UNIT Five

Alterations in the Respiratory System

CHAPTER 19

Structure and Function of the Respiratory System

Respiration provides the body with a means of gas exchange. It is the process whereby oxygen from the air is transferred to the blood and carbon dioxide is eliminated from the body. The nervous system controls the movement of the respiratory muscles and adjusts the rate of breathing so that it matches the needs of the body during various levels of activity. The content in this chapter focuses on the structure and function of the respiratory system as it relates to these aspects of respiration. The function of the red blood cell in the transport of oxygen is discussed in Chapter 13.

STRUCTURAL ORGANIZATION OF THE RESPIRATORY SYSTEM

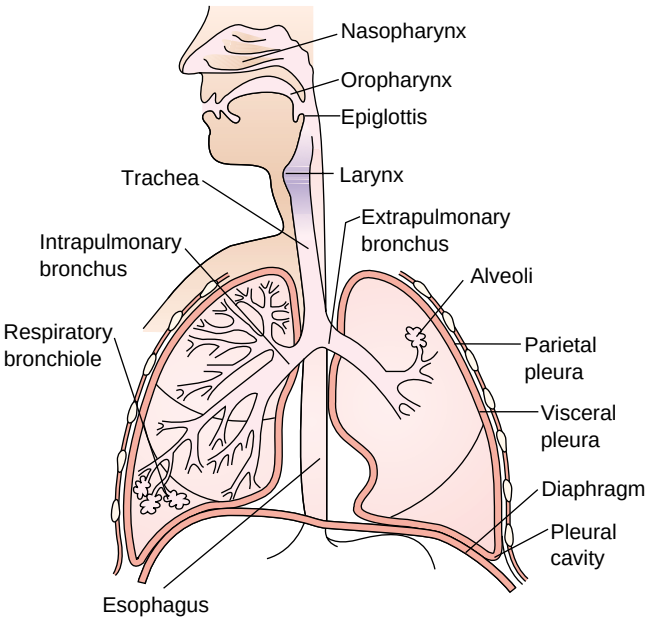
The respiratory system consists of the air passages and the lungs. Functionally, the respiratory system can be divided into two parts: the *conducting airways*, through which air moves as it passes between the atmosphere and the lungs, and the *respiratory tissues* of the lungs, where gas exchange takes place.

The Conducting Airways

The conducting airways consist of the nasal passages, mouth and pharynx, larynx, trachea, bronchi, and bronchioles (Fig. 19-1). The air we breathe is warmed, filtered, and moistened as it moves through these structures. Heat is transferred to the air from the blood flowing through the walls of the respiratory passages; the mucociliary blanket removes foreign materials; and water from the mucous membranes is used to moisten the air.

The conducting airways are lined with a pseudostratified columnar epithelium that contains a mosaic of mucus-secreting goblet cells and cells that contain hairlike projections called *cilia* (Fig. 19-2). The larger bronchi contain additional mucus-secreting glands that connect to the epithelium through long epithelial ducts. The epithelial layer gradually becomes thinner as it moves from the pseudostratified epithelium of the bronchi to cuboidal epithelium of the bronchioles and then to squamous epithelium of the alveoli. The mucus produced by the goblet cells in the conducting airways forms a layer, called the *mucociliary blanket*, that protects the respiratory system by entrapping dust and other foreign particles that enter the airways. The cilia, which constantly are in motion, move the mucociliary blanket with its entrapped particles in an escalator-like fashion toward the oropharynx, from which it is expectorated or swallowed. The function of the mucociliary blanket in clearing the lower airways and alveoli is optimal at normal oxygen levels and is impaired in situations of low and high oxygen levels. It is impaired by drying, such as breathing heated but unhumidified indoor air during winter. Cigarette smoking slows down or paralyzes the motility of the cilia. This slowing allows the residue from tobacco smoke, dust, and other particles to accumulate in the lungs, decreasing the efficiency of this pulmonary defense system.

The airways are kept moist by water contained in the mucous layer. Moisture is added to the air as it moves through the conducting airways. The capacity of the air to contain moisture or water vapor without condensation increases as the temperature rises. Thus, the air in the alveoli, which is maintained at body temperature, usually contains considerably more water vapor than the atmospheric-temperature air that we breathe. The difference between the water vapor contained in the air we breathe and that found in the alveoli is drawn from the moist surface of the mucous membranes that line the conducting airways and is a source of insensible water loss (see Chapter 6). Under normal conditions, approximately 1 pint of water per day is lost in humidifying the air breathed. During fever, the water vapor in the lungs increases, causing more water to be lost from the respiratory mucosa. In addition, fever usually is accompanied by an increase in respiratory rate so that more air passes through the airways, withdrawing moisture from its mucosal surface. As a result, respiratory secretions thicken, preventing free movement of the cilia and impairing the protective function of the mucociliary defense system. This is particularly true in persons whose water intake is inadequate.



■ **FIGURE 19-1** ■ Structures of the respiratory system.

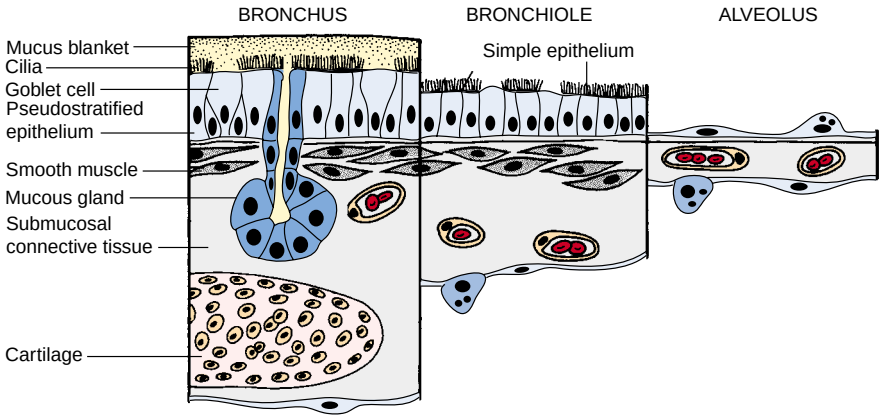
Nasopharyngeal Airways

The nose is the preferred route for the entrance of air into the respiratory tract during normal breathing. As air passes through the nasal passages, it is filtered, warmed, and humidified. The outer nasal passages are lined with coarse hairs, which filter and trap dust and other large particles from the air. The upper portion of the nasal cavity is lined with mucous membrane that contains a rich network of small blood vessels; this portion of the nasal cavity supplies warmth and moisture to the air we breathe.

The mouth serves as an alternative airway when the nasal passages are plugged or when there is a need for the exchange of large amounts of air, as occurs during exercise. The oropharynx extends posteriorly from the soft palate to the epiglottis. The oropharynx is the only opening between the nose and mouth and the lungs. Both swallowed food on its way to the esophagus and air on its way to the larynx pass through it. Obstruction of the oropharynx leads to immediate cessation of ventilation. Neural control of the tongue and pharyngeal muscles may be impaired in coma and certain types of neurologic disease. In these conditions, the tongue falls back into the pharynx and obstructs the airway, particularly if the person is lying on his or her back. Swelling of the pharyngeal structures caused by injury, infection, or severe allergic reaction also predisposes a person to airway obstruction, as does the presence of a foreign body.

Laryngotracheal Airways

The larynx connects the oropharynx with the trachea. The walls of the larynx are supported by firm cartilaginous structures that prevent collapse during inspiration. The functions of the larynx can be divided into two categories: those associated with speech and those associated with protecting the lungs from substances other than air. The larynx is located in a strate-

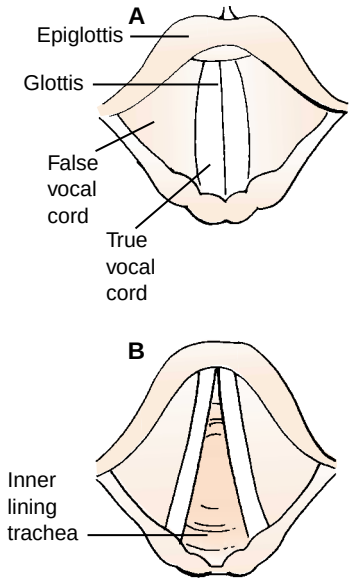


■ **FIGURE 19-2** ■ Airway wall structure: bronchus, bronchiole, and alveolus. The bronchial wall contains pseudostratified epithelium, smooth muscle cells, mucous glands, connective tissue, and cartilage. In smaller bronchioles, a simple epithelium is found, cartilage is absent, and the wall is thinner. The alveolar wall is designed for gas exchange, rather than structural support. (From Weibel E.R., Taylor R.C. [1988]. Design and structure of the human lung. In Fishman A.P. [ed.]. *Pulmonary diseases and disorders.* Vol. 1. [p. 14]. New York: McGraw-Hill. Reproduced with permission of the McGraw-Hill Companies)

gic position between the upper airways and the lungs and sometimes is referred to as the "watchdog of the lungs."

The cavity of the larynx is divided into two pairs of two-by-two folds of mucous membrane stretching from front to back with an opening in the midline (Fig. 19-3). The upper pair of folds, called the *vestibular folds*, has a protective function. The lower pair of folds has cordlike margins; they are termed the *vocal folds* because their vibrations are required for making vocal sounds. The true vocal folds and the elongated opening between them are called the *glottis*. A complex set of muscles controls the opening and closing of the glottis. Speech involves the intermittent release of expired air and opening and closing of the glottis. The epiglottis, which is located above the vocal folds, is a large, leaf-shaped piece of cartilage that is covered with epithelium. During swallowing, the free edges of the epiglottis move downward to cover the larynx, thus routing liquids and foods into the esophagus.

In addition to opening and closing the glottis for speech, the vocal folds of the larynx can perform a sphincter function in closing off the airways. When confronted with substances other than air, the laryngeal muscles contract and close off the airway. At the same time, the cough reflex is initiated as a means of removing a foreign substance from the airway. If the swallowing mechanism is partially or totally paralyzed, food and fluids can enter the airways instead of the esophagus when a person attempts to swallow. These substances are not easily removed; and when they are pulled into the lungs, they can cause a serious inflammatory condition called *aspiration pneumonia*.



■ **FIGURE 19-3** ■ Epiglottis and vocal cords viewed above with (**A**) glottis closed and (**B**) glottis open.

Tracheobronchial Tree

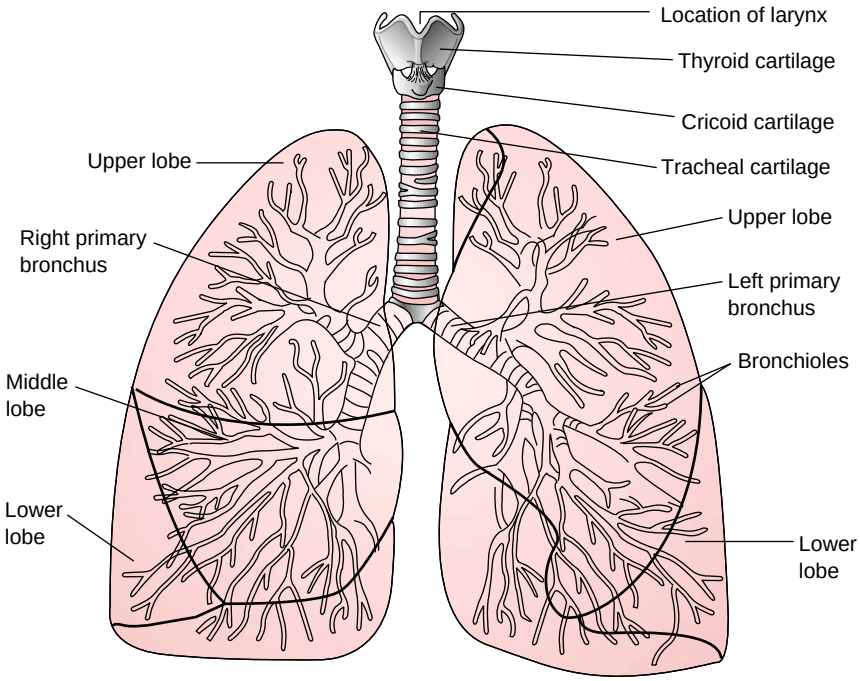
The tracheobronchial tree, which consists of the trachea, bronchi, and bronchioles, can be viewed as a system of branching tubes (Fig. 19-5). It is similar to a tree whose branches become smaller and more numerous as they divide. There are approximately 23 levels of branching, beginning with the conducting airways and ending with the respiratory airways, where gas exchange takes place (Fig. 19-5).

The trachea, or windpipe, is a continuous tube that connects the larynx and the major bronchi of the lungs (see Fig. 19-4). The walls of the trachea are supported by horseshoe-shaped cartilages, which prevent it from collapsing when the pressure in the thorax becomes negative.

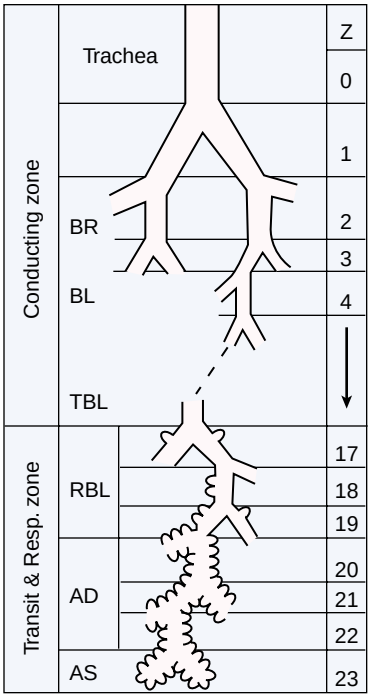
The trachea divides to form the right and the left primary bronchi. Each bronchus enters the lung through a slit called the hilus. The structure of the primary bronchi is similar to that of the trachea in that these airways are supported by cartilaginous rings.

Each primary bronchus divides into *secondary*, or *lobular*, *bronchi*, which supply each of the lobes of the lungs—three in the right lung and two in the left. The right middle lobe bronchus is of relatively small diameter and length and sometimes bends sharply near its bifurcation. It is surrounded by a collar of lymph nodes that drain the middle and the lower lobe and is particularly subject to obstruction. The secondary bronchi divide to form the segmental bronchi, which supply the bronchopulmonary segments of the lung. These segments are identified according to their location in the lung (*e.g.*, the apical segment of the right upper lobe) and are the smallest named units in the lung. Lung lesions such as atelectasis and pneumonia often are localized to a particular bronchopulmonary segment.

The bronchi continue to branch, forming smaller bronchi, until they become the terminal bronchioles, the smallest of



■ **FIGURE 19-4** ■ Larynx, trachea, and bronchial tree (anterior view).



■ **FIGURE 19-5** ■ Idealization of the human airways. The first 16 generations of branching (Z) make up the conducting airways, and the last seven constitute the respiratory zone (or transitional and respiratory zone). BR, bronchus; BL, bronchiole; TBL, terminal bronchiole; RBL, respiratory bronchiole; AD, alveolar ducts; AS, alveolar sacs. (Weibel E.R. [1962]. *Morphometry of the human lung* [p. 111]. Berlin: Springer-Verlag)

the conducting airways. As these bronchi branch and become smaller, this cartilaginous support becomes thinner and then disappears at the level of the respiratory bronchioles. Between the cartilaginous support and the mucosal surface are two criss-crossing layers of smooth muscle that wind in opposite directions (Fig. 19-6). Bronchospasm, or contraction of these muscles, causes narrowing of the bronchioles and impairs air flow. The epithelial lining of conducting airways gradually becomes reduced from pseudostratified epithelium in the bronchi to a thin layer of tightly joined epithelial cells in the alveoli.

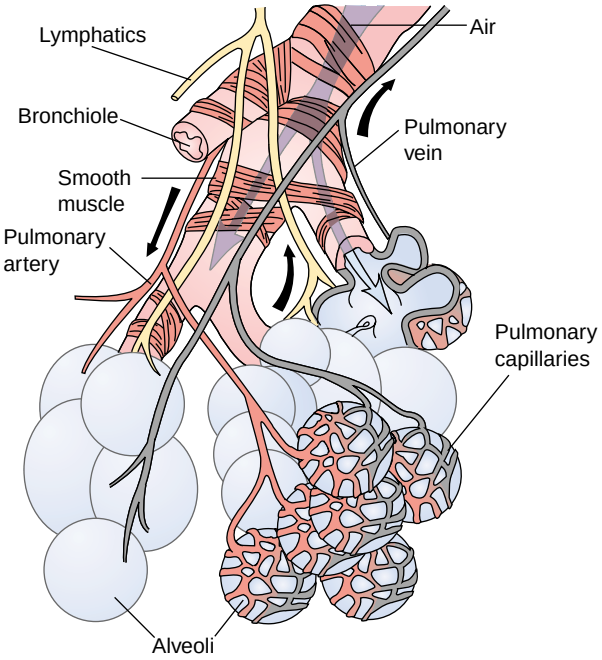
The Lungs and Respiratory Airways

The lungs are soft, spongy, cone-shaped organs located side by side in the chest cavity (see Fig. 19-1). They are separated from each other by the *mediastinum* (*i.e.*, the space between the lungs) and its contents—the heart, blood vessels, lymph nodes, nerve fibers, thymus gland, and esophagus. The upper part of the lung, which lies against the top of the thoracic cavity, is called the *apex*, and the lower part, which lies against the diaphragm, is called the *base*. The lungs are divided into lobes: three in the right lung and two in the left (see Fig. 19-4).

The lungs are the functional structures of the respiratory system. In addition to their gas exchange function, they inactivate vasoactive substances such as bradykinin; they convert angiotensin I to angiotensin II; and they serve as a reservoir for blood storage. Heparin-producing cells are particularly abundant in the capillaries of the lung, where small clots may be trapped.

Respiratory Lobules

The gas exchange function of the lung takes place in the lobules of the lungs. Each lobule, which is the smallest functional unit of the lung, is supplied by a branch of a terminal bron-



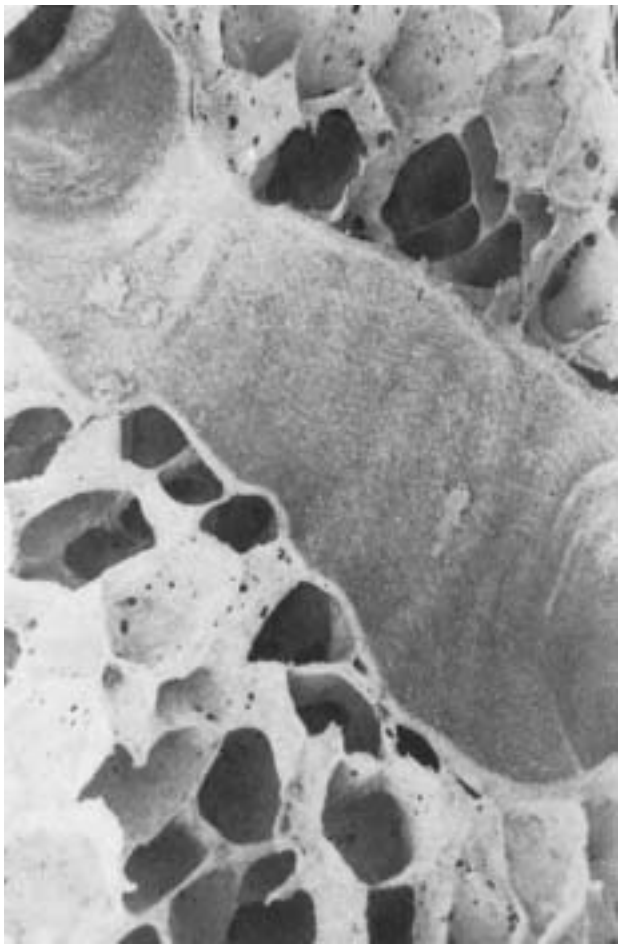
■ **FIGURE 19-6** ■ Lobule of the lung, showing the bronchial smooth muscle fibers, pulmonary blood vessels, and lymphatics.

chiole, an arteriole, the pulmonary capillaries, and a venule (see Fig. 19-6). Gas exchange takes place in the terminal respiratory bronchioles and the alveolar ducts and sacs. Blood enters the lobules through a pulmonary artery and exits through a pulmonary vein. Lymphatic structures surround the lobule and aid in the removal of plasma proteins and other particles from the interstitial spaces.

Unlike larger bronchi, the respiratory bronchioles are lined with simple epithelium, rather than ciliated pseudostratified epithelium. The respiratory bronchioles also lack the cartilaginous support of the larger airways. Instead, they are attached to the elastic spongework of tissue that contains the alveolar air spaces. When the air spaces become stretched during inspiration, the bronchioles are pulled open by expansion of the surrounding tissue.

The alveolar sacs are cup-shaped, thin-walled structures that are separated from each other by thin alveolar septa. Most of the septa are occupied by a single network of capillaries so that blood is exposed to air on both sides. There are approximately 300 million alveoli in the adult lung, with a total surface area of approximately 50 to 100 m^2. Unlike the bronchioles, which are tubes with their own separate walls, the alveoli are interconnecting spaces that have no separate walls (Fig. 19-7). As a result of this arrangement, there is a continual mixing of air in the alveolar structures.

The alveolar structures are composed of two types of cells: type I alveolar cells and type II alveolar cells (Fig. 19-8). The type I alveolar cells are flat squamous epithelial cells across which gas exchange takes place. The type II alveolar cells produce surfactant, a lipoprotein substance that decreases the surface tension in the alveoli. The alveoli also contain alveolar macrophages, which are responsible for the removal of offending substances from the alveolar epithelium.

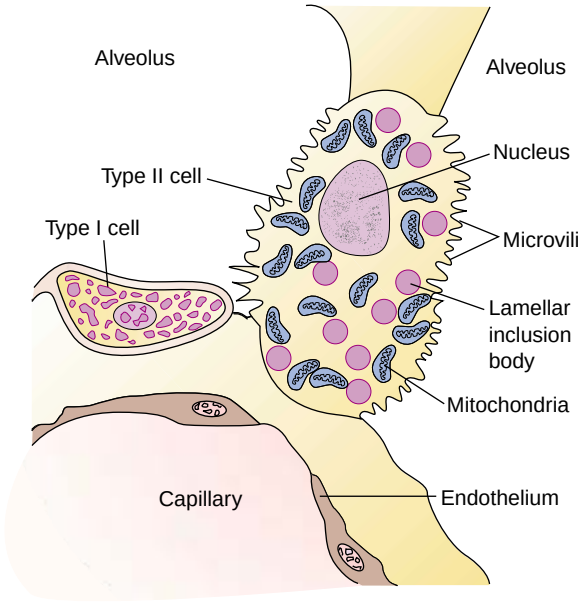


■ **FIGURE 19-7** ■ Close-up of a cross-section of a small bronchus and surrounding alveoli. (Courtesy of Janice A. Nowell, University of California, Santa Cruz)

Lung Circulation

The lungs are provided with a dual blood supply: the pulmonary and bronchial circulations. The pulmonary circulation arises from the pulmonary artery and provides for the gas exchange function of the lungs. Deoxygenated blood leaves the right heart through the pulmonary artery, which divides into a left pulmonary artery that enters the left lung and a right pulmonary artery that enters the right lung. Return of oxygenated blood to the heart occurs by way of the pulmonary veins, which empty into the left atrium.

The bronchial circulation distributes blood to the conducting airways and supporting structures of the lung. The bronchial circulation has a secondary function of warming and humidifying incoming air as it moves through the conducting airways. The bronchial arteries arise from the thoracic aorta and enter the lungs with the major bronchi, dividing and subdividing along with the bronchi as they move out into the lung, supplying them and other lung structures with oxygen. The capillaries of the bronchial circulation drain into the bronchial veins, the larger of which empties into the vena cava. The smaller of the bronchial veins empties into the pulmonary veins. This blood is unoxygenated because the bronchial circulation does



■ **FIGURE 19-8** ■ Schematic drawing of the two types of alveolar cells and their relation to alveoli and capillaries. Alveolar type I cells comprise most of the alveolar surface. Alveolar type II cells are located in the corner between two adjacent alveoli. Also shown are endothelial cells that line the pulmonary capillaries. (Rhoades R.A., Tanner G.A. [1996]. *Medical physiology* [p. 362]. Boston: Little, Brown).

not participate in gas exchange. As a result, this blood dilutes the oxygenated blood returning to the left side of the heart.

Pleura

A thin, transparent, double-layered serous membrane, called the *pleura*, lines the thoracic cavity and encases the lungs. The outer parietal layer lies adjacent to the chest wall, and the inner visceral layer adheres to the outer surface of the lung (see Fig. 19-1). The parietal pleura forms part of the mediastinum and lines the inner wall of the thoracic or chest cavity. A thin film of serous fluid separates the two pleural layers, and this allows the two layers to glide over each other and yet hold together, so there is no separation between the lungs and the chest wall. The pleural cavity is a potential space in which serous fluid or inflammatory exudate can accumulate. The term *pleural effusion* is used to describe an abnormal collection of fluid or exudate in the pleural cavity.

In summary, the respiratory system consists of the air passages and the lungs, where gas exchange takes place. Functionally, the air passages of the respiratory system can be structurally divided into two parts: the conducting airways, through which air moves as it passes into and out of the lungs, and the respiratory tissues, where gas exchange actually takes place. The conducting airways include the nasal passages, mouth and nasopharynx, larynx, and tracheobronchial tree. Air is warmed, filtered, and humidified as it passes through these structures.

The lungs are the functional structures of the respiratory system. In addition to their gas exchange function, they inactivate vasoactive substances such as bradykinin; they convert angiotensin I to angiotensin II; and they serve as a reservoir for blood. The lobules, which are the functional units of the lung, consist of the respiratory bronchioles, alveoli, and pulmonary capillaries. It is here that gas exchange takes place. Oxygen from the alveoli diffuses across the alveolar capillary membrane into the blood, and carbon dioxide from the blood diffuses into the alveoli.

The lungs are provided with a dual blood supply: the pulmonary circulation provides for the gas exchange function of the lungs, and the bronchial circulation distributes blood to the conducting airways and supporting structures of the lung. The lungs are encased in a thin, transparent, double-layered serous membrane called the *pleura*. The pressure in the pleural space, which is negative in relation to alveolar pressure, prevents the lungs from collapsing.

EXCHANGE OF GASES BETWEEN THE ATMOSPHERE AND THE LUNGS

Basic Properties of Gases

The air we breathe is made up of a mixture of gases, mainly nitrogen and oxygen. These gases exert a combined pressure called the *atmospheric pressure*. The pressure at sea level is defined as 1 atmosphere, which is equal to 760 millimeters of mercury (mm Hg) or 14.7 pounds per square inch (PSI). When measuring respiratory pressures, atmospheric pressure is assigned a value of 0. A respiratory pressure of +15 mm Hg means that the pressure is 15 mm Hg above atmospheric pressure, and a respiratory pressure of −15 mm Hg is 15 mm Hg less than atmospheric pressure. Respiratory pressures often are expressed in centimeters of water (cm H_2O) because of the small pressures involved (1 mm Hg = 1.35 cm H_2O pressure).

The pressure exerted by a single gas in a mixture is called the *partial pressure*. The capital letter "P" followed by the chemical symbol of the gas (PO_2) is used to denote its partial pressure. The law of partial pressures states that the total pressure of a mixture of gases, as in the atmosphere, is equal to the sum of the partial pressures of the different gases in the mixture. If the concentration of oxygen at 760 mm Hg (1 atmosphere) is 20%, its partial pressure is 152 mm Hg (760×0.20).

Water vapor is different from other types of gases; its partial pressure is affected by temperature but not atmospheric pressure. The relative humidity refers to the percentage of moisture in the air compared with the amount that the air can hold without causing condensation (100% saturation). Warm air holds more moisture than cold air. This is the reason that precipitation in the form of rain or snow commonly occurs when the relative humidity is high and there is a sudden drop in atmospheric temperature. The air in the alveoli, which is 100% saturated at normal body temperature, has a water vapor pressure of 47 mm Hg. The water vapor pressure must be included in the sum of the total pressure of the gases in the alveoli (*i.e.*, the total pressure of the other gases in the alveoli is 760 − 47 = 713 mm Hg).

Air moves between the atmosphere and the lungs because of a pressure difference. According to the laws of physics, the pressure of a gas varies inversely with the volume of its container, provided the temperature remains constant. If equal amounts of a gas are placed in two different-size containers, the pressure of the gas in the smaller container is greater than the pressure in the larger container. The movement of gases is always from the container with the greater pressure to the one with the lesser pressure. The chest cavity can be viewed as a volume container. During inspiration, the size of the chest cavity increases and air moves into the lungs; during expiration, air moves out as the size of the chest cavity decreases.

Ventilation and the Mechanics of Breathing

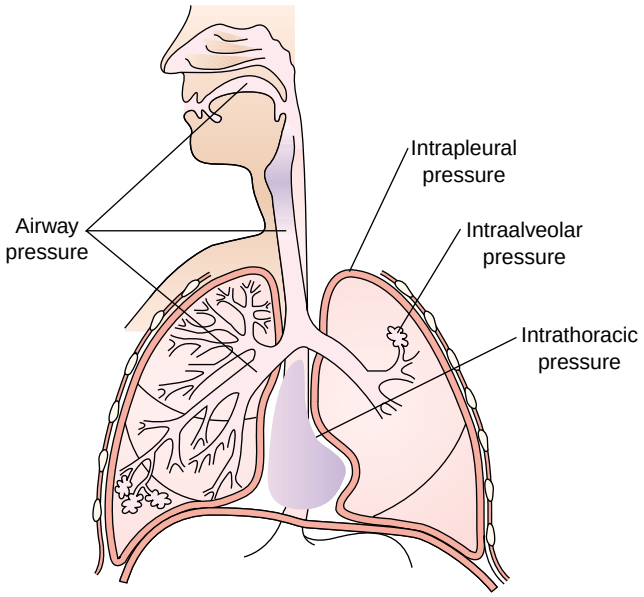
Ventilation is concerned with the movement of gases into and out of the lungs. It relies on a system of open airways and the respiratory pressures created as the movements of the respiratory muscles change the size of the chest cage. The degree to which the lungs inflate and deflate depends on the respiratory pressures inflating the lung, compliance of the lungs, and airway resistance.

Respiratory Pressures

The pressure inside the airways and alveoli of the lungs is called the *intrapulmonary pressure* or *alveolar pressure*. The gases in this area of the lungs are in communication with atmospheric pressure (Fig. 19-9). When the glottis is open and air is not moving into or out of the lungs, as occurs just before inspiration or expiration, the intrapulmonary pressure is zero or equal to atmospheric pressure.

The pressure in the pleural cavity is called the *intrapleural pressure*. The intrapleural pressure is always negative in relation to alveolar pressure, approximately –4 mm Hg between breaths when the glottis is open and the alveolar spaces are open to the atmosphere. The lungs and the chest wall have elastic properties, each pulling in the opposite direction. If removed from the chest, the lungs would contract to a smaller size, and the chest wall, if freed from the lungs, would expand. The opposing forces of the chest wall and lungs create a pull against the visceral and parietal layers of the pleura, causing the pressure in the pleural cavity to become negative. During inspiration, the elastic recoil of the lungs increases, causing intrapleural pressure to become more negative than during expiration. Without the negative intrapleural pressure holding the lungs against the chest wall, their elastic recoil properties would cause them to collapse. Although the intrapleural pressure of the inflated lung is always negative in relation to alveolar pressure, it may become positive in relation to atmospheric pressure (*e.g.*, during forced expiration and coughing).

The *intrathoracic pressure* is the pressure in the thoracic cavity. It is essentially equal to intrapleural pressure and is the pressure to which the lungs, heart, and great vessels are exposed. Forced expiration against a closed glottis (Valsalva maneuver) compresses the air in the thoracic cavity and produces marked increases in intrathoracic and intrapleural pressures.



■ **FIGURE 19-9** ■ Partitioning of respiratory pressures.

The Chest Cage and Respiratory Muscles

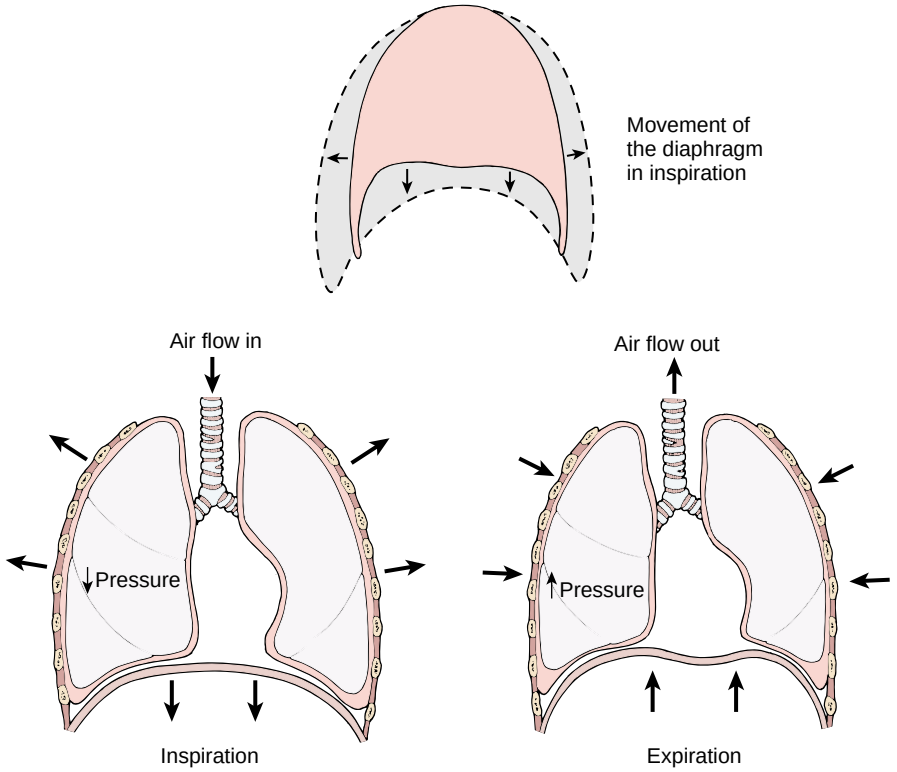
The lungs and major airways share the chest cavity with the heart, great vessels, and esophagus. The chest cavity is a closed compartment bounded on the top by the neck muscles and at the bottom by the diaphragm. The outer walls of the chest cavity are formed by 12 pairs of ribs, the sternum, the thoracic vertebrae, and the intercostal muscles that lie between the ribs. Mechanically, the act of breathing depends on the fact that the chest cavity is a closed compartment whose only opening to the exterior is the trachea.

Ventilation consists of inspiration and expiration. During *inspiration*, the size of the chest cavity increases, the intrathoracic pressure becomes more negative, and air is drawn into the lungs. *Expiration* occurs as the elastic components of the chest wall and lung structures that were stretched during inspiration recoil, causing the size of the chest cavity to decrease and the pressure in the chest cavity to increase (Fig. 19-10).

Inspiration. The diaphragm is the principal muscle of inspiration. When the diaphragm contracts, the abdominal contents are forced downward and the chest expands from top to bottom (Fig. 19-10). The diaphragm is innervated by the phrenic nerve roots, which arise from the cervical level of the spinal cord, mainly from C4 but also from C3 and C5.

The external intercostal muscles, which also aid in inspiration, connect to the adjacent ribs and slope downward and forward (Fig. 19-11). When they contract, they raise the ribs and rotate them slightly so that the sternum is pushed forward; this enlarges the chest from side to side and from front to back. The intercostal muscles receive their innervation from nerves that exit the central nervous system at the thoracic level of the spinal cord. Paralysis of these muscles usually does not have a serious effect on respiration because of the effectiveness of the diaphragm.

The accessory muscles of inspiration include the scalene muscles and the sternocleidomastoid muscles. The scalene muscles elevate the first two ribs, and the sternocleidomastoid muscles raise the sternum to increase the size of the chest cavity. These muscles contribute little to quiet breathing but



■ **FIGURE 19-10** ■ Movement of the diaphragm and changes in chest volume and pressure during inspiration and expiration. (**A**) Movement of diaphragm and expansion of the chest cavity during inspiration. (**B**) During inspiration, contraction of the diaphragm and expansion of the chest cavity produce a decrease in intrathoracic pressure, causing air to move into the lungs. (**C**) During expiration, relaxation of the diaphragm and chest cavity produce an increase in intrathoracic pressure, causing air to move out of the lungs.

contract vigorously during exercise. For the accessory muscles to assist in ventilation, they must be stabilized in some way. For example, persons with bronchial asthma often brace their arms against a firm object during an attack as a means of stabilizing their shoulders so that the attached accessory muscles can exert their full effect on ventilation. The head commonly is bent backward so that the scalene and sternocleidomastoid muscles can elevate the ribs more effectively. Other muscles that play a minor role in inspiration are the alae nasi, which produce flaring of the nostrils during obstructed breathing.

Expiration. Expiration is largely passive. It occurs as the elastic components of the chest wall and lung structures that were stretched during inspiration recoil, causing air to leave the lungs as the intrathoracic pressure increases. When needed, the abdominal and the internal intercostal muscles can be used to increase expiratory effort (see Fig. 19-11). The increase in intra-abdominal pressure that accompanies the forceful contraction of the abdominal muscles pushes the diaphragm upward and results in an increase in intrathoracic pressure. The internal intercostal muscles move inward, which pulls the chest downward, increasing expiratory effort.

Lung Compliance

Lung compliance refers to the ease with which the lungs can be inflated. It is determined by the elastin and collagen fibers of the lung, its water content, and surface tension. Compliance can be appreciated by comparing the ease of blowing up a new balloon that is stiff and noncompliant with one that has been previously blown up and stretched.

Specifically, lung compliance describes the change in lung volume that can be accomplished with a given change in respiratory pressure. The normal compliance of both lungs in the average adult is approximately 200 mL/cm H_2O. This means that every time the transpulmonary pressure increases by 1 cm/H_2O, the lung volume expands by 200 mL. It would take more pressure to move the same amount of air into a noncompliant lung.

Changes in Elastin/Collagen Composition of Lung Tissue. Lung tissue is made up of elastin and collagen fibers. The elastin fibers are easily stretched and increase the ease of lung inflation, whereas the collagen fibers resist stretching and make lung inflation more difficult. In lung diseases such as interstitial lung disease and pulmonary fibrosis, the lungs become stiff and noncompliant as the elastin fibers are replaced with scar tissue. Pulmonary congestion and edema produce a reversible decrease in pulmonary compliance.

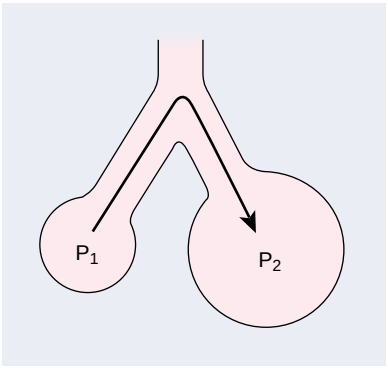
Elastic recoil describes the ability of the elastic components of the lung to recoil to their original position after having been stretched. Overstretching the airways, as occurs with emphysema, causes the elastic components of the lung to lose their recoil, making the lung easier to inflate but more difficult to deflate because of its inability to recoil.

Surface Tension. An important factor in lung compliance is the *surface tension* in the alveoli. The alveoli are lined with a thin film of liquid, and it is at the interface between this liquid film and the alveolar air that surface tension develops. This is because the forces that hold the liquid film molecules together are stronger than those that hold the air molecules together. In the alveoli, excess surface tension causes the liquid film to contract, making lung inflation more difficult.

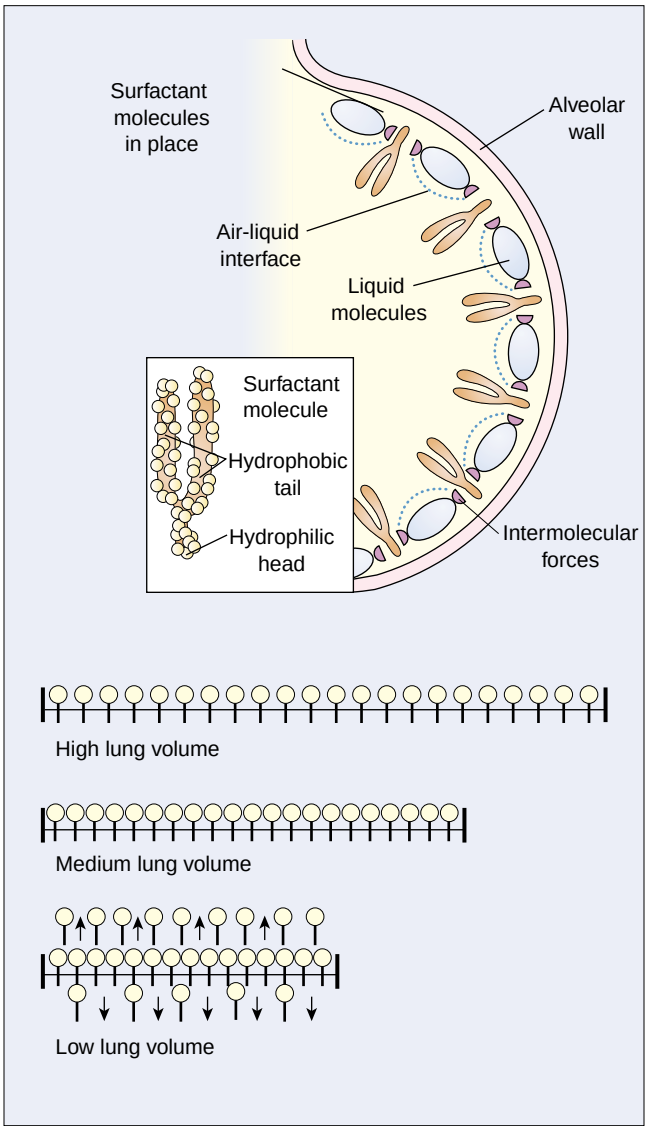
The pressure in the alveoli (which are modeled as spheres with open airways projecting from them) can be predicted using Laplace's law (pressure = 2 × surface tension/radius). If the surface tension were equal throughout the lungs, the alveoli with the smallest radii would have the greatest pressure, and this would cause them to empty into the larger alveoli (Fig. 19-12). The reason this does not occur is because of special surface tension-lowering molecules, called *surfactant*, that line the inner surface of the alveoli.

Surfactant is a complex mixture of lipoproteins (largely phospholipids) and small amounts of carbohydrates that is synthesized in the type II alveolar cells. The surfactant molecule has two ends: a hydrophobic (water-insoluble) tail and a hydrophilic (water-soluble) head (Fig. 19-13). The hydrophilic head of the surfactant molecule attaches to the liquid molecules and the hydrophobic tail to the gas molecules, interrupting the intermolecular forces that are responsible for creating the surface tension.

Surfactant exerts four important effects on lung inflation: (1) it lowers the surface tension; (2) it increases lung compliance and ease of inflation; (3) it provides for stability and more even inflation of the alveoli; and (4) it assists in preventing pulmonary edema by keeping the alveoli dry. Without surfactant, lung inflation would be extremely difficult, requiring an intrapleural pressure of –20 to –30 mm Hg, compared with the –3 to –5 mm Hg pressure that normally is needed. The surfactant molecules are more densely packed in the small alveoli



■ **FIGURE 19-12** ■ Law of Laplace (P = 2 T/r, P = pressure, T = tension, r = radius). The effect of the radius on the pressure and movement of gases in the alveolar structures is depicted. Air moves from P_1 with a small radius and higher pressure to P_2 with its larger radius and lower pressure.



■ **FIGURE 19-13** ■ (**Top**) Alveolar wall depicting surface tension resulting from the intramolecular forces in the air–liquid film interface; the surfactant molecule with its hydrophobic tail and hydrophilic head; and its function in reducing surface tension by disrupting the intermolecular forces. (**Bottom**) The surface concentration of surfactant molecules at high, medium, and low lung volumes.

than in larger alveoli, where the density of the molecules is less. Therefore, surfactant reduces the surface tension more effectively in the small alveoli, which have the greatest tendency to collapse, providing for stability and more even distribution of ventilation. Surfactant also helps to keep the alveoli dry and prevent pulmonary edema. This is because water is pulled out of the pulmonary capillaries into the alveoli when increased surface tension causes the alveoli to contract.

The type II alveolar cells that produce surfactant do not begin to mature until the 26th to 28th week of gestation; consequently, many premature infants have difficulty producing sufficient amounts of surfactant. This can lead to alveolar collapse and severe respiratory distress. This condition, called *infant respiratory distress syndrome*, is the single most common cause of respiratory disease in premature infants. Surfactant dysfunction also is possible in the adult. This usually occurs as the result of severe injury or infection and can contribute to the development of a condition called *acute respiratory distress syndrome* (see Chapter 21).

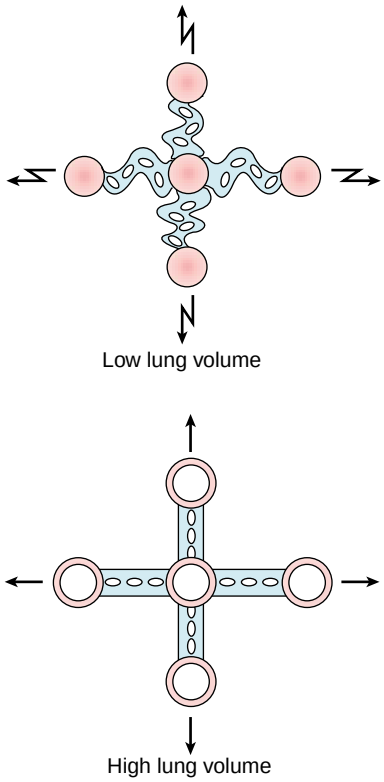
Airway Resistance

The volume of air that moves into and out of the air exchange portion of the lungs is directly related to the pressure difference between the lungs and the atmosphere and inversely related to the resistance that the air encounters as it moves through the airways. The effects of airway resistance on airflow can be illustrated using *Poiseuille's law*. According to Poiseuille's law, the resistance to flow is inversely related to the fourth power of the radius ($R = 1/r^4$). If the radius is reduced by one half, the resistance increases 16-fold ($2 \times 2 \times 2 \times 2 = 16$). Because the resistance of the airways is inversely proportional to the fourth power of the radius, small changes in airway caliber, such as those caused by pulmonary secretions or bronchospasm, can produce a marked increase in airway resistance.

Airway resistance is also affected by lung volumes, being less during inspiration than during expiration. This is because elastic-type fibers connect the outside of the airways to the surrounding lung tissues. As a result, these airways are pulled open as the lungs expand during inspiration, and they become narrower as the lungs deflate during expiration (Fig. 19-14). This is one of the reasons that persons with conditions that increase airway resistance, such as bronchial asthma, usually have less difficulty during inspiration than during expiration.

Airway Compression. Airflow through the collapsible airways in the lungs depends on the distending airway (intrapulmonary) pressures that hold the airways open and the external (intrapleural or intrathoracic) pressures that surround and compress the airways. The difference between these two pressures (airway pressure minus intrathoracic pressure) is called the *transpulmonary pressure*. For airflow to occur, the distending pressure inside the airways must be greater than the compressing pressure outside the airways (Fig. 19-15).

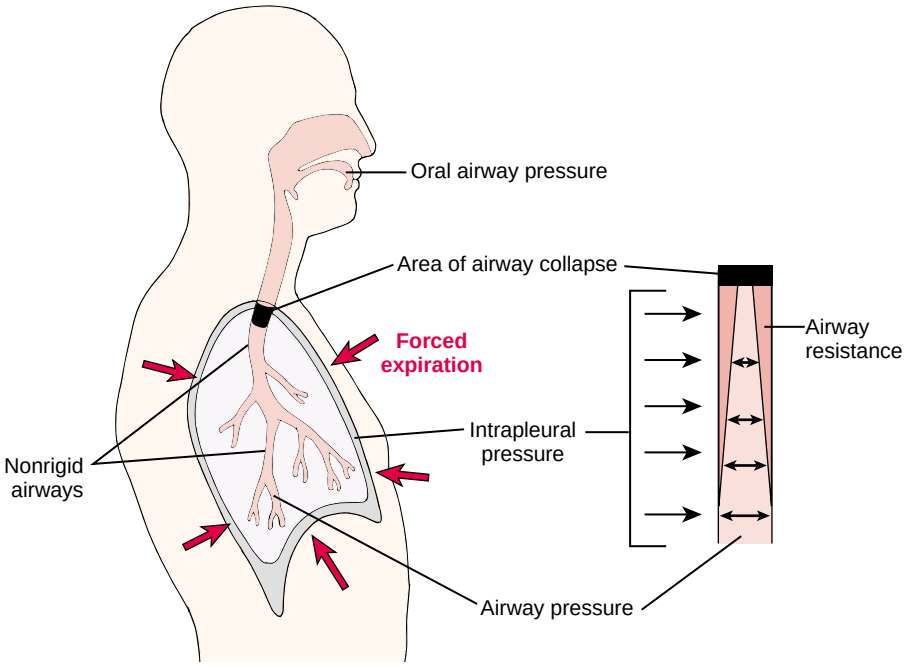
During forced expiration, the transpulmonary pressure is decreased because of a disproportionate increase in the intrathoracic pressure compared with airway pressure. The resistance that air encounters as it moves out of the lungs causes a further drop in airway pressure. If this drop in airway pressure is sufficiently great, the surrounding intrathoracic pressure will compress the collapsible airways (*i.e.*, those that lack cartilaginous support), causing airflow to be interrupted and air to be trapped in the alveoli (Fig. 19-15). Although this type of airway compression usually is seen only during forced expiration in persons with normal respiratory function, it may occur during normal breathing in persons with lung disease. For example, in conditions that increase airway resistance, such as chronic obstructive airway disease (COPD), the pressure drop along the smaller airways is magnified, and an increase in intra-airway pressure is needed to maintain airway patency (see Chapter 20). Measures such as pursed-lip breathing increase airway pressure and improve expiratory flow rates in persons with COPD.



■ **FIGURE 19-14** ■ Interaction of tissue forces on airways during low and high lung volumes. At low lung volumes, the tissue forces tend to fold and place less tension on the airways and they become smaller; during high lung volumes, the tissue forces are stretched and pull the airways open.

Lung Volumes

Lung volumes, or the amount of air exchanged during ventilation, can be subdivided into three components: (1) the tidal volume (TV), (2) the inspiratory reserve volume (IRV), and (3) the expiratory reserve volume (ERV). The TV, usually about 500 mL, is the amount of air that moves into and out of the lungs during a normal breath (Fig. 19-6). The IRV is the maximum amount of air that can be inspired in excess of the normal TV, and the ERV is the maximum amount that can be exhaled in excess of the normal TV. Approximately 1200 mL of air always remains in the lungs after forced expiration; this air is the *residual volume* (RV). The RV increases with age because there is more trapping of air in the lungs at the end of expiration. These volumes can be measured using an instrument called a *spirometer*.

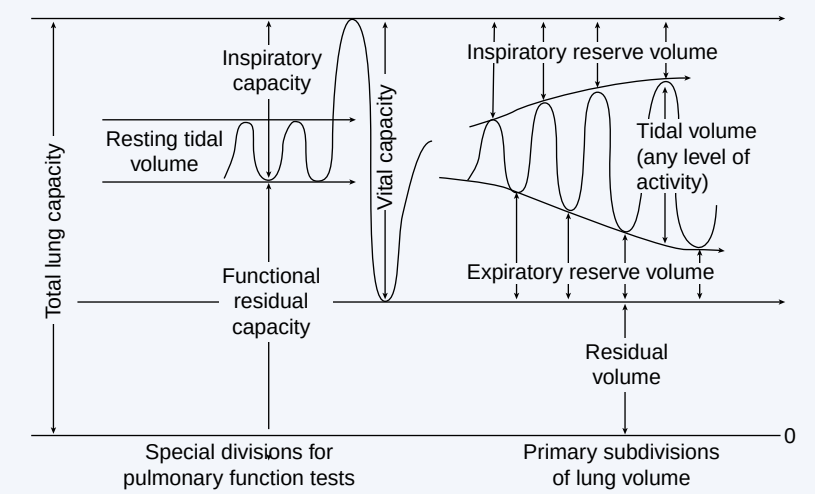


■ **FIGURE 19-15** ■ Mechanism that limits maximal expiratory flow rate. (**A**) Airway patency and airflow in the nonrigid airways of the lungs rely on a transpulmonary pressure gradient in which airway pressure is greater than intrapleural pressure. (**B**) Airway resistance normally produces a drop in airway pressure as air moves out of the lungs. The increased intrapleural pressure that occurs with forced expiration produces airway collapse in the nonrigid airways at the point where intrapleural pressure exceeds airway pressure.

Lung capacities include two or more lung volumes. The *vital capacity* (VC) equals the IRV plus the TV plus the ERV and is the amount of air that can be exhaled from the point of maximal inspiration. The *inspiratory capacity* (IC) equals the TV plus the IRV. It is the amount of air a person can breathe in beginning at the normal expiratory level and distending the lungs to the maximal amount. The *functional residual capacity* (FRC) is the sum of the RV and ERV; it is the volume of air that remains in the lungs at the end of normal expiration. The *total lung capacity* (TLC) is the sum of all the volumes in the lungs. The RV cannot be measured with the spirometer because this air cannot be expressed from the lungs. It is measured by indirect methods, such as the helium dilution methods, the nitrogen washout methods, or body plethysmography. Lung volumes and capacities are summarized in Table 19-1.

Pulmonary Function Studies

The previously described lung volumes and capacities are anatomic or static measures, determined by lung volumes and measured without relation to time. The spirometer also is used to measure dynamic lung function (*i.e.*, ventilation with respect to time); these tests often are used in assessing pulmonary function (Table 19-2). The *maximum voluntary ventilation* measures the volume of air that a person can move into and out of the lungs during maximum effort lasting for a specific period of time. This measurement usually is converted to liters per minute. Two other useful tests are the forced vital capacity (FVC) and the *forced expiratory volume* (FEV). The FVC involves full inspiration to total lung capacity followed by forceful maximal expiration. Obstruction of airways produces a FVC that is lower than that observed with more slowly performed vital



■ **FIGURE 19-16** ■ A tracing of respiratory volumes and capacities made with the use of a spirometer.

TABLE 19-1 Lung Volumes and Capacities

Volume	Symbol	Measurement
Tidal volume (about 500 mL at rest)	TV	Amount of air that moves into and out of the lungs with each breath
Inspiratory reserve volume (about 3000 mL)	IRV	Maximum amount of air that can be inhaled from the point of maximal expiration
Expiratory reserve volume (about 1100 mL)	ERV	Maximum volume of air that can be exhaled from the resting end-expiratory level
Residual volume (about 1200 mL)	RV	Volume of air remaining in the lungs after maximal expiration. This volume cannot be measured with the spirometer; it is measured indirectly using methods such as the helium dilution method, the nitrogen washout technique, or body plethysmography.
Functional residual capacity (about 2300 mL)	FRC	Volume of air remaining in the lungs at end-expiration (sum of RV and ERV)
Inspiratory capacity (about 3500 mL)	IC	Sum of IRV and TV
Vital capacity (about 4600 mL)	VC	Maximal amount of air that can be exhaled from the point of maximal inspiration
Total lung capacity (about 5800 mL)	TLC	Total amount of air that the lungs can hold; it is the sum of all the volume components after maximal inspiration. This value is about 20% to 25% less in females than in males.

capacity measurements. The forced expiratory volume (FEV) is the expiratory volume achieved in a given time period. The $FEV_{1.0}$ is the forced expiratory volume that can be exhaled in 1 second. The $FEV_{1.0}$ frequently is expressed as a percentage of the FVC. The $FEV_{1.0}$ and FVC are used in the diagnosis of obstructive lung disorders.

Efficiency and the Work of Breathing

The *minute volume*, or total ventilation, is the amount of air that is exchanged in 1 minute. It is determined by the metabolic needs of the body. The minute volume is equal to the TV multiplied by the respiratory rate. During normal activity it is about 6000 mL (500 mL TV × respiratory rate of 12 breaths per minute). The efficiency of breathing is determined by matching the TV and respiratory rate in a manner that provides an optimal minute volume while minimizing the work of breathing.

The work of breathing is determined by the amount of effort required to move air through the conducting airways and by the ease of lung expansion or compliance. Expansion of the lungs is difficult for persons with stiff and noncompliant lungs; they usually find it easier to breathe if they keep their TV low and breathe at a more rapid rate (*e.g.*, 300 × 20 = 6000 mL) to achieve their minute volume and meet their oxygen needs. In contrast, persons with obstructive airway disease usually find it less difficult to inflate their lungs but expend more energy in moving air through the airways. As a result, these persons take deeper breaths and breathe at a slower rate (*e.g.*, 600 × 10 = 6000 mL) to achieve their oxygen needs.

In summary, the movement of air between the atmosphere and the lungs follows the laws of physics as they relate to gases. The air in the alveoli contains a mixture of gases, including nitrogen, oxygen, carbon dioxide, and water vapor. With the exception of water vapor, each gas exerts a pressure that is determined by the atmospheric pressure and the concentration of the gas in the mixture. Water vapor pressure is affected by temperature but not atmospheric pressure. Air moves into the lungs along a pressure gradient. The pressure inside the airways and alveoli of the lungs is called *intrapulmonary* (or *alveolar*) *pressure*; the pressure in the pleural cavity is called *pleural pressure*; and the pressure in the thoracic cavity is called *intrathoracic pressure*.

Breathing is the movement of gases between the atmosphere and the lungs. It requires a system of open airways and pressure changes resulting from the action of the respiratory

TABLE 19-2 Pulmonary Function Tests

Test	Symbol	Measurement*
Maximal voluntary ventilation	MVV	Maximum amount of air that can be breathed in a given time
Forced vital capacity	FVC	Maximum amount of air that can be rapidly and forcefully exhaled from the lungs after full inspiration. The expired volume is plotted against time.
Forced expiratory volume achieved in 1 second	$FEV_{1.0}$	Volume of air expired in the first second of FVC
Percentage of forced vital capacity	$FEV_{1.0}$/FVC%	Volume of air expired in the first second, expressed as a percentage of FVC

*By convention, all the lung volumes and rates of flow are expressed in terms of body temperature and pressure and saturated with water vapor (BTPS), which allows for a comparison of the pulmonary function data from laboratories with different ambient temperatures and altitudes.

muscles in changing the volume of the chest cage. The diaphragm is the principal muscle of inspiration, assisted by the external intercostal muscles. The scalene and sternocleidomastoid muscles elevate the ribs and act as accessory muscles for inspiration. Expiration is largely passive, aided by the elastic recoil of the respiratory muscles that were stretched during inspiration. When needed, the abdominal and internal intercostal muscles can be used to increase expiratory effort.

Lung compliance describes the ease with which the lungs can be inflated. It reflects the elasticity of the lung tissue and the surface tension in the alveoli. Surfactant molecules, produced by type II alveolar cells, reduce the surface tension in the lungs, thereby increasing lung compliance. Airway resistance refers to the impediment to flow that the air encounters as it moves through the airways. The minute volume, which is determined by the metabolic needs of the body, is the amount of air that is exchanged in 1 minute (*i.e.*, respiratory rate and TV). The efficiency and work of breathing are determined by factors such as impaired lung compliance and airway diseases that increase the work involved in maintaining the minute volume. Lung volumes and lung capacities can be measured using a spirometer. Pulmonary function studies are used to assess ventilation with respect to time.

EXCHANGE AND TRANSPORT OF GASES

The primary functions of the lungs are oxygenation of the blood and removal of carbon dioxide. Pulmonary gas exchange is conventionally divided into three processes: (1) ventilation or the flow of gases into and out of the alveoli of the lungs, (2) perfusion or flow of blood in the adjacent pulmonary capillaries, and (3) diffusion or transfer of gases between the alveoli and the pulmonary capillaries. The efficiency of gas exchange requires that alveolar ventilation occur adjacent to perfused pulmonary capillaries.

Ventilation

Ventilation refers to the exchange of gases in the respiratory system. There are two types of ventilation: pulmonary and alveolar. *Pulmonary ventilation* refers to the total exchange of gases between the atmosphere and the lungs. *Alveolar ventilation* is the exchange of gases within the gas exchange portion of the lungs. Ventilation requires a system of open airways and a pressure difference that moves air into and out of the lungs. It is affected by body position and lung volume as well as by disease conditions that affect the heart and respiratory system.

Distribution of Ventilation

The distribution of ventilation between the base (bottom) and apex (top) of the lung varies with body position and the effects of gravity on intrapleural pressure. Compliance reflects the change in volume that occurs with a change in intrapleural pressure. It is less in fully expanded alveoli, which have difficulty accommodating more air, and greater in alveoli that are less inflated. In the seated or standing position, gravity exerts a downward pull on the lung, causing intrapleural pressure at the apex of the lung to become more negative. As a result, the alveoli at the apex of the lung are more fully expanded and less compliant than those at the base of the lung. The same holds true for lung expansion in the dependent portions of the lung in the supine or lateral position. In the supine position, ventilation in the lowermost (posterior) parts of the lung exceeds that in the uppermost (anterior) parts. In the lateral position (*i.e.*, lying on the side), the dependent lung is better ventilated.

The distribution of ventilation also is affected by lung volumes. During full inspiration (high lung volumes) in the seated or standing position, the airways are pulled open and air moves into the more compliant portions of the lower lung. At low lung volumes, the opposite occurs. At functional residual capacity (see Fig. 19-16), the pleural pressure at the base of the lung exceeds airway pressure, compressing the airways so that ventilation is greatly reduced. In contrast, the airways in the apex of the lung remain open, and this area of the lung is well ventilated.

Perfusion

The term *perfusion* is used to describe the flow of blood through the pulmonary capillary bed. The primary functions of the pulmonary circulation are to perfuse or provide blood flow to the gas exchange portion of the lung and to facilitate gas exchange. The pulmonary circulation serves several important functions in addition to gas exchange. It filters all the blood that moves from the right to the left side of the circulation; it removes most of the thromboemboli that might form; and it serves as a reservoir of blood for the left side of the heart.

The gas exchange function of the lungs requires a continuous flow of blood through the respiratory portion of the lungs. Deoxygenated blood enters the lung through the pulmonary artery, which has its origin in the right side of the heart and enters the lung at the hilus, along with the primary bronchus. The pulmonary arteries branch in a manner similar to that of the airways. The small pulmonary arteries accompany the bronchi as they move down the lobules and branch to supply the capillary network that surrounds the alveoli (see Fig. 19-6). The oxygenated capillary blood is collected in the small pulmonary veins of the lobules, and then it moves to the larger veins to be collected in the four large pulmonary veins that empty into the left atrium.

Distribution of Blood Flow

As with ventilation, the distribution of pulmonary blood flow is affected by body position and gravity. In the upright position, the distance of the upper apices of the lung above the level of the heart may exceed the perfusion capabilities of the mean pulmonary arterial pressure (approximately 12 mm Hg); therefore, blood flow in the upper part of the lungs is less than that in the base or bottom part of the lungs. In the supine position, the lungs and the heart are at the same level, and blood flow to the apices and base of the lungs becomes more uniform. In this position, blood flow to the posterior or dependent portions (*e.g.*, bottom of the lung when lying on the side) exceeds flow in the anterior or nondependent portions of the lungs. In persons with left-sided heart failure, congestion develops in the dependent portions of the lungs exposed to increased blood flow.

Effects of Hypoxia

The blood vessels in the pulmonary circulation undergo marked vasoconstriction when they are exposed to hypoxia. The precise mechanism for this response is unclear. When alveolar oxygen levels drop below 60 mm Hg, marked vasoconstriction may occur, and at very low oxygen levels, the local flow may be almost abolished. In regional hypoxia, as occurs with a localized airway obstruction (*e.g.*, atelectasis), vasoconstriction is localized to a specific region of the lung. Vasoconstriction has the effect of directing blood flow away from the hypoxic regions of the lungs. When alveolar hypoxia no longer exists, blood flow is restored.

Generalized hypoxia causes vasoconstriction throughout the lung. Generalized vasoconstriction occurs when the partial pressure of oxygen is decreased at high altitudes, or it can occur in persons with chronic hypoxia caused by lung disease. Prolonged hypoxia can lead to pulmonary hypertension and increased workload on the right heart. A low blood pH also produces vasoconstriction, especially when alveolar hypoxia is present (*e.g.*, during circulatory shock).

Diffusion

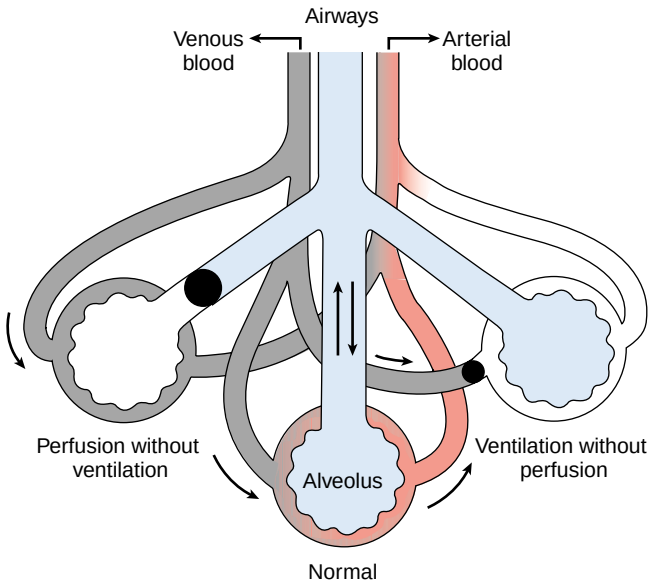
Diffusion refers to the movement of gases in the alveoli and across the alveolar capillary membrane. Diffusion of gases in the lung is affected by the difference in the pressure of gas across the membrane, the surface area that is available for diffusion, and the thickness of the alveolar capillary membrane through which the gas must pass. Administration of high concentrations of oxygen increases the pressure difference between the two sides of the membrane and increases the diffusion of the gas. Diseases that destroy lung tissue and the surface area for diffusion and those that increase the thickness of the alveolar-capillary membrane adversely influence the diffusing capacity of the lungs. For example, the removal of one lung reduces the diffusing capacity by one half. The thickness of the alveolar-capillary membrane and the distance for diffusion are increased in persons with pulmonary edema or pneumonia. The characteristics of the gas and its molecular weight and solubility constitute the diffusion coefficient and determine how rapidly the gas diffuses through the respiratory membranes. For example, carbon dioxide diffuses 20 times more rapidly than oxygen because of its greater solubility in the respiratory membranes.

Matching of Ventilation and Perfusion

The gas exchange properties of the lung depend on matching ventilation and perfusion, ensuring that equal amounts of air and blood are entering the respiratory portion of the lungs (Fig. 19-17). There are two factors that may interfere with the matching of ventilation and perfusion: (1) dead air space and (2) shunt.

Dead Air Space

Dead space refers to the air that must be moved with each breath but does not participate in gas exchange. The movement of air through dead space contributes to the work of breathing but not to gas exchange. There are two types of dead space: that contained in the conducting airways, called the *anatomic dead space*, and that contained in the respiratory portion of the lung, called the *alveolar dead space*. The volume of anatomic airway dead space is fixed at approximately 150 to 200 mL, depending on body size. It constitutes air contained in the nose, pharynx, trachea, and bronchi. The creation of an opening in the trachea to facilitate ventilation (tracheostomy) decreases anatomic dead space ventilation because air does not have to move through the nasal and oral airways. Alveolar dead space, normally about 5 to 10 mL, constitutes alveolar air that does not participate in gas exchange. When alveoli are ventilated but deprived of blood



■ **FIGURE 19-17** ■ Matching of ventilation and perfusion. (**Center**) Normal matching of ventilation and perfusion; (**left**) perfusion without ventilation (*i.e.*, shunt); (**right**) ventilation without perfusion (*i.e.*, dead air space).

KEY CONCEPTS

MATCHING OF VENTILATION AND PERFUSION

- Exchange of gases between the air in the alveoli and the blood in pulmonary capillaries requires a matching of ventilation and perfusion.
- Dead air space refers to air that is moved with each breath but is not ventilated. Anatomic dead space is that contained in the conducting airways that normally do not participate in gas exchange. Alveolar dead space results from alveoli that are ventilated but not perfused.
- Shunt refers to blood that moves from the right to the left side of the circulation without being oxygenated. With an anatomic shunt, blood moves from the venous to the arterial side of the circulation without going through the lungs. Physiologic shunting results from blood moving through unventilated parts of the lung.

flow, they do not contribute to gas exchange and thereby constitute alveolar dead space.

The *physiologic dead space* includes the anatomic dead space plus alveolar dead space. In persons with normal respiratory function, physiologic dead space is about the same as anatomic dead space. Only in lung disease does physiologic dead space increase.

Shunt

Shunt refers to blood that moves from the right to the left side of the circulation without being oxygenated. There are two types of shunts: physiologic and anatomic. In a *physiologic shunt*, there is mismatching of ventilation and perfusion, resulting in insufficient ventilation to provide the oxygen needed to oxygenate the blood flowing through the alveolar capillaries. Physiologic shunting of blood usually results from destructive lung disease that impairs ventilation or from heart failure that interferes with movement of blood through sections of the lungs. In an *anatomic shunt*, blood moves from the venous to the arterial side of the circulation without moving through the lungs. Anatomic intracardiac shunting of blood caused by congenital heart defects is discussed in Chapter 17.

Mismatching of Ventilation and Perfusion

Mismatching of ventilation and perfusion occurs when there is perfusion without ventilation or ventilation without perfusion (see Figure 19-17). Perfusion without ventilation (shunt) results in a low ventilation–perfusion ratio. This is the type of situation that occurs when there is incomplete expansion of the lung, such as in atelectasis (Chap-ter 21). Ventilation without perfusion (dead air space) results in a high ventilation–perfusion ratio. An example of this type of situation is pulmonary embolism, when a blood clot obstructs flow (Chapter 21). The PO_2 in the arterial blood leaving the pulmonary circulation reflects mixing of blood from areas of shunt and dead air space.

Gas Transport

The lungs enable inhaled air to come in contact with blood flowing through the pulmonary capillaries so that exchange of gases between the external environment and the internal environment of the body can occur. The lungs restore the oxygen content of the arterial blood and remove carbon dioxide from the venous blood.

The blood carries oxygen and carbon dioxide in the dissolved state and in combination with hemoglobin. Carbon dioxide also is converted to bicarbonate and transported in that form. The amount of a gas that can dissolve in plasma is determined by two factors: the solubility of the gas in the plasma and the partial pressure of the gas in the alveoli. Oxygen and carbon dioxide dissolve in plasma. The gases that are dissolved in plasma are similar to the carbon dioxide that is dissolved in a capped bottle of a carbonated drink. In the case of the carbonated drink, increased pressure is used to increase the dissolved carbon dioxide to the drink. When the bottle cap is removed and the pressure reduced, tiny bubbles can be seen as the gas moves from the dissolved to the gaseous state.

In the clinical setting, blood gas measurements are used to determine the level of the partial pressure of oxygen (PO_2) and carbon dioxide (PCO_2) in the blood. Arterial blood commonly is used for measuring blood gases. Venous blood is not used because venous levels of oxygen and carbon dioxide reflect the metabolic demands of the tissues, rather than the gas exchange function of the lungs. The PO_2 of arterial blood normally is greater than 80 mm Hg, and the PCO_2 is in the range of 35 to 45 mm Hg. Normally, the arterial blood gases are the same or nearly the same as the partial pressure of the gases in the alveoli. The arterial PO_2 often is written PaO_2, and the alveolar PO_2 as PAO_2, with the same types of designations being used for PCO_2. This text uses PO_2 and PCO_2 to designate both arterial and alveolar levels of the gases.

Oxygen Transport

Oxygen is transported in two forms: (1) in chemical combination with hemoglobin and (2) in the dissolved state. The hemoglobin in red blood cells serves as a transport vehicle for oxygen. It binds oxygen in the pulmonary capillaries and releases it in the tissue capillaries. As oxygen moves into or out of the red blood cells, it dissolves in the plasma. It is the dissolved form of oxygen that leaves the capillary, crosses cell membranes, and participates in cell metabolism. Only approximately 1% of the oxygen in the blood is carried in the dissolved state; the remainder is carried in combination with hemoglobin. The oxygen content of the blood (measured in milliliters per 100 milliliters of blood) includes the oxygen carried by hemoglobin and dissolved oxygen.

Hemoglobin Transport. Hemoglobin is a highly efficient carrier of oxygen, and approximately 98% to 99% of the oxygen used by body tissues is carried in this manner. Hemoglobin with bound oxygen is called *oxyhemoglobin*, and when oxygen is removed, it is called *deoxygenated* or *reduced hemoglobin*. Each gram of hemoglobin carries approximately 1.34 mL of oxygen when it is fully saturated. This means that a person with a hemoglobin of 14 g/100 mL carries 18.8 mL of oxygen per 100 mL of blood. In the lungs, oxygen moves across the alveolar-capillary membrane, through the plasma, and into

KEY CONCEPTS

OXYGEN TRANSPORT

- Oxygen is transported in chemical combination with hemoglobin and as a gas dissolved in the plasma.
- Hemoglobin, which is the main transporter for oxygen, binds oxygen as it passes through the lungs and releases it as it moves through the tissues.
- The amount of oxygen that is carried as a dissolved gas is determined by the partial pressure of the gas in the lungs.
- The oxygen content of the blood, or the amount of oxygen that is available to the tissues, represents the total amount of oxygen carried by the hemoglobin plus the amount of oxygen that is carried in the dissolved state.

the red blood cell, where it forms a loose and reversible bond with the hemoglobin molecule. In normal lungs, this process is rapid, so that even with a fast heart rate, the hemoglobin is almost completely saturated with oxygen during the short time it spends in the pulmonary capillaries.

The oxygenated hemoglobin is transported in the arterial blood to the peripheral capillaries, where the oxygen is released and made available to the tissues for use in cell metabolism. As the oxygen moves out of the capillaries in response to the needs of the tissues, the hemoglobin saturation, which usually is approximately 95% to 97% as the blood leaves the left side of the heart, drops to approximately 75% as the mixed venous blood returns to the right side of the heart.

Dissolved Oxygen. The partial pressure of oxygen (PO_2) represents the level of dissolved oxygen in plasma. The amount of gas that can be dissolved in a liquid depends on the solubility of the gas and its pressure. The solubility of oxygen in plasma is fixed and very small. For every 1 mm Hg of PO_2 present in the alveoli, 0.003 mL of oxygen becomes dissolved in 100 mL of plasma. This means that at a normal alveolar PO_2 of 100 mm Hg, the blood carries only 0.3 mL of dissolved oxygen in each 100 mL of plasma. This amount is very small compared with the amount that can be carried in an equal amount of blood when oxygen is attached to hemoglobin.

Although the amount of oxygen carried in plasma under normal conditions is small, it can become a life-saving mode of transport in carbon monoxide poisoning, when most of the hemoglobin sites are occupied by carbon monoxide and are unavailable for transport of oxygen. The use of a hyperbaric chamber, in which 100% oxygen can be administered at high atmospheric pressures, increases the amount of oxygen that can be carried in the dissolved state.

Oxygen-Hemoglobin Dissociation. Oxygen that remains bound to hemoglobin cannot participate in tissue metabolism. The efficiency of the oxygen dissociation transport system depends on the ability of the hemoglobin molecule to bind oxygen in the lungs and release it, as it is needed in the tissues. The *affinity* of hemoglobin refers to its capacity to bind oxygen. Hemoglobin binds oxygen more readily when its affinity is increased and releases it more readily when its affinity is decreased. As described in Chapter 13, the hemoglobin molecule is composed of four polypeptide chains bound to an iron-containing heme group. Because oxygen binds to the iron atom, each hemoglobin molecule can bind four molecules of oxygen. When oxygen is bound to all four of the heme groups, the hemoglobin molecule is said to be fully *saturated*. Hemoglobin is partially saturated when it contains only one, two, or three molecules of oxygen.

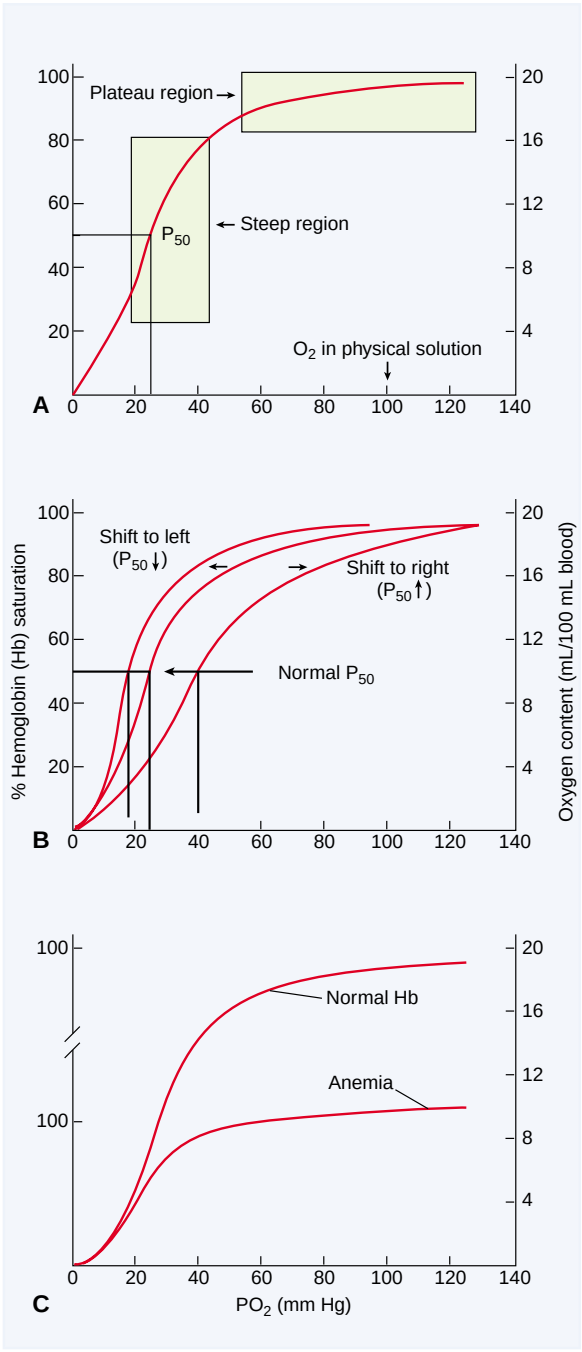
Hemoglobin's affinity for oxygen is influenced by pH, carbon dioxide concentration, and temperature. Hemoglobin binds oxygen more strongly under conditions of increased pH (alkalosis), decreased carbon dioxide concentration, and decreased body temperature, and releases it more readily under conditions of decreased pH (acidosis), increased carbon dioxide concentration, and fever. Conditions that decrease affinity and favor unloading of oxygen reflect the level of tissue metabolism and need for oxygen. For example, increased tissue metabolism generates carbon dioxide and metabolic acids, thereby decreasing the affinity of hemoglobin for oxygen. Heat also is a byproduct of tissue metabolism, explaining the effect of fever on oxygen binding. Red blood cells contain a metabolic intermediate called 2,3-diphosphoglycerate (2,3-DPG) that also affects the affinity of hemoglobin for oxygen. An increase in 2,3-DPG enhances unloading of oxygen from hemoglobin at the tissue level. An increase in 2,3-DPG occurs with exercise and the hypoxia that occurs with high altitude and chronic lung disease.

The relation between the oxygen carried in combination with hemoglobin and the PO_2 of the blood is described by the *oxygen-hemoglobin dissociation curve*, which is shown in Figure 19-18A. The x axis depicts the PO_2; the left y axis, hemoglobin saturation, and the right y axis, the oxygen content or total amount of oxygen in the blood, including the dissolved oxygen and that carried by the hemoglobin. There are three important things to observe about the relationships among PO_2, hemoglobin saturation, and oxygen content. First, PO_2 is the dissolved oxygen. It reflects the partial pressure of the gas in the lung (*i.e.*, the PO_2 is approximately 100 mm Hg when room air is being breathed but can rise to 200 mm Hg or higher when oxygen-enriched air is breathed). Second, hemoglobin saturation reflects the amount of oxygen that is carried by the hemoglobin. Third, it is the oxygen content of the blood, rather than the PO_2, or even hemoglobin saturation, that determines the amount of oxygen that is delivered to the tissues. An anemic person may have a normal PO_2 and hemoglobin saturation level but decreased oxygen content because of the lower amount of hemoglobin for binding oxygen (Fig. 19-18C).

The oxygen-hemoglobin dissociation curve has a flat top portion representing binding of oxygen by the hemoglobin in the lungs and a steep portion representing its release into the tissue capillaries. The S shape of the curve reflects the effect that oxygen saturation has on the affinity of hemoglobin for oxygen. At approximately 100 mm Hg PO_2, a plateau occurs, at which point the hemoglobin is approximately 98% saturated. Increasing the alveolar PO_2 above this level does not increase the hemoglobin saturation. Even at high altitudes, when the partial pressure of oxygen is considerably decreased, the hemoglobin remains relatively well saturated. For example, at 60 mm Hg PO_2, the hemoglobin is still approximately 89% saturated.

The steep portion of the dissociation curve—between 60 and 40 mm Hg—represents the removal of oxygen from the hemoglobin as it moves through the tissue capillaries. This portion of the curve shows that there is considerable transfer of oxygen from hemoglobin to the tissues with only a small drop in PO_2, thereby ensuring a gradient for oxygen to move into body cells. The tissues normally remove approximately 5 mL of oxygen per 100 mL of blood, and the hemoglobin of mixed venous blood is approximately 75% saturated as it returns to the right side of the heart.

Hemoglobin can be regarded as an oxygen buffer system that regulates oxygen pressure in the tissues. Hemoglobin affinity for oxygen must change with the metabolic needs of the tissues. This change is represented by a shift to the right or left in the dissociation curve, as shown in Figure 19-18B. The P_{50} represents the PO_2 at a hemoglobin of 50%. It can be used



■ **FIGURE 19-18** ■ Oxygen-hemoglobin dissociation curve (oxygen content at hemoglobin of 14 gm/dL). (**A**) Left boxed area represents the steep portion of the curve where oxygen is released from hemoglobin (Hb) to the tissues, and the top boxed area the plateau of the curve where oxygen is loaded onto hemoglobin in the lung. P_{50} partial pressure of oxygen required to saturate 50% of hemoglobin with oxygen. (**B**) The effect of body temperature, arterial PCO_2, and pH on hemoglobin affinity for oxygen as indicated by a shift in the curve and position of the P_{50}. A shift of the curve to the right due to an increase in temperature, PCO_2, or decreased pH favors release of oxygen to the tissues. A decrease in temperature, PCO_2, or increase in pH shifts the curve to the left. (**C**) Effect of anemia on the oxygen-carrying capacity of blood. The hemoglobin can be completely saturated, but the oxygen content of the blood is reduced. (Adapted from Rhoades R.A., Tanner G.A. [1996]. *Medical physiology.* Boston: Little, Brown)

to determine whether the dissociation curve has shifted to the right or to the left. A *shift to the right* indicates that the tissue PO_2 is greater for any given level of hemoglobin saturation and represents reduced affinity of the hemoglobin for oxygen at any given PO_2. It usually is caused by conditions such as fever or acidosis or by an increase in PCO_2, which reflects increased tissue metabolism. High altitude and conditions such as pulmonary insufficiency, heart failure, and severe anemia also cause the oxygen dissociation curve to shift to the right.

A *shift to the left* in the oxygen dissociation curve represents enhanced affinity of hemoglobin for oxygen and occurs in situations associated with a decrease in tissue metabolism, such as alkalosis, decreased body temperature, and decreased carbon dioxide levels.

Carbon Dioxide Transport

Carbon dioxide is transported in the blood in three forms: as dissolved carbon dioxide (10%), attached to hemoglobin (30%), and as bicarbonate (60%). Acid-base balance is influenced by the amount of dissolved carbon dioxide and the bicarbonate level in the blood (see Chapter 6).

As carbon dioxide is formed during the metabolic process, it diffuses out of cells into the tissue spaces and then into the capillaries. The amount of dissolved carbon dioxide that can be carried in plasma is determined by the partial pressure of the gas and its solubility coefficient (0.03 mL/100 mL/1 mm Hg PCO_2). Carbon dioxide is 20 times more soluble in plasma than oxygen. Thus, the dissolved state plays a greater role in transport of carbon dioxide compared with oxygen.

Most of the carbon dioxide diffuses into the red blood cells, where it forms carbonic acid or combines with hemoglobin. Carbonic acid (H_2CO_3) is formed when carbon dioxide combines with water ($CO_2 + H_2O = H^+ + HCO_3^-$). The process is catalyzed by an enzyme called *carbonic anhydrase,* which greatly increases the rate of the reaction. Carbonic acid readily ionizes to form a bicarbonate (HCO_3^-) and a hydrogen (H^+) ion. The hydrogen ion that is generated combines with the hemoglobin, which is a powerful acid-base buffer, and the bicarbonate ion diffuses into plasma in exchange for a chloride ion.

In addition to the carbonic anhydrase-mediated reaction with water, carbon dioxide reacts directly with hemoglobin to form *carbaminohemoglobin*. The combination of carbon dioxide with hemoglobin is a reversible reaction that involves a loose bond, which allows transport of carbon dioxide from tissues to the lungs, where it is released into the alveoli for exchange with the external environment. The release of oxygen from hemoglobin in the tissues enhances the binding of carbon dioxide to hemoglobin; in the lungs, the combining of oxygen with hemoglobin displaces carbon dioxide. The binding of carbon dioxide to hemoglobin is determined by the acidic nature of hemoglobin. Binding with carbon dioxide causes the hemoglobin to become a stronger acid. In the lungs, the highly acidic hemoglobin has a lesser tendency to form carbaminohemoglobin, and carbon dioxide is released from hemoglobin into the alveoli. In the tissues, the release of oxygen from hemoglobin causes hemoglobin to become less acid, thereby increasing its ability to combine with carbon dioxide and form carbaminohemoglobin.

In summary, the primary functions of the lungs are oxygenation of the blood and removal of carbon dioxide. Pulmonary gas exchange is conventionally divided into three processes: ventilation, or the flow of gases into the alveoli of the lungs; perfusion, or movement of blood through the adjacent pulmonary capillaries; and diffusion, or transfer of gases between the alveoli and the pulmonary capillaries.

Ventilation is the movement of air between the atmosphere and the lungs. Pulmonary ventilation refers to the total exchange of gases between the atmosphere and the lungs, and alveolar ventilation refers to ventilation in the gas exchange portion of the lungs. The distribution of alveolar ventilation and pulmonary capillary blood flow varies with lung volume and body position. In the upright position and at high lung volumes, ventilation is greatest in the lower parts of the lungs. The upright position also produces a decrease in blood flow to the upper parts of the lung, resulting from the distance above the level of the heart and the low mean arterial pressure in the pulmonary circulation.

The diffusion of gases in the lungs is influenced by four factors: the surface area available for diffusion; the thickness of the alveolar-capillary membrane, through which the gases diffuse; the differences in the partial pressure of the gas on either side of the membrane; and the characteristics of the gas. The efficiency of gas exchange requires matching of ventilation and perfusion so that equal amounts of air and blood enter the respiratory portion of the lungs. Two factors—dead air space and shunt—interfere with matching of ventilation and perfusion and do not contribute to gas exchange. Dead air space occurs when areas of the lungs are ventilated but not perfused. Shunt is the condition under which areas of the lungs are perfused but not ventilated.

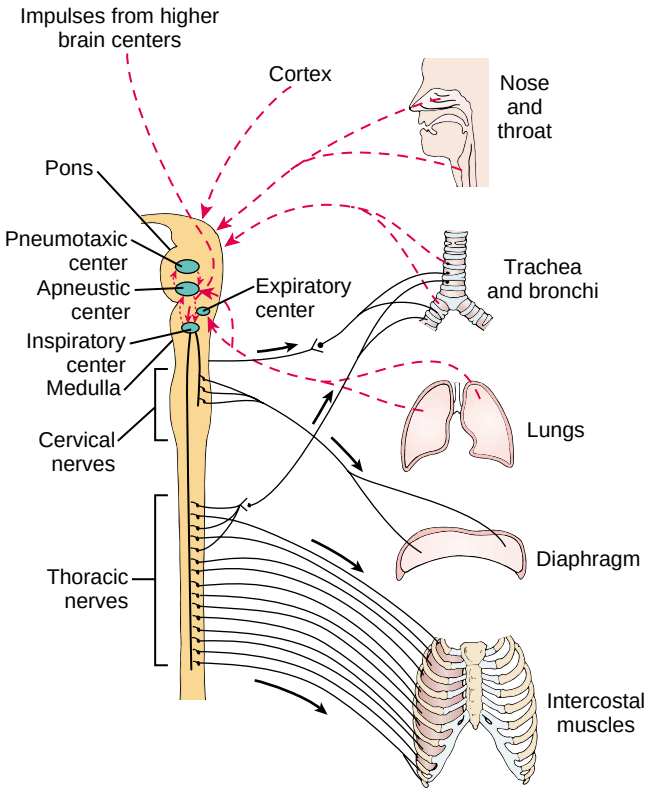
The blood transports oxygen to the cells and returns carbon dioxide to the lungs. Oxygen is transported in two forms: in chemical combination with hemoglobin and physically dissolved in plasma (PO_2). Hemoglobin is an efficient carrier of oxygen, and approximately 98% to 99% of oxygen is transported in this manner. Carbon dioxide is carried in three forms: carbaminohemoglobin (30%), dissolved carbon dioxide (10%), and bicarbonate (60%).

CONTROL OF BREATHING

Unlike the heart, which has inherent rhythmic properties and can beat independently of the nervous system, the muscles that control respiration require continuous input from the nervous system. Movement of the diaphragm, intercostal muscles, sternocleidomastoid, and other accessory muscles that control ventilation is integrated by neurons located in the pons and medulla. These neurons are collectively referred to as the *respiratory center* (Fig. 19-19).

Respiratory Center

The medullary respiratory center consists of two groups of neurons involved in initiating inspiration and expiration and incorporating afferent impulses into the motor responses of the respiratory muscles. The first, or inspiratory area, which is located in the dorsal region of the medulla, controls the activity of the phrenic nerves that innervate the diaphragm and another group of neurons, which innervate the spinal motor neurons of the intercostals and abdominal muscles. The second group of neurons is concerned with the expiratory phase of respiration.



■ **FIGURE 19-19** ■ Schematic representation of activity in the respiratory center. Impulses traveling over afferent neurons (*red dashed lines*) communicate with central neurons, which activate efferent neurons that supply the muscles of respiration. Respiratory movements can be altered by a variety of stimuli.

The pacemaker properties of the respiratory center result from the cycling of the two groups of respiratory neurons in the pons: the *pneumotaxic center* in the upper pons and the *apneustic center* in the lower pons. These two groups of neurons contribute to the function of the respiratory center in the medulla. The apneustic center has an excitatory effect on inspiration, tending to prolong inspiration. The pneumotaxic center switches inspiration off, assisting in the control of respiratory rate and inspiratory volume. Brain injury that damages the connection between the pneumotaxic and apneustic centers results in an irregular breathing pattern that consists of prolonged inspiratory gasps interrupted by expiratory efforts.

Axons from the neurons in the respiratory center cross in the midline and descend in the ventrolateral columns of the spinal cord. The tracts that control expiration and inspiration are spatially separated in the cord, as are the tracts that transmit specialized reflexes (*i.e.*, coughing and hiccupping) and voluntary control of ventilation. Only at the level of the spinal cord are the respiratory impulses integrated to produce a reflex response.

The control of breathing has automatic and voluntary components. The automatic regulation of ventilation is controlled by input from two types of sensors or receptors: chemoreceptors and lung receptors. *Chemoreceptors* monitor blood levels of oxygen, carbon dioxide, and pH and adjust ventilation to meet the changing metabolic needs of the body. *Lung receptors* monitor breathing patterns and lung function. Voluntary regulation of ventilation integrates breathing with voluntary acts, such as speaking, blowing, and singing. These voluntary acts, initiated by the motor and premotor cortex, cause temporary suspension of automatic breathing. The automatic and voluntary components of respiration are regulated by afferent impulses that come to the respiratory center from a number of sources. Afferent input from higher brain centers is evidenced by the fact that a person can consciously alter the depth and rate of respiration. Fever, pain, and emotion exert their influence through lower brain centers. Vagal afferents from sensory receptors in the lungs and airways are integrated in the dorsal area of the respiratory center.

Chemoreceptors

Tissue needs for oxygen and the removal of carbon dioxide are regulated by chemoreceptors that monitor blood levels of these gases. Input from these sensors is transmitted to the respiratory center, and ventilation is adjusted to maintain the arterial blood gases within a normal range.

There are two types of chemoreceptors: central and peripheral. The most important chemoreceptors for sensing changes in blood carbon dioxide content are the *central chemoreceptors*. These receptors are located in chemosensitive regions near the respiratory center in the medulla and are bathed in cerebrospinal fluid. Although the central chemoreceptors monitor carbon dioxide levels, the actual stimulus for these receptors is provided by hydrogen ions in the cerebrospinal fluid (CSF). The CSF is separated from the blood by the blood-brain barrier, which permits free diffusion of carbon dioxide but not bicarbonate or hydrogen ions. The carbon dioxide combines rapidly with water to form carbonic acid, which dissociates into hydrogen and bicarbonate ions. The carbon dioxide content in the blood regulates ventilation through its effect on the pH of the extracellular fluid of the brain. The central chemoreceptors are extremely sensitive to short-term changes in carbon dioxide. An increase in plasma carbon dioxide levels increases ventilation, reaching its peak within a minute or so and then declining if the carbon dioxide level remains elevated. Thus, persons with chronically elevated levels of carbon dioxide no longer have a response to this stimulus for increased ventilation but rely on the stimulus provided by a decrease in blood oxygen levels.

The *peripheral chemoreceptors* are located in the carotid and aortic bodies, which are found at the bifurcation of the common carotid arteries and in the arch of the aorta, respectively. These chemoreceptors monitor arterial blood oxygen levels. Although the peripheral chemoreceptors also monitor carbon dioxide, they play a much more important role in monitoring oxygen levels. These receptors exert little control over ventilation until the PO_2 has dropped below 60 mm Hg. Thus, hypoxia is the main stimulus for ventilation in persons with chronically elevated levels of carbon dioxide. If these patients are given oxygen therapy at a level sufficient to increase the PO_2 above that needed to stimulate the peripheral chemoreceptors, their ventilation may be seriously depressed.

Lung Receptors

Lung and chest wall receptors provide information on the status of breathing in terms of airway resistance and lung expansion. There are three types of lung receptors: stretch, irritant, and juxtacapillary receptors.

Stretch receptors are located in the smooth muscle layers of the conducting airways. They respond to changes in pressure in the walls of the airways. When the lungs are inflated, these receptors inhibit inspiration and promote expiration. They are important in establishing breathing patterns and minimizing the work of breathing by adjusting respiratory rate and TV to accommodate changes in lung compliance and airway resistance.

The *irritant receptors* are located between the airway epithelial cells. They are stimulated by noxious gases, cigarette smoke, inhaled dust, and cold air. Stimulation of the irritant receptors leads to airway constriction and a pattern of rapid, shallow breathing. This pattern of breathing probably protects respiratory tissues from the damaging effects of toxic inhalants. It also is thought that the mechanical stimulation of these receptors may ensure more uniform lung expansion by initiating periodic sighing and yawning. It is possible that these receptors are involved in the bronchoconstriction response that occurs in some persons with bronchial asthma.

The *juxtacapillary* or *J receptors* are located in the alveolar wall, close to the pulmonary capillaries. It is thought that these receptors sense lung congestion. These receptors may be responsible for the rapid, shallow breathing that occurs with pulmonary edema, pulmonary embolism, and pneumonia.

Cough Reflex

Coughing is a neurally mediated reflex that protects the lungs from the accumulation of secretions and from entry of irritating and destructive substances. It is one of the primary defense mechanisms of the respiratory tract. The cough reflex is initiated by receptors located in the tracheobronchial wall; these receptors are extremely sensitive to irritating substances and to the presence of excess secretions. Afferent impulses from these receptors are transmitted through the vagus to the medullary center, which integrates the cough response.

Coughing itself requires the rapid inspiration of a large volume of air (usually about 2.5 L), followed by rapid closure of the glottis and forceful contraction of the abdominal and expiratory muscles. As these muscles contract, intrathoracic pressures are elevated to levels of 100 mm Hg or more. The rapid opening of the glottis at this point leads to an explosive expulsion of air.

Many conditions can interfere with the cough reflex and its protective function. The reflex is impaired in persons whose abdominal or respiratory muscles are weak. This problem can be caused by disease conditions that lead to muscle weakness or paralysis, by prolonged inactivity, or as an outcome of surgery involving these muscles. Bed rest interferes with expansion of the chest and limits the amount of air that can be taken into the lungs in preparation for coughing, making the cough weak and ineffective. Disease conditions that prevent effective closure of

the glottis and laryngeal muscles interfere with production of the marked increase in intrathoracic pressure that is needed for effective coughing. For example, the presence of a nasogastric tube may prevent closure of the upper airway structures and may fatigue the receptors for the cough reflex that are located in the area. The cough reflex also is impaired when there is depressed function of the medullary centers in the brain that integrate the cough reflex. Interruption of the central integration aspect of the cough reflex can arise as the result of disease of this part of the brain or the action of drugs that depress the cough center.

Although the cough reflex is a protective mechanism, frequent and prolonged coughing can be exhausting and painful and can exert undesirable effects on the cardiovascular and respiratory systems and on the elastic tissues of the lungs. This is particularly true in young children and elderly persons.

In summary, the respiratory system requires continuous input from the nervous system. Movement of the diaphragm, intercostal muscles, and other respiratory muscles is controlled by neurons of the respiratory center located in the pons and medulla. The control of breathing has automatic and voluntary components. Voluntary respiratory control is needed for integrating breathing and actions such as speaking, blowing, and singing. These acts, which are initiated by the motor and premotor cortex, cause temporary suspension of automatic breathing.

The automatic regulation of ventilation is controlled by two types of receptors: lung receptors, which protect respiratory structures, and chemoreceptors, which monitor the gas exchange function of the lungs by sensing changes in blood levels of carbon dioxide, oxygen, and pH. There are three types of lung receptors: stretch receptors, which monitor lung inflation; irritant receptors, which protect against the damaging effects of toxic inhalants; and J receptors, which are thought to sense lung congestion. There are two groups of chemoreceptors: central and peripheral. The central chemoreceptors are the most important in sensing changes in carbon dioxide levels, and the peripheral chemoreceptors function in sensing arterial blood oxygen levels.

The cough reflex protects the lungs from the accumulation of secretions and from the entry of irritating and destructive substances; it is one of the primary defense mechanisms of the respiratory tract.

REVIEW QUESTIONS

- State the difference between the conducting and the respiratory airways.
- Describe the function of the mucociliary blanket.
- Define the term *water vapor pressure* and cite the source of water for humidification of air as it moves through the airways.
- State the function of the two types of alveolar cells and use Laplace's law to explain the need for surfactant in maintaining the inflation of small alveoli.
- State the definition of intrathoracic, intrapleural, and intraalveolar pressures, and state how each of these pressures changes in relation to atmospheric pressure during inspiration and expiration.
- Explain why ventilation and perfusion must be matched and describe their relation to dead air space and shunt.
- Explain the difference between PO_2 and hemoglobin-bound oxygen and O_2 saturation and content and explain the effect of administering 40% oxygen on O_2 saturation and PO_2.
- Explain the significance of a shift to the right and a shift to the left in the oxygen-hemoglobin dissociation curve.
- Describe the function of the chemoreceptors and lung receptors in the regulation of ventilation.
- Trace the integration of the cough reflex from stimulus to explosive expulsion of air that constitutes the cough.

Visit the Connection site at connection.lww.com/go/porth for links to chapter-related resources on the Internet.

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