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The Respiratory System

Far from self-sustaining, the body depends on the external environment, both as a source of substances the body needs to survive and as a catch basin for its wastes. The trillions of cells making up the body require a continuous supply of oxygen to carry out their vital functions. We cannot do without oxygen for even a little while, as we can without food or water.

As cells use oxygen, they give off carbon dioxide, a waste product the body must get rid of. They also generate dangerous free radicals, the inescapable by-products of living in a world full of oxygen. But let's get to the topic of this chapter, the respiratory system.

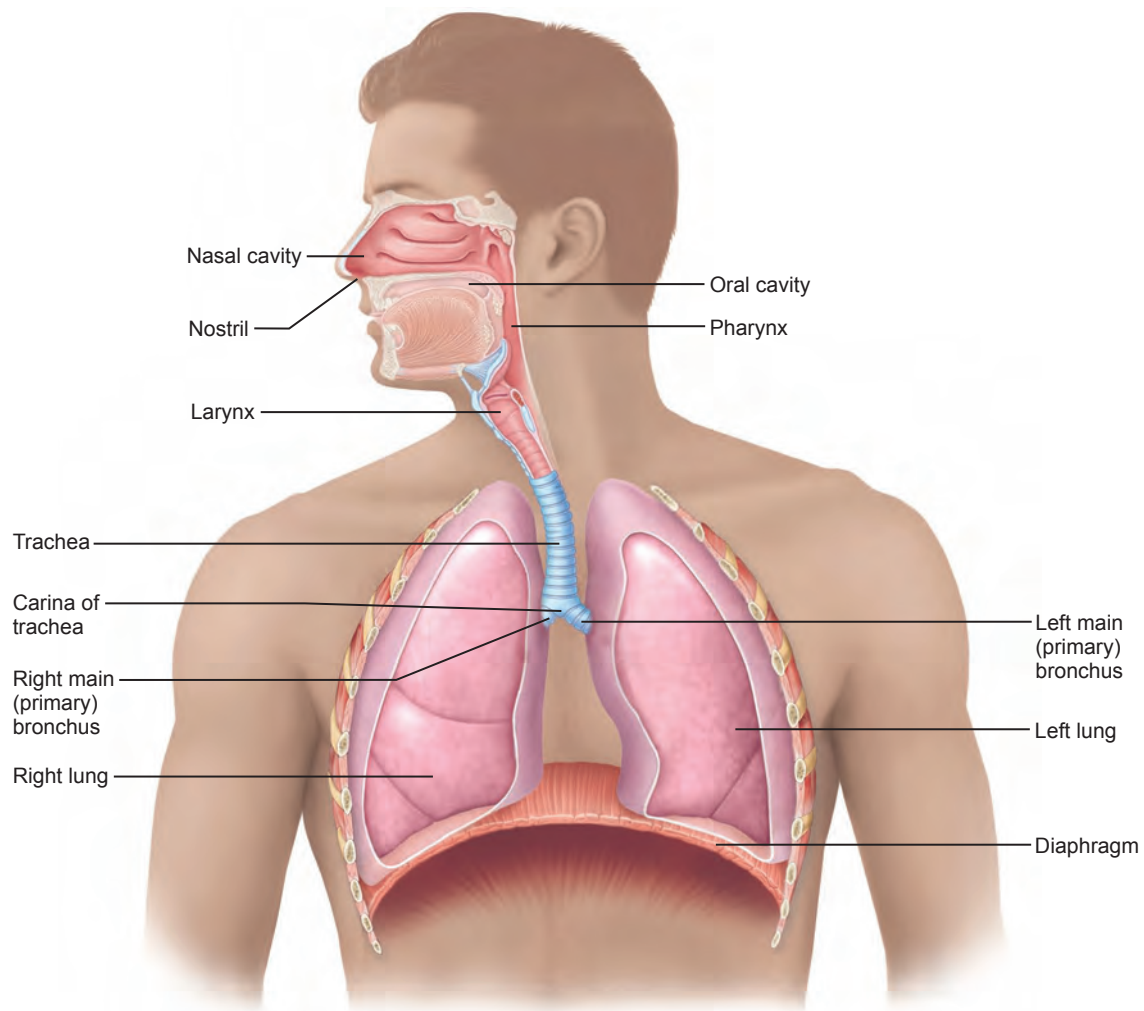


Figure 22.1 The major respiratory organs in relation to surrounding structures.

The major function of the **respiratory system** is to supply the body with oxygen and dispose of carbon dioxide. To accomplish this function, at least four processes, collectively called **respiration**, must happen:

1. **Pulmonary ventilation:** movement of air into and out of the lungs so that the gases there are continuously changed and refreshed (commonly called breathing).
2. **External respiration:** movement of oxygen from the lungs to the blood and of carbon dioxide from the blood to the lungs.
3. **Transport of respiratory gases:** transport of oxygen from the lungs to the tissue cells of the body, and of carbon dioxide from the tissue cells to the lungs. This transport is accomplished by the cardiovascular system using blood as the transporting fluid.
4. **Internal respiration:** movement of oxygen from blood to the tissue cells and of carbon dioxide from tissue cells to blood.

Only the first two processes are the special responsibility of the respiratory system (**Figure 22.1**), but it cannot accomplish its primary goal of obtaining oxygen and eliminating carbon

dioxide unless the third and fourth processes also occur. As you can see, the respiratory and circulatory systems are closely coupled, and if either system fails, the body's cells begin to die from oxygen starvation.

The actual use of oxygen and production of carbon dioxide by tissue cells, known as *cellular respiration*, is the cornerstone of all energy-producing chemical reactions in the body. We discuss cellular respiration, which is not a function of the respiratory system, in the metabolism section of Chapter 24.

Because it moves air, the respiratory system is also involved with the sense of smell and with speech.

Functional Anatomy of the Respiratory System

- ▶ Identify the organs forming the respiratory passageway(s) in descending order until the alveoli are reached.
- ▶ Describe the location, structure, and function of each of the following: nose, paranasal sinuses, pharynx, and larynx.
- ▶ List and describe several protective mechanisms of the respiratory system.

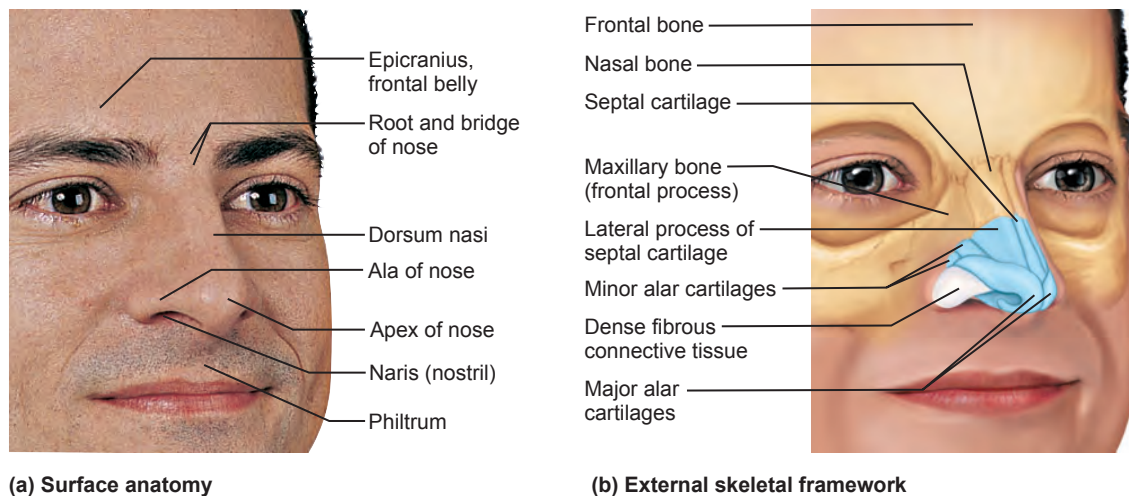


Figure 22.2 The external nose.

The respiratory system includes the *nose*, *nasal cavity*, and *paranasal sinuses*; the *pharynx*; the *larynx*; the *trachea*; the *bronchi* and their smaller branches; and the *lungs*, which contain the terminal air sacs, or *alveoli* (Figure 22.1). Functionally, the system consists of two zones. The **respiratory zone**, the actual site of gas exchange, is composed of the respiratory bronchioles, alveolar ducts, and alveoli, all microscopic structures. The **conducting zone** includes all other respiratory passageways, which provide fairly rigid conduits for air to reach the gas exchange sites. The conducting zone organs also cleanse, humidify, and warm incoming air. As a result, air reaching the lungs has fewer irritants (dust, bacteria, etc.) than when it entered the system, and it is warm and damp, like the air of the tropics. The functions of the major organs of the respiratory system are summarized in [Table 22.1](#).

In addition to these organs, some authorities also include the respiratory muscles (diaphragm, etc.) as part of this system. Although we will consider how these skeletal muscles bring about the volume changes that promote ventilation, we continue to classify them as part of the *muscular system*.

The Nose and Paranasal Sinuses

The nose is the only externally visible part of the respiratory system. Unlike the eyes and lips, facial features often referred to poetically, the nose is usually an irreverent target. We are urged to keep our nose to the grindstone and to keep it out of other people's business. Considering its important functions, however, it deserves more esteem. The nose (1) provides an airway for respiration, (2) moistens and warms entering air, (3) filters and cleans inspired air, (4) serves as a resonating chamber for speech, and (5) houses the olfactory (smell) receptors.

The structures of the nose are divided into the *external nose* and the internal *nasal cavity* for ease of consideration. The surface features of the external nose include the *root* (area between the eyebrows), *bridge*, and *dorsum nasi* (anterior

margin), the latter terminating in the *apex* (tip of the nose) (Figure 22.2a). Just inferior to the apex is a shallow vertical groove called the *philtrum* (fil'trum). The external openings of the nose, the *nostrils* or *nares* (na'rēz), are bounded laterally by the flared *alae*.

The skeletal framework of the external nose is fashioned by the nasal and frontal bones superiorly (forming the bridge and root, respectively), the maxillary bones laterally, and flexible plates of hyaline cartilage (the alar and septal cartilages, and the lateral processes of the septal cartilage) inferiorly (Figure 22.2b). Noses vary a great deal in size and shape, largely because of differences in the nasal cartilages. The skin covering the nose's dorsal and lateral aspects is thin and contains many sebaceous glands.

The internal **nasal cavity** lies in and posterior to the external nose. During breathing, air enters the cavity by passing through the **nostrils**, or **nares** (Figure 22.2a and Figure 22.3c). The nasal cavity is divided by a midline **nasal septum**, formed anteriorly by the septal cartilage and posteriorly by the vomer bone and perpendicular plate of the ethmoid bone (see Figure 7.14b, p. 213). The nasal cavity is continuous posteriorly with the nasal portion of the pharynx through the **posterior nasal apertures**, also called the *choanae* (ko-a'ne; "funnels").

The roof of the nasal cavity is formed by the ethmoid and sphenoid bones of the skull. The floor is formed by the *palate*, which separates the nasal cavity from the oral cavity below. Anteriorly, where the palate is supported by the palatine bones and processes of the maxillary bones, it is called the **hard palate**. The unsupported posterior portion is the muscular **soft palate**.

The part of the nasal cavity just superior to the nostrils, called the **nasal vestibule**, is lined with skin containing sebaceous and sweat glands and numerous hair follicles. The hairs, or **vibrissae** (vi-bris'e; *vibro* = to quiver), filter coarse particles (dust, pollen) from inspired air. The rest of the nasal cavity is lined with two types of mucous membrane. The **olfactory epithelium** (**mucosa**), lining the slitlike superior region of the

TABLE 22.1 Principal Organs of the Respiratory System

| STRUCTURE | DESCRIPTION, GENERAL AND DISTINCTIVE FEATURES | FUNCTION |
|-------------------|--|---|
| Nose | Jutting external portion is supported by bone and cartilage. Internal nasal cavity is divided by midline nasal septum and lined with mucosa. Roof of nasal cavity contains olfactory epithelium. | Produces mucus; filters, warms, and moistens incoming air; resonance chamber for speech Receptors for sense of smell |
| Paranasal sinuses | Mucosa-lined, air-filled cavities in cranial bones surrounding nasal cavity. | Same as for nasal cavity; also lighten skull |
| Pharynx | Passageway connecting nasal cavity to larynx and oral cavity to esophagus. Three subdivisions: nasopharynx, oropharynx, and laryngopharynx. Houses tonsils (lymphoid tissue masses involved in protection against pathogens). | Passageway for air and food Facilitates exposure of immune system to inhaled antigens |
| Larynx | Connects pharynx to trachea. Has framework of cartilage and dense connective tissue. Opening (glottis) can be closed by epiglottis or vocal folds. Houses vocal folds (true vocal cords). | Air passageway; prevents food from entering lower respiratory tract Voice production |
| Trachea | Flexible tube running from larynx and dividing inferiorly into two main bronchi. Walls contain C-shaped cartilages that are incomplete posteriorly where connected by trachealis muscle. | Air passageway; cleans, warms, and moistens incoming air |
| Bronchial tree | Consists of right and left main bronchi, which subdivide within the lungs to form lobar and segmental bronchi and bronchioles. Bronchiolar walls lack cartilage but contain complete layer of smooth muscle. Constriction of this muscle impedes expiration. | Air passageways connecting trachea with alveoli; cleans, warms, and moistens incoming air |
| Alveoli | Microscopic chambers at termini of bronchial tree. Walls of simple squamous epithelium are underlain by thin basement membrane. External surfaces are intimately associated with pulmonary capillaries. Special alveolar cells produce surfactant. | Main sites of gas exchange Reduces surface tension; helps prevent lung collapse |
| Lungs | Paired composite organs that flank mediastinum in thorax. Composed primarily of alveoli and respiratory passageways. Stroma is fibrous elastic connective tissue, allowing lungs to recoil passively during expiration. | House respiratory passages smaller than the main bronchi |
| Pleurae | Serous membranes. Parietal pleura lines thoracic cavity; visceral pleura covers external lung surfaces. | Produce lubricating fluid and compartmentalize lungs |

nasal cavity, contains smell receptors. The balance of the nasal cavity mucosa, the **respiratory mucosa**, is a pseudostratified ciliated columnar epithelium, containing scattered *goblet cells*, that rests on a lamina propria richly supplied with *mucous* and *serous glands*. (Mucous cells secrete mucus, and serous cells secrete a watery fluid containing enzymes.)

Each day, these glands secrete about a quart (or a liter) of mucus containing *lysozyme*, an antibacterial enzyme. The sticky mucus traps inspired dust, bacteria, and other debris, while lysozyme attacks and destroys bacteria chemically. The epithelial cells of the respiratory mucosa also secrete *defensins*, natural antibiotics that help get rid of invading microbes. Additionally, the high water content of the mucus film acts to humidify the inhaled air.

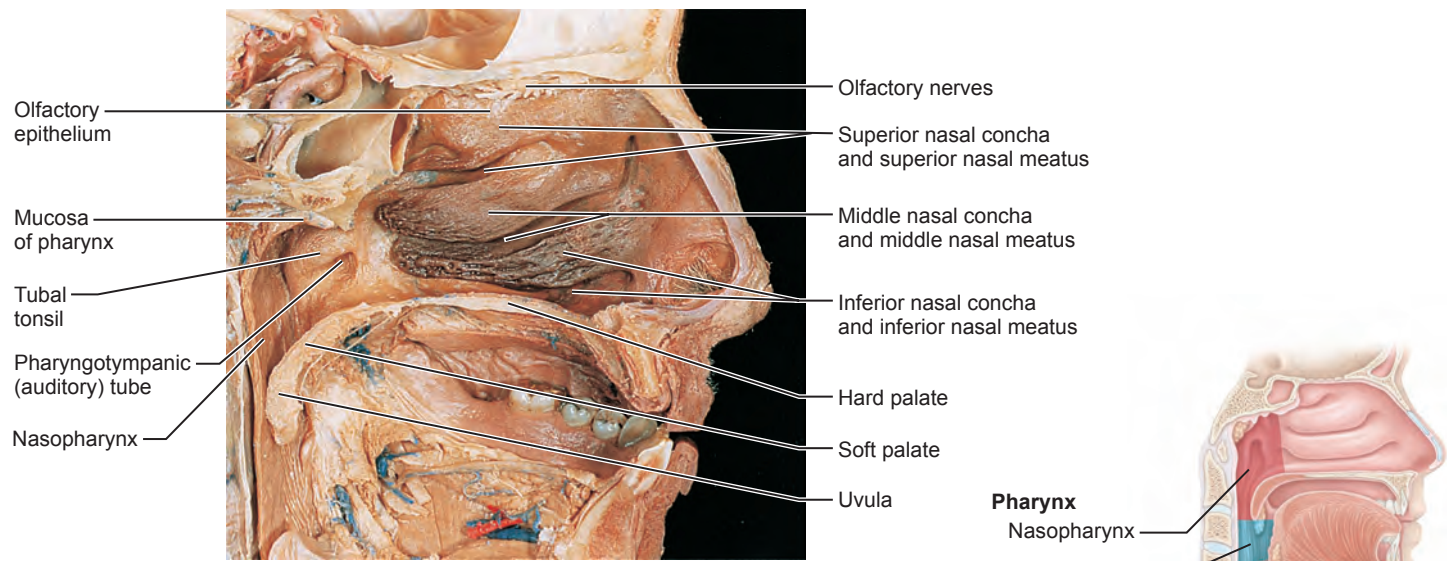
The ciliated cells of the respiratory mucosa create a gentle current that moves the sheet of contaminated mucus posteriorly toward the throat, where it is swallowed and digested by stomach juices. We are usually unaware of this important action of our nasal cilia, but when exposed to cold air they become sluggish, allowing mucus to accumulate in the nasal cavity and

then dribble out the nostrils. This along with the fact that water vapor in expired air tends to condense at these lower temperatures helps explain why you might have a “runny” nose on a crisp, wintry day.

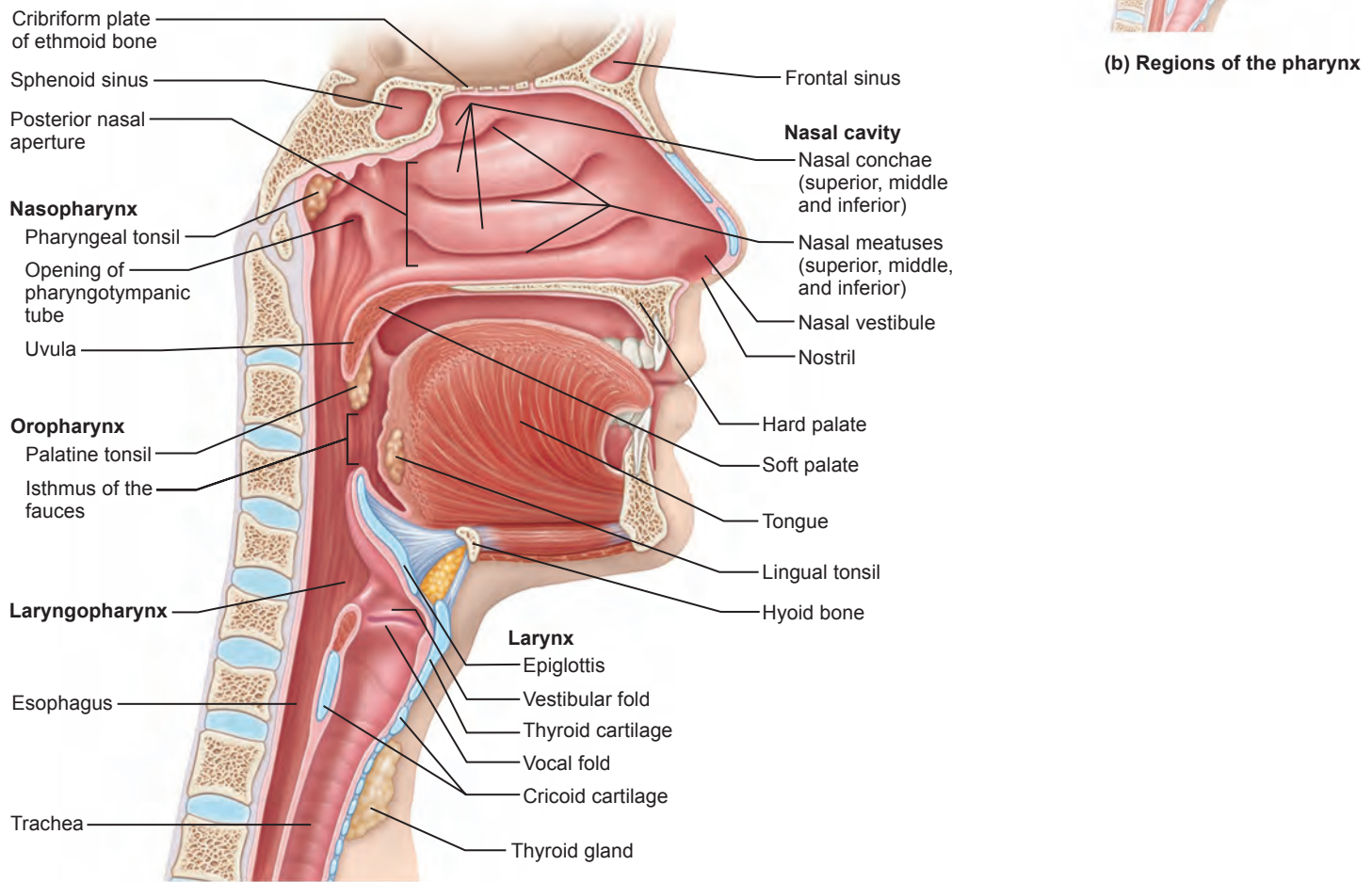
The nasal mucosa is richly supplied with sensory nerve endings, and contact with irritating particles (dust, pollen, and the like) triggers a sneeze reflex. The sneeze forces air outward in a violent burst—a somewhat crude way of expelling irritants from the nose.

Rich plexuses of capillaries and thin-walled veins underlie the nasal epithelium and warm incoming air as it flows across the mucosal surface. When the inspired air is cold, the vascular plexus becomes engorged with blood, thereby intensifying the air-heating process. Because of the abundance and superficial location of these blood vessels, nosebleeds are common and often profuse.

Protruding medially from each lateral wall of the nasal cavity are three scroll-like mucosa-covered projections, the *superior*, *middle*, and *inferior nasal conchae* (kong'ke) (Figure 22.3). The groove inferior to each concha is a *nasal meatus* (me-a'tus). The



(a) Photograph



(c) Illustration

Figure 22.3 The upper respiratory tract. Midsagittal section of the head and neck. (See also *A Brief Atlas of the Human Body*, Figure 47.)

curved conchae greatly increase the mucosal surface area exposed to the air and enhance air turbulence in the cavity. The gases in inhaled air swirl through the twists and turns, but heavier, nongaseous particles tend to be deflected onto the mucus-coated surfaces, where they become trapped. As a result, few particles larger than 6 μm make it past the nasal cavity.

The conchae and nasal mucosa not only function during inhalation to filter, heat, and moisten the air, but also act during exhalation to reclaim this heat and moisture. In other words, the inhaled air cools the conchae, then during exhalation these cooled conchae precipitate moisture and extract heat from the humid air flowing over them. This reclamation process minimizes the amount of moisture and heat lost from the body through breathing, helping us to survive in dry and cold climates.

The nasal cavity is surrounded by a ring of **paranasal sinuses** (Figure 22.3c). They are located in the frontal, sphenoid, ethmoid, and maxillary bones (see Figure 7.15, p. 216). The sinuses lighten the skull, and together with the nasal cavity they warm and moisten the air. The mucus they produce ultimately flows into the nasal cavity, and the suctioning effect created by nose blowing helps drain the sinuses.

HOMEOSTATIC IMBALANCE

Cold viruses, streptococcal bacteria, and various allergens can cause **rhinitis** (ri-ni'tis), inflammation of the nasal mucosa accompanied by excessive mucus production, nasal congestion, and postnasal drip. The nasal mucosa is continuous with that of the rest of the respiratory tract, explaining the typical nose to throat to chest progression of colds. Because the mucosa extends tentacle-like into the nasolacrimal (tear) ducts and paranasal sinuses, nasal cavity infections often spread to those regions, causing **sinusitis** (inflamed sinuses). When the passageways connecting the sinuses to the nasal cavity are blocked with mucus or infectious material, the air in the sinus cavities is absorbed. The result is a partial vacuum and a **sinus headache** localized over the inflamed areas. ■

The Pharynx

The funnel-shaped **pharynx** (far'ingks) connects the nasal cavity and mouth superiorly to the larynx and esophagus inferiorly. Commonly called the *throat*, the pharynx vaguely resembles a short length of garden hose as it extends for about 13 cm (5 inches) from the base of the skull to the level of the sixth cervical vertebra (Figure 22.1).

From superior to inferior, the pharynx is divided into three regions—the **nasopharynx**, **oropharynx**, and **laryngopharynx** (Figure 22.3b). The muscular pharynx wall is composed of skeletal muscle throughout its length (see Table 10.3, pp. 334–335). However, the cellular composition of its mucosa varies from one pharyngeal region to another.

The Nasopharynx

The **nasopharynx** is posterior to the nasal cavity, inferior to the sphenoid bone, and superior to the level of the soft palate. Because it lies above the point where food enters the body, it serves

only as an air passageway. During swallowing, the soft palate and its pendulous **uvula** (u'vu-lah; “little grape”) move superiorly, an action that closes off the nasopharynx and prevents food from entering the nasal cavity. (When we giggle, this sealing action fails and fluids being swallowed can end up spraying out the nose.)

The nasopharynx is continuous with the nasal cavity through the posterior nasal apertures (Figure 22.3c). Its pseudostratified ciliated epithelium takes over the job of propelling mucus where the nasal mucosa leaves off. High on its posterior wall is the **pharyngeal tonsil** (far-rin'je-al) (or **adenoids**), which traps and destroys pathogens entering the nasopharynx in air.

HOMEOSTATIC IMBALANCE

Infected and swollen adenoids block air passage in the nasopharynx, making it necessary to breathe through the mouth. As a result, the air is not properly moistened, warmed, or filtered before reaching the lungs. When the adenoids are chronically enlarged, both speech and sleep may be disturbed. ■

The **pharyngotympanic (auditory) tubes**, which drain the middle ear cavities and allow middle ear pressure to equalize with atmospheric pressure, open into the lateral walls of the nasopharynx (Figure 22.3a). A ridge of pharyngeal mucosa, referred to as a **tubal tonsil**, arches over each of these openings. Because of their strategic location, the tubal tonsils help protect the middle ear against infections likely to spread from the nasopharynx. The pharyngeal tonsil, superoposterior and medial to the tubal tonsils, also plays this protective role.

The Oropharynx

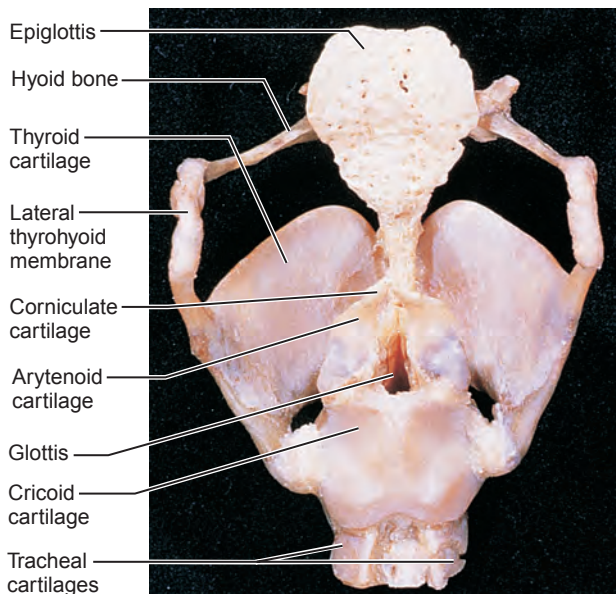
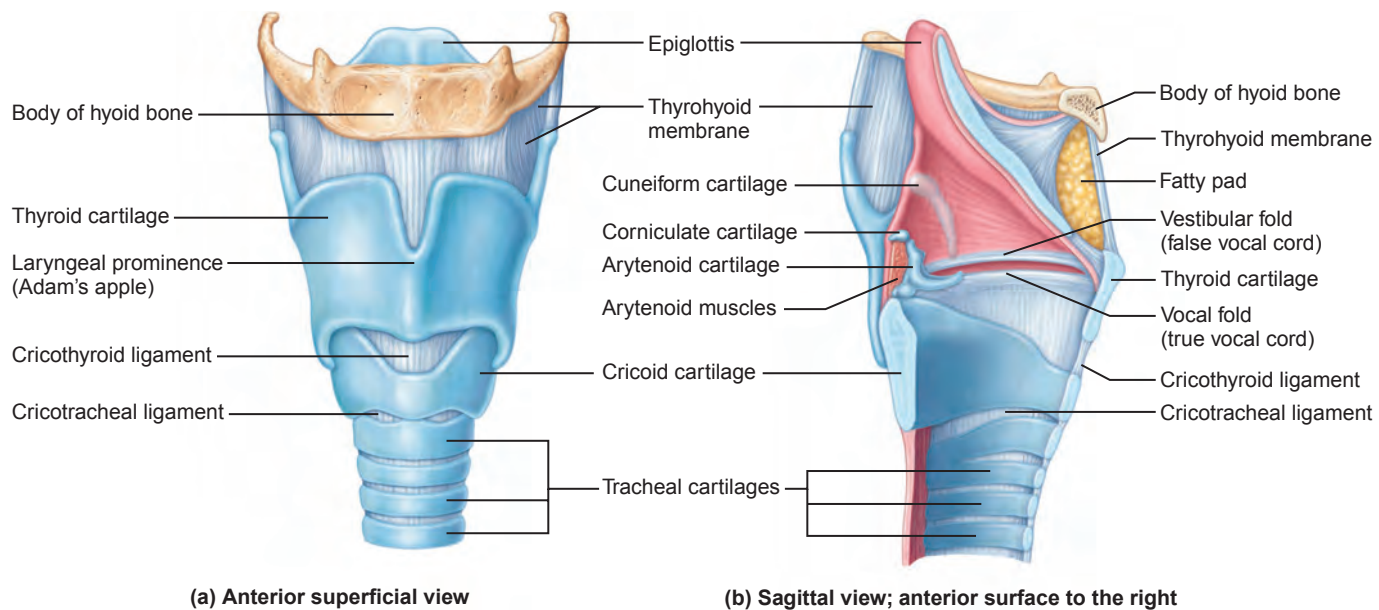
The **oropharynx** lies posterior to the oral cavity and is continuous with it through an archway called the **isthmus of the fauces** (faw'sēz; “throat”) (Figure 22.3c). Because the oropharynx extends inferiorly from the level of the soft palate to the epiglottis, both swallowed food and inhaled air pass through it.

As the nasopharynx blends into the oropharynx, the epithelium changes from pseudostratified columnar to a more protective stratified squamous epithelium. This structural adaptation accommodates the increased friction and greater chemical trauma accompanying food passage.

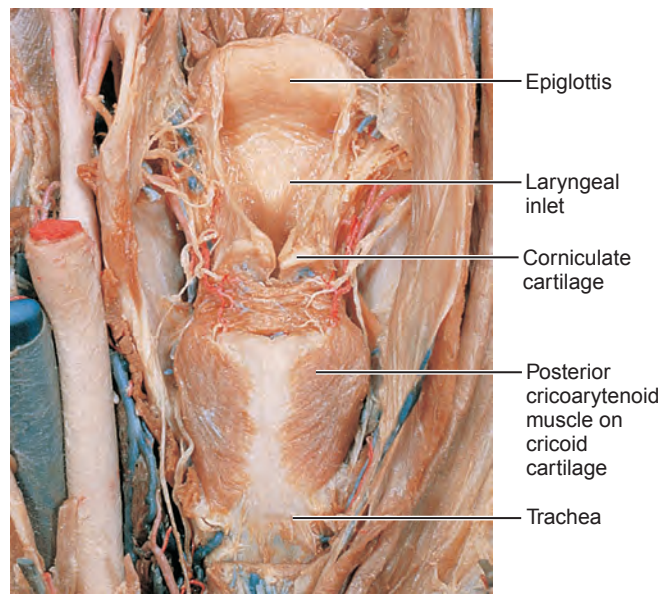
The paired **palatine tonsils** lie embedded in the oropharyngeal mucosa of the lateral walls of the fauces. The **lingual tonsil** covers the posterior surface of the tongue.

The Laryngopharynx

Like the oropharynx above it, the **laryngopharynx** (lah-ring'go-far'ingks) serves as a passageway for food and air and is lined with a stratified squamous epithelium. It lies directly posterior to the upright epiglottis and extends to the larynx, where the respiratory and digestive pathways diverge. At that point the laryngopharynx is continuous with the esophagus posteriorly. The esophagus conducts food and fluids to the stomach; air enters the larynx anteriorly. During swallowing, food has the “right of way,” and air passage temporarily stops.



(c) Photograph of cartilaginous framework of the larynx, posterior view



(d) Photograph of posterior aspect

Figure 22.4 The larynx.

The Larynx

Basic Anatomy

The **larynx** (lar'ingks), or voice box, extends for about 5 cm (2 inches) from the level of the third to the sixth cervical vertebra. Superiorly it attaches to the hyoid bone and opens into the laryngopharynx. Inferiorly it is continuous with the trachea (Figure 22.3c).

The larynx has three functions. Its two main tasks are to provide a *patent* (open) airway and to act as a switching mechanism to route air and food into the proper channels. Because it houses

the vocal folds (vocal cords), the third function of the larynx is voice production.

The framework of the larynx is an intricate arrangement of nine cartilages connected by membranes and ligaments (Figure 22.4). Except for the epiglottis, all laryngeal cartilages are hyaline cartilages. The large, shield-shaped **thyroid cartilage** is formed by the fusion of two cartilage plates. The midline **laryngeal prominence** (lah-rin'je-al), which marks the fusion point, is obvious externally as the *Adam's apple*. The thyroid cartilage is typically larger in males than in females because male sex hormones stimulate its growth during puberty. Inferior to the thyroid cartilage is the ring-shaped

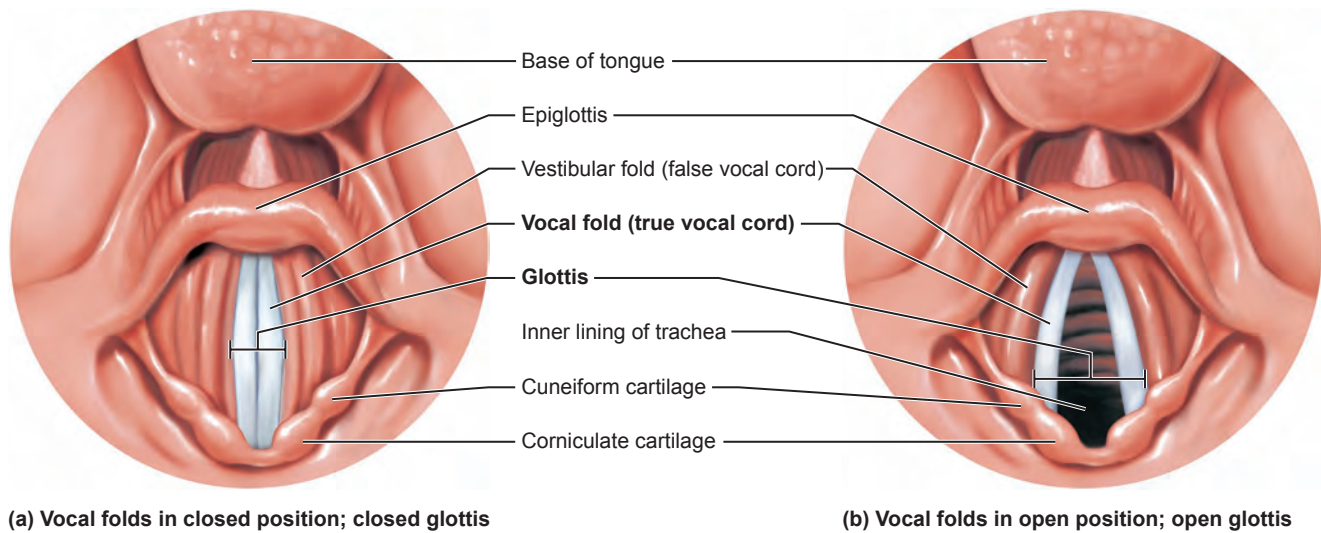


Figure 22.5 Movements of the vocal folds. Drawings of superior views of the larynx and vocal folds, as if seen through a laryngoscope.

cricoid cartilage (kri'koid), perched atop and anchored to the trachea inferiorly.

Three pairs of small cartilages, **arytenoid** (ar'i-te'noid), **cuneiform** (ku-ne'i-form), and **corniculate cartilages**, form part of the lateral and posterior walls of the larynx. The most important of these are the pyramid-shaped arytenoid cartilages, which anchor the vocal folds.

The ninth cartilage, the flexible, spoon-shaped **epiglottis** (ep'i-glot'is; "above the glottis"), is composed of elastic cartilage and is almost entirely covered by a taste bud-containing mucosa. The epiglottis extends from the posterior aspect of the tongue to its anchoring point on the anterior rim of the thyroid cartilage (Figure 22.4b and c).

When only air is flowing into the larynx, the inlet to the larynx is open wide and the free edge of the epiglottis projects upward. During swallowing, the larynx is pulled superiorly and the epiglottis tips to cover the laryngeal inlet. Because this action keeps food out of the lower respiratory passages, the epiglottis has been called the guardian of the airways. Anything other than air entering the larynx initiates the cough reflex, which acts to expel the substance. This protective reflex does not work when we are unconscious, so it is never a good idea to administer liquids when attempting to revive an unconscious person.

Lying under the laryngeal mucosa on each side are the **vocal ligaments**, which attach the arytenoid cartilages to the thyroid cartilage. These ligaments, composed largely of elastic fibers, form the core of mucosal folds called the **vocal folds**, or **true vocal cords**, which appear pearly white because they lack blood vessels (Figure 22.5).

The vocal folds vibrate, producing sounds as air rushes up from the lungs. The vocal folds and the medial opening between them through which air passes are called the **glottis**. Superior to the vocal folds is a similar pair of mucosal folds called the **vestibular folds**, or **false vocal cords**. These play no direct part in sound production but help to close the glottis when we swallow.

The superior portion of the larynx, an area subject to food contact, is lined by stratified squamous epithelium. Below the vocal folds the epithelium is a pseudostratified ciliated columnar type that acts as a dust filter. The power stroke of its cilia is directed upward toward the pharynx so that mucus is continually moved *away* from the lungs. We help to move mucus up and out of the larynx when we "clear our throat."

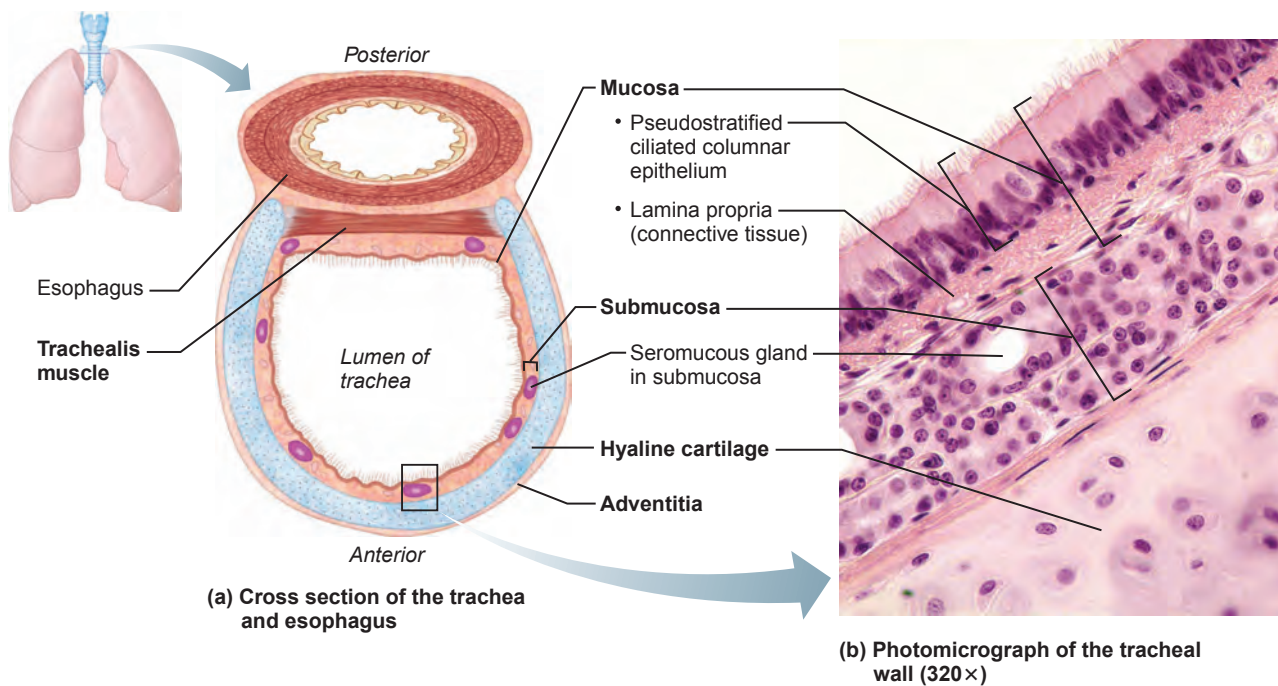
Voice Production

Speech involves the intermittent release of expired air and the opening and closing of the glottis. The length of the vocal folds and the size of the glottis change with the action of the intrinsic laryngeal muscles that clothe the cartilages. Most of these muscles move the arytenoid cartilages. As the length and tension of the vocal folds change, the pitch of the sound varies. Generally, the tenser the vocal folds, the faster they vibrate and the higher the pitch.

As a boy's larynx enlarges during puberty, his vocal folds become longer and thicker. Because this causes them to vibrate more slowly, his voice becomes deeper. Until the young man learns to control his newly enlarged vocal folds, his voice "cracks."

Loudness of the voice depends on the force with which the airstream rushes across the vocal folds. The greater the force, the stronger the vibration and the louder the sound. The vocal folds do not move at all when we whisper, but they vibrate vigorously when we yell. The power source for creating the airstream is the muscles of the chest, abdomen, and back.

The vocal folds actually produce buzzing sounds. The perceived quality of the voice depends on the coordinated activity of many structures above the glottis. For example, the entire length of the pharynx acts as a resonating chamber, to amplify and enhance the sound quality. The oral, nasal, and sinus cavities also contribute to vocal resonance. In addition, good enunciation depends on the "shaping" of sound into recognizable consonants and vowels by muscles in the pharynx, tongue, soft palate, and lips.



(c) Scanning electron micrograph of cilia in the trachea (2500 \times)

Figure 22.6 Tissue composition of the tracheal wall. In the scanning electron micrograph in (c), the cilia appear as yellow, grasslike projections. Mucus-secreting goblet cells (orange) with short microvilli are interspersed between the ciliated cells.

HOMEOSTATIC IMBALANCE

Inflammation of the vocal folds, or **laryngitis**, causes the vocal folds to swell, interfering with their vibration. This produces a change in the voice tone, hoarseness, or in severe cases inability to speak above a whisper. Laryngitis is also caused by overuse of the voice, very dry air, bacterial infections, tumors on the vocal folds, and inhalation of irritating chemicals. ■

Sphincter Functions of the Larynx

Under certain conditions, the vocal folds act as a sphincter that prevents air passage. During abdominal straining associated with defecation, the glottis closes to prevent exhalation and the abdominal muscles contract, causing the intra-abdominal pressure to rise. These events, collectively known as **Valsalva's maneuver**, help empty the rectum and can also splint (stabilize) the body trunk when one lifts a heavy load.

The Trachea

The **trachea** (tra'ke-ah), or *windpipe*, descends from the larynx through the neck and into the mediastinum. It ends by dividing into the two main bronchi at midthorax (see Figure 22.1). In humans, it is 10–12 cm (about 4 inches) long and 2 cm (3/4 inch) in diameter, and very flexible and mobile. Interestingly, early anatomists mistook the trachea for a rough-walled artery (*trachea* = rough).

The tracheal wall consists of several layers that are common to many tubular body organs—the *mucosa*, *submucosa*, and *adventitia*—plus a layer of hyaline cartilage (Figure 22.6). The **mucosa** has the same goblet cell-containing pseudostratified epithelium that occurs throughout most of the respiratory tract. Its cilia continually propel debris-laden mucus toward the pharynx. This epithelium rests on a fairly thick lamina propria that has a rich supply of elastic fibers.

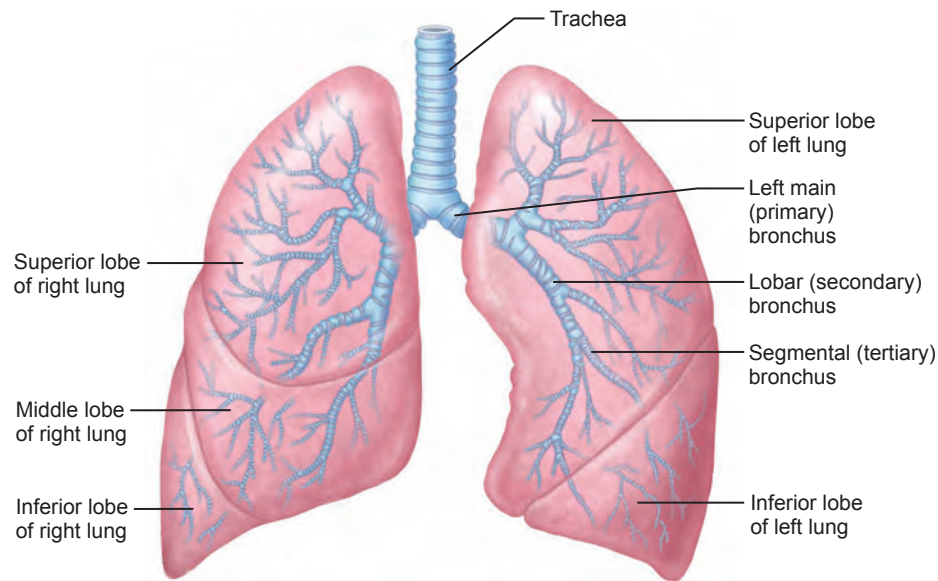


Figure 22.7 Conducting zone passages. The air pathway inferior to the larynx consists of the trachea and the main, lobar, and segmental bronchi, which branch into the smaller bronchi and bronchioles until the terminal bronchioles of the lungs are reached.

HOMEOSTATIC IMBALANCE

Smoking inhibits and ultimately destroys cilia, after which coughing is the only means of preventing mucus from accumulating in the lungs. For this reason, smokers with respiratory congestion should avoid medications that inhibit the cough reflex. ■

The **submucosa**, a connective tissue layer deep to the mucosa, contains seromucous glands that help produce the mucus “sheets” within the trachea. The submucosa is supported by 16 to 20 C-shaped rings of hyaline cartilage encased by the **adventitia**, the outermost layer of connective tissue (Figure 22.6).

The trachea’s elastic elements make it flexible enough to stretch and move inferiorly during inspiration and recoil during expiration, but the cartilage rings prevent it from collapsing and keep the airway patent despite the pressure changes that occur during breathing. The open posterior parts of the cartilage rings, which abut the esophagus (Figure 22.6a), are connected by smooth muscle fibers of the **trachealis muscle** and by soft connective tissue. Because this portion of the tracheal wall is not rigid, the esophagus can expand anteriorly as swallowed food passes through it. Contraction of the trachealis muscle decreases the trachea’s diameter, causing expired air to rush upward from the lungs with greater force. This action helps to expel mucus from the trachea when we cough by accelerating the exhaled air to speeds of 100 mph!

The last tracheal cartilage is expanded, and a spar of cartilage, called the **carina** (kar-ri’nah; “keel”), projects posteriorly from its inner face, marking the point where the trachea branches into the two *main bronchi*. The mucosa of the carina is highly sensitive and violent coughing is triggered when a foreign object makes contact with it.

By the time incoming air reaches the end of the trachea, it is warm, cleansed of most impurities, and saturated with water vapor.

HOMEOSTATIC IMBALANCE

Tracheal obstruction is life threatening. Many people have suffocated after choking on a piece of food that suddenly closed off their trachea. The **Heimlich maneuver**, a procedure in which air in the victim’s lungs is used to “pop out,” or expel, an obstructing piece of food, has saved many people from becoming victims of “café coronaries.” The maneuver is simple to learn and easy to do. However, it is best learned by demonstration because cracked ribs are a distinct possibility when it is done incorrectly. ■

CHECK YOUR UNDERSTANDING

1. Air moving from the nose to the trachea passes by a number of structures. List (in order) as many of these structures as you can.
2. Which structure seals the larynx when we swallow?
3. Which structural features of the trachea allow it to expand and contract, yet keep it from collapsing?

For answers, see Appendix G.

The Bronchi and Subdivisions

- Distinguish between conducting and respiratory zone structures.
- Describe the makeup of the respiratory membrane, and relate structure to function.

The air passageways in the lungs branch and branch again, about 23 times overall. This branching pattern of airways is often called the **bronchial** or **respiratory tree** (Figure 22.7). The

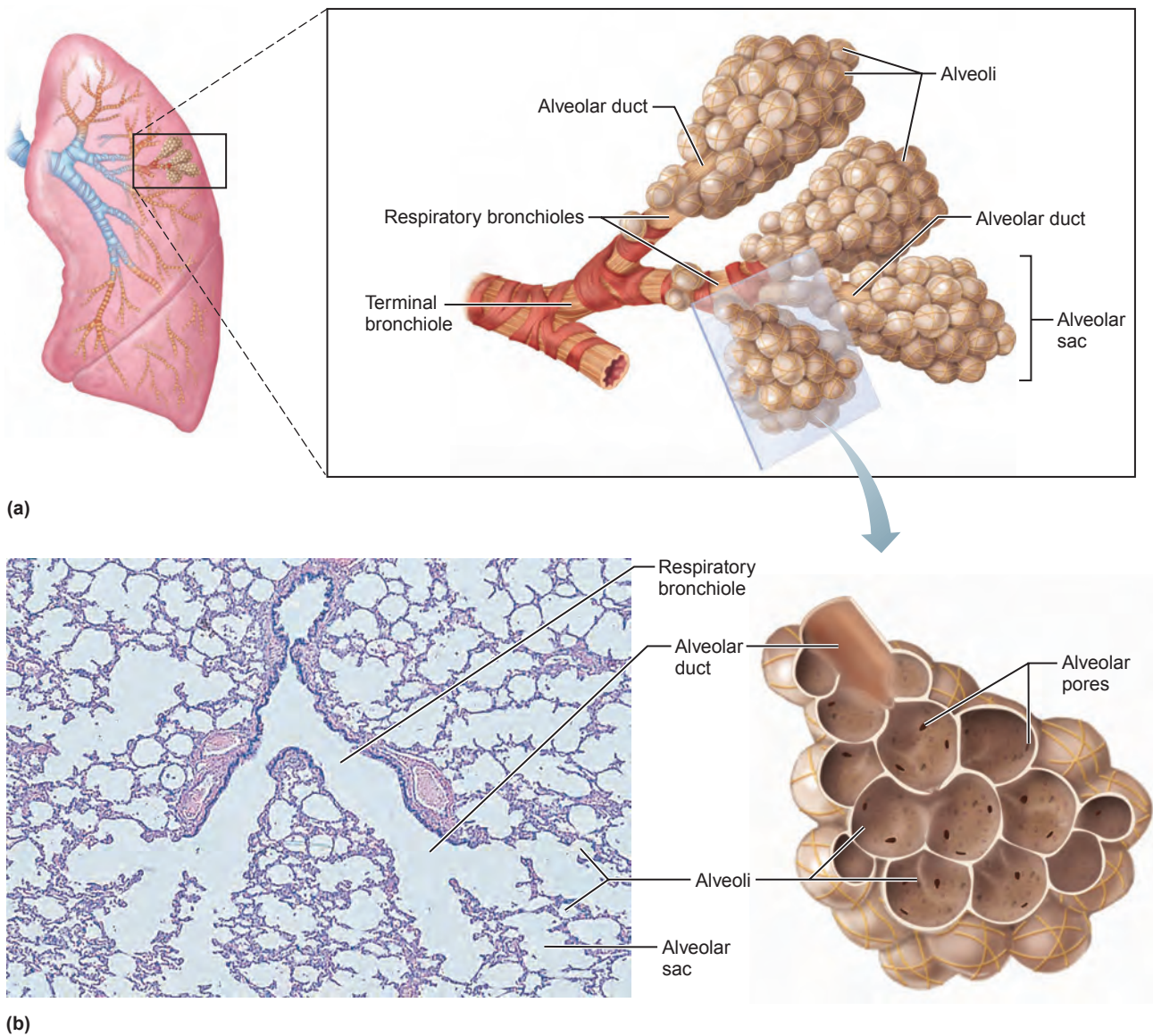


Figure 22.8 Respiratory zone structures. (a) Diagrammatic view of respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli. (b) Photomicrograph of a section of human lung, showing the respiratory structures that form the final divisions of the bronchial tree (70x). Notice the thinness of the alveolar walls.

bronchial tree is the site where conducting zone structures give way to respiratory zone structures (Figure 22.8).

Conducting Zone Structures

The trachea divides to form the **right and left main (primary) bronchi** (brong'ki) approximately at the level of T₇ in an erect (standing) person. Each bronchus runs obliquely in the mediastinum before plunging into the medial depression (hilum) of the lung on its own side (Figure 22.7). The right main bronchus is wider, shorter, and more vertical than the left. Consequently, it is the more common site for an inhaled foreign object to become lodged.

Once inside the lungs, each main bronchus subdivides into **lobar (secondary) bronchi**—three on the right and two on the

left—each supplying one lung lobe. The lobar bronchi branch into third-order **segmental (tertiary) bronchi**, which divide repeatedly into smaller and smaller bronchi (fourth-order, fifth-order, etc.). Passages smaller than 1 mm in diameter are called **bronchioles** (“little bronchi”), and the tiniest of these, the **terminal bronchioles**, are less than 0.5 mm in diameter.

The tissue composition of the walls of the main bronchi mimics that of the trachea, but as the conducting tubes become smaller, the following structural changes occur:

- 1. Support structures change.** The cartilage rings are replaced by irregular *plates* of cartilage, and by the time the bronchioles are reached, supportive cartilage is no longer present in the tube walls. However, elastic fibers are found in the tube walls throughout the bronchial tree.

- 2. Epithelium type changes.** The mucosal epithelium thins as it changes from pseudostratified columnar to columnar and then to cuboidal in the terminal bronchioles. Cilia are sparse, and mucus-producing cells are absent in the bronchioles. For this reason, most airborne debris found at or below the level of the bronchioles must be removed by macrophages in the alveoli.
- 3. Amount of smooth muscle increases.** The relative amount of smooth muscle in the tube walls increases as the passageways become smaller. A complete layer of circular smooth muscle in the bronchioles and the lack of supporting cartilage (which would hinder constriction) allows the bronchioles to provide substantial resistance to air passage under certain conditions (as we will describe later).

Respiratory Zone Structures

Defined by the presence of thin-walled air sacs called **alveoli** (al-ve'o-li; *alveol* = small cavity), the respiratory zone begins as the terminal bronchioles feed into **respiratory bronchioles** within the lung (Figure 22.8). Protruding from these smallest bronchioles are scattered alveoli. The respiratory bronchioles lead into winding **alveolar ducts**, whose walls consist of diffusely arranged rings of smooth muscle cells, connective tissue fibers, and outpocketing alveoli. The alveolar ducts lead into terminal clusters of alveoli called **alveolar sacs**.

Many people mistakenly equate alveoli, the site of gas exchange, with alveolar sacs, but they are not the same thing. The alveolar sac is analogous to a bunch of grapes, and the alveoli are the individual grapes. The 300 million or so gas-filled alveoli in the lungs account for most of the lung volume and provide a tremendous surface area for gas exchange.

The Respiratory Membrane The walls of the alveoli are composed primarily of a single layer of squamous epithelial cells, called **type I cells**, surrounded by a flimsy basement membrane. The thinness of their walls is hard to imagine, but a sheet of tissue paper is 15 times thicker. The external surfaces of the alveoli are densely covered with a “cobweb” of pulmonary capillaries (Figure 22.9). Together, the alveolar and capillary walls and their fused basement membranes form the **respiratory membrane**, a 0.5- μm -thick *air-blood barrier* that has gas on one side and blood flowing past on the other (Figure 22.9c). Gas exchanges occur readily by simple diffusion across the respiratory membrane— O_2 passes from the alveolus into the blood, and CO_2 leaves the blood to enter the gas-filled alveolus.

Scattered amid the type I squamous cells that form the major part of the alveolar walls are cuboidal **type II cells** (Figure 22.9c). The type II cells secrete a fluid containing a detergent-like substance called *surfactant* that coats the gas-exposed alveolar surfaces. (We describe surfactant’s role in reducing the surface tension of the alveolar fluid later in this chapter.) Recently, type II cells have been shown to secrete a number of antimicrobial proteins that are important elements of innate immunity.

The alveoli have three other significant features: (1) They are surrounded by fine elastic fibers of the same type that surround

the entire bronchial tree. (2) Open **alveolar pores** connecting adjacent alveoli allow air pressure throughout the lung to be equalized and provide alternate air routes to any alveoli whose bronchi have collapsed due to disease. (3) Remarkably efficient **alveolar macrophages** crawl freely along the internal alveolar surfaces.

Although huge numbers of infectious microorganisms are continuously carried into the alveoli, alveolar surfaces are usually sterile. Because the alveoli are “dead ends,” aged and dead macrophages must be prevented from accumulating in them. Most macrophages simply get swept up by the ciliary current of superior regions and carried passively to the pharynx. In this manner, we clear and swallow over 2 million alveolar macrophages per hour!

The Lungs and Pleurae

- Describe the gross structure of the lungs and pleurae.

The paired **lungs** occupy all of the thoracic cavity except the mediastinum, which houses the heart, great blood vessels, bronchi, esophagus, and other organs (Figure 22.10).

Gross Anatomy of the Lungs

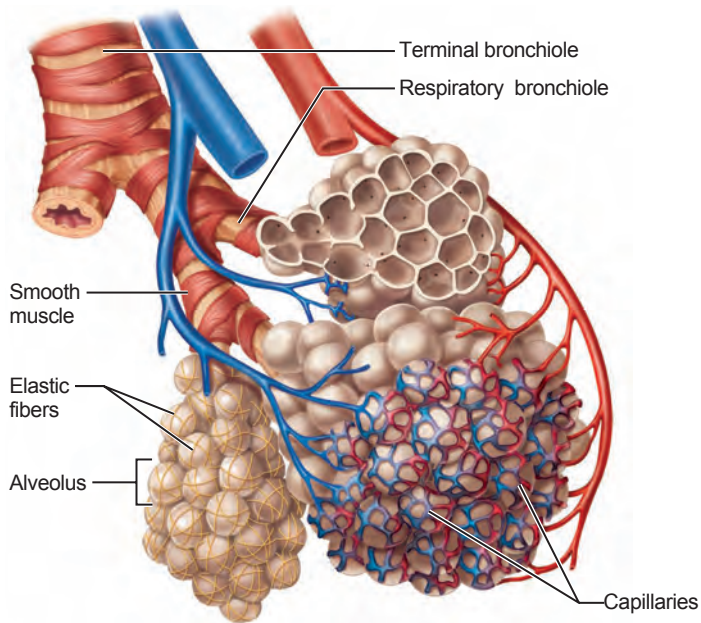
Each cone-shaped lung is surrounded by pleurae and connected to the mediastinum by vascular and bronchial attachments, collectively called the lung **root**. The anterior, lateral, and posterior lung surfaces lie in close contact with the ribs and form the continuously curving **costal surface**. Just deep to the clavicle is the **apex**, the narrow superior tip of the lung. The concave, inferior surface that rests on the diaphragm is the **base**.

On the mediastinal surface of each lung is an indentation, the **hilum**, through which pulmonary and systemic blood vessels, bronchi, lymphatic vessels, and nerves enter and leave the lungs. Each main bronchus plunges into the hilum on its own side and begins to branch almost immediately. All conducting and respiratory passageways distal to the main bronchi are found in the lungs.

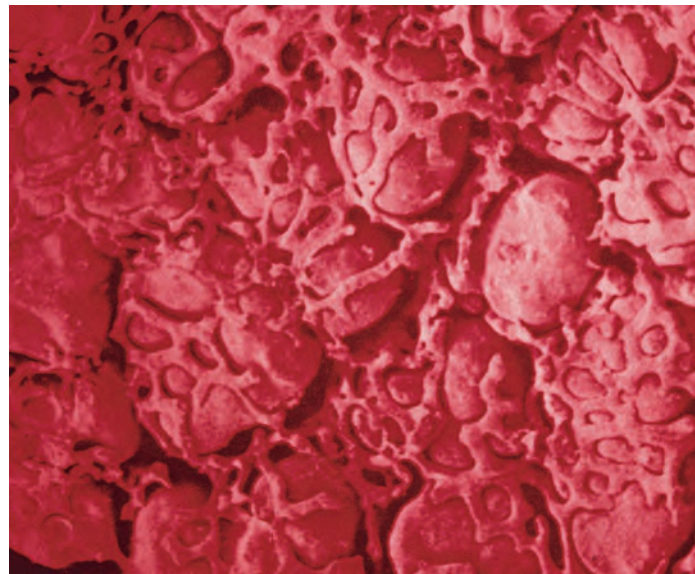
The two lungs differ slightly in shape and size because the apex of the heart is slightly to the left of the median plane. The left lung is smaller than the right, and the **cardiac notch**—a concavity in its medial aspect—is molded to and accommodates the heart (Figure 22.10a). The left lung is subdivided into superior and inferior **lobes** by the *oblique fissure*, whereas the right lung is partitioned into superior, middle, and inferior lobes by the *oblique* and *horizontal fissures*.

Each lobe contains a number of pyramid-shaped **bronchopulmonary segments** separated from one another by connective tissue septa. Each segment is served by its own artery and vein and receives air from an individual segmental (tertiary) bronchus. Initially each lung contains ten bronchopulmonary segments arranged in similar (but not identical) patterns (Figure 22.11). Subsequent fusion of adjacent segmental arteries reduces the number in the left lung to eight or nine segments.

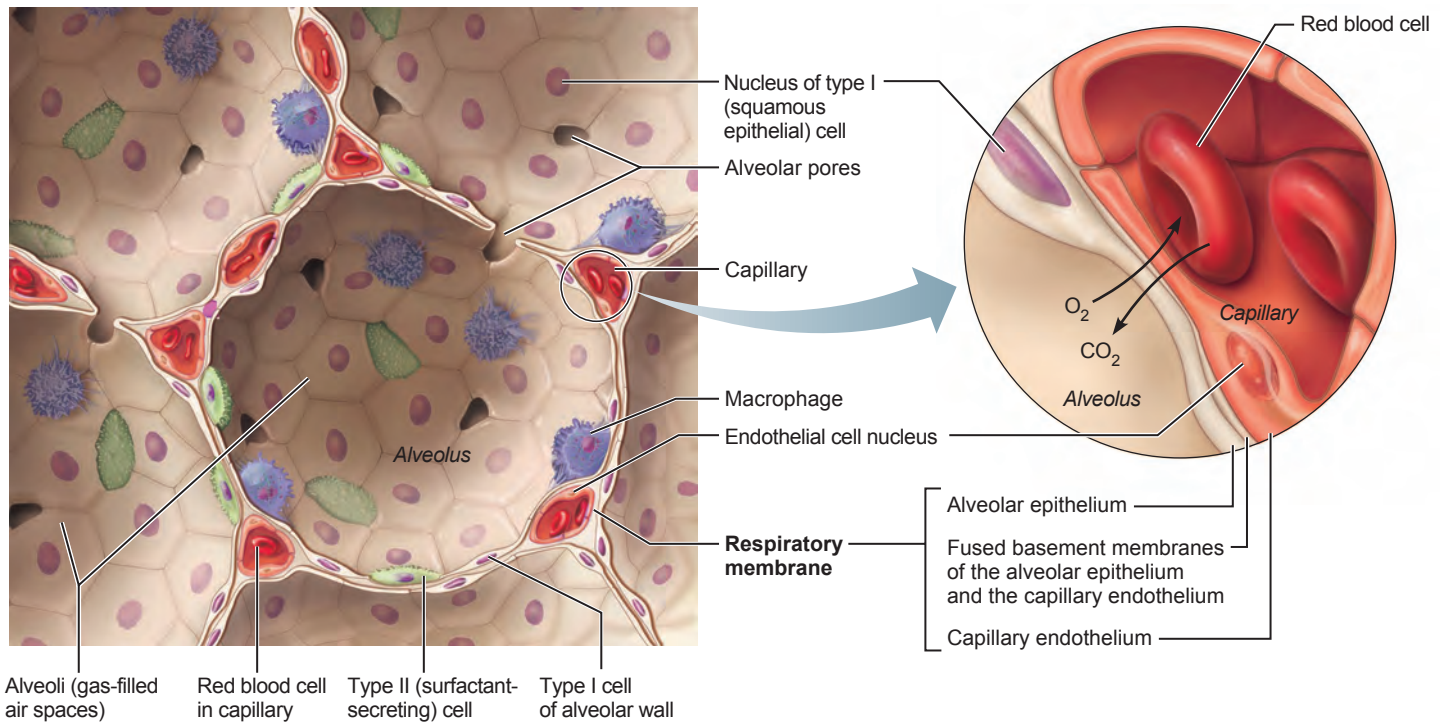
The bronchopulmonary segments are clinically important because pulmonary disease is often confined to one or a few



(a) Diagrammatic view of capillary-alveoli relationships



(b) Scanning electron micrograph of casts of alveoli and associated pulmonary capillaries (300x)



(c) Detailed anatomy of the respiratory membrane

Figure 22.9 Alveoli and the respiratory membrane. Elastic fibers and capillaries surround all alveoli, but for clarity they are shown only on some alveoli in (a).

SOURCE: (b) Kessel and Kardou/Visuals Unlimited.

segments. Their connective tissue partitions allow diseased segments to be surgically removed without damaging neighboring healthy segments or impairing their blood supply.

The smallest subdivisions of the lung visible with the naked eye are the **lobules**, which appear at the lung surface as hexa-

gons ranging from the size of a pencil eraser to the size of a penny (Figure 22.10b). Each lobule is served by a large bronchiole and its branches. In most city dwellers and in smokers, the connective tissue that separates the individual lobules is blackened with carbon.

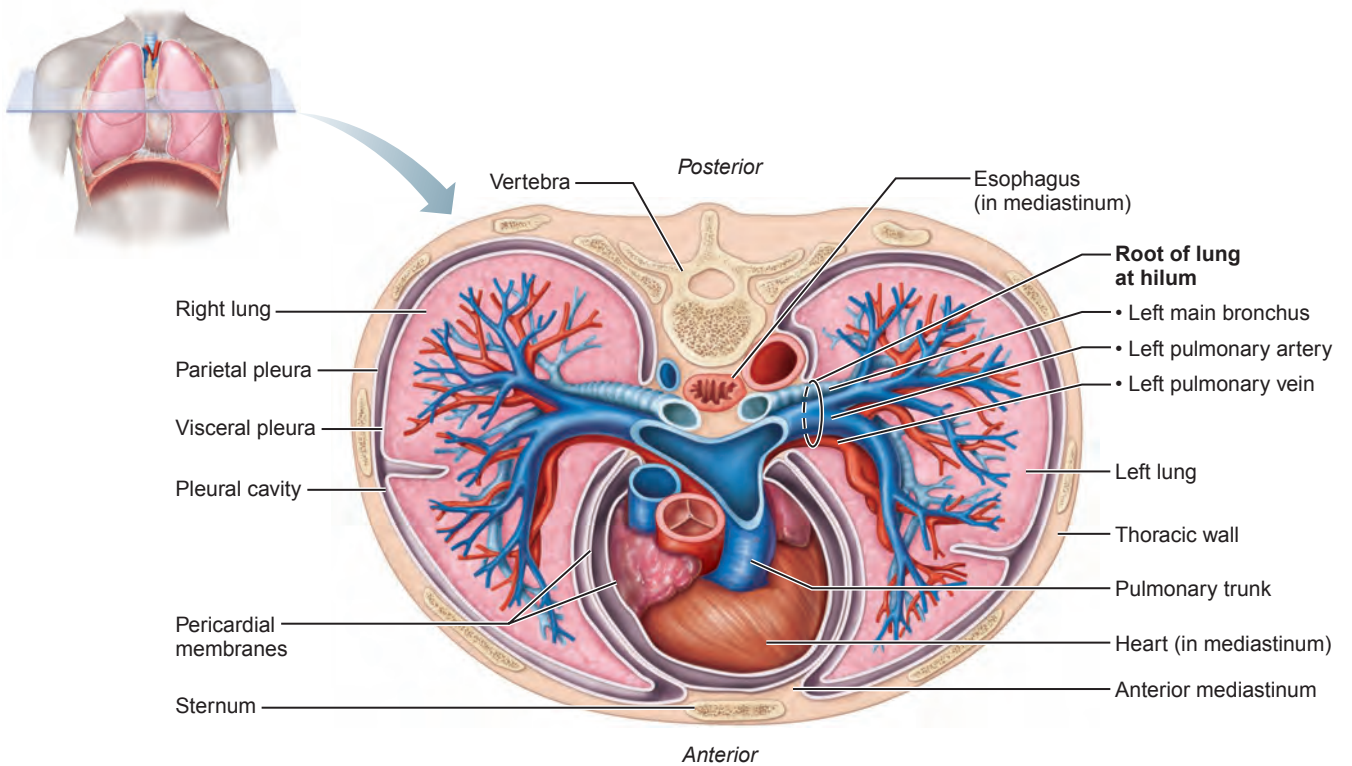
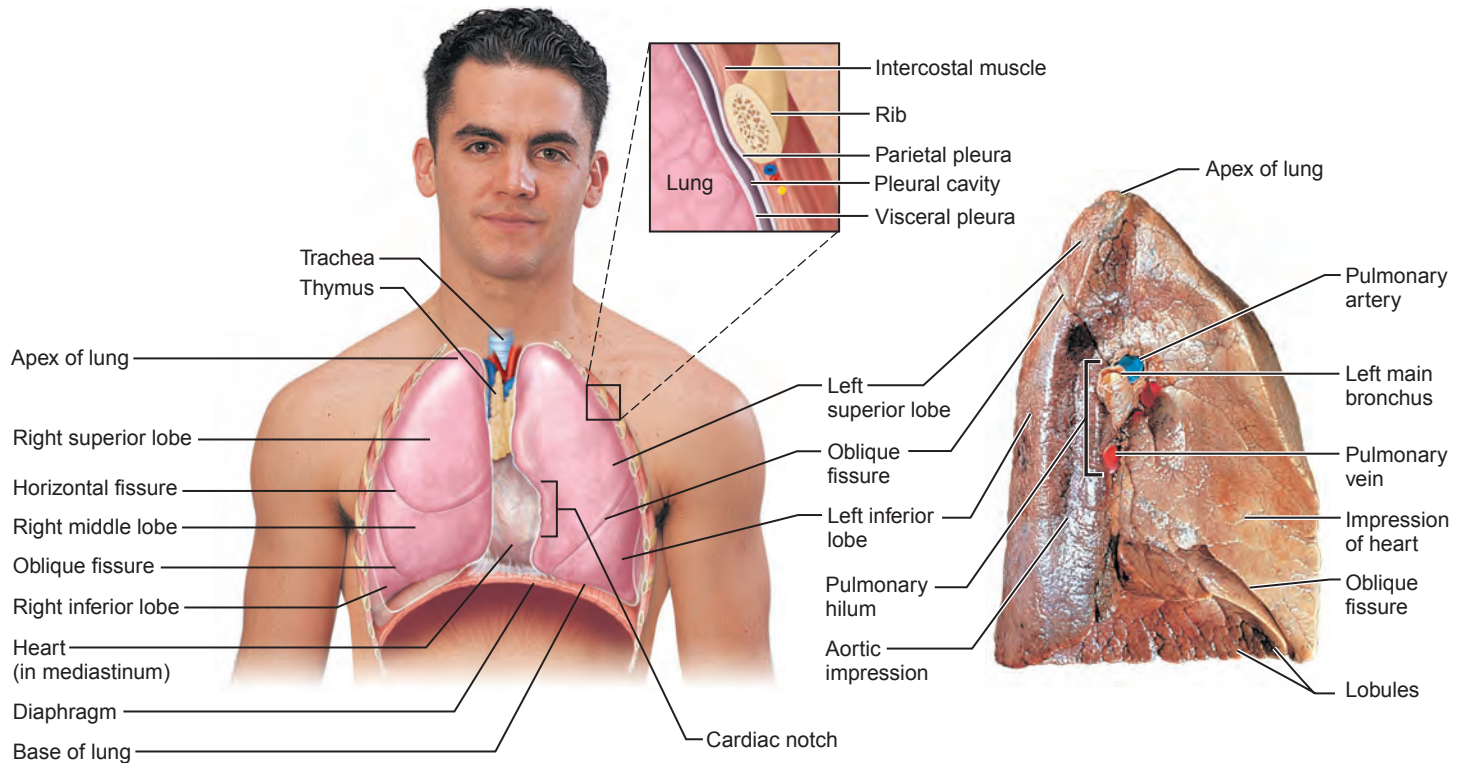


Figure 22.10 Anatomical relationships of organs in the thoracic cavity. In (c), the size of the pleural cavity is exaggerated for clarity.

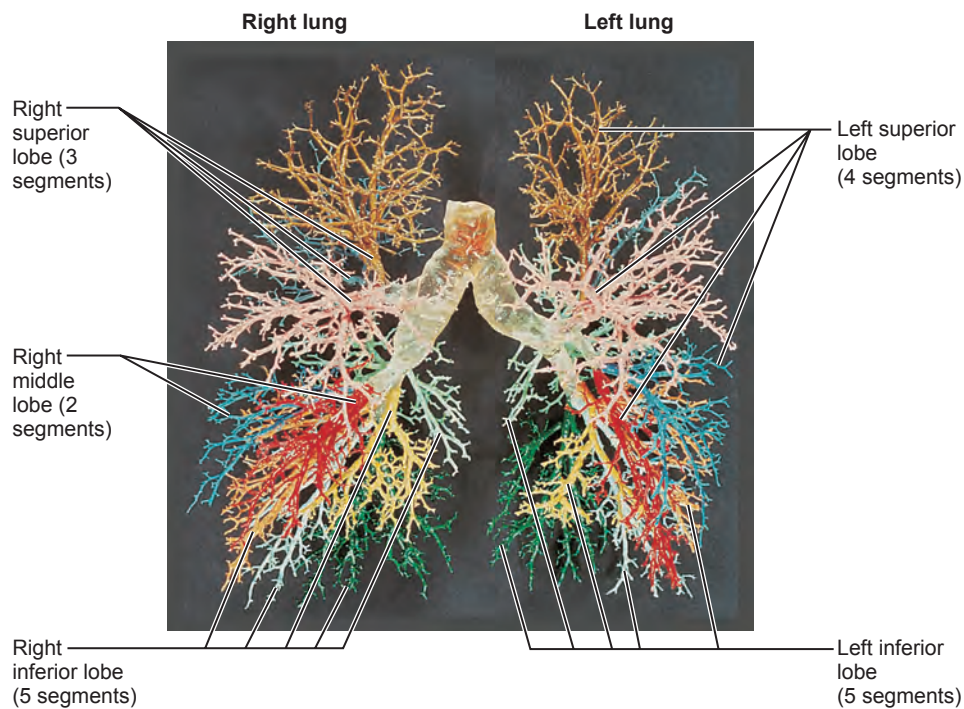


Figure 22.11 A cast of the bronchial tree. The individual bronchopulmonary segments have been painted different colors.

As we mentioned earlier, the lungs consist largely of air spaces. The balance of lung tissue, or its **stroma** (literally “mattress” or “bed”), is mostly elastic connective tissue. As a result, the lungs are soft, spongy, elastic organs that together weigh just over 1 kg (2.2 lb). The elasticity of healthy lungs helps to reduce the work of breathing, as we will describe shortly.

Blood Supply and Innervation of the Lungs

The lungs are perfused by two circulations, the pulmonary and the bronchial, which differ in size, origin, and function. Systemic venous blood that is to be oxygenated in the lungs is delivered by the **pulmonary arteries**, which lie anterior to the main bronchi (Figure 22.10c). In the lungs, the pulmonary arteries branch profusely along with the bronchi and finally feed into the **pulmonary capillary networks** surrounding the alveoli (see Figure 22.9a).

Freshly oxygenated blood is conveyed from the respiratory zones of the lungs to the heart by the **pulmonary veins**. Their tributaries course back to the hilum both with the corresponding bronchi and in the connective tissue septa separating the bronchopulmonary segments.

In contrast to the pulmonary circulation, the **bronchial arteries** provide oxygenated systemic blood to lung tissue. They arise from the aorta, enter the lungs at the hilum, and then run along the branching bronchi. They provide a high-pressure, low-volume supply of oxygenated blood to all lung tissues except the alveoli, which receive blood from the low-pressure, high-volume pulmonary circulation. Some systemic venous blood is drained from the lungs by the tiny bronchial veins, but there are multiple anastomoses between the two circulations, and most venous blood returns to the heart via the pulmonary veins.

Because *all* of the body’s blood passes through the lungs about once each minute, the lung capillary endothelium is an ideal location for enzymes that act on materials in the blood. Examples include *angiotensin converting enzyme*, which activates an important blood pressure hormone, and enzymes that inactivate certain prostaglandins.

The lungs are innervated by parasympathetic and sympathetic motor fibers, and visceral sensory fibers. These nerve fibers enter each lung through the **pulmonary plexus** on the lung root and run along the bronchial tubes and blood vessels in the lungs. Parasympathetic fibers constrict the air tubes, whereas the sympathetic nervous system dilates them.

The Pleurae

The **pleurae** (ploo’re; “sides”) form a thin, double-layered serosa. The layer called the **parietal pleura** covers the thoracic wall and superior face of the diaphragm (Figure 22.10a, c). It continues around the heart and between the lungs, forming the lateral walls of the mediastinal enclosure and snugly enclosing the lung root. From here, the pleura extends as the layer called the **visceral pleura** to cover the external lung surface, dipping into and lining its fissures.

The pleurae produce **pleural fluid**, which fills the slitlike **pleural cavity** between them. This lubricating secretion allows the lungs to glide easily over the thorax wall during our breathing movements. Although the pleurae slide easily across each other, their separation is strongly resisted by the surface tension of the pleural fluid. Consequently, the lungs cling tightly to the thorax wall and are forced to expand and recoil passively as the volume of the thoracic cavity alternately increases and decreases during breathing.

The pleurae also help divide the thoracic cavity into three chambers—the central mediastinum and the two lateral pleural compartments, each containing a lung. This compartmentalization helps prevent one mobile organ (for example, the lung or heart) from interfering with another. It also limits the spread of local infections.

HOMEOSTATIC IMBALANCE

Pleurisy (ploō'ri-se), inflammation of the pleurae, often results from pneumonia. Inflamed pleurae become rough, resulting in friction and stabbing pain with each breath. As the disease progresses, the pleurae may produce an excessive amount of fluid. This increased fluid relieves the pain caused by pleural surfaces rubbing together, but may exert pressure on the lungs and hinder breathing movements.

Other fluids that may accumulate in the pleural cavity include blood (leaked from damaged blood vessels) and blood filtrate (the watery fluid that oozes from the lung capillaries when left-sided heart failure occurs). The general term for fluid accumulation in the pleural cavity is *pleural effusion*. ■

CHECK YOUR UNDERSTANDING

4. What features of the alveoli and their respiratory membranes suit them to their function of exchanging gases by diffusion?
5. A 3-year-old boy is brought to the emergency department after aspirating (inhaling) a peanut. Bronchoscopy confirms the suspicion that the peanut is lodged in a bronchus and then it is successfully extracted. Which main bronchus was the peanut most likely to be in? Why?
6. The lungs are perfused by two different circulations. Name these circulations and indicate their roles in the lungs.

For answers, see Appendix G.

Mechanics of Breathing

Breathing, or **pulmonary ventilation**, consists of two phases: **inspiration**, the period when air flows into the lungs, and **expiration**, the period when gases exit the lungs.

Pressure Relationships in the Thoracic Cavity

- Explain the functional importance of the partial vacuum that exists in the intrapleural space.

Before we can begin to describe the breathing process, it is important to understand that *respiratory pressures are always described relative to atmospheric pressure (P_{atm})*, which is the pressure exerted by the air (gases) surrounding the body. At sea level, atmospheric pressure is 760 mm Hg (the pressure exerted by a column of mercury 760 mm high). This pressure can also be expressed in atmosphere units: atmospheric pressure = 760 mm Hg = 1 atm.

A negative respiratory pressure in any respiratory area, such as -4 mm Hg, indicates that the pressure in that area is lower than atmospheric pressure by 4 mm Hg ($760 - 4 = 756$ mm Hg).

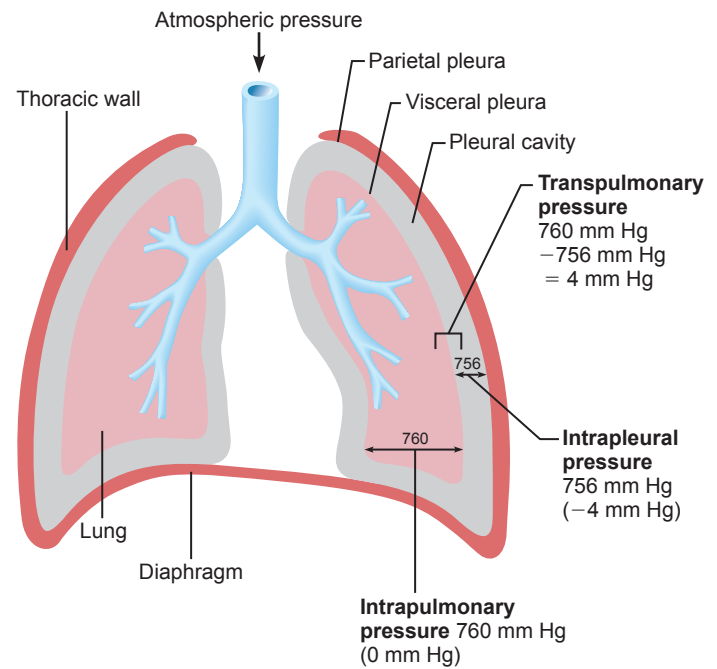


Figure 22.12 Intrapulmonary and intrapleural pressure relationships. Differences in pressure relative to atmospheric pressure (760 mm Hg) are given in parentheses. Values shown are at the end of a normal expiration. For illustration, the size of the pleural cavity has been greatly exaggerated.

A positive respiratory pressure is higher than atmospheric pressure, and zero respiratory pressure is equal to atmospheric pressure. Now we are ready to examine the pressure relationships that normally exist in the thoracic cavity.

Intrapulmonary Pressure

The **intrapulmonary** (intra-alveolar) **pressure** (P_{pul}) is the pressure in the alveoli. Intrapulmonary pressure rises and falls with the phases of breathing, but it *always* eventually equalizes with the atmospheric pressure (**Figure 22.12**).

Intrapleural Pressure

The pressure in the pleural cavity, the **intrapleural pressure** (P_{ip}), also fluctuates with breathing phases, but is always about 4 mm Hg less than P_{pul} . That is, P_{ip} is *always* negative relative to P_{pul} .

How is this negative intrapleural pressure established? In other words, what causes it? Let's examine the forces that exist in the thorax to see if we can answer these questions. First of all, we know there are opposing forces. Two forces act to pull the lungs (visceral pleura) away from the thorax wall (parietal pleura) and cause lung collapse:

1. **The lungs' natural tendency to recoil.** Because of their elasticity, lungs always assume the smallest size possible.
2. **The surface tension of the alveolar fluid.** The molecules of the fluid lining the alveoli attract each other and this produces *surface tension* that constantly acts to draw the alveoli to their smallest possible dimension.

However, these lung-collapsing forces are opposed by the natural elasticity of the chest wall, a force that tends to pull the thorax outward and to enlarge the lungs.

So which force wins? The answer is neither in a healthy person, because of the strong adhesive force between the parietal and visceral pleurae. Pleural fluid secures the pleurae together in the same way a drop of water holds two glass slides together. The pleurae slide from side to side easily, but they remain closely apposed, and separating them requires extreme force. The net result of the dynamic interplay between these forces is a negative P_{ip} .

The amount of pleural fluid in the pleural cavity must remain minimal in order for the negative P_{ip} to be maintained. The pleural fluid is actively pumped out of the pleural cavity into the lymphatics continuously. If it wasn't, fluid would accumulate in the intrapleural space (remember, fluids move from high to low pressure), producing a positive pressure in the pleural cavity.

We cannot overemphasize the importance of negative pressure in the intrapleural space and the tight coupling of the lungs to the thorax wall. Any condition that equalizes P_{ip} with the intrapulmonary (or atmospheric) pressure causes *immediate lung collapse*. It is the **transpulmonary pressure**—the difference between the intrapulmonary and intrapleural pressures ($P_{pul} - P_{ip}$)—that keeps the air spaces of the lungs open or, phrased another way, keeps the lungs from collapsing. Moreover, *the size of the transpulmonary pressure determines the size of the lungs at any time*—the greater the transpulmonary pressure, the larger the lungs.

HOMEOSTATIC IMBALANCE

Atelectasis (at'ĕ-lik'tah-sis), or lung collapse, occurs when a bronchiole becomes plugged (as may follow pneumonia). Its associated alveoli then absorb all of their air and collapse. Atelectasis can also occur when air enters the pleural cavity either through a chest wound, or due to rupture of the visceral pleura, which allows air to enter the pleural cavity from the respiratory tract. The presence of air in the pleural cavity is referred to as a **pneumothorax** (nu'mo-tho'raks; "air thorax"). The condition is reversed by drawing air out of the intrapleural space with chest tubes, which allows the pleurae to heal and the lung to re-inflate and resume its normal function. Note that because the lungs are in separate cavities, one lung can collapse without interfering with the function of the other. ■

Pulmonary Ventilation

- ▶ Relate Boyle's law to events of inspiration and expiration.
- ▶ Explain the relative roles of the respiratory muscles and lung elasticity in producing the volume changes that cause air to flow into and out of the lungs.

Pulmonary ventilation, consisting of inspiration and expiration, is a mechanical process that depends on volume changes in the thoracic cavity. A rule to keep in mind throughout the following

discussion is that *volume changes lead to pressure changes*, and pressure changes lead to the *flow of gases* to equalize the pressure.

The relationship between the pressure and volume of a gas is given by **Boyle's law**: At constant temperature, the pressure of a gas varies inversely with its volume. That is,

$$P_1 V_1 = P_2 V_2$$

where P is the pressure of the gas, V is its volume, and subscripts 1 and 2 represent the initial and resulting conditions respectively.

Gases always *fill* their container. Consequently, in a large container, the molecules in a given amount of gas will be far apart and the pressure will be low. But if the volume of the container is reduced, the gas molecules will be forced closer together and the pressure will rise. A good example is an inflated automobile tire. The tire is hard and strong enough to bear the weight of the car because air is compressed to about one-third of its atmospheric volume in the tire, providing the high pressure. Now let's see how this relates to inspiration and expiration.

Inspiration

Visualize the thoracic cavity as a gas-filled box with a single entrance at the top, the tubelike trachea. The volume of this box is changeable and can be increased by enlarging all of its dimensions, thereby decreasing the gas pressure inside it. This drop in pressure causes air to rush into the box from the atmosphere, because gases always flow down their pressure gradients.

The same thing happens during normal quiet inspiration, when the **inspiratory muscles**—the diaphragm and external intercostal muscles—are activated. Here's how quiet inspiration works:

1. **Action of the diaphragm.** When the dome-shaped diaphragm contracts, it moves inferiorly and flattens out (**Figure 22.13**, top). As a result, the superior-inferior dimension (height) of the thoracic cavity increases.
2. **Action of the intercostal muscles.** Contraction of the external intercostal muscles lifts the rib cage and pulls the sternum superiorly (**Figure 22.13**, top). Because the ribs curve downward as well as forward around the chest wall, the broadest lateral and anteroposterior dimensions of the rib cage are normally directed obliquely downward. But when the ribs are raised and drawn together, they swing outward, expanding the diameter of the thorax both laterally and in the anteroposterior plane. This is much like the action that occurs when a curved bucket handle is raised—it moves outward as it moves upward.

Although these actions expand the thoracic dimensions by only a few millimeters along each plane, this is enough to increase thoracic volume by almost 500 ml—the usual volume of air that enters the lungs during a normal quiet inspiration. Of the two types of inspiratory muscles, the diaphragm is far more important in producing the volume changes that lead to normal quiet inspiration.

As the thoracic dimensions increase during inspiration, the lungs are stretched and the intrapulmonary volume increases. As

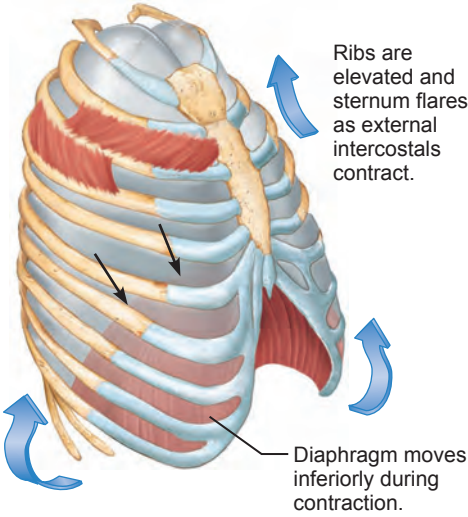
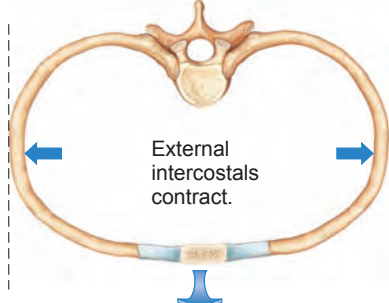
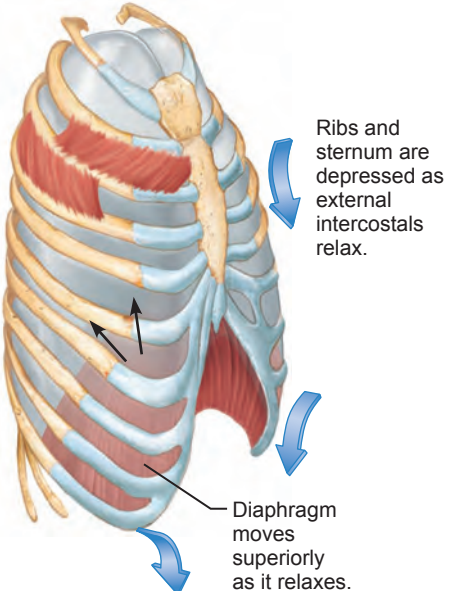
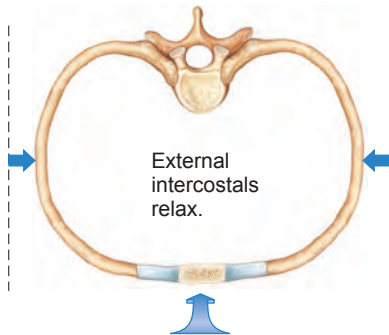
| | Sequence of events | Changes in anterior-posterior and superior-inferior dimensions | Changes in lateral dimensions (superior view) |
|-------------|---|---|--|
| Inspiration | <ol style="list-style-type: none"> ① Inspiratory muscles contract (diaphragm descends; rib cage rises). ↓ ② Thoracic cavity volume increases. ↓ ③ Lungs are stretched; intrapulmonary volume increases. ↓ ④ Intrapulmonary pressure drops (to -1 mm Hg). ↓ ⑤ Air (gases) flows into lungs down its pressure gradient until intrapulmonary pressure is 0 (equal to atmospheric pressure). |  <p>Ribs are elevated and sternum flares as external intercostals contract.</p> <p>Diaphragm moves inferiorly during contraction.</p> |  <p>External intercostals contract.</p> |
| Expiration | <ol style="list-style-type: none"> ① Inspiratory muscles relax (diaphragm rises; rib cage descends due to recoil of costal cartilages). ↓ ② Thoracic cavity volume decreases. ↓ ③ Elastic lungs recoil passively; intrapulmonary volume decreases. ↓ ④ Intrapulmonary pressure rises (to $+1$ mm Hg). ↓ ⑤ Air (gases) flows out of lungs down its pressure gradient until intrapulmonary pressure is 0. |  <p>Ribs and sternum are depressed as external intercostals relax.</p> <p>Diaphragm moves superiorly as it relaxes.</p> |  <p>External intercostals relax.</p> |

Figure 22.13 Changes in thoracic volume and sequence of events during inspiration and expiration. The sequence of events in the left column includes volume changes during inspiration (top) and expiration (bottom). The lateral views in the middle column show changes in the superior-inferior dimension (as the diaphragm alternately contracts and relaxes) and in the anterior-posterior dimension (as the external intercostal muscles alternately contract and relax). The superior views of transverse thoracic sections in the right column show lateral dimension changes resulting from alternate contraction and relaxation of the external intercostal muscles.

a result, P_{pul} drops about 1 mm Hg relative to P_{atm} . Anytime the intrapulmonary pressure is less than the atmospheric pressure ($P_{pul} < P_{atm}$), air rushes into the lungs along the pressure gradient. Inspiration ends when $P_{pul} = P_{atm}$. During the same period, P_{ip} declines to about -6 mm Hg relative to P_{atm} (Figure 22.14).

During the *deep* or *forced inspirations* that occur during vigorous exercise and in some chronic obstructive pulmonary diseases, the thoracic volume is further increased by activity of accessory muscles. Several muscles, including the scalenes and sternocleidomastoid muscles of the neck and the pectoralis

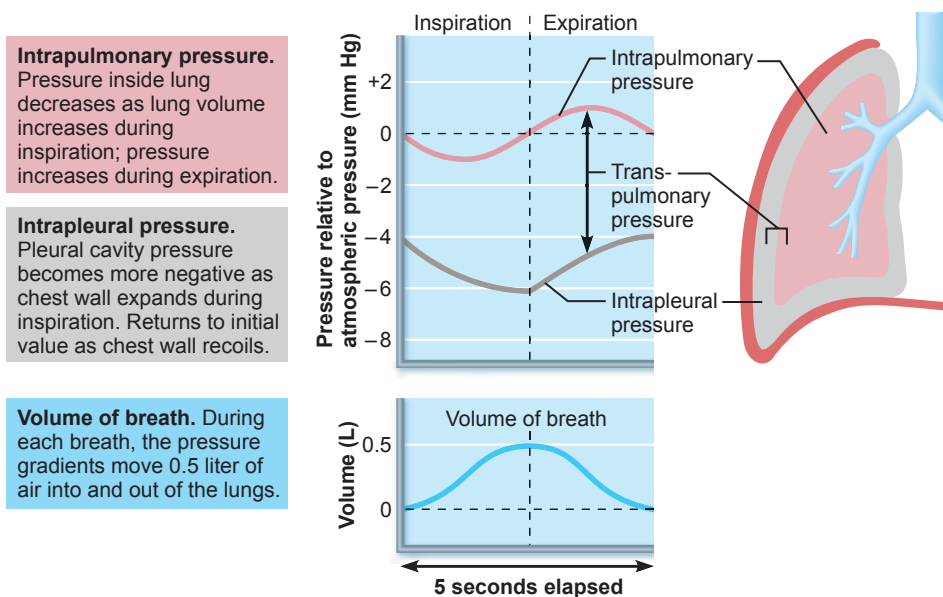


Figure 22.14 Changes in intrapulmonary and intrapleural pressures during inspiration and expiration. Notice that normal atmospheric pressure (760 mm Hg) is given a value of 0 on the scale.

minor of the chest, raise the ribs even more than occurs during quiet inspiration. Additionally, the back extends as the thoracic curvature is straightened by the erector spinae muscles.

Expiration

Quiet expiration in healthy individuals is a passive process that depends more on lung elasticity than on muscle contraction. As the inspiratory muscles relax and resume their resting length, the rib cage descends and the lungs recoil (Figure 22.13, bottom). As a result, both the thoracic and intrapulmonary volumes decrease. This volume decrease compresses the alveoli, and P_{pul} rises to about 1 mm Hg above atmospheric pressure (Figure 22.14). When $P_{pul} > P_{atm}$, the pressure gradient forces gases to flow out of the lungs.

Forced expiration is an active process produced by contraction of abdominal wall muscles, primarily the oblique and transversus muscles. These contractions (1) increase the intra-abdominal pressure, which forces the abdominal organs superiorly against the diaphragm, and (2) depress the rib cage. The internal intercostal muscles also help to depress the rib cage and decrease thoracic volume.

Control of accessory muscles of expiration is important when precise regulation of air flow from the lungs is desired. For instance, the ability of a trained vocalist to hold a musical note depends on the coordinated activity of several muscles normally used in forced expiration.

CHECK YOUR UNDERSTANDING

7. What is the driving force for ventilation?
8. What causes the intrapulmonary pressure to decrease during inspiration?

9. What causes the partial vacuum (negative pressure) inside the pleural cavity? What happens to a lung if air enters the pleural cavity? What is the clinical name for this condition?

For answers, see Appendix G.

Physical Factors Influencing Pulmonary Ventilation

- List several physical factors that influence pulmonary ventilation.

As we have seen, the lungs are stretched during inspiration and recoil passively during expiration. The inspiratory muscles consume energy to enlarge the thorax. Energy is also used to overcome various factors that hinder air passage and pulmonary ventilation. We examine these factors next.

Airway Resistance

The major *nonelastic* source of resistance to gas flow is friction, or drag, encountered in the respiratory passageways. The relationship between gas flow (F), pressure (P), and resistance (R) is given by the following equation:

$$F = \frac{\Delta P}{R}$$

Notice that the factors determining gas flow in the respiratory passages and blood flow in the cardiovascular system are equivalent. The amount of gas flowing into and out of the alveoli is directly proportional to ΔP , the *difference* in pressure, or the pressure gradient, between the external atmosphere and the alveoli. Normally, very small differences in pressure produce large changes in the volume of gas flow. The average pressure

gradient during normal quiet breathing is 2 mm Hg or less, and yet it is sufficient to move 500 ml of air in and out of the lungs with each breath.

But, as the equation also indicates, gas flow changes *inversely* with resistance. In other words, gas flow decreases as resistance increases. As in the cardiovascular system, resistance in the respiratory tree is determined mostly by the diameters of the conducting tubes. However, as a rule, airway resistance is insignificant for two reasons:

1. Airway diameters in the first part of the conducting zone are huge, relative to the low viscosity of air.
2. As the airways get progressively smaller, there are progressively more branches. As a result, although individual bronchioles are tiny, there are an enormous number of them in parallel, so the total cross-sectional area is huge.

Consequently, the greatest resistance to gas flow occurs in the medium-sized bronchi (Figure 22.15). At the terminal bronchioles, gas flow stops and diffusion takes over as the main force driving gas movement, so resistance is no longer an issue.

HOMEOSTATIC IMBALANCE

Smooth muscle of the bronchiolar walls is exquisitely sensitive to neural controls and certain chemicals. For example, inhaled irritants activate a reflex of the parasympathetic division of the nervous system that causes vigorous constriction of the bronchioles and dramatically reduces air passage. During an *acute asthma attack*, histamine and other inflammatory chemicals can cause such strong bronchoconstriction that pulmonary ventilation almost completely stops, regardless of the pressure gradient. Conversely, epinephrine released during sympathetic nervous system activation or administered as a drug dilates bronchioles and reduces airway resistance. Local accumulations of mucus, infectious material, or solid tumors in the passageways are important sources of airway resistance in those with respiratory disease.

Whenever airway resistance rises, breathing movements become more strenuous, but such compensation has its limits. When the bronchioles are severely constricted or obstructed, even the most magnificent respiratory efforts cannot restore ventilation to life-sustaining levels. ■

Alveolar Surface Tension

At any gas-liquid boundary, the molecules of the liquid are more strongly attracted to each other than to the gas molecules. This unequal attraction produces a state of tension at the liquid surface, called **surface tension**, that (1) draws the liquid molecules closer together and reduces their contact with the dissimilar gas molecules, and (2) resists any force that tends to increase the surface area of the liquid.

Water is composed of highly polar molecules and has a very high surface tension. As the major component of the liquid film that coats the alveolar walls, water is always acting to reduce the alveoli to their smallest possible size, as we noted earlier. If the film were pure water, the alveoli would collapse between breaths. But the alveolar film contains **surfactant** (ser-fak'tant),

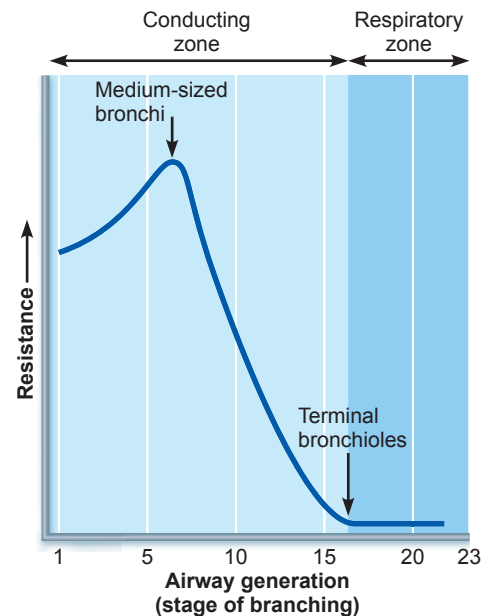


Figure 22.15 Resistance in respiratory passageways. Airway resistance peaks in the medium-sized bronchi and then declines sharply as the total cross-sectional area of the airways increases rapidly.

a detergent-like complex of lipids and proteins produced by the type II alveolar cells. Surfactant decreases the cohesiveness of water molecules, much the way a laundry detergent reduces the attraction of water for water, allowing water to interact with and pass through fabric. As a result, the surface tension of alveolar fluid is reduced, and less energy is needed to overcome those forces to expand the lungs and discourage alveolar collapse. Breaths that are deeper than normal stimulate type II cells to secrete more surfactant.

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When too little surfactant is present, surface tension forces can collapse the alveoli. Once this happens, the alveoli must be completely reinflated during each inspiration, an effort that uses tremendous amounts of energy. This is the problem faced by newborns with **infant respiratory distress syndrome (IRDS)**, a condition peculiar to premature babies. Since inadequate pulmonary surfactant is produced until the last two months of fetal development, babies born prematurely often are unable to keep their alveoli inflated between breaths. IRDS is treated by spraying natural or synthetic surfactant into the newborn's respiratory passageways. In addition, devices that maintain a positive airway pressure throughout the respiratory cycle are often used to keep the alveoli open between breaths. In severe cases, mechanical ventilators are required.

Many IRDS survivors suffer from *bronchopulmonary dysplasia*, a chronic lung disease, during childhood and beyond. This condition is believed to result from inflammatory injury to respiratory zone structures caused by mechanical ventilation of the premature newborn's delicate lungs. ■

Lung Compliance

Healthy lungs are unbelievably stretchy, and this distensibility is referred to as **lung compliance**. Specifically, lung compliance (C_L) is a measure of the change in lung volume (ΔV_L) that occurs with a given change in the transpulmonary pressure [$\Delta(P_{pul} - P_{ip})$]. This relationship is stated as

$$C_L = \frac{\Delta V_L}{\Delta(P_{pul} - P_{ip})}$$

The more a lung expands for a given rise in transpulmonary pressure, the greater its compliance. Said another way, the higher the lung compliance, the easier it is to expand the lungs at any given transpulmonary pressure.

Lung compliance is determined largely by two factors: (1) distensibility of the lung tissue and (2) alveolar surface tension. Because lung distensibility is generally high and alveolar surface tension is kept low by surfactant, the lungs of healthy people tend to have high compliance, which favors efficient ventilation.

Lung compliance is diminished by a decrease in the natural resilience of the lungs. Chronic inflammation, or infections such as tuberculosis, can cause nonelastic scar tissue to replace normal lung tissue (*fibrosis*). Another factor that can decrease lung compliance is a decrease in production of surfactant. The lower the lung compliance, the more energy is needed just to breathe.

Since the lungs are contained within the thoracic cavity, we also need to consider the compliance (distensibility) of the thoracic wall. Factors that decrease the compliance of the thoracic wall hinder the expansion of the lungs. The total compliance of the respiratory system is comprised of lung compliance and thoracic wall compliance.

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Deformities of the thorax, ossification of the costal cartilages (common during old age), and paralysis of the intercostal muscles all reduce total respiratory compliance by hindering thoracic expansion. ■

Respiratory Volumes and Pulmonary Function Tests

- ▶ Explain and compare the various lung volumes and capacities.
- ▶ Define dead space.
- ▶ Indicate types of information that can be gained from pulmonary function tests.

The amount of air flushed in and out of the lungs depends on the conditions of inspiration and expiration. Consequently, several respiratory volumes can be described. Specific combinations of these respiratory volumes, called *respiratory capacities*, are measured to gain information about a person's respiratory status.

Respiratory Volumes

The four **respiratory volumes** of interest are tidal, inspiratory reserve, expiratory reserve, and residual. The values recorded in **Figure 22.16a** (and used in the following text) represent normal values for a healthy 20-year-old male weighing about 70 kg (155 lb). Figure 22.16b provides average values for males and females.

During normal quiet breathing, about 500 ml of air moves into and then out of the lungs with each breath. This respiratory volume is the **tidal volume (TV)**. The amount of air that can be inspired forcibly beyond the tidal volume (2100 to 3200 ml) is called the **inspiratory reserve volume (IRV)**.

The **expiratory reserve volume (ERV)** is the amount of air—normally 1000 to 1200 ml—that can be evacuated from the lungs after a tidal expiration. Even after the most strenuous expiration, about 1200 ml of air remains in the lungs; this is the **residual volume (RV)**, which helps to keep the alveoli patent (open) and to prevent lung collapse.

Respiratory Capacities

The **respiratory capacities** include inspiratory capacity, functional residual capacity, vital capacity, and total lung capacity (Figure 22.16). As noted, the respiratory capacities always consist of two or more lung volumes.

The **inspiratory capacity (IC)** is the total amount of air that can be inspired after a tidal expiration, so it is the sum of TV and IRV. The **functional residual capacity (FRC)** represents the amount of air remaining in the lungs after a tidal expiration and is the combined RV and ERV.

Vital capacity (VC) is the total amount of exchangeable air. It is the sum of TV, IRV, and ERV. In healthy young males, VC is approximately 4800 ml. The **total lung capacity (TLC)** is the sum of all lung volumes and is normally around 6000 ml. As indicated in Figure 22.16b, lung volumes and capacities (with the possible exception of TV) tend to be smaller in women than in men because of women's smaller size.

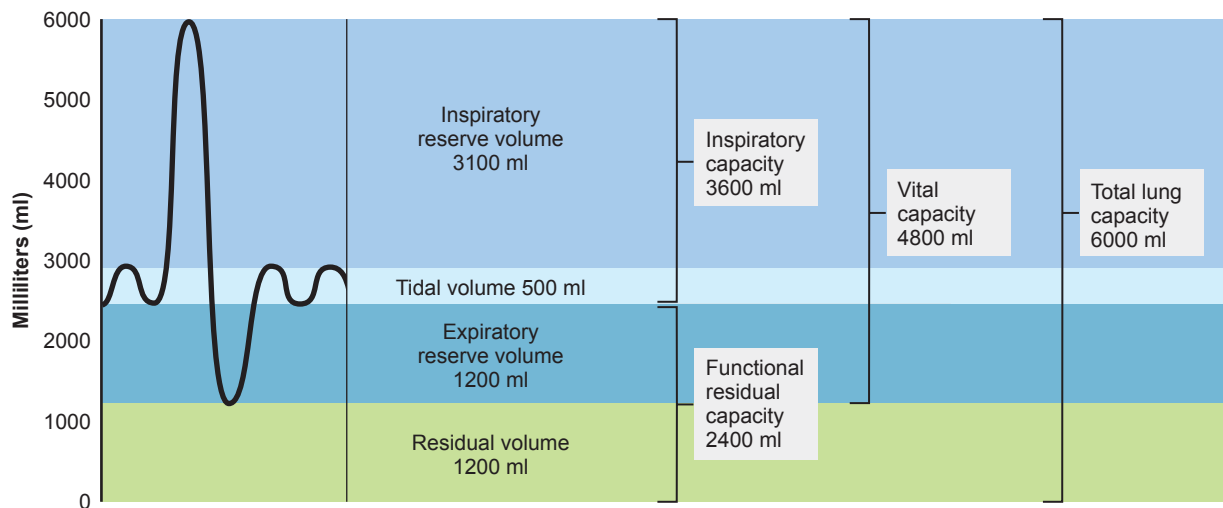
Dead Space

Some of the inspired air fills the conducting respiratory passageways and never contributes to gas exchange in the alveoli. The volume of these conducting zone conduits, which make up the **anatomical dead space**, typically amounts to about 150 ml. (The rule of thumb is that the anatomical dead space volume in a healthy young adult is equal to 1 ml per pound of ideal body weight.) This means that if TV is 500 ml, only 350 ml of it is involved in alveolar ventilation. The remaining 150 ml of the tidal breath is in the anatomical dead space.

If some alveoli cease to act in gas exchange (due to alveolar collapse or obstruction by mucus, for example), the **alveolar dead space** is added to the anatomical dead space, and the sum of the nonuseful volumes is referred to as **total dead space**.

Pulmonary Function Tests

Because the various lung volumes and capacities are often abnormal in people with pulmonary disorders, they are routinely measured in such patients. The original clinical measuring



(a) Spirographic record for a male

| | Measurement | Adult male average value | Adult female average value | Description |
|------------------------|------------------------------------|--------------------------|----------------------------|--|
| Respiratory volumes | Tidal volume (TV) | 500 ml | 500 ml | Amount of air inhaled or exhaled with each breath under resting conditions |
| | Inspiratory reserve volume (IRV) | 3100 ml | 1900 ml | Amount of air that can be forcefully inhaled after a normal tidal volume inhalation |
| | Expiratory reserve volume (ERV) | 1200 ml | 700 ml | Amount of air that can be forcefully exhaled after a normal tidal volume exhalation |
| | Residual volume (RV) | 1200 ml | 1100 ml | Amount of air remaining in the lungs after a forced exhalation |
| Respiratory capacities | Total lung capacity (TLC) | 6000 ml | 4200 ml | Maximum amount of air contained in lungs after a maximum inspiratory effort: $TLC = TV + IRV + ERV + RV$ |
| | Vital capacity (VC) | 4800 ml | 3100 ml | Maximum amount of air that can be expired after a maximum inspiratory effort: $VC = TV + IRV + ERV$ |
| | Inspiratory capacity (IC) | 3600 ml | 2400 ml | Maximum amount of air that can be inspired after a normal expiration: $IC = TV + IRV$ |
| | Functional residual capacity (FRC) | 2400 ml | 1800 ml | Volume of air remaining in the lungs after a normal tidal volume expiration: $FRC = ERV + RV$ |

(b) Summary of respiratory volumes and capacities for males and females

Figure 22.16 Respiratory volumes and capacities. Idealized spirographic record of respiratory volumes in (a) is for a healthy young 70-kg adult male.

device, a **spirometer** (spi-rom'ě-ter), was a simple but cumbersome instrument utilizing a hollow bell inverted over water. Now patients simply blow into a small electronic measuring device.

Spirometry is most useful for evaluating losses in respiratory function and for following the course of certain respiratory diseases. It cannot provide a specific diagnosis, but it can distinguish between *obstructive pulmonary disease* involving increased airway resistance (such as chronic bronchitis) and *restrictive disorders* involving a reduction in total lung capacity resulting from structural or functional changes in the lungs. (These changes might be due to diseases such as tuberculosis, or to fibrosis due to exposure to certain environmental agents such as asbestos). Increases in TLC, FRC, and RV may occur as a result

of hyperinflation of the lungs in obstructive disease, whereas VC, TLC, FRC, and RV are reduced in restrictive diseases, which limit lung expansion.

More information can be obtained about a patient's ventilation status by assessing the rate at which gas moves into and out of the lungs. The **minute ventilation** is the total amount of gas that flows into or out of the respiratory tract in 1 minute. During normal quiet breathing, the minute ventilation in healthy people is about 6 L/min (500 ml per breath multiplied by 12 breaths per minute). During vigorous exercise, the minute ventilation may reach 200 L/min.

Two other useful tests are FVC and FEV. **FVC**, or **forced vital capacity**, measures the amount of gas expelled when a subject takes a deep breath and then forcefully exhales maximally and as

TABLE 22.2 Effects of Breathing Rate and Depth on Alveolar Ventilation of Three Hypothetical Patients

| BREATHING PATTERN OF HYPOTHETICAL PATIENT | DEAD SPACE VOLUME (DSV) | TIDAL VOLUME (TV) | RESPIRATORY RATE* | MINUTE VENTILATION (MVR) | ALVEOLAR VENTILATION (AVR) | % EFFECTIVE VENTILATION (AVR/MVR) |
|---|-------------------------|-------------------|-------------------|--------------------------|----------------------------|-----------------------------------|
| I—Normal rate and depth | 150 ml | 500 ml | 20/min | 10,000 ml/min | 7000 ml/min | 70% |
| II—Slow, deep breathing | 150 ml | 1000 ml | 10/min | 10,000 ml/min | 8500 ml/min | 85% |
| III—Rapid, shallow breathing | 150 ml | 250 ml | 40/min | 10,000 ml/min | 4000 ml/min | 40% |

* Respiratory rate values are artificially adjusted to provide equivalent minute ventilation as a baseline for comparison of alveolar ventilation.

rapidly as possible. FEV, or **forced expiratory volume**, determines the amount of air expelled during specific time intervals of the FVC test. For example, the volume exhaled during the first second is FEV₁. Those with healthy lungs can exhale about 80% of the FVC within 1 second. Those with obstructive pulmonary disease exhale considerably less than 80% of the FVC within 1 second, while those with restrictive disease can exhale 80% or more of FVC in 1 second even though their FVC is reduced.

Alveolar Ventilation

Minute ventilation values provide a rough yardstick for assessing respiratory efficiency, but the **alveolar ventilation rate (AVR)** is a better index of effective ventilation. The AVR takes into account the volume of air wasted in the dead space and measures the flow of fresh gases in and out of the alveoli during a particular time interval. AVR is computed with this equation:

$$\text{AVR} = \text{frequency} \times (\text{TV} - \text{dead space})$$

(ml/min) (breaths/min) (ml/ breath)

In healthy people, AVR is usually about 12 breaths per minute times the difference of 500 – 150 ml per breath, or 4200 ml/min.

Because anatomical dead space is constant in a particular individual, increasing the volume of each inspiration (breathing depth) enhances AVR and gas exchange more than raising the

respiratory rate. AVR drops dramatically during rapid shallow breathing because most of the inspired air never reaches the exchange sites. Furthermore, as tidal volume approaches the dead space value, effective ventilation approaches zero, regardless of how fast a person is breathing. The effects of breathing rate and breathing depth on alveolar ventilation are summarized for three hypothetical patients in [Table 22.2](#).

Nonrespiratory Air Movements

Many processes other than breathing move air into or out of the lungs, and these processes may modify the normal respiratory rhythm. Most of these **nonrespiratory air movements** result from reflex activity, but some are produced voluntarily. The most common of these movements are described in [Table 22.3](#).

CHECK YOUR UNDERSTANDING

- Resistance in the airways is typically low. Why? (Give at least two reasons.)
- Premature infants often lack adequate surfactant. How does this affect their ability to breathe?
- Explain why slow, deep breaths ventilate the alveoli more effectively than do rapid, shallow breaths.

For answers, see Appendix G.

TABLE 22.3 Nonrespiratory Air (Gas) Movements

| MOVEMENT | MECHANISM AND RESULT |
|----------|--|
| Cough | Taking a deep breath, closing glottis, and forcing air superiorly from lungs against glottis; glottis opens suddenly and a blast of air rushes upward. Can dislodge foreign particles or mucus from lower respiratory tract and propel such substances superiorly. |
| Sneeze | Similar to a cough, except that expelled air is directed through nasal cavities as well as through oral cavity; depressed uvula routes air upward through nasal cavities. Sneezes clear upper respiratory passages. |
| Crying | Inspiration followed by release of air in a number of short expirations. Primarily an emotionally induced mechanism. |
| Laughing | Essentially same as crying in terms of air movements produced. Also an emotionally induced response. |
| Hiccups | Sudden inspirations resulting from spasms of diaphragm; believed to be initiated by irritation of diaphragm or phrenic nerves, which serve diaphragm. Sound occurs when inspired air hits vocal folds of closing glottis. |
| Yawn | Very deep inspiration, taken with jaws wide open; not believed to be triggered by levels of oxygen or carbon dioxide in blood. Ventilates all alveoli (not the case in normal quiet breathing). |

Gas Exchanges Between the Blood, Lungs, and Tissues

- ▶ State Dalton's law of partial pressures and Henry's law.
- ▶ Describe how atmospheric and alveolar air differ in composition, and explain these differences.
- ▶ Relate Dalton's and Henry's laws to events of external and internal respiration.

As you've discovered, during *external respiration* oxygen enters and carbon dioxide leaves the blood in the lungs by diffusion. At the body tissues, where the process is called *internal respiration*, the same gases move in opposite directions, also by diffusion. To understand these processes, let's examine some of the physical properties of gases and consider the composition of alveolar gas.

Basic Properties of Gases

Two more gas laws provide most of the information we need—*Dalton's law of partial pressures* reveals how a gas behaves when it is part of a mixture of gases, and *Henry's law* will help us understand movement of gases into and out of solution.

Dalton's Law of Partial Pressures

Dalton's law of partial pressures states that the total pressure exerted by a mixture of gases is the sum of the pressures exerted independently by each gas in the mixture. Further, the pressure exerted by each gas—its **partial pressure**—is directly proportional to the percentage of that gas in the gas mixture.

As indicated in **Table 22.4**, nitrogen makes up about 79% of air, and the partial pressure of nitrogen (P_{N_2}) is $78.6\% \times 760$ mm Hg, or 597 mm Hg. Oxygen, which accounts for nearly 21% of the atmosphere, has a partial pressure (P_{O_2}) of 159 mm Hg ($20.9\% \times 760$ mm Hg). Together nitrogen and oxygen contribute about 99% of the total atmospheric pressure. Air also contains 0.04% carbon dioxide, up to 0.5% water vapor, and insignificant amounts of inert gases (such as argon and helium).

At high altitudes, where the atmosphere is less influenced by gravity, partial pressures decline in direct proportion to the decrease in atmospheric pressure. For example, at 10,000 feet above sea level where the atmospheric pressure is 523 mm Hg, P_{O_2} is 110 mm Hg. Moving in the opposite direction, atmospheric pressure increases by 1 atm (760 mm Hg) for each 33 feet of descent (in water) below sea level. At 99 feet below sea level, the total pressure exerted on the body is equivalent to 4 atm, or 3040 mm Hg, and the partial pressure exerted by each component gas is also quadrupled.

Henry's Law

According to **Henry's law**, when a gas is in contact with a liquid, that gas will dissolve in the liquid in proportion to its partial pressure. Accordingly, the greater the concentration of a particular gas in the gas phase, the more and the faster that gas will go into solution in the liquid. At equilibrium, the gas partial pressures in the two phases are the same. If, however, the partial pressure of the gas later becomes greater in the liquid than in the adjacent gas phase, some of the dissolved gas molecules will reenter the gaseous phase. So the direction and amount of movement of a gas is determined by its partial pressure in the two phases. This flexible situation is exactly what occurs when gases are exchanged in the lungs and tissues.

How much of a gas will dissolve in a liquid at any given partial pressure also depends on the *solubility* of the gas in the liquid and on the *temperature* of the liquid. The gases in air have very different solubilities in water (and in plasma). Carbon dioxide is most soluble. Oxygen is only 1/20 as soluble as CO_2 , and N_2 is only half as soluble as O_2 . For this reason, at a given partial pressure, much more CO_2 than O_2 dissolves in water, and practically no N_2 goes into solution.

The effect of increasing the liquid's temperature is to decrease gas solubility. Think of club soda, which is produced by forcing CO_2 gas to dissolve in water under high pressure. If you take the cap off a refrigerated bottle of club soda and allow it to stand at room temperature, in just a few minutes you will have plain water—all the CO_2 gas will have escaped from solution.

TABLE 22.4 Comparison of Gas Partial Pressures and Approximate Percentages in the Atmosphere and in the Alveoli

| GAS | ATMOSPHERE (SEA LEVEL) | | ALVEOLI | |
|--------|------------------------|--------------------------|------------------------|--------------------------|
| | APPROXIMATE PERCENTAGE | PARTIAL PRESSURE (mm Hg) | APPROXIMATE PERCENTAGE | PARTIAL PRESSURE (mm Hg) |
| N_2 | 78.6 | 597 | 74.9 | 569 |
| O_2 | 20.9 | 159 | 13.7 | 104 |
| CO_2 | 0.04 | 0.3 | 5.2 | 40 |
| H_2O | 0.46 | 3.7 | 6.2 | 47 |
| | 100.0% | 760 | 100.0% | 760 |

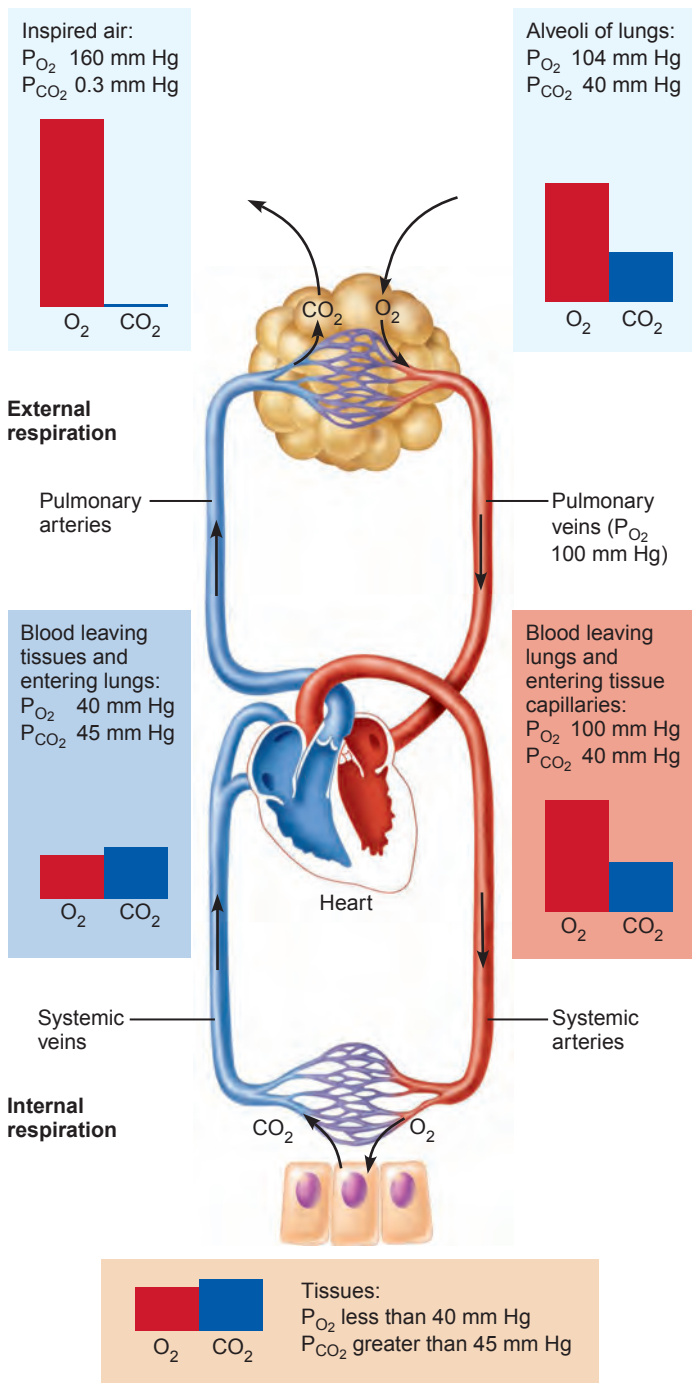


Figure 22.17 Partial pressure gradients promoting gas movements in the body. Top: Gradients promoting O_2 and CO_2 exchange across the respiratory membrane in the lungs. Bottom: Gradients promoting gas movements across systemic capillary membranes in body tissues. (Note that the small decrease in P_{O_2} in blood leaving lungs is due to partial dilution of pulmonary capillary blood with less oxygenated blood.)

Hyperbaric oxygen chambers provide clinical applications of Henry's law. These chambers contain O_2 gas at pressures higher than 1 atm and are used to force greater-than-normal amounts of O_2 into the blood of patients suffering from carbon monoxide poisoning or tissue damage following radiation therapy. Hyper-

baric therapy is also used to treat individuals with gas gangrene, because the anaerobic bacteria causing this infection cannot live in the presence of high O_2 levels. Scuba diving provides another illustration of Henry's law—if divers rise rapidly from the depths, dissolved nitrogen forms bubbles in their blood, causing “the bends.”

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Although breathing O_2 gas at 2 atm is not a problem for short periods, **oxygen toxicity** develops rapidly when P_{O_2} is greater than 2.5–3 atm. Excessively high O_2 concentrations generate huge amounts of harmful free radicals, resulting in profound CNS disturbances, coma, and death. ■

Composition of Alveolar Gas

As shown in Table 22.4, the gaseous makeup of the atmosphere is quite different from that in the alveoli. The atmosphere is almost entirely O_2 and N_2 ; the alveoli contain more CO_2 and water vapor and much less O_2 . These differences reflect the effects of (1) gas exchanges occurring in the lungs (O_2 diffuses from the alveoli into the pulmonary blood and CO_2 diffuses in the opposite direction), (2) humidification of air by conducting passages, and (3) the mixing of alveolar gas that occurs with each breath. Because only 500 ml of air is inspired with each tidal inspiration, gas in the alveoli is actually a mixture of newly inspired gases and gases remaining in the respiratory passageways between breaths.

The alveolar partial pressures of O_2 and CO_2 are easily changed by increasing breathing depth and rate. A high AVR brings more O_2 into the alveoli, increasing alveolar P_{O_2} and rapidly eliminating CO_2 from the lungs.

External Respiration

During external respiration (pulmonary gas exchange) dark red blood flowing through the pulmonary circuit is transformed into the scarlet river that is returned to the heart for distribution by systemic arteries to all body tissues. This color change is due to O_2 uptake and binding to hemoglobin in red blood cells (RBCs), but CO_2 exchange (unloading) is occurring equally fast.

The following three factors influence the movement of oxygen and carbon dioxide across the respiratory membrane:

1. Partial pressure gradients and gas solubilities
2. Matching of alveolar ventilation and pulmonary blood perfusion
3. Structural characteristics of the respiratory membrane

Let's look at these factors one by one in the sections that follow.

Partial Pressure Gradients and Gas Solubilities

Partial pressure gradients of O_2 and CO_2 drive the diffusion of these gases across the respiratory membrane. A steep oxygen partial pressure gradient exists across the respiratory membrane because the P_{O_2} of deoxygenated blood in the pulmonary arteries is only 40 mm Hg, as opposed to a P_{O_2} of approximately 104 mm Hg in the alveoli. As a result, O_2 diffuses rapidly from the alveoli into the pulmonary capillary blood (Figure 22.17). Equilibrium—that is, a P_{O_2} of 104 mm Hg on both sides of the respiratory membrane—

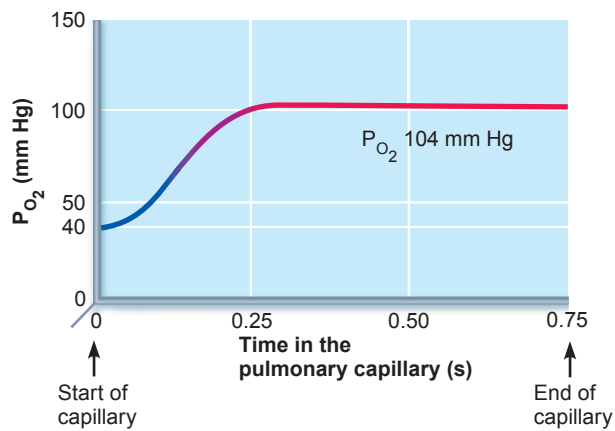


Figure 22.18 Oxygenation of blood in the pulmonary capillaries at rest. Note that the time from blood entering the pulmonary capillaries (indicated by 0) until the P_{O_2} is 104 mm Hg is approximately 0.25 second.

usually occurs in 0.25 second, which is about one-third the time a red blood cell is in a pulmonary capillary (Figure 22.18). The lesson here is that the blood can flow through the pulmonary capillaries three times as quickly and still be adequately oxygenated.

Carbon dioxide diffuses in the opposite direction along a much gentler partial pressure gradient of about 5 mm Hg (45 mm Hg to 40 mm Hg) until equilibrium occurs at 40 mm Hg. Carbon dioxide is then expelled gradually from the alveoli during expiration.

Even though the O_2 pressure gradient for oxygen diffusion is much steeper than the CO_2 gradient, equal amounts of these gases are exchanged. Why? The reason is because CO_2 is 20 times more soluble in plasma and alveolar fluid than O_2 .

Ventilation-Perfusion Coupling

For gas exchange to be efficient, there must be a close match, or coupling, between the amount of gas reaching the alveoli, known as *ventilation*, and the blood flow in pulmonary capillaries, known as *perfusion*. As we explained in Chapter 19, local autoregulatory mechanisms continuously respond to alveolar conditions.

Specifically, in alveoli where ventilation is inadequate, P_{O_2} is low, as Figure 22.19a shows. As a result, the terminal arterioles constrict, and blood is redirected to respiratory areas where P_{O_2} is high and oxygen pickup may be more efficient.

In alveoli where ventilation is maximal, pulmonary arterioles dilate, increasing blood flow into the associated pulmonary capillaries, as Figure 22.19b shows. Notice that the autoregulatory mechanism controlling pulmonary vascular muscle is the

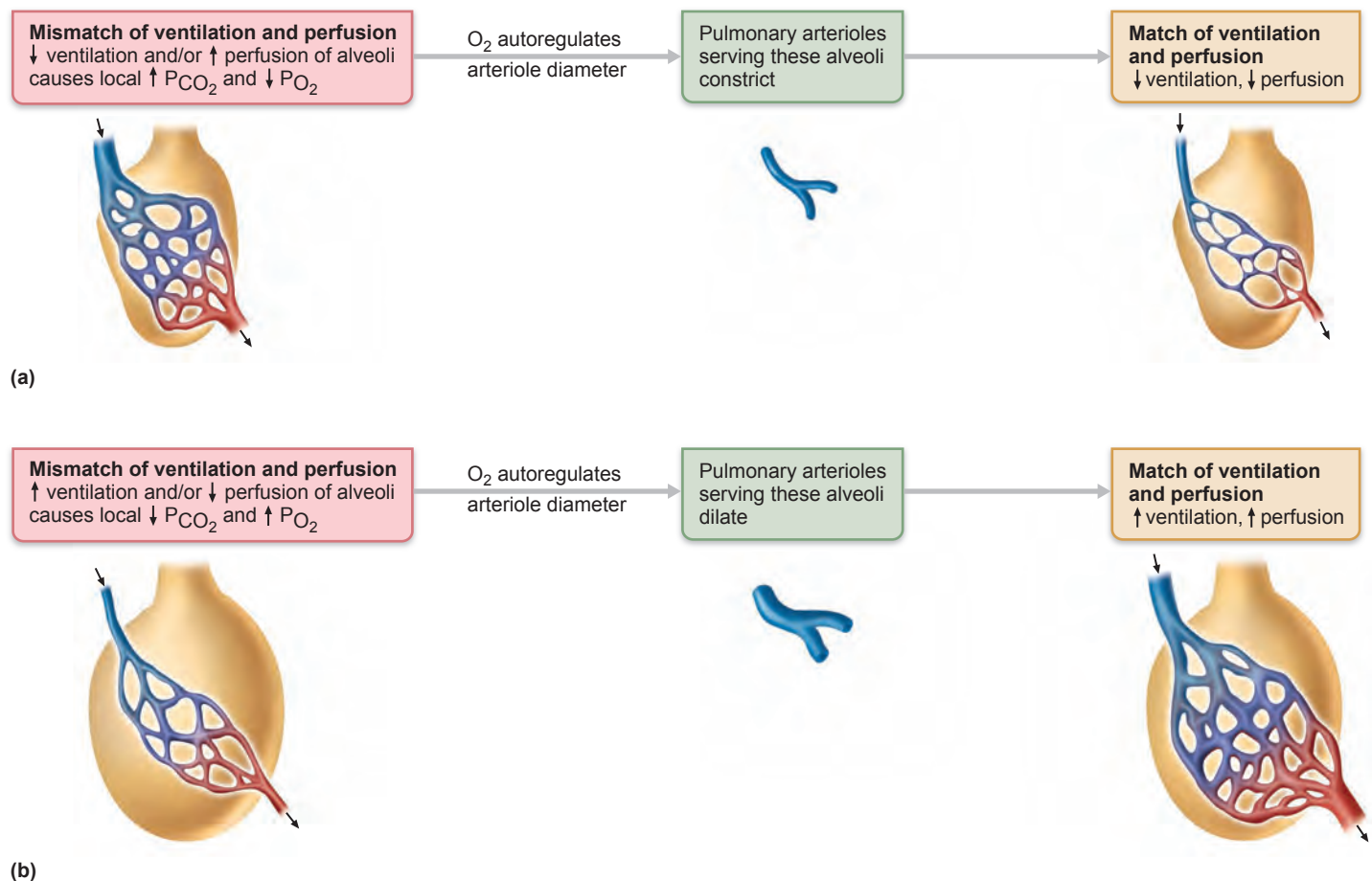


Figure 22.19 Ventilation-perfusion coupling. Autoregulatory events result in local matching of blood flow (perfusion) through the pulmonary capillaries with the amount of alveolar ventilation.

opposite of the mechanism controlling most arterioles in the systemic circulation.

While changes in alveolar P_{O_2} affect the diameter of pulmonary blood vessels (arterioles), changes in alveolar P_{CO_2} cause changes in the diameters of the *bronchioles*. Bronchioles servicing areas where alveolar CO_2 levels are high dilate, allowing CO_2 to be eliminated from the body more rapidly. Bronchioles servicing areas where P_{CO_2} is low constrict.

As a result of changing the diameter of local bronchioles and arterioles, alveolar ventilation and pulmonary perfusion are synchronized. Poor alveolar ventilation results in low oxygen and high carbon dioxide levels in the alveoli. Consequently, the pulmonary arterioles constrict and the airways dilate, bringing blood flow and air flow into closer physiological match. High P_{O_2} and low P_{CO_2} in the alveoli cause bronchioles servicing the alveoli to constrict, and promote flushing of blood into the pulmonary capillaries.

Although these homeostatic mechanisms provide appropriate conditions for efficient gas exchange, they never completely balance ventilation and perfusion in every alveolus due to other factors. In particular, (1) gravity causes regional variations in both blood and air flow in the lungs, and (2) the occasional alveolar duct plugged with mucus creates unventilated areas. These factors, together with the shunting of blood from bronchial veins, account for the slight drop in P_{O_2} from alveolar air (104 mm Hg) to pulmonary venous blood (100 mm Hg), as shown in Figure 22.17.

Thickness and Surface Area of the Respiratory Membrane

In healthy lungs, the respiratory membrane is only 0.5 to 1 μm thick, and gas exchange is usually very efficient.

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The effective thickness of the respiratory membrane increases dramatically if the lungs become waterlogged and edematous, as in pneumonia or left heart failure (see p. 687). Under such conditions, even the total time (0.75 s) that red blood cells are in transit through the pulmonary capillaries may not be enough for adequate gas exchange, and body tissues begin to suffer from oxygen deprivation. ■

The greater the surface area of the respiratory membrane, the more gas can diffuse across it in a given time period. The alveolar surface area is enormous in healthy lungs. Spread flat, the total gas exchange surface of these tiny sacs in an adult male's lungs is about 90 m^2 , approximately 40 times greater than the surface area of his skin!

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In certain pulmonary diseases, the alveolar surface area actually functioning in gas exchange is drastically reduced. This reduction occurs in emphysema, when the walls of adjacent alveoli break down and the alveolar chambers become larger. It also occurs when tumors, mucus, or inflammatory material blocks gas flow into the alveoli. ■

Internal Respiration

In internal respiration, involving capillary gas exchange in body tissues, the partial pressure and diffusion gradients are reversed from the situation we have just described for external respiration and pulmonary gas exchange. However, the factors promoting gas exchanges between the systemic capillaries and the tissue cells are essentially identical to those acting in the lungs (see Figure 22.17). Tissue cells continuously use O_2 for their metabolic activities and produce CO_2 . Because P_{O_2} in the tissues is always lower than that in the systemic arterial blood (40 mm Hg versus 100 mm Hg), O_2 moves rapidly from the blood into the tissues until equilibrium is reached. At the same time, CO_2 moves quickly along its pressure gradient into the blood. As a result, venous blood draining the tissue capillary beds and returning to the heart has a P_{O_2} of 40 mm Hg and a P_{CO_2} of 45 mm Hg.

In summary, the gas exchanges that occur between the blood and the alveoli and between the blood and the tissue cells take place by simple diffusion driven by the partial pressure gradients of O_2 and CO_2 that exist on the opposite sides of the exchange membranes.

CHECK YOUR UNDERSTANDING

- You are given a sealed container of water and air. The P_{CO_2} and P_{O_2} in the air are both 100 mm Hg. What are the P_{CO_2} and P_{O_2} in the water? Which gas has more molecules dissolved in the water? Why?
- P_{O_2} in the alveoli is about 56 mm Hg lower than in the inspired air. Explain this difference.
- Suppose a patient is receiving oxygen by mask. Are the arterioles leading into the O_2 -enriched alveoli dilated or constricted? What is the advantage of this response?

For answers, see Appendix G.

Transport of Respiratory Gases by Blood

We have considered external and internal respiration consecutively to emphasize their similarities, but keep in mind that it is the blood that transports O_2 and CO_2 between these two exchange sites.

Oxygen Transport

- Describe how oxygen is transported in the blood, and explain how oxygen loading and unloading is affected by temperature, pH, BPG, and P_{CO_2} .

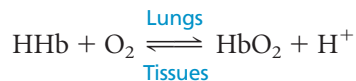
Molecular oxygen is carried in blood in two ways: bound to hemoglobin within red blood cells and dissolved in plasma. Oxygen is poorly soluble in water, so only about 1.5% of the oxygen transported is carried in the dissolved form. Indeed, if this were the *only* means of oxygen transport, a P_{O_2} of 3 atm or a cardiac output of 15 times normal would be required to provide the oxygen levels needed by body tissues! This problem, of course,

has been solved by hemoglobin, and 98.5% of the oxygen ferried from the lungs to the tissues is carried in a loose chemical combination with hemoglobin.

Association of Oxygen and Hemoglobin

As we described in Chapter 17, hemoglobin (Hb) is composed of four polypeptide chains, each bound to an iron-containing heme group (see Figure 17.4). Because the iron atoms bind oxygen, each hemoglobin molecule can combine with four molecules of O₂, and oxygen loading is rapid and reversible.

The hemoglobin-oxygen combination, called **oxyhemoglobin** (ok'si-he'mo-glo'bin), is written **HbO₂**. Hemoglobin that has released oxygen is called **reduced hemoglobin**, or **deoxyhemoglobin**, and is written **HHb**. Loading and unloading of O₂ can be indicated by a single reversible equation:



After the first O₂ molecule binds to iron, the Hb molecule changes shape. As a result, it more readily takes up two more O₂ molecules, and uptake of the fourth is even more facilitated. When all four heme groups are bound to O₂, a hemoglobin molecule is said to be *fully saturated*. When one, two, or three oxygen molecules are bound, hemoglobin is *partially saturated*. By the same token, unloading of one oxygen molecule enhances the unloading of the next, and so on. In this way, the *affinity* (binding strength) of hemoglobin for oxygen changes with the extent of oxygen saturation, and both loading and unloading of oxygen are very efficient.

The rate at which Hb reversibly binds or releases O₂ is regulated by P_{O₂}, temperature, blood pH, P_{CO₂}, and blood concentration of an organic chemical called BPG. These factors interact to ensure adequate deliveries of O₂ to tissue cells.

Influence of P_{O₂} on Hemoglobin Saturation The relationship between the degree of hemoglobin saturation and the P_{O₂} of blood is not linear, because the affinity of hemoglobin for O₂ changes with O₂ binding, as we just described. The **oxygen-hemoglobin dissociation curve** shows this relationship (Figure 22.20). This S-shaped curve has a steep slope for P_{O₂} values between 10 and 50 mm Hg and then flattens out (plateaus) between 70 and 100 mm Hg.

Under normal resting conditions (P_{O₂} = 100 mm Hg), arterial blood hemoglobin is 98% saturated, and 100 ml of systemic arterial blood contains about 20 ml of O₂. This *oxygen content* of arterial blood is written as 20 vol % (volume percent). As arterial blood flows through the systemic capillaries, about 5 ml of O₂ per 100 ml of blood is released, yielding an Hb saturation of 75% and an O₂ content of 15 vol % in venous blood.

The nearly complete saturation of Hb in arterial blood explains why breathing deeply increases both the alveolar and arterial blood P_{O₂} but causes very little increase in the O₂ saturation of hemoglobin. Remember, P_{O₂} measurements indicate only the amount of O₂ dissolved in plasma, not the amount bound to hemoglobin. However, P_{O₂} values are a good index of lung function, and when arterial P_{O₂} is significantly less than alveolar P_{O₂} some degree of respiratory impairment exists.

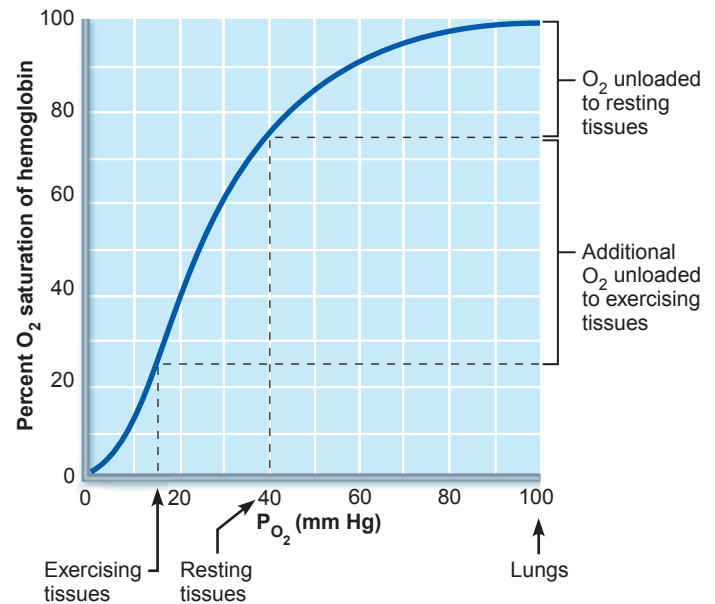


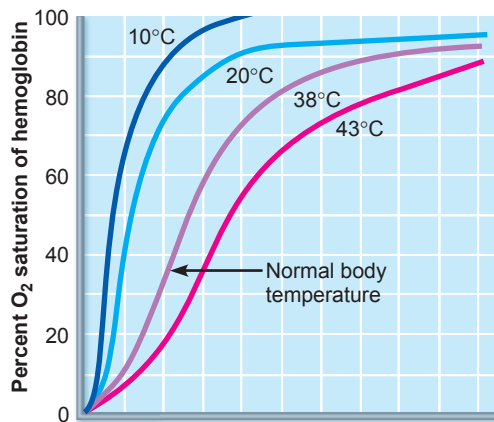
Figure 22.20 Oxygen-hemoglobin dissociation curve. Hb saturation changes as blood P_{O₂} changes. Notice that hemoglobin is almost completely saturated at a P_{O₂} of 70 mm Hg. Rapid loading and unloading of O₂ to and from hemoglobin occur at P_{O₂} values in the steep portion of the curve. In the systemic circuit, approximately 25% of Hb-bound O₂ is unloaded to resting tissues. Thus, hemoglobin of venous blood from resting tissue is still about 75% saturated with oxygen after one round through the body. During exercise, P_{O₂} can drop as low as 15 mm Hg, causing an additional 50% unloading and leaving the Hb only 25% saturated.

The oxygen-hemoglobin dissociation curve in Figure 22.20 reveals two other important facts. First, Hb is almost completely saturated at a P_{O₂} of 70 mm Hg, and further increases in P_{O₂} produce only small increases in O₂ binding. The adaptive value of this is that O₂ loading and delivery to the tissues can still be adequate when the P_{O₂} of inspired air is well below its usual levels, a situation common at higher altitudes and in people with cardiopulmonary disease.

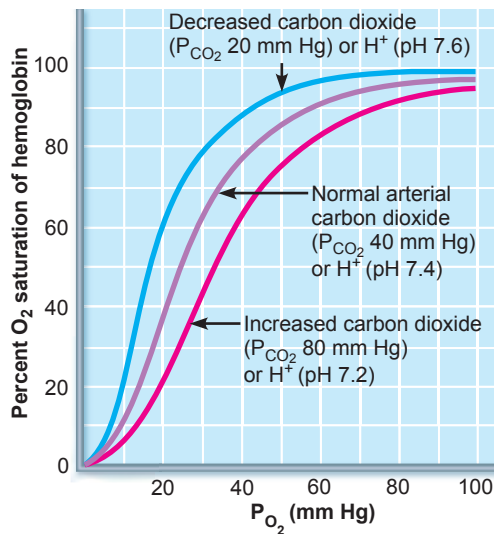
Second, because most O₂ *unloading* occurs on the steep portion of the curve, a small drop in P_{O₂} will cause a large increase in unloading. Normally, only 20–25% of bound oxygen is unloaded during one systemic circuit, and substantial amounts of O₂ are still available in venous blood (the *venous reserve*). Consequently, if O₂ drops to very low levels in the tissues, as might occur during vigorous exercise, much more O₂ will dissociate from hemoglobin to be used by the tissue cells without any increase in respiratory rate or cardiac output.

Influence of Other Factors on Hemoglobin Saturation Temperature, blood pH, P_{CO₂}, and the amount of BPG in the blood all influence hemoglobin saturation at a given P_{O₂}. BPG (2,3-bisphosphoglycerate), which binds reversibly with hemoglobin, is produced by red blood cells (RBCs) as they break down glucose by the anaerobic process called glycolysis.

All of these factors influence Hb saturation by modifying hemoglobin's three-dimensional structure, and thereby changing its affinity for O₂. Generally speaking, an *increase* in



(a)



(b)

Figure 22.21 Effect of temperature, P_{CO_2} , and blood pH on the oxygen-hemoglobin dissociation curve. Oxygen unloading is enhanced at conditions of (a) increased temperature, (b) increased P_{CO_2} , and/or hydrogen ion concentration (decreased pH), causing the dissociation curve to shift to the right. This response is called the Bohr effect.

temperature, P_{CO_2} , H^+ , or BPG levels in blood decreases Hb's affinity for O_2 , enhancing oxygen unloading from the blood. This is shown by the rightward shift of the oxygen-hemoglobin dissociation curve in Figure 22.21. (The purple lines represent normal body conditions, and the red lines show the shift to the right.)

Conversely, a decrease in any of these factors increases hemoglobin's affinity for oxygen, decreasing oxygen unloading. This change shifts the dissociation curve to the left (as the blue lines show in Figure 22.21).

If you give a little thought to how these factors might be related, you'll realize that they all tend to be at their highest levels in the systemic capillaries where oxygen unloading is the goal. As cells metabolize glucose and use O_2 , they release CO_2 , which increases the P_{CO_2} and H^+ levels in the capillary blood. Both declining blood pH (acidosis) and increasing P_{CO_2}

weaken the Hb- O_2 bond, a phenomenon called the **Bohr effect**. As a result, oxygen unloading is enhanced where it is most needed.

Additionally, heat is a by-product of metabolic activity, and active tissues are usually warmer than less active ones. A rise in temperature affects hemoglobin's affinity for O_2 both directly and indirectly (via its influence on RBC metabolism and BPG synthesis). Collectively, these factors see to it that Hb unloads much more O_2 in the vicinity of hard-working tissue cells.

HOMEOSTATIC IMBALANCE

Whatever the cause, inadequate oxygen delivery to body tissues is called **hypoxia** (hi-pok'se-ah). This condition is observed more easily in fair-skinned people because their skin and mucosae take on a bluish cast (become *cyanotic*) when Hb saturation falls below 75%. In dark-skinned individuals, this color change can be observed only in the mucosae and nail beds.

Classification of hypoxia based on cause is as follows:

- **Anemic hypoxia** reflects poor O_2 delivery resulting from too few RBCs or from RBCs that contain abnormal or too little Hb.
- **Ischemic (stagnant) hypoxia** results when blood circulation is impaired or blocked. Congestive heart failure may cause bodywide ischemic hypoxia, whereas emboli or thrombi block oxygen delivery only to tissues distal to the obstruction.
- **Histotoxic hypoxia** occurs when body cells are unable to use O_2 even though adequate amounts are delivered. This variety of hypoxia is the consequence of metabolic poisons, such as cyanide.
- **Hypoxemic hypoxia** is indicated by reduced arterial P_{O_2} . Possible causes include disordered or abnormal ventilation-perfusion coupling, pulmonary diseases that impair ventilation, and breathing air containing scant amounts of O_2 .

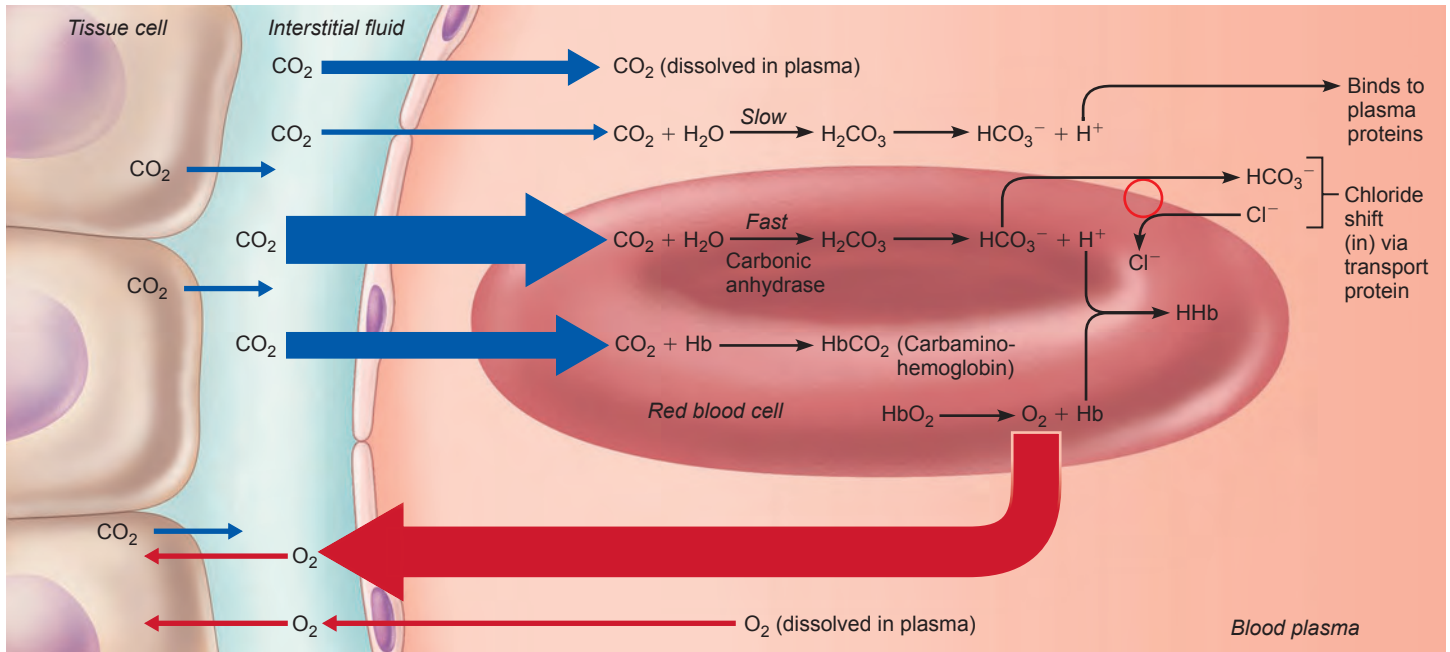
Carbon monoxide poisoning is a unique type of hypoxemic hypoxia, and a leading cause of death from fire. Carbon monoxide (CO) is an odorless, colorless gas that competes vigorously with O_2 for heme binding sites. Moreover, because Hb's affinity for CO is more than 200 times greater than its affinity for oxygen, CO is a highly successful competitor. Even at minuscule partial pressures, carbon monoxide can displace oxygen.

CO poisoning is particularly dangerous because it does not produce the characteristic signs of hypoxia—cyanosis and respiratory distress. Instead the victim is confused and has a throbbing headache. In rare cases, fair skin becomes cherry red (the color of the Hb-CO complex), which the eye of the beholder interprets as a healthy “blush.” Patients with CO poisoning are given hyperbaric therapy (if available) or 100% O_2 until the CO has been cleared from the body. ■

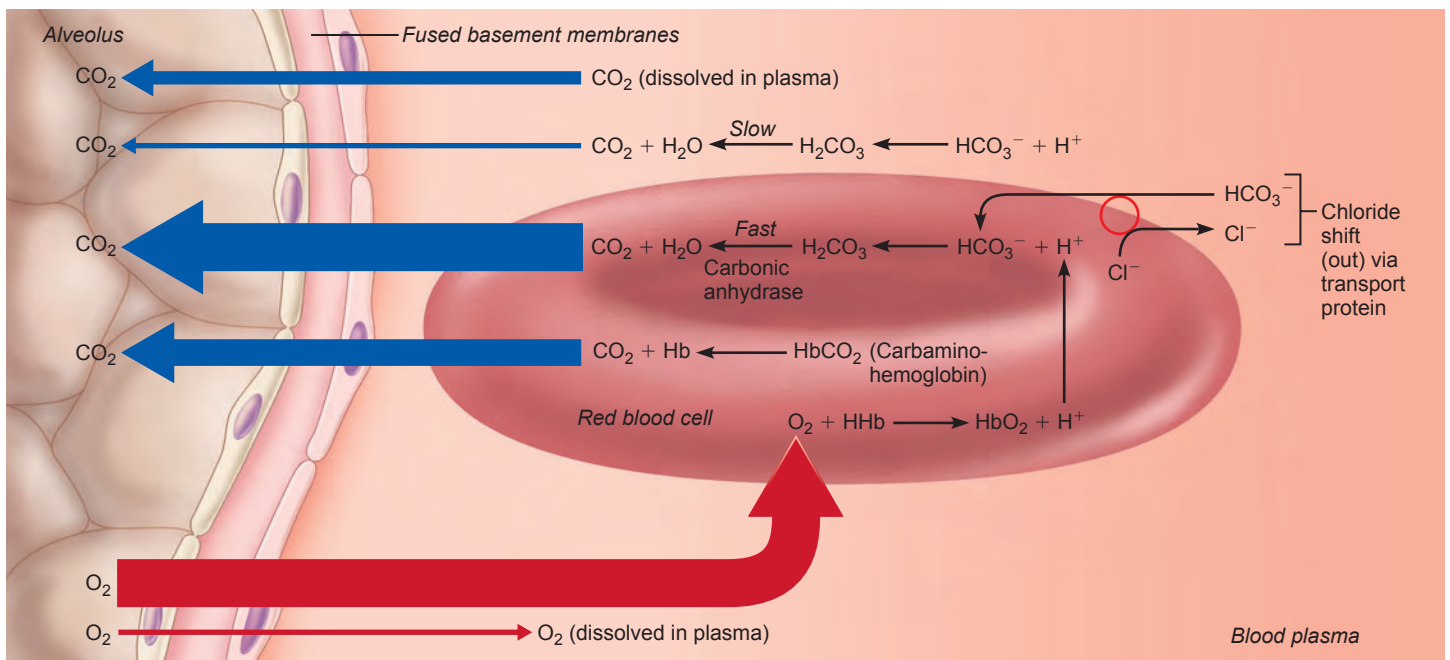
Carbon Dioxide Transport

- Describe carbon dioxide transport in the blood.

Normally active body cells produce about 200 ml of CO_2 each minute—exactly the amount excreted by the lungs. Blood



(a) Oxygen release and carbon dioxide pickup at the tissues



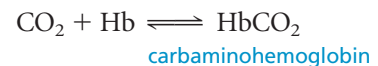
(b) Oxygen pickup and carbon dioxide release in the lungs

Figure 22.22 Transport and exchange of CO₂ and O₂. Relative sizes of the transport arrows indicate the proportionate amounts of O₂ and CO₂ moved by each method. (Reduced hemoglobin is HHb.)

transports CO₂ from the tissue cells to the lungs in three forms (**Figure 22.22**):

- 1. Dissolved in plasma (7–10%).** The smallest amount of CO₂ is transported simply dissolved in plasma.
- 2. Chemically bound to hemoglobin (just over 20%).** In this form, dissolved CO₂ is bound and carried in the

RBCs as **carbaminohemoglobin** (kar-bam"i-no-he"mo-glo'bin):

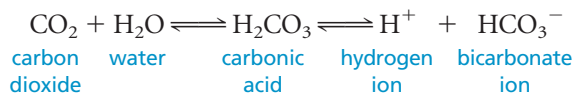


This reaction is rapid and does not require a catalyst. Carbon dioxide transport in RBCs does not compete with

oxyhemoglobin transport because carbon dioxide binds directly to the amino acids of *globin* (and not to the heme).

CO₂ loading and unloading to and from Hb are directly influenced by the P_{CO₂} and the degree of Hb oxygenation. Carbon dioxide rapidly dissociates from hemoglobin in the lungs, where the P_{CO₂} of alveolar air is lower than that in blood. Carbon dioxide is loaded in the tissues, where the P_{CO₂} is higher than that in the blood. Deoxygenated hemoglobin combines more readily with carbon dioxide than does oxygenated hemoglobin, as we will see in the discussion of the Haldane effect below.

3. **As bicarbonate ion in plasma** (about 70%). Most carbon dioxide molecules entering the plasma quickly enter the RBCs, where most of the reactions that prepare carbon dioxide for transport as **bicarbonate ions** (HCO₃⁻) in plasma occur. As illustrated in Figure 22.22a, when dissolved CO₂ diffuses into the RBCs, it combines with water, forming carbonic acid (H₂CO₃). H₂CO₃ is unstable and dissociates into hydrogen ions and bicarbonate ions:



Although this reaction also occurs in plasma, it is thousands of times faster in RBCs because they (and not plasma) contain **carbonic anhydrase** (kar-bon'ik an-hi'drās), an enzyme that reversibly catalyzes the conversion of carbon dioxide and water to carbonic acid. Hydrogen ions released during the reaction (as well as CO₂ itself) bind to Hb, triggering the Bohr effect. In this way CO₂ loading enhances O₂ release. Because of the buffering effect of Hb, the liberated H⁺ causes little change in pH under resting conditions. As a result, blood becomes only slightly more acidic (the pH declines from 7.4 to 7.34) as it passes through the tissues.

Once generated, HCO₃⁻ moves quickly from the RBCs into the plasma, where it is carried to the lungs. To counterbalance the rapid outrush of these anions from the RBCs, chloride ions (Cl⁻) move from the plasma into the RBCs. This ion exchange process, called the **chloride shift**, occurs via facilitated diffusion through a RBC membrane protein.

In the lungs, the process is reversed (Figure 22.22b). As blood moves through the pulmonary capillaries, its P_{CO₂} declines from 45 mm Hg to 40 mm Hg. For this to occur, CO₂ must first be freed from its “bicarbonate housing.” HCO₃⁻ reenters the RBCs (and Cl⁻ moves into the plasma) and binds with H⁺ to form carbonic acid, which is then split by carbonic anhydrase to release CO₂ and water. This CO₂, along with that released from hemoglobin and from solution in plasma, then diffuses along its partial pressure gradient from the blood into the alveoli.

The Haldane Effect

The amount of carbon dioxide transported in blood is markedly affected by the degree of oxygenation of the blood. The lower the P_{O₂} and the lower the extent of Hb saturation with oxygen, the more CO₂ that can be carried in the blood.

This phenomenon, called the **Haldane effect**, reflects the greater ability of reduced hemoglobin to form carbaminohemoglobin and to buffer H⁺ by combining with it. As CO₂ enters the systemic bloodstream, it causes more oxygen to dissociate from Hb (Bohr effect). The dissociation of O₂ allows more CO₂ to combine with Hb (Haldane effect).

The Haldane effect encourages CO₂ exchange in both the tissues and lungs. In the pulmonary circulation, the situation that we just described is reversed—uptake of O₂ facilitates release of CO₂ (Figure 22.22b). As Hb becomes saturated with O₂, the H⁺ released combines with HCO₃⁻, helping to unload CO₂ from the pulmonary blood.

Influence of CO₂ on Blood pH

Typically, the H⁺ released during carbonic acid dissociation is buffered by Hb or other proteins within the RBCs or in plasma. The HCO₃⁻ generated in the red blood cells diffuses into the plasma, where it acts as the *alkaline reserve* part of the blood's carbonic acid–bicarbonate buffer system.

The **carbonic acid–bicarbonate buffer system** is very important in resisting shifts in blood pH, as shown in the equation in point 3 concerning CO₂ transport. For example, if the hydrogen ion concentration in blood begins to rise, excess H⁺ is removed by combining with HCO₃⁻ to form carbonic acid (a weak acid). If H⁺ concentration drops below desirable levels in blood, carbonic acid dissociates, releasing hydrogen ions and lowering the pH again.

Changes in respiratory rate or depth can produce dramatic changes in blood pH by altering the amount of carbonic acid in the blood. Slow, shallow breathing allows CO₂ to accumulate in the blood. As a result, carbonic acid levels increase and blood pH drops. Conversely, rapid, deep breathing quickly flushes CO₂ out of the blood, reducing carbonic acid levels and increasing blood pH. In this way, respiratory ventilation can provide a fast-acting system to adjust blood pH (and P_{CO₂}) when it is disturbed by metabolic factors. Respiratory adjustments play a major role in the acid-base balance of the blood, as we will discuss in Chapter 26.

CHECK YOUR UNDERSTANDING

16. Rapidly metabolizing tissues generate large amounts of CO₂ and H⁺. How does this affect O₂ unloading? What is this effect called?
17. List the three ways CO₂ is transported in blood and state approximate percentages of each.
18. What is the relationship between CO₂ and pH in the blood? Explain.

For answers, see Appendix G.

Control of Respiration

Although our tidelike breathing seems so beautifully simple, its control is more complex than you might think. Higher brain centers, chemoreceptors, and other reflexes all modify the basic respiratory rhythms generated in the brain stem.

Neural Mechanisms

► Describe the neural controls of respiration.

The control of respiration primarily involves neurons in the reticular formation of the medulla and pons. Because the medulla sets the respiratory rhythm, we will begin there.

Medullary Respiratory Centers

Clustered neurons in two areas of the medulla oblongata appear to be critically important in respiration. These are (1) the **dorsal respiratory group (DRG)**, located dorsally near the root of cranial nerve IX, and (2) the **ventral respiratory group (VRG)**, a network of neurons that extends in the ventral brain stem from the spinal cord to the pons-medulla junction (Figure 22.23).

The VRG appears to be a rhythm-generating and integrative center. It contains groups of neurons that fire during inspiration and others that fire during expiration in a dance of mutual inhibition. When its inspiratory neurons fire, a burst of impulses travels along the **phrenic** and **intercostal nerves** to excite the diaphragm and external intercostal muscles, respectively (Figure 22.23). As a result, the thorax expands and air rushes into the lungs. When the VRG's expiratory neurons fire, the output stops, and expiration occurs passively as the inspiratory muscles relax and the lungs recoil.

This cyclic on/off activity of the inspiratory and expiratory neurons repeats continuously and produces a respiratory rate of 12–15 breaths per minute, with inspiratory phases lasting about 2 seconds followed by expiratory phases lasting about 3 seconds. This normal respiratory rate and rhythm is referred to as **eupnea** (ūp-ne'ah; *eu* = good, *pne* = breath). During severe hypoxia, VRG networks generate gasping (perhaps in a last-ditch effort to restore O₂ to the brain). Respiration stops completely when a certain cluster of VRG neurons is completely suppressed, as by an overdose of morphine or alcohol.

Until recently, it was thought that the DRG acts as an inspiratory center, performing many of the tasks now known to be performed by the VRG. We now know that in almost all mammals including humans, the DRG integrates input from peripheral stretch and chemoreceptors (which we will describe shortly) and communicates this information to the VRG. It may seem surprising, but many of the details of this system so essential to life are still being worked out.

Pontine Respiratory Centers

Although the VRG generates the basic respiratory rhythm, the pontine respiratory centers influence and modify the activity of medullary neurons. For example, pontine centers appear to smooth out the transitions from inspiration to expiration, and vice versa. When lesions are made in its superior region, inspirations become very prolonged, a phenomenon called *apneustic breathing*.

The **pontine respiratory group**, formerly called the *pneumotaxic center* (noo'mo-tak'sik), and other pontine centers transmit impulses to the VRG of the medulla (Figure 22.23). This input modifies and fine-tunes the breathing rhythms generated by the VRG during certain activities such as vocalization, sleep,

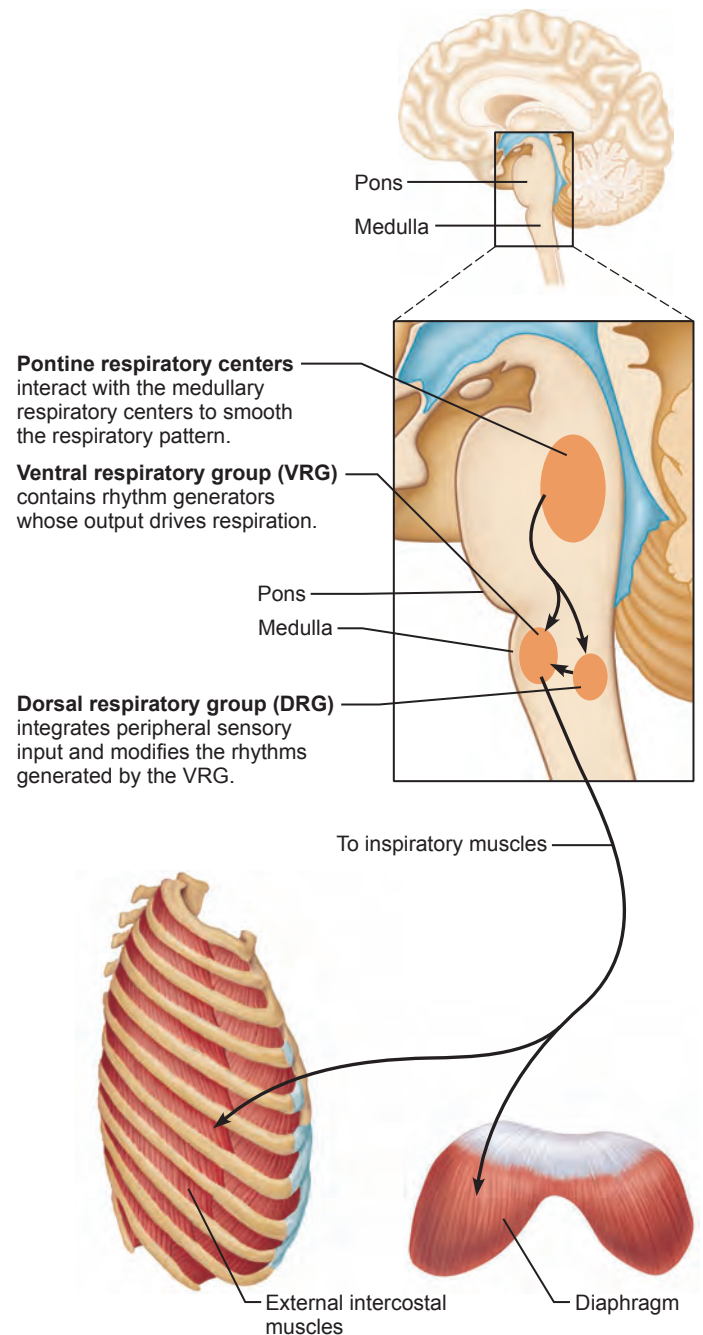


Figure 22.23 Locations of respiratory centers and their postulated connections. The efferent pathway shown here is incomplete. Medullary neurons communicate with lower motor neurons in the spinal cord, but these are omitted for simplicity.

and exercise. As you would expect from these functions, the pontine respiratory centers, like the DRG, receive input from higher brain centers and from various sensory receptors in the periphery.

Genesis of the Respiratory Rhythm

There is little question that breathing is rhythmic, but we still cannot fully explain the origin of its rhythm. One hypothesis is that there are *pacemaker neurons*, which have intrinsic (automatic)

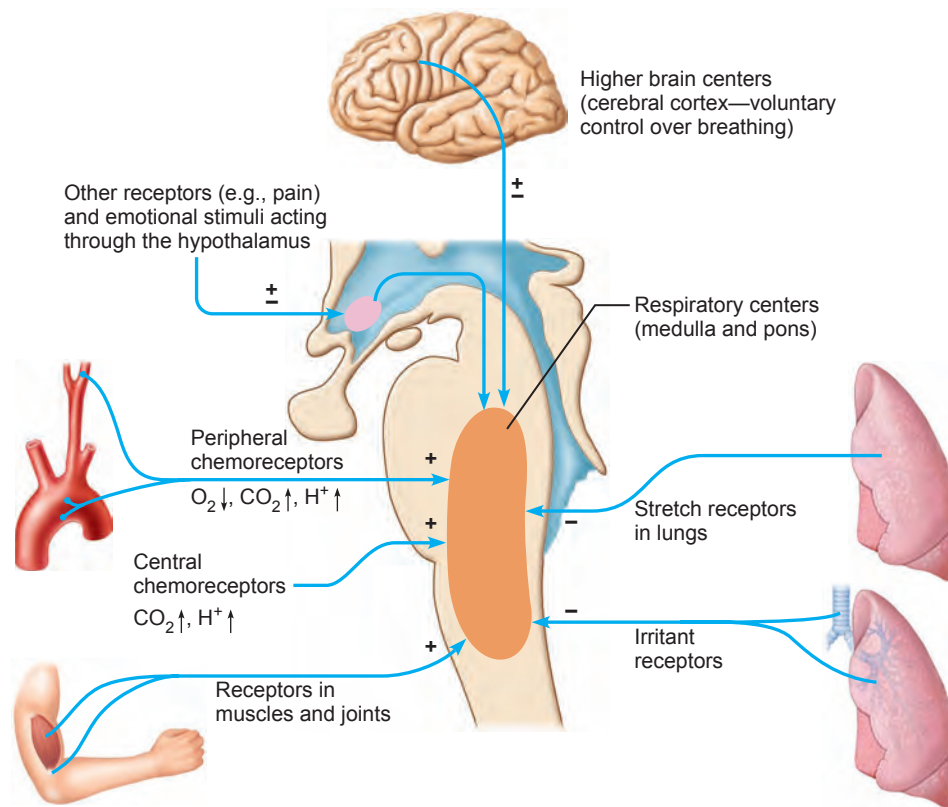


Figure 22.24 Neural and chemical influences on brain stem respiratory centers.

Excitatory influences (+) increase the frequency of impulses sent to the muscles of respiration and recruit additional motor units, resulting in deeper, faster breathing. Inhibitory influences (–) have the reverse effect. In some cases, the impulses may be excitatory or inhibitory (±), depending on which receptors or brain regions are activated. The cerebral cortex also directly innervates respiratory muscle motor neurons (not shown).

rhythmicity like the pacemaker cells found in the heart. Pacemaker-like activity has been demonstrated in certain VRG neurons, but suppressing their activity does not abolish breathing. This leads us to the second (and more widely accepted) hypothesis: Normal respiratory rhythm is a result of reciprocal inhibition of interconnected neuronal networks in the medulla. Rather than a single set of pacemaker neurons, there are two sets that inhibit each other and so cycle their activity to generate the rhythm.

Factors Influencing Breathing Rate and Depth

- ▶ Compare and contrast the influences of arterial pH, arterial partial pressures of oxygen and carbon dioxide, lung reflexes, volition, and emotions on respiratory rate and depth.

Inspiratory depth is determined by how actively the respiratory center stimulates the motor neurons serving the respiratory muscles. The greater the stimulation, the greater the number of motor units excited and the greater the force of respiratory muscle contractions. Respiratory rate is determined by how long the inspiratory center is active or how quickly it is switched off.

Depth and rate of breathing can be modified in response to changing body demands. The respiratory centers in the medulla and pons are sensitive to both excitatory and inhibitory stimuli. We describe these stimuli next and they are summarized in **Figure 22.24**.

Chemical Factors

Among the factors that influence breathing rate and depth, the most important are changing levels of CO_2 , O_2 , and H^+ in arterial blood. Sensors responding to such chemical fluctuations, called **chemoreceptors**, are found in two major body locations. The **central chemoreceptors** are located throughout the brain stem, including the ventrolateral medulla. The **peripheral chemoreceptors** are found in the aortic arch and carotid arteries.

Influence of P_{CO_2} Of all the chemicals influencing respiration, CO_2 is the most potent and the most closely controlled. Normally, arterial P_{CO_2} is 40 mm Hg and is maintained within ± 3 mm Hg of this level by an exquisitely sensitive homeostatic mechanism that is mediated mainly by the effect that rising CO_2 levels have on the central chemoreceptors of the brain stem (**Figure 22.25**).

As P_{CO_2} levels rise in the blood, a condition referred to as **hypercapnia** (hi''per-kap'ne-ah), CO_2 accumulates in the brain. As CO_2 accumulates, it is hydrated to form carbonic acid. The acid dissociates, H^+ is liberated, and the pH drops. This is the same reaction that occurs when CO_2 enters RBCs (see p. 834). The increase in H^+ excites the central chemoreceptors, which make abundant synapses with the respiratory regulatory centers. As a result, the depth and rate of breathing are increased. This enhanced alveolar ventilation quickly flushes CO_2 out of the blood, increasing blood pH.

An elevation of only 5 mm Hg in arterial P_{CO_2} results in a doubling of alveolar ventilation, even when arterial O_2 levels and pH are unchanged. When P_{O_2} and pH are below normal, the response to elevated P_{CO_2} is even greater. Increased ventilation is normally self-limiting, ending when homeostatic blood P_{CO_2} levels are restored.

Notice that while rising blood CO_2 levels act as the initial stimulus, it is rising levels of H^+ generated within the brain that prod the *central* chemoreceptors into increased activity. (CO_2 readily diffuses across the blood-brain barrier between the brain and the blood, but H^+ does not.) In the final analysis, control of breathing during rest is aimed primarily at *regulating the H^+ concentration in the brain.*

HOMEOSTATIC IMBALANCE

Hyperventilation is an increase in the rate and depth of breathing that exceeds the body's need to remove CO_2 . A person experiencing an anxiety attack may hyperventilate involuntarily to the point where he or she becomes dizzy or faints. This happens because low CO_2 levels in the blood (**hypocapnia**) cause cerebral blood vessels to constrict, reducing brain perfusion and producing cerebral ischemia. Earlier symptoms of hyperventilation are tingling and involuntary muscle spasms (tetany) in the hands and face caused by blood Ca^{2+} levels falling as pH rises. Such attacks may be averted by breathing into a paper bag because then the air being inspired is expired air, rich in carbon dioxide, which causes carbon dioxide to be retained in the blood. ■

When P_{CO_2} is abnormally low, respiration is inhibited and becomes slow and shallow. In fact, periods of **apnea** (breathing cessation) may occur until arterial P_{CO_2} rises and again stimulates respiration.

Sometimes swimmers voluntarily hyperventilate so that they can hold their breath longer during swim meets. This is incredibly dangerous for the following reasons. Blood O_2 content rarely drops much below 60% of normal during regular breath-holding, because as P_{O_2} drops, P_{CO_2} rises enough to make breathing unavoidable. However, strenuous hyperventilation can lower P_{CO_2} so much that a lag period occurs before it rebounds enough to stimulate respiration again. This lag may allow oxygen levels to fall well below 50 mm Hg, causing the swimmer to black out (and perhaps drown) before he or she has the urge to breathe.

Influence of P_{O_2} Cells sensitive to arterial O_2 levels are found in the peripheral chemoreceptors, that is, in the **aortic bodies** of

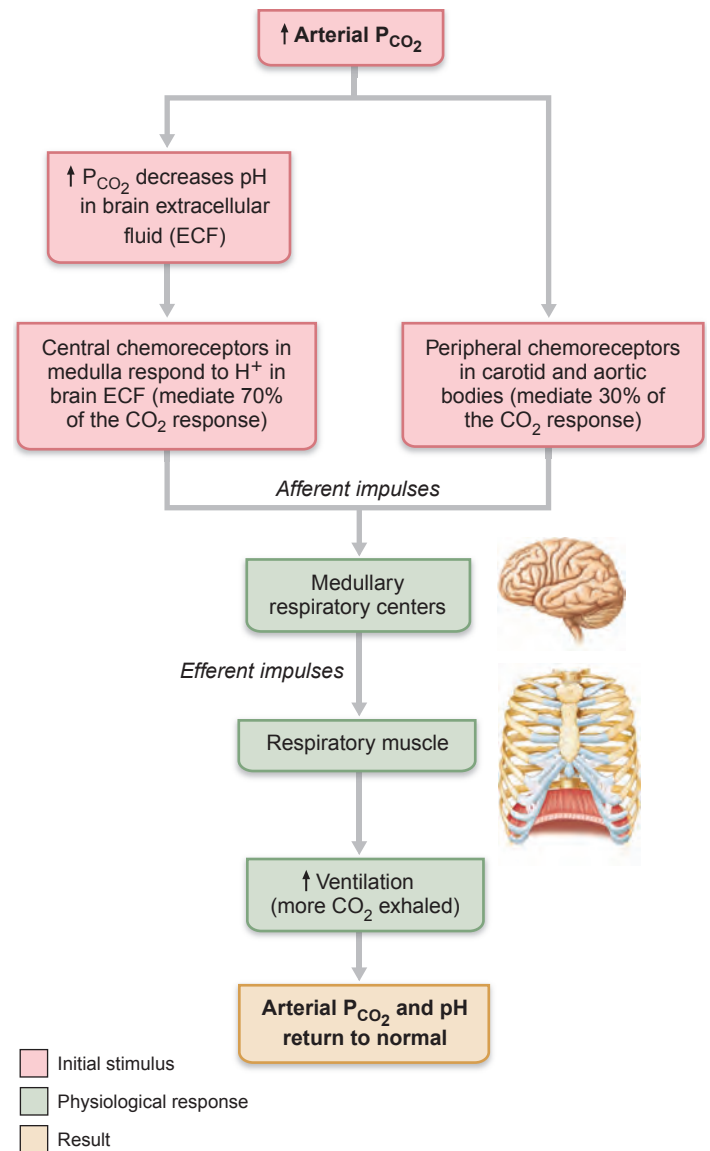


Figure 22.25 Negative feedback mechanism by which changes in P_{CO_2} and blood pH regulate ventilation.

the aortic arch and in the **carotid bodies** at the bifurcation of the common carotid arteries (**Figure 22.26**). Those in the carotid bodies are the main oxygen sensors.

Under normal conditions, the effect of declining P_{O_2} on ventilation is slight and mostly limited to enhancing the sensitivity of peripheral receptors to increased P_{CO_2} . Arterial P_{O_2} must drop *substantially*, to at least 60 mm Hg, before O_2 levels become a major stimulus for increased ventilation. This is not as strange as it may appear. Remember, there is a huge reservoir of O_2 bound to Hb, and Hb remains almost entirely saturated unless or until the P_{O_2} of alveolar gas and arterial blood falls below 60 mm Hg. The brain stem centers then begin to suffer from O_2 starvation, and their activity is depressed. At the same time, the peripheral chemoreceptors become excited and stimulate the respiratory centers to increase ventilation, even if P_{CO_2} is normal.

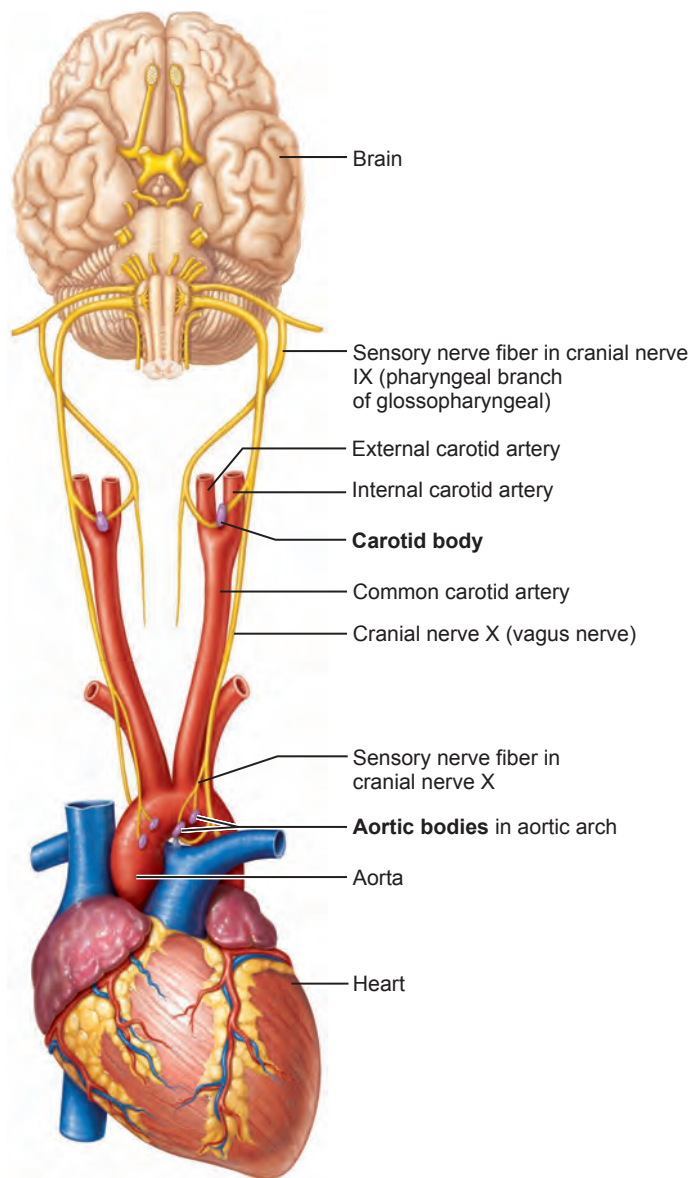


Figure 22.26 Location and innervation of the peripheral chemoreceptors in the carotid and aortic bodies.

In this way, the peripheral chemoreceptor system can maintain ventilation when alveolar O_2 levels are low even though brain stem centers are depressed by hypoxia.

Influence of Arterial pH Changes in arterial pH can modify respiratory rate and rhythm even when CO_2 and O_2 levels are normal. Because little H^+ diffuses from the blood into the brain, the direct effect of arterial H^+ concentration on central chemoreceptors is insignificant compared to the effect of H^+ generated by elevations in P_{CO_2} . The increased ventilation that occurs in response to falling arterial pH is mediated through the peripheral chemoreceptors.

Although changes in P_{CO_2} and H^+ concentration are interrelated, they are distinct stimuli. A drop in blood pH may reflect CO_2 retention, but it may also result from metabolic causes, such as accumulation of lactic acid during exercise or of fatty

acid metabolites (ketone bodies) in patients with poorly controlled diabetes mellitus. Regardless of cause, as arterial pH declines, respiratory system controls attempt to compensate and raise the pH by eliminating CO_2 (and carbonic acid) from the blood by increasing respiratory rate and depth.

Summary of Interactions of P_{CO_2} , P_{O_2} , and Arterial pH

Although every cell in the body must have O_2 to live, the body's need to rid itself of CO_2 is the most important stimulus for breathing in a healthy person. However, CO_2 does not act in isolation, and various chemical factors enforce or inhibit one another's effects. These interactions are summarized here:

1. **Rising CO_2 levels are the most powerful respiratory stimulant.** As CO_2 is hydrated in brain tissue, liberated H^+ acts directly on the central chemoreceptors, causing a reflexive increase in breathing rate and depth. Low P_{CO_2} levels depress respiration.
2. **Under normal conditions, blood P_{O_2} affects breathing only indirectly by influencing peripheral chemoreceptor sensitivity to changes in P_{CO_2} .** Low P_{O_2} augments P_{CO_2} effects, and high P_{O_2} levels diminish the effectiveness of CO_2 stimulation.
3. **When arterial P_{O_2} falls below 60 mm Hg, it becomes the major stimulus for respiration, and ventilation is increased via reflexes initiated by the peripheral chemoreceptors.** This may increase O_2 loading into the blood, but it also causes hypocapnia (low P_{CO_2} blood levels) and an increase in blood pH, both of which inhibit respiration.
4. **Changes in arterial pH resulting from CO_2 retention or metabolic factors act indirectly through the peripheral chemoreceptors to promote changes in ventilation, which in turn modify arterial P_{CO_2} and pH.** Arterial pH does not influence the central chemoreceptors directly.

Influence of Higher Brain Centers

Hypothalamic Controls Acting through the hypothalamus and the rest of the limbic system, strong emotions and pain send signals to the respiratory centers, modifying respiratory rate and depth. For example, have you ever touched something cold and clammy and gasped? That response was mediated through the hypothalamus. So too is the breath holding that occurs when we are angry and the increased respiratory rate that occurs when we are excited. A rise in body temperature acts to increase the respiratory rate, while a drop in body temperature produces the opposite effect. Sudden chilling of the body (a dip in the North Atlantic Ocean in late October) can cause cessation of breathing (apnea)—or at the very least, leave you gasping.

Cortical Controls Although the brain stem respiratory centers normally regulate breathing involuntarily, we can also exert conscious (volitional) control over the rate and depth of our breathing. We can choose to hold our breath or to take an extra-deep breath, for example. During voluntary control, the cerebral motor cortex sends signals to the motor neurons that stimulate the respiratory muscles, bypassing the medullary centers.

Our ability to voluntarily hold our breath is limited, however, because the brain stem respiratory centers automatically reinitiate breathing when the blood concentration of CO_2 reaches critical levels. That explains why drowning victims typically have water in their lungs.

Pulmonary Irritant Reflexes

The lungs contain receptors that respond to an enormous variety of irritants. When activated, these receptors communicate with the respiratory centers via vagal nerve afferents. Accumulated mucus, inhaled debris such as dust, or noxious fumes stimulate receptors in the bronchioles that promote reflex constriction of those air passages. The same irritants stimulate a cough when present in the trachea or bronchi, and a sneeze when present in the nasal cavity.

The Inflation Reflex

The visceral pleurae and conducting passages in the lungs contain numerous stretch receptors that are vigorously stimulated when the lungs are inflated. These receptors signal the medullary respiratory centers via afferent fibers of the vagus nerves, sending inhibitory impulses that end inspiration and allow expiration to occur. As the lungs recoil, the stretch receptors become quiet, and inspiration is initiated once again. This reflex, called the **inflation reflex**, or **Hering-Breuer reflex** (her'ing broy'er), is thought to be more a protective response (to prevent excessive stretching of the lungs) than a normal regulatory mechanism.

CHECK YOUR UNDERSTANDING

19. Which brain stem respiratory area is thought to generate the respiratory rhythm?
20. Which chemical factor in blood normally provides the most powerful stimulus to breathe? Which chemoreceptors are most important for this response?

For answers, see Appendix G.

Respiratory Adjustments

- ▶ Compare and contrast the hyperpnea of exercise with hyperventilation.
- ▶ Describe the process and effects of acclimatization to high altitude.

Exercise

Respiratory adjustments during exercise are geared both to intensity and duration of the exercise. Working muscles consume tremendous amounts of O_2 and produce large amounts of CO_2 , and so ventilation can increase 10- to 20-fold during vigorous exercise. This increase in ventilation in response to metabolic needs is called **hyperpnea** (hi'perp-ne'ah).

How does it differ from hyperventilation? The respiratory changes in hyperpnea do not lead to significant changes in

blood O_2 and CO_2 levels. By contrast, hyperventilation is excessive ventilation, and is characterized by low P_{CO_2} and alkalosis.

Exercise-enhanced ventilation does *not* appear to be prompted by rising P_{CO_2} and declining P_{O_2} and pH in the blood for two reasons. First, ventilation increases abruptly as exercise begins, followed by a gradual increase, and then a steady state of ventilation. When exercise stops, there is an initial small but abrupt decline in ventilation rate, followed by a gradual decrease to the pre-exercise value. Second, although venous levels change, arterial P_{CO_2} and P_{O_2} levels remain surprisingly constant during exercise. In fact, P_{CO_2} may decline to below normal and P_{O_2} may rise slightly because of the efficiency of the respiratory adjustments. Our present understanding of the mechanisms that produce these observations is sketchy, but the most accepted explanation is as follows.

The abrupt increase in ventilation that occurs as exercise begins reflects interaction of three neural factors:

1. Psychological stimuli (our conscious anticipation of exercise)
2. Simultaneous cortical motor activation of skeletal muscles and respiratory centers
3. Excitatory impulses reaching respiratory centers from proprioceptors in moving muscles, tendons, and joints

The subsequent gradual increase and then plateauing of respiration probably reflect the rate of CO_2 delivery to the lungs (the “ CO_2 flow”). The small but abrupt decrease in ventilation that occurs as exercise ends reflects the shutting off of the three neural factors listed above. The subsequent gradual decline to baseline ventilation likely reflects a decline in the CO_2 flow that occurs as the oxygen deficit is being repaid. The rise in lactic acid levels that contributes to O_2 deficit is *not* a result of inadequate respiratory function, because alveolar ventilation and pulmonary perfusion are as well matched during exercise as during rest (hemoglobin remains fully saturated). Rather, it reflects cardiac output limitations or inability of the skeletal muscles to further increase their oxygen consumption.

In light of this fact, the practice of inhaling pure O_2 by mask, used by some football players to replenish their “oxygen-starved” bodies as quickly as possible, is useless. The panting athlete *does* have an O_2 deficit, but inspiring extra oxygen will not help, because the shortage is in the muscles—not the lungs.

High Altitude

Most people live between sea level and an altitude of approximately 2400 m (8000 feet). In this range, differences in atmospheric pressure are not great enough to cause healthy people any problems when they spend brief periods in the higher-altitude areas. However, when you travel quickly from sea level to elevations above 8000 ft, where atmospheric pressure and P_{O_2} are lower, your body responds with symptoms of *acute mountain sickness* (AMS)—headaches, shortness of breath, nausea, and dizziness. AMS is common in travelers to ski resorts such as Vail, Colorado (8120 ft), and Brian Head, Utah (a heart-pounding 9600 ft). In severe cases of AMS, lethal pulmonary and cerebral edema may occur.

When you move on a *long-term* basis from sea level to the mountains, your body begins to make respiratory and hematopoietic adjustments via an adaptive response called **acclimatization**. As we have already explained, decreases in arterial P_{O_2} cause the peripheral chemoreceptors to become more responsive to increases in P_{CO_2} , and a substantial decline in P_{O_2} directly stimulates the peripheral chemoreceptors. As a result, ventilation increases as the brain attempts to restore gas exchange to previous levels. Within a few days, the minute ventilation stabilizes at a level 2–3 L/min higher than the sea level rate. Increased ventilation also reduces arterial CO_2 levels, so the P_{CO_2} of individuals living at high altitudes is typically below 40 mm Hg (its value at sea level).

High-altitude conditions always result in lower-than-normal hemoglobin saturation levels because less O_2 is available to be loaded. For example, at about 19,000 ft above sea level, O_2 saturation of arterial blood is only 67% (compared to nearly 98% at sea level). But Hb unloads only 20–25% of its oxygen at sea level, which means that even at the reduced saturations at high altitudes, the O_2 needs of the tissues are still met adequately under resting conditions. Additionally, at high altitudes hemoglobin's affinity for O_2 is reduced because of increases in BPG concentration, with the result that more O_2 is released to the tissues during each circulatory round.

Although the tissues in a person at high altitude receive adequate oxygen under normal conditions, problems arise when all-out efforts are demanded of the cardiovascular and respiratory systems (as discovered by athletes competing in the 1968 Summer Olympics on the high mesa of Mexico City, at 7370 ft). Unless a person is fully acclimatized, such conditions almost guarantee that body tissues will become severely hypoxic.

When blood O_2 levels decline, the kidneys accelerate production of erythropoietin, which stimulates bone marrow production of RBCs (see Chapter 17, p. 639). This phase of acclimatization, which occurs slowly, provides long-term compensation for living at high altitudes.

22 CHECK YOUR UNDERSTANDING

21. An injured soccer player arrives by ambulance in the emergency room. She is in obvious distress, breathing rapidly. Her blood P_{CO_2} is 26 mm Hg and pH is 7.5. Is she suffering from hyperventilation or hyperpnea? Explain.
22. What long-term adjustments does the body make when living at high altitude?

For answers, see Appendix G.

Homeostatic Imbalances of the Respiratory System

- ▶ Compare the causes and consequences of chronic bronchitis, emphysema, asthma, tuberculosis, and lung cancer.

The respiratory system is particularly vulnerable to infectious diseases because it is wide open to airborne pathogens. Many of

these inflammatory conditions, such as rhinitis and laryngitis, were considered earlier in the chapter. Here we turn our attention to the most disabling disorders: *chronic obstructive pulmonary disease (COPD)*, *asthma*, *tuberculosis*, and *lung cancer*. COPD and lung cancer are living proof of the devastating effects of cigarette smoking on the body. Long known to promote cardiovascular disease, cigarettes are perhaps even more effective at destroying the lungs.

Chronic Obstructive Pulmonary Disease

The **chronic obstructive pulmonary diseases (COPD)**, exemplified best by emphysema and chronic bronchitis, are a major cause of death and disability in North America. The key physiological feature of these diseases is an irreversible decrease in the ability to force air out of the lungs. These diseases also share other common features (**Figure 22.27**):

1. More than 80% of patients have a history of smoking.
2. **Dyspnea** (disp-ne'ah), difficult or labored breathing often referred to as "air hunger," occurs and gets progressively more severe.
3. Coughing and frequent pulmonary infections are common.
4. Most COPD victims develop respiratory failure manifested as **hypoventilation** (insufficient ventilation in relation to metabolic needs, causing CO_2 retention), respiratory acidosis, and hypoxemia.

Emphysema is distinguished by permanent enlargement of the alveoli, accompanied by destruction of the alveolar walls. Invariably the lungs lose their elasticity. This has three important consequences: (1) Accessory muscles must be enlisted to breathe, and victims are perpetually exhausted because breathing requires 15–20% of their total body energy supply (as opposed to 5% in healthy individuals). (2) For complex reasons, the bronchioles open during inspiration but collapse during expiration, trapping huge volumes of air in the alveoli. This hyperinflation leads to development of a permanently expanded "barrel chest" and flattens the diaphragm, thus reducing ventilation efficiency. (3) Damage to the pulmonary capillaries as the alveolar walls disintegrate increases resistance in the pulmonary circuit, forcing the right ventricle to overwork and consequently become enlarged. In addition to cigarette smoking, hereditary factors (e.g., alpha-1 antitrypsin deficiency) cause emphysema in some patients.

In **chronic bronchitis**, inhaled irritants lead to chronic excessive mucus production by the mucosa of the lower respiratory passageways and to inflammation and fibrosis of that mucosa. These responses obstruct the airways and severely impair lung ventilation and gas exchange. Pulmonary infections are frequent because bacteria thrive in the stagnant pools of mucus. However, the degree of dyspnea is usually moderate compared to that of emphysema sufferers. In addition to the major factor of cigarette smoking, environmental pollution may contribute to the development of chronic bronchitis.

In the clinical setting you might see two very different patterns that represent the extremes of patients with COPD. One pattern has traditionally been called the "pink puffer": these patients work so hard maintaining adequate ventilation that they

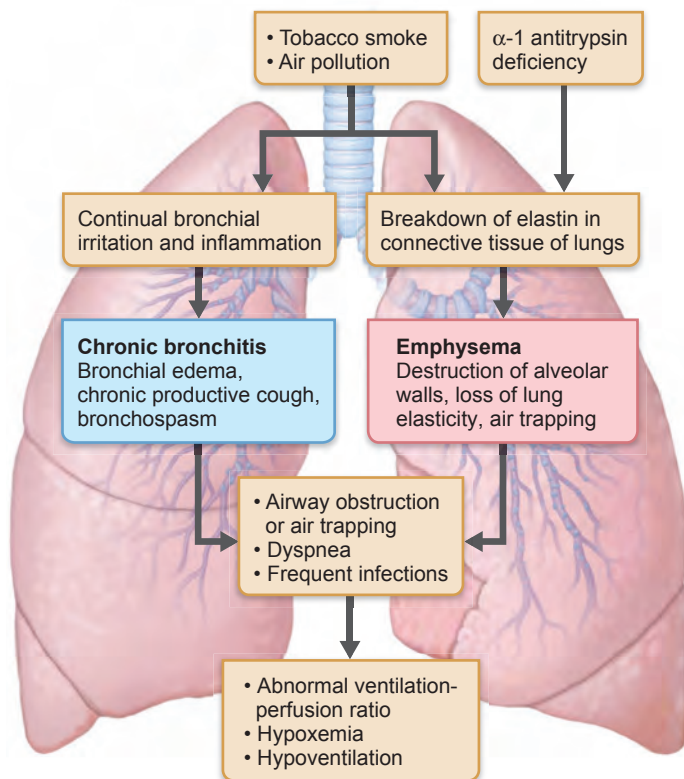


Figure 22.27 The pathogenesis of COPD.

lose weight, becoming thin but still having nearly normal blood gases. In contrast, “blue bloaters,” commonly of stocky build, become sufficiently hypoxic that they are obviously cyanotic. The hypoxia causes constriction of pulmonary blood vessels, which leads to pulmonary hypertension and right-sided heart failure. Traditionally, “pink puffers” were associated with emphysema while “blue bloaters” were associated with chronic bronchitis.

As usual, things are not that clear-cut. It turns out that patients with the same underlying disease can display either one of these two clinical patterns, and this may depend on a third factor—the strength of their innate respiratory drive. Most COPD patients fall in between these two clinical extremes.

COPD is routinely treated with bronchodilators and corticosteroids in aerosol form (inhalers). Severe dyspnea and hypoxia mandate oxygen use. For a few patients, surgical treatment for COPD, called *lung volume reduction surgery*, may be beneficial. In this procedure, part of the grossly enlarged lungs is removed to give the remaining lung tissue room to expand. While this surgery does not prolong life, it can offer certain COPD patients increased exercise capability and a higher quality of life, although at a high cost.

COPD patients in acute respiratory distress are commonly given oxygen. This oxygen must be administered with care, however. In some of these patients, giving pure oxygen can increase the blood P_{CO_2} (and lower blood pH) to life-threatening levels. It was once thought that this was due to the sudden loss of a hypoxic drive. The *hypoxic drive* hypothesis proposed that

chemoreceptor responses to CO_2 adapt to chronically high P_{CO_2} (essentially becoming nonfunctional), leaving only oxygen starvation to trigger adequate ventilation. However, this doesn't seem to be the case—oxygen administration barely changes ventilation. Instead, two other factors provide an explanation. First, oxygen dilates pulmonary arterioles, increasing perfusion and worsening an already poor ventilation-perfusion mismatch. Second, oxygen drives more CO_2 off of hemoglobin (the Haldane effect), dumping it into alveoli from which it cannot be removed because of the underlying disease. This whole problem can be avoided simply by using the minimum concentration of oxygen that relieves the patient's hypoxia.

Asthma

Asthma is characterized by episodes of coughing, dyspnea, wheezing, and chest tightness—alone or in combination. Most acute attacks are accompanied by a sense of panic. Although sometimes classed with COPD because it is an obstructive disorder, asthma is marked by acute exacerbations followed by symptom-free periods—that is, the obstruction is *reversible*.

The cause of asthma has been hard to pin down. Initially it was viewed as a consequence of bronchospasm triggered by various factors such as cold air, exercise, or allergens. However, when it was discovered that bronchoconstriction has relatively little effect on air flow through normal lungs, researchers probed more deeply and found that in asthma, active inflammation of the airways comes first. The airway inflammation is an immune response under the control of $T_{\text{H}2}$ cells, a subset of T lymphocytes that, by secreting certain interleukins, stimulate the production of IgE and recruit inflammatory cells (notably eosinophils) to the site.

Once someone has allergic asthma, the inflammation persists even during symptom-free periods and makes the airways hypersensitive to almost any irritant. (The most common triggers are in the home—the allergens from dust mites, cockroaches, cats, dogs, and fungi.) Once the airway walls are thickened with inflammatory exudate, the effect of bronchospasm is vastly magnified and can dramatically reduce air flow.

About one in ten people in North America suffer from asthma—children more than adults. Over the past 20 years, the number of cases of asthma has risen dramatically, an increase which may now be plateauing. While asthma remains a major health problem, better treatment options have begun to reduce the number of deaths due to asthma. Instead of merely treating the symptoms of asthma with fast-acting bronchodilators, we now treat the underlying inflammation using inhaled corticosteroids. New approaches to limiting the airway inflammation include antileukotrienes and antibodies against the patient's own IgE class of antibodies.

Tuberculosis

Tuberculosis (TB), the infectious disease caused by the bacterium *Mycobacterium tuberculosis*, is spread by coughing and primarily enters the body in inhaled air. TB mostly affects the

lungs but can spread through the lymphatics to affect other organs. One-third of the world's population is infected, but most people never develop active TB because a massive inflammatory and immune response usually contains the primary infection in fibrous, or calcified, nodules (tubercles) in the lungs. However, the bacteria survive in the nodules and when the person's immunity is weakened, they may break out and cause symptomatic TB, involving fever, night sweats, weight loss, a racking cough, and coughing up blood.

Until the 1930s, TB was responsible for one-third of all deaths among 20- to 45-year-old adults in the U.S. With the advent of antibiotics in the 1940s, this killer was put into retreat and its prevalence declined dramatically. During the mid-1980s, there was an alarming increase in TB due to TB-infected HIV patients. This trend has now been brought under control and TB rates in the U.S. are again decreasing.

Of potential concern are deadly strains of drug-resistant (even multidrug-resistant) TB that develop when treatment is incomplete or inadequate. Such strains are found elsewhere in the world and have appeared in North America. Ideal breeding grounds for such strains are shelters for the homeless with their densely packed populations. The TB bacterium grows very slowly and drug therapy entails a 12-month course of antibiotics. The transient nature of shelter populations makes it difficult to track TB patients and ensure they take their medications for the full 12 months. The threat of TB epidemics is so real that health centers in some cities are detaining such patients in sanatoriums against their will for as long as it takes to complete a cure.

Lung Cancer

Lung cancer is the leading cause of cancer death for both men and women in North America, causing more deaths than breast, prostate, and colorectal cancer combined. This is tragic, because lung cancer is largely preventable—nearly 90% of lung cancers are the result of smoking. The cure rate for lung cancer is notoriously low, with most victims dying within one year of diagnosis. The overall five-year survival of those with lung cancer is about 17%. Because lung cancer is aggressive and metastasizes rapidly and widely, most cases are not diagnosed until they are well advanced.

Lung cancer appears to follow closely the oncogene-activating steps outlined in *A Closer Look* in Chapter 4. Ordinarily, nasal hairs, sticky mucus, and cilia do a fine job of protecting the lungs from chemical and biological irritants, but when a person smokes, these defenses are overwhelmed and eventually stop functioning. In particular, smoking paralyzes the cilia that clear mucus from the airways, allowing irritants and pathogens to accumulate. The “cocktail” of free radicals and other carcinogens in tobacco smoke eventually translates into lung cancer.

The three most common types of lung cancer are (1) **squamous cell carcinoma** (25–30% of cases), which arises in the epithelium of the bronchi or their larger subdivisions and tends to form masses that may cavitate (hollow out) and bleed, (2) **adenocarcinoma** (about 40%), which originates in peripheral lung areas as solitary nodules that develop from bronchial

glands and alveolar cells, and (3) **small cell carcinoma** (about 20%), which contains round lymphocyte-sized cells that originate in the main bronchi and grow aggressively in small grape-like clusters within the mediastinum. Subsequent metastasis from the mediastinum is especially rapid. Some small cell carcinomas cause problems beyond their effects on the lungs because they become ectopic sites of hormone production. For example, some secrete ACTH (leading to Cushing's syndrome) or ADH (which results in the syndrome of inappropriate ADH secretion, or SIADH; see p. 608).

Complete removal of the diseased lung has the greatest potential for prolonging life and providing a cure. However, this choice is open to few lung cancer patients because the cancer has often metastasized before it is discovered. In most cases, radiation therapy and chemotherapy are the only options, but these have low success rates.

Fortunately, there are several new therapies on the horizon. These include (1) antibodies that target specific growth factors or other molecules required by the tumor or that deliver toxic agents directly to the tumor, (2) cancer vaccines to stimulate the immune system to fight the tumor, and (3) various forms of gene therapy to replace the defective genes that make tumor cells divide continuously. As clinical trials progress, we will learn which of these approaches is most effective.

Developmental Aspects of the Respiratory System

- ▶ Trace the embryonic development of the respiratory system.
- ▶ Describe normal changes that occur in the respiratory system from infancy to old age.

Because embryos develop in a cephalocaudal (head-to-tail) direction, the upper respiratory structures appear first. By the fourth week of development, two thickened plates of ectoderm, the **olfactory placodes** (plak'ōds), are present on the anterior aspect of the head (**Figure 22.28**). These quickly invaginate to form **olfactory pits** that form the nasal cavities. The olfactory pits then extend posteriorly to connect with the developing pharynx, which forms at the same time from the endodermal germ layer.

The epithelium of the lower respiratory organs develops as an outpocketing of the foregut endoderm, which becomes the pharyngeal mucosa. This protrusion, called the **laryngo-tracheal bud**, is present by the fifth week of development. The proximal part of the bud forms the tracheal lining, and its distal end splits and forms the mucosae of the bronchi and all their subdivisions, including (eventually) the lung alveoli. Mesoderm covers these endoderm-derived linings and forms the walls of the respiratory passageways and the stroma of the lungs.

By 28 weeks, the respiratory system has developed sufficiently to allow a baby born prematurely to breathe on its own. As we noted earlier, infants born before this time tend to exhibit infant respiratory distress syndrome resulting from inadequate surfactant production.

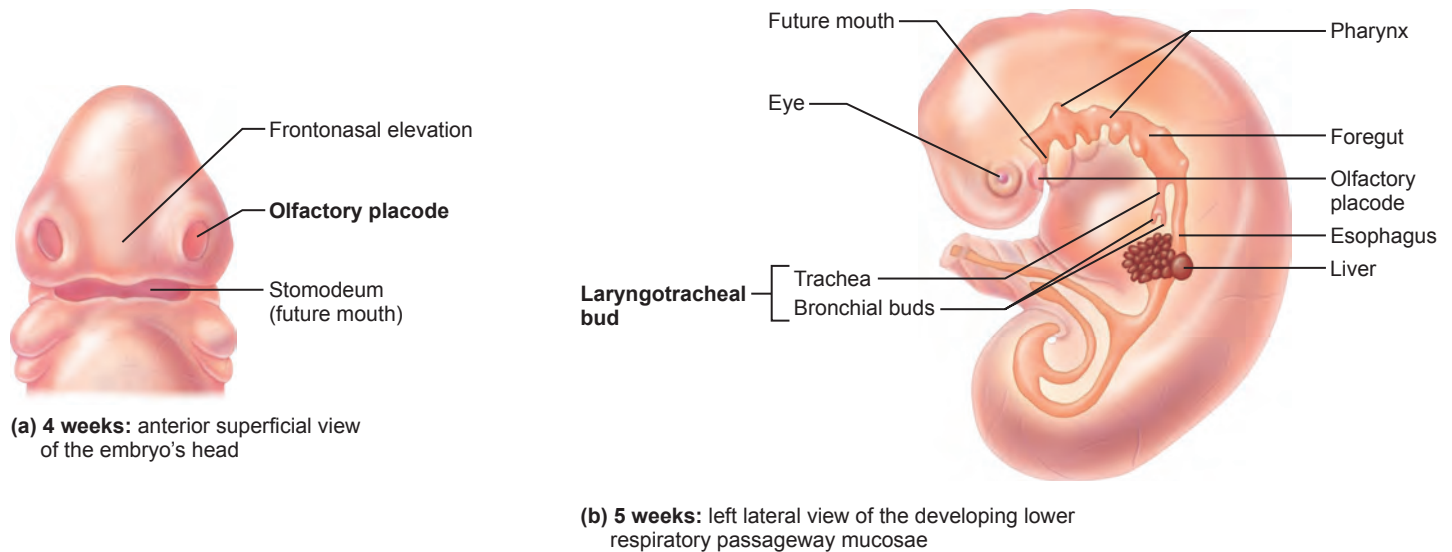


Figure 22.28 Embryonic development of the respiratory system.

During fetal life, the lungs are filled with fluid and all respiratory exchanges are made by the placenta. Vascular shunts cause circulating blood to largely bypass the lungs (see Chapter 28). At birth, the fluid-filled pathway empties, and the respiratory passageways fill with air. As the P_{CO_2} in the baby's blood rises, the respiratory centers are excited, causing the baby to take its first breath. The alveoli inflate and begin to function in gas exchange, but it is nearly two weeks before the lungs are fully inflated.

HOMEOSTATIC IMBALANCE

Important birth defects of the respiratory system include *cleft palate* (described in Chapter 7) and *cystic fibrosis*. **Cystic fibrosis (CF)**, the most common lethal genetic disease in North America, strikes in one out of every 2400 births. CF causes secretion of abnormally viscous mucus that clogs the respiratory passages, providing a breeding ground for airborne bacteria that predisposes the child to respiratory infections. It appears that infection of CF victims' lungs with the bacterium *Pseudomonas aeruginosa* trips a genetic switch that causes the disabled cells to churn out oceans of abnormal mucin (the primary component of mucus). The bacteria then feed on the stagnant pools of mucus and keep sending signals to the cells to make more. Toxins released by the bacteria and the local inflammatory reaction set up by the immune response both damage the lungs. Unable to reach the bacteria embedded in the mucus, the immune cells begin to attack the lung tissue, turning the air sacs into bloated cysts.

Repeated cycles of infection, chronic inflammation, and resulting tissue damage eventually result in such extensive damage that it can be treated only by a lung transplant. The disease also impairs food digestion by clogging ducts that deliver pancreatic enzymes and bile to the small intestine, and sweat glands of CF patients produce an extremely salty perspiration.

At the root of CF is a faulty gene that codes for the *CFTR* (cystic fibrosis transmembrane conductance regulator) *protein*. The

normal CFTR protein works as a membrane channel to control Cl^- flow in and out of cells. In those with the mutated gene, CFTR lacks an essential amino acid and so it gets “stuck” in the endoplasmic reticulum, unable to reach the membrane and perform its normal role. Consequently, less Cl^- is secreted and less water follows, resulting in the thick mucus typical of CF.

Conventional therapy for CF has been mucus-dissolving drugs, “clapping” the chest to loosen the thick mucus, and antibiotics to prevent infection. The basic goal of CF research is to restore normal salt and water movements by (1) introducing normal CFTR genes into respiratory tract mucosa cells, (2) prodding another channel protein to take over the duties of transporting Cl^- , and (3) developing techniques to free the CFTR protein from the ER. Suppressing the inflammatory response in the lungs is another goal. Among anti-inflammatory agents being tested is a fatty acid found in fish oils, docosahexaenoic acid (DHA). A novel and surprisingly simple approach involves inhaling hypertonic saline droplets. This draws water into the mucus, making it more liquid. Alone or in combination, these therapies provide new hope to patients with CF. ■

The respiratory rate is highest in newborn infants (40–80 respirations per minute). At five years of age it is around 25 per minute, and in adults it is between 12 and 18 per minute. In old age, the rate often increases again. At birth, only about one-sixth of the final number of alveoli are present. The lungs continue to mature and more alveoli are formed until young adulthood. However, if a person begins smoking in the early teens, the lungs never completely mature, and those additional alveoli are lost forever.

In infants, the ribs take a nearly horizontal course. For this reason, infants rely almost entirely on descent of the diaphragm to increase thoracic volume for inspiration. By the second year, the ribs are positioned more obliquely, and the adult form of breathing is established.

System Connections

Homeostatic Interrelationships Between the Respiratory System and Other Body Systems



Nervous System

- Respiratory system provides oxygen needed for normal neuronal activity and disposes of carbon dioxide
- Medullary and pontine centers regulate respiratory rate and depth; stretch receptors in lungs and chemoreceptors provide feedback

Endocrine System

- Respiratory system provides oxygen and disposes of carbon dioxide; angiotensin converting enzyme in lungs converts angiotensin I to angiotensin II
- Epinephrine dilates the bronchioles; testosterone promotes laryngeal enlargement in pubertal males; glucocorticoids promote surfactant production

Cardiovascular System

- Respiratory system provides oxygen and disposes of carbon dioxide; carbon dioxide present in blood as HCO_3^- and H_2CO_3 contributes to blood buffering
- Blood is the transport medium for respiratory gases

Lymphatic System/Immunity

- Respiratory system provides oxygen and disposes of carbon dioxide; tonsils in pharynx house immune cells
- Lymphatic system helps to maintain blood volume required for respiratory gas transport; immune system protects respiratory organs from bacteria, bacterial toxins, viruses, protozoa, fungi, and cancer

Digestive System

- Respiratory system provides oxygen and disposes of carbon dioxide
- Digestive system provides nutrients needed by respiratory system organs

Urinary System

- Respiratory system provides oxygen and disposes of carbon dioxide to provide short-term pH homeostasis
- Kidneys dispose of metabolic wastes of respiratory system organs (other than carbon dioxide) and maintain long-term pH homeostasis

Reproductive System

- Respiratory system provides oxygen and disposes of carbon dioxide

Integumentary System

- Respiratory system provides oxygen and disposes of carbon dioxide
- Skin protects respiratory system organs by forming surface barriers

Skeletal System

- Respiratory system provides oxygen and disposes of carbon dioxide
- Bones protect lungs and bronchi by enclosure

Muscular System

- Respiratory system provides oxygen needed for muscle activity and disposes of carbon dioxide
- Activity of the diaphragm and intercostal muscles essential for producing volume changes that lead to pulmonary ventilation; regular exercise increases respiratory efficiency

The Respiratory System and Interrelationships with the Cardiovascular, Lymphatic/Immune, and Muscular Systems

Every day we inhale and exhale nearly 10,000 L of air. This accomplishes two things—it supplies the body with the oxygen it needs to oxidize food and release energy, and it expels carbon dioxide, the major waste product of that process. As crucial as breathing is, most of us don't think very often about the importance of having fresh air on call. But the phenomenon of gasping for air is familiar to every athlete. Indeed, the respiratory rate of a competitive swimmer may jump to over 40 breaths/min and the amount of air inhaled per breath may soar from the usual 500 ml to as much as 6 to 7 L.

The respiratory system is beautifully engineered for its function. Its alveoli are flushed with new air more than 15,000 times each day and the alveolar walls are so indescribably thin that red blood cells moving single-file through the pulmonary capillaries can make the gaseous “swaps” with the air-filled alveoli within a fraction of a second. Although every cell in the body depends on this system for the oxygen it needs to live, the respiratory system interactions that we will consider here are those it has with the cardiovascular, lymphatic/immune, and muscular systems.

Cardiovascular System

The interaction between the respiratory and cardiovascular systems is so intimate that these two systems are inseparable. Respiratory system organs, as important as they are, can make only the external gas exchanges, those that occur in the lungs. Although all body cells depend on the respiratory system to provide needed oxygen, they pick up that oxygen not from the lungs but from the blood. Thus, without blood to act as the intermediary and the heart and blood vessels to act as the hardware to pump the blood around the body, all the efforts of the respiratory system would be useless.

In turn, angiotensin converting enzyme on lung capillary endothelium plays an important role in blood pressure regulation.

Lymphatic System/Immunity

Of all body systems, only the respiratory system is completely exposed to the external environment (yes, the skin is exposed but its exposed parts are all dead). Because air contains a rich mix of potentially dangerous inhabitants (bacteria, viruses, fungi, asbestos fibers, etc.), the respiratory system is continuously at risk for infection or damage from external agents. Lymphoid outposts help protect the respiratory tract and enhance the defenses (cilia, mucus) that the respiratory system itself erects. Particularly well situated to apprehend intruders at the oral-nasal-pharynx junction are the palatine, pharyngeal, lingual, and tubal tonsils. Their macrophages engulf foreign antigens and they provide sites where lymphocytes are sensitized to mount immune responses.

Muscular System

Skeletal muscle cells, like other body cells, need oxygen to live. The notable part of this interaction is that most respiratory compensations that occur service increased muscular activity. (It is difficult to think of incidents where this is not the case—the exceptions concern disease conditions.) When we are at rest, the respiratory system operates at basal levels, but any time physical activity becomes more vigorous, the respiratory rhythm picks up the beat to match supply with need and to maintain the acid-base balance of the blood.

Respiratory System

Case study: Barbara Joley was in the bus that was hit broadside. When she was freed from the wreckage, she was deeply cyanotic and her respiration had stopped. Her heart was still beating, but her pulse was fast and thready. The emergency medical technician reported that when Barbara was found, her head was cocked at a peculiar angle and it looked like she had a fracture at the level of the C₂ vertebra. The following questions refer to these observations.

1. How might the “peculiar” head position explain Barbara's cessation of breathing?
2. What procedures (do you think) should have been initiated immediately by the emergency personnel?
3. Why is Barbara cyanotic? Explain cyanosis.

4. Assuming that Barbara survives, how will her accident affect her lifestyle in the future?

Barbara survived transport to the hospital and notes recorded at admission included the following observations.

- Right thorax compressed; ribs 7 to 9 fractured
- Right lung atelectasis

Relative to these notes:

5. What is atelectasis and why is only the right lung affected?
6. How do the recorded injuries relate to the atelectasis?
7. What treatment will be done to reverse the atelectasis? What is the rationale for this treatment?

(Answers in Appendix G)

HOMEOSTATIC IMBALANCE

Most respiratory system problems are the result of external factors—for example, viral or bacterial infections or obstruction of the trachea by a piece of food. For many years, bacterial pneumonia was one of the worst killers in North America. Antibiotics have greatly decreased its lethality, but it is still a dangerous disease, particularly in the elderly. By far the most problematic diseases *at present* are those described earlier: COPD, asthma, lung cancer, and multidrug-resistant tuberculosis. ■

The maximum amount of oxygen we can use during aerobic metabolism, $\dot{V}_{O_2\max}$, declines about 9% per decade in inactive people beginning in their mid-20s. In those that remain active, $\dot{V}_{O_2\max}$ still declines but much less. As we age, the thoracic wall becomes more rigid and the lungs gradually lose their elasticity, resulting in a decreasing ability to ventilate the lungs. Vital capacity declines by about one-third by the age of 70. Blood O_2 levels decline slightly, and many old people tend to become hypoxic during sleep and exhibit *sleep apnea* (temporary cessation of breathing during sleep).

The number of glands in the nasal mucosa decreases as does blood flow to this mucosa. For this reason, the nose dries and produces a thick mucus that makes us want to clear our throat.

Additionally, many of the respiratory system's protective mechanisms become less effective with age. Ciliary activity of the mucosa decreases, and the macrophages in the lungs become sluggish. The net result is that the elderly are more at risk for respiratory tract infections, particularly pneumonia and influenza.

CHECK YOUR UNDERSTANDING

23. What distinguishes the obstruction in asthma from that in chronic bronchitis?
24. What is the underlying defect in cystic fibrosis?
25. List two reasons for the decline in vital capacity seen with age.

For answers, see Appendix G.

Lungs, bronchial tree, heart, and connecting blood vessels— together, these organs fashion a remarkable system that ensures that blood is oxygenated and relieved of carbon dioxide and that all tissue cells have access to these services. Although the cooperation of the respiratory and cardiovascular systems is obvious, all organ systems of the body depend on the functioning of the respiratory system, as summarized in *Making Connections* on pp. 844–845.

RELATED CLINICAL TERMS

Adult respiratory distress syndrome (ARDS) A dangerous lung condition that can develop after severe illness or injury to the body. Neutrophils leave the body's capillaries in large numbers and then secrete chemicals that increase capillary permeability. The capillary-rich lungs are heavily affected. As the lungs fill with the fluids of edema, the patient suffocates. Even with mechanical ventilation, ARDS is hard to control and often lethal.

Adenoidectomy (adenotonsillectomy) Surgical removal of an infected pharyngeal tonsil (adenoids).

Aspiration (as"pī-ra'shun) (1) The act of inhaling or drawing something into the lungs or respiratory passages. Pathological aspiration in which vomit or excessive mucus is drawn into the lungs may occur when a person is unconscious or anesthetized; turning the head to one side is preventive. (2) Withdrawal of fluid by suction (use of an aspirator); done during surgery to keep an area free of blood or other body fluids; mucus is aspirated from the trachea of tracheotomy patients.

Bronchoscopy (scopy = viewing) Use of a viewing tube inserted through the nose or mouth to examine the internal surface of the main bronchi in the lung. Forceps attached to the tip of the tube can remove trapped objects or take samples of mucus for examination.

Cheyne-Stokes breathing (chān'stōks) Abnormal breathing pattern sometimes seen just before death (the "death rattle") and in people with combined neurological and cardiac disorders. It consists of bursts of tidal volume breaths (increasing and then decreasing in depth) alternating with periods of apnea. Trauma and hypoxia of the brain stem centers, as well as P_{CO_2} imbalances between arterial blood and brain, may be causative factors.

Deviated septum Condition in which the nasal septum takes a more lateral course than usual and may obstruct breathing; often manifests in old age or from nose trauma.

Endotracheal tube A thin plastic tube threaded into the trachea through the nose or mouth; used to deliver oxygen to patients who are breathing inadequately, in a coma, or under anesthesia.

Epistaxis (ep"i-stak'sis; *epistazo* = to bleed at the nose) Nosebleed; commonly follows trauma to the nose or excessive nose blowing. Most nasal bleeding is from the highly vascularized anterior septum and can be stopped by pinching the nostrils closed or packing them with cotton.

Nasal polyps Mushroomlike benign neoplasms of the nasal mucosa; sometimes caused by infections, but most often cause is unknown; may block air flow.

Orthopnea (or"thop-ne'ah; *ortho* = straight, upright) Inability to breathe in the horizontal (lying down) position.

Otorhinolaryngology (o"to-ri"no-lar'in-gol'o-je; *oto* = ear; *rhino* = nose) Branch of medicine that deals with diagnosis and treatment of diseases of the ears, nose, and throat.

Pneumonia Infectious inflammation of the lungs, in which fluid accumulates in the alveoli; the eighth most common cause of death in the United States. Most of the more than 50 different varieties of pneumonia are viral or bacterial.

Pulmonary embolism Obstruction of the pulmonary artery or one of its branches by an embolus (most often a blood clot that has been carried from the lower limbs and through the right side of the heart into the pulmonary circulation). Symptoms are chest pain, productive bloody cough, tachycardia, and rapid, shallow breathing. Can cause sudden death unless treated quickly; usual treatment is oxygen by mask, pain relievers, and anticoagulant