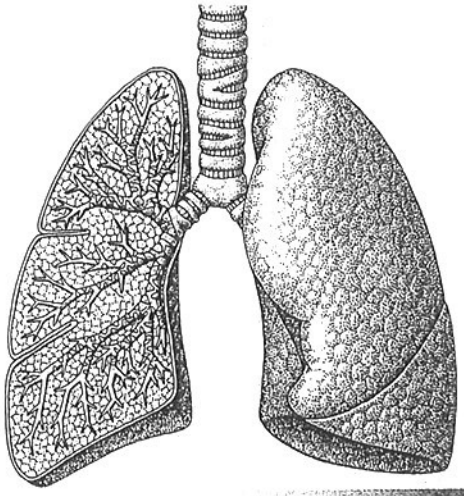

17 Respiratory Physiology

CHAPTER OUTLINE

BACKGROUND BASICS

Ciliated and exchange epithelia (p. 57)
Pressure, volume, flow, and resistance (p. 387)
Pulmonary circulation (p. 385)
pH and buffers (p. 25)
Law of mass action (p. 85)
Cerebrospinal fluid (p. 237)
Hydrogen bonds and surface tension (p. 22)
Capillary filtration (p. 439)
Simple diffusion (p. 117)
Autonomic and somatic motor neurons (p. 308)
Structure of the brain stem (p. 244)
Elastic recoil (p. 62)
Red blood cells and hemoglobin (p. 460)
Blood-brain barrier (p. 241)
Velocity of flow (p. 390)

Imagine covering the playing surface of a racquetball court (about 75 m^2) with thin plastic wrap, then crumpling up the wrap and stuffing it into a 3-liter soft drink bottle. Impossible? Maybe so, if you use plastic wrap and a drink bottle. But the lungs of a 70-kg man have a gas exchange surface the size of that plastic wrap, compressed into a volume that is less than the size of the bottle. This tremendous area for gas exchange is needed to supply the trillions of cells in the body with adequate amounts of oxygen.

Aerobic metabolism in animal cells depends on a steady supply of oxygen and nutrients from the environment, coupled with the removal of carbon dioxide and other wastes. In small, simple aquatic animals, these needs can be met by simple diffusion across the body surface. The rate of diffusion is limited by distance, however, and as a result, most multicelled animals use specialized respiratory organs associated with a circulatory system. Respiratory organs take a variety of forms, but all possess a large surface area compressed into a small space.

Besides needing a large exchange surface, humans and other terrestrial animals face an additional physiological challenge, that of dehydration. Their exchange surfaces must be thin and moist to allow gases to pass from air into solution, yet at the same time they must be protected to prevent

drying out from exposure to air. Some terrestrial animals such as the slug, a shell-less snail, meet the challenge of dehydration with behavioral adaptations that restrict them to humid environments and nighttime activities. However, a more common solution is anatomical: an internalized respiratory epithelium. Human lungs are enclosed within the chest cavity to control their contact with the outside air. Internalization creates a humid environment for the exchange of gases with the blood and protects the exchange surface from damage.

Internalized lungs create another problem, however: how to exchange air between the atmosphere and the exchange surface deep within the body. Air flow requires a muscular pump to create pressure gradients. Thus, in more complex animals, the respiratory system consists of two separate components: a muscular pump and a thin, moist exchange surface. In humans, the pump is the musculoskeletal structure of the thorax, and the lungs themselves consist of the exchange epithelium and associated blood vessels.

The primary functions of the respiratory system are:

1. *Exchange of gases between the atmosphere and the blood.* Oxygen is brought into the body for distribution to the tissues, and carbon dioxide wastes produced by metabolism are eliminated.
2. *Homeostatic regulation of body pH.*
3. *Protection from inhaled pathogens and irritating substances.* Like all epithelia that contact the external environment, the epithelium found in the respiratory system is well supplied with mechanisms to trap and destroy potentially harmful substances before they can enter the body.
4. *Vocalization.* Air moving across the vocal cords creates vibrations used for speech, singing, and other forms of communication.

In addition to serving these functions, the respiratory system is also a source of significant losses of water and heat from the body. These losses must be balanced using homeostatic compensations.

This chapter examines how the respiratory system carries out these functions by exchanging air between the environment and the interior of the lungs. In addition, it examines how the circulatory and respiratory systems cooperate to move oxygen and carbon dioxide between the lungs and the cells of the body.

THE RESPIRATORY SYSTEM

The word *respiration* can have several meanings (Fig. 17-1 ■). **Cellular respiration** refers to the intracellular reaction of oxygen with organic molecules to produce carbon dioxide, water, and energy in the form of ATP (∞ p. 91). **External respiration,** the topic of this chapter, is the interchange of gases between the environment and the body's cells. External respiration can be subdivided into four integrated processes:

1. The exchange of air between the atmosphere and the lungs. This process is known as **ventilation,** or breathing. **Inspiration** is the movement of air into the lungs; **expiration** is the movement of air out of the lungs.
2. The exchange of oxygen and carbon dioxide between the lungs and the blood.
3. The transport of oxygen and carbon dioxide by the blood.
4. The exchange of the gases between blood and the cells.

External respiration requires the coordinated functioning of the respiratory and cardiovascular systems. The **respiratory system** is composed of the structures involved in ventilation and gas exchange (Fig. 17-2 ■). It consists of:

1. The **conducting system** of passages, or **airways,** that lead from the environment to the exchange surface of the **lungs.**
2. The **alveoli,** the exchange surface of the lungs, where oxygen and carbon dioxide transfer between air and the blood.
3. The bones and muscles of the **thorax** (chest) that assist in ventilation.

The respiratory system can be divided into two parts. The **upper respiratory tract** consists of the mouth, nasal cavity, pharynx, larynx, and trachea. The **lower respiratory tract** consists of the two bronchi, their branches, and the lungs. It is also known as the thoracic portion of the respiratory system because it is enclosed in the thorax.

The Musculoskeletal structure of the thorax acts as a pump creating pressure gradients for air movement.

Problem

Emphysema

"Diagnosis: COPD (blue bloater)," reads Edna Wilson's patient chart. COPD—chronic obstructive pulmonary disease—is a name given to diseases in which air exchange is impaired by narrowing of the airways. Most people with COPD have emphysema or chronic bronchitis or a combination of the two. Individuals in whom chronic bronchitis predominates are nicknamed "blue bloaters," owing to the bluish tinge of their skin and a tendency to be overweight. "Pink puffers" suffer more from emphysema. They tend to be thin, have normal (pink) skin coloration, and breathe shallow, rapid breaths. Because COPD is commonly caused by smoking, most people can avoid the disease simply by not smoking. Unfortunately, Edna has been a hard-core smoker for 35 of her 47 years.

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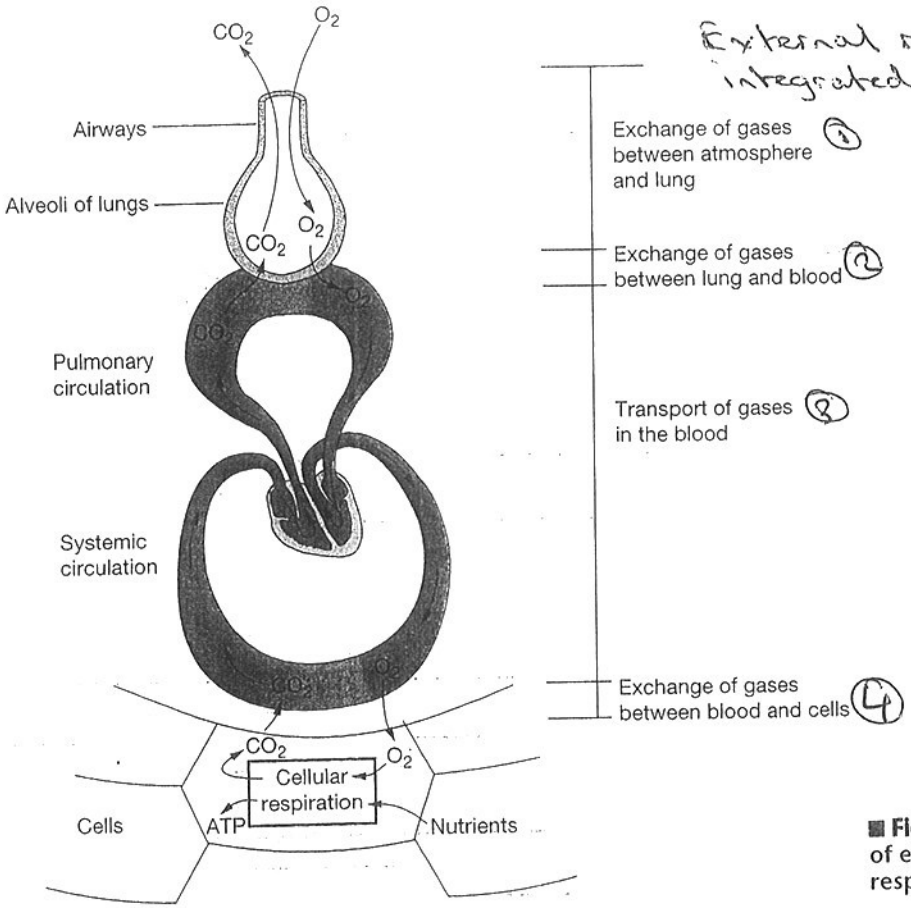

■ **Figure 17-1** Overview of external and cellular respiration

The Bones and Muscles of the Thorax Surround the Lungs

The thorax, or chest cavity, is bounded by the bones of the spine and rib cage and their associated muscles. Together the bones and muscles are called the *thoracic cage*. The ribs and spine form the sides and top of the cage (the *chest wall*), and a dome-shaped sheet of skeletal muscle, the **diaphragm,** forms the floor (Fig. 17-2a ■). Two sets of **intercostal muscles,** internal and external, connect the 12 pairs of ribs. Additional muscles, the **sternocleidomastoids** and the **scalenes,** run from the head and neck to the sternum and first two ribs.

Functionally, the thorax is a sealed container filled with three membranous bags, or sacs. One, the pericardial sac, contains the heart. The other two bags, the *pleural sacs*, contain the lungs [*pleura*, rib, or side]. The esophagus and the thoracic blood vessels and nerves pass between the pleural sacs (Fig. 17-2d ■).

The Lungs Are Enclosed in the Pleural Sacs

The lungs (Fig. 17-2b ■) consist of light, spongy tissue whose volume is mostly occupied by air-filled spaces. These irregular cone-shaped organs nearly fill the thoracic cavity, with their bases resting on the curved diaphragm. Rigid conducting airways, the bronchi, connect the lungs to the main airway, the trachea.

Each lung is contained within a double-walled pleural sac whose membranes line the inside of the thorax and cover the outer surface of the lungs (Fig. 17-3 ■, p. 480). The pleural membranes, or **pleura,** contain several layers of elastic connective tissue and numerous capillaries. The opposing layers of pleural membrane are held together by a thin film of **pleural fluid** whose total volume is only a few milliliters. The result is similar to an air-filled balloon (the lung) surrounded by a water-filled balloon (the pleural sac). Most illustrations exaggerate the volume of the pleural fluid, but you can appreciate its thinness if you imagine spreading 3 mL of water evenly over the surface of a 3-liter soft drink bottle.

Pleural fluid serves several purposes. First, it creates a moist, slippery surface so that the opposing membranes can slide across one another as the lungs move within the thorax. The second important function of pleural fluid is to hold the lungs tight against the thoracic wall. To visualize this arrangement, think of two panes of glass stuck together by a thin film of water. You can slide the panes back and forth across each other, but you cannot pull them apart because of the cohesiveness of the water (∞ p. 22). A similar fluid bond between the

pleural membranes makes the lungs "stick" to the thoracic cage and holds them stretched in a partially inflated state, even at rest.

The Airways of the Conducting System Connect the Lungs with the Environment

Air enters the upper respiratory tract through the mouth and nose and passes into the **pharynx,** a common passageway for food, liquids, and air [*pharynx*, throat]. From the pharynx, air flows through the **larynx** into the **trachea,** or windpipe (Fig. 17-2b ■). The larynx contains the **vocal cords,** connective tissue bands that tighten to create sound when air moves past them.

The trachea is a semiflexible tube held open by 15 to 20 C-shaped cartilage rings (Fig. 17-2e ■). It extends down into the thorax, where it branches (division 1) into a pair of **primary bronchi,** one *bronchus* to each lung. Within the lungs, the bronchi branch repeatedly (divisions 2–11) into progressively smaller bronchi (Fig. 17-2b, e ■). Like the trachea, the bronchi are semirigid tubes supported by cartilage.

Within the lungs, the smallest bronchi branch to become **bronchioles,** small collapsible passageways with smooth muscle walls. The bronchioles continue branching (divisions 12–23) until the *terminal bronchioles* end at the exchange epithelium of the lung.

The diameter of the airways becomes progressively smaller from the trachea to the bronchioles, but as the individual airways get narrower, their numbers increase (Fig. 17-4 ■, p. 480). As a result, the total cross-sectional area increases with each division of the airways. Total cross-sectional area is lowest in the upper respiratory tract and greatest in the bronchioles, analogous to the increase in cross-sectional area that occurs from the aorta to the capillaries. Velocity of air flow is therefore highest in the trachea and lowest in the terminal bronchioles (∞ p. 390).

The Alveoli Are the Site of Gas Exchange

The bulk of lung tissue consists of exchange sacs known as alveoli [*alveus*, a concave vessel, singular *alveolus*]. The alveoli are grapelike clusters at the ends of the terminal bronchioles (Fig. 17-2f, g ■). Their primary function is the exchange of gases between air in the alveoli and the blood.

Each tiny alveolus is composed of a single layer of thin exchange epithelium (Fig. 17-2g ■). Two types of epithelial cells are found in the alveoli, and they occur in roughly equal numbers. The larger **type I alveolar cells** are very thin so that gases can diffuse rapidly through them. The smaller but thicker **type II alveolar cells** synthesize and secrete a chemical known as surfactant. Surfactant mixes with the thin fluid lining of the alveoli to ease the expansion of the lungs during breathing.

The thin walls of the alveoli do not contain muscle, because muscle fibers would block rapid gas exchange. As a result, lung tissue itself cannot contract. However, connective tissue between the alveolar epithelial cells does contain many elastin fibers that contribute to elastic recoil when lung tissue is stretched.

The intimate link between the respiratory and cardiovascular systems is demonstrated by the close association of the alveoli with an extensive network of capillaries. These blood vessels cover 80%–90% of the alveolar surface, forming an almost continuous "sheet" of blood in close contact with the air-filled alveoli (Fig. 17-2f ■). Gas exchange in the lungs occurs by diffusion through the thin alveolar type I cells to the capillaries. In much of the exchange area, the basement membrane underlying the alveolar epithelium has fused with that of the capillary endothelium, and only a small amount of interstitial fluid is present. The proximity of capillary blood to air in the alveolus is essential for the rapid exchange of gases.

The Pulmonary Circulation Is a High-Flow, Low-Pressure System

The pulmonary circulation begins with the pulmonary trunk that receives low-oxygen blood from the right ventricle, then divides into two pulmonary arteries, one to each lung (∞ Fig. 14-1, p. 386). Oxygenated blood from the lungs returns to the left atrium via the pulmonary veins.

At any given moment, the pulmonary circulation contains about 0.5 liters of blood, or 10% of the total blood volume. About 75 mL of this amount is found in the capillaries, where gas exchange takes place, with the remainder in the pulmonary arteries and veins. The rate of blood flow through the lungs is quite high when compared with other tissues (∞ p. 436) because the lungs receive the entire cardiac output of the right ventricle, 5 L/min. This means that as much blood flows through the lungs in one minute as flows through the rest of the body in the same amount of time!

Despite the high flow rate, blood pressure in the pulmonary circulation is low. Pulmonary arterial blood pressure averages 25/8 mm Hg, compared with the average systemic arterial blood pressure of 120/80 mm Hg. The right ventricle does not have to pump as forcefully to create blood flow through the lungs because the resistance of the pulmonary circulation is low. This low

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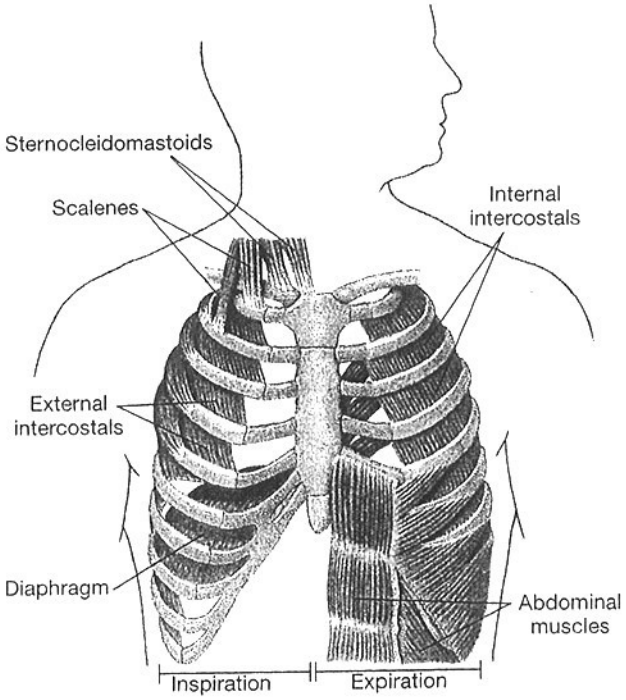
Patients with chronic bronchitis have excessive mucus production and general inflammation of the entire respiratory tract. The mucus narrows the airways and makes breathing difficult.

Question 1: What does narrowing of the airways do to the resistance of the airways to air flow? (Hint: The relationship between radius and resistance is the same for air flow as it was for blood flow in the circulatory system; ∞ p. 387.)

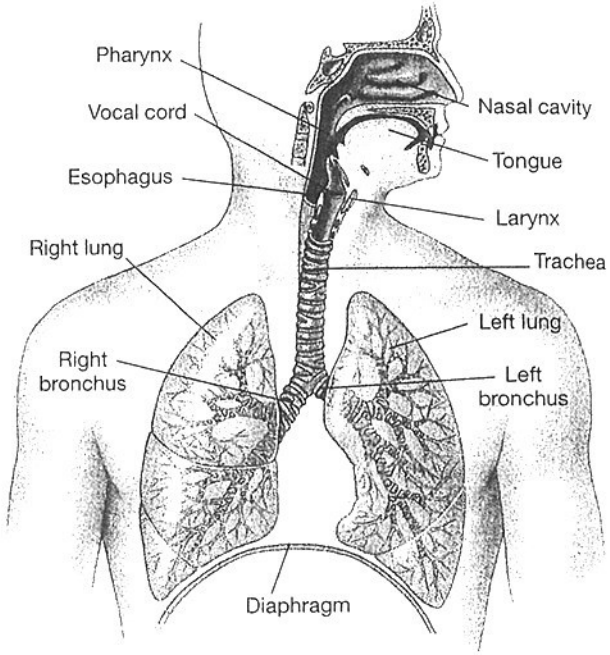
Anatomy Summary Respiratory System

Figure 17-2

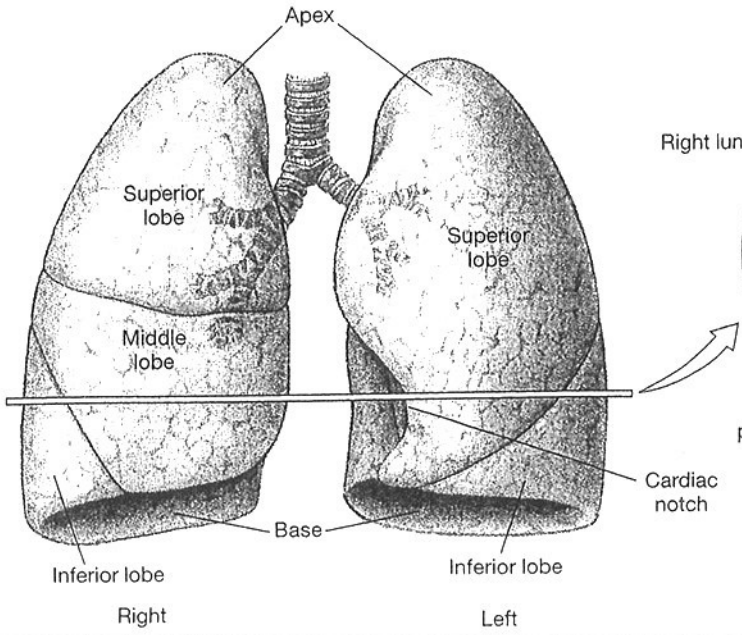
(a) Muscles used for ventilation
The muscles of inspiration include the diaphragm, external intercostals, sternocleidomastoids, and scalenes. The muscles of expiration include the internal intercostals and the abdominals.



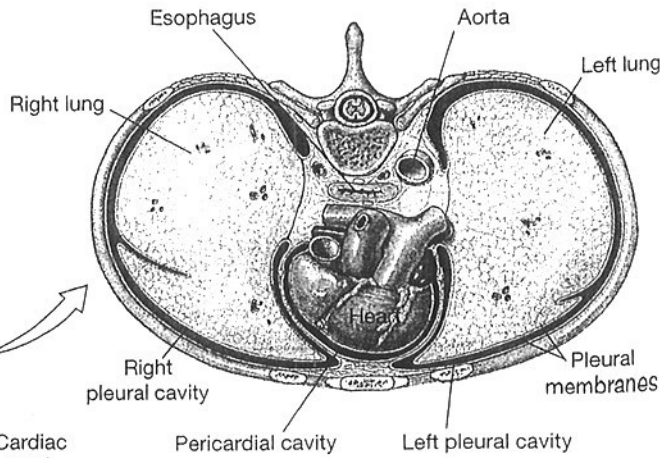
(b) The respiratory system
The respiratory system consists of the upper respiratory system (mouth, nasal cavity, pharynx, larynx) and the lower respiratory system (trachea, bronchi, lungs). The lower respiratory system is enclosed in the thorax, bounded by the ribs, spine, and diaphragm.



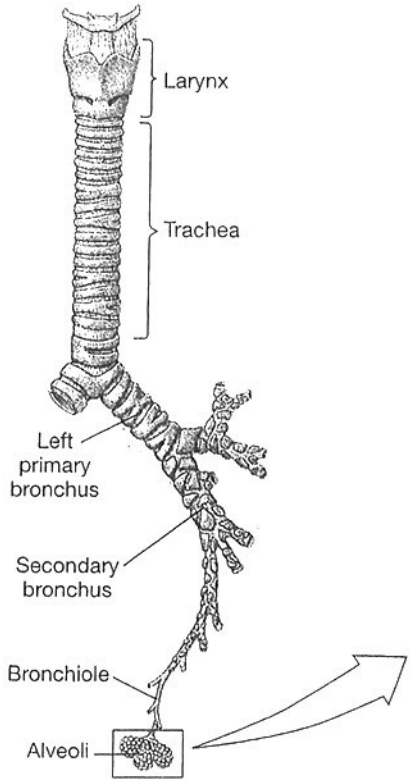
(c) External anatomy of lungs
Externally, the right lung is divided into three lobes and the left lung into two.



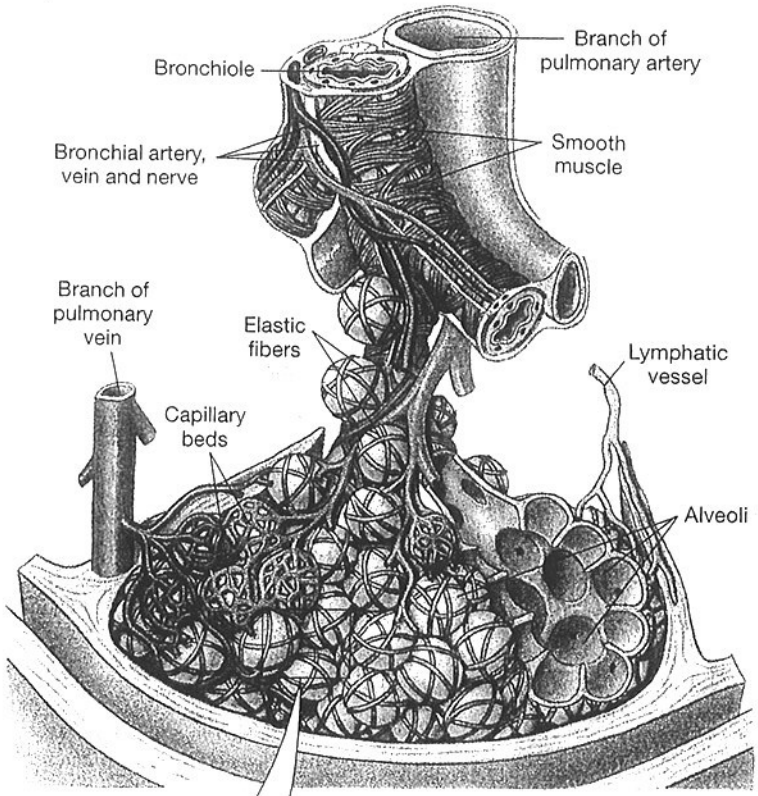
(d) Sectional view of chest
Each lung is enclosed in two pleural membranes. The pleural fluid and space is much smaller than illustrated. The esophagus and aorta pass through the thorax between the pleural sacs.



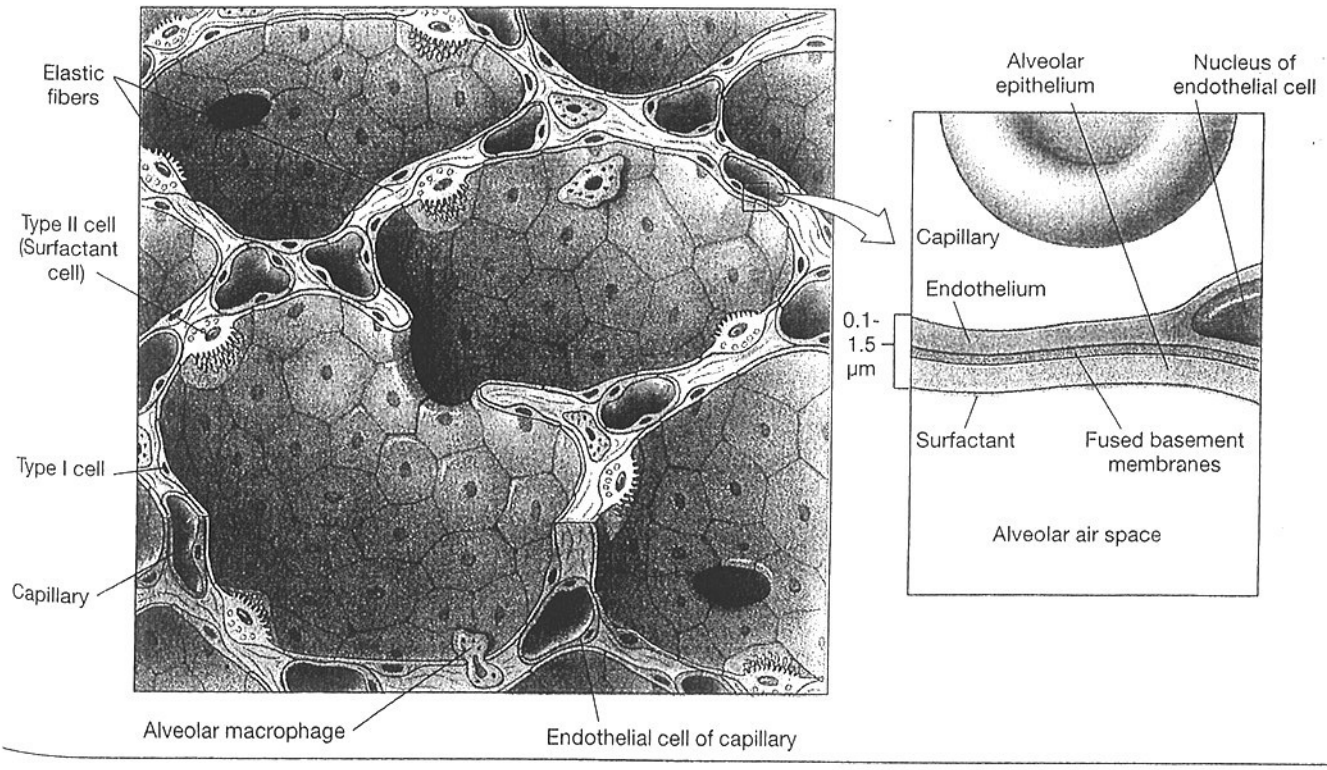
(e) Branching of airways
The trachea branches into two bronchi, one to each lung. Each bronchus branches 22 more times, finally terminating in a cluster of alveoli.

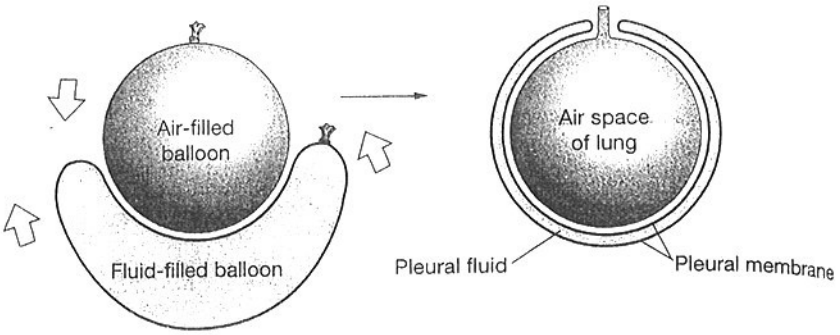


(f) Structure of lung lobule
Each cluster of alveoli is surrounded by elastic fibers and a network of capillaries.



(g) Alveolar structure
The alveoli are composed of type I cells for gas exchange and type II cells that synthesize surfactant. Alveolar macrophages ingest foreign material that reaches the aveoli.





■ **Figure 17-3 The relationship between the pleural sac and the lung** The pleural sac forms a double membrane surrounding the lung, similar to a fluid-filled balloon surrounding an air-filled balloon. The pleural fluid has a much smaller volume than is suggested by this illustration.

resistance can be attributed to the shorter total length of the pulmonary blood vessels and the distensibility and large cross-sectional area of pulmonary arterioles.

Because mean blood pressure is low in the pulmonary capillaries, the net hydraulic pressure forcing fluid out of the capillary into the interstitial space is also low (∞ p. 439). Filtered fluid from the pulmonary capillaries is efficiently removed by the lymphatic system, and only a small amount of fluid is found in the interstitial space of the lung. As a result, the distance between alveolus and capillary is small, and gases diffuse rapidly between them.

In the next section, we begin our discussion of respiratory physiology with a review of the laws of physics and chemistry that govern the behavior of gases.

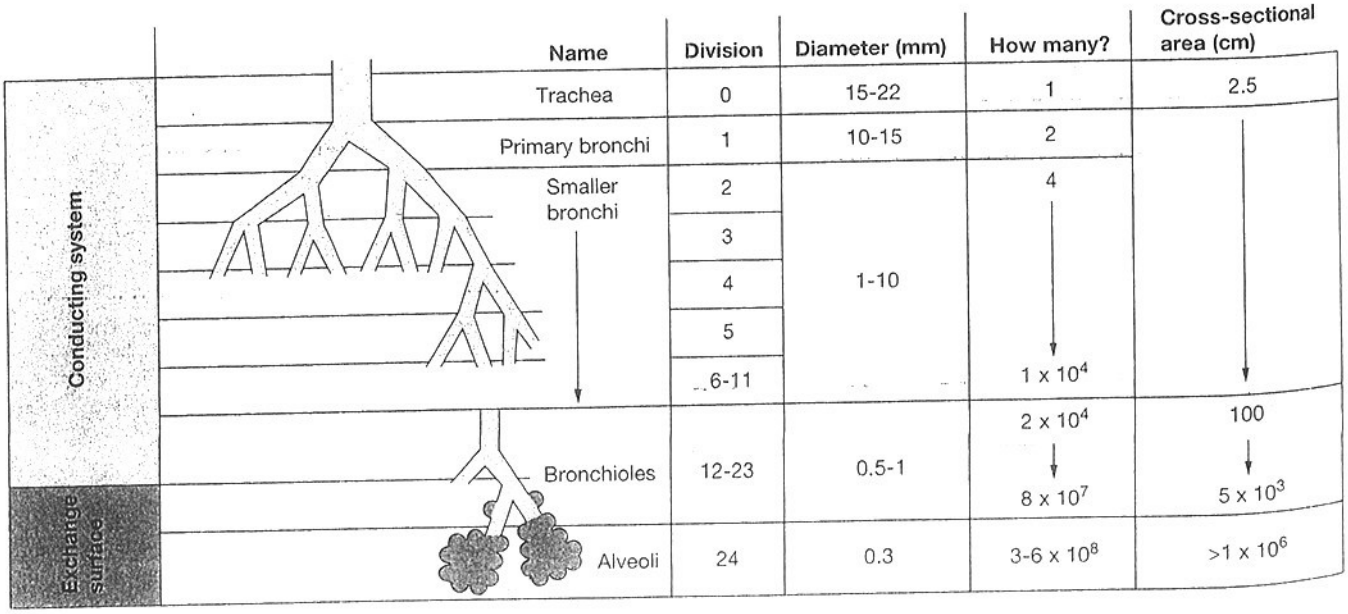
✓ A person has left ventricular failure but normal right ventricular function. As a result, blood pools in the pulmonary circulation, doubling pulmonary capillary hydraulic pressure. What happens to fluid flow across the walls of the pulmonary capillaries?

GAS LAWS

Air flow in the respiratory system is very similar to blood flow in the cardiovascular system in many respects, although blood is a noncompressible liquid and air is a compressible mixture of gases. Blood pressure and environmental air pressure (**atmospheric pressure**) are both reported in millimeters of mercury (mm Hg).* At sea level, atmospheric pressure is 760 mm Hg.

One convention that we will follow in this book is the designation of atmospheric pressure as 0 mm Hg. Because atmospheric pressure varies with altitude and because very few people live exactly at sea level, this convention allows us to compare pressure differences that occur during ventilation without correcting for altitude. Subatmospheric pressures are designated by negative numbers, and higher-than-atmospheric pressures are written as positive numbers.

*Respiratory physiologists sometimes report gas pressures in units of centimeters of water: 1 cm H_2O = 1.3 mm Hg.



■ **Figure 17-4 Branching of the airways**

TABLE 17-1 Gas Laws

1. The total pressure of a mixture of gases is the sum of the pressures of the individual gases (Dalton's Law).
2. Gases, singly or in a mixture, move from areas of higher pressure to areas of lower pressure.
3. If the volume of a container of gas changes, the pressure of the gas will change in an inverse manner (Boyle's Law).
4. The amount of a gas that will dissolve in a liquid is determined by the partial pressure of the gas and the gas's solubility in the liquid.

The rules that govern the behavior of gases in air and solution are summarized in Table 17-1. These rules ovide the basis for the exchange of oxygen and carbon oxide between the environment and cells. They are scussed briefly in the paragraphs below.

ir Is a Mixture of Gases

ıe atmosphere surrounding the earth is a mixture of ses and water vapor. **Dalton's Law** states that the total essure of a mixture of gases is the sum of the pressures the individual gases. Thus, in dry air at an atmosıeric pressure of 760 mm Hg, 78% of the total pressure due to nitrogen molecules, 21% to oxygen molecules, d so on (Table 17-2).

n respiratory physiology, we are concerned not only th total atmospheric pressure but also with the indiıual pressures of oxygen and carbon dioxide. The essure of a single gas species is known as its **partial essure,** abbreviated P_{gas}. To find the partial pressure a gas, multiply the atmospheric pressure (P_{atm}) by the s's relative contribution (%):

Partial pressure of an atmospheric gas = $P_{atm} \times$ % of gas in atmosphere

Partial pressure of oxygen = 760 mm Hg × 21%

$P_{O_2} = 760 \times 0.21 = 160$ mm Hg

us, the P_{O_2}, or partial pressure of oxygen, in dry air at ı level is 160 mm Hg. The pressure of an individual s is determined only by its relative abundance in the xture and is independent of the molecular size or ight of the gas.

The actual partial pressure of gases varies slightly depending on how much water vapor is in the air. Water pressure "dilutes" the contribution of other gases to the total pressure. Table 17-2 compares the partial pressures of some atmospheric gases in dry air and at 100% humidity.

Gases Move from Areas of Higher Pressure to Areas of Lower Pressure

Air flow occurs whenever there is a pressure gradient. Air flow, like blood flow, moves from areas of higher pressure to areas of lower pressure. Meteorologists predict the weather by knowing that areas of high atmospheric pressure move in to replace areas of low pressure. In ventilation, flow of air down pressure gradients explains why air exchanges between the environment and the lungs. The movement of the thorax during breathing creates alternating conditions of high and low pressure within the lungs.

Movement down pressure gradients also applies to a single gas. Oxygen moves from areas of higher oxygen partial pressure (P_{O_2}) to areas of lower oxygen partial pressure. The simple diffusion of oxygen and carbon dioxide between lung and blood, or between blood and cells, depends on pressure gradients for these gases. Respiratory physiologists talk about the partial pressure of oxygen or carbon dioxide in the body rather than the concentration of the gas in solution because this measure allows direct comparison with the partial pressures of the gases in air.

Pressure-Volume Relationships of Gases Are Described by Boyle's Law

The pressure exerted by a gas or mixture of gases in a sealed container is created by the collisions of the moving gas molecules with the walls of the container and with each other. If the size of the container is reduced, the collisions will become more frequent and the pressure will rise. This relationship can be expressed by the following equation:

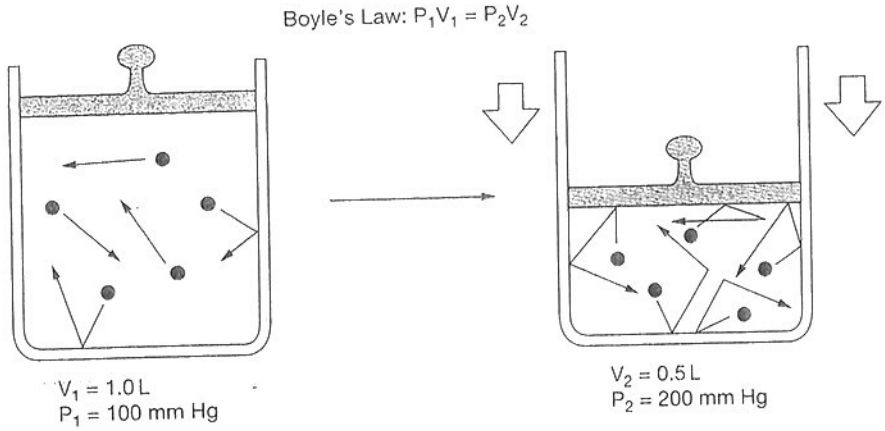
$P_1V_1 = P_2V_2$ where P represents pressure and V represents volume

For example, start with a 1-liter container (V_1) of a gas whose pressure is 100 mm Hg (P_1). One side of the container moves in to decrease the volume to 0.5 L (Fig. 17-5 ■).

BLE 17-2 Partial Pressures of Some Atmospheric Gases at 25° C and 760 mm Hg

ıs	*Partial Pressure in Atmospheric Air, Dry*	*Partial Pressure in Atmospheric Air, 100% Humidity*
itrogen (N_2)	593 mm Hg	575 mm Hg
‹ygen (O_2)	160 mm Hg	152 mm Hg
ırbon dioxide (CO_2)	0.25 mm Hg	0.24 mm Hg
ater vapor	0 mm Hg	23.8 mm Hg

760 mmHg



■ **Figure 17-5 Boyle's Law** A decrease in the volume of a gas causes more collisions between the gas molecules and between gas molecules and the container. The higher number of collisions results in an increase in the pressure exerted by the gas. Boyle's Law assumes that the temperature and number of gas molecules remain constant.

What happens to the pressure of the gas? According to the equation,

$$P_1V_1 = P_2V_2$$
$$100 \text{ mm Hg} \times 1 \text{ L} = P_2 \times 0.5 \text{ L}$$
$$P_2 = 200 \text{ mm Hg}$$

If the volume is reduced by one-half, the pressure doubles. If the volume were to double, the pressure would be reduced by one-half. This relationship between pressure and volume was first noted by Robert Boyle in the 1600s and has been called **Boyle's Law** of gases.

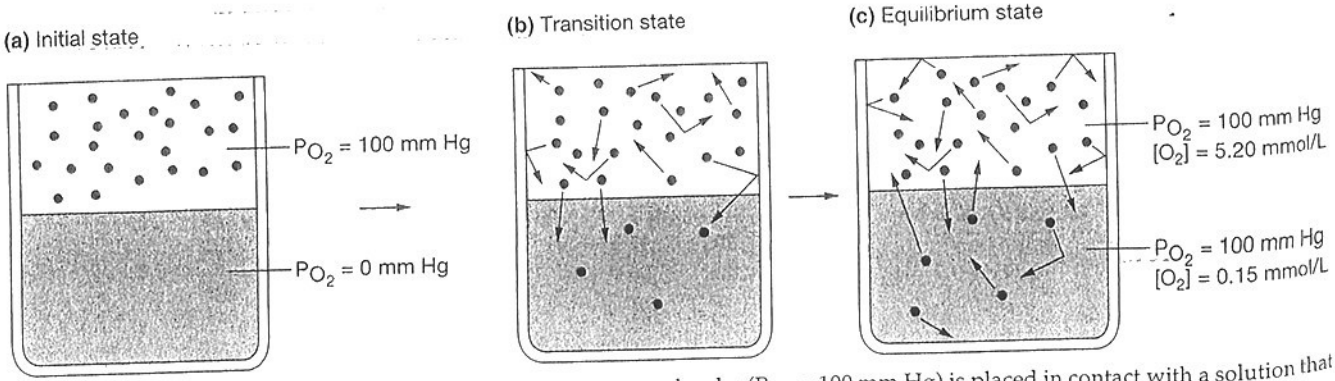
In the respiratory system, changes in the volume of the chest cavity during ventilation cause pressure gradients that create air flow. When the chest increases in volume, the intrathoracic pressure drops and air flows into the respiratory system. When the chest decreases in volume, the pressure rises and air flows out into the atmosphere. This movement of air is called *bulk flow* because the entire gas mixture is moving rather than merely one or two gas species.

The Solubility of a Gas in a Liquid Depends on the Pressure and Solubility of the Gas and on the Temperature

When a gas is placed in contact with water, if there is a pressure gradient, the gas molecules move from one phase to the other. If the gas pressure is higher in the water than in the gaseous phase, gas molecules will leave the water. If the gas pressure is higher in the gaseous phase than in the water, the gas will dissolve into the water. The movement of gas molecules from air into solution is directly proportional to three factors: (1) the pressure gradient of the individual gas, (2) the solubility of the gas in the given liquid, and (3) temperature. Because temperature is relatively constant in mammals, we will ignore its contribution in this discussion.

The ease with which a gas dissolves in a solution is its **solubility.** If a gas is very soluble, large numbers of gas molecules will go into solution at low partial pressures. With less soluble gases, high partial pressures may cause only a few molecules of the gas to dissolve.

For example, imagine a closed container half-filled with water and half-filled with oxygen (Fig. 17-6 ■). Initially, the gas has a P_{O_2} of 100 mm Hg and the water has no oxygen dissolved in it (P_{O_2} = 0 mm Hg). As the gas phase stays in contact with the water, the moving oxygen molecules in the gas diffuse into the water and dissolve. This process will continue until equilibrium is reached. At equilibrium, the movement of oxygen into the water is equal to the movement of oxygen back into the air. We refer to the amount of oxygen that dissolves in the water at any given P_{O_2} as the partial pressure of the gas in solution. Thus, if the gaseous phase has a P_{O_2} of 100 mm Hg, at equilibrium the water will also have a P_{O_2} of 100 mm Hg.



■ **Figure 17-6 Gases in solution** (a) Gas containing oxygen molecules (P_{O_2} = 100 mm Hg) is placed in contact with a solution that contains no oxygen molecules (P_{O_2} = 0 mm Hg). (b) Oxygen molecules move down their pressure gradient and dissolve in the solution. (c) At equilibrium, the P_{O_2} of the gas and solution are equal, and net movement of oxygen molecules between the gas and liquid phases stops. But the concentration of oxygen in the two phases is not equal. The amount of oxygen that dissolves depends on the solubility of oxygen in the solution as well as on the partial pressure of the gas.

Note that this does *not* mean that the concentration of oxygen is the same in the air and in the water. The concentration of dissolved oxygen also depends on the solubility of oxygen. For example, when the P_{O_2} of both air and water is 100 mm Hg, the concentration of oxygen in the air is 5.2 mmoles/L air, whereas the concentration of oxygen in the water is only 0.15 mmoles/L water. As you can see, oxygen is not very soluble in aqueous solutions; its insolubility is one reason for the evolution of oxygen-carrying molecules in blood.

Carbon dioxide is about 20 times as soluble in water as oxygen is. At a P_{CO_2} of 100 mm Hg, the CO_2 concentration in air is 5.2 mmoles/L of air and its concentration in solution is 3.0 mmoles/L of water.

✓ A saline solution is exposed to a gas mixture with equal partial pressures of O_2 and CO_2. What information do you need to know to predict if equal amounts of O_2 and CO_2 will dissolve in the saline?

✓ If nitrogen is 78% of atmospheric air, what is the partial pressure of nitrogen (P_{N_2}) when the dry atmospheric pressure is 720 mm Hg?

VENTILATION

The first exchange in respiratory physiology is ventilation, or breathing, the movement of air between the environment and the alveoli.

The Airways Warm, Humidify, and Filter Inspired Air

The upper airways and the bronchi do more than simply serve as passageways for air. They play an important role in conditioning air before it reaches the alveoli. Conditioning has three components:

1. Warming air to 37° C so that core body temperature will not change and alveoli will not be damaged by cold air,
2. Adding water vapor until the air reaches 100% humidity so that the moist exchange epithelium will not dry out,
3. Filtering out foreign material so that viruses, bacteria, and inorganic particles will not reach the alveoli.

Inhaled air is warmed and moistened by heat and water from the mucosal lining of the airways. Under normal circumstances, by the time air reaches the trachea, it has been conditioned to 37° C and 100% humidity. Breathing through the mouth is not nearly as effective at warming and moistening air as breathing through the nose. If you exercise outdoors in very cold weather, you may be familiar with the ache in your chest that results from breathing cold air through your mouth. Filtration of air takes place in the trachea and bronchi as well. These airways are lined with a ciliated epithelium that secretes both mucus and a dilute saline solution (Fig. 17-7 ■). The cilia themselves are bathed in a watery saline layer covered by a sticky layer of mucus. The mucus is secreted by *goblet cells* in the epithelium (∞ p. 60). Mucus traps most inhaled particles larger than 2 μm, and its immunoglobulins disable many inhaled microorganisms. The mucus layer is continuously moved toward the pharynx by the upward beating of the cilia, a process called the *mucus escalator*. Once mucus reaches the pharynx, it is swallowed, so acid and enzymes in the stomach can destroy any remaining microorganisms.

Secretion of the watery layer beneath the mucus is a critical step in the mucus escalator. Without the watery layer, the cilia would become trapped in the thick, sticky mucus and cease to function. This is what happens in the inherited disease *cystic fibrosis*. A genetic error in one amino acid creates a defective Cl^- channel protein that is unable to secrete chloride ions, an essential step in saline secretion (∞ p. 113).

✓ Cigarette smoking paralyzes the cilia in the epithelial lining of the airways. Why would paralysis of the cilia cause smokers to develop a cough?

During Ventilation, Air Flows because of Pressure Gradients

Air flows into and out of the lungs because of pressure gradients created by a pump, just as blood flows in the cardiovascular system because of the pumping action of the heart. In the respiratory system, most lung tissue is thin exchange epithelium, so the muscles of the thoracic cage and diaphragm function as the pump. When these muscles contract, moving the rib cage and diaphragm, the lungs move also, held to the inside of the thoracic cage by the pleural fluid.

Breathing is an active process that uses muscle contraction to create pressure gradients. The primary muscles involved in quiet breathing are the diaphragm, the intercostals, and the scalenes. During forced breathing, other muscles of the chest and abdomen may be recruited to assist. Examples of situations in which breathing is forced include exercise, playing a wind instrument, and blowing up a balloon.

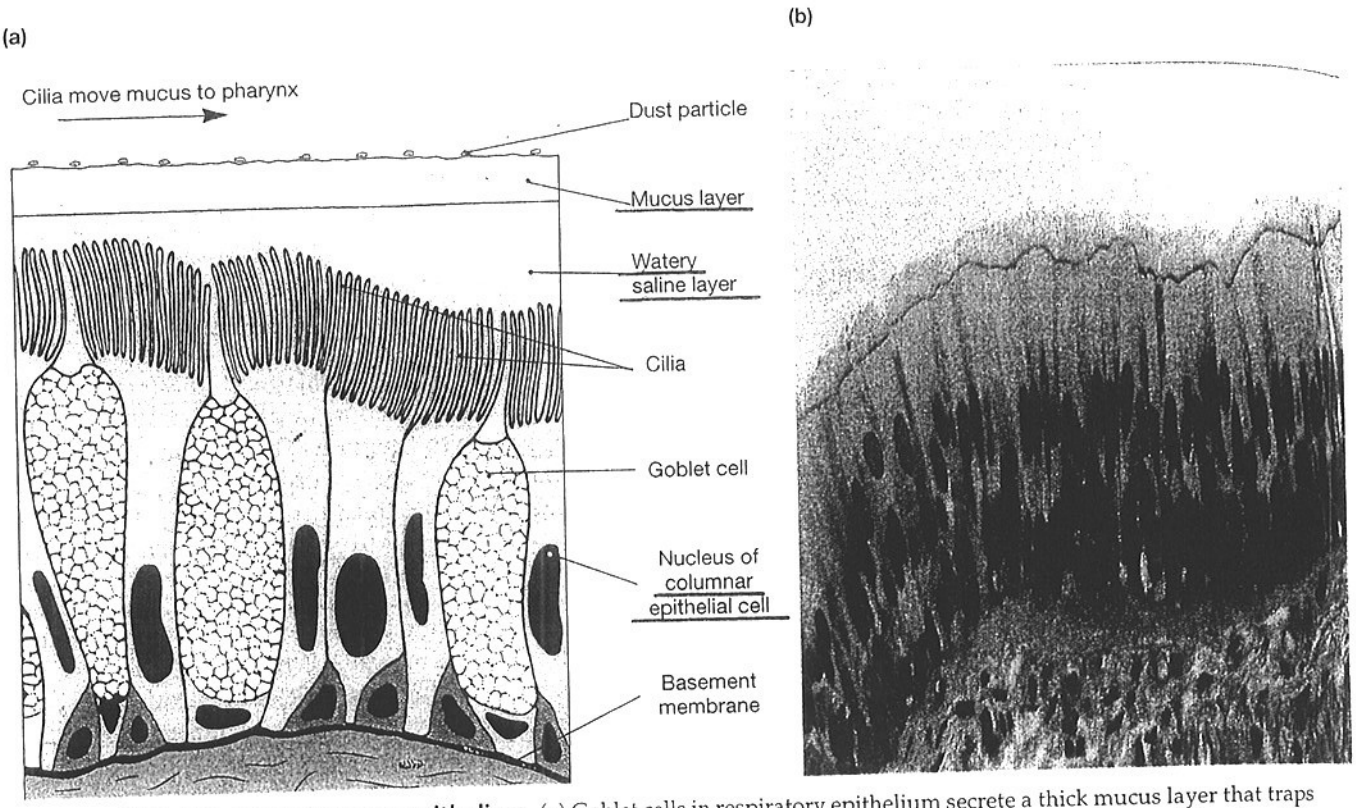
Air flow in the respiratory tract obeys the same rule as blood flow in the cardiovascular system:

$$\text{Flow} \propto \Delta P/R$$

continued from page 477

Smokers usually develop chronic bronchitis before they develop emphysema. Cigarette smoke paralyzes the cilia that sweep debris and mucus out of the airways. Without the action of cilia, mucus and debris pool in the airways, leading to a chronic cough. Eventually, breathing becomes difficult.

Question 2: Why do people with chronic bronchitis have a higher-than-normal rate of respiratory infections?



■ **Figure 17-7 Ciliated respiratory epithelium** (a) Goblet cells in respiratory epithelium secrete a thick mucus layer that traps inhaled particles. The mucus floats on top of a saline solution that allows the cilia to push the mucus upward toward the pharynx, where it is swallowed. (b) This scanning electron micrograph shows the cilia of the trachea and some mucus drops.

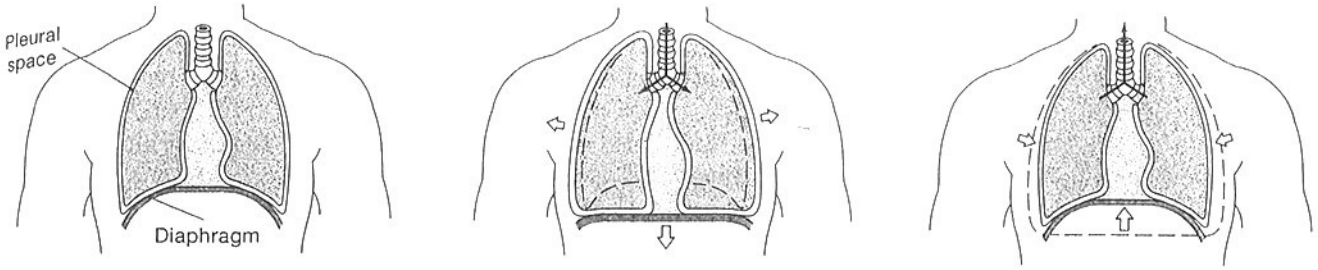
This equation means that (1) air flows in response to a pressure gradient (ΔP) and that (2) flow decreases as the resistance (R) of the system to flow increases. Before we discuss resistance, let us consider how the respiratory system creates a pressure gradient.

Pressures in the respiratory system can be measured either in the air spaces of the lungs (**intrapulmonary pressure**) or within the pleural fluid (**intrapleural pressure**). Because atmospheric pressure is relatively constant, pressure in the lungs must be higher or lower than atmospheric pressure in order for air to flow between the environment and the alveoli. The respiratory system ends in a dead end, so the direction of air flow reverses. Air flows into the lungs when you inhale (inspiration) and out of the lungs when you exhale (expiration). A single **respiratory cycle** consists of an inspiration followed by an expiration. The pressure-volume relationships of Boyle's Law provide the basis for pulmonary ventilation.

Inspiration Occurs When Intrapulmonary Pressure Decreases

During inspiration, somatic motor neurons trigger contraction of the diaphragm and the inspiratory muscles. When the diaphragm contracts, it loses its dome shape and drops down toward the abdomen. In quiet breathing, the diaphragm drops about 1.5 cm. This movement increases the volume of the thoracic cavity by flattening its floor (Fig. 17-8 ■). Between 60% and 75% of the inspiratory volume change during normal quiet breathing is caused by contraction of the diaphragm. The remaining 25% to 40% of the volume change is due to movement of the rib cage. Contraction of the external intercostal and scalene muscles swings the ribs upward and out. The movement of the ribs during inspiration has been likened to a pump handle lifting up and away from the pump (the ribs moving up and away from the spine) and to the movement of a pair of bucket handles as they lift away from the sides of a bucket (ribs moving outward in a lateral direction). The combination of these two movements broadens the rib cage in all directions (Fig. 17-9 ■). As the volume of the thoracic cavity increases, pressure decreases and air flows into the lungs.

For many years, quiet breathing was attributed solely to the action of the diaphragm and the external intercostal muscles. It was thought that the scalenes and sternocleidomastoid muscles were active only during deep breathing. But in recent years, studies of patients with neuromuscular disorders have changed our understanding of how these accessory muscles contribute to quiet breathing. It now appears that without lifting of the sternum and upper ribs by the scalenes, contraction of the diaphragm during inspiration pulls the lower ribs inward. This action decreases the volume of the thoracic cage and works against inspiration. Because we know that the lower ribs move up and out in normal quiet breathing, the scalenes must assist quiet inspiration. New



(a) At rest, diaphragm is relaxed.

(b) Diaphragm contracts, thoracic volume increases.

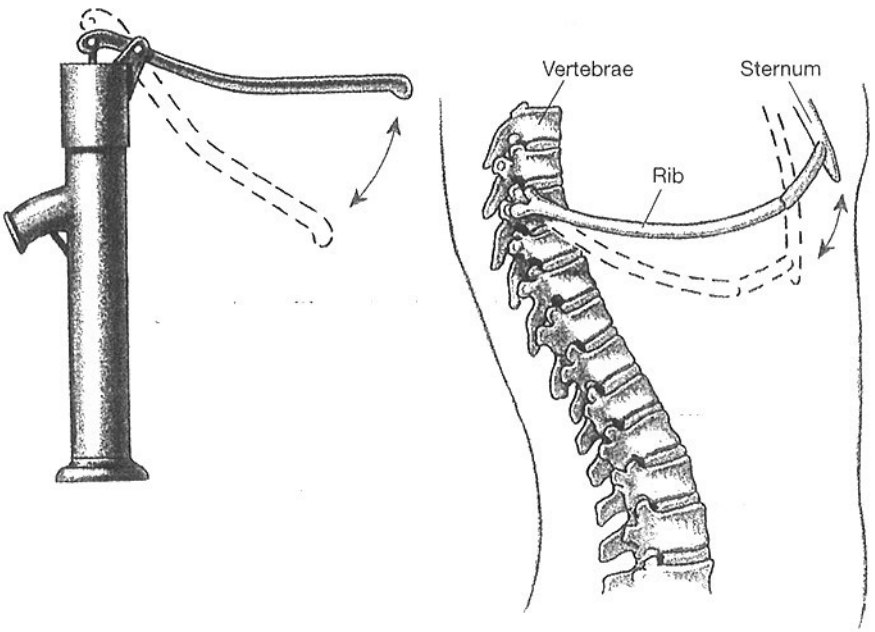
(c) Diaphragm relaxes, thoracic volume decreases.

■ Figure 17-8 Movement of the diaphragm

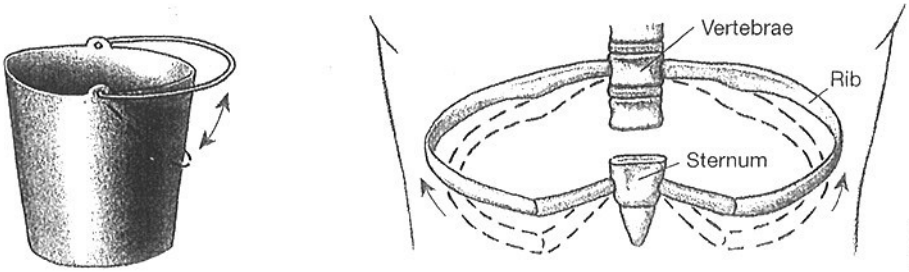
evidence also downplays the role of the external intercostal muscles during quiet breathing. However, the external intercostals play an increasingly important role as respiratory activity increases. Because the exact contribution of the external intercostals and scalenes varies depending upon the type of breathing, we will group these muscles together and call them the *inspiratory muscles*.

Now let us follow intrapulmonary pressure as it changes during a single inspiration. At the start of an inspiration, the brief pause between breaths, intrapulmonary pressure is equal to atmospheric pressure and there is no air flow (Fig. 17-10 ■, point A_1). As inspiration begins, the muscles of the thoracic cage contract and the volume of the thorax increases. With the increase in volume, intrapulmonary pressure falls about 1 mm Hg below atmospheric pressure (−1 mm Hg) and air begins to flow into the alveoli. The volume changes faster than air can flow, so intrapulmonary pressure reaches its lowest value about halfway through inspiration (point A_2). As air flows into the alveoli, the pressure gradually rises

(a) "Pump handle" motion increases anterior-posterior dimension of rib cage



(b) "Bucket handle" motion increases lateral dimension of rib cage



■ Figure 17-9 Movement of the rib cage during inspiration

until the thoracic cage stops expanding, just before the end of inspiration. Air movement continues for a fraction of a second longer, until the pressure inside the lungs equalizes with atmospheric pressure (point A_3). At the end of inspiration, the volume of air in the lungs is at its maximum for the respiratory cycle (point C_2) and intrapulmonary pressure is equal to atmospheric pressure.

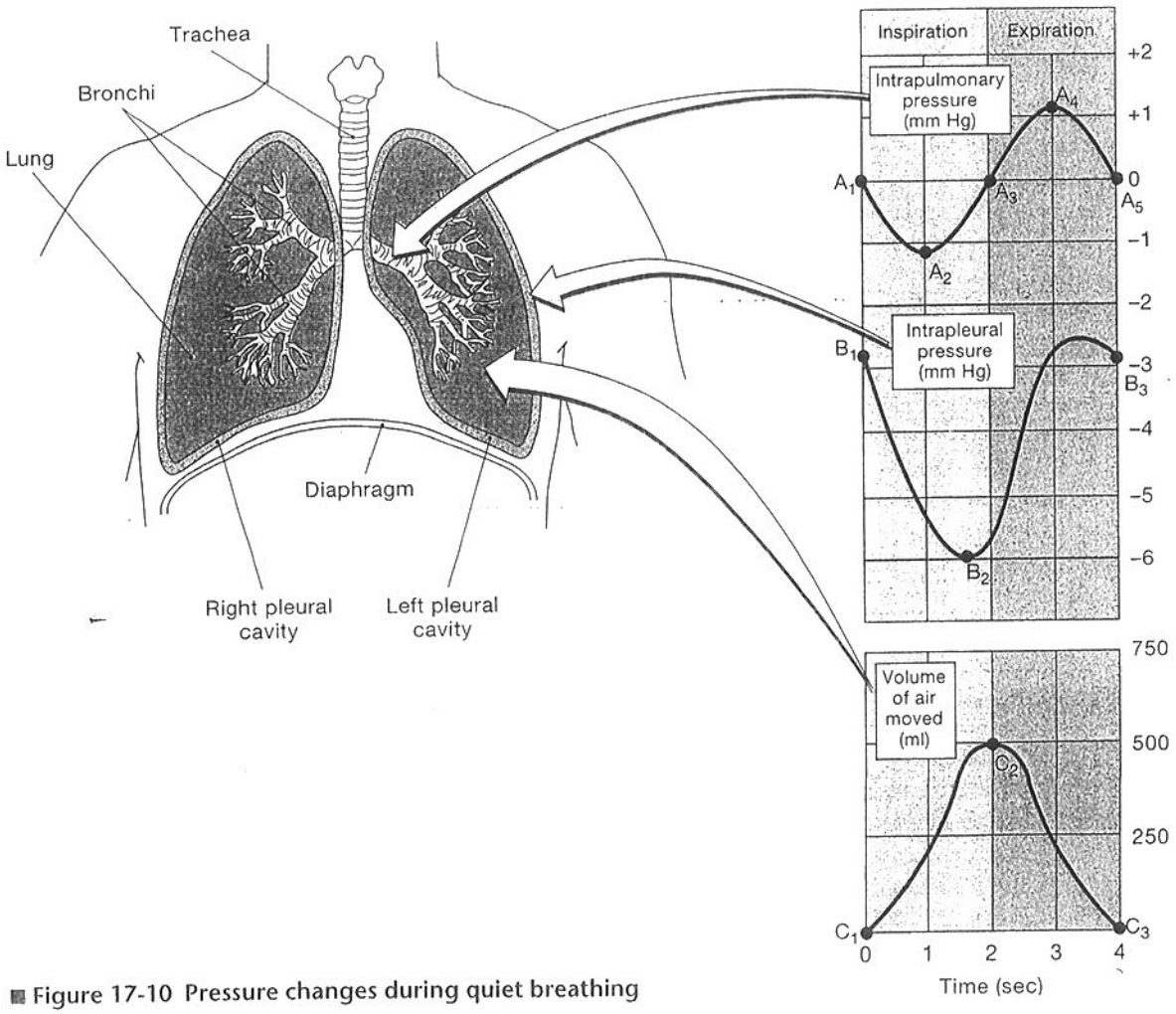
You can demonstrate this phenomenon by taking a deep breath and stopping the movement of your chest at the end of inspiration. (Do not "hold your breath," because doing so causes the opening of the pharynx to close and prevents air flow). If you do this correctly, you will notice that air flow stops after you freeze the inspiratory movement. This exercise shows that, at the end of inspiration, air pressure in the alveoli is equal to atmospheric pressure.

Expiration Occurs When Intrapulmonary Pressure Exceeds Atmospheric Pressure

At the end of inspiration, impulses from somatic motor neurons to the inspiratory muscles cease and the muscles relax. The elastic recoil of the stretched muscle fibers returns the diaphragm and rib cage to their original relaxed positions, just as a stretched elastic waistband recoils when released. Muscle recoil is reinforced by the elastic recoil of the pleura and the lung tissue itself. Because expiration during quiet breathing involves passive elastic recoil rather than active muscle contraction, it is called **passive expiration.**

As the volume of the thorax decreases during expiration, air pressure in the lungs increases, reaching about 1 mm Hg above atmospheric pressure at its maximum (Fig. 17-10 ■, point A_4). Intrapulmonary pressure is now higher than atmospheric pressure, so air flow reverses and air moves out of the lungs. At the end of expiration, air movement ceases when the intrapulmonary pressure is again equal to atmospheric pressure (point A_5). The volume of air in the lungs reaches its minimum for the respiratory cycle (point C_3). At this point, the respiratory cycle has ended and is ready to begin again with the next breath.

The pressure differences shown in Figure 17-10 ■ apply to quiet breathing. During exercise or forced heavy breathing, these values will become proportionately larger. **Active expiration** occurs during voluntary exhalations and when ventilation exceeds 30–40 breaths per minute. (Normal resting ventilation rate is 12–20 breaths per minute for an adult.) Active expiration uses a different set of muscles from those used during inspiration, namely the internal intercostal muscles and the



■ Figure 17-10 Pressure changes during quiet breathing

abdominal muscles. These muscles are collectively called the *expiratory muscles*.

The internal intercostal muscles line the inside of the rib cage. When they contract, they pull the ribs inward, reducing the volume of the thoracic cavity. To feel this action, place your hands on your rib cage. Forcefully blow as much air out of your lungs as you can, noting the movement of your hands as you do so.

The internal and external intercostals act as antagonistic muscle groups (∞ p. 326) to alter the position and volume of the rib cage during ventilation, but the diaphragm has no antagonistic muscles. Therefore, the abdominal muscles become active during active expiration to supplement the activity of the intercostals. Contraction of abdominal muscles during active expiration pulls the lower rib cage inward and decreases abdominal volume. The displaced intestines and liver push the diaphragm up into the thoracic cavity, passively decreasing the chest volume even more. This is why when you are doing abdominal exercises in an aerobics class, the instructor tells you to blow air out as you lift your head and shoulders. The active process of blowing air out helps you contract your abdominals, the very muscles you are trying to strengthen. The diaphragm stays relaxed during active expiration because contraction would move it downward and would work against the abdominal muscles that are trying to push the diaphragm upward.

Any neuromuscular disease that weakens skeletal muscles or damages their motor neurons can adversely affect ventilation. With decreased ventilation, less fresh air enters the lungs. In addition, loss of the ability to cough increases the risk of pneumonia and other infections. Examples of diseases that affect the motor control of ventilation include **myasthenia gravis**, an illness in which the acetylcholine receptors of the motor end plate of skeletal muscles are destroyed, and **polio** (poliomyelitis), a viral illness that sometimes paralyzes the respiratory muscles.

✓ Scarlett O'Hara was trying to squeeze herself into a corset with an 18-inch waist. Was she more successful when she took a deep breath and held it or when she blew all the air out of her lungs? Why?

✓ Why would loss of the ability to cough increase the risk of respiratory infections? (Hint: What does coughing do to mucus in the airways?)

Intrapleural Pressure Changes during Ventilation

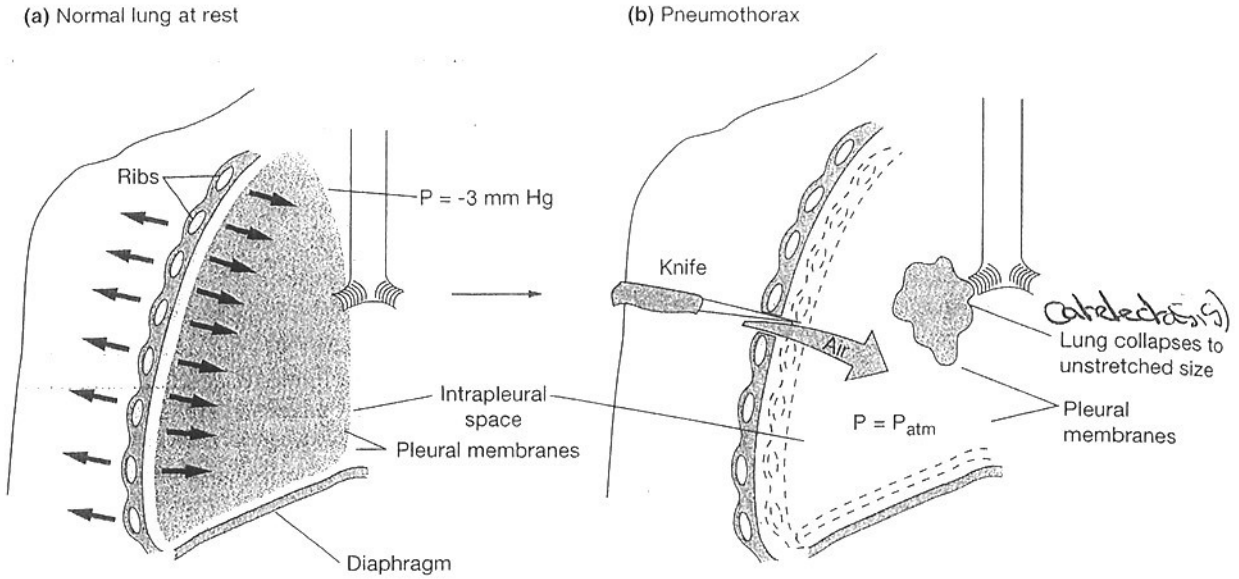
Ventilation requires that the lungs, which are unable to expand and contract on their own, move in association with the contraction and relaxation of the thorax. As discussed earlier in this chapter, the lungs are "stuck" to the thoracic cage by the pleural fluid, the fluid between the two pleural membranes.

The intrapleural pressure, pressure within the fluid between the pleural membranes, is normally subatmospheric. This subatmospheric pressure arises during development, when the thoracic cage with its associated pleural membrane grows more rapidly than the lung with its associated pleural membrane. The two pleural membranes are held together by the pleural fluid bond, so the elastic lungs are forced to stretch to conform to the larger volume of the thoracic cavity. At the same time, however, elastic recoil of the lungs creates an inwardly directed force that attempts to pull the lungs away from the chest wall (Fig. 17-11a ■). The combination of the outward pull of the thoracic cage and inward recoil of the elastic lungs creates an intrapleural pressure of about −3 mm Hg.

You can create a similar situation with a syringe half-filled with fluid and capped with a plugged-up needle. Begin with the fluid inside the syringe at atmospheric pressure. Now pick up the syringe and hold the barrel (the chest wall) in one hand while you try to withdraw the plunger (the elastic lung pulling away from the chest wall). As you pull on the plunger, the volume inside the barrel increases slightly, but the cohesive forces between the water molecules cause the fluid inside the syringe to resist expansion. The pressure within the barrel, which was initially equal to atmospheric pressure, decreases slightly as you pull on the plunger. If you release the plunger, it snaps back to its resting position, restoring atmospheric pressure inside the syringe.

But what happens to subatmospheric intrapleural pressure if an opening is made between the sealed pleural cavity and the atmosphere? A knife thrust between the ribs, a broken rib that punctures the pleural membrane, or any event that opens the pleural cavity to the atmosphere will allow air to flow in down its pressure gradient, just as air enters when you break the seal on a vacuum-packed can. Air in the pleural cavity breaks the fluid bond holding the lung to the chest wall. The elastic lung collapses to an unstretched state, like a deflated balloon, while the chest wall expands outward (Fig. 17-11b ■). This condition, called **pneumothorax** [*pneuma*, air + *thorax*, chest], results in a collapsed lung that is unable to function normally. Pneumothorax can occur spontaneously if a congenital *bleb*, or weakened section of lung tissue, ruptures, allowing air from inside the lung to enter the pleural cavity. Correction of a pneumothorax has two components: removing as much air from the pleural cavity as possible with a suction pump, and sealing the hole to prevent more air from entering. Any air remaining in the cavity will gradually be absorbed into the blood, restoring the pleural fluid bond and reinflating the lung.

Pressures in the pleural fluid vary during a respiratory cycle. At the beginning of inspiration, intrapleural pressure is about −3 mm Hg (Fig. 17-10 ■, point B_1). As inspiration proceeds, the pleural membranes and lungs follow the thoracic cage because of the pleural fluid bond. But the elastic lung tissue resists being stretched. The lungs attempt to pull farther away from the chest wall, causing the intrapleural pressure to become even more negative (Fig. 17-10 ■, point B_2). Because this



■ **Figure 17-11 Pressure in the pleural cavity** (a) Elastic recoil of the normal lung at rest creates an inward pull while the elastic recoil of the chest wall tries to pull the chest wall outward. Pressure in the fluid between the pleural membranes is subatmospheric. (b) If the sealed pleural cavity is opened to the atmosphere, air flows into the cavity. The lung collapses to its unstretched size, and the rib cage expands slightly. This condition is called pneumothorax.

process is difficult to visualize, return to the analogy of the fluid-filled syringe with the blocked needle. You can pull the plunger out a small distance without much effort, but if you try to pull it out farther, it is harder to do because of the cohesiveness of the fluid. The increased amount of work you do trying to pull out the plunger is paralleled by the work your muscles must do when they contract for inspiration. The bigger the breath, the more work is required to "stretch" the pleural fluid and the elastic lung.

By the end of quiet inspiration, when lungs are fully expanded, intrapleural pressure drops to around −6 mm Hg (point B_2). During exercise or other powerful inspirations, intrapleural pressure may reach −18 mm Hg.

With expiration, the thoracic cage returns to its resting position. The lungs are released from their extra-stretched position, and the intrapleural pressure returns to its normal value of −3 mm Hg (point B_3). Notice that intrapleural pressure never equilibrates with the atmosphere because the pleural cavity is a closed compartment.

The pressure gradients required for air flow are created by the work of skeletal muscle contraction. Normally, about 3%–5% of the body's energy expenditure is used for quiet breathing. During exercise, the energy required for breathing increases substantially. The two factors that have the greatest influence on the amount of work needed for breathing are (1) the stretchability, or compliance, of the lungs and (2) the resistance of the airways to air flow.

✓ A person has periodic spastic contractions of the diaphragm, otherwise known as hiccups. What happens to intrapleural and intrapulmonary pressure when a person hiccups?

✓ A stabbing victim is brought into the emergency room with a knife wound between the ribs on the left side of his chest. What has probably happened to his left lung? To his right lung? Why does the left side of his rib cage seem larger than the right side?

Lung Compliance and Elastance May Change in Disease States

Adequate ventilation depends on the ability of the lungs to expand normally. Most of the work of breathing goes into overcoming the resistance of the elastic lungs and the thoracic cage to stretch. Clinically, the ability of the lung to stretch is called **compliance.** A high-compliance lung stretches easily, just as a compliant person is easy to persuade. A low-compliance lung requires more force from the inspiratory muscles to stretch it. Compliance is different from **elastance** (elasticity). The fact that a lung stretches easily (high compliance) does not necessarily mean that it will return to its resting volume when the stretching force is released (elastance). For example, you may have had a pair of gym shorts in which the elastic waistband was easy to stretch but lacking in elasticity, making the shorts impossible to keep around your waist. Analogous problems may occur in the respiratory system. For example, *emphysema* is a disease in which the elastin fibers normally found in lung tissue are destroyed. Destruction of the elastin fibers results in lungs that exhibit high compliance and stretch easily during inspiration. However, these lungs also have decreased elastance, and therefore they do not recoil to their resting position during expiration. To understand the importance of elastic recoil to expiration, think of an inflated balloon and an inflated plastic bag. The balloon

is similar to the normal lung. Its elastic walls squeeze on the air inside the balloon, thereby increasing the internal air pressure. When the neck of the balloon is opened to the atmosphere, elastic recoil causes air to flow out of the balloon. The inflated plastic bag, on the other hand, is like the lung of an individual with emphysema. It has high compliance and is easily inflated, but it has little elastic recoil. If the inflated plastic bag is opened to the atmosphere, most of the air remains inside the bag.

A decrease in lung compliance will also affect ventilation because more work must be expended to stretch a stiff lung. Pathological conditions in which compliance is reduced are called **restrictive lung diseases.** In these conditions, the energy expenditure required to stretch stiff, less-compliant lungs can far exceed the normal range. Two common causes of decreased compliance are inelastic scar tissue formed in fibrotic lung diseases and inadequate production of surfactant in the alveoli.

Fibrotic Lung Disease Fibrotic lung diseases often result from the chronic inhalation of fine particulate matter that escapes the mucus lining of the airways and reaches the exchange epithelium of the alveoli. The only protective mechanism in that region of the respiratory system is removal by wandering alveolar macrophages (Fig. 17-2g ■). These phagocytic cells patrol the alveoli, engulfing any airborne particles that have managed to reach the exchange surface. If the particles are organic, the macrophages digest them with lysosomal enzymes. But if the particles are inorganic and cannot be digested, an inflammatory process ensues. Intracellular accumulation of the particles causes the macrophage to secrete growth factors that stimulate fibroblasts in the connective tissue of the lung. The fibroblasts produce collagen that forms inelastic, fibrous scar tissue. Large amounts of scar tissue reduce the compliance of the lung. The proliferation of inelastic scar tissue in the lung is called **fibrotic lung disease,** or **fibrosis.** Inorganic particles that can trigger fibrosis include asbestos, coal dust, silicon, and even dust and pollutants from urban areas.

Surfactant Decreases the Work of Breathing

For years, physiologists assumed that elastin and other elastic fibers were the primary source of resistance to stretch in the lung. But studies comparing the work required to expand air-filled and saline-filled lungs showed that air-filled lungs are much harder to inflate, so the lung tissue itself must contribute less to resistance than we thought. Another property of the normal air-filled lung, not present in a saline-filled lung, creates most of the resistance to stretch.

This property is **surface tension,** created by the thin fluid layer between the alveolar cells and the air. At any air-fluid interface, the surface of a liquid behaves as if it is under tension, like a thin membrane being stretched. This surface tension arises because of the hydrogen bonds between water molecules. The surface molecules are attracted to other water molecules beside and beneath them, but not to the air. If water is isolated in a drop, it will take on a rounded shape (∞ Fig. 2-10, p. 24). If water is in the shape of a bubble, as it is when it lines the alveoli, surface tension exerts a force directed toward the center of the bubble.

The **Law of LaPlace** is an expression of the force, or pressure, created by a fluid sphere or bubble. In physiology, the sphere is analogous to a fluid-lined alveolus. The Law of LaPlace states that the pressure within a fluid-lined alveolus depends on two factors: the surface tension of the fluid and the radius of the alveolus. This relationship is expressed by the equation

$P = 2 \cdot T/r$ where P is the pressure inside the alveolus

T is the surface tension of the fluid lining the alveolus

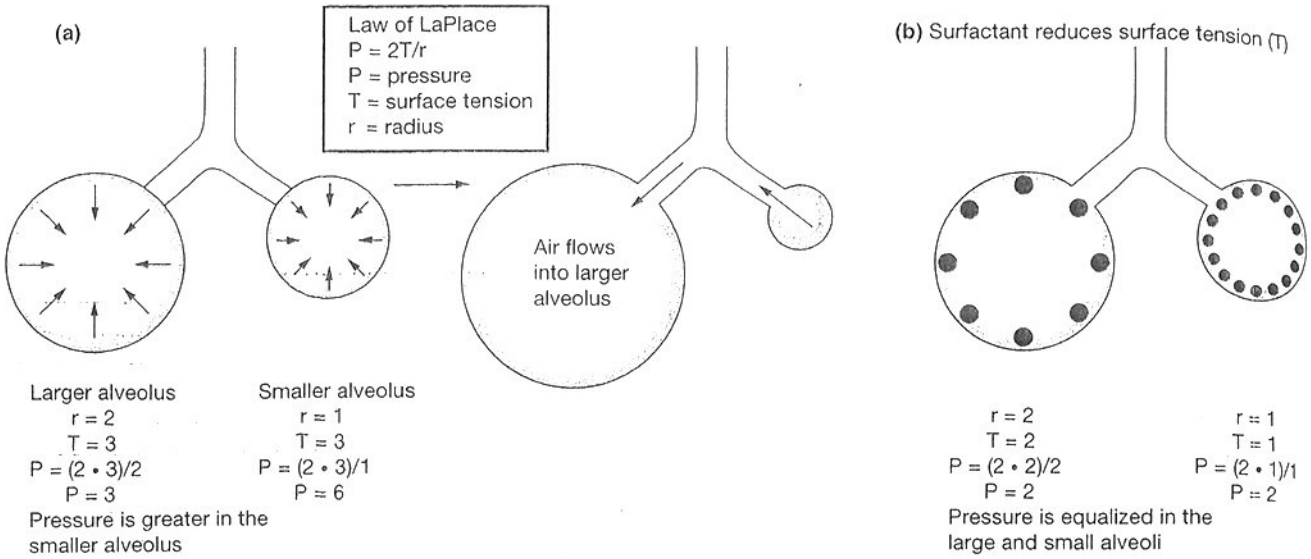
r is the radius of the alveolus

two alveoli have different diameters but are lined by fluids with the same surface tension, the pressure inside the smaller alveolus will be greater (Fig. 17-12a ■). If the two alveoli are connected to each other, air will flow from the higher-pressure small alveolus to the lower-pressure large alveolus. This movement of air causes the smaller alveolus to collapse, while the larger alveolus increases in volume.

Thus, the presence of fluid lining the alveoli creates surface tension that increases the resistance of the lung to stretch. This surface tension also makes the alveoli behave like elastic bubbles or inflated balloons that, once expanded, tend to collapse. Consequently, surface tension has the potential to increase the work needed to expand the alveoli with each breath.

Normally, however, our lungs secrete a chemical called a surfactant that reduces surface tension. **Surfactants** are molecules that disrupt cohesive forces between water molecules. For example, in dishwasher rinses, surfactants keep rinse water from beading up on the dishes. In the lungs, surfactant decreases the surface tension of the fluid lining the alveoli and prevents small alveoli from collapsing. Surfactant is more concentrated in smaller alveoli, making the surface tension in the smaller alveoli less than that in larger alveoli (Fig. 17-12b ■). Lower surface tension equalizes the pressure among different sizes of alveoli and keeps the smaller alveoli from collapsing when their air flows into larger, lower-pressure alveoli. With lower surface tension, the work needed to expand the alveoli with each breath is also greatly reduced.

Human surfactant is a mixture containing lipoproteins such as *dipalmitoylphosphatidylcholine.* Surfactant is manufactured and secreted into the alveolar air space by the type II alveolar cells (see Fig. 17-2g ■). Normally, surfactant synthesis begins about the twenty-fifth week of fetal development under the influence of various hormones. Production usually reaches adequate levels by the thirty-second week (about eight weeks before normal delivery). Babies who are born prematurely without adequate concentrations of surfactant in their alveoli



■ **Figure 17-12 Surfactant prevents the collapse of alveoli** (a) Air pressure within the alveoli is determined by the Law of LaPlace. If two alveoli have the same surface tension, the small alveolus will have higher pressure and will collapse as its air flows into the larger alveolus. (b) Surfactant decreases surface tension in the fluid lining the alveoli. Smaller alveoli have a higher concentration of surfactant so their surface tension is lower. The higher concentration of surfactant in smaller alveoli equalizes the pressure between smaller and larger alveoli.

develop *newborn respiratory distress syndrome (NRDS)*. In addition to "stiff" (low-compliance) lungs that require tremendous effort to expand with each breath, babies with NRDS also have alveoli that collapse.

Resistance of the Airways to Air Flow Is Determined Primarily by Airway Diameter

The other factor besides compliance that influences the work of breathing is the resistance of the respiratory system to air flow. According to Poiseuille's Law (∞ p. 389), parameters that contribute to resistance are:

1. The length of the system (L)
2. The viscosity of the substance flowing through the system (η)
3. The radius of the tubes in the system (r)

The equation that expresses the relation of those parameters is

$$R \propto L\eta/r^4$$

Because the length of the respiratory system is constant, we can ignore that variable. The viscosity of air is also

✓ Coal miners who spend years inhaling fine coal dust have much of their alveolar surface area covered with scarlike tissue. What happens to their lung compliance as a result?

✓ When a baby takes its first breath, what happens to the alveoli if surfactant is not present?

Respiratory Distress Syndrome and Surfactant The clue to what creates additional resistance in an air-filled alveolus came from studies of premature babies with newborn respiratory distress syndrome (NRDS). From their first breath, NRDS babies have difficulty keeping their lungs inflated. With each breath, their lungs collapse and they must use a tremendous amount of energy to expand them again for the next breath. Unless treatment is initiated rapidly, about 50% of these infants die. When President and Mrs. John Fitzgerald Kennedy's son was born with NRDS in the 1960s, the physicians could do little but administer oxygen and hope that the baby's lungs would mature before hypoxia and exertion overwhelmed him. Now the prognosis for NRDS babies is much better. Amniotic fluid can be sampled to assess if the baby's lungs are producing adequate amounts of surfactant. If they are not, and if delivery cannot be delayed, the NRDS baby can be treated by artificial ventilation that forces air into the lungs and keeps the alveoli open. The latest treatment is the aerosol administration of artificial surfactant until the baby's lungs mature enough to produce their own.

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Emphysema is characterized by a loss of elastin, the elastic fibers that help the alveoli recoil during expiration. Researchers believe that elastin is destroyed by proteases released by immune system cells, which work overtime in smokers to rid the lungs of irritants. People with emphysema have no difficulty inhaling air; however, because their alveoli have lost elastic recoil, expiration—normally a passive process—requires conscious effort. They literally have to work to push air out of their lungs.

Question 3: Name the muscles that patients with emphysema use to exhale forcefully.

ıost constant, although you may have noticed that it s harder to breathe in a sauna filled with steam than room with normal humidity. Water droplets in the ım increase the viscosity of the steamy air, thereby easing its resistance to flow. Viscosity also changes htly with atmospheric pressure, increasing as pres- increases. Divers breathing high-pressure com- sed air may feel a little more resistance to air flow, reas someone at high altitude may feel less resis- e. Despite these exceptions, viscosity plays very lit- ole in resistance to air flow.

cause length and viscosity are essentially constant he respiratory system, the radius (or diameter) of irways is the primary determinant of airway resis- e. Normally, however, the work needed to overcome esistance of the airways to air flow is small com- d with the work needed to overcome the resistance e lungs and thoracic cage to stretch.

arly 90% of airway resistance normally can be outed to the trachea and bronchi, rigid structures the smallest total cross-sectional area of the air- s. These structures are supported by cartilage and , so their diameters normally do not change, and resistance to air flow is constant. However, mucus mulation from allergies or infections can dramati- increase resistance. If you have ever tried breath- hrough your nose when you have a cold, you can eciate how the narrowing of an upper airway limits ow!

bronchioles normally do not contribute signifi- y to airway resistance because their total cross-sec- l area is about 2000 times that of the trachea. But, ıse the bronchioles are collapsible tubes, a decrease ir diameter can suddenly turn them into a signifi- source of airway resistance. **Bronchoconstriction** ases resistance to air flow and decreases the nt of fresh air that reaches the alveoli. Bronchioles, rterioles, are subject to reflex control by the ner- system and by hormones. However, most minute- nute changes in bronchiolar diameter occur in nse to paracrines.

on dioxide in the airways is the primary paracrine ffects bronchiolar diameter. Increased concentrations of carbon dioxide in expired air relax bronchiolar smooth muscle and cause **bronchodilation.** On the other hand, *histamine* is a paracrine that acts as a powerful bronchoconstrictor. This chemical is released by mast cells (∞ p. 147) in response to tissue damage or allergic reactions. In severe allergic reactions, large amounts of histamine may lead to widespread bronchoconstriction and difficulty breathing. Immediate medical treatment in these patients is imperative.

The primary neural control of bronchioles comes from parasympathetic neurons that cause bronchoconstriction, a reflex designed to protect the lower respiratory tract from inhaled irritants. There is no significant sympathetic innervation of the bronchioles in humans. However, smooth muscle in the bronchioles is well supplied with β_2 receptors that respond to epinephrine. Stimulation of β_2 receptors relaxes airway smooth muscle and results in bronchodilation. This reflex is used therapeutically in the treatment of asthma and various allergic reactions characterized by histamine release and bronchoconstriction. Factors that alter airway resistance are summarized in Table 17-3.

✓ A cancerous lung tumor has grown into the walls of a group of bronchioles, narrowing their lumens. What has happened to the resistance to air flow in these bronchioles?

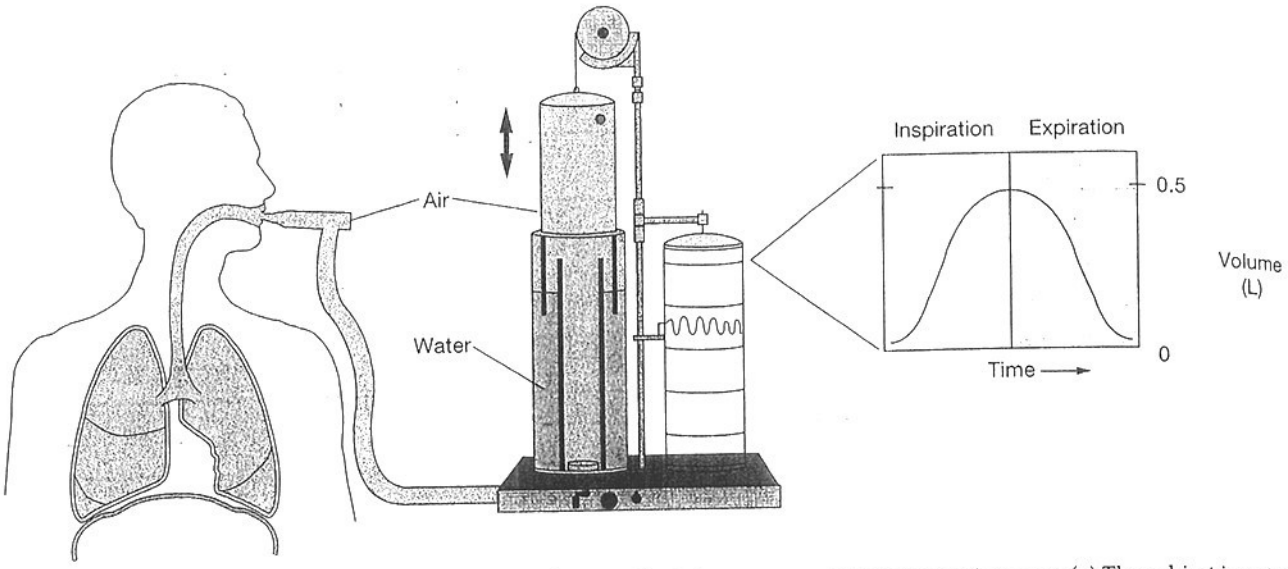
✓ Why does it feel more difficult to breathe in a steam room than outside in drier air?

Pulmonary Function Tests Measure Lung Volume during Ventilation

One method that physiologists use to assess a person's pulmonary function is to measure how much air the person moves during quiet breathing and with maximum effort. Many **pulmonary function tests** use a **spirometer,** an instrument that measures the volume of air moving with each breath (Fig. 17-13 ■). Although pulmonary function tests are relatively simple to perform, they have considerable diagnostic value. For example, in asthma, the bronchioles are constricted.

E 17-3 Factors That Affect Airway Resistance

r	*Affected by*	*Mediated by*
th of the system	Constant; not a factor	
sity of air	Usually constant. Humidity and altitude may alter slightly.	
ıeter of airways		
er airways	Physical obstruction	Mucus and other factors
ıchioles	Bronchoconstriction	Parasympathetic neurons (muscarinic receptors) Histamine
	Bronchodilation	Carbon dioxide Epinephrine (β_2 receptors)



■ **Figure 17-13 The recording spirometer** Lung volumes and air flow are recorded using a spirometer. (a) The subject inserts a mouthpiece that is attached to an inverted bell filled with air or oxygen. The volume of the bell and the volume of the subject's respiratory tract create a closed system. When the subject inhales, air moves from the bell into the lungs. The volume of the bell decreases, and the pen rises on the tracing. When the subject exhales, air moves from the lungs back into the bell, and its volume increases. This increase causes the pen to drop on the tracing. In addition to measuring lung volumes, spirometers can be used to determine the *rate* of air movement during forced expiration. Most clinical spirometers today have been computerized, but the spirometer illustrated is still widely used in student laboratories.

They tend to collapse and close off before a forced expiration is completed, reducing both the amount and rate of air flow. Diseases in which air flow during expiration is diminished owing to narrowing of the bronchioles are known as **obstructive lung diseases.** Emphysema and chronic bronchitis are sometimes called *chronic obstructive pulmonary disease*, or *COPD*, because of their ongoing, or chronic, nature.

Lung volumes The air moved during breathing can be divided into four lung volumes: tidal volume, inspiratory reserve volume, expiratory reserve volume, and residual volume. These volumes are diagrammed in Figure 17-14 ■ and described below. The numerical values given represent average volumes for the 70-kg man; the volumes for women are typically about 20% less. Each paragraph below begins with the instructions that you would be given if you were being tested for these volumes.

"Breathe quietly." The volume of air that moves in a single normal inspiration or expiration is known as the **tidal volume** (V_T). Average tidal volume during quiet breathing is 500 mL. Tidal volume will vary with the age, sex, and height of the individual.

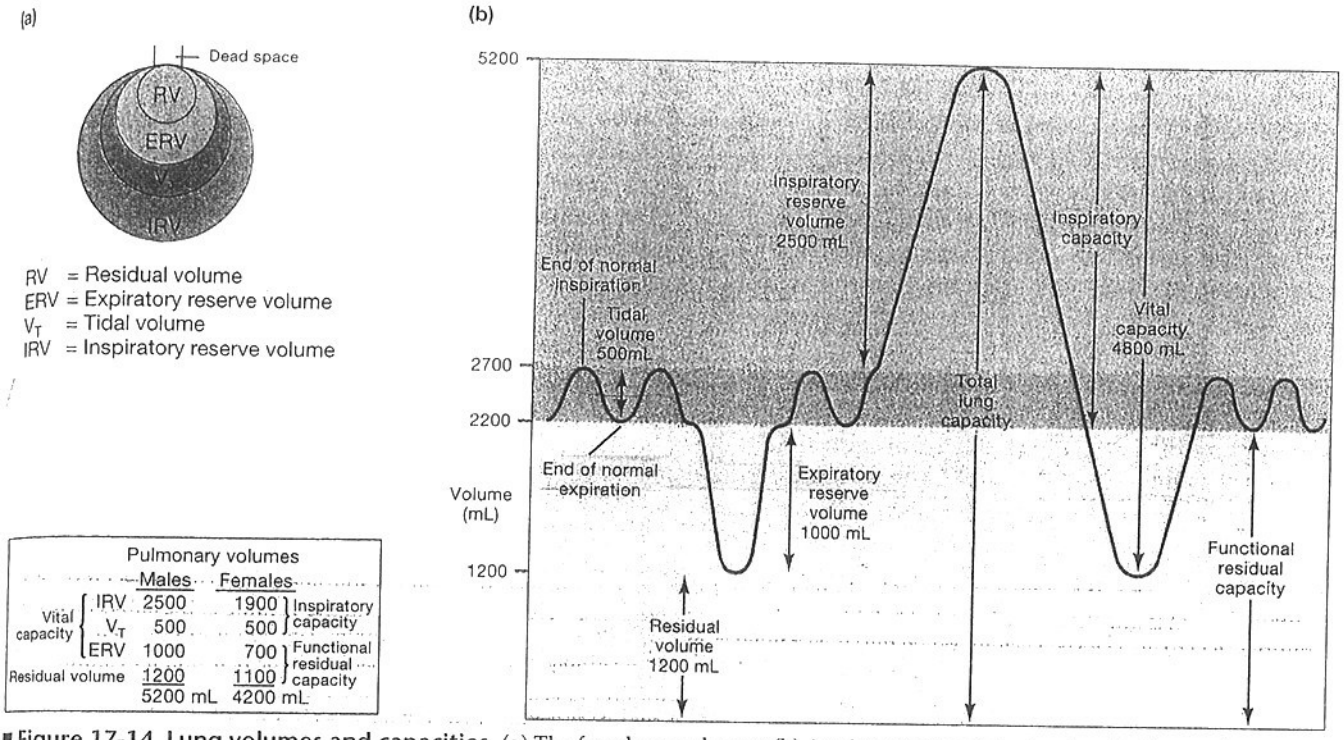
"Now, at the end of a quiet inspiration, take in as much additional air as you possibly can." The additional volume you inspire above the tidal volume represents your **inspiratory reserve volume** (IRV). In a 70-kg man, this volume is about 2500 mL, a fivefold increase over the normal tidal volume.

"Now stop at the end of a normal exhalation, then exhale as much air as you possibly can." The amount of air exhaled after the end of a normal expiration is the **expiratory reserve volume** (ERV), which averages about 1000 mL.

The fourth volume is one that cannot be measured directly. Even if you blow out as much air as you can, air still remains in the lungs and the airways. The volume of air in the respiratory system after maximal exhalation, about 1200 mL, is called the **residual volume** (RV). Most of this residual volume exists because the lungs are held stretched against the thoracic wall by the pleural fluid.

Lung capacities Sums of two or more lung volumes are called **capacities.** Adding the inspiratory reserve vol-

Asthma Asthma is an obstructive lung disease characterized by bronchoconstriction and airway edema, which increase airway resistance and decrease air flow. Patients complain of shortness of breath (*dyspnea*), and when they are asked to exhale forcefully, a wheezing sound is heard as air whistles through the narrowed lower airways. The severity of asthma attacks ranges from mild to life-threatening. Asthma is an inflammatory condition that is often associated with allergies. It can also be triggered by exercise (exercise-induced asthma) and by rapid changes in the temperature or humidity of inspired air. At the cellular level, a variety of chemical signals may be responsible for inducing bronchoconstriction, including acetylcholine, histamine, substance P (a neuropeptide), and leukotrienes secreted by mast cells, macrophages, and eosinophils. Asthma is treated with inhaled and oral medications that include β_2-adrenergic agonists, anti-inflammatory drugs, and a new leukotriene antagonist.



Pulmonary volumes

		Males	Females	
Vital capacity	IRV	2500	1900	Inspiratory capacity
	V_T	500	500	
	ERV	1000	700	Functional residual capacity
Residual volume		1200	1100	
		5200 mL	4200 mL	

Figure 17-14 Lung volumes and capacities (a) The four lung volumes. (b) A spirometer tracing showing the lung volumes and capacities.

ume, the expiratory reserve volume, and the tidal volume gives a measure of the **vital capacity** (VC). Vital capacity represents the maximum amount of air that can be voluntarily moved into or out of the respiratory system with one breath. To measure vital capacity, you would instruct the person to take in as much air as possible, then blow it all out. Vital capacity decreases with age.

The vital capacity plus the residual volume yields the **total lung capacity** (TLC). Other capacities of importance in pulmonary medicine include the inspiratory capacity (tidal volume plus inspiratory reserve volume) and the functional residual capacity (expiratory reserve volume plus residual volume).

Auscultation of breath sounds Auscultation of breath sounds is an important diagnostic technique in pulmonary medicine, just as auscultation of heart sounds is used in cardiovascular diagnosis (∞ p. 413). But breath sounds are more complicated to interpret owing to a wide range of normal variation. In general, breath sounds are distributed evenly over the lungs and resemble a quiet "whoosh" made by flowing air. In conditions in which air flow is reduced, such as pneumothorax, breath sounds may be diminished or absent. Abnormal sounds include a variety of squeaks, pops, wheezes, or bubbling sounds caused by fluid and secretions in the airways or alveoli. Inflammation of the pleural membrane results in a crackling or grating sound known as a *friction rub*. It is caused by swollen, inflamed pleural membranes rubbing against each other, and it disappears when fluid again separates them.

✓ Restrictive lung disease decreases the compliance of the lung. How will the inspiratory reserve volume change in patients with a restrictive lung disease?

✓ Chronic obstructive lung disease causes patients to lose the ability to exhale fully. How does residual volume change in these patients?

✓ If vital capacity decreases with age but total lung capacity does not change, what volume must be changing? In which direction?

The Effectiveness of Ventilation Is Determined by the Rate and Depth of Breathing

You may recall that the efficiency of the heart is measured by the cardiac output, which is calculated by multiplying heart rate by stroke volume. Likewise, we can estimate the effectiveness of ventilation by calculating the **total pulmonary ventilation**, the volume of air moved into and out of the lungs each minute. Total pulmonary ventilation, also known as the *minute volume*, is calculated as follows:

Ventilation rate × tidal volume (V_T) = total pulmonary ventilation

The normal ventilation rate for an adult is 12–20 breaths per minute. Using the average tidal volume of 500 mL and the slowest ventilation rate, we get

12 breaths/min × 500 mL/breath = 6000 mL/min, or 6 L/min

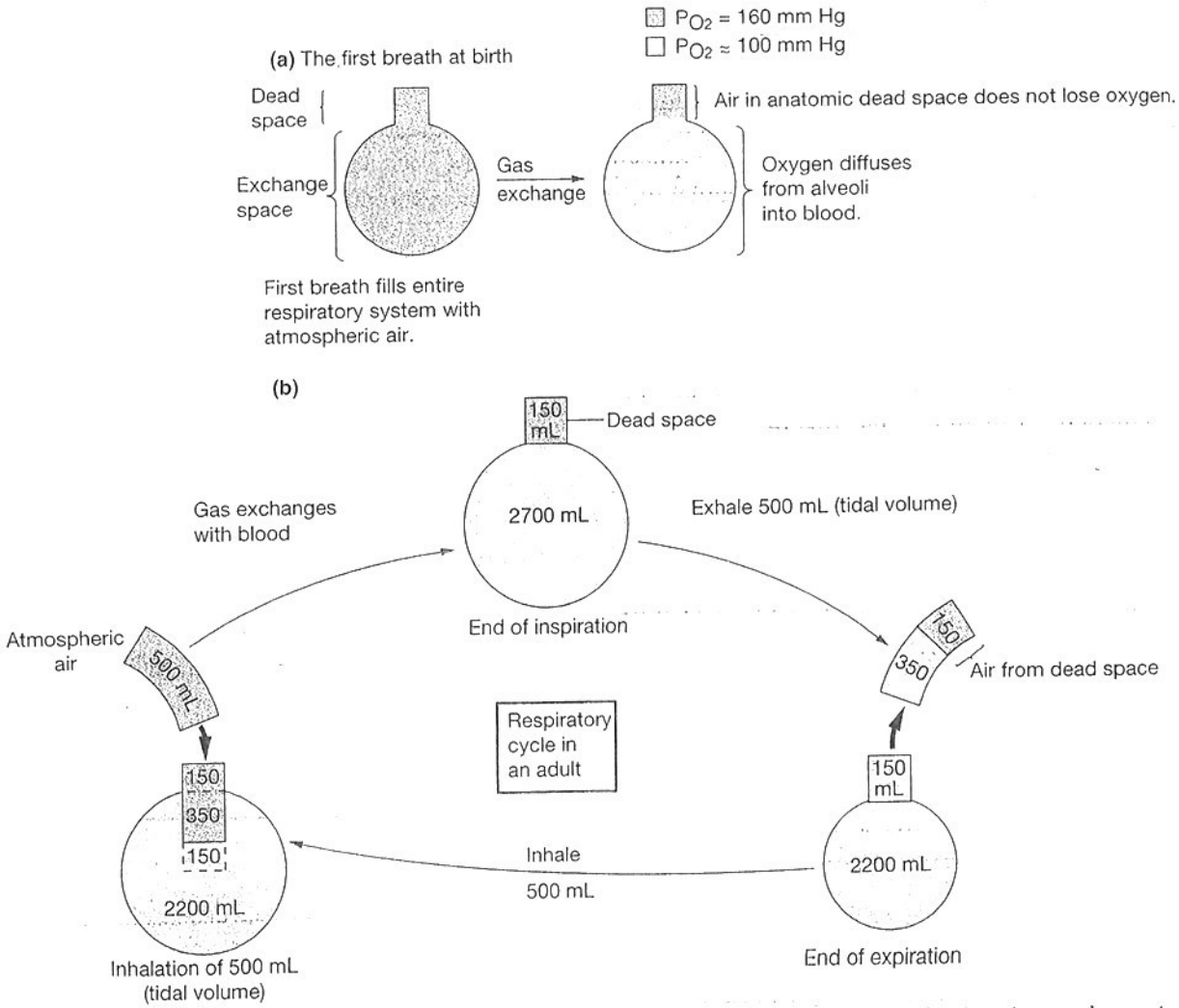
Total pulmonary ventilation represents the physical movement of air into and out of the respiratory tract. But it is not necessarily a good indicator of how much fresh air reaches the alveolar exchange surface. Some air that enters the respiratory system does not reach the alveoli because part of every breath remains in the conducting airways, such as the trachea and bronchi. Because the conducting airways do not exchange gases with the blood, they are known as the **anatomic dead space.** Anatomic dead space averages about 150 mL.

To illustrate the difference between air that enters the airways and fresh air that reaches the alveoli, let us consider a typical breath bringing 500 mL of fresh air into the respiratory system (Fig. 17-15b ■). The entering air displaces the 150 mL of stale air in the anatomic dead space, sending it into the alveoli. The first 350 mL of the fresh air also enters the alveoli. The last 150 mL of inspired air remains in the dead space. Consequently, only 350 mL of fresh air enters the alveoli with each breath. This 350 mL mixes with 2200 mL of air already in the lungs (the functional residual capacity; see Fig. 17-14 ■).

Because a significant portion of inspired air never reaches an exchange surface, a more accurate indicator of the efficiency of ventilation is **alveolar ventilation,** the amount of air that reaches the alveoli each minute. Alveolar ventilation is calculated by multiplying the ventilation rate by the volume of air that reaches the alveoli:

Ventilation rate × (tidal volume − dead space volume) = alveolar ventilation

Using the same ventilation rate and tidal volume as above and a dead space volume of 150 mL yields an alveolar ventilation of



■ **Figure 17-15 Total pulmonary and alveolar ventilation** (a) Air that remains in the conducting airways does not exchange gases with the blood. The conducting airways are also called the dead space for this reason. (b) In adults, the dead space is about 150 mL. When a breath of 500 mL is exhaled, the first 150 mL of air comes from the dead space and the remaining 350 mL is alveolar air. At the end of expiration, the dead space is filled with alveolar air. The next inspiration brings 500 mL of fresh air into the respiratory system. However, the first 150 mL of air to move into the lungs is the 150 mL of "stale" alveolar air that was in the dead space. Only 350 mL of fresh air enters the alveoli. The remaining 150 mL of fresh air remains in the dead space.

TABLE 17-4 Effects of Breathing Pattern on Alveolar Ventilation

Tidal Volume (mL)	Respiratory Rate (breaths/min)	Total Pulmonary Ventilation (mL/min)	Fresh Air to Alveoli (mL) (tidal volume − dead space volume*)	Alveolar Ventilation (mL/min)
500 (normal)	12 (normal)	6000	350	4200
300 (shallow)	20 (rapid)	6000	150	3000
750 (deep)	8 (slow)	6000	600	4800

*Dead space volume is assumed to be 150 mL.

12 breaths/min × (500 mL/breath − 150 mL/breath) = alveolar ventilation

12 breaths/min × 350 mL/breath = 4200 mL/min

Thus, at 12 breaths per minute, the alveolar ventilation is 4.2 L/min. Although 6 L/min of fresh air entered the respiratory system, only 4.2 L reached the alveoli.

Alveolar ventilation can be drastically affected by changes in the rate or depth of breathing. Table 17-4 shows that three people can have the same total pulmonary ventilation (minute volume) but dramatically different alveolar ventilation. Maximum voluntary ventilation, which involves breathing as deeply and quickly as possible, may increase total pulmonary ventilation to as much as 170 L/min. Table 17-5 describes various patterns of ventilation.

Gas Composition in the Alveoli Varies Little during Normal Breathing

How much will a change in alveolar ventilation affect the amount of fresh air and oxygen that reaches the alveoli? Figure 17-16 ■ is a graph showing how P_{O_2} and P_{CO_2} vary with hyper- and hypoventilation. As alveolar ventilation increases above normal levels (**hyperventilation**), alveolar P_{O_2} rises to about 120 mm Hg and alveolar P_{CO_2} falls to around 20 mm Hg. During **hypoventilation**, when less fresh air enters the alveoli, alveolar P_{O_2} decreases and alveolar P_{CO_2} increases.

Although a dramatic change in alveolar ventilation pattern will affect gas partial pressures in the alveoli, the P_{O_2} and P_{CO_2} in the alveoli change surprisingly little during normal quiet breathing. Alveolar P_{O_2} is fairly constant at 100 mm Hg, and alveolar P_{CO_2} stays close to 40 mm Hg. Intuitively, one might think that P_{O_2} would increase when fresh air first enters the alveoli, then decrease steadily as oxygen leaves to enter the blood. Instead, we find only very small swings in P_{O_2} because (1) the amount of oxygen that enters the alveoli with each breath is roughly equal to the amount of oxygen that enters the blood, and (2) the amount of fresh air that enters the lungs with each breath is only a little more than 10% of the total lung volume at the end of inspiration.

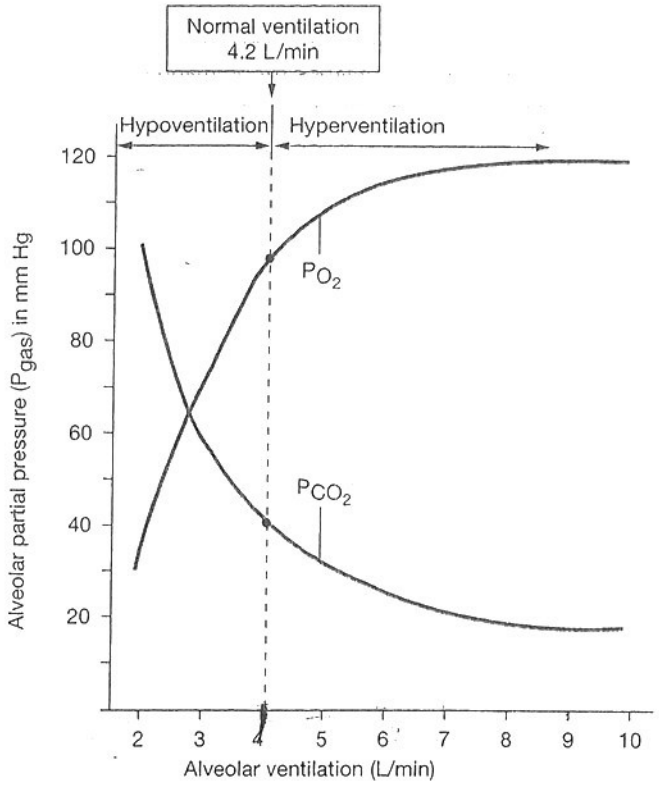
✓ If a person increased the depth of breathing (i.e., increased his tidal volume), what do you predict would happen to his alveolar P_{O_2}?

Ventilation Is Matched to Alveolar Blood Flow

Moving oxygen from the atmosphere to the alveolar exchange surface is only the first step in external respiration. Next there must be normal gas exchange across the alveolar-capillary interface. Finally, blood flow (*perfusion*) past the alveoli must be adequate to pick up the available oxygen. Matching ventilation into groups of alveoli with blood flow past those alveoli is a two-part

TABLE 17-5 Types and Patterns of Ventilation

Name	Description	Examples
Eupnea	Normal quiet breathing	
Hyperpnea	Increased respiratory rate and/or volume in response to increased metabolism	Exercise
Hyperventilation	Increased respiratory rate and/or volume without increased metabolism	Emotional hyperventilation; blowing up a balloon
Hypoventilation	Decreased alveolar ventilation	Shallow breathing; asthma; restrictive lung disease
Tachypnea	Rapid breathing; usually increased respiratory rate with decreased depth	Panting
Dyspnea	Difficulty breathing (a subjective feeling sometimes described as "air hunger")	Various pathologies or hard exercise
Apnea	Cessation of breathing	Voluntary breath-holding; depression of CNS control centers



■ **Figure 17-16 Effect of changing alveolar ventilation on P_{O_2} and P_{CO_2} in the alveoli**

process involving local regulation of both air flow and blood flow.

Alterations in blood flow in the lungs depend almost exclusively on properties of the capillaries and on local factors such as the concentrations of oxygen and carbon dioxide in the lung tissue. Capillaries in the lungs are unusual because they are collapsible. If the pressure of blood flowing through the capillaries falls below a certain point, the capillaries close off, diverting blood to other pulmonary capillary beds with higher pressure. In a person at rest, some capillary beds found in the apex (top) of the lung are closed off, whereas capillary beds at the base of the lung have higher hydraulic pressure because of gravity and remain open. Consequently, blood flow is diverted toward the base of the lung. During exercise, when blood pressure rises, the closed apical capillary beds open, ensuring that the increased cardiac output will be fully oxygenated as it passes through the lungs. The ability of the lungs to recruit additional capillary beds during exercise is an example of the reserve capacity of the body.

At the local level, the body attempts to match air and blood flow in each section of the lung by regulating the diameters of the arterioles and the bronchioles. Bronchiolar diameter is mediated primarily by CO_2 levels in exhaled air passing through them (Table 17-6). An increase in the P_{CO_2} of expired air causes the bronchioles to dilate. A decrease in the P_{CO_2} of expired air causes bronchioles to constrict.

Although there is some autonomic innervation of the pulmonary arterioles, there is no evidence for neural

TABLE 17-6 Local Control of Arterioles and Bronchioles by Oxygen and Carbon Dioxide

Gas Composition	*Bronchioles*	*Pulmonary Arterioles*	*Systemic Arterioles*
P_{CO_2} increases	Dilate	(Constrict)	Dilate
P_{CO_2} decreases	Constrict	(Dilate)	Constrict
P_{O_2} increases	(Constrict)	Dilate	Constrict
P_{O_2} decreases	(Dilate)	Constrict	Dilate

Note: Responses in parentheses indicate weak responses.

control of pulmonary blood flow. The resistance of pulmonary arterioles to blood flow is regulated primarily by the oxygen content of the interstitial fluid around the arteriole (Fig. 17-17 ■). If the ventilation of alveoli in an area of the lung is diminished, the tissue P_{O_2} in that area decreases. The arterioles respond to lower P_{O_2} by constricting. Vasoconstriction diverts blood away from the underventilated region to better-ventilated parts of the lung.

On the other hand, if P_{O_2} in the lung becomes higher than normal, the alveoli in that region are being overventilated relative to the blood flow past them. The arterioles supplying those alveoli dilate to bring in additional blood that can pick up the extra oxygen.

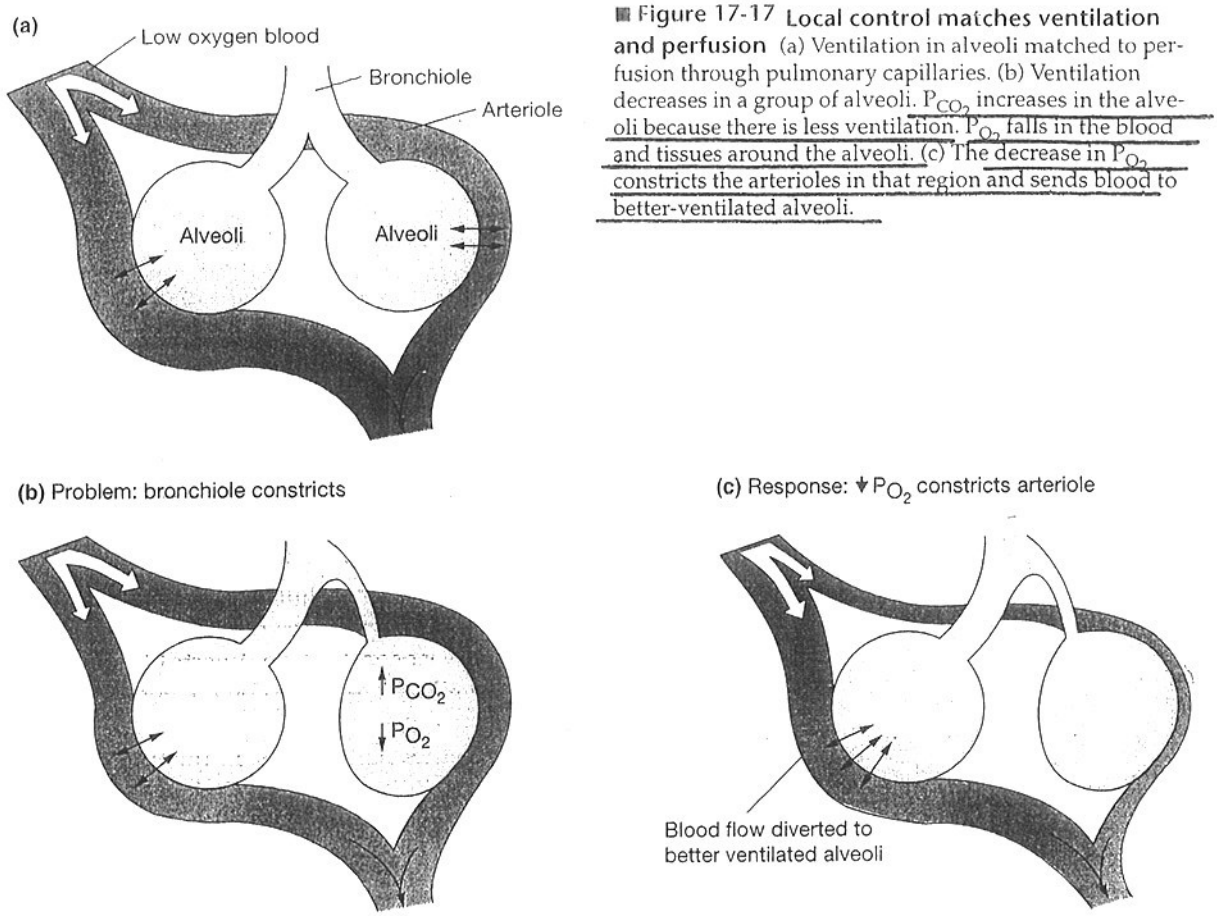
Note that constriction of pulmonary arterioles in response to low P_{O_2} is exactly the opposite of what occurs in the systemic circulation (∞ p. 434). In the systemic circulation, a decrease in the concentration of oxygen in the tissues causes the arterioles to dilate, bringing more blood to metabolically active tissues that are consuming oxygen.

One important point must be noted here. Local control mechanisms are not effective regulators of air and blood flow under all circumstances. If blood flow is blocked in one pulmonary artery, or if air flow is blocked at the level of the larger airways, local responses that shunt air or blood to other parts of the lung are ineffective because no place in the lung has normal ventilation or perfusion.

✓ If a tumor in the lung tissue decreases blood flow in one small section of the lung to a minimum, what happens to P_{O_2} in those alveoli and in the surrounding tissue? What happens to P_{CO_2} in the same region? What is the compensatory response of the bronchioles in that region? Will the compensation bring ventilation in that section of the lung back to normal? Explain.

GAS EXCHANGE IN THE LUNGS

The diffusion of gases between the alveoli and the blood obeys the rules for simple diffusion introduced in Chapter 5 (∞ p. 117):



■ **Figure 17-17 Local control matches ventilation and perfusion** (a) Ventilation in alveoli matched to perfusion through pulmonary capillaries. (b) Ventilation decreases in a group of alveoli. P_{CO_2} increases in the alveoli because there is less ventilation. P_{O_2} falls in the blood and tissues around the alveoli. (c) The decrease in P_{O_2} constricts the arterioles in that region and sends blood to better-ventilated alveoli.

1. The rate of diffusion across membranes is directly proportional to the partial pressure (concentration) gradient.
2. The rate of diffusion across membranes is directly proportional to the available surface area.
3. The rate of diffusion across membranes is inversely proportional to the thickness of the membrane.
4. Diffusion is most rapid over short distances.

Normally, gas exchange in the lungs is rapid and goes to equilibrium, but a change in any of the parameters listed above has the potential to limit diffusion significantly. Pathological changes in these factors that affect gas exchange are discussed briefly below.

The Partial Pressure Gradient Is the Primary Factor Influencing Gas Exchange

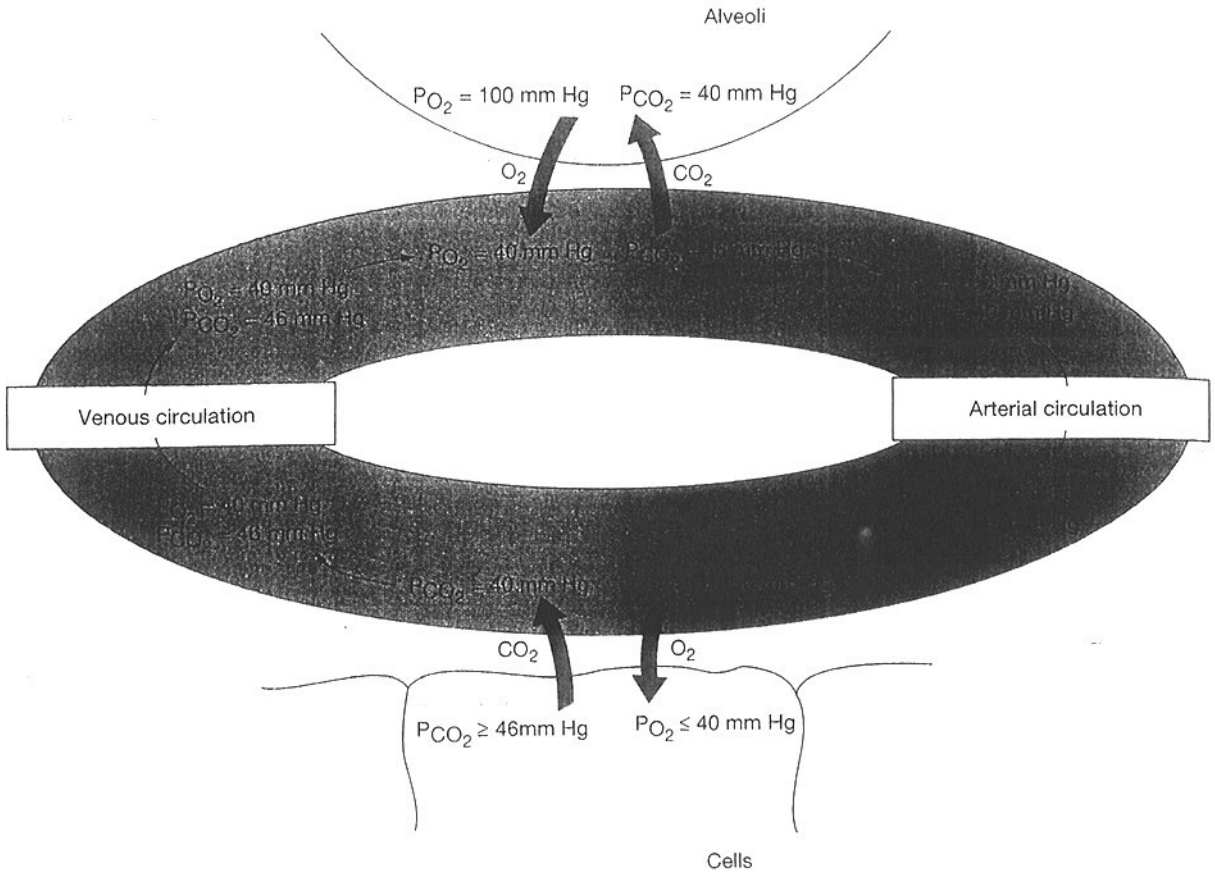
As you learned earlier in the chapter, the amount of oxygen or carbon dioxide that dissolves in the plasma depends on both the pressure gradient and the solubility of the gas. Because solubility is normally constant, the primary determinant of gas exchange is the partial pressure gradient of the gas across the alveolar-capillary membrane.

The gas laws state that individual gases flow from regions of higher partial pressure to regions of lower partial pressure. This rule governs the exchange of oxygen and carbon dioxide at the lungs and tissues (Fig. 17-18 ■). Normal alveolar P_{O_2} is 100 mm Hg, whereas the P_{O_2} of systemic venous blood arriving at the lungs is 40 mm Hg. Oxygen therefore moves from the alveoli into the capillaries. The reverse process occurs with carbon dioxide. Alveolar P_{CO_2} is 40 mm Hg, whereas the P_{CO_2} of systemic venous blood entering the lungs is 46 mm Hg. Carbon dioxide thus moves from the plasma into the alveoli.

Although oxygen and carbon dioxide diffuse across two cell layers (capillary and alveolus) and through the interstitial fluid, exchange is very rapid because (1) the distance is small and (2) the gases are both water- and lipid-soluble. Diffusion of carbon dioxide and oxygen reaches equilibrium in less than one second. By the time blood leaves the alveoli, it has a P_{O_2} of 100 mm Hg and a P_{CO_2} of 40 mm Hg, identical to the partial pressures of those two gases in the alveoli.

Any factor that decreases alveolar P_{O_2} decreases the pressure gradient and results in less oxygen entering the blood. If alveolar P_{O_2} is low, there are two questions to ask: (1) Is the composition of the inspired air normal? and (2) Is alveolar ventilation adequate?

The main factor that affects the oxygen content of inspired air is altitude. The partial pressure of oxygen in air decreases along with total atmospheric pressure as



■ Figure 17-18 Gas exchange at the alveoli and cells

you move from sea level (760 mm Hg) to higher altitudes. At the summit of Mt. Everest, an altitude of 8848 M, atmospheric pressure is only 253 mm Hg, and atmospheric P_{O_2} is only 53 mm Hg. As a result, alveolar and arterial P_{O_2} fall from 100 mm Hg to 35 mm Hg, a value barely large enough to sustain life!

If the composition of the inspired air is normal but alveolar P_{O_2} is low, then the cause is a decrease in alveolar ventilation. Low alveolar ventilation is also known as hypoventilation and is characterized by less fresh air entering the alveoli. Pathological factors that cause alveolar hypoventilation include increased airway resistance (asthma; Fig. 17-19e ■), decreased lung compliance (fibrosis; Fig. 17-19c ■), and overdoses of drugs or alcohol that depress the central nervous system and slow the ventilation rate.

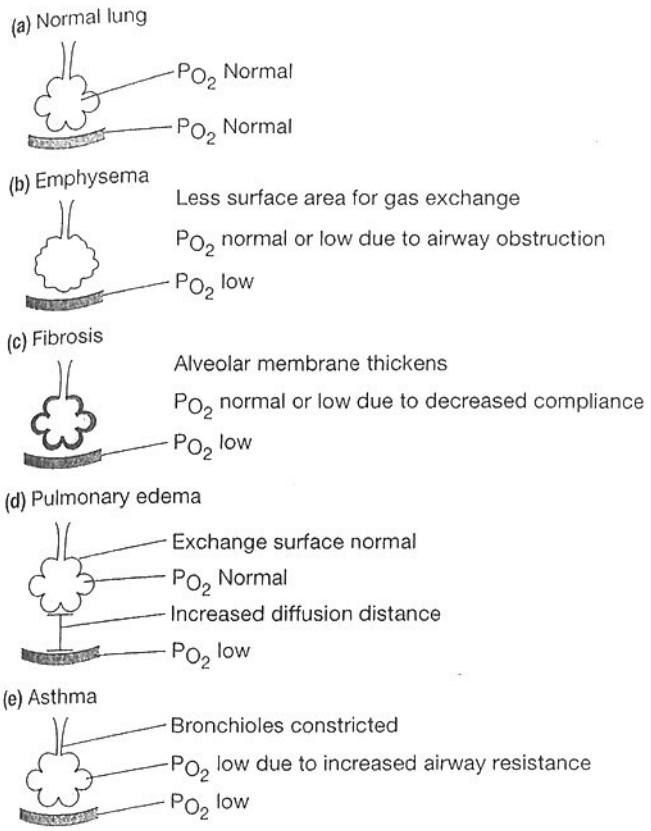
Gas Exchange Can Be Affected by Changes in the Alveolar Membrane

In some situations, alveolar P_{O_2} is normal but the P_{O_2} of the arterial blood leaving the lungs is low. In these cases, there is a problem with the exchange of gases between the alveoli and the blood. Factors that adversely affect gas exchange include (1) a decrease in the amount of alveolar surface area that is available for gas exchange and (2) an increase in the diffusion distance between the alveoli and the blood.

Physical loss of alveolar surface area is demonstrated dramatically in emphysema, a degenerative lung disease most often caused by cigarette smoking. The irritating effect of smoke in the alveoli activates alveolar macrophages that release proteolytic enzymes. These enzymes destroy the elastic fibers of the lung, as discussed earlier, and kill cells, breaking down the walls of the alveoli. The result is a high-compliance/low-elastic recoil lung with fewer and larger alveoli and less surface area for gas exchange (Fig. 17-19b ■).

Any change in the alveolar membrane that alters its properties will slow gas exchange. For example, in fibrotic lung diseases, deposition of scar tissue thickens the alveolar membrane (Fig. 17-19c ■). Diffusion of gases through this scar tissue is much slower than normal. However, the lungs have a built-in reserve capacity. As a result, one-third of the exchange epithelium must be incapacitated before arterial P_{O_2} falls significantly.

A situation in which the diffusion distance between alveoli and blood increases is **pulmonary edema,** characterized by excessive interstitial fluid volume in the lungs. Normally, only small amounts of interstitial fluid are found in the lungs, owing to low pulmonary blood pressure and effective lymph drainage. But if pulmonary blood pressure rises for some reason such as left ventricular failure or mitral valve dysfunction, capillary hydraulic pressure increases. Fluid filtration out of the capillary increases to



■ **Figure 17-19 Pulmonary pathologies that affect alveolar ventilation and gas exchange** (a) Normal lung. (b) In emphysema, destruction of alveoli results in less surface area for gas exchange. (c) In fibrotic lung diseases, thickening of the alveolar membrane from scar tissue will slow gas exchange. In addition, the loss of lung compliance may decrease alveolar ventilation, causing lower alveolar P_{O_2}. (d) In pulmonary edema, excess fluid in the interstitial space will increase the diffusion distance between the alveoli and the blood. P_{CO_2} in the arterial blood may be normal because of the higher solubility of carbon dioxide, but P_{O_2} is likely to be decreased. In addition, edema may cause a loss of compliance. (e) In asthma, narrowing of the bronchioles will cause a decrease in alveolar ventilation.

the point that the lymphatics become unable to remove all the fluid (Fig. 17-19d ■). Excess fluid accumulates in the pulmonary interstitial space and may even leak across the alveolar membrane, collecting inside the alveoli. The increased diffusion distance does not usually affect carbon dioxide exchange because carbon dioxide is relatively soluble in body fluids. Oxygen, however, is much less soluble and is unable to cross the increased diffusion distance as easily. Subsequently, oxygen exchange diminishes. In these cases, it is not unusual to find normal arterial P_{CO_2} accompanying decreased arterial P_{O_2}.

If the diffusion of oxygen from alveolus to blood is significantly impaired, **hypoxia,** or too little oxygen in the cells, results. Hypoxia frequently goes hand in hand with **hypercapnia,** elevated concentrations of carbon dioxide. These two conditions are clinical signs, not diseases, and the clinician must gather additional information to pinpoint their cause.

The Pulse Oximeter One important clinical indicator of the effectiveness of gas exchange in the lungs is the amount of oxygen in arterial blood. Previously, obtaining an arterial blood sample was difficult and painful because it meant finding an accessible artery (most blood is drawn from superficial veins rather than from arteries, which lie deeper within the body). Recently, scientists developed instruments that quickly and painlessly measure blood oxygen levels through the surface of the skin on a finger. The pulse oximeter clips onto the tip of a finger and, within seconds, gives a digital reading of arterial hemoglobin saturation by measuring light absorbance of the tissue at two wavelengths. Transcutaneous oxygen sensors measure dissolved oxygen (P_{O_2}) using a variant of traditional gas-measuring electrodes. Both methods have their limitations but are popular because they give a rapid, noninvasive means of estimating arterial oxygen concentration.

✓ Why does left ventricular failure or mitral valve dysfunction cause elevated pulmonary blood pressure? (Hint: ∞ p. 415.)

✓ If alveolar ventilation increases, what do you predict will happen to arterial P_{O_2}? To arterial P_{CO_2}? To venous P_{O_2} and P_{CO_2}? Explain.

GAS EXCHANGE IN THE TISSUES

Diffusion of gases between the blood and the cells also depends on the pressure gradient between the two compartments. Arterial blood reaching the systemic capillaries has a P_{O_2} of 100 mm Hg and a P_{CO_2} of 40 mm Hg (Fig. 17-18 ■). The cells are continuously using oxygen and producing carbon dioxide through cellular respiration, so their P_{O_2} is ≤40 mm Hg and their P_{CO_2} is ≥ 46 mm Hg. The lower P_{O_2} in the cells sets up a gradient favoring diffusion of oxygen from the plasma into the cells. Conversely, higher P_{CO_2} in the cells than in the capillary blood allows carbon dioxide to diffuse out of the cells into the capillary. Just as at the alveoli, exchange is rapid and goes to equilibrium. Blood in the systemic venous circulation has an average P_{O_2} of 40 mm Hg and a P_{CO_2} of 46 mm Hg. Gas exchange at the tissue level may be affected slightly by tissue edema, but it usually proceeds without interference.

continued from page 490

Edna has been admitted to the hospital for tests related to her COPD. One of the tests is a hematocrit, an indicator of the number of red blood cells in her blood. The results of this test show that Edna has higher-than-normal numbers of red blood cells.

Question 4: Why does Edna have an increased hematocrit? (Hint: Because of Edna's COPD, her arterial P_{O_2} is low.)

GAS TRANSPORT IN THE BLOOD

Now that we have examined the role of the respiratory system in gas exchange, let us turn our attention to the transport of oxygen and carbon dioxide in the blood. The gases are transported either dissolved in the plasma or within the red blood cells.

Hemoglobin Transports Most Oxygen to the Tissues

The presence of adequate amounts of hemoglobin in the blood is essential for normal gas transport. Oxygen in the blood is transported two ways: dissolved in the plasma and bound to hemoglobin (Hb). This fact can be summarized in the following statement:

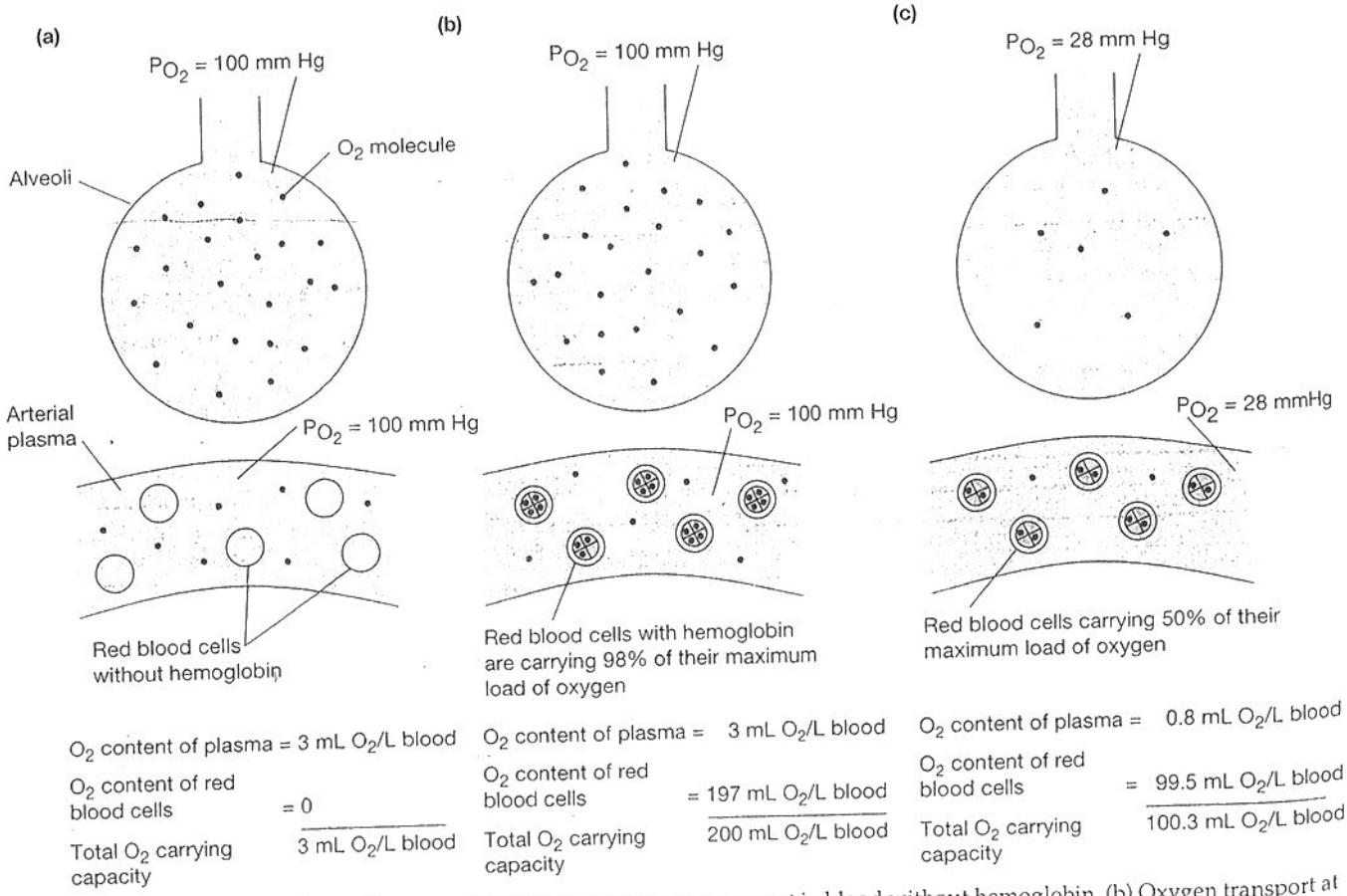
> Total blood oxygen content = amount dissolved in plasma + amount bound to hemoglobin

Because of the low solubility of oxygen in aqueous solutions, only 3 mL of O_2 will dissolve in the plasma fraction of 1 liter of arterial blood (Fig. 17-20 ■). Thus, with a typical cardiac output of 5 L blood/min, about 15 mL of dissolved oxygen reaches the systemic tissues each minute. This amount cannot begin to meet the needs of the tissues, however. Oxygen consumption at rest is about 250 mL/min, and that figure increases dramatically with exercise. Thus, the body is heavily dependent on the oxygen carried by hemoglobin.

More than 98% of the oxygen in a given volume of blood is transported inside the red blood cells, where it is bound to hemoglobin. At normal hemoglobin levels, oxygen in the red blood cells amounts to about 197 mL/L blood. When the oxygen bound to hemoglobin is added to that dissolved in the plasma, the total oxygen content of whole blood jumps from 3 mL/L to 200 mL/L. If the cardiac output remains 5 L/min, oxygen delivery jumps to almost 1000 mL/min, nearly four times the oxygen consumption of the tissues at rest.

The amount of oxygen that binds to hemoglobin depends on two factors: (1) the P_{O_2} of the plasma surrounding the red blood cells and (2) the number of potential oxygen-binding sites available within the red blood cells. The P_{O_2} of the plasma is the primary factor that determines how many hemoglobin binding sites are occupied by oxygen. Arterial plasma P_{O_2} is established by the composition of the inspired air, the alveolar ventilation rate, and the efficiency of gas exchange between lung and blood, as you learned in previous sections.

The number of potential binding sites depends on the total number of hemoglobin molecules in the blood. Clinically, this number can be estimated either by count-



■ **Figure 17-20 Hemoglobin and oxygen transport** (a) Oxygen transport in blood without hemoglobin. (b) Oxygen transport at normal P_{O_2} in blood with hemoglobin. (c) Oxygen transport at reduced P_{O_2} in blood with hemoglobin.

ing the red blood cells and quantifying the amount of hemoglobin per red blood cell (*mean corpuscular hemoglobin*) or by simply determining the blood hemoglobin content (g Hb/dL whole blood). Any pathology that decreases the amount of hemoglobin in the cells or the number of red blood cells will adversely affect the blood's oxygen-transporting capacity.

People who have lost large amounts of blood need to replace hemoglobin for oxygen transport. The ideal replacement for blood loss is a blood transfusion, but in emergencies this is not always possible. Saline infusions can replace lost blood volume, but saline, like plasma, cannot transport sufficient quantities of oxygen and carbon dioxide. Researchers are currently trying to find artificial oxygen carriers to replace hemoglobin. In times of large-scale disasters, these hemoglobin substitutes will eliminate the need to establish blood type before giving transfusions for blood loss.

Each Hemoglobin Molecule Binds Up to Four Oxygen Molecules

Less than 2% of the oxygen in arterial blood is carried dissolved in the plasma. The remaining oxygen is bound to hemoglobin molecules inside circulating red blood cells. A hemoglobin molecule is composed of four globin subunits, each centered around a heme group whose central iron atom binds reversibly with an oxygen molecule (∞ p. 462). The iron-oxygen interaction is a weak bond, and the two molecules can be easily separated without altering either the hemoglobin or the oxygen. Because there are four iron atoms in a hemoglobin molecule, each hemoglobin molecule has the potential to bind four oxygen molecules. Hemoglobin (Hb) bound to oxygen is known as *oxyhemoglobin*, abbreviated HbO_2. (It would be more accurate to show the actual number of oxygen molecules carried on each heme molecule: $Hb(O_2)_{1-4}$, but, because the number bound varies from molecule to molecule, we will use the simpler abbreviation.) The reversible reaction of oxygen binding to hemoglobin at the lungs can be summarized as

$$Hb + O_2 \rightleftharpoons HbO_2$$

The amount of oxygen bound to hemoglobin depends primarily on the P_{O_2} of the surrounding plasma (Fig. 17-20 ■). Dissolved O_2 in the plasma diffuses into the red blood cell, where it binds to hemoglobin. Binding effectively removes dissolved O_2 from the plasma so that more oxygen can diffuse in from the alveoli. The transfer of oxygen from air to plasma into red blood cells and onto hemoglobin occurs so rapidly that blood leaving the alveoli normally picks up as much oxygen as the P_{O_2} of the plasma and number of red blood cells permit.

It is possible to calculate what percentage of potential oxygen-binding sites are actually carrying O_2 by knowing how much oxygen is actually bound to hemoglobin and the maximum amount of oxygen that it can bind. The amount of oxygen bound to hemoglobin at any given P_{O_2} is expressed as a percentage:

(Actual amount of O_2 bound / maximum that could be bound) × 100 = percent saturation of hemoglobin

The **percent saturation of hemoglobin** refers to the percent of available binding sites that are bound to oxygen. If all binding sites of all hemoglobin molecules are occupied by oxygen molecules, the blood is 100% oxygenated, or *saturated* with oxygen. If half the available binding sites are carrying oxygen, the hemoglobin is 50% saturated, and so on.

The relationship between the plasma P_{O_2} and oxygen-hemoglobin binding can be explained with the following analogy. The hemoglobin molecules carrying oxygen are like students moving books from an old library to a new one. Each student (a hemoglobin molecule) can carry a maximum of four books (100% saturation). The librarian in charge controls how many books (O_2 molecules) each student will carry, just as P_{O_2} determines the amount of oxygen that binds to hemoglobin. At the same time, the total number of books being carried depends on the number of available students, just as the amount of oxygen delivered to the tissues depends on the number of available hemoglobin molecules. For example, if there are 100 students and the librarian gives each of them four books, then 400 books will be carried to the new library. If the librarian has only three books for each (decreased P_{O_2}), then only 300 books will go to the new library, even though each student can carry four

Blood Substitutes Physiologists have been attempting to find a substitute for blood ever since 1878, when an intrepid scientist named T. Gaillard Thomas transfused whole milk in place of blood. Although milk seems an unlikely replacement for blood, it has two important properties: proteins to provide colloid osmotic pressure and molecules (emulsified lipids) capable of binding to oxygen. In the development of hemoglobin substitutes, oxygen transport is the most difficult property to mimic. A hemoglobin solution would seem to be the obvious answer, but hemoglobin that is not compartmentalized in red blood cells behaves differently than hemoglobin that is. First, the quaternary structure changes so that the four-subunit (tetramer) form is in equilibrium with a smaller two-subunit (dimer) form. The smaller version of hemoglobin is easily excreted by the kidneys, so almost half a dose of hemoglobin solution disappears from the blood in 2–4 hours. Second, hemoglobin found outside the red blood cells does not release oxygen as easily in peripheral tissues. Investigators are making progress by polymerizing hemoglobin into larger, more stable molecules and loading these hemoglobin polymers into phospholipid liposomes (∞ p. 109). By encapsulating hemoglobin into these artificial red blood cells, researchers hope to extend the life span of the blood substitute and make its properties approach those of real blood.

(decreased percent saturation of hemoglobin). If the librarian is handing out four books per student but only 50 students show up (fewer hemoglobin molecules), then only 200 books will get to the new library, even though the students will be carrying the maximum number of books they can carry.

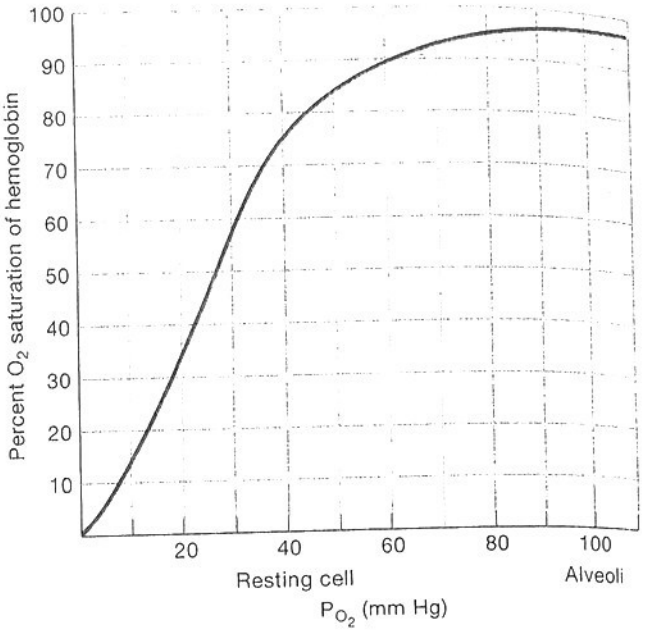
Once arterial blood reaches the tissues, the exchange process that took place in the lungs reverses. As dissolved oxygen diffuses out of the plasma into the cells, the resultant drop in plasma P_{O_2} disturbs the equilibrium of the oxygen-hemoglobin binding reaction by removing oxygen from the left side of the equation. The reaction shifts to the left according to the Law of Mass Action (∞ p. 85), and the hemoglobin molecules release their oxygen stores. Like oxygen loading at the lungs, this process takes place very rapidly and goes to equilibrium. The amount of oxygen unloaded from hemoglobin at a cell is determined primarily by the P_{O_2} of the cell, which in turn reflects its metabolic activity.

The Oxygen-Hemoglobin Dissociation Curve Shows the Relationship between P_{O_2} and Hemoglobin Binding of Oxygen

The physical relationship between P_{O_2} and oxygen binding to hemoglobin can be studied *in vitro* in the laboratory. Samples of hemoglobin are exposed to varying P_{O_2} levels, and the amount of oxygen that binds is determined quantitatively. The results of these *in vitro* binding studies are graphically represented by **oxyhemoglobin dissociation curves,** such as the one shown in Figure 17-21 ■. The shape of the oxyhemoglobin dissociation curve reflects the properties of the hemoglobin molecule and its affinity for oxygen. If you look at the curve, you will see that at the normal alveolar and arterial P_{O_2} of 100 mm Hg, 98% of the hemoglobin is bound to oxygen. Because the curve is nearly flat at higher P_{O_2} levels (i.e., slope approaches zero), large changes in P_{O_2} will cause only minor changes in the percent saturation. Although hemoglobin is about 98% saturated at a P_{O_2} of 100 mm Hg, 100% saturation does not occur until the P_{O_2} reaches nearly 250 mm Hg, a partial pressure far higher than anything we encounter in everyday life.

The flattened portion of the dissociation curve at higher dissolved oxygen levels also means that P_{O_2} at the alveoli can drop significantly without having a major effect on hemoglobin saturation. As long as P_{O_2} in the pulmonary capillaries stays above 60 mm Hg, hemoglobin will be more than 90% saturated and near-normal levels of oxygen transport will be maintained.

Once the P_{O_2} drops below 60 mm Hg, the dissociation curve develops a steeper slope. The steep slope means that a small decrease in P_{O_2} causes a relatively large amount of oxygen to be released by hemoglobin. For example, if P_{O_2} falls from 100 mm Hg to 60 mm Hg, the percent saturation of hemoglobin goes from 98% saturation to about 88% saturation, a decrease of 10%. This is equivalent to a saturation change of 2.5% for each 10 mm Hg change. If P_{O_2} falls further, from 60 to 40 mm Hg, the percent saturation goes from 88% to 75%, a decrease of 6.5% for each 10 mm Hg. Notice that the slope of the curve is greater in the 40–60 mm Hg range than in the 60–100 mm Hg range. If P_{O_2} decreases from 40 mm Hg to 20 mm Hg, the slope of the curve becomes even steeper. Hemoglobin saturation declines from 75% to 35%, a change of 20% for each 10 mm Hg.



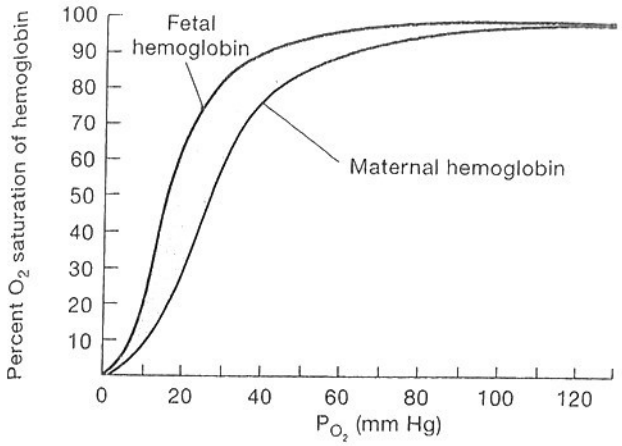
Graph question:
(a) When the P_{O_2} is 20 mm Hg, what is the percent O_2 saturation of hemoglobin?
(b) At what P_{O_2} is hemogoblin 50% saturated with O_2?

■ **Figure 17-21 Oxygen-hemoglobin dissociation curve**

Note that at a P_{O_2} of 40 mm Hg, the partial pressure of resting cells, hemoglobin is still 75% saturated and has released only one-fourth of the oxygen it is capable of carrying. This is another example of the built-in reserve capacity of the body. The 75% of the oxygen that remains bound serves as a reservoir that cells can draw upon to meet their needs as metabolism increases. If metabolically active tissues use additional oxygen and their P_{O_2} decreases, additional oxygen is released by hemoglobin. At a P_{O_2} of 20 mm Hg, an average value for exercising muscle, hemoglobin saturation drops to about 35%. With a 20 mm Hg decrease in P_{O_2} (40 mm Hg to 20 mm Hg), hemoglobin releases an additional 40% of the oxygen it is capable of carrying.

Temperature, pH, and Metabolites Affect Oxygen-Hemoglobin Binding

Although P_{O_2} is the primary factor influencing oxygen transport by hemoglobin, any factor that changes the configuration of the hemoglobin protein may affect its



Graph question:
- Because of incomplete gas exchange across the thick membranes of the placenta, hemoglobin in fetal blood leaving the placenta is 80% saturated with oxygen. What is the P_{O_2} of that placental blood?
- Blood in the vena cava of the fetus has a P_{O_2} around 10 mm Hg. What is the percent O_2 saturation of maternal hemoglobin at the same P_{O_2}?

Figure 17-22 Differences in the oxygen-binding properties of maternal and fetal hemoglobin

ability to bind oxygen. In humans, physiological changes in pH, P_{CO_2}, and temperature of the blood all affect the oxygen-binding capability of hemoglobin.

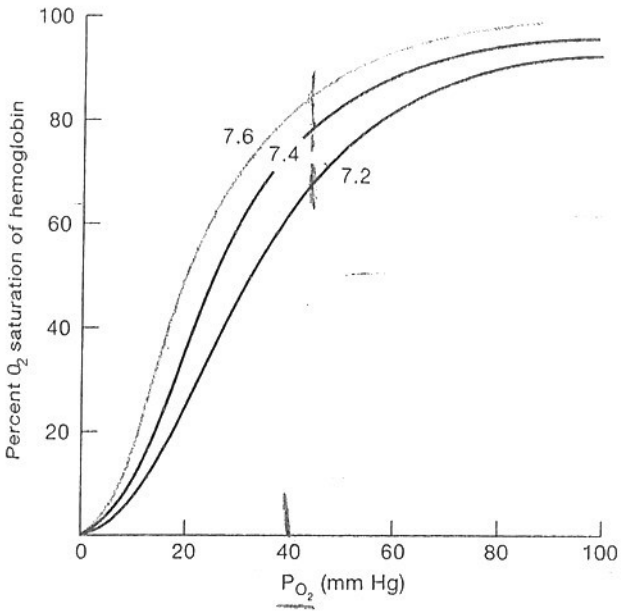
Changes in binding affinity are reflected by changes in the shape of the oxygen-hemoglobin dissociation curve. For example, fetal hemoglobin has a unique protein chain for two of its subunits, giving it a different binding affinity for oxygen that is more appropriate for binding oxygen in the low-oxygen environment of the placenta. The different binding affinity is reflected by the different shape of the fetal oxygen-hemoglobin dissociation curve (Fig. 17-22 ■).

Physiological changes in temperature, P_{CO_2}, or H^+ concentration also affect the oxygen-binding capacity of hemoglobin. Increases in temperature, P_{CO_2}, or H^+ concentration decrease the affinity of hemoglobin molecules for oxygen and shift the oxygen-hemoglobin dissociation curve to the right (Fig. 17-23 ■). Decreases in those parameters increase binding affinity and shift the curve to the left. Notice, however, that the changes are much more pronounced in the steep part of the curve. This means that oxygen binding at the lungs will not be greatly affected by temperature, pH, and P_{CO_2}, but oxygen delivery at the tissues will be significantly altered.

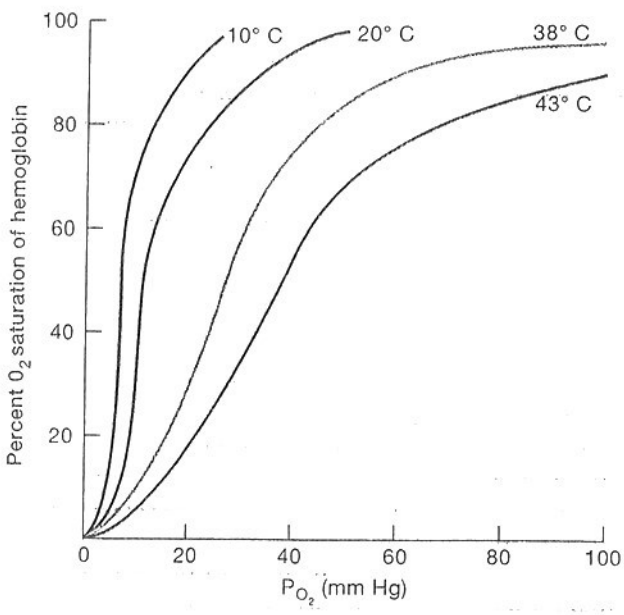
Let us examine one specific example, the shift that takes place when pH goes from 7.4 (normal) to 7.2 (more

Bohr effect.

(a) Effect of pH



(b) Effect of temperature



Graph question: At a P_{O_2} of 20 mm Hg, how much more oxygen is released at an exercising muscle cell whose pH is 7.2 than by a cell with a pH of 7.4? What happens to oxygen release when the exercising muscle cell warms up?

Figure 17-23 Physical factors such as pH and temperature affect oxygen binding to hemoglobin.

acidic). A pH of 7.2 is lower than normal for the body (normal range 7.38–7.42) but is compatible with life. At a P_{O_2} of 40 mm Hg and pH of 7.2, hemoglobin molecules release 15% more oxygen than they do at a pH of 7.4. Lesser changes in pH also shift the curve to the right but not to the same extent. Anaerobic exercise is one example of a situation in which body pH decreases. Anaerobic metabolism in exercising muscle fibers produces lactic acid, which in turn releases H^+ into the cytoplasm and extracellular fluid. As pH falls owing to increasing H^+ concentrations, the affinity of hemoglobin for oxygen decreases and the oxygen-hemoglobin dissociation curve shifts to the right. This shift shows that more oxygen is being released at the tissues as the blood becomes more acidic (pH decreases). A shift in the hemoglobin saturation curve that results from a change in pH is called the **Bohr effect.**

One other factor that affects oxygen-hemoglobin binding is **2,3-diphosphoglycerate (2,3-DPG),** a compound made from an intermediate of the glycolysis pathway. By mechanisms not well understood, **chronic hypoxia** (extended periods of low oxygen) triggers an increase in 2,3-DPG production in red blood cells. Like H^+ and CO_2, 2,3-DPG lowers the binding affinity of hemoglobin and causes the dissociation curve to shift to the right. Ascent to high altitude and anemia are two situations that trigger increased 2,3-DPG production.

Figure 17-24 ■ summarizes the factors that influence oxygen transport in the blood.

High Altitude In 1981 a group of 20 physiologists, physicians, and climbers, supported by 42 Sherpa assistants, formed the American Medical Research Expedition to Mt. Everest. The purpose of the expedition was to study human physiology at extreme altitudes, starting with the base camp at 5400 M and continuing on to the summit at 8848 M. Starting with the work of these scientists and adding studies of people who reside at high altitudes, we now have a good picture of the physiology of high-altitude acclimatization. The body's immediate homeostatic response to the hypoxia of high altitude is hyperventilation. Hyperventilation enhances alveolar ventilation, raising the alveolar and arterial P_{O_2}. However, it also causes lower plasma P_{CO_2} and increases pH, causing a state of alkalosis. The pH change in turn increases the affinity of hemoglobin for oxygen, seen on the oxygen-hemoglobin saturation curve as a left shift (Fig. 17-23■). Increased oxygen-hemoglobin binding might seem counterproductive, but in reality it allows the hemoglobin to pick up more oxygen at the lower P_{O_2} of the lungs. After an acclimatization period of hours to days, the production of 2,3-DPG by red blood cells increases, shifting the oxygen-hemoglobin saturation curve back to the right and offsetting the effects of the respiratory alkalosis. Thus, at altitudes up to 6300 M, the hemoglobin saturation curve is essentially normal.

The hypoxia of high altitude also triggers the release of the hormone erythropoietin from the kidney and liver. This hormone stimulates red blood cell production. Even though the P_{O_2} of the blood remains low, the total oxygen-carrying capacity is thus increased. In some individuals, the increased hematocrit (polycythemia) that results from living at high altitudes may be maladaptive. Hematocrits greater than 45% increase the viscosity of the blood enough to impede blood flow to the brain and peripheral tissues. The decrease in blood flow counteracts the increased oxygen-carrying capacity of the blood. Altitude-induced polycythemia is considered to be the cause of the condition known as chronic mountain sickness, with symptoms of headache, fatigue, mental status changes, and poor exercise tolerance. People who exhibit symptoms of elevated hematocrits may be helped by phlebotomy (blood withdrawal). In Leadville, Colorado (3100 M), the 60 people who suffer from chronic mountain sickness are the main donors to the local blood bank!

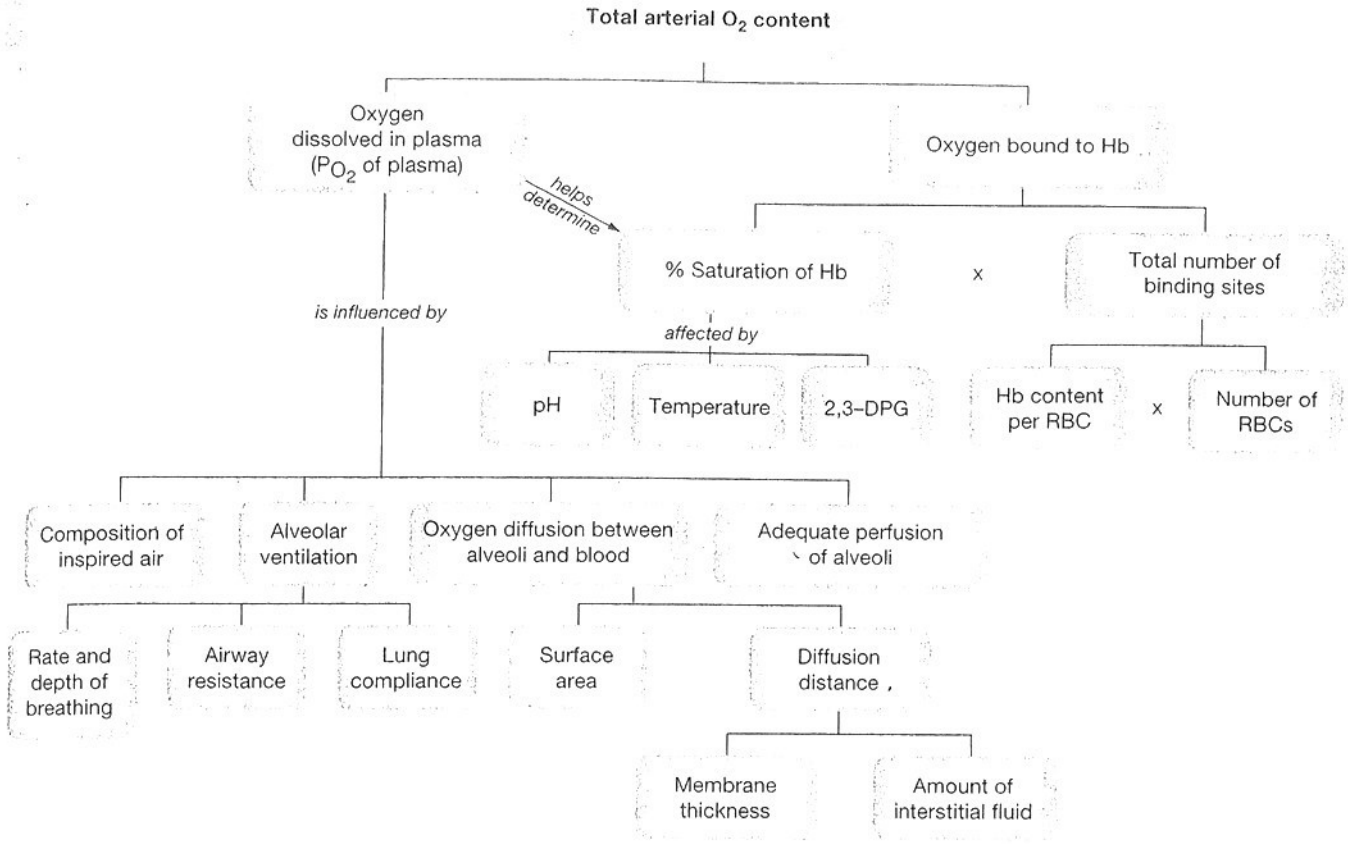
✓ A muscle that is actively contracting may have an intracellular P_{O_2} of 25 mm Hg. What happens to oxygen binding to hemoglobin at this P_{O_2}? What is the P_{O_2} of the venous blood leaving the active muscle?

Carbon Dioxide Is Transported Dissolved in Plasma, Bound to Hemoglobin, and as Bicarbonate Ions

Gas transport in the blood is a two-way process. Carbon dioxide produced as a by-product of cellular respiration is picked up in the tissues and conveyed to the lungs. Removal of carbon dioxide from the body is an essential part of external respiration. Elevated P_{CO_2} (hypercapnia) leads to increased plasma H^+ concentrations and the pH disturbance known as *acidosis* (see Chapter 19). Abnormally high P_{CO_2} levels can also depress the function of the central nervous system, causing confusion, coma, or even death.

Although carbon dioxide is more soluble in body fluids than is oxygen, the cells produce more carbon dioxide than can be carried dissolved in the plasma. Venous plasma with a P_{CO_2} of 46 mm Hg contains about 0.3 mL CO_2/100 mL blood. This represents only about 7% of the carbon dioxide carried by venous blood. The remaining 93% of carbon dioxide that enters the systemic capillaries diffuses into the red blood cells. There, it either binds directly to hemoglobin ($Hb \cdot CO_2$) or is converted to bicarbonate ion, as explained below. Figure 17-25 ■ summarizes carbon dioxide transport in the blood.

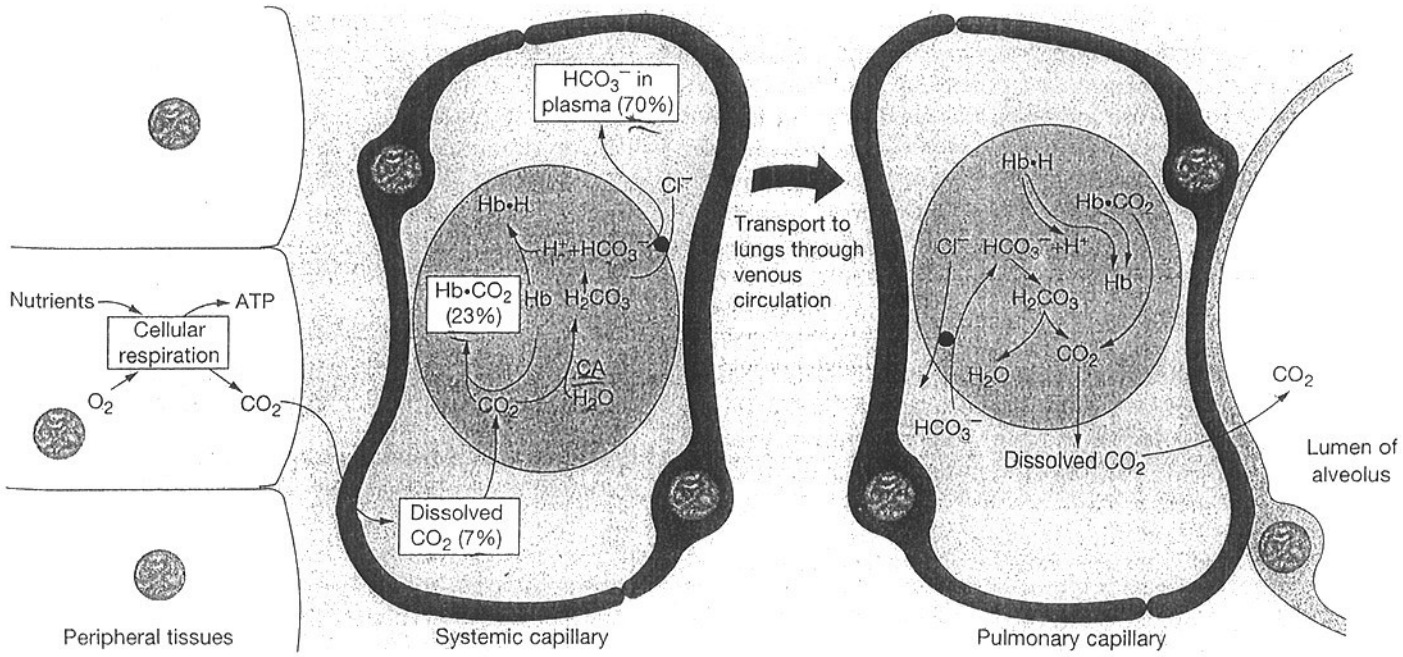
About 70% of the carbon dioxide molecules that enter the circulation are transported to the lungs as bicarbonate ions (HCO_3^-) dissolved in the plasma. The conversion of carbon dioxide to bicarbonate serves two purposes: (1) It provides an additional means by which carbon dioxide can be transported from cells to lungs, and (2) the bicarbonate is available to act as a buffer for metabolic acids (☞ p. 26), thereby helping stabilize the body's pH. Rapid production of bicarbonate from car-



■ Figure 17-24 Factors contributing to the total oxygen content of arterial blood

bon dioxide depends on the presence of **carbonic anhydrase**, an enzyme found concentrated in red blood cells.

Dissolved carbon dioxide in plasma diffuses into the red blood cells, where it reacts with water in the presence of carbonic anhydrase to form carbonic acid. Carbonic acid then dissociates into a hydrogen ion and a bicarbonate ion. The equation for the reaction is written as follows:



■ Figure 17-25 Carbon dioxide transport

$$CO_2 + H_2O \xrightleftharpoons{\text{carbonic anhydrase}} \underbrace{H_2CO_3}_{\text{carbonic acid}} \rightleftharpoons H^+ + HCO_3^-$$

Because of the dissociation of carbonic acid, we may ignore the intermediate step and summarize the reaction as:

$$CO_2 + H_2O \xrightleftharpoons{\text{carbonic anhydrase}} H^+ + HCO_3^-$$

This reaction is reversible. The rate in either direction depends on the relative concentrations of the substrates and obeys the Law of Mass Action. When carbon dioxide moves into the red blood cells, the reaction goes to the right, producing more acid and bicarbonate until a new equilibrium state is reached (Fig. 17-25 ■). (Water is always in excess in the body, so water concentration plays no role in the dynamic equilibrium of this reaction.) In order to keep the reaction going, the products of the reaction, H^+ and HCO_3^-, must be removed from the cytoplasm of the red blood cell.

Removal of free H^+ and HCO_3^- from the red blood cells is accomplished in two separate steps. Hemoglobin is a buffer and binds hydrogen ions (Hb • H). This binding keeps the intracellular concentration of free H^+ low. At the same time, bicarbonate ions produced from carbon dioxide move out of the red blood cell via an antiport transport protein (∞ p. 122). This transport process, known as the **chloride shift,** exchanges one HCO_3^- for one Cl^-. The one-for-one exchange maintains electrical neutrality so that the cell's membrane potential is not affected. As H^+ and HCO_3^- levels in the red blood cell fall, carbon dioxide continues to form carbonic acid. The resultant drop in plasma P_{CO_2} allows more carbon dioxide to diffuse out of cells and into the plasma.

The buffering of H^+ by hemoglobin is an important step that prevents large changes in the body's pH. If blood P_{CO_2} is elevated much above normal, the hemoglobin buffer is not adequate to soak up all of the H^+ produced from the reaction of carbon dioxide and water. In those cases, the excess H^+ remains in the plasma, causing the condition known as **respiratory acidosis.** Further information on the role of the respiratory system in maintaining pH homeostasis is found in Chapter 19.

Although most carbon dioxide that enters the red blood cells is converted to bicarbonate ions, about 23% of the carbon dioxide molecules in venous blood bind directly to hemoglobin. When oxygen leaves its binding sites on the hemoglobin molecule, carbon dioxide binds with the free hemoglobin at exposed amino groups (NH_2), forming **carbaminohemoglobin.** This reaction can be summarized as

$$CO_2 + Hb \rightleftharpoons Hb \cdot CO_2 \text{ (carbaminohemoglobin)}$$

The formation of carbaminohemoglobin is facilitated by the presence of H^+ produced from carbon dioxide because decreased pH in red blood cells decreases the binding affinity of hemoglobin for oxygen.

When venous blood reaches the lungs, the processes that took place in the systemic capillaries proceed in reverse (Fig. 17-25 ■). The P_{CO_2} of the alveoli is lower than that in the venous blood. Carbon dioxide diffuses out of the plasma into the alveoli, and the plasma P_{CO_2} begins to decline. The decrease in plasma P_{CO_2} allows dissolved carbon dioxide to diffuse out of the red blood cells. As carbon dioxide levels in the red blood cells decrease, the equilibrium of the CO_2-bicarbonate reaction is disturbed. Removal of carbon dioxide causes the reaction to proceed from right to left. Hydrogen ions leave the hemoglobin molecules. The chloride shift reverses: Chloride ions return to the plasma in exchange for bicarbonate ions that move back into the red blood cells. The bicarbonate and H^+ re-form into carbonic acid that is converted into water and carbon dioxide. The carbon dioxide is then free to diffuse out of the red blood cell and into the alveoli.

Summary of Gas Transport

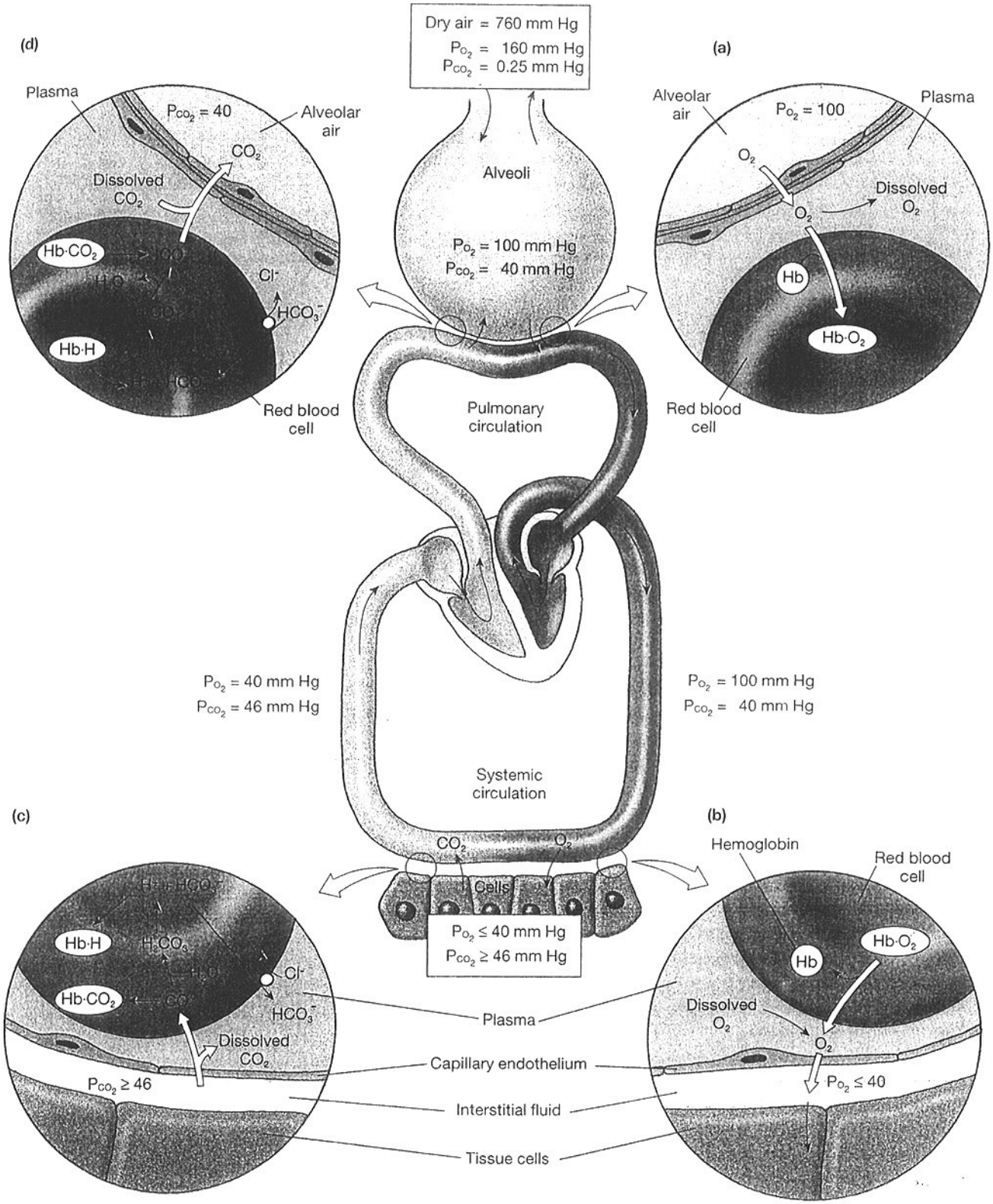
Figure 17-26 ■ summarizes the transport of carbon dioxide and oxygen in the blood. Oxygen diffuses down its pressure gradient from the alveoli into the plasma and, from there, into the red blood cells. Hemoglobin binds oxygen molecules, increasing the amount of oxygen that can be transported to the cells. At the cells, the process reverses. P_{O_2} in the cells is lower than that in the arterial blood, so O_2 diffuses from the plasma to the cells. The drop in plasma P_{O_2} causes hemoglobin to release oxygen, giving up additional oxygen to enter the cells. Carbon dioxide from aerobic metabolism simultaneously enters the blood, dissolving in the plasma. From there, it enters the red blood cells, where most is converted to bicarbonate ion and H^+. The bicarbonate is returned to the plasma in exchange for a chloride ion, while the H^+ binds to hemoglobin. A small fraction of the carbon dioxide also binds directly to hemoglobin. At the lungs, the process reverses as carbon dioxide diffuses out into the alveoli.

In order to understand fully how the respiratory system coordinates delivery of oxygen to the lungs with its transport in the circulation, we will now consider the central nervous system control of ventilation.

✓ How would an obstruction of the airways affect the body's pH?

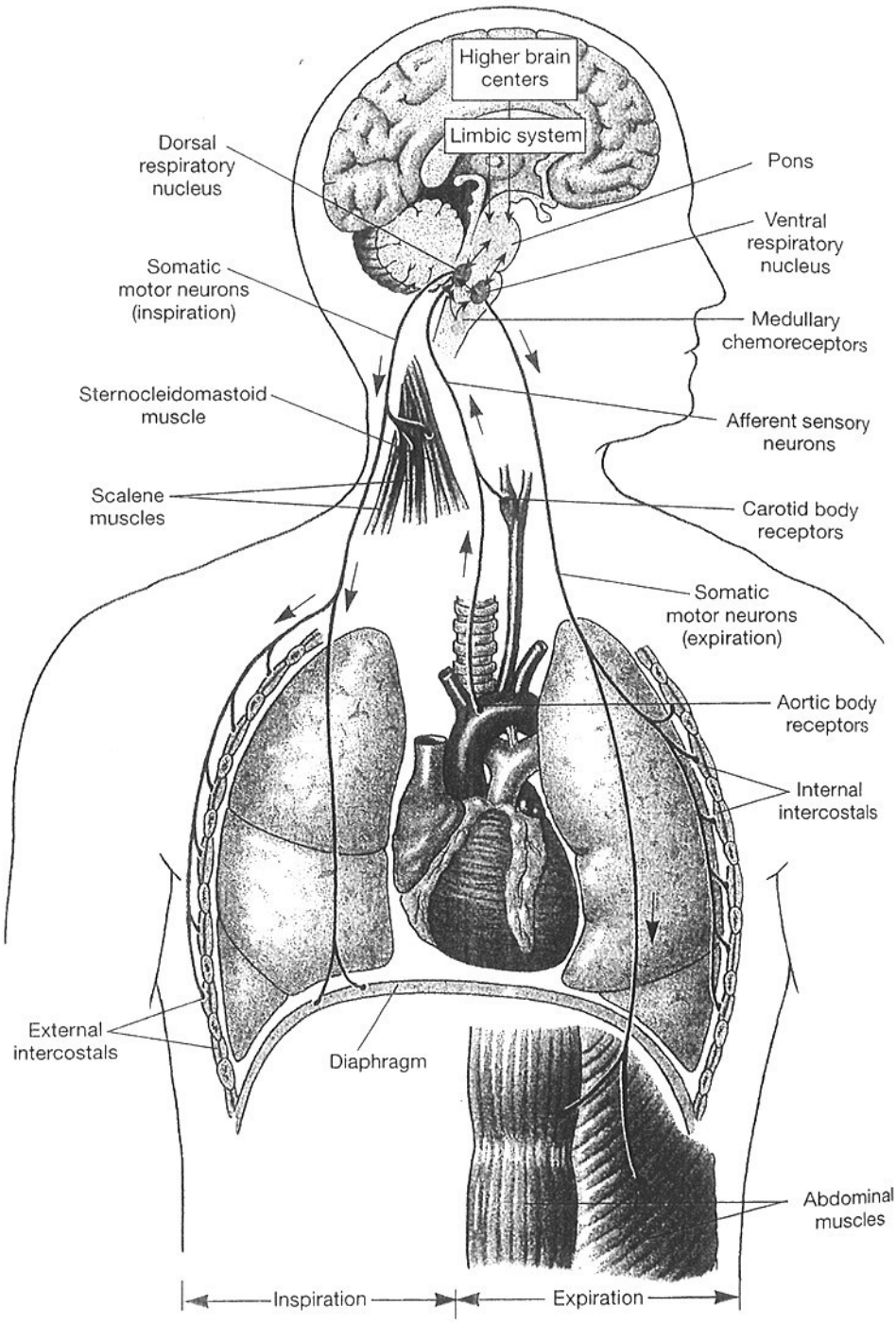
REGULATION OF VENTILATION

Breathing is a rhythmic process that occurs without conscious thought. In that respect, it resembles the rhythmic beating of the heart. However, skeletal muscles, unlike autorhythmic cardiac muscles, are not able to contract spontaneously. Instead, skeletal muscle contraction must be initiated by somatic motor neurons, which in turn are controlled by the central nervous system. In the respiratory system, contraction of the diaphragm and intercostals is initiated by control neu-



■ **Figure 17-26 Summary of gas transport** (a) Oxygen exchange between alveoli and blood. (b) Oxygen exchange from blood to cells. (c) Carbon dioxide exchange from cells to blood. (d) Carbon dioxide exchange from blood to alveoli.

rons in the medulla oblongata (Fig. 17-27 ■). These control neurons take the form of a network, or **central pattern generator,** that has intrinsic rhythmic activity (∞ p. 374). It has been postulated that the rhythmic activity arises from a pacemaker neuron, a single neuron with an unstable membrane potential that periodically reaches threshold. However, to date, no pacemaker has been definitively identified, and scientists now believe that the rhythmicity arises within a network of neurons with unstable membrane potentials.



■ **Figure 17-27 Reflex control of ventilation** Control centers in the brain stem regulate activity in somatic motor neurons leading to the muscles that control ventilation. Chemoreceptors in the brain stem and arteries monitor blood gases and H^+ concentrations and influence ventilation.

Direct study of the brain centers controlling ventilation is difficult because of the complexity of the neuronal network and its anatomical location. Consequently, some of our understanding of the control of ventilation has come from observing patients with brain damage. Other information has come from experiments in which the neural connections between major parts of the brain stem were severed. In order to better understand the complex relationships between the parts of the brain that control ventilation, let us review some of these clinical and experimental findings and see what deductions researchers made about the control of rhythmic breathing.

1. *Observation.* If the brain stem is severed below the medulla, all respiratory movement ceases. If the brain stem is cut above the level of the pons, ventilation is normal.

   Hypothesis 1. The control centers for ventilation lie in the medulla or the pons or both.

2. *Observation.* If the medulla is completely separated from the pons and higher brain centers, ventilation becomes gasping and irregular in depth, but the respiratory rhythm remains.

Hypothesis 2. The primary control center for ventilation lies in the medulla.

Hypothesis 3. The medulla contains neurons that set the rhythm of ventilation.

Hypothesis 4. The normal smooth pattern of ventilation depends on communication between neurons in the pons and the medulla.

From these observations and hypotheses, the following model for the control of ventilation has been proposed. Some parts of the model are well supported with experimental evidence; other aspects are still under investigation. The model states that:

1. Respiratory neurons in the medulla control inspiration and expiration.
2. Neurons in the pons influence the rate and depth of ventilation.
3. The rhythmic pattern of breathing arises from a network of spontaneously discharging neurons.
4. Ventilation is subject to modulation by various chemical factors and by higher brain centers. (The experimental evidence for this point will be discussed later.)

Respiratory Neurons in the Medulla Control Inspiration and Expiration

The classic descriptions of the brain's respiratory control of ventilation divided groups of neurons into various control centers. The most recent descriptions have become less specific about assigning function to particular centers and now simply refer to the network of neurons in the brain stem as the central pattern generator. The central pattern generator is unique in that it functions automatically throughout a person's life, and yet it can be controlled voluntarily, up to a point. Complicated synaptic interactions between neurons in the network create the rhythmic cycles of inspiration and expiration, influenced continuously by sensory input from receptors for CO_2, O_2, and H^+. Ventilation pattern depends in large part on the levels of those three substances in the blood.

Although there is still much to be learned about the central pattern generator, we do know that respiratory neurons are found concentrated in two nuclei in the medulla oblongata. The **dorsal respiratory group** (DRG) contains mostly **inspiratory neurons** (I neurons) that control the external intercostal muscles and the diaphragm (Fig. 17-27 ■). The **ventral respiratory group** (VRG) contains neurons that control the muscles used for active expiration (E neurons) and for greater-than-normal inspiration (I+ neurons), such as occurs during vigorous exercise.

During quiet respiration, the inspiratory neurons of the dorsal respiratory group gradually increase stimulation of the inspiratory muscles for 2 seconds. This increase is sometimes called ramping because of the shape of the graph of inspiratory neuron activity (Fig. 17-28 ■). A few inspiratory neurons fire to begin the ramp. The firing of these neurons recruits other inspiratory neurons to fire in an apparent positive feedback loop. As more neurons fire, more skeletal muscle fibers are recruited. The rib cage expands smoothly as the diaphragm contracts. At the end of 2 seconds, the inspiratory neurons abruptly stop firing and the respiratory muscles relax. Over the next 3 seconds, passive expiration occurs because of elastic recoil of the inspiratory muscles and the elastic lung tissue. However, there is some motor neuron activity during passive expiration, suggesting that perhaps muscles in the upper airways contract to slow the flow of air out of the respiratory system.

The expiratory neurons and I+ neurons of the ventral respiratory group remain mostly inactive during quiet respiration. They function primarily during forced breathing, when inspiratory movements are exaggerated, or during active expiration. In forced breathing, the increased activity of dorsal respiratory group inspiratory neurons in some way activates the I+ neurons of the ventral respiratory group. These I+ neurons in turn stimulate accessory inspiratory muscles such as the sternocleidomastoid. Contraction of the accessory inspiratory muscles enhances expansion of the thorax by raising the sternum and upper ribs.

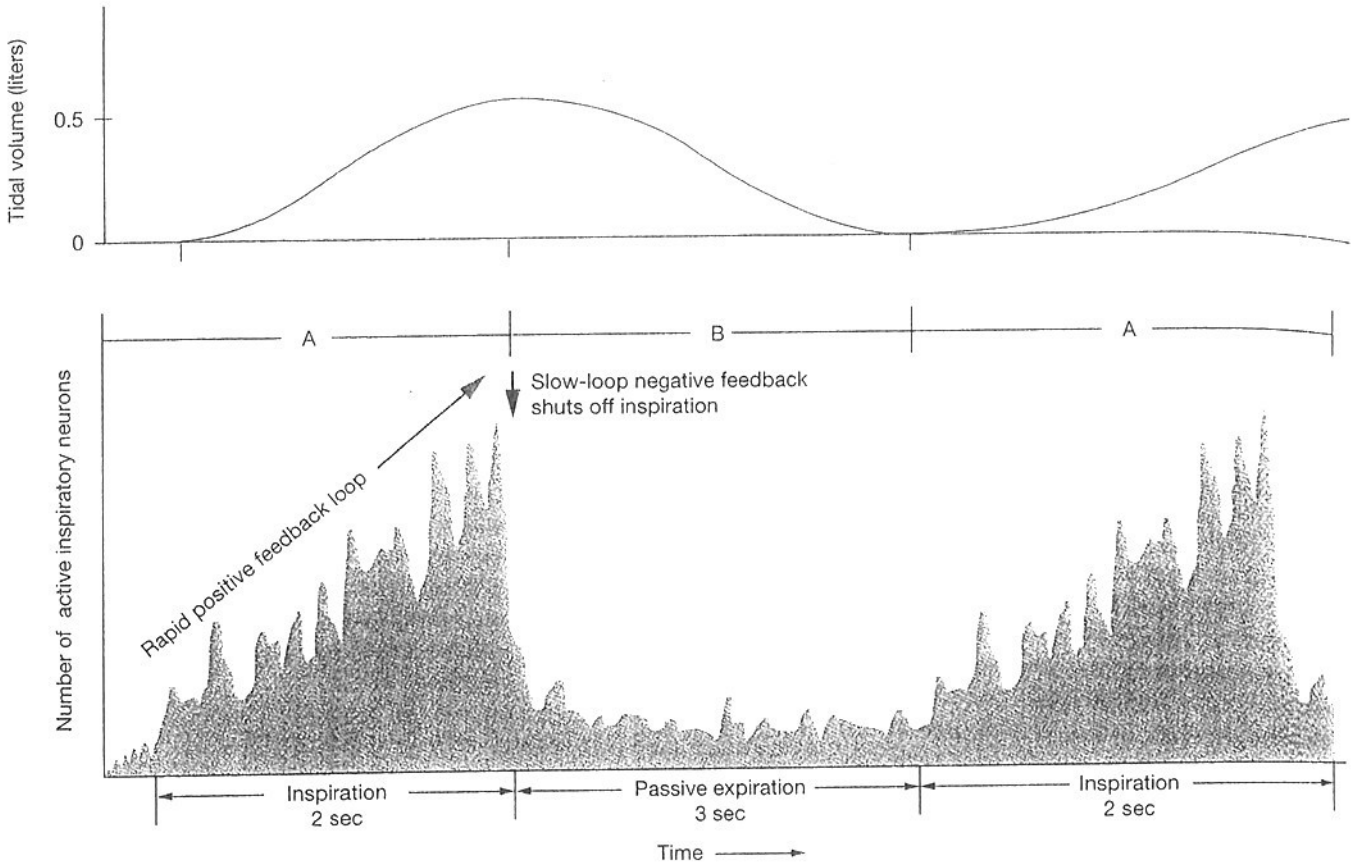
In active expiration, expiratory (E) neurons from the ventral respiratory group activate the internal intercostal and abdominal muscles. There seems to be reciprocal inhibition between the inspiratory and expiratory neurons. The I neurons inhibit the E neurons during inspiration, whereas the E neurons inhibit I neurons during active expiration.

The cycling of respiratory activity is controlled through the neurons of the brain stem. However, activity in these neurons is subject to continuous modulation as gas levels in the blood change.

Carbon Dioxide, Oxygen, and pH Influence Ventilation

Sensory input from two sets of chemoreceptors modifies the rhythmicity of the central pattern generator, triggering reflex changes in ventilation. Carbon dioxide is the primary stimulus for changes in ventilation, with oxygen and plasma pH playing lesser roles. The chemoreceptors for oxygen and carbon dioxide are strategically associated with the arterial circulation. If too little oxygen is present in the arterial blood destined for the tissues, the rate and depth of breathing increase. Or, if the rate of carbon dioxide production by the cells exceeds the rate of carbon dioxide removal by the lungs, ventilation is intensified to match carbon dioxide removal to production. These homeostatic reflexes operate constantly, keeping arterial P_{O_2} and P_{CO_2} within a narrow range.

Peripheral chemoreceptors located in the carotid and aortic bodies sense changes in the oxygen concentration and pH of the plasma (Fig. 17-27 ■). The carotid and

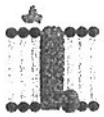


■ **Figure 17-28 Rhythmic breathing** During inspiration, the activity of inspiratory neurons increases steadily, apparently through a positive feedback mechanism. At the end of inspiration, the activity shuts off abruptly and expiration takes place through elastic recoil of the muscles and elastic lung tissue.

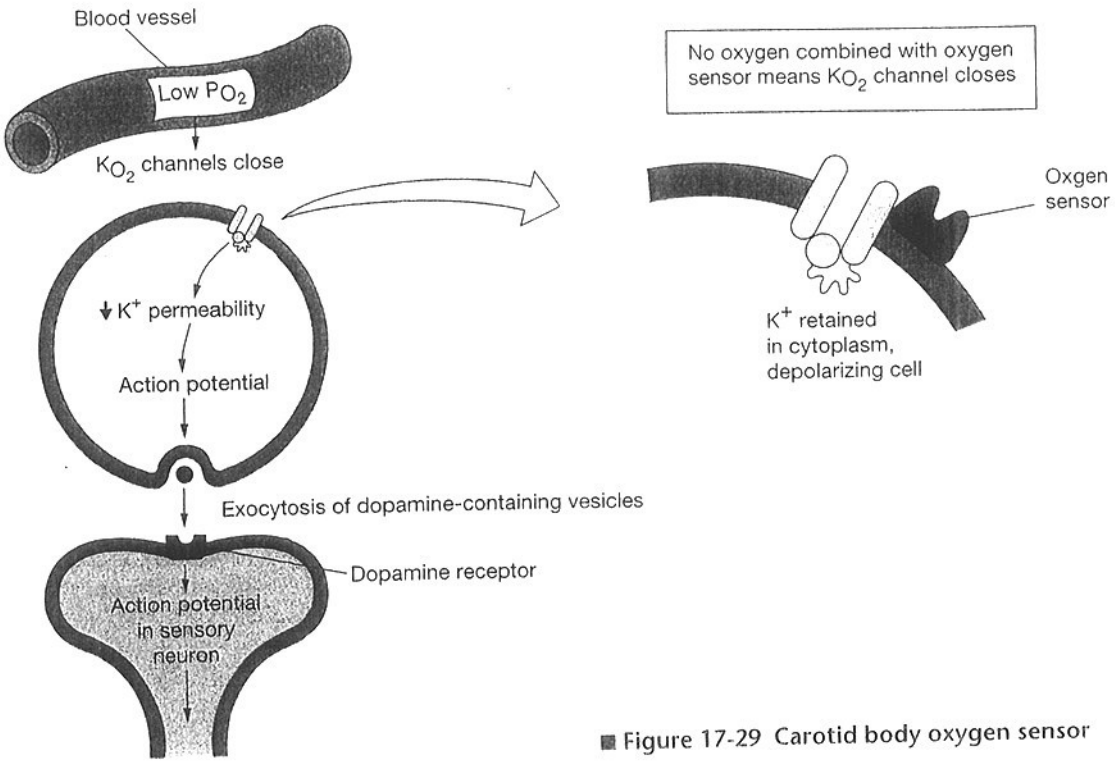
aortic bodies also contain the baroreceptors involved in reflex control of blood pressure (∞ p. 443). The **central chemoreceptors** monitor cerebrospinal fluid (CSF) composition and respond to changes in the concentration of CO_2 in the cerebrospinal fluid. These receptors lie on the ventral surface of the medulla, close to neurons involved in respiratory control.

The carotid and aortic bodies The carotid and aortic chemoreceptors are sensitive to the P_{O_2} and pH of arterial blood. When these receptors are activated by decreases in P_{O_2} or pH, they send action potentials through sensory neurons to the brain stem. Sensory information is integrated within the medullary control centers, and the centers respond by sending signals through somatic motor neurons to the skeletal muscles that control ventilation. The response to decreased P_{O_2} and decreased pH is the same: an increase in ventilation.

Under most circumstances, oxygen is not an important factor in modulating ventilation. Arterial P_{O_2} must drop below 60 mm Hg before ventilation is stimulated. This decrease in P_{O_2} is equivalent to ascending to an altitude of 3000 m. (For reference, Denver is located at an altitude of 1609 m.) Because the peripheral chemoreceptors respond only to dramatic changes in arterial P_{O_2}, they



The Carotid Oxygen Sensors The carotid and aortic bodies contain chemoreceptors that adjust ventilation in response to changes in blood levels of oxygen. But what is the mechanism that translates dissolved oxygen concentrations into electrical signals? In the last decade, researchers have come closer to answering that question. Cells in the carotid bodies called **glomus cells** [*glomus*, a ball-shaped mass] have been identified as the chemoreceptors (Fig. 17-29 ■). The glomus cells contain gated potassium channels, called K_{O_2} channels, that are oxygen-sensitive. An oxygen sensor on the extracellular fluid side of the cell membrane is associated with the channel. When the sensor is combined with oxygen, the channel stays open and K^+ leaves the cell, hyperpolarizing it. If oxygen levels in the blood decrease, fewer of the sensors are combined with O_2 and more of the K_{O_2} channels close. The resultant decrease in potassium permeability depolarizes the cells, causing them to fire repetitive action potentials. The action potentials open voltage-gated calcium channels in the glomus cell membrane, allowing Ca^{2+} to enter the cells. Just as in the axon terminal, calcium entry triggers exocytosis of secretory vesicles containing a neurotransmitter, in this case dopamine. Dopamine initiates action potentials in sensory neurons leading to the central nervous system, signaling the respiratory control centers to increase ventilation.



■ **Figure 17-29 Carotid body oxygen sensor**

do not play a role in the everyday regulation of ventilation. However, unusual physiological conditions (such as ascending to high altitude) and pathological conditions such as chronic obstructive pulmonary disease (COPD) can reduce arterial P_{O_2} to low levels that activate the peripheral chemoreceptors.

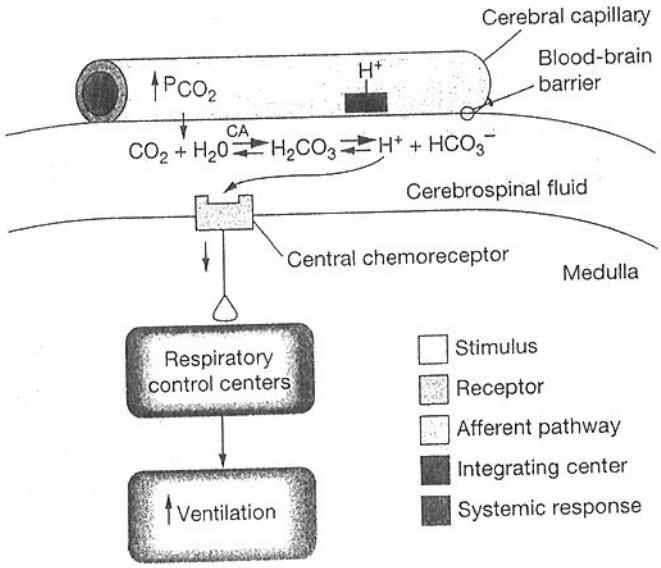
The peripheral chemoreceptors in the carotid and aortic bodies are more responsive to increases in plasma H^+ concentrations than to changes in P_{O_2}. Any condition that reduces plasma pH, including an increase in plasma P_{CO_2}, stimulates ventilation by way of peripheral chemoreceptors.

Central chemoreceptors The most important chemical controller of ventilation is carbon dioxide, mediated through central H^+ chemoreceptors located in the medulla (Fig. 17-30 ■). These receptors set the respiratory pace, providing continuous input into the central pattern generator.

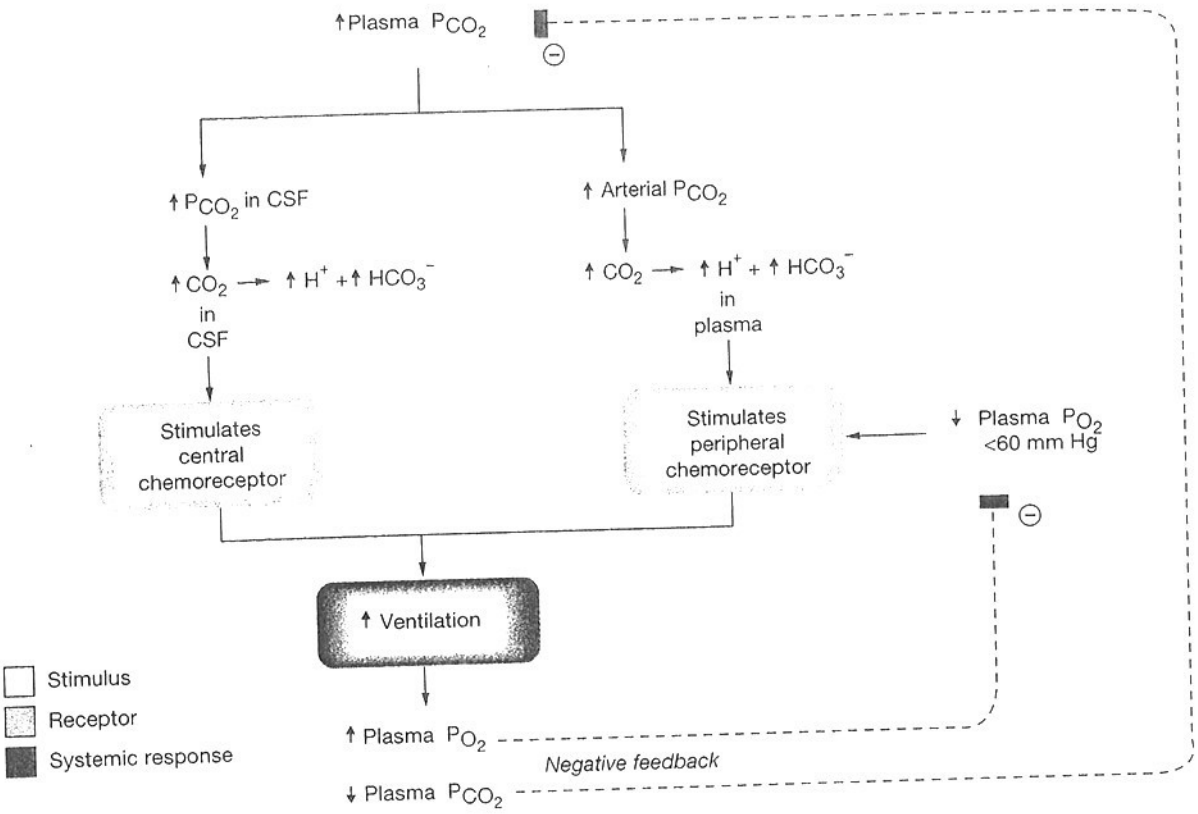
When arterial P_{CO_2} increases, carbon dioxide crosses the blood-brain barrier quite rapidly, resulting in activation of the central chemoreceptors. The receptors signal the central pattern generator to increase the rate and depth of ventilation, thereby increasing alveolar ventilation and removing carbon dioxide from the blood (Fig. 17-31 ■).

Although we say that the central chemoreceptors respond to carbon dioxide, they actually sense changes in the H^+ concentration of the cerebrospinal fluid. These H^+ ions are formed from carbon dioxide that has diffused across the blood-brain barrier into the cerebrospinal fluid ($CO_2 + H_2O \rightleftharpoons H^+ + HCO_3^-$). Free H^+ in the plasma is unable to cross the blood-brain barrier, however, so H^+ from lactic acid and other metabolic acids has no direct effect on the central chemoreceptors.

Decreases in arterial P_{CO_2} also influence ventilation. If alveolar P_{CO_2} falls, as it might owing to hyperventilation, plasma P_{CO_2} declines, as does P_{CO_2} in the cerebrospinal fluid. As a result, central chemoreceptor activity declines, and the central pattern generator slows the ventilation rate. With decreased ventilation, carbon dioxide begins to accumulate in alveoli and the plasma. Eventually, the arterial P_{CO_2} rises above the threshold level for the



■ **Figure 17-30 Central chemoreceptors** The central chemoreceptors are located in the medulla, facing the cerebrospinal fluid. Carbon dioxide can diffuse across the blood-brain barrier, but free H^+ in the plasma cannot. Once in the cerebrospinal fluid, the carbon dioxide is converted to bicarbonate and H^+. The hydrogen ions thus produced stimulate the central chemoreceptors, causing an increase in ventilation.



■ **Figure 17-31 Chemoreceptor reflex**

chemoreceptors. At that point, the receptors fire, and the central pattern generator again increases ventilation.

The central chemoreceptors initially respond strongly to an increase in plasma P_{CO_2} by increasing ventilation. However, if P_{CO_2} remains elevated for several days, ventilation decreases. This adaptation to elevated P_{CO_2} occurs because the blood-brain barrier begins to transport bicarbonate ions into the cerebrospinal fluid. The bicarbonate acts as a buffer, removing H^+ from the cerebrospinal fluid and decreasing H^+ stimulation of the central pattern generator.

Fortunately for people with chronic lung diseases, the response of peripheral chemoreceptors to low arterial oxygen remains intact over time, even though the central chemoreceptors adapt to high P_{CO_2}. In some situations, low P_{O_2} becomes the only chemical stimulus for ventilation. For example, patients with severe chronic lung disease such as emphysema have chronic hypercapnia and hypoxia. Their arterial P_{CO_2} may rise to 50–55 mm Hg, while their P_{O_2} falls to 45–50 mm Hg. Because these levels are chronic, the central chemoreceptors gradually adapt to the elevated P_{CO_2}. Most of the chemical stimulus for ventilation then comes from low P_{O_2}, sensed by the carotid and aortic chemoreceptors. If these patients are given too much oxygen, they may stop breathing because their chemical stimulus for ventilation is eliminated.

On occasion, homeostatic compensation for decreased P_{O_2} will adversely affect plasma P_{CO_2} levels. For example, at altitudes above 3000 m, the P_{O_2} of inspired air drops below 60 mm Hg. This decrease in P_{O_2} activates the carotid and aortic bodies and increases ventilation in an attempt to bring arterial P_{O_2} back into a normal range. But, because the inspired air is low in oxygen, hyperventilation cannot significantly increase arterial P_{O_2}. However, hyperventilation will cause arterial P_{CO_2} to decrease. The decrease in arterial P_{CO_2}, monitored by the central chemoreceptors, then *depresses* ventilation. Within a few days, acclimatization to the lower arterial P_{CO_2} takes place, so ventilation again increases.

Mechanoreceptor Reflexes Protect the Lungs from Inhaled Irritants

In addition to the chemoreceptor reflexes that help regulate ventilation, there are protective reflexes that respond to physical injury or irritation of the respiratory tract and to overinflation of the lungs. The major protective reflex is bronchoconstriction, mediated through parasympathetic neurons that innervate bronchiolar smooth muscle. Inhaled particles or noxious gases stimulate **irritant receptors** in the airway mucosa. The irritant receptors send signals through sensory neurons to control centers in the central nervous system that trigger bronchoconstriction. Protective reflex responses also include coughing and sneezing.

The **Hering-Breuer inflation reflex** is designed to prevent overexpansion of the lungs during strenuous exercise. If tidal volume exceeds 1 liter, stretch receptors in the lung

continued from page 499

Edna is discharged from the hospital after three days with prescriptions for bronchodilator drugs (to keep her airways open) and the nicotine patch (to help her stop smoking). Four days later, however, she becomes dizzy and confused. She falls in her kitchen, but manages to dial 9-1-1. The paramedics who arrive ask her if she has any medical conditions. She replies that she has COPD. The paramedics start Edna on high-flow oxygen and prepare to transport her to the hospital. A paramedic-in-training, along for the ride, asks one of the paramedics about the danger of giving oxygen to Edna. "Thinking has changed on that," the paramedic replies. "Experts think it's more dangerous to withhold oxygen from these patients, especially if they have severe hypercapnia, like this patient."

Question 5: Without performing blood tests, why does the paramedic suspect that Edna has severe hypoxia and hypercapnia (abnormally high levels of P_{CO_2})?

signal the brain stem to terminate inspiration. However, because normal tidal volume is only 500 mL, this reflex does not operate during quiet breathing and mild exertion.

Higher Brain Centers Affect Patterns of Ventilation

Conscious and unconscious thought processes also affect respiratory activities. Higher centers in the hypothalamus and cerebrum can alter the activity of the central pattern generator and change ventilation rate and depth. Voluntary control of ventilation falls into this category. But higher brain center control is not a *requirement* for ventilation. Even if the brain stem above the pons is severely damaged, essentially normal respiratory cycles continue.

Respiration can also be affected by stimulation of portions of the limbic system. As a result, emotional and autonomic activities such as fear and excitement may affect the pace and depth of respiration. In some of these situations, the neural pathway goes directly to the somatic motor neurons, bypassing the central pattern generator in the brain stem.

Although we can temporarily alter our respiratory performance, we cannot override the chemoreceptor reflexes. Holding one's breath is a good example. We can hold our breath voluntarily only until elevated P_{CO_2} in the blood and cerebrospinal fluid activates the chemoreceptor reflex, forcing us to inhale. Small children having temper tantrums sometimes attempt to manipulate parents by threatening to hold their breath until they die. However, the chemoreceptor reflexes make it impossible for the children to carry out that threat. Extremely strong-willed children can continue holding their breath until they turn blue and pass out from hypoxia, but once they are unconscious, normal breathing will automatically resume.

Breathing is intimately linked to cardiovascular function. The integrating centers for both functions are located in the brain stem, and interneurons project between the two centers, allowing signaling back and forth. In Chapter 19, we will examine the integration of cardiovascular, respiratory, and renal function as the three systems work together to maintain fluid and acid-base homeostasis. But first, in Chapter 18, we examine the physiology of the kidneys.

CHAPTER REVIEW

Chapter Summary

1. Aerobic metabolism in living cells consumes oxygen and produces carbon dioxide. (p. 474)
2. Gas exchange requires a thin, moist, internalized exchange surface with a large surface area, a pump to move air between the atmosphere and the exchange surface, and a circulatory system to transport gases between the exchange surface and the cells. (p. 474)
3. The functions of the respiratory system in addition to gas exchange include pH regulation, vocalization, and protection from foreign substances. (p. 475)

The Respiratory System

4. **Cellular respiration** refers to the metabolic processes of the cell that consume oxygen and nutrients and produce energy. **External respiration** is the exchange of gases between the atmosphere and the cells. It includes ventilation, gas exchange at the lung surface and at the cells, and transport of gases in the blood. **Ventilation** is the movement of air into and out of the lungs. (p. 475)
5. The **respiratory system** is composed of the anatomical structures involved in ventilation and gas exchange in the lungs. (p. 475)
6. The **upper respiratory tract** includes the mouth, nasal cavity, **pharynx**, **larynx**, and **trachea**. The **lower respiratory** tract includes the bronchi, bronchioles, and exchange surfaces of the alveoli. (p. 475)
7. The thoracic cage is bounded by the ribs, spine, and **diaphragm**. Two sets of **intercostal muscles** connect the ribs. The respiratory muscles are skeletal muscles innervated by somatic motor neurons. (p. 476)
8. The lungs are paired air-filled organs, each contained within a double-walled pleural sac. A small quantity of **pleural fluid** lies between the pleural membranes. (p. 476)
9. Air passes through the upper respiratory system to the **trachea**. In the **thorax**, the trachea divides to form the two **primary bronchi** that enter the lungs. Each primary

bronchus divides into progressively smaller bronchi and finally into **bronchioles,** small collapsible passageways that deliver air to the respiratory exchange surfaces. (p. 477)

10. Bronchioles terminate in **alveoli,** air sacs composed mostly of thin-walled **type I alveolar cells** for gas exchange. **Type II alveolar cells** produce surfactant. A network of capillaries surrounds each alveolus. (p. 477)
11. Blood flow through the lungs is equal to the cardiac output. Resistance to blood flow in the pulmonary circulation is low, and pulmonary arterial pressure averages 25/8 mm Hg. (p. 477)

Gas Laws

12. The total pressure of a mixture is the sum of the pressures of the individual gases in the mixture (**Dalton's Law**). The pressure contributed by a single gas such as oxygen or carbon dioxide is known as its **partial pressure** (P_{O_2} and P_{CO_2}, respectively). (p. 480)
13. Bulk flow of air occurs down pressure gradients, as does the movement of individual gas species. Gases move from areas of higher pressure of the gas to areas of lower pressure. (p. 481)
14. The body creates pressure gradients and air flow by changing the volume of the thorax. The inverse relationship between pressure and volume is called **Boyle's Law.** (p. 482)
15. The amount of a gas that will dissolve in a liquid is proportional to the partial pressure of the gas and to the **solubility** of the gas in the liquid. Carbon dioxide is 20 times more soluble in body fluids than oxygen. (p. 482)

Ventilation

16. The upper respiratory system is lined with a ciliated epithelium with mucus-secreting goblet cells. The sticky mucus traps dust and microorganisms, filtering out harmful particles. The cilia move the mucus toward the pharynx, where it is swallowed. Evaporation of water from the mucus humidifies the incoming air. (p. 483)
17. Air flow in the respiratory system is directly proportional to the pressure gradient and inversely related to the resistance of the airways to flow. (p. 483)
18. A single **respiratory cycle** consists of an inspiration and an expiration. (p. 484)
19. During **inspiration,** air flows into the lungs as the thoracic cavity enlarges and the **intrapulmonary pressure** drops. Inspiration requires contraction of the inspiratory muscles and the diaphragm. (p. 484)
20. Air flows out during **expiration,** when the volume of the thoracic cavity decreases and the intrapulmonary pressure increases. Expiration is usually passive, resulting from elastic recoil of the skeletal muscles and lungs. (p. 486)
21. **Active expiration** requires contraction of the internal intercostal and abdominal muscles. (p. 486)
22. Intrapleural pressures during ventilation normally remain subatmospheric because the pleural cavity is a sealed compartment. (p. 487)
23. **Compliance** is the ease with which the chest wall and lungs expand. Loss of compliance increases the work of breathing. **Elastance** is the ability of a stretched lung to resume its normal volume. (p. 488)
24. **Surfactant** is a chemical secreted by type II alveolar cells. It decreases surface tension in the fluid that lines the alveoli and prevents the smaller alveoli from collapsing into the larger ones. (p. 489)
25. The diameter of the bronchioles is an important factor affecting air flow. Smaller diameter causes higher resistance to flow. (p. 490)
26. Carbon dioxide in expired air is the main controller of bronchiolar diameter. Increased CO_2 dilates bronchioles. Parasympathetic neurons cause **bronchoconstriction** in response to irritant stimuli in the airways. There is no significant sympathetic innervation of bronchioles, but epinephrine will cause **bronchodilation.** (p. 491)
27. The **tidal volume** is the amount of air taken in during a single normal inspiration. **Vital capacity** is the tidal volume plus the **expiratory** and **inspiratory reserve volumes.** The air left in the lungs at the end of maximum expiration is the **residual volume.** (p. 492)
28. **Total pulmonary ventilation** is the tidal volume times the ventilation rate. **Alveolar ventilation** is a more accurate indicator of air supply to the alveoli. Alveolar ventilation is ventilation rate times (tidal volume minus dead space volume). (p. 493)
29. Gas composition in the alveoli changes very little during a normal respiratory cycle. **Hyperventilation** increases alveolar P_{O_2} and decreases alveolar P_{CO_2}. **Hypoventilation** has the opposite effect. (p. 495)
30. Air flow is matched to blood flow around the alveoli by local mechanisms. Carbon dioxide dilates bronchioles, and decreased oxygen levels constrict pulmonary arterioles. The response of pulmonary arterioles to low oxygen is opposite that of the systemic arterioles. (p. 495)

Gas Exchange in the Lungs

31. Oxygen and carbon dioxide move between the alveoli and blood by simple diffusion. Factors that affect partial pressure gradients at the alveoli include the composition of the inspired air and the effectiveness of alveolar ventilation. (p. 496)
32. Gas exchange between the alveoli and blood is affected by changes in the surface area available for diffusion, the thickness of the alveolar membrane, and the diffusion distance across the interstitial space. (p. 498)
33. Normal alveolar and arterial P_{O_2} is 100 mm Hg, and normal P_{CO_2} is 40 mm Hg. (p. 499)

Gas Exchange in the Tissues

34. Gas exchange in the tissues depends on the pressure gradient between the blood and the cells. Venous blood leaving the tissues has an average P_{O_2} of ≤40 mm Hg and an average P_{CO_2} of ≥46 mm Hg. (p. 499)

Gas Transport in the Blood

35. Oxygen and carbon dioxide that enter the blood first dissolve in the plasma. Their solubility, however, is limited, and red blood cells assist with gas transport. (p. 500)
36. More than 98% of the oxygen carried in the blood is found inside the red blood cells bound to hemoglobin. (p. 501)
37. The P_{O_2} of the plasma determines how much oxygen will bind to hemoglobin. At alveolar P_{O_2}, hemoglobin is almost fully saturated with oxygen. At the peripheral tissues, hemoglobin releases variable amounts of oxygen depending on the P_{O_2} of the tissue. (p. 501)
38. Oxygen-hemoglobin binding is affected by pH, temperature, and **2,3-diphosphoglycerate (2,3-DPG),** a red blood cell metabolite. More oxygen will be released if the pH drops (**Bohr effect**), the temperature rises, or the red blood cells generate 2,3-DPG owing to hypoxia. (p. 502)
39. About 7% of the carbon dioxide transported in the blood is dissolved in the plasma. Another 23% is bound as **carbaminohemoglobin** within the red blood cells. (p. 504)
40. The remaining 70% of blood carbon dioxide is converted to carbonic acid by the enzyme **carbonic anhydrase** inside the red blood cells. Carbonic acid then dissociates into H^+ and HCO_3^-. The H^+ ions are buffered by hemoglobin. The HCO_3^- leaves the red blood cell in exchange for a chloride ion (the **chloride shift**). Once in the plasma, HCO_3^- acts as a buffer. (p. 505)

Regulation of Ventilation

41. Respiratory control resides in a network of neurons in the pons and medulla oblongata. This network is known as the **central pattern generator.** (p. 506)
42. Inspiratory neurons are concentrated in the **dorsal respiratory group** of the medulla. They control somatic motor neurons to the inspiratory muscles and the diaphragm. The **ventral respiratory group** of neurons assists in greater-than-normal inspiration and active expiration. Normal passive expiration occurs when the inspiratory neurons cease firing. (p. 509)
43. Carbon dioxide is the primary stimulus for changes in ventilation. **Central chemoreceptors** in the medulla facing the cerebrospinal fluid respond to changes in P_{CO_2} via changes in CSF H^+ concentrations. An increase in arterial P_{CO_2} increases ventilation. (p. 509)
44. **Peripheral chemoreceptors** in the carotid and aortic bodies monitor P_{O_2} and pH in the blood. Ventilation increases with a decrease in pH or if P_{O_2} falls below 60 mm Hg. (p. 510)
45. Protective reflexes monitored by peripheral mechanoreceptors prevent injury to the lungs from overinflation or irritants. (p. 512)
46. Conscious and unconscious thought processes can affect respiratory activity. (p. 513)

Questions

LEVEL ONE Reviewing Facts and Terms

1. List four functions of the respiratory system.
2. Give two different definitions for the word *respiration.*
3. Which sets of muscles are used for normal quiet inspiration? For normal quiet expiration? For active expiration?
4. What is the function of pleural fluid?
5. Name the anatomical structures that an oxygen molecule passes on its way from the atmosphere to the blood.
6. Diagram the structure of an alveolus and give the function of each part. How are capillaries associated with an alveolus?
7. Trace the path of the pulmonary circulation. About how much blood is found here at any given moment? What is a typical arterial blood pressure for the pulmonary circuit and how does this compare to that of the systemic circulation?
8. List three factors that influence the movement of gas molecules from air into solution. Which of these factors is usually not significant in humans?
9. What happens to inspired air as it is conditioned during its passage through the airways?
10. During inspiration, most of the volume change of the chest is due to movement of the _____.
11. Describe the changes in intra-alveolar and intrapleural pressure during one respiratory cycle.
12. What is the function of surfactant?
13. Of the three factors that contribute to the resistance of air flow through a tube, which plays the largest role in changing resistance in the human respiratory system?
14. Match the following items with their correct effect on the bronchioles:

(a) histamine	1. bronchoconstriction
(b) epinephrine	2. bronchodilation
(c) acetylcholine	3. no effect
(d) increased P_{CO_2}	

15. Define these four terms and explain how they relate to one another: tidal volume, inspiratory reserve volume,

residual volume, expiratory reserve volume. Give an average value for each volume in a young male. List some factors that explain differing values among different individuals.

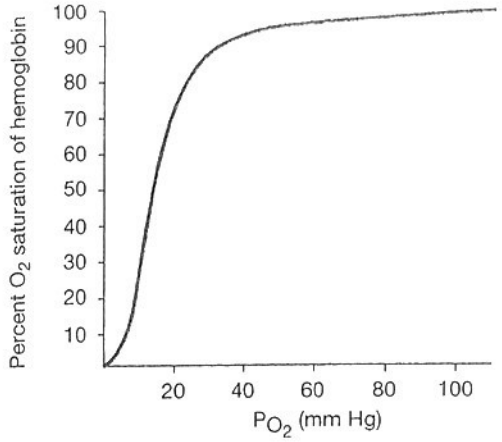
16. More than _____% of the oxygen in arterial blood is transported bound to hemoglobin. How is the remaining oxygen transported to the cells?
17. Name four factors that affect the amount of oxygen that binds to hemoglobin. Which of these four factors is the most important?
18. Describe the structure of a hemoglobin molecule. What element is essential for hemoglobin synthesis?
19. The centers for control of ventilation are found in the _____ and _____ of the brain. The dorsal and ventral respiratory groups of neurons control what processes, respectively? What is a central pattern generator?
20. Name the chemoreceptors that influence ventilation and explain how they do so. What chemical is the most important controller of ventilation?
21. Describe the protective reflexes of the respiratory system. What does the Hering-Breuer reflex prevent? How is it initiated?

LEVEL TWO Reviewing Concepts

22. **Concept map:** Draw an alveolus and adjacent capillary similar to that shown in Figure 17-20. Write in the partial pressures of oxygen and carbon dioxide for the arterial and venous blood and the air. Draw arrows showing diffusion of the gases. Relate the four rules governing diffusion to the figure. Indicate how at least three different pulmonary pathologies can interfere with gas exchange.
23. A container of gas with a moveable piston has a volume of 500 mL and a pressure of 60 mm Hg. The piston is moved and the new pressure is measured as 150 mm Hg. What is the new volume of the container?
24. You have a mixture of gases in dry air, with an atmospheric pressure of 760 mm Hg. Calculate the partial pressure of each gas for each of the examples below:
    a. 21% oxygen, 78% nitrogen, 0.3% carbon dioxide
    b. 40% oxygen, 13% nitrogen, 45% carbon dioxide, 2% hydrogen
    c. 10% oxygen, 15% nitrogen, 1% argon, 25% carbon dioxide
25. Compare and contrast the following sets of concepts:
    a. compliance and elastance
    b. inspiration and expiration
    c. intrapleural and intra-alveolar pressures
    d. total pulmonary ventilation and alveolar ventilation
    e. transport of oxygen and carbon dioxide in arterial blood
26. Neelesh is helping his mother clean a dusty attic. As he watches the dust particles dance in a sunbeam, it occurs to him that he is inhaling many particles like these. When do these particles end up in his body? Explain.
27. Define the following terms: pneumothorax, spirometer, hypoxia, COPD, auscultation, hypoventilation, hypercapnia, bronchoconstriction, minute volume.
28. The cartoon coyote is blowing up a balloon as part of an attempt to once more catch a roadrunner. He first breathes in as much air as he can, then blows out all that he can into the balloon. The volume of air in the balloon is equal to the _____ _____ of the coyote's lungs. This volume can be measured directly, as above, or by adding what respiratory volumes together? In 10 years, when the coyote is still chasing the roadrunner, will he still be able to put as much air into the balloon in one breath? Explain.
29. Define these terms and explain how they differ: oxyhemoglobin, carbaminohemoglobin, hemoglobin saturation, carbonic anhydrase, polycythemia, erythropoietin.

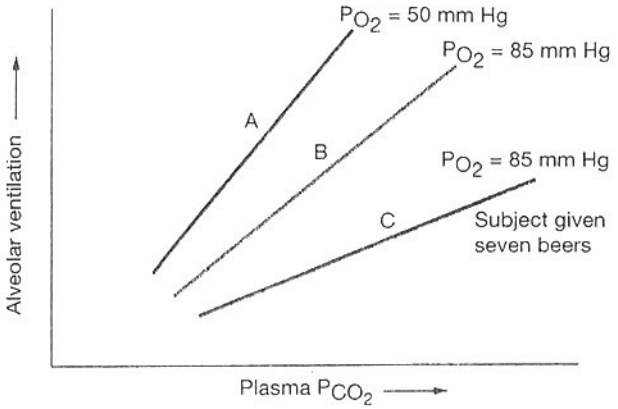
LEVEL THREE Problem Solving

30. Li is a tiny woman, with a tidal volume of 400 mL and a respiratory rate of 12 breaths per minute at rest. What is her total pulmonary ventilation? Just before a physiology exam, her ventilation increases to 18 breaths per minute from nervousness. Now what is her total pulmonary ventilation? Assuming her dead space is 120 mL, what is her alveolar ventilation in each case?
31. Marco tries to hide at the bottom of a swimming hole by breathing through a garden hose that greatly increases his dead space. What happens to the following parameters in his arterial blood, and why?
    a. P_{CO_2} b. P_{O_2} c. bicarbonate ion d. pH
32. A hospitalized patient with severe chronic obstructive lung disease has a P_{CO_2} of 55 mm Hg and a P_{O_2} of 50 mm Hg. To elevate his blood oxygen, he is given pure oxygen through a nasal tube. The patient immediately stops breathing. Explain why this might occur.
33. You are a physiologist on the manned space flight to a distant planet. You find intelligent humanoid creatures inhabiting the planet, and they willingly submit to your tests. Some of the data you have collected are described below:
    a. The graph below shows the oxygen dissociation curve for the oxygen-carrying pigment in the blood of the humanoid named Bzork. Bzork's normal alveolar P_{O_2} is 85 mm Hg. His normal cell P_{O_2} is 20 mm Hg but drops to 10 mm Hg with exercise.



(1) What is the percent saturation for Bzork's oxygen-carrying pigment in blood at the alveoli? At an exercising cell?
(2) What conclusions can you draw about Bzork's oxygen requirement during normal activity and during exercise, based on the graph?

b. The next experiment on Bzork involves his ventilatory response to different conditions. The data from that experiment are graphed below. Line A represents ventilation with an alveolar P_{O_2} of 50 mm Hg. Line B represents ventilation with an alveolar P_{O_2} of 85 mm Hg. Line C represents ventilation with an alveolar P_{O_2} of 85 mm Hg after Bzork has been given beer to drink. Interpret the results of experiments A and C.



Problem Conclusion

In this running problem, you learned about chronic obstructive pulmonary disease.

Further check your understanding of this running problem by checking your answers against those in the summary table.

Question	*Facts*	*Integration and Analysis*
1 What does narrowing of the airways do to the resistance of the airways to air flow?	The relationship between radius and resistance is the same for air flow as it was for blood flow in the circulatory system: As radius decreases, resistance increases (⟸ p. 389).	When resistance increases, the body must use more energy to create air flow or blood flow.
2 Why do people with chronic bronchitis have a higher-than-normal rate of respiratory infections?	Cigarette smoke paralyzes the cilia that sweep debris and mucus out of the airways. Without the action of cilia, mucus and trapped particles pool in the airways.	Because of the lack of the ciliary "housekeeping," bacteria can become established in the lower respiratory tract more easily.
3 Name the muscles that patients with emphysema use to exhale forcefully.	Normal expiration depends on elastic recoil of muscles and elastic tissue in the lungs.	Forceful expiration uses the internal intercostal muscles and the abdominal muscles.
4 Why does Edna have an increased hematocrit?	The body is heavily dependent on the oxygen carried by hemoglobin in red blood cells. Because of Edna's COPD, her arterial P_{O_2} is low. The major stimulus for red blood cell synthesis is hypoxia.	Low arterial oxygen levels will trigger the synthesis of additional red blood cells. This provides more binding sites for oxygen transport.
5 Without performing blood tests, why does the paramedic suspect that Edna has severe hypoxia and hypercapnia (abnormally high levels of P_{CO_2})?	Abnormally high P_{CO_2} or low P_{O_2} can depress the function of the central nervous system.	Edna's altered mental state suggests lack of oxygen to the brain or excessively high CO_2 levels.