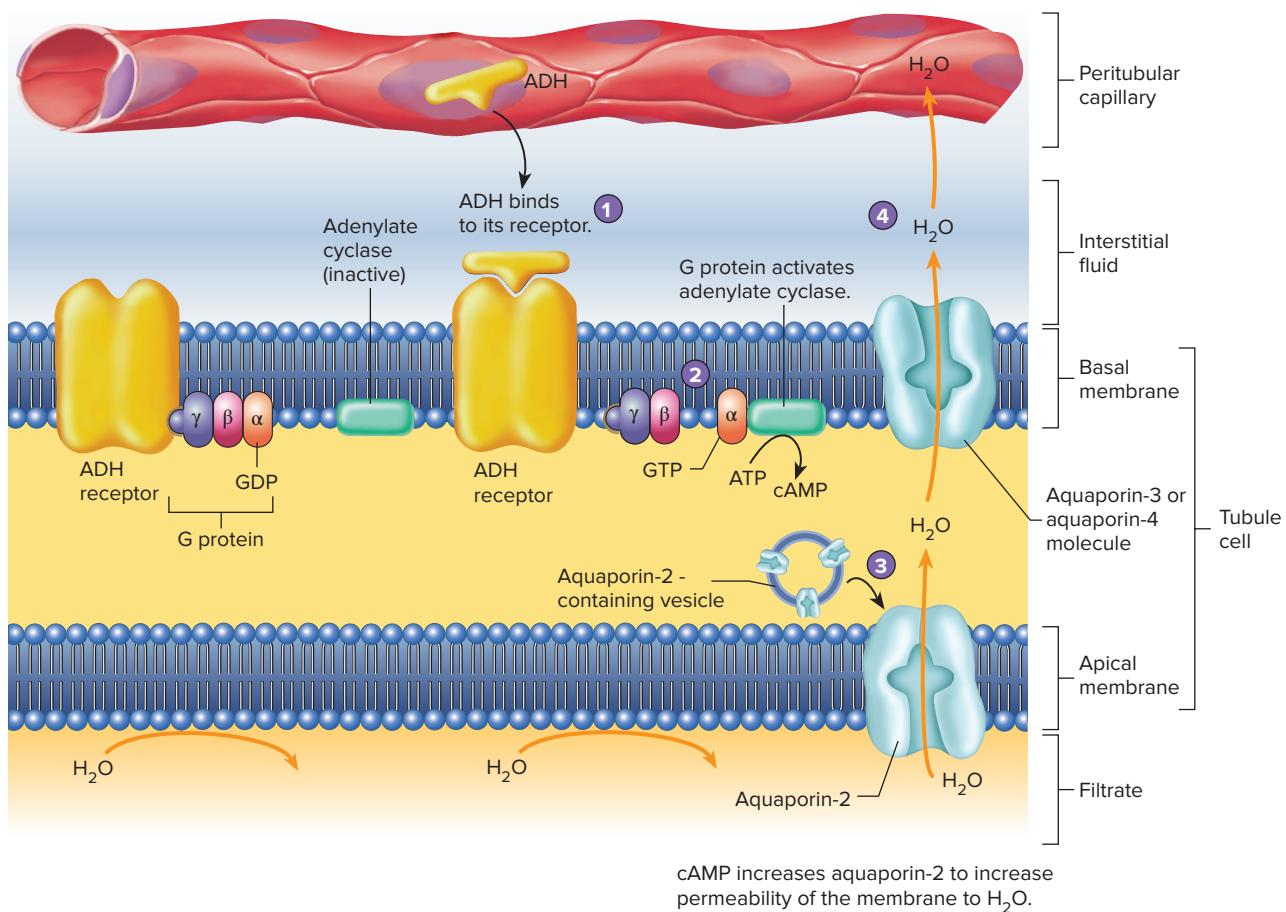
capillary pressure. The increased glomerular capillary pressure damages the glomerular basement membrane, causing it to thicken and become more permeable. The glomerular basement membrane is also damaged by the production of glycoproteins called **advanced glycosylation end products (AGEs)**. AGEs are produced when glucose forms irreversible cross-links with kidney and plasma proteins. The AGEs stimulate the secretion of growth factors from glomerular cells, which promote glomerular basement membrane thickening.

Because the glomerular basement membrane in patients with diabetes mellitus is more permeable than normal, plasma proteins cross the filtration membrane and enter the urine. The initial amount of protein entering the urine is small, a condition called microalbuminuria (mī'krō-al-boō-min-ū'rē-ă). However, as the number of functional nephrons in the kidney decreases, microalbuminuria eventually progresses to overt proteinuria (prō-tē-noo'rē-ă), the secretion of more than 300 mg albumin/day. By the time overt proteinuria has developed, which

may take 10–15 years, the number of functional nephrons has decreased to less than 10% of normal, and the kidneys are no longer able to excrete adequate amounts of waste products. This condition is called **end-stage renal disease (ESRD)**. In ESRD, renal failure has worsened to the point that kidney function is less than 10% of normal. Unless ESRD is treated by hemodialysis or kidney transplantation, the patient dies.

The use of **angiotensin-converting enzyme (ACE) inhibitors** slows or, in some cases, even halts the progression of proteinuria and end-stage renal disease. ACE inhibitors prevent the formation of angiotensin II; consequently, arterial blood pressure and glomerular capillary pressure remain within their normal ranges. When ACE inhibitors are used in combination with drugs called **angiotensin receptor blockers (ARBs)**, which prevent angiotensin II molecules from binding to their receptors, proteinuria decreases up to 45%. People with type 2 diabetes who maintain their blood glucose within normal levels have a much lower incidence of diabetic nephropathy and ESRD.

FUNDAMENTAL Figure



- ① ADH moves from the peritubular capillaries and binds to ADH receptors in the plasma membranes of the distal convoluted tubule cells and the collecting duct cells.
- ② When ADH binds to its receptor, a G protein mechanism is activated, which in turn activates adenylate cyclase.
- ③ Adenylate cyclase increases the rate of cAMP synthesis. Cyclic AMP promotes the insertion of aquaporin-2 containing cytoplasmic vesicles into the apical membranes of the distal convoluted tubules and collecting ducts, thereby increasing their permeability to water. Water then moves by osmosis out of the distal convoluted tubules and collecting ducts into the tubule cells through the aquaporin-2 water channels.
- ④ Water exits the tubule cells and enters the interstitial fluid through aquaporin-3 and aquaporin-4 water channels in the basal membranes.

PROCESS FIGURE 26.18 Effect of Antidiuretic Hormone (ADH) on Renal Tubule Water Movement

Increased blood solute concentration affects hypothalamic neurons, and decreased blood pressure affects baroreceptors. In response to either of these stimuli, the posterior pituitary secretes ADH, which increases water reabsorption by the kidneys.

? In response to severely low blood pressure, ADH is secreted. How does ADH secretion help return blood pressure to its set point? How might blood pressure respond in an individual who has excess ADH secretion, a condition known as syndrome of inappropriate ADH secretion?

whereas a substantial change in blood pressure is required to alter ADH secretion. Thus, ADH is more important in regulating blood osmolality than it is in regulating blood pressure.

Predict 3

Ethyl alcohol inhibits ADH secretion. Given this information, describe the mechanism by which alcoholic beverages affect urine production.

Production of Concentrated Urine

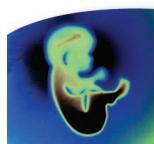
Filtrate enters the distal convoluted tubules after passing through the loops of Henle. From the distal convoluted tubule, filtrate then passes through the collecting ducts. ADH increases the permeability of the distal convoluted tubule and the collecting ducts to water. When ADH is present, water moves by osmosis out of the distal convoluted tubule and collecting duct into the more concentrated interstitial fluid.

ADH increases the permeability of the apical membranes of the distal convoluted tubules and collecting ducts to water by binding to membrane-bound receptors. This activates a G protein mechanism that increases cAMP synthesis inside these cells. Cyclic AMP promotes the insertion of aquaporins into the apical membrane (figure 26.18). **Aquaporins** are water channel proteins that increase the permeability of the distal convoluted tubule and the collecting duct to water. There are multiple forms of aquaporins. In cells of the distal convoluted tubules and collecting ducts, the basal membranes contain aquaporin molecules—aquaporin-3 and aquaporin-4—that are insensitive to ADH. These aquaporin molecules provide channels for water to exit from the collecting duct cells into the interstitial fluid. Aquaporin-2 molecules regulate water movement into the cells. In cells that have not been exposed to ADH, the aquaporin-2 molecules are found in the membranes of vesicles in the cytoplasm (see figure 3.1). In response to ADH, the increased cAMP initiates the incorporation of the membranes of vesicles containing aquaporin-2 channels into the apical membrane. Thus, when ADH is present, water moves by osmosis out of the distal convoluted tubules and collecting

ducts; conversely, when ADH is absent, water remains in the distal convoluted tubules and collecting ducts to become urine (figure 26.19). Abnormal aquaporin-2 genes can result in excessive urine production because these genes code for abnormal aquaporin-2 molecules that do not function normally. Thus, the number of functional aquaporins decreases, and water remains in the renal tubule.

The filtrate flows into the distal convoluted tubules and collecting ducts that pass through the kidney medulla with its high concentration of solutes. When ADH is present, water moves by osmosis from the distal convoluted tubules and the collecting ducts into the interstitial fluid. By the time the filtrate has reached the end of the collecting ducts, another 19% of the filtrate has been reabsorbed. Thus, 1% of the filtrate remains as urine, and 99% of the filtrate has been reabsorbed. The osmolality of the filtrate at the ends of the collecting ducts is approximately 1200 mOsm/kg (see figure 26.16).

In addition to the dramatic decrease in filtrate volume and the increase in filtrate osmolality, a marked alteration occurs in the filtrate composition. Waste products, such as creatinine and urea, and excess ions, such as K^+ , H^+ , phosphate, and sulfate, are at a



Clinical Impact 26.2

Diuretics

Diuretics (dī-ū-ret'iks) are chemicals that increase the rate of urine production. Although the definition is simple, a number of physiological mechanisms are involved.

Diuretics are used to treat hypertension, as well as several types of edema caused by congestive heart failure, cirrhosis of the liver, and other anomalies. However, treatment with diuretics can lead to complications, including dehydration and electrolyte imbalances.

The varying degree of diuretic chemical types is outlined in the following descriptions, along with their physiological mechanisms. The action of **carbonic anhydrase** (kar-bō'ik an-hī'drās) inhibitors reduces the rate of H^+ secretion and the reabsorption of bicarbonate ion (HCO_3^-). As H^+ is secreted into the renal tubule, it combines with HCO_3^- to form carbonic acid. Carbonic acid dissociates into water and CO_2 , which can diffuse across the wall of the renal tubule. Reduced H^+ secretion causes HCO_3^- to remain in the renal tubule. The HCO_3^- increases tubular osmotic pressure, causing osmotic diuresis. The diuretic effect is useful in treating conditions such as glaucoma and altitude sickness. However, with long-term

use, carbonic anhydrase inhibitors tend to lose their diuretic effect.

Sodium ion reabsorption inhibitors include thiazide-type diuretics. They promote the loss of Na^+ , Cl^- , and water in the urine. These diuretics are sometimes given to people who have hypertension. The increased loss of water in the urine lowers blood volume and thus blood pressure. Other inhibitors of Na^+ reabsorption, such as bumetanide, furosemide, and ethacrynic acid, specifically inhibit transport in the ascending limb of the loop of Henle. These diuretics are frequently used to treat congestive heart failure, cirrhosis of the liver, and renal disease. A possible side effect of these drugs is increased excretion of K^+ in the urine.

Certain **potassium-sparing diuretics** act on the distal convoluted tubules and the collecting ducts to reduce the exchange between Na^+ and K^+ . Potassium-sparing diuretics are used to diminish the loss of K^+ in the urine, thereby preserving, or “sparing,” these ions. Some potassium-sparing diuretic drugs act by competitive inhibition of aldosterone, whereas others inhibit the symporters for Na^+ in apical membranes of cells in the distal convoluted tubules and collecting ducts. Both types result

in Na^+ diuresis and K^+ retention. A side effect of prolonged treatment with certain diuretics is K^+ depletion. These diuretics are inhibitors of Na^+-Cl^- symporters in the ascending limb of the loop of Henle. To prevent K^+ depletion, potassium-sparing diuretics are commonly used in combination with Na^+-Cl^- symport inhibitors.

Osmotic diuretics freely pass into the filtrate and undergo limited reabsorption by the renal tubule. These diuretics increase urine volume by elevating the osmotic concentration of the filtrate, thus reducing the amount of water moving by osmosis out of the renal tubule. Urea, mannitol, and glycerine have been used as osmotic diuretics and can be effective in treating patients who have cerebral edema and edema in acute renal failure (see table 26.5).

Xanthines (zan'thēnz), including caffeine and related substances, act as diuretics partly because they increase renal blood flow and the rate of glomerular filtrate formation. They also influence the renal tubule by decreasing Na^+ and Cl^- reabsorption.

Alcohol acts as a diuretic, although it is not used clinically for that purpose. It inhibits ADH secretion from the posterior pituitary and results in increased urine volume.



Case STUDY 26.2

Diabetes Insipidus

Two infants were born to different families within the same week. Not long after the newborns arrived home from the hospital, their respective parents noticed that their diapers were excessively wet hour after hour throughout the day and night. In addition, both infants were irritable, had slight fevers, and had vomited, even though they had not eaten for several feedings. The parents took the babies to their pediatricians. Subsequently, blood tests indicated that both infants had high blood Na^+ levels. Following water deprivation tests, which monitor plasma levels of ADH, the physicians diagnosed nephrogenic diabetes insipidus. One infant was found to have an ADH receptor abnormality, whereas the other was diagnosed with an aquaporin-2 abnormality.

The term *diabetes* refers to a disease state characterized by polyuria, excess production of urine. There are two major causes of diabetes: (1) inadequate production of or response to insulin, called diabetes mellitus

(see chapter 18), and (2) inadequate production of or response to ADH, called diabetes insipidus. Diabetes insipidus is a relatively rare disease that occurs in two varieties: **Central diabetes insipidus (CDI)** is caused by failure of ADH secretion, and **nephrogenic diabetes insipidus (NDI)** results when ADH secretion is normal but the ADH receptor, or the response to ADH, in the kidney is abnormal. Consequently, the G protein mechanism, which normally functions in the insertion of the aquaporin-2 water channel protein in the apical membranes, does not operate. In most cases, NDI results from an inherited condition that affects the function of the ADH receptor. NDI can also be acquired, but that usually happens later in life and can be due to several factors, including the use of certain prescription drugs or the existence of an underlying systemic disease.

Treatment of NDI includes ensuring a plentiful supply of water, following a low-sodium and sometimes a low-protein diet, and using thia-

zide diuretics (Na^+ reabsorption inhibitors) in combination with a potassium-sparing diuretic.

► Predict 4

Use your knowledge of kidney physiology and figure 26.18 to answer the following questions.

- Why did the two infants have high blood Na^+ levels and dilute urine?
- Predict how the infants' plasma levels of ADH changed during the water deprivation test, given the diagnosis of NDI. (Hint: See section 26.4.)
- Why does an abnormal aquaporin-2 gene result in excessive urine production?
- Predict plasma levels of ADH following a water deprivation test in an individual with central diabetes insipidus.
- Why is treatment with a thiazide diuretic helpful to patients with NDI? (Hint: See Clinical Impact 26.2.)

much higher concentration in urine than in the original filtrate because water has been removed from the filtrate. Overall, the processes of reabsorption and secretion are selective so that, in the end, beneficial substances are retained in the body and toxic substances are eliminated.

Production of Dilute Urine

If ADH is not present or its concentration is low, the distal convoluted tubules and collecting ducts are less permeable to water. This lowered permeability dampens water reabsorption. The concentration of the urine produced is less than 1200 mOsm/kg, and

the volume is increased. The volume of this more dilute urine can be much larger than 1% of the filtrate formed each day. If no ADH is secreted, the osmolality of the urine may be close to the osmolality of the filtrate in the distal convoluted tubule, and the volume of urine may approach 20–30 L/day, which is the same volume as ten to fifteen 2-liter soda bottles per day (figure 26.19).

In a healthy person, even when the kidneys produce dilute urine, the concentration of waste products in the urine is large enough to maintain homeostasis. Again, as with the production of concentrated urine, beneficial substances are retained, and both toxic substances and excess water are eliminated.



Clinical GENETICS 26.2

Nephrogenic Diabetes Insipidus

There are three types of inherited nephrogenic diabetes insipidus (NDI). X-linked NDI, the most common form, affects more males than females. X-linked NDI is caused by a mutation in the V_2 ADH receptor gene on the X chromosome. Mutations in this gene result in defective ADH receptors, which prevent a normal response to ADH in the kidneys.

Autosomal recessive NDI is more rare than the X-linked form, and it affects males and females equally. This form of NDI requires both parents to be carriers for an abnormal aquaporin-2 gene. For children to have autosomal recessive NDI, they must inherit a recessive allele from each parent. In autosomal recessive NDI, there is a 25% chance that each child of heterozygous parents will have NDI.

Autosomal dominant NDI is the most rare form of NDI, and it affects males and females equally. With this form, only one parent must have a dominant allele for an abnormal aquaporin-2 gene, but that parent will also have symptoms of NDI. There is a 50% chance that each child will have NDI.

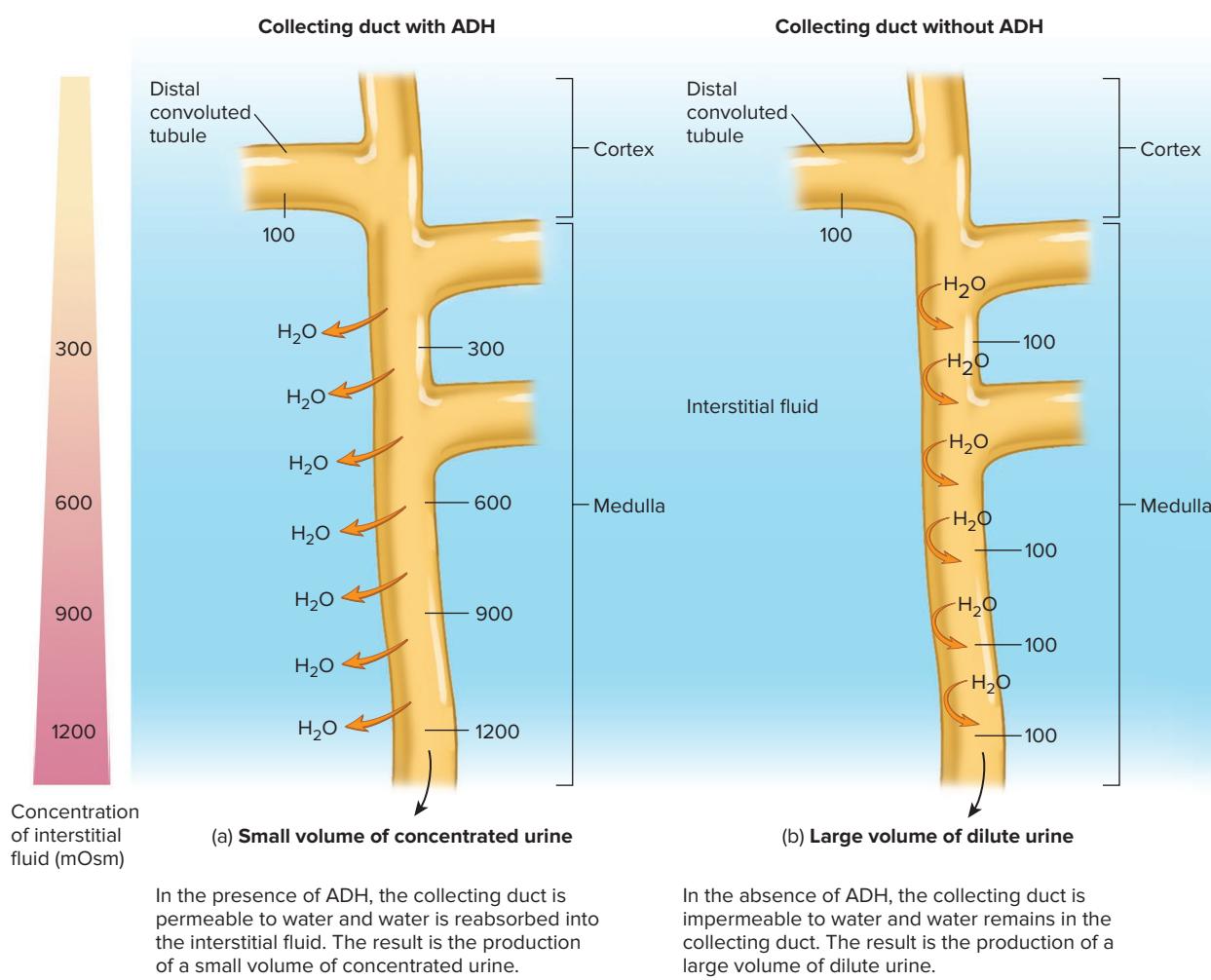


FIGURE 26.19 Effect of ADH on Urine Concentration and Volume

(a) When ADH is available, it increases the permeability of the collecting duct to water. (b) Without ADH, the collecting duct is impermeable to water.

Predict 5

Amanda, an inexperienced runner, competed in her first marathon last spring in Phoenix, Arizona. During the run, the temperature reached 35°C (95°F) with 30% humidity. Amanda drank very little water during the race. When she finished 4½ hours later, she was dizzy and disoriented and had an increased heart rate. She was also very pale. Friends took her to a hospital, where the doctor diagnosed severe dehydration and prescribed IV fluids. Amanda did not urinate until nearly 12 hours later. Explain the physiological responses that resulted in her reduced urine production. (*Hint:* See section 21.9.)

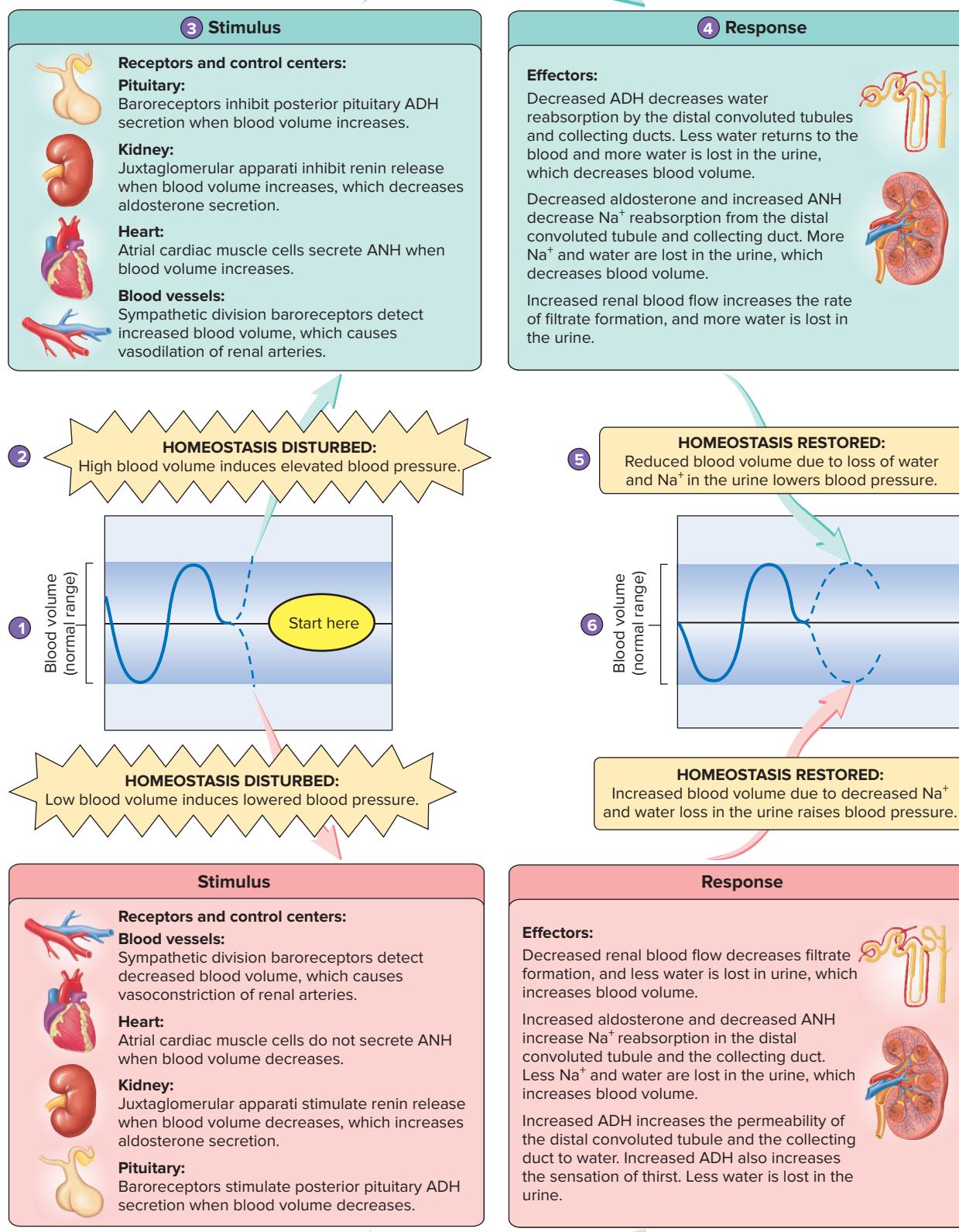
Atrial Natriuretic Hormone

Atrial natriuretic (nā'trē-ū-ret'ik) hormone (ANH) is a hormone secreted by cells in the right atrium of the heart when they are stretched more than normal. Increased stretch of the right atrium occurs when blood volume is higher than usual (see chapter 21). Atrial natriuretic hormone decreases blood volume through inhibition of Na⁺ reabsorption in the kidney tubules. ANH also inhibits ADH secretion from the posterior pituitary gland. Increased ANH

secretion increases the volume of urine produced, which lowers blood volume and thus blood pressure. Atrial natriuretic hormone also dilates arteries and veins, which reduces peripheral resistance and lowers blood pressure. Thus, venous return and blood volume decrease in the right atrium. Figure 26.20 provides a summary of the hormonal mechanisms that regulate kidney function and their effects on blood volume and blood pressure.

ASSESS YOUR PROGRESS

35. Where is ADH produced? What factors stimulate an increase in ADH secretion?
36. How does ADH affect urine volume and concentration?
37. Describe how the presence of ADH causes the production of a small volume of concentrated urine.
38. How does the absence of ADH cause the production of a large volume of dilute urine?
39. Where is atrial natriuretic hormone produced, and how does it affect urine production?



HOMEOSTASIS FIGURE 26.20 Regulation of Blood Pressure

(1) Blood volume is in the normal range. (2) Blood volume increases outside the normal range, which causes homeostasis to be disturbed. (3) The control centers respond to the change in blood volume. (4) The control centers cause ADH and aldosterone secretion to decrease, which reduced water reabsorption. The control centers also cause dilation of renal arteries, which increases urine production. The heart secretes ANH, which also increases urine production. (5) These changes cause blood volume to decrease. (6) Blood volume returns to the normal range and homeostasis is restored. Observe the responses to a decrease in blood volume outside the normal range by following the red arrows.

26.5 Plasma Clearance and Tubular Maximum

LEARNING OUTCOMES



After reading this section, you should be able to

- A. Define plasma clearance and show how it is calculated.
- B. Describe why inulin is used to estimate GFR through plasma clearance.
- C. Explain how plasma clearance is used to calculate renal plasma flow.
- D. Define tubular load and tubular maximum.

A clinician who is concerned that a patient's kidney function is declining will measure the GFR by determining plasma clearance. **Plasma clearance** is a calculated value representing the volume of plasma that is cleared of a specific substance each minute. For example, if the clearance value is 100 mL/min for a substance, the substance is completely removed from 100 mL of plasma each minute. The plasma clearance can be calculated for any substance that enters the blood according to the following formula:

$$\text{Plasma clearance} = \frac{\text{Quantity of substance in urine (mL/min)}}{\text{Concentration of substance in urine} \times \text{Concentration of substance in plasma}} \quad (26.5)$$

Plasma clearance can be used to estimate GFR if the appropriate substance is monitored (see table 26.2). Such a substance must have the following characteristics: (1) It must pass through the filtration membrane of the renal corpuscle as freely as water or other small molecules, (2) it must not be reabsorbed, (3) it must not be secreted into the renal tubule, and (4) it must not be either metabolized or produced in the kidneys. **Inulin** (in'ū-lin; not to be confused with the hormone insulin) is a nonphysiological polysaccharide that has these characteristics. As filtrate forms, the filtrate has the same concentration of inulin as plasma; however, as the filtrate flows through the renal tubule, none of the inulin gets reabsorbed. Thus, inulin gets steadily removed from the blood as it passes through the kidney. The rate of inulin removal, called plasma clearance, is equal to the GFR.

GFR is reduced when a kidney fails. Therefore, measurement of the GFR can indicate the degree of kidney damage. The clearance value for urea and creatinine can also be used clinically. One advantage of using these substances is that they are naturally occurring metabolites, so foreign substances do not have to be injected. A high plasma concentration and a lower-than-normal clearance value for urea and creatinine indicate a reduced GFR and kidney failure. Creatinine clearance can also be used to monitor the progress of GFR changes in people experiencing kidney failure.

Plasma clearance can also be used to calculate renal plasma flow (see table 26.2). However, substances with the following characteristics must be used: (1) The substance must pass through the filtration membrane of the renal corpuscle, and (2) it must be

secreted into the renal tubule at a sufficient rate that very little of it remains in the blood as the blood leaves the kidney. Para-aminohippuric acid (PAH) meets these requirements (see section 26.3). As blood flows through the kidney, essentially all the PAH is either filtered or secreted into the renal tubule. The clearance calculation for PAH is equal to the volume of plasma flowing through the kidney each minute. Also, if the hematocrit is known, the total volume of blood flowing through the kidney each minute can be calculated easily.

In addition, the concept of plasma clearance can be used to help determine how drugs or other substances are excreted by the kidney. A plasma clearance value greater than the inulin clearance value suggests that the substance is secreted by the tubule into the filtrate.

The **tubular load** is the total amount of a substance that passes through the filtration membrane into the renal tubule each minute. Normally, glucose is almost completely reabsorbed from the tubule by active transport. However, the tubule's capacity to actively transport glucose across the epithelium of the tubule is limited. If the tubular load is greater than the tubule's capacity to reabsorb it, the excess glucose remains in the urine.

The **tubular maximum** is the maximum rate at which a substance can be actively reabsorbed (figure 26.21). Each substance that is reabsorbed has its own tubular maximum, determined by the number of active transport carrier proteins and the rate at which they are able to transport molecules of the substance. For example, in people who have diabetes mellitus, the tubular load for glucose can exceed the tubular maximum by a substantial amount, thus allowing glucose to appear in the urine. Urine volume is also greater than normal because the glucose molecules in the filtrate increase the osmolality of the filtrate in the tubule and reduce the effectiveness of water reabsorption by osmosis.

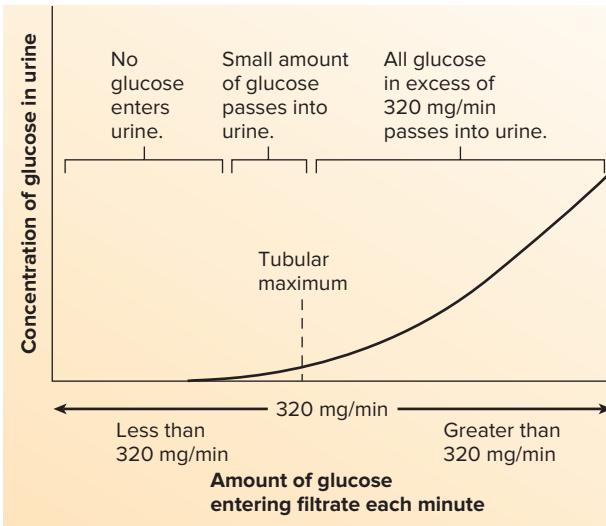


FIGURE 26.21 Tubular Maximum for Glucose

As the concentration of glucose increases in the filtrate, it reaches a point that exceeds the renal tubule's ability to actively reabsorb it. That concentration is called the tubular maximum. Beyond that concentration, the excess glucose enters the urine.

Predict 6

A person is suspected of having chronic renal failure. To assess kidney function, urea clearance is measured and found to be very low. Explain what a very low urea clearance indicates for this patient. Compare that with the effect of chronic renal failure on the tendency for the blood K^+ level to be higher than normal and the blood Na^+ level to be lower than normal.

ASSESS YOUR PROGRESS

40. What is plasma clearance, and how is it calculated?
41. Explain why plasma clearance of inulin can be used to estimate GFR.
42. Describe how PAH is used to determine renal plasma flow.
43. Explain the significance of tubular load and tubular maximum.

26.6 Urine Movement

LEARNING OUTCOMES

After reading this section, you should be able to

- A. Describe the anatomy and histology of the ureters, urinary bladder, and urethra.
- B. Explain the flow of urine from the nephron to the urinary bladder.
- C. Discuss the micturition reflex.

Anatomy and Histology of the Ureters and Urinary Bladder

The **ureters** are tubes through which urine flows from the kidneys to the urinary bladder. The ureters extend inferiorly and medially from the renal pelvis and exit the kidney at the renal hilum. The ureters descend through the abdominal cavity and enter the urinary bladder (figure 26.22; see figures 26.1 and 26.2). The **urinary bladder** is a hollow, muscular container that lies in the pelvic cavity just posterior to the symphysis pubis. The ureters enter on its posterolateral surface. In males, the urinary bladder is just anterior to the rectum; in females, it is just anterior to the vagina and inferior and anterior to the uterus. Its volume increases and decreases, depending on how much or how little urine is stored in it.

The **urethra**, which transports urine to the outside of the body, exits the urinary bladder inferiorly and anteriorly (figure 26.22, center). The triangular area of the urinary bladder's posterior wall between the two ureters and the urethra on the urinary bladder's anterior wall is called the **trigone** (*tri'gōn*). This region is histologically unique. The trigone does not expand with the urinary bladder wall as it fills. This causes the trigone to act as a funnel for emptying the urinary bladder. **Cystitis** (*sist'i'tis*) is an inflammation of the urinary bladder, which usually results from a bacterial infection. Typically, bacteria from outside the body enter the bladder. Infection by the bacterium *E. coli* is the most common cause of cystitis.

Transitional epithelium lines both the ureters and the urinary bladder. Transitional epithelium is specialized, so that the cells

slide past one another, and the number of cell layers decreases as the volume of the ureters and urinary bladder increases. The rest of the walls of these structures consists of a lamina propria, a muscular coat, and a fibrous adventitia (figure 26.22b,c). The wall of the urinary bladder is much thicker than the wall of a ureter because it consists of layers of primarily smooth muscle, sometimes called the **detrusor** (*dī-troo'ser*) **muscle**. Contraction of this smooth muscle forces urine out of the urinary bladder. The epithelium itself ranges from four or five cells thick when the urinary bladder is empty to two or three cells thick when it is distended. The urethra is lined with stratified or pseudostratified columnar epithelium.

At the junction of the urinary bladder and the urethra, smooth muscle forms an **internal urethral sphincter** that prevents urine leakage from the urinary bladder. In males, the internal urethral sphincter contracts to keep semen from entering the urinary bladder during sexual intercourse (see chapter 28). The specific anatomy and physiology of the internal urethral sphincter is more clearly detailed for the male urethra. For the female urethra, the details are not as well established. Females clearly have smooth muscle fibers within the wall of the urethra at the neck of the bladder. These smooth muscle fibers assist with preventing urine leakage, but whether these fibers form a distinct sphincter is still under scrutiny.

Both males and females have a well-defined **external urethral sphincter**. The external urethral sphincter is formed of skeletal muscle that surrounds the urethra as the urethra extends through the pelvic floor. The external urethral sphincter allows a person to voluntarily start or stop the flow of urine through the urethra.

In males, the urethra extends to the end of the penis, where it opens to the outside (see chapter 28). The female urethra is much shorter (approximately 4 cm) than the male urethra (approximately 20 cm) and opens into the vestibule anterior to the vaginal opening.

Urine Flow Through the Nephron and Ureters

Pressure decreases in the renal tubule as filtrate moves along it during urine production. Hydrostatic pressure from filtrate averages 10 mm Hg in the Bowman capsule and drops to nearly 0 mm Hg in the renal pelvis. This pressure gradient forces the filtrate to flow from the Bowman capsule through the renal tubule into the renal pelvis. Because the hydrostatic pressure is 0 mm Hg in the renal pelvis, no pressure gradient exists to force urine to flow through the ureters to the urinary bladder. However, the circular smooth muscle in the walls of the ureters undergoes peristaltic waves of contractions (see chapter 24), which force urine through the ureters. The peristaltic waves progress from the region of the renal pelvis to the urinary bladder. They occur from once every few seconds to once every 2–3 minutes. Parasympathetic stimulation increases their frequency, and sympathetic stimulation decreases it.

The peristaltic contractions of each ureter proceed at a velocity of approximately 3 cm/s and can generate pressures in excess of 50 mm Hg. Where the ureters penetrate the urinary bladder, they run obliquely through the trigone. Pressure inside the urinary bladder compresses that part of the ureter to prevent urine from backing up into the ureters.



MICROBES In Your Body 26.1

Can Bacteria Actually Help Cure Urinary Bladder Cancer?

In the United States, there are more than 60,000 new cases of urinary bladder cancer diagnosed each year; it is the ninth-leading type of cancer. The majority of urinary bladder cancer is transitional cell carcinoma, which is cancer of the endothelial cell lining of the urinary bladder. However, if the cancer is detected and treated before it penetrates the urinary bladder's muscular wall or spreads to other areas of the body, the 5-year survival rate is 77%. Reliable treatments can resolve these cases relatively quickly. Surprisingly, the most common treatment for early-stage urinary bladder cancer tumors is the introduction of a fluid containing live tuberculosis-causing bacteria into the urinary bladder. We will examine the causes of and screening tests for urinary bladder cancer and explore how a bacterium serves as an anticancer treatment for urinary bladder cancer.

At least 50% of urinary bladder cancer cases can be attributed to cigarette smoking, even 10 years or more after a person has quit smoking. About 30% of cases are due to exposure to environmental carcinogens, such as certain industrial dyes or hair dyes used by professional hairdressers. The remaining cases are often due to a combination of factors, none of which are well understood.

In about 80–90% of urinary bladder cancer cases, the first sign is blood in the urine, called macrohematuria. Sometimes, pain with urination or a change in urination frequency is also an indicator of possible cancer. However, confirmation is usually done with a procedure called **cystoscopy** (si-stos'kuh-peē), in which a catheter is inserted into the urinary bladder to view the wall and collect cells, which are then examined under a microscope to look for abnormalities in appearance.

The treatments for urinary bladder cancer are dependent on how deeply the tumor has penetrated into the urinary bladder wall. In earlier stages, treatment is more effective. If the tumor is quite small and shallow in the endothelium, a process called transurethral resection of the bladder tumor (TURBT) can be used to scrape the cancerous cells off the urinary bladder wall. In other cases, in which the tumor is superficial but somewhat more advanced than the earliest stage, immunotherapy with intravesicular (inside the urinary bladder) delivery of a medicine known as Bacillus Calmette-Guérin (BCG) is used. BCG was originally developed in 1906 as a vaccine against the bacterial disease tuberculosis. BCG is a live, attenuated (weakened) strain of *Mycobacterium bovis*, the bacterium that causes tuberculosis in cattle, but it can infect other organisms, including humans. BCG was used as an anticancer therapeutic after results from animal experiments demonstrated its effectiveness.

Tuberculosis and humans have a long history together. The disease was originally called “consumption” because one of its side effects in untreated patients is extreme weight loss. Human tuberculosis is caused by the bacterium *Mycobacterium tuberculosis*. Due to their cellular composition, members of the *Mycobacterium* genus are notoriously difficult to kill, including destruction by our body’s immune system. Ironically, this characteristic is what makes tuberculosis bacteria effective at helping kill cancer cells. Urinary bladder cancer is the only cancer treated with BCG. Because the BCG fluid is isolated within the urinary bladder, other organs in the body are not usually exposed to the bacteria.

Members of the *Mycobacterium* genus have cell walls with higher lipid content than other bacteria. It is this lipid content that protects them once they are phagocytosed by macrophages or taken up by cancer cells. Once the infected cells have the bacteria inside, these cells then display the bacterial antigens. Display of the bacterial antigens induces destruction of the infected cells by the immune system (see chapter 22). Since the bacteria used in BCG are live, although attenuated, they can infect other body tissues if they enter the blood. If this happens, patients develop an illness called acute disseminated (widespread) tuberculosis and become contagious to others. Fortunately, development of tuberculosis is a rare occurrence for BCG recipients. Treatments are terminated once white blood cells are detectable in the patient’s urine, indicating that an immunological reaction is occurring in the urinary bladder. The average treatment time is about 6 weeks. The BCG urinary bladder cancer treatment is an elegant example of how knowledge of body systems can be applied in an unexpected way: purposefully infecting a patient with bacteria so cancer cells are destroyed by the patient’s immune system.

► Predict 7

Based on your knowledge of the micturition reflex and using figure 26.23, predict how treatment with BCG and induction of an immunological response in the urinary bladder might affect action potential frequency in sensory neurons located in the wall of the urinary bladder. Would there be a higher or lower frequency of action potentials? How would a patient interpret a change in action potential frequency in relation to the urge to urinate?

When no urine is present in the urinary bladder, internal pressure is about 0 mm Hg; even when the urine volume is 100 mL, pressure rises to only 10 mm Hg. Pressure continues to rise slowly as volume increases to approximately 300 mL, but above volumes of 400 mL the pressure rises rapidly.

Micturition Reflex

The flow of urine from the kidney to the urinary bladder through the ureter is relatively continuous. The urinary bladder acts as a reservoir for urine until it can be eliminated relatively quickly at an appropriate time and place. The urinary bladder can stretch to hold a large urine volume. At its maximum volume, the urinary bladder

can contain 1 L (about 1 quart) of urine, but discomfort becomes noticeable when urine volume exceeds approximately 500 mL. The urinary bladder’s capacity to distend is due to three factors:

1. The wall of the urinary bladder contains large folds, similar to those of the stomach, which unfold to enlarge the lumen.
2. The lining of the urinary bladder is transitional epithelium, which stretches.
3. The smooth muscle wall of the urinary bladder, with the exception of the trigone, also stretches to accommodate fluid. As urine enters the urinary bladder, it lifts and expands superiorly to accommodate the fluid.

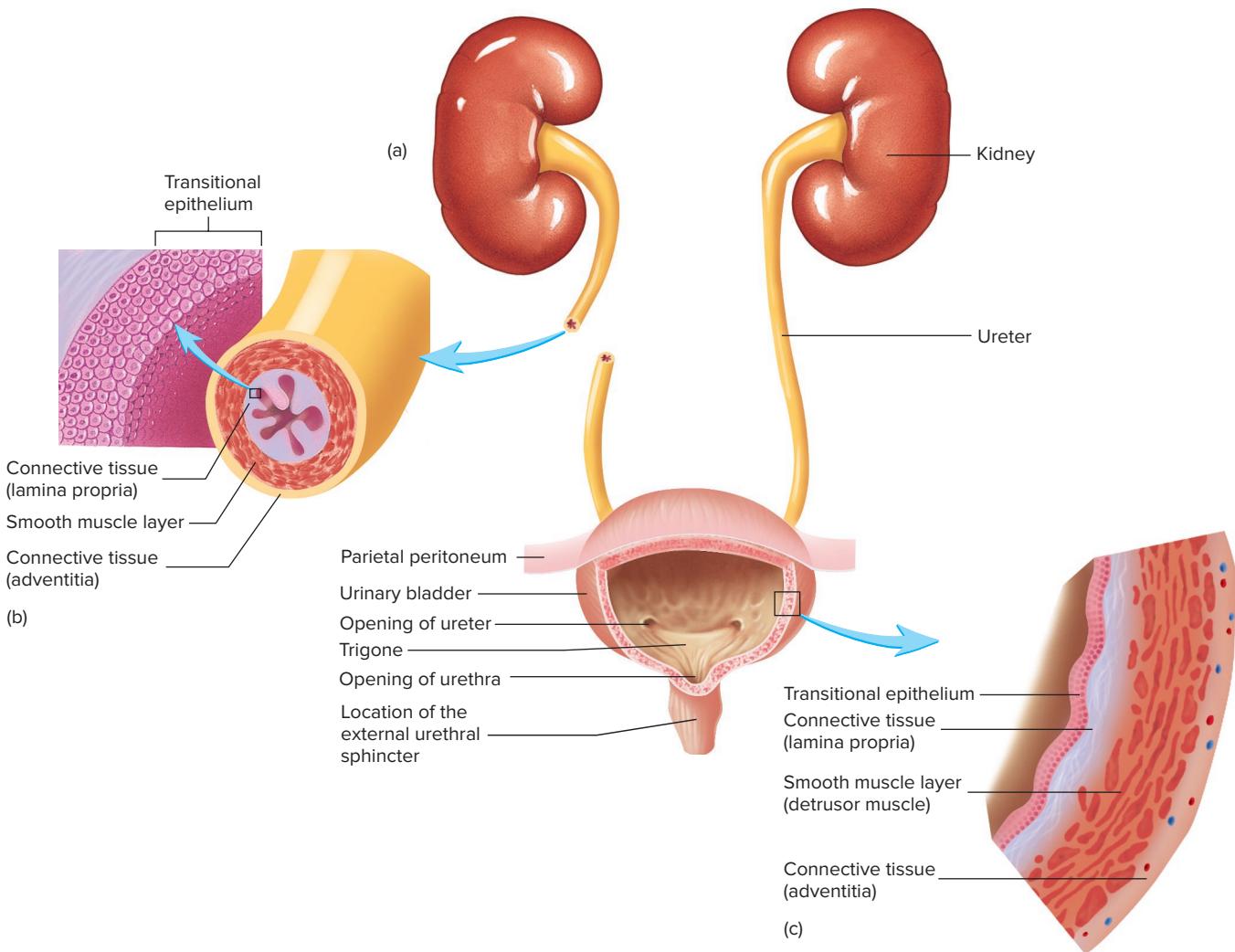


FIGURE 26.22 Ureters and Urinary Bladder

(a) Ureters extend from the pelvis of the kidney to the urinary bladder. (b) The walls of the ureters and the urinary bladder are lined with transitional epithelium, which is surrounded by a connective tissue layer (lamina propria), smooth muscle layers, and a fibrous adventitia. (c) Section through the wall of the urinary bladder.

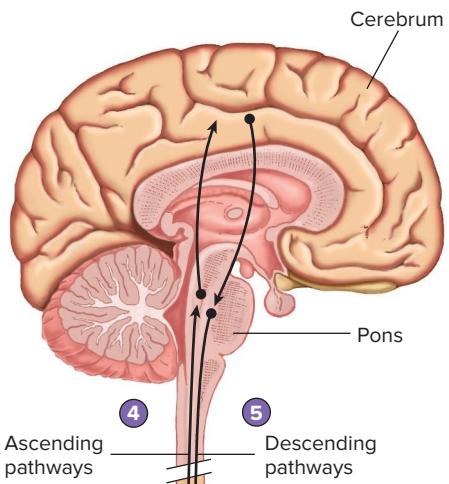
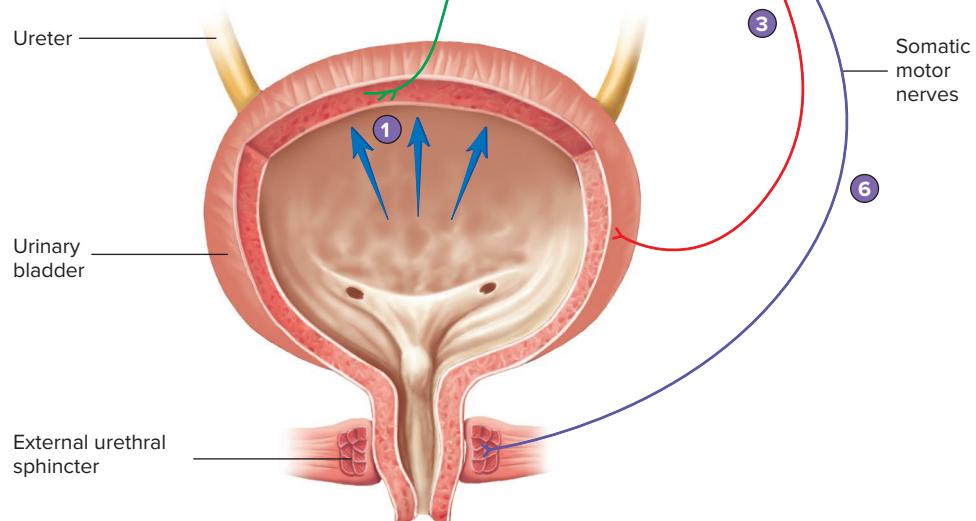
Urination is called **micturition** (mik'-choo-rish'un). The **micturition reflex** is activated when the urinary bladder wall is stretched as urine fills the urinary bladder. Integration of the micturition reflex occurs in the sacral region of the spinal cord and is modified by centers in the pons and cerebrum.

Urine filling the urinary bladder stimulates stretch receptors, which produce action potentials. The action potentials are carried by sensory neurons to the sacral segments of the spinal cord through the pelvic nerves. In response, action potentials travel to the urinary bladder through parasympathetic fibers in the pelvic nerves (figure 26.23). The parasympathetic action potentials cause the smooth muscle of the urinary bladder (the detrusor muscle) to contract. In addition, decreased somatic motor action potentials cause the external urethral sphincter, which consists of skeletal muscle, to relax. Urine flows from the urinary bladder when the pressure there is great enough to force the urine through the urethra while the external urethral sphincter is relaxed. The micturition reflex normally produces a series of contractions of the urinary bladder.

Action potentials carried by sensory neurons from stretch receptors in the urinary bladder wall also ascend the spinal cord to a micturition center in the pons and to the cerebrum. The micturition reflex integrated in the spinal cord is automatic, but it is either stimulated or inhibited by descending action potentials sent to the sacral region of the spinal cord. For example, higher brain centers prevent micturition by sending action potentials from the cerebrum and pons through spinal pathways to inhibit the spinal micturition reflex. Consequently, parasympathetic stimulation of the urinary bladder is inhibited, and somatic motor neurons that keep the external urethral sphincter contracted are stimulated. The micturition reflex, integrated in the spinal cord, predominates in infants. The ability to inhibit micturition voluntarily develops at the age of 2–3 years; subsequently, the influence of the pons and cerebrum on the spinal micturition reflex predominates.

The slow increase in internal pressure helps explain why there is little urge to urinate when the urinary bladder contains less than 300 mL. As stated previously, though, the pressure in the urinary

- ① Urine in the urinary bladder stretches the bladder wall.
- ② Action potentials produced by stretch receptors are carried along pelvic nerves (green line) to the sacral region of the spinal cord.
- ③ Action potentials are carried by parasympathetic nerves (red line) to contract the smooth muscles of the urinary bladder.
- ④ Ascending pathways carry an increased frequency of action potentials up the spinal cord to the pons and cerebrum when the urinary bladder becomes stretched. This increases the conscious urge to urinate.
- ⑤ Descending pathways carry action potentials to the sacral region of the spinal cord to tonically inhibit the micturition reflex, preventing automatic urination when the bladder is full. Descending pathways facilitate the reflex when stretch of the urinary bladder produces the conscious urge to urinate. This reinforces the micturition reflex.
- ⑥ The brain voluntarily controls the external urethral sphincter through somatic motor nerves (purple line), causing the sphincter to relax or constrict.



PROCESS FIGURE 26.23 Micturition Reflex

The micturition reflex is under parasympathetic regulation. **AP|R**

? How might the urinary bladder be affected by damage to spinal cord nerves in the sacrum?

bladder increases rapidly once its volume exceeds approximately 400 mL. In addition, the frequency of action potentials conducted by the ascending spinal pathways to the pons and cerebrum also increases, resulting in a stronger urge to urinate.

Voluntary initiation of micturition requires an increase in action potentials sent from the cerebrum to facilitate the micturition reflex and to voluntarily relax the external urethral sphincter. In addition, voluntary contraction of the abdominal

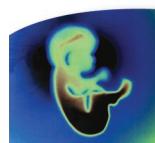
muscles increases abdominal pressure and thereby enhances the micturition reflex by increasing the pressure applied to the urinary bladder wall.

Normally, the urge to urinate results from stretch of the urinary bladder wall, but irritation of the urinary bladder or the urethra by a bacterial infection or some other condition can also initiate the urge to urinate, even if the urinary bladder is nearly empty.

If the spinal cord is damaged *above* the sacral region, no micturition reflex exists for a time; however, if the urinary bladder is emptied frequently, the micturition reflex eventually regains the ability to cause the urinary bladder to empty. Although a typical micturition reflex may exist, the person has no conscious control over its onset or duration. This condition is called **automatic bladder**.

On the other hand, if the spinal cord is damaged *in* the sacral region of the spinal cord, it eliminates the micturition reflex altogether. The urinary bladder is unable to contract even though the external urethral sphincter is relaxed. The urinary bladder fills to capacity, and urine is forced in a slow dribble through the external urethral sphincter.

In elderly people and in patients with damage to the brainstem or spinal cord, there is a reduction in inhibitory action potentials to the sacral region of the spinal cord. Without this inhibition, the sacral centers are hyperexcitable, and even a small amount of urine in the urinary bladder can elicit an uncontrollable micturition reflex.



Clinical IMPACT 26.3

Kidney Stones

Kidney stones are hard objects usually found in the pelvis of the kidney. They are typically 2–3 mm in diameter, with either a smooth or a jagged surface, but occasionally a large, branching kidney stone, called a **staghorn stone**, forms in the renal pelvis. About 1% of all autopsies reveal kidney stones, and many stones never cause symptoms. The symptoms associated with kidney stones occur when a stone passes into the ureter, resulting in referred pain down the back, side, and groin area. The ureter contracts around the stone, causing the stone to irritate the epithelium and produce bleeding, which appears as blood in the urine, a condition called **hematuria**. In addition to causing intense pain, kidney stones can block the ureter, cause ulceration in the ureter, and increase the probability of bacterial infection.

About 65% of all kidney stones are composed of calcium oxylate mixed with calcium phosphate, whereas another 15% are magnesium ammonium phosphate and 10% are uric acid or cystine; approximately 2.5% of each kidney stone is composed of mucoprotein.

The cause of kidney stones is usually obscure. Predisposing conditions include concentrated urine and an abnormally high calcium concentration in the urine, although the cause of the high calcium concentration is usually unknown. Magnesium ammonium phosphate stones are often found in people with recurrent kidney infections, and uric acid stones are common in people suffering from gout. Severe kidney stones must be surgically removed from the kidney. However, traditional surgical procedures have mainly been replaced by **lithotripsy** (lith’ō-trip-sē), in which kidney stones are pulverized using ultrasound or lasers.

ASSESS YOUR PROGRESS

44. What are the functions of the ureters, urinary bladder, and urethra? Describe their structure, including the epithelial lining of their inner surfaces.
45. What is the trigone?
46. What force moves urine through the nephron and ureters?
47. Explain the ability of the urinary bladder to distend.
48. Describe the micturition reflex. How is voluntary control of micturition accomplished?

26.7 Effects of Aging on the Kidneys

LEARNING OUTCOME

After reading this section, you will be able to

- A. Describe the effects of aging on the kidneys.

Aging causes the kidneys to gradually decrease in size. This decrease can begin as early as age 20 but becomes obvious by age 50 and continues throughout the remainder of life. The decrease in kidney size appears to be related to changes in the blood vessels of the kidney. The amount of blood flowing through the kidneys gradually decreases. Starting at age 20, there appears to be an approximately 10% decrease every 10 years. Small arteries, including the afferent and efferent arterioles, become irregular and twisted. Functional glomeruli are destroyed. By age 80, 40% of the glomeruli are not functioning. About 30% of the glomeruli that stop functioning no longer have a lumen through which blood flows. Other glomeruli thicken and assume a structure similar to that of arterioles. Some renal tubules and collecting ducts become thicker, shorter, and more irregular in structure. The capacity to secrete and absorb declines, and whole nephrons stop functioning. The kidney's ability to concentrate urine gradually declines. Eventually, changes in the kidney increase the risk for dehydration because of the kidney's reduced ability to produce a concentrated urine. The ability to eliminate uric acid, urea, creatine, and toxins from the blood also decreases.

An age-related loss of responsiveness to ADH and to aldosterone occurs. The kidney decreases renin secretion and has a reduced ability to participate in vitamin D synthesis, which contributes to Ca^{2+} deficiency, osteoporosis, and bone fractures.

Recall that one-third of one kidney is required to maintain homeostasis, and the additional kidney tissue beyond this constitutes a reserve capacity. Therefore, the age-related changes in the kidney reduce the kidney's reserve capacity. As the functional kidney mass is reduced substantially in older people, high blood pressure, atherosclerosis, and diabetes have greater adverse effects.

ASSESS YOUR PROGRESS

49. Discuss the effect of aging on the kidneys. Why do the kidneys gradually decrease in size?



Background Information

A large piece of machinery overturned at a construction site, severely crushing Roger's legs. Because Roger was trapped for several hours, his blood pressure decreased to very low levels (hypotension) due to blood loss, edema in the inflamed tissues, and emotional shock. Doctors administered both intravenous saline solutions and blood transfusions to return his blood pressure to its normal range. Twenty-four hours after the accident, however, Roger's urine volume began to decrease. His urinary Na^+ concentration increased, but his urine osmolality decreased. In addition, cellular debris was evident in his urine.

For approximately 7 days, Roger required renal dialysis to maintain his blood volume and ion concentrations within normal ranges. After about 3 weeks, his kidney function slowly began to improve, although many months passed before it was back to normal. In Roger's case, the events after 24 hours are consistent with acute renal failure caused by prolonged low blood pressure and lack of blood flow to the kidneys. The reduced blood flow was severe enough to cause damage to the epithelial lining of the renal tubules. The period of reduced urine volume resulted from the tubule damage. Dead and damaged tubule cells sloughed off into the tubules and blocked them, so that filtrate could not flow through. In addition, the filtrate leaked from the blocked or partially blocked tubules back into the interstitial spaces and therefore back into the blood. As a result, the amount of filtrate that became urine was markedly reduced.

Blood levels of urea and creatine usually increase due to reduced filtrate formation and reduced function of the tubule epithelium. A small amount of urine is produced that has a high Na^+ concentration,

although the osmolality is usually close to the concentration of the body fluids. The kidney is not able to reabsorb Na^+ , nor can it effectively concentrate urine.

Treatments for Renal Failure

Hemodialysis (*hē'mō-dī-al'i-sis*) is used when a person is suffering from severe acute or chronic kidney failure. The procedure substitutes for the excretory functions of the kidney. Hemodialysis is based on blood flow through tubes composed of a selectively permeable membrane. Blood is usually taken from an artery, passed through tubes of the dialysis machine, and then returned to a vein (figure 26.24). On the outside of the dialysis tubes is a fluid, called dialysis fluid, which contains the same concentration of solutes as normal plasma, except for the metabolic waste products. As a consequence, the metabolic wastes diffuse from the blood to the dialysis fluid. The dialysis membrane has pores that are too small to allow plasma proteins to pass through them, and because the dialysis fluid contains the same beneficial solutes as the plasma, the net movement of these substances is zero. **Peritoneal** (*per'i-tō-nē'äl*) **dialysis** is sometimes used to treat kidney failure. The principles by which peritoneal dialysis works are the same as for hemodialysis, but the dialysis fluid flows through a tube inserted into the peritoneal cavity. The visceral and parietal peritonea act as the dialysis membrane. Waste products diffuse from the blood vessels beneath the peritoneum, across the peritoneum, and into the dialysis fluid.

Kidney transplants are sometimes performed on people who have severe renal failure. Often, the donor has suffered an accidental death and had granted permission to have his or her kidneys used for transplantation. The major cause of kidney transplant failure is rejection by the recipient's immune system. Physicians therefore attempt to match the immune

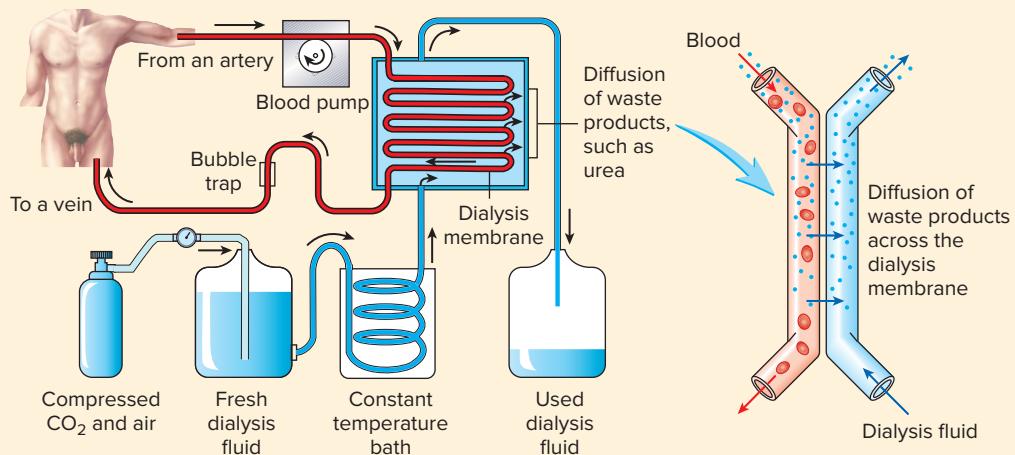
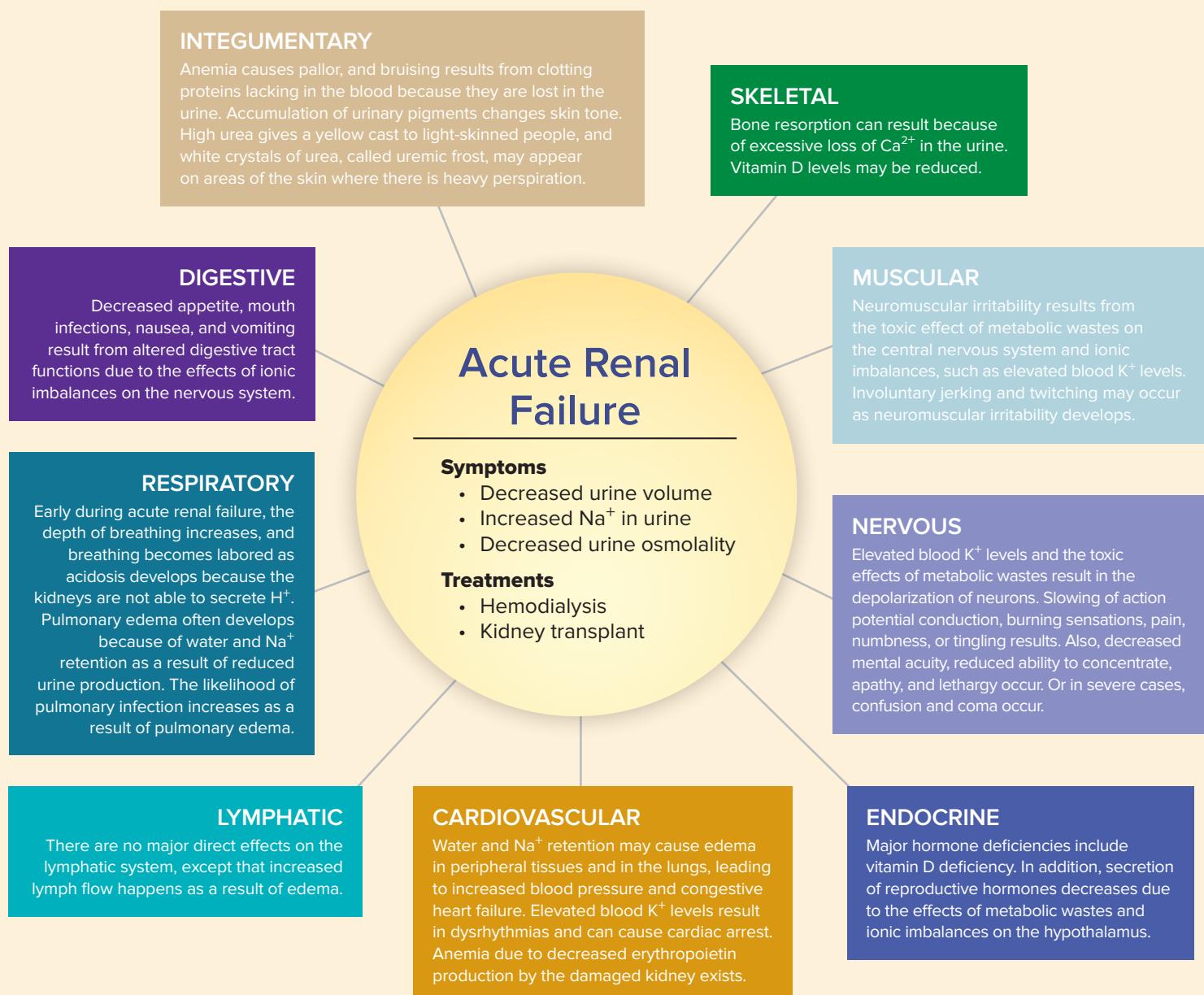


FIGURE 26.24 Hemodialysis

During hemodialysis, blood flows through a system of tubes composed of a selectively permeable membrane. Dialysis fluid, which has a composition similar to that of normal blood (except that the concentration of waste products is very low), flows in the opposite direction on the outside of the dialysis tubes. Waste products, such as urea, diffuse from the blood into the dialysis fluid. Other substances, such as Na^+ , K^+ , and glucose, can diffuse from the blood into the dialysis fluid if they are present in higher-than-normal concentrations, because these substances are present in the dialysis fluid at the same concentrations found in normal blood.

**FIGURE 26.25 Acute Renal Failure**

Acute renal failure has significant effects on other other organ systems in the body, as this diagram illustrates.

characteristics of the donor and recipient to reduce the tendency for rejection. Even with careful matching, recipients have to take medication for the rest of their lives to suppress their immune reactions. In most cases, the transplanted kidney functions well, and the tendency of the recipient's immune system to reject the transplanted kidney can be controlled. Figure 26.25 demonstrates the effects on other organ systems of acute renal failure.

► Predict 8

Nine days after the accident, Roger began to appear pale, became dizzy on standing, and was very weak and lethargic. His hematocrit was elevated and his heart was arrhythmic. Explain these manifestations.

TABLE 26.5 Representative Diseases and Disorders of the Urinary System

Kidney Disorders	Description
Inflammation of the Kidneys	
Glomerulonephritis (glō-mār'ū-lō-ne-frī'tis)	Inflammation of the filtration membrane within the renal corpuscle, causing an increase in the filtration membrane's permeability; plasma proteins and blood cells enter the filtrate, which increases urine volume due to increased osmotic concentration of the filtrate
Acute glomerulonephritis	Often occurs 1–3 weeks after a severe bacterial infection, such as "strep throat"; normally subsides after several days
Chronic glomerulonephritis	Long-term, progressive process whereby the filtration membrane thickens and is eventually replaced by connective tissue; the kidneys become nonfunctional
Pyelonephritis (pi'ē-lō-ne-frī'tis)	Often begins as a bacterial, usually <i>E. coli</i> , infection of the renal pelvis, which spreads to the rest of the kidney; the infection can destroy nephrons, dramatically reducing the kidney's ability to concentrate urine
Renal Failure	
Acute renal failure	Can result from any condition that interferes with kidney function
Chronic renal failure	Occurs when damage to the kidney is rapid and extensive; leads to accumulation of wastes in the blood; if renal failure is complete, death can occur in 1–2 weeks
	Caused by permanent damage to so many nephrons that the remaining nephrons are inadequate for normal kidney function; can result from chronic glomerulonephritis, trauma to the kidneys, tumors, or kidney stones

Answer

Learn to Predict

We read in this chapter that chronic renal failure is caused by a decrease in the number of functional nephrons in the kidneys, which is common in type 2 diabetics, such as Bobbie. Renal failure is most likely the result of damage to the glomerular basement membrane due to increased glomerular pressure and the production of advanced glycosylation end products, both of which are common side effects of type 2 diabetes.

Because Bobbie's renal failure means her kidneys have a dramatically reduced filtration function, we would expect Bobbie's blood tests to reveal high levels of glucose, K⁺, and creatinine and low levels of Na⁺. In addition, the creatinine clearance rate would be below normal, and there would be substantial protein in the urine. The increased blood glucose level results from a decrease in the tubular maximum for glucose reabsorption due to fewer functional nephrons. Similarly, the tubular maximum for Na⁺ is decreased, and the kidneys' ability to secrete K⁺ also decreases.

Consequently, blood Na⁺ levels decrease and blood K⁺ levels increase. The low creatinine clearance rate is consistent with a decreased number of functional nephrons, and protein in the urine reflects the increased permeability of the filtration membrane in the remaining nephrons. The puffiness of Bobbie's face indicates that fluid is being retained, which is consistent with the increase in blood pressure.

The consequences for Bobbie are severe. She needs to take precautions to make it easier for the remaining nephrons to maintain homeostasis—for example, by carefully regulating her blood glucose and controlling the hypertension. If her condition continues to worsen, she may have to resort to dialysis and consider a kidney transplant.

Answers to the odd-numbered Predict questions from this chapter appear in appendix E.

Summary

26.1 Functions of the Urinary System

1. The urinary system consists of the kidneys, ureters, urinary bladder, and urethra.
2. The urinary system eliminates wastes; regulates blood volume, ion concentration, and pH; and is involved with red blood cell and vitamin D production.

26.2 Kidney Anatomy and Histology

Location and External Anatomy of the Kidneys

1. A kidney lies behind the peritoneum on the posterior abdominal wall on each side of the vertebral column.
2. The renal capsule surrounds each kidney, and adipose tissue and the renal fascia engulf each kidney and anchor it to the abdominal wall.

- Blood vessels and nerves enter and exit the kidney at the hilum, on the medial side of each kidney, which opens into the renal sinus, containing fat and connective tissue.

Internal Anatomy and Histology of the Kidneys

- The two major regions of the kidney are the cortex and the medulla.
 - The renal columns extend toward the medulla between the renal pyramids.
 - The renal pyramids of the medulla project to the minor calyces.
- The minor calyces open into the major calyces, which open into the renal pelvis. The renal pelvis leads to the ureter.
- The functional unit of the kidney is the nephron. The parts of a nephron are the renal corpuscle, the proximal convoluted tubule, the loop of Henle, and the distal convoluted tubule.
 - The renal corpuscle consists of the Bowman capsule and the glomerulus. Materials leave the blood in the glomerulus and enter the Bowman capsule through the filtration membrane.
 - The renal tubule empties through the distal convoluted tubule into a collecting duct.
- The juxtaglomerular apparatus consists of the macula densa (part of the distal convoluted tubule) and the juxtaglomerular cells of the afferent arteriole.

Arteries and Veins of the Kidneys

- Arteries branch as follows: renal artery to segmental artery to interlobar artery to arcuate artery to interlobular artery to afferent arteriole.
- Afferent arterioles supply the glomeruli.
- Efferent arteries from the glomeruli supply the peritubular capillaries and vasa recta.
- Veins form from the peritubular capillaries as follows: interlobular vein to arcuate vein to interlobar vein to renal vein.

26.3 Urine Production

Urine is produced by filtration, tubular reabsorption, and tubular secretion.

Filtration

- The renal filtrate is plasma minus blood cells and blood proteins. Most (99%) of the filtrate is reabsorbed.
- The filtration membrane is composed of a fenestrated endothelium, a basement membrane, and the slitlike pores formed by podocytes.
- Filtration pressure is responsible for filtrate formation.
 - Filtration pressure is glomerular capillary pressure minus capsular hydrostatic pressure minus blood colloid osmotic pressure.
 - Filtration pressure changes are primarily caused by changes in glomerular capillary pressure.

Regulation of Glomerular Filtration Rate

- Two important mechanisms regulating GFR are autoregulation and sympathetic stimulation.
- Autoregulation dampens systemic blood pressure changes by altering afferent arteriole diameter.
- Sympathetic stimulation decreases afferent arteriole diameter.

Tubular Reabsorption

- Filtrate is reabsorbed by passive transport, including simple diffusion and facilitated diffusion. Filtrate is also reabsorbed through active transport and symport. Materials move from the renal tubule into the peritubular capillaries.

- Specialization of tubule segments
 - The thin segment of the loop of Henle is specialized for passive transport.
 - The rest of the renal tubules and collecting ducts perform active transport, symport, and passive transport.

- Substances transported
 - Active transport moves mainly Na^+ across the wall of the renal tubule. Other ions and molecules are moved primarily by symport.
 - Passive transport moves water, urea, and lipid-soluble, nonpolar compounds.

Tubular Secretion

- Substances enter the proximal or distal convoluted tubules and the collecting ducts.
- Hydrogen ions, K^+ , and some substances not produced in the body are secreted by antiport mechanisms.

Urine Concentration Mechanism

- The vasa recta, the loop of Henle, and the distribution of urea are responsible for the concentration gradient in the medulla. The concentration gradient is necessary for the production of concentrated urine.
- Production of urine
 - In the proximal convoluted tubule, Na^+ and other substances are removed by active transport. Water follows passively, filtrate volume is reduced 65%, and the filtrate concentration is 300 mOsm/L.
 - In the descending limb of the loop of Henle, water exits passively and solute enters. The filtrate volume is reduced 15%, and the osmolality of the filtrate concentration is 1200 mOsm/kg.
 - In the ascending limb of the loop of Henle, Na^+ , Cl^- , and K^+ are actively transported out of the filtrate, but water remains because this segment of the renal tubule is impermeable to water. The osmolality of the filtrate concentration is 100 mOsm/kg.

26.4 Regulation of Urine Concentration and Volume

Hormonal Mechanisms

- Aldosterone, produced in the adrenal cortex, affects Na^+ and Cl^- transport in the distal convoluted tubule and collecting ducts.
 - A decrease in aldosterone results in less Na^+ reabsorption and an increase in urine concentration and volume. An increase in aldosterone results in greater Na^+ reabsorption and a decrease in urine concentration and volume.
 - Aldosterone production is stimulated by angiotensin II, increased blood K^+ concentration, and decreased blood Na^+ concentration.
- Renin, produced by the kidneys, causes the production of angiotensin II.
 - Angiotensin II acts as a vasoconstrictor and stimulates aldosterone secretion, causing a decrease in urine production and an increase in blood volume.
 - Decreased blood pressure or decreased Na^+ concentration stimulates renin production.
- ADH, secreted by the posterior pituitary, increases water permeability in the distal convoluted tubules and collecting ducts.
 - ADH decreases urine volume, increases blood volume, and thus increases blood pressure.
 - ADH release is stimulated by increased blood osmolality or decreased blood pressure.
 - Water movement out of the distal convoluted tubules and collecting ducts is regulated by ADH. If ADH is absent, water is not reabsorbed, and a dilute urine is produced. If ADH is present, water moves out, and a concentrated urine is produced.

4. Atrial natriuretic hormone, produced by the heart when blood pressure increases, inhibits ADH production and reduces the kidney's ability to concentrate urine.

26.5 Plasma Clearance and Tubular Maximum

1. Plasma clearance is the volume of plasma that is cleared of a specific substance each minute.
2. Tubular load is the total amount of a substance that enters the renal tubule each minute.
3. Tubular maximum is the fastest rate at which a substance is reabsorbed from the renal tubule.

26.6 Urine Movement

Anatomy and Histology of the Ureters and Urinary Bladder

1. Structure
 - The walls of the ureter and urinary bladder consist of the epithelium, the lamina propria, a muscular coat, and a fibrous adventitia.
 - The transitional epithelium permits changes in size.

2. Function

- The ureters transport urine from the kidney to the urinary bladder.
- The urinary bladder stores urine.

Urine Flow Through the Nephron and Ureters

1. Hydrostatic pressure forces urine through the nephron.
2. Peristalsis moves urine through the ureters.

Micturition Reflex

1. Stretch of the urinary bladder stimulates a reflex that causes the urinary bladder to contract and inhibits the urethral sphincters.
2. Higher brain centers can stimulate or inhibit the micturition reflex.

26.7 Effects of Aging on the Kidneys

1. The kidneys gradually decrease in size due to a decrease in renal blood flow.
2. The number of functional nephrons decreases.
3. Renin secretion and vitamin D synthesis decrease.
4. The renal tubule's ability to secrete and absorb declines.

REVIEW AND COMPREHENSION



1. Which of these is *not* a general function of the kidneys?
 - a. regulation of blood volume
 - b. regulation of solute concentration in the blood
 - c. regulation of the pH of the extracellular fluid
 - d. regulation of vitamin A synthesis
 - e. regulation of red blood cell synthesis
2. The cortex of the kidney contains the

a. hilum.	c. adipose tissue.	e. renal pelvis.
b. glomeruli.	d. renal pyramids.	
3. Given these structures:

(1) major calyx	(3) renal papilla
(2) minor calyx	(4) renal pelvis

Choose the arrangement that lists the structures in order as urine leaves the collecting duct and travels to the ureter.

4. Which of these structures contain(s) blood?

a. glomerulus	d. Bowman capsule
b. vasa recta	e. Both a and b are correct.
c. distal convoluted tubule	
5. The juxtaglomerular cells of the _____ and the macula densa cells of the _____ form the juxtaglomerular apparatus.
 - a.fferent arteriole, proximal convoluted tubule
 - b.fferent arteriole, distal convoluted tubule
 - c.efferent arteriole, proximal convoluted tubule
 - d.efferent arteriole, distal convoluted tubule
6. Given these blood vessels:

(1) afferent arteriole	(3) glomerulus
(2) efferent arteriole	(4) peritubular capillaries

Choose the correct order as blood passes from an interlobular artery to an interlobular vein.

- a. 1,2,3,4
- b. 1,3,2,4
- c. 2,1,4,3
- d. 3,2,4,1
- e. 4,3,1,2

7. Which of these processes is responsible for kidney function?
 - a. filtration
 - b. secretion
 - c. reabsorption
 - d. Both a and b are correct.
 - e. All of these are correct.
8. The amount of plasma that enters the Bowman capsule per minute is the

a. GFR.	c. renal fraction.
b. renal plasma flow.	d. renal blood flow.
9. If the glomerular capillary pressure is 40 mm Hg, the capsular hydrostatic pressure is 10 mm Hg, and the blood colloid osmotic pressure within the glomerulus is 30 mm Hg, the filtration pressure is
 - 20 mm Hg.
 - 0 mm Hg.
 - 20 mm Hg.
 - 60 mm Hg.
 - 80 mm Hg.
10. Which of these conditions reduces filtration pressure in the glomerulus?
 - a. elevated blood pressure
 - b. constriction of the afferent arterioles
 - c. decreased plasma protein in the glomerulus
 - d. dilation of the afferent arterioles
 - e. decreased capsular hydrostatic pressure
11. If blood pressure increases by 50 mm Hg
 - a. the afferent arterioles constrict.
 - b. glomerular capillary pressure increases by 50 mm Hg.
 - c. GFR increases dramatically.
 - d. efferent arterioles constrict.
 - e. All of these are correct.
12. Glucose is usually completely reabsorbed from the filtrate by the time the filtrate has reached the

a. end of the proximal convoluted tubule.
b. bend of the loop of Henle.
c. end of the distal convoluted tubule.
d. end of the collecting duct.
e. Bowman capsule.

13. The greatest volume of water is reabsorbed from the renal tubule by the
 a. proximal convoluted tubule. c. distal convoluted tubule.
 b. loop of Henle. d. collecting duct.
14. Water leaves the renal tubule by
 a. active transport. d. facilitated diffusion.
 b. filtration into the capillary network. e. symport.
 c. osmosis.
15. Potassium ions enter the _____ by _____.
 a. proximal convoluted tubule, diffusion
 b. proximal convoluted tubule, active transport
 c. distal convoluted tubule, diffusion
 d. distal convoluted tubule, antiport
16. Reabsorption of most solute molecules from the proximal convoluted tubule is linked to the active transport of Na^+ across the
 a. apical membrane and out of the cell.
 b. apical membrane and into the cell.
 c. basal membrane and out of the cell.
 d. basal membrane and into the cell.
17. Which of these ions is used to symport amino acids, glucose, and other solutes through the apical membrane of tubule cells?
 a. K^+ b. Na^+ c. C^- d. Ca^{2+} e. Mg^{2+}
18. Which of the following contributes to the formation of a hyperosmotic environment in the medulla of the kidney?
 a. the effects of ADH on water permeability of the ascending limb of the loop of Henle
 b. the impermeability of the ascending limb of the loop of Henle to water
 c. the symport of Na^+ , K^+ , and Cl^- out of the ascending limb of the loop of Henle
 d. Both a and c are correct.
 e. Both b and c are correct.
19. At which of these sites is the osmolality of the filtrate at its lowest (lowest concentration)?
 a. glomerular capillary d. initial section of the distal convoluted tubule
 b. proximal convoluted tubule e. collecting duct
 c. bend of the loop of Henle
20. Increased aldosterone causes
 a. increased reabsorption of Na^+ .
 b. decreased blood volume.
 c. decreased reabsorption of Cl^- .
 d. increased permeability of the distal convoluted tubule to water.
 e. increased volume of urine.
21. Juxtaglomerular cells are involved in the secretion of
 a. ADH. c. aldosterone.
 b. angiotensin. d. renin.
22. Angiotensin II
 a. causes vasoconstriction. d. increases the sensation of thirst.
 b. stimulates aldosterone secretion. e. All of these are correct.
 c. stimulates ADH secretion.
23. ADH governs the
 a. Na^+ pump of the proximal convoluted tubules.
 b. water permeability of the loop of Henle.
 c. Na^+ pump of the vasa recta.
 d. water permeability of the distal convoluted tubules and collecting ducts.
 e. Na^+ reabsorption in the proximal convoluted tubule.
24. A decrease in blood osmolality results in
 a. increased ADH secretion.
 b. increased permeability of the collecting ducts to water.
 c. decreased urine osmolality.
 d. decreased urine output.
 e. All of these are correct.
25. The amount of a substance that passes through the filtration membrane into the renal tubule per minute is the
 a. renal plasma flow. c. plasma clearance.
 b. tubular load. d. tubular maximum.
26. The urinary bladder
 a. is composed of skeletal muscle.
 b. is lined by simple columnar epithelium.
 c. is connected to the outside of the body by the ureter.
 d. is located in the pelvic cavity.
 e. has two urethras and one ureter attached to it.

Answers appear in appendix F.

CRITICAL THINKING

- To relax after an anatomy and physiology examination, Rob goes to a local bistro and drinks 2 quarts of low-sodium beer. What effect does this beer have on urine concentration and volume? Explain the mechanisms involved.
- Harry is doing yard work one hot summer day and refuses to drink anything until he is finished. He then drinks glass after glass of plain water. Assuming that he drinks enough water to replace all the water he lost as sweat, how does this much water affect urine concentration and volume? Explain the mechanisms involved.
- A patient has the following symptoms: slight increase in extracellular fluid volume, large decrease in plasma sodium concentration, very concentrated urine, and cardiac fibrillation. An imbalance of what hormone is responsible for these symptoms? Are the symptoms caused by oversecretion or undersecretion of the hormone?
- Propose several ways to decrease the GFR.
- Design a kidney that can produce hyposmotic urine, which is less concentrated than plasma, or hyperosmotic urine, which is more

concentrated than plasma, by the active transport of water instead of Na^+ . Assume that the kidney's anatomical structure is the same as that in humans, but feel free to change anything else you choose.

- If only a very small amount of urea, instead of its normal concentration, were present in the interstitial fluid of the kidney, how would the kidney's ability to concentrate urine be affected?
- Some patients with hypertension are kept on a low-salt (low-sodium) diet. Propose an explanation for this therapy.
- Marvin was driving too fast on a remote mountain road at 3 a.m. when his car left the road and rolled down a steep hill. Marvin sustained numerous cuts and bruises. When medical help arrived 2 hours later, his systolic blood pressure was 70 mm Hg, and his pulse was weak (thready). Intravenous saline was administered immediately, and plasma and then whole blood were administered in the emergency room. After another hour, Marvin's blood pressure had returned to normal and he no longer appeared pale. While he was in the hospital, Marvin's urine volume decreased to less than 30 mL/h (<400 mL/day). A blood sample



indicated elevated blood levels of urea, creatinine, and uric acid. He also exhibited hyperkalemia and some cardiac arrhythmia, and his arterial pH was <7.35 (below normal). Over the next few days, his red blood cell count decreased and he bruised easily. His jugular veins were distended, and there was some peripheral and pulmonary edema. From the following list, select the conditions that applied to Marvin at this time.

- (1) hypoxic injury to the kidney
 - (2) increased reabsorption of wastes
 - (3) decreased H⁺ secretion
 - (4) decreased K⁺ secretion
 - (5) increased HCO₃⁻ reabsorption
 - (6) decreased erythropoietin secretion
- | | | |
|----------------|--------------|----------|
| a. 1,2,3,4,5,6 | c. 1,2,3,4 | e. 1,2,6 |
| b. 2,3,4,5 | d. 1,2,3,4,6 | |
9. Which of the following will help compensate for the low pH of the patient in question 8?
- a. increased respiration
 - b. increased HCO₃⁻ reabsorption

- c. increased H⁺ secretion
- d. All of these are correct.
- e. Both a and b are correct.

10. Renin-secreting tumors are usually found in the kidneys but rarely in other organs, such as the liver, lungs, pancreas, and ovaries. Predict the effects of renin-secreting tumors on blood K⁺ levels, and explain the effects on action potential conduction in nerves and muscle tissues.
11. Even though mutations of aquaporin-3 and aquaporin-4 in the collecting duct have not been described in the literature, if mutations occurred that resulted in a reduced number of these aquaporins in the cells of the collecting ducts, how would urine volume and concentration be affected? Would ADH be an effective treatment?

Answers to the odd-numbered questions appear in appendix G.